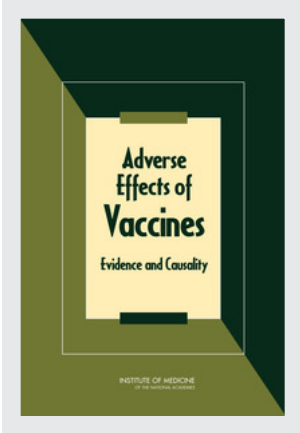


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## Adverse Effects of Vaccines: Evidence and Causality (2012)

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894 pages | 6 x 9 | HARDBACK  
ISBN 978-0-309-21435-3 | DOI 10.17226/13164

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### SUGGESTED CITATION

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Institute of Medicine 2012. *Adverse Effects of Vaccines: Evidence and Causality*. Washington, DC: The National Academies Press.  
<https://doi.org/10.17226/13164>.

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# Adverse Effects of Vaccines

## Evidence and Causality

Committee to Review Adverse Effects of Vaccines  
Board on Population Health and Public Health Practice  
Kathleen Stratton, Andrew Ford, Erin Rusch, and Ellen Wright Clayton,  
*Editors*

INSTITUTE OF MEDICINE  
*OF THE NATIONAL ACADEMIES*

THE NATIONAL ACADEMIES PRESS  
Washington, D.C.  
[www.nap.edu](http://www.nap.edu)

THE NATIONAL ACADEMIES PRESS 500 Fifth Street, N.W. Washington, DC 20001

NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This study was supported by Contract No. HHS230200446009I, Task Order 13 between the National Academy of Sciences and the Health Resources and Services Administration of the U.S. Department of Health and Human Services. The Centers for Disease Control and Prevention and the National Vaccine Program Office also provided support through that contract. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the author(s) and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

#### Library of Congress Cataloging-in-Publication Data

Institute of Medicine (U.S.). Committee to Review Adverse Effects of Vaccines.

Adverse effects of vaccines : evidence and causality / Committee to Review Adverse Effects of Vaccines, Board on Population Health and Public Health Practice ; Kathleen Stratton ... [et al.], editors.

p. ; cm.

Includes bibliographical references and index.

ISBN 978-0-309-21435-3 (hardcover) — ISBN 978-0-309-21436-0 (PDF)

I. Stratton, Kathleen R. II. Title.

[DNLM: 1. Vaccines—adverse effects. 2. Bacterial Infections—prevention & control. 3. Causality. 4. Virus Diseases—prevention & control. QW 805]

615.3'72—dc23

2012007052

Additional copies of this report are available from the National Academies Press, 500 Fifth Street, N.W., Keck 360, Washington, DC 20001; (800) 624-6242 or (202) 334-3313; Internet, <http://www.nap.edu>.

For more information about the Institute of Medicine, visit the IOM home page at: [www.iom.edu](http://www.iom.edu).

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Printed in the United States of America

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Suggested citation: IOM (Institute of Medicine). 2012. *Adverse effects of vaccines: Evidence and causality*. Washington, DC: The National Academies Press.

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Willing is not enough; we must do.”*

—Goethe



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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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**Chris Wilson**, The Bill & Melinda Gates Foundation

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by **Charles C. J. Carpenter**, The Miriam Hospital, and **Floyd E. Bloom**, The Scripps Research Institute. Appointed by the National Research Council and Institute of Medicine, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

## Preface

Vaccines are widely recognized as one of the greatest public health successes of the last century, significantly reducing morbidity and mortality from a variety of bacteria and viruses. Diseases that were once the cause of many outbreaks, common causes of loss of health and life, are now rarely seen, because they have been prevented by vaccines. However, vaccines can in rare cases themselves cause illness. A rare potential for harm can loom large when people no longer experience or fear the targeted disease. In this regard, the public opinion of vaccines can be a victim of their success. The Institute of Medicine (IOM) was charged by Congress when it enacted the National Childhood Vaccine Injury Act in 1986 with reviewing the literature regarding the adverse events associated with vaccines covered by the program, a charge which the IOM has addressed 11 times in the past 25 years. Following in this tradition, the task of this committee was to assess dispassionately the scientific evidence about whether eight different vaccines cause adverse events (AE), a total of 158 vaccine-AE pairs, the largest study undertaken to date, and the first comprehensive review since 1994.

The committee had a herculean task, requiring long and thoughtful discussions of our approach to analyzing the studies culled from more than 12,000 peer-reviewed articles in order to reach our conclusions, which are spelled out in the chapters that follow. In the process, we learned some lessons that may be of value for future efforts to evaluate vaccine safety. One is that some issues simply cannot be resolved with currently available epidemiologic data, excellent as some of the collections and studies are. Particularly for rare events, we look to the day when electronic medical records truly are universal and when society reaches a broad-based con-

sensus about how these records may be used to detect very rare adverse events from vaccines as well as other drugs and medical interventions. Even then, challenges will remain. Some adverse events caused by vaccines are also caused by the natural infection. These effects often cannot be detected by epidemiologic methods, which typically cannot distinguish between the adverse events that are caused by the vaccine itself and the decrease in adverse events due to the decreased rate of natural infection. In addition, even very large epidemiologic studies may not detect or rule out rare events. Subgroup analysis or more focused epidemiologic studies, informed by as yet incomplete knowledge of the biologic mechanisms of vaccine-induced injury, may be required.

Examining mechanistic evidence to assess causation is also challenging. Many of the case reports the committee reviewed simply cited a temporal relation between vaccine administration and an adverse event. Association, however, does not equal causation. More is required. The proof can be relatively straightforward, as when vaccine-specific virus is recovered from the cerebrospinal fluid of a patient who develops viral meningitis a few weeks after receiving the vaccine. Alleged adverse effects that appear to be immune mediated, as many of them are, are more challenging, in part because the biology is not completely understood. One potentially useful line of inquiry as science advances is to assess whether the vaccine recipient who suffers harm had a preexisting susceptibility to that particular adverse event as such studies may provide insight into the mechanisms by which such events occur. The committee is aware of the work funded by the Centers for Disease Control and Prevention (CDC) to study such individuals and looks forward to their findings. Most individuals, for example, who develop invasive infection from live vaccine viruses have demonstrated immunodeficiencies. Our work was also complicated by the wide variation in the case reports regarding what other tests had been done to rule out other potential causes. To improve the utility of these reports, periodically convening a group of experts to suggest guidelines, based on the best available science, for providing mechanistic evidence that a particular adverse event was caused by a vaccine may be useful. These guidelines could be made available on the Web, and perhaps more important, shared with clinicians who report cases to the Vaccine Adverse Event Reporting System so their reports can be as complete and useful as possible.

The value of dialogue between both epidemiologic and mechanisms approaches cannot be overstated. Epidemiologic studies can identify particular at-risk groups, who can then be examined with more in depth testing to explore predisposing factors. The findings of such studies can then inform more focused epidemiologic research as well as efforts to reduce risks. These conversations between different types of research can be difficult, but the results are worth it.

Although the committee is optimistic that more can and will be known about vaccine safety in the future, the limitations of the currently available peer-reviewed data meant that, more often not, we did not have sufficient scientific information to conclude whether a particular vaccine caused a specific rare adverse event. Where the data were inadequate to reach a scientifically defensible conclusion about causation, the committee specifically chose not to say which way the evidence “leaned,” reasoning that such indications would violate our analytic framework. Some readers doubtless will be disappointed by this level of rigor. The committee particularly counsels readers not to interpret a conclusion of inadequate data to accept or reject causation as evidence either that causation is either present or absent. Inadequate data to accept or reject causation means just that—inadequate. It is also important to recognize what our task was not. We were not charged with assessing the benefits of vaccines, with weighing benefits and costs, or with deciding how, when, and to whom vaccines should be administered. The committee was not charged with making vaccine policy. We did receive calls to stride into this contentious debate, but others, such as the Food and Drug Administration and the CDC, are tasked with formulating recommendations for use that balance the risk of vaccines with the benefits, with studying the safety of the vaccines during pre-release trials, and monitoring them closely once the vaccine is in use in the population.

Our work could not have been accomplished without the concerted efforts of the committee members who did their work carefully with good cheer and open minds. The committee’s talented and intrepid staff, Trevonne Walford, Erin Rusch, and Andrew Ford, led by the wisdom and experience of Kathleen Stratton, could not have been more wonderful to work with or more essential to the committee’s task.

Ellen Wright Clayton, *Chair*  
Committee to Review Adverse Effects of Vaccines



# Contents

|                                      |    |
|--------------------------------------|----|
| SUMMARY                              | 1  |
| Charge to the Committee, 2           |    |
| Assessing the Weight of Evidence, 10 |    |
| Causality Assessment, 14             |    |
| Causality Conclusions, 17            |    |
| Susceptibility, 24                   |    |
| Concluding Comment, 24               |    |
| References, 24                       |    |
| 1 INTRODUCTION                       | 27 |
| Charge to the Committee, 30          |    |
| Committee Process, 36                |    |
| Outline of the Report, 36            |    |
| References, 36                       |    |
| 2 APPROACH                           | 39 |
| Literature Searching, 40             |    |
| Weight of Evidence, 42               |    |
| Causality Assessment, 48             |    |
| Special Considerations, 54           |    |
| References, 54                       |    |

|   |  |     |
|---|--|-----|
| 3 | EVALUATING BIOLOGICAL MECHANISMS OF ADVERSE EVENTS                     | 57  |
|   | Latency Between Antigen Exposure and Peak Adaptive Immune Response, 57 |     |
|   | Immune-Mediated Mechanisms, 59   |     |
|   | Viral Activity, 76   |     |
|   | Injection-Related Adverse Events, 78                                   |     |
|   | Coagulation and Hypercoagulable States, 81                             |     |
|   | Increased Susceptibility, 82   |     |
|   | Alterations in Brain Development, 85                                   |     |
|   | Contribution of Animal Models, 89                                      |     |
|   | References, 91   |     |
| 4 | MEASLES, MUMPS, AND RUBELLA VACCINE                                    | 103 |
|   | Introduction, 103  |     |
|   | Measles Inclusion Body Encephalitis, 108                               |     |
|   | Encephalitis and Encephalopathy, 111                                   |     |
|   | Febrile Seizures, 119  |     |
|   | Afebrile Seizures, 133   |     |
|   | Meningitis, 137  |     |
|   | Ataxia, 143  |     |
|   | Autism, 145  |     |
|   | Acute Disseminated Encephalomyelitis, 153                              |     |
|   | Transverse Myelitis, 154   |     |
|   | Optic Neuritis, 156  |     |
|   | Neuromyelitis Optica, 158  |     |
|   | Multiple Sclerosis Onset in Adults, 159                                |     |
|   | Multiple Sclerosis Onset in Children, 164                              |     |
|   | Guillain-Barré Syndrome, 165   |     |
|   | Chronic Inflammatory Disseminated Polyneuropathy, 166                  |     |
|   | Opsoclonus Myoclonus Syndrome, 167                                     |     |
|   | Brachial Neuritis, 168   |     |
|   | Anaphylaxis, 169   |     |
|   | Transient Arthralgia in Women, 174                                     |     |
|   | Transient Arthralgia in Children, 182                                  |     |
|   | Chronic Arthralgia in Women, 190                                       |     |
|   | Chronic Arthritis in Women, 195  |     |
|   | Chronic Arthropathy in Children, 199                                   |     |
|   | Arthropathy in Men, 201  |     |
|   | Type 1 Diabetes, 204   |     |
|   | Hepatitis, 211   |     |
|   | Chronic Fatigue Syndrome, 212  |     |
|   | Fibromyalgia, 213  |     |

|   |   |     |
|---|---|-----|
|   | Hearing Loss, 214   |     |
|   | Concluding Section, 217   |     |
|   | References, 222   |     |
| 5 | VARICELLA VIRUS VACCINE   | 239 |
|   | Introduction, 239   |     |
|   | Disseminated Oka VZV Without Other Organ Involvement, 242                 |     |
|   | Disseminated Oka VZV with Other Organ Involvement, 249                    |     |
|   | Vaccine-Strain Viral Reactivation Without Other Organ<br>Involvement, 256 |     |
|   | Vaccine-Strain Viral Reactivation with Other Organ<br>Involvement, 261    |     |
|   | Encephalopathy, 267   |     |
|   | Seizures, 268   |     |
|   | Cerebellar Ataxia, 269  |     |
|   | Acute Disseminated Encephalomyelitis, 271                                 |     |
|   | Transverse Myelitis, 272  |     |
|   | Guillain-Barré Syndrome, 273  |     |
|   | Small Fiber Neuropathy, 274   |     |
|   | Anaphylaxis, 275  |     |
|   | Onset or Exacerbation of Arthropathy, 278                                 |     |
|   | Stroke, 279   |     |
|   | Thrombocytopenia, 281   |     |
|   | Concluding Section, 282   |     |
|   | References, 285   |     |
| 6 | INFLUENZA VACCINE   | 293 |
|   | Introduction, 293   |     |
|   | Encephalitis and Encephalopathy, 296                                      |     |
|   | Seizures, 301   |     |
|   | Acute Disseminated Encephalomyelitis, 308                                 |     |
|   | Transverse Myelitis, 309  |     |
|   | Optic Neuritis, 310   |     |
|   | Neuromyelitis Optica, 314   |     |
|   | Multiple Sclerosis Onset in Adults, 314                                   |     |
|   | Multiple Sclerosis Relapse in Adults, 318                                 |     |
|   | Guillain-Barré Syndrome, 321  |     |
|   | Chronic Inflammatory Disseminated Polyneuropathy, 334                     |     |
|   | Bell's Palsy, 335   |     |
|   | Brachial Neuritis, 340  |     |
|   | Small Fiber Neuropathy, 340   |     |
|   | Anaphylaxis, 341  |     |



|   |  |     |
|---|--|-----|
|   | Inactivated Influenza Vaccine and Asthma Exacerbation or Reactive Airway Disease Episodes in Children and Adults, 345                      |     |
|   | Live Attenuated Influenza Vaccine and Asthma Exacerbation or Reactive Airway Disease Episodes in Children Younger Than 5 Years of Age, 356 |     |
|   | Live Attenuated Influenza Vaccine and Asthma Exacerbation or Reactive Airway Disease Episodes in Persons 5 Years of Age or Older, 366      |     |
|   | Onset or Exacerbation of Systemic Lupus Erythematosus, 373   |     |
|   | Onset or Exacerbation of Vasculitis, 379   |     |
|   | Polyarteritis Nodosa, 383  |     |
|   | Onset or Exacerbation of Arthropathy, 384  |     |
|   | Stroke, 386  |     |
|   | Myocardial Infarction, 387   |     |
|   | Fibromyalgia, 389  |     |
|   | All-Cause Mortality, 390   |     |
|   | Oculorespiratory Syndrome, 391   |     |
|   | Concluding Section, 401  |     |
|   | References, 405  |     |
| 7 | HEPATITIS A VACCINE  | 421 |
|   | Introduction, 421  |     |
|   | Acute Disseminated Encephalomyelitis, 423  |     |
|   | Transverse Myelitis, 424   |     |
|   | Multiple Sclerosis, 425  |     |
|   | Guillain-Barré Syndrome, 426   |     |
|   | Chronic Inflammatory Disseminated Polyneuropathy, 427  |     |
|   | Bell's Palsy, 427  |     |
|   | Anaphylaxis, 428   |     |
|   | Autoimmune Hepatitis, 429  |     |
|   | Concluding Section, 430  |     |
|   | References, 432  |     |
| 8 | HEPATITIS B VACCINE  | 435 |
|   | Introduction, 435  |     |
|   | Encephalitis and Encephalopathy, 437   |     |
|   | Seizures, 438  |     |
|   | Acute Disseminated Encephalomyelitis, 440  |     |
|   | Transverse Myelitis, 442   |     |
|   | Optic Neuritis, 443  |     |
|   | Neuromyelitis Optica, 446  |     |
|   | Multiple Sclerosis Onset in Adults, 447  |     |
|   | Multiple Sclerosis Onset in Children, 454  |     |

|    |   |     |
|----|---|-----|
|    | Multiple Sclerosis Relapse in Adults, 455   |     |
|    | Multiple Sclerosis Relapse in Children, 457   |     |
|    | First Demyelinating Event in Adults, 458  |     |
|    | First Demyelinating Event in Children, 464  |     |
|    | Guillain-Barré Syndrome, 465  |     |
|    | Chronic Inflammatory Disseminated Polyneuropathy, 466                               |     |
|    | Brachial Neuritis, 467  |     |
|    | Anaphylaxis, 468  |     |
|    | Erythema Nodosum, 469   |     |
|    | Onset or Exacerbation of Systemic Lupus Erythematosus, 471                          |     |
|    | Onset or Exacerbation of Vasculitis, 473  |     |
|    | Onset or Exacerbation of Polyarteritis Nodosa, 477                                  |     |
|    | Onset or Exacerbation of Psoriatic Arthritis, 479                                   |     |
|    | Onset or Exacerbation of Reactive Arthritis, 480                                    |     |
|    | Onset or Exacerbation of Rheumatoid Arthritis, 482                                  |     |
|    | Onset or Exacerbation of Juvenile Idiopathic Arthritis, 485                         |     |
|    | Type 1 Diabetes, 488  |     |
|    | Fibromyalgia, 490   |     |
|    | Concluding Section, 490   |     |
|    | References, 494   |     |
| 9  | HUMAN PAPILLOMAVIRUS VACCINE  | 505 |
|    | Introduction, 505   |     |
|    | Acute Disseminated Encephalomyelitis, 507   |     |
|    | Transverse Myelitis, 508  |     |
|    | Neuromyelitis Optica, 509   |     |
|    | Multiple Sclerosis, 510   |     |
|    | Guillain-Barré Syndrome, 511  |     |
|    | Chronic Inflammatory Disseminated Polyneuropathy, 512                               |     |
|    | Brachial Neuritis, 512  |     |
|    | Amyotrophic Lateral Sclerosis, 513  |     |
|    | Anaphylaxis, 515  |     |
|    | Transient Arthralgia, 516   |     |
|    | Pancreatitis, 517   |     |
|    | Thromboembolic Events, 519  |     |
|    | Hypercoagulable States, 520   |     |
|    | Concluding Section, 520   |     |
|    | References, 522   |     |
| 10 | DIPHThERIA TOXOID–, TETANUS TOXOID–, AND<br>ACELLULAR PERTUSSIS–CONTAINING VACCINES | 525 |
|    | Introduction, 525   |     |
|    | Encephalitis and Encephalopathy, 534  |     |

|   |            |
|---|------------|
| Infantile Spasms, 537                                 |            |
| Seizures, 539   |            |
| Ataxia, 544   |            |
| Autism, 545   |            |
| Acute Disseminated Encephalomyelitis, 546             |            |
| Transverse Myelitis, 547                              |            |
| Optic Neuritis, 549                                   |            |
| Multiple Sclerosis Onset in Adults, 550               |            |
| Multiple Sclerosis Relapse in Adults, 554             |            |
| Multiple Sclerosis Relapse in Children, 555           |            |
| Guillain-Barré Syndrome, 557                          |            |
| Chronic Inflammatory Disseminated Polyneuropathy, 558 |            |
| Opsoclonus Myoclonus Syndrome, 560                    |            |
| Bell's Palsy, 561                                     |            |
| Anaphylaxis, 563                                      |            |
| Chronic Urticaria, 565                                |            |
| Serum Sickness, 566                                   |            |
| Arthropathy, 567                                      |            |
| Type 1 Diabetes, 571                                  |            |
| Myocarditis, 579                                      |            |
| Fibromyalgia, 581                                     |            |
| Sudden Infant Death Syndrome, 581                     |            |
| Immune Thrombocytopenic Purpura, 582                  |            |
| Concluding Section, 584                               |            |
| References, 589                                       |            |
| <b>11 MENINGOCOCCAL VACCINE</b>                       | <b>599</b> |
| Introduction, 599                                     |            |
| Encephalitis and Encephalopathy, 602                  |            |
| Acute Disseminated Encephalomyelitis, 603             |            |
| Transverse Myelitis, 604                              |            |
| Multiple Sclerosis, 605                               |            |
| Guillain-Barré Syndrome, 606                          |            |
| Chronic Inflammatory Disseminated Polyneuropathy, 607 |            |
| Anaphylaxis, 608                                      |            |
| Chronic Headache, 610                                 |            |
| Concluding Section, 610                               |            |
| References, 612                                       |            |
| <b>12 INJECTION-RELATED ADVERSE EVENTS</b>            | <b>615</b> |
| Complex Regional Pain Syndrome, 615                   |            |
| Deltoid Bursitis, 618                                 |            |
| Syncope, 620  |            |

|  |            |
|--|------------|
| CONTENTS   | <i>xix</i> |
| Concluding Section, 624  |            |
| References, 626  |            |
| 13 CONCLUDING COMMENTS   | 629        |
| References, 633  |            |
| APPENDIXES   |            |
| A GLOSSARY   | 635        |
| B LIST OF ADVERSE EVENTS   | 649        |
| C LITERATURE SEARCH STRATEGY   | 655        |
| D CAUSALITY CONCLUSION TABLES  | 673        |
| E REFERENCES   | 749        |
| F COMMITTEE BIOSKETCHES  | 827        |
| G MEETING AGENDAS  | 835        |
| INDEX  | 839        |
| FIGURES  |            |
| S-1 Epidemiologic and mechanistic evidence reviewed by the committee, 11   |            |
| S-2 Strength of evidence that determined the causality conclusions, 16   |            |
| 2-1 Epidemiologic and mechanistic evidence reviewed by the committee, 41   |            |
| 2-2 Strength of evidence that determined the causality conclusions, 51   |            |
| 3-1 Present and past environmental exposures, 83   |            |
| TABLES   |            |
| S-1 Adverse Events and Causality Conclusions Included in the Vaccine Chapters, 3                                     |            |
| S-2 Summary of Causality Conclusions, 19   |            |
| 1-1 Adverse Events Included in the Vaccine Chapters, 31  |            |
| 4-1 Studies Included in the Weight of Epidemiologic Evidence for MMR Vaccine and Encephalopathy or Encephalitis, 114 |            |
| 4-2 Studies Included in the Weight of Epidemiologic Evidence for MMR Vaccine and Febrile Seizures, 125               |            |

- 4-3 Studies Included in the Weight of Epidemiologic Evidence for MMR Vaccine and Afebrile Seizures, 135
- 4-4 Studies Included in the Weight of Epidemiologic Evidence for MMR Vaccine and Meningitis, 140
- 4-5 Studies Included in the Weight of Epidemiologic Evidence for MMR Vaccine and Autism, 149
- 4-6 Studies Included in the Weight of Epidemiologic Evidence for MMR Vaccine and MS Onset in Adults, 162
- 4-7 Studies Included in the Weight of Epidemiologic Evidence for MMR Vaccine and Transient Arthralgia in Women, 177
- 4-8 Studies Included in the Weight of Epidemiologic Evidence for MMR Vaccine and Transient Arthralgia in Children, 186
- 4-9 Studies Included in the Weight of Epidemiologic Evidence for MMR Vaccine and Chronic Arthralgia in Women, 192
- 4-10 Studies Included in the Weight of Epidemiologic Evidence for MMR Vaccine and Chronic Arthritis in Women, 197
- 4-11 Studies Included in the Weight of Epidemiologic Evidence for MMR Vaccine and Arthropathy in Men, 203
- 4-12 Studies Included in the Weight of Epidemiologic Evidence for MMR Vaccine and Type 1 Diabetes, 208
- 4-13 Summary of Epidemiologic Assessments, Mechanistic Assessments, and Causality Conclusions for Measles, Mumps, and Rubella Vaccine, 218
  
- 5-1 Summary of Epidemiologic Assessments, Mechanistic Assessments, and Causality Conclusions for Varicella Vaccine, 283
  
- 6-1 Influenza Vaccines Licensed and Available in the United States, 297
- 6-2 Studies Included in the Weight of Epidemiologic Evidence for Influenza Vaccine and Seizures, 305
- 6-3 Studies Included in the Weight of Epidemiologic Evidence for Influenza Vaccine and Optic Neuritis, 312
- 6-4 Studies Included in the Weight of Epidemiologic Evidence for Influenza Vaccine and MS Onset in Adults, 317
- 6-5 Studies Included in the Weight of Epidemiologic Evidence for Influenza Vaccine and MS Relapse in Adults, 320
- 6-6 Studies Included in the Weight of Epidemiologic Evidence for Influenza Vaccine and GBS, 328
- 6-7 Studies Included in the Weight of Epidemiologic Evidence for Influenza Vaccine and Bell's Palsy, 338
- 6-8 Studies Included in the Weight of Epidemiologic Evidence for Inactivated Influenza Vaccine and Asthma Exacerbation or Reactive Airway Disease Episodes in Children and Adults, 351

- 6-9 Studies Included in the Weight of Epidemiologic Evidence for Live Attenuated Influenza Vaccine and Asthma Exacerbation or Reactive Airway Disease Episodes in Children Younger Than 5 Years of Age, 362
- 6-10 Studies Included in the Weight of Epidemiologic Evidence for Live Attenuated Influenza Vaccine and Asthma Exacerbation or Reactive Airway Disease Episodes in Persons 5 Years of Age or Older, 370
- 6-11 Studies Included in the Weight of Epidemiologic Evidence for Influenza Vaccine and Exacerbation of SLE, 376
- 6-12 Studies Included in the Weight of Epidemiologic Evidence for Influenza Vaccine and Exacerbation of Vasculitis, 381
- 6-13 Studies Included in the Weight of Epidemiologic Evidence for Influenza Vaccine and Oculorespiratory Syndrome, 395
- 6-14 Summary of Epidemiologic Assessments, Mechanistic Assessments, and Causality Conclusions for Influenza Vaccine, 402
  
- 7-1 Summary of Epidemiologic Assessments, Mechanistic Assessments, and Causality Conclusions for Hepatitis A Vaccine, 431
  
- 8-1 Studies Included in the Weight of Epidemiologic Evidence for Hepatitis B Vaccine and Optic Neuritis, 445
- 8-2 Studies Included in the Weight of Epidemiologic Evidence for Hepatitis B Vaccine and MS Onset in Adults, 451
- 8-3 Studies Included in the Weight of Epidemiologic Evidence for Hepatitis B Vaccine and First Demyelinating Event in Adults, 461
- 8-4 Summary of Epidemiologic Assessments, Mechanistic Assessments, and Causality Conclusions for Hepatitis B Vaccine, 491
  
- 9-1 Summary of Epidemiologic Assessments, Mechanistic Assessments, and Causality Conclusions for HPV Vaccine, 521
  
- 10-1 Diphtheria Toxoid-, Tetanus Toxoid-, and Acellular Pertussis-Containing Vaccines Licensed and Available in the United States, 531
- 10-2 Studies Included in the Weight of Epidemiologic Evidence for Diphtheria Toxoid-, Tetanus Toxoid-, and Acellular Pertussis-Containing Vaccines and Seizures, 542
- 10-3 Studies Included in the Weight of Epidemiologic Evidence for Diphtheria Toxoid-, Tetanus Toxoid-, and Acellular Pertussis-Containing Vaccines and MS Onset in Adults, 552

- 10-4 Studies Included in the Weight of Epidemiologic Evidence for Diphtheria Toxoid–, Tetanus Toxoid–, and Acellular Pertussis–Containing Vaccines and Arthropathy, 569
- 10-5 Studies Included in the Weight of Epidemiologic Evidence for Diphtheria Toxoid–, Tetanus Toxoid–, and Acellular Pertussis–Containing Vaccines and Type 1 Diabetes, 575
- 10-6 Summary of Epidemiologic Assessments, Mechanistic Assessments, and Causality Conclusions for Diphtheria Toxoid (DT)–, Tetanus Toxoid (TT)–, and Acellular Pertussis (aP)–Containing Vaccines, 585
  
- 11-1 Summary of Epidemiologic Assessments, Mechanistic Assessments, and Causality Conclusions for Meningococcal Vaccine, 611
  
- 12-1 Summary of Epidemiologic Assessments, Mechanistic Assessments, and Causality Conclusions for Injection-Related Adverse Events, 625
  
- B-1 Adverse Events Included in the Vaccine Chapters, 650
  
- D-1 Causality Conclusions Organized by Chapter and Adverse Event, 674
- D-2 Causality Conclusions Organized by Adverse Event and Chapter, 689
- D-3 Causality Conclusions Organized by Causality Conclusion, Adverse Event, and Chapter, 704
- D-4 Causality Conclusions Organized by Epidemiologic Assessment, Adverse Event, and Chapter, 719
- D-5 Causality Conclusions Organized by Mechanistic Assessment, Adverse Event, and Chapter, 734

## Acronyms

|       |  |
|-------|--|
| AAP   | American Academy of Pediatrics   |
| AAV   | ANCA-associated vasculitis   |
| ACIP  | Advisory Committee on Immunization Practices   |
| ADEM  | acute disseminated encephalomyelitis   |
| ADI-R | autism diagnostic index—revised  |
| ADOS  | autism diagnostic observational schedule   |
| ADRAC | Adverse Drug Reactions Advisory Committee<br>(Australia)   |
| AE    | adverse event  |
| AIDS  | acquired immune deficiency syndrome  |
| ALL   | acute lymphoblastic leukemia   |
| ALS   | amyotrophic lateral sclerosis  |
| ALT   | alanine aminotransferase   |
| AMAN  | acute motor axonal neuropathy  |
| ANA   | anti-nuclear antibodies  |
| ANCA  | antineutrophil cytoplasmic antibody  |
| aP    | acellular pertussis  |
| BPV   | bovine papillomavirus  |
| BU    | Boston University  |
| BVAS  | Birmingham Vasculitis Activity Score   |
| CAIV  | cold-adapted influenza virus <i>or</i> cold-adapted, trivalent<br>intranasal influenza virus vaccine |
| CDC   | Centers for Disease Control and Prevention   |



|              |  |
|--------------|--|
| CI           | confidence interval  |
| CIDP         | chronic inflammatory disseminated polyneuropathy                               |
| CNS          | central nervous system   |
| CRPS         | complex regional pain syndrome   |
| CSF          | cerebrospinal fluid  |
| DMSS         | Defense Medical Surveillance System  |
| DNA          | deoxyribonucleic acid  |
| DSM          | <i>Diagnostic and Statistical Manual of Psychological Disorders</i>            |
| DT           | diphtheria and tetanus toxoids   |
| DTaP         | diphtheria toxoid, tetanus toxoid, acellular pertussis                         |
| DTP          | diphtheria toxoid, tetanus toxoid, pertussis                                   |
| DTwP         | diphtheria toxoid, tetanus toxoid, whole cell pertussis                        |
| EAE          | experimental allergic encephalomyelitis  |
| EIA          | enzyme immunoassay   |
| ELISA        | enzyme linked immunosorbent assay  |
| ER           | emergency room   |
| EURODIAB ACE | European diabetes: aetiology of childhood diabetes on an epidemiological basis |
| Fc           | Constant region  |
| FDA          | U.S. Food and Drug Administration  |
| FEV          | forced expiratory volume   |
| FHA          | filamentous hemagglutinin  |
| FOIA         | Freedom of Information Act   |
| FUS/TLS      | fused in sarcoma/translocated in liposarcoma                                   |
| GBS          | Guillain-Barré syndrome  |
| GHC          | Group Health Cooperative   |
| GM-CSF       | granulocyte/macrophage colony-stimulating factor                               |
| GPRD         | General Practice Research Database   |
| HAI          | hemagglutination inhibition assay  |
| HAV          | hepatitis A virus  |
| HBIG         | hepatitis B immune globulin  |
| HBsAg        | hepatitis B surface antigen  |
| HBV          | hepatitis B virus  |
| HBVP         | hepatitis B virus polymerase   |
| HHS          | U.S. Department of Health and Human Services                                   |
| HiB          | <i>Haemophilus influenzae</i> type B   |
| HIV          | human immunodeficiency virus   |

|        |   |
|--------|---|
| HLA    | human leukocyte antigen                         |
| HMO    | health maintenance organization                 |
| HPMG   | HealthPartners Medical Group                    |
| HPV    | human papillomavirus                            |
| HRSA   | Health Resources and Services Administration    |
| HTLV   | human T-lymphotropic virus                      |
| HZ     | herpes zoster                                   |
| ICD    | International Classification of Diseases        |
| IDDM   | insulin dependent diabetes mellitus             |
| Ig     | immunoglobulin                                  |
| IL     | interleukin                                     |
| IOM    | Institute of Medicine                           |
| IPV    | inactivated poliovirus vaccine                  |
| ITP    | immune thrombocytopenic purpura                 |
| JIA    | juvenile idiopathic arthritis                   |
| KIDSEP | French Kids Sclérose en Plaques                 |
| KP     | Kaiser Permanente                               |
| KPMCP  | Kaiser Permanente Medical Care Program          |
| LAIV   | live attenuated influenza virus                 |
| LOS    | lipo-oligosaccharide                            |
| MAC    | membrane attack complex                         |
| MBP    | myelin basic protein                            |
| MCC    | Measles Control Campaign                        |
| MCO    | medical care organization                       |
| MHC    | major histocompatibility complex                |
| MHC    | Ministry of Health Mother-Child Health (Israel) |
| MIT    | Massachusetts Institute of Technology           |
| MMR    | measles, mumps, rubella                         |
| MMRV   | measles, mumps, rubella, and varicella          |
| MPO    | myeloperoxidase                                 |
| MPSV   | meningococcal polysaccharide vaccine            |
| MR     | measles-rubella                                 |
| MRI    | magnetic resonance imaging                      |
| MS     | multiple sclerosis                              |
| NCES   | National Childhood Encephalopathy Study         |
| NCK    | Northern California Kaiser                      |
| NCKP   | Northern California Kaiser Permanente           |

|         |  |
|---------|--|
| NCVIA   | National Childhood Vaccine Injury Act                                    |
| NK      | natural killer   |
| NMO     | neuromyelitis optica   |
| OMS     | opsoclonus myoclonus syndrome  |
| OPV     | oral polio vaccine   |
| ON      | optic neuritis   |
| OR      | odds ratio   |
| ORS     | oculorespiratory syndrome  |
| PAMP    | pathogen-associated molecular pattern                                    |
| PAN     | polyarteritis nodosa   |
| PCR     | polymerase chain reaction  |
| PDD     | pervasive developmental disorder   |
| PEF     | peak expiratory flow   |
| PFU     | plaque-forming unit  |
| PR3     | proteinase 3   |
| PRP     | polyribosylribitol phosphate   |
| PRR     | pattern recognition receptor   |
| RA      | rheumatoid arthritis   |
| RCT     | randomized controlled trial  |
| RNA     | ribonucleic acid   |
| RR      | relative risk  |
| RT-PCR  | reverse transcription polymerase chain reaction                          |
| SAFEVIC | Surveillance of Adverse Events following Vaccination<br>in the Community |
| SAFEVSS | Serious Adverse Events Following Vaccination<br>Surveillance Scheme      |
| SIDS    | sudden infant death syndrome   |
| SIP     | sympathetically independent pain   |
| SLE     | systemic lupus erythematosus   |
| SLEDAI  | SLE Disease Activity Index   |
| SMP     | sympathetically maintained pain  |
| SSPE    | subacute sclerosing panencephalitis                                      |
| SWHP    | Scott & White Health Plan  |
| TCR     | T cell receptor  |
| TF      | tissue factor  |
| TIV     | trivalent inactivated influenza vaccine                                  |
| TT      | tetanus toxoid   |

ACRONYMS

*xxvii*

|       |   |
|-------|---|
| VAERS | Vaccine Adverse Event Reporting System        |
| VAS   | visual analogue score                         |
| VICP  | National Vaccine Injury Compensation Program  |
| VIS   | Vaccine Information Statement                 |
| VLP   | virus like particle                           |
| VSD   | Vaccine Safety Datalink                       |
| VZV   | varicella zoster virus                        |
| VZVIP | Varicella Zoster Virus Identification Program |
| WAES  | Worldwide Adverse Experience System           |
| WHO   | World Health Organization                     |



## Summary

Congress passed the National Childhood Vaccine Injury Act (P.L. 99-660) in 1986. The legislation was intended to bolster vaccine research and development through federal coordination of vaccine efforts in government by providing relief to vaccine manufacturers who reported at the time that financial burdens from awards in the tort system threatened their financial viability. The legislation was also intended to address concerns about the safety of vaccines through a multipronged approach involving instituting a compensation program financed by an excise tax on covered vaccines, setting up a passive surveillance system for vaccine adverse events, and providing information to consumers.

Sections 312 and 313 of the legislation required the secretary of the U.S. Department of Health and Human Services to consult with the Institute of Medicine (IOM) to conduct a review of the scientific literature related to a set of serious adverse events<sup>1</sup> following immunizations recommended for use in children. Two reports were issued (IOM, 1991, 1994). These reports contain a framework for causality assessment of adverse events following vaccination. The reports embraced all vaccines covered by the National Vaccine Injury Compensation Program (VICP) up to that point: diphtheria- and tetanus-toxoids and whole cell pertussis (DTwP) vaccine<sup>2</sup> and other tetanus toxoid-containing vaccines; measles, mumps, and rubella

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<sup>1</sup>Adverse *events* are distinguished from adverse *effects* in that an event is something that occurs but may not be causally associated, whereas an adverse *effect* implies causation. All adverse effects are adverse events, but not all adverse events are adverse effects.

<sup>2</sup>Acellular pertussis vaccine (aP) has replaced whole cell pertussis vaccine in the United States.

(MMR) vaccines; *Haemophilus influenzae* type B vaccine; hepatitis B vaccine; and both inactivated and oral polio vaccines.<sup>3</sup> The reports informed the secretary's review of the Vaccine Injury Table. The reports have also been referenced extensively as a source of definitive scientific understanding of the evidence by Special Masters in decisions regarding injuries not listed on the Vaccine Injury Table.

The IOM was subsequently asked to review specific vaccine safety concerns in a series of reports requested by the Centers for Disease Control and Prevention (CDC). These reports (IOM, 2001a,b, 2002a,b, 2003a,b, 2004a,b) included causality assessments similar to the previous IOM reports, but included other conclusions and recommendations regarding research, communications, and policy review.

### CHARGE TO THE COMMITTEE

In 2009 the IOM entered into a contract with the Health Resources and Services Administration (HRSA)<sup>4</sup> to convene a committee of experts to review the epidemiologic, clinical, and biological evidence regarding adverse health events associated with specific vaccines covered by the VICP. The committee was composed of individuals with expertise in pediatrics, internal medicine, neurology, immunology, immunotoxicology, neurobiology, rheumatology, epidemiology, biostatistics, and law.

The vaccines to be reviewed included varicella zoster vaccine; influenza vaccines;<sup>5</sup> hepatitis B vaccine; human papillomavirus vaccine (HPV); tetanus toxoid-containing vaccines other than those containing the whole cell pertussis component; measles, mumps, and rubella vaccines; hepatitis A vaccine; and meningococcal vaccines. It is expected that the report will provide the scientific basis for review and adjudication of claims of vaccine injury by the VICP.

HRSA presented a list of specific adverse events for the committee to review (see Table S-1). The selection criteria was described at the first committee meeting (Johann-Liang, 2009) as including the vast majority of adverse events in the claims for compensation. The committee added adverse events to the list if it identified epidemiologic studies or case reports for an adverse event not originally assigned by HRSA. These additions were all-cause mortality and seizures following influenza vaccine; optic neuritis

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<sup>3</sup>Vaccines are included in the VICP if they are recommended by the CDC for routine administration in children and are subject to an excise tax. Adults who experience an adverse reaction to one of these "childhood" vaccines are also covered by the program.

<sup>4</sup>The CDC and the National Vaccine Program Office also provided funds for the project via the contract with HRSA.

<sup>5</sup>The 2009 H1N1 influenza vaccine is covered by the Countermeasures Injury Compensation Program, and evidence about its safety is not covered in this report.

TABLE S-1 Adverse Events and Causality Conclusions Included in the Vaccine Chapters

| Adverse Event   | DT-, TT-, and aP-     |                             |                             |                               |                               |                       |                                |                                  |                                     |   |   |   |
|---|-----------------------|-----------------------------|-----------------------------|-------------------------------|-------------------------------|-----------------------|--------------------------------|----------------------------------|-------------------------------------|---|---|---|
|   | MMR Vaccine Chapter 4 | Varicella Vaccine Chapter 5 | Influenza Vaccine Chapter 6 | Hepatitis A Vaccine Chapter 7 | Hepatitis B Vaccine Chapter 8 | HPV Vaccine Chapter 9 | Containing Vaccines Chapter 10 | Meningococcal Vaccine Chapter 11 | Injection-Related Events Chapter 12 |   |   |   |
| Disseminated Oka VZV without Other Organ Involvement  | CS                    |                             |                             |                               |                               |                       |                                |                                  |                                     |   |   |   |
| Disseminated Oka VZV with Subsequent Infection Resulting in Pneumonia, Meningitis, or Hepatitis     | CS <sup>a</sup>       |                             |                             |                               |                               |                       |                                |                                  |                                     |   |   |   |
| Vaccine Strain Viral Reactivation without Other Organ Involvement                                   | CS                    |                             |                             |                               |                               |                       |                                |                                  |                                     |   |   |   |
| Vaccine Strain Viral Reactivation with Subsequent Infection Resulting in Meningitis or Encephalitis | CS                    |                             |                             |                               |                               |                       |                                |                                  |                                     |   |   |   |
| Measles Inclusion Body Encephalitis   | CS <sup>a,b</sup>     |                             |                             |                               |                               |                       |                                |                                  |                                     |   |   |   |
| Encephalitis  | I                     | I                           | I                           | I                             | I                             | I                     | I                              | I                                | I                                   | I | I | I |
| Encephalopathy  | I                     | I                           | I                           | I                             | I                             | I                     | I                              | I                                | I                                   | I | I | I |
| Infantile Spasms  | I                     |                             |                             |                               |                               |                       |                                |                                  |                                     |   |   |   |

*continued*



TABLE S-1 Continued

| Adverse Event                        | MMR Vaccine Chapter 4 | Varicella Vaccine Chapter 5 | Influenza Vaccine Chapter 6 | Hepatitis A Vaccine Chapter 7 | Hepatitis B Vaccine Chapter 8 | HPV Vaccine Chapter 9 | DT-, TT-, and aP-   |                                  | Injection-Related Events Chapter 12 |
|--------------------------------------|-----------------------|-----------------------------|-----------------------------|-------------------------------|-------------------------------|-----------------------|---------------------|----------------------------------|-------------------------------------|
|                                      |                       |                             |                             |                               |                               |                       | Vaccines Chapter 10 | Meningococcal Vaccine Chapter 11 |                                     |
| Febrile Seizures                     | CS                    |                             |                             |                               |                               |                       |                     |                                  |                                     |
| Afebrile Seizures                    | I                     |                             |                             |                               |                               |                       |                     |                                  |                                     |
| Seizures                             | I                     | I <sup>c</sup>              |                             |                               |                               |                       |                     |                                  |                                     |
| Meningitis                           | I <sup>c</sup>        |                             |                             |                               |                               |                       |                     |                                  |                                     |
| Cerebellar Ataxia                    | I                     |                             |                             |                               |                               |                       |                     |                                  |                                     |
| Ataxia                               | I                     |                             |                             |                               |                               |                       |                     |                                  |                                     |
| Autism                               | FR                    |                             |                             |                               |                               |                       |                     |                                  |                                     |
| Acute Disseminated Encephalomyelitis | I                     | I                           | I                           | I                             | I                             | I                     | I                   | I                                | I                                   |
| Transverse Myelitis                  | I                     | I                           | I                           | I                             | I                             | I                     | I                   | I                                | I                                   |
| Optic Neuritis                       | I <sup>c</sup>        |                             | I <sup>c</sup>              |                               | I <sup>c</sup>                |                       |                     | I <sup>c</sup>                   |                                     |
| Neuromyelitis Optica                 | I <sup>c</sup>        |                             | I                           | I                             | I                             | I                     |                     |                                  |                                     |
| Multiple Sclerosis Onset in Adults   | I                     | I                           | I                           | I                             | I                             | I                     |                     | I                                |                                     |
| Multiple Sclerosis Onset in Children | I                     |                             |                             |                               | I                             |                       |                     |                                  |                                     |
| Multiple Sclerosis Relapse in Adults |                       |                             | I                           |                               | I                             |                       |                     |                                  | I                                   |

|  |    |  |    |    |    |    |  |  |    |                |  |  |                 |  |    |  |  |  |  |  |  |                 |   |    |
|--|----|--|----|----|----|----|--|--|----|----------------|--|--|-----------------|--|----|--|--|--|--|--|--|-----------------|---|----|
| Multiple Sclerosis Relapse in Children           |    |  |    | I  |    |    |  |  |    | I              |  |  |                 |  |    |  |  |  |  |  |  |                 | I |    |
| Multiple Sclerosis                               |    |  |    |    |    |    |  |  |    | I              |  |  |                 |  |    |  |  |  |  |  |  |                 |   | I  |
| First Demyelinating Event in Adults              |    |  |    |    |    |    |  |  |    | I              |  |  |                 |  |    |  |  |  |  |  |  |                 |   |    |
| First Demyelinating Event in Children            |    |  |    |    |    |    |  |  |    | I              |  |  |                 |  |    |  |  |  |  |  |  |                 |   |    |
| Guillain-Barré Syndrome                          | I  |  | I  | I  | I  | I  |  |  |    | I              |  |  |                 |  |    |  |  |  |  |  |  |                 |   | I  |
| Chronic Inflammatory Disseminated Polyneuropathy | I  |  | I  | I  | I  | I  |  |  |    | I              |  |  |                 |  |    |  |  |  |  |  |  |                 |   | I  |
| Opsoclonus Myoclonus Syndrome                    | I  |  |    |    |    |    |  |  |    |                |  |  |                 |  |    |  |  |  |  |  |  |                 |   | I  |
| Bell's Palsy                                     |    |  |    |    |    |    |  |  | FR |                |  |  |                 |  |    |  |  |  |  |  |  |                 |   | I  |
| Brachial Neuritis                                | I  |  |    |    |    |    |  |  | I  |                |  |  |                 |  |    |  |  |  |  |  |  |                 | I |    |
| Amyotrophic Lateral Sclerosis                    |    |  |    |    |    |    |  |  |    |                |  |  |                 |  |    |  |  |  |  |  |  |                 |   | I  |
| Small Fiber Neuropathy                           |    |  |    |    |    |    |  |  |    | I <sup>c</sup> |  |  |                 |  |    |  |  |  |  |  |  |                 |   |    |
| Anaphylaxis                                      | CS |  | CS | CS | CS | CS |  |  |    | I              |  |  | CS <sup>d</sup> |  | FA |  |  |  |  |  |  | CS <sup>e</sup> |   | CS |
| Chronic Urticaria                                |    |  |    |    |    |    |  |  |    |                |  |  |                 |  |    |  |  |  |  |  |  |                 | I |    |
| Serum Sickness                                   |    |  |    |    |    |    |  |  |    |                |  |  |                 |  |    |  |  |  |  |  |  |                 |   | I  |

TABLE S-1 Continued

| Adverse Event  | MMR Vaccine<br>Chapter 4 | Varicella Vaccine<br>Chapter 5 | Influenza Vaccine<br>Chapter 6 | Hepatitis A Vaccine<br>Chapter 7 | Hepatitis B Vaccine<br>Chapter 8 | HPV Vaccine<br>Chapter 9 | DT-, TT-, and aP-<br>Containing Vaccines<br>Chapter 10 | Meningococcal Vaccine<br>Chapter 11 | Injection-Related Events<br>Chapter 12 |
|--|--------------------------|--------------------------------|--------------------------------|----------------------------------|----------------------------------|--------------------------|--|-------------------------------------|--|
| Inactivated Influenza Vaccine and Asthma   |                          |                                | FR                             |                                  |                                  |                          |  |                                     |  |
| Exacerbation or Reactive Airway Disease Episodes in Children and Adults                  |                          |                                |                                |                                  |                                  |                          |  |                                     |  |
| Live Attenuated Influenza Vaccine and Asthma   |                          |                                | I                              |                                  |                                  |                          |  |                                     |  |
| Exacerbation or Reactive Airway Disease Episodes in Children Younger Than 5 Years of Age |                          |                                |                                |                                  |                                  |                          |  |                                     |  |
| Live Attenuated Influenza Vaccine and Asthma   |                          |                                | I                              |                                  |                                  |                          |  |                                     |  |
| Exacerbation or Reactive Airway Disease Episodes in Persons 5 Years of Age or Older      |                          |                                |                                |                                  |                                  |                          |  |                                     |  |
| Erythema Nodosum   |                          |                                |                                |                                  |                                  |                          |  | I <sup>c</sup>                      |  |
| Systemic Lupus Erythematosus   |                          |                                | I                              |                                  |                                  |                          |  | I                                   |  |
| Vasculitis   |                          |                                | I                              |                                  |                                  |                          |  | I                                   |  |
| Polyarthritis Nodosa   |                          |                                | I                              |                                  |                                  |                          |  | I                                   |  |

|                                  |                 |   |
|----------------------------------|-----------------|---|
| Psoriatic Arthritis              | I               |   |
| Reactive Arthritis               | I               |   |
| Rheumatoid Arthritis             | I               |   |
| Juvenile Idiopathic Arthritis    | I               |   |
| Transient Arthralgia in Women    | FA <sup>1</sup> |   |
| Transient Arthralgia in Children | FA              |   |
| Transient Arthralgia             |                 | I |
| Chronic Arthralgia in Women      | I               |   |
| Chronic Arthritis in Women       | I               |   |
| Chronic Arthropathy in Children  | I               |   |
| Arthropathy in Men               | I               |   |
| Arthropathy                      | I               | I |
| Type 1 Diabetes                  | FR              | I |
| Autoimmune Hepatitis             |                 | I |
| Myocarditis                      |                 | I |
| Pancreatitis                     |                 | I |

*continued*

TABLE S-1 Continued

| Adverse Event                   | MMR Vaccine Chapter 4 | Varicella Vaccine Chapter 5 | Influenza Vaccine Chapter 6 | Hepatitis A Vaccine Chapter 7 | Hepatitis B Vaccine Chapter 8 | HPV Vaccine Chapter 9 | DT-, TT-, and aP- Vaccines Chapter 10 | Meningococcal Vaccine Chapter 11 | Injection-Related Events Chapter 12 |
|---------------------------------|-----------------------|-----------------------------|-----------------------------|-------------------------------|-------------------------------|-----------------------|---------------------------------------|----------------------------------|-------------------------------------|
| Hepatitis                       | I                     |                             |                             |                               |                               |                       |                                       |                                  |                                     |
| Thromboembolic Events           |                       |                             |                             |                               |                               | I                     |                                       |                                  |                                     |
| Stroke                          |                       | I <sup>c</sup>              | I                           |                               |                               |                       |                                       |                                  |                                     |
| Hypercoagulable States          |                       |                             |                             |                               |                               | I                     |                                       |                                  |                                     |
| Myocardial Infarction           |                       |                             | I                           |                               |                               |                       |                                       |                                  |                                     |
| Chronic Fatigue Syndrome        | I                     |                             |                             |                               |                               |                       |                                       |                                  |                                     |
| Chronic Headache                |                       |                             |                             |                               |                               |                       | I                                     |                                  |                                     |
| Fibromyalgia                    | I                     |                             | I                           |                               | I                             |                       | I                                     |                                  |                                     |
| Sudden Infant Death Syndrome    |                       |                             |                             |                               |                               |                       | I                                     |                                  |                                     |
| Hearing Loss                    | I                     |                             |                             |                               |                               |                       |                                       |                                  |                                     |
| All Cause Mortality             |                       |                             | I <sup>c</sup>              |                               |                               |                       |                                       |                                  |                                     |
| Oculorespiratory Syndrome       |                       |                             | FA <sup>g</sup>             |                               |                               |                       |                                       |                                  |                                     |
| Thrombocytopenia                |                       | I                           |                             |                               |                               |                       |                                       |                                  |                                     |
| Immune Thrombocytopenic Purpura |                       |                             |                             |                               |                               |                       | I                                     |                                  |                                     |
| Complex Regional Pain Syndrome  |                       |                             |                             |                               |                               |                       |                                       |                                  | I                                   |

Deltoid Bursitis

CS

Synopsis

CS

NOTE: CS = convincingly supports a causal relationship; FA = favors acceptance of a causal relationship; FR = favors rejection of a causal relationship; I = inadequate to accept or reject a causal relationship.

<sup>a</sup> The committee attributes causation to individuals with demonstrated immunodeficiencies.

<sup>b</sup> The committee attributes causation to the measles component of the vaccine.

<sup>c</sup> Although not originally charged to the committee by the sponsor, the committee considered this adverse event in its review of the literature.

<sup>d</sup> The committee attributes causation to yeast-sensitive individuals.

<sup>e</sup> The committee attributes causation to the tetanus toxoid vaccine. The evidence is inadequate to accept or reject a causal relationship between anaphylaxis and diphtheria toxoid or acellular pertussis vaccine.

<sup>f</sup> The committee attributes causation to the rubella component of the vaccine.

<sup>g</sup> The committee attributes causation to two particular vaccines used in three particular years in Canada.

following MMR, influenza, hepatitis B, and DTaP vaccines; neuromyelitis optica and meningitis following MMR vaccine; erythema nodosum following hepatitis B vaccine; and stroke and small fiber neuropathy following varicella vaccine.

It is important to note that the committee was *not* tasked with assessing the benefits (effectiveness) of vaccines or any policy issues related to vaccination. The committee's task is focused only on an assessment of the risk of vaccines.

## ASSESSING THE WEIGHT OF EVIDENCE

Two streams of evidence support the committee's causality conclusions: epidemiologic evidence derived from studies of populations (most often based on observational designs but randomized trials when available), and mechanistic evidence derived primarily from biological and clinical studies in animals and individual humans (see Figure S-1). Some studies provide evidence capable of addressing both epidemiologic and mechanistic questions. Drawing from both sources of evidence to support causal inference is well established in the literature.

The committee made three assessments for each relationship reviewed. The first assessment applies to the weight of evidence from the epidemiologic literature; the second applies to the weight of evidence from the mechanistic literature. Each individual article (or findings within an article if more than one outcome or vaccine was studied) was evaluated for its strengths and weaknesses. The committee then synthesized the body of evidence of each type (epidemiologic or mechanistic) and assigned a "weight-of-evidence" for each. These weights-of-evidence represent the committee's assessment of the quality and quantity of evidence. The two weight-of-evidence assessments contributed to the third assessment, a conclusion about the causal relationship.

### Weight of Epidemiologic Evidence

Each peer-reviewed epidemiologic study was evaluated for its methodologic limitations (e.g., flawed measurement of either vaccine administration or adverse event, or failure to adequately control confounding variables) and for the precision of the reported results (e.g., the width of the 95% confidence interval around an effect estimate, reflecting the statistical power to detect a significantly increased risk of an adverse event). A specific study involving multiple outcomes or vaccines could have fewer limitations for the analysis of some vaccines or some outcomes than for others. Small clinical studies can be well conducted but the low number of subjects may limit the ability to detect most adverse events. Although most efficacy studies

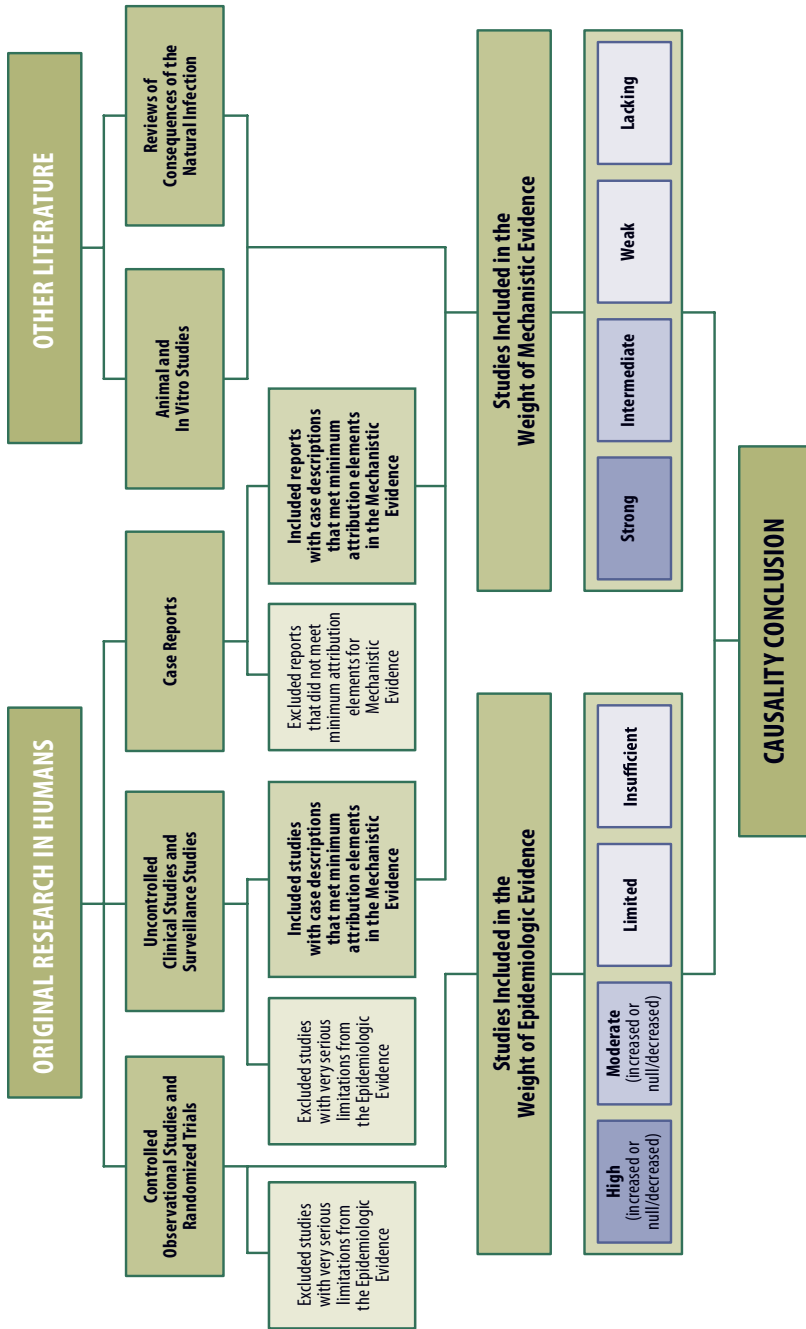


FIGURE S-1 Epidemiologic and mechanistic evidence reviewed by the committee.



include a safety component, the results are often nonspecific (e.g., “no serious adverse events were detected”). The committee was rigorous in assessing the strengths and weaknesses of each epidemiologic study. Some studies reviewed are likely the most reasonably methodologically sound given the nature of the exposure and the outcomes, even if the studies have some residual limitation due to the challenges that often attend such research. Summary paragraphs describe the epidemiologic evidence (as well as the mechanistic evidence and in some circumstances the causality conclusion) more fully than can be captured with the formal and consistent wording of the assessments used in this report.

The committee used a summary classification scheme that incorporates both the quality and quantity of the individual epidemiologic studies and the consistency of the group of studies in terms of direction of effect (i.e., whether the vaccine increases risk, decreases risk, or has no effect on risk). Integral to the assessment is the confidence the committee has that the true effect lies close to the average overall effect estimate for the body of evidence (i.e., collection of reports) reviewed (Schunemann et al., 2011).

The four weight-of-evidence assessments for the epidemiologic evidence are

- **High:** Two or more studies with negligible methodological limitations that are consistent in terms of the direction of the effect, and taken together provide high confidence.
- **Moderate:** One study with negligible methodological limitations, or a collection of studies generally consistent in terms of the direction of the effect, that provides moderate confidence.
- **Limited:** One study or a collection of studies lacking precision or consistency that provides limited, or low, confidence.
- **Insufficient:** No epidemiologic studies of sufficient quality.

Assessments of high and moderate include a direction of effect. These are to indicate increased risk of the adverse event, decreased risk of the adverse event, or no change in risk of the adverse event or “null.” Assessments of limited or insufficient include no direction of effect.

### **Weight of Mechanistic Evidence**

The committee assessed the mechanisms by which the vaccine could cause a specific adverse event by identifying and evaluating clinical and biological evidence. First, the committee searched for evidence in the peer-reviewed literature that a vaccine was or may be a cause of an adverse event in one or more persons (from case reports or clinical studies) in a reasonable time period after the vaccination. Then the committee looked

for other information from the clinical and biological (human, animal, or in vitro studies) literature that would provide evidence of a pathophysiological process or mechanism that is reasonably likely to cause the adverse event or to occur in response to a specific immunization. Chapter 3 contains a discussion of the major mechanisms the committee invokes as possible explanations of how a given adverse event can occur after vaccination.

The committee identified many case reports in the literature describing adverse events following vaccination. For the purposes of this report, *case report* refers to a description of an individual patient; one publication could describe multiple case reports. The committee evaluated each case report using a well-established set of criteria called *attribution elements* for case evaluation (Miller et al., 2000). At a minimum, for a case to factor into the weight-of-evidence assessment, it had to include specific mention of the vaccine administered, evidence of a clinician-diagnosed health outcome, and a specified and reasonable time interval (i.e., temporality or latency) between vaccination and symptoms. Case descriptions that did not have the three basic elements described above were not considered in the mechanistic weight-of-evidence assessments. These three criteria were only necessary but not sufficient to affect the weight of mechanistic evidence. After identifying cases with the three basic elements, the committee looked for evidence in the case descriptions and in other clinical or biological literature of a possible operative mechanism(s) that would support a judgment that the vaccination was related to the adverse event. See Chapter 3 for a description of possible mechanisms identified by the committee.

An important attribute in the evaluation of the clinical evidence from case reports is *rechallenge*, an adverse event that occurred after more than one administration of a particular vaccine in the same individual. Each challenge in a patient, however, must meet the same attributes of reasonable latency, documentation of vaccination receipt, and clinician diagnosis of the health outcome. The value of any case report is much greater if the clinical workup eliminated well-accepted alternative explanations for the condition, thus increasing the possibility that the vaccine could be associated with the adverse event. A particularly strong piece of evidence in the case description is laboratory-confirmed isolation of a vaccine strain virus in the patient.

The committee follows the convention of previous IOM committees in considering the effects of the natural infection as one type, albeit minor, of clinical or biological evidence in support of mechanisms.<sup>6</sup> Other evidence,

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<sup>6</sup>The committee relied on standard textbooks of infectious disease or internal medicine for this evaluation; the committee did not review original research to come to this determination. This is consistent with previous IOM committees tasked with reviewing evidence of causality for vaccine safety. Evidence consisting only of parallels with the natural infections is never sufficient to merit a conclusion other than the evidence is inadequate to accept or reject a causal relationship.

described above, provided much stronger evidence in support of the mechanistic assessment. Evidence from animal studies is also informative if the model of the disease (adverse outcome) is well established as applicable to humans, or if the basic immunology of the vaccine reaction is well understood. In vitro studies can also be informative, but such data were eyed with skepticism regarding their relationship to the human experience.

The committee developed categories for the mechanistic weight-of-evidence assessment. Each assessment includes consideration of the clinical information from case reports and consideration of clinical and experimental evidence from other sources. The four weight-of-evidence assessments for the mechanistic evidence are

- **Strong:** One or more cases in the literature, for which the committee concludes the vaccine *was* a contributing cause of the adverse event, based on an overall assessment of attribution in the available cases and clinical, diagnostic, or experimental evidence consistent with relevant biological response to vaccine.
- **Intermediate:** At least two cases, taken together, for which the committee concludes the vaccine *may be* a contributing cause of the adverse event, based on an overall assessment of attribution in the available cases and clinical, diagnostic, or experimental evidence consistent with relevant biological response to vaccine. On occasion, the committee reviewed evidence consisting of at least two cases that, taken together, while *suggestive*, are nonetheless insufficient to conclude that the vaccine may be a contributing cause of the adverse event. This evidence has been categorized as “low-intermediate.”
- **Weak:** Insufficient evidence from cases in the literature for the committee to conclude the vaccine may be a contributing cause of the adverse event, based on an overall assessment of attribution in the available cases and clinical, diagnostic, or experimental evidence consistent with relevant biological response to vaccine.
- **Lacking:** No clinical, diagnostic, or experimental evidence consistent with relevant biological response to vaccine, regardless of the presence of individual cases in the literature.

### CAUSALITY ASSESSMENT

The committee adopted the approach to causation developed by previous IOM committees. Implicit in these categories is that “the absence of evidence is not evidence of absence.” That is, the committee began its assessment from the position of neutrality; until all evidence was reviewed, it presumed neither causation nor lack of causation. The committee then

moved from that position only when the combination of epidemiologic evidence and mechanistic evidence suggested a more definitive assessment regarding causation, either that vaccines might or might not pose an increased risk of an adverse effect. The categories of causation used by the committee are the following:

- *Evidence convincingly supports<sup>7</sup> a causal relationship*—This applies to relationships in which the causal link is convincing, as with the oral polio vaccine and vaccine-associated paralytic polio.
- *Evidence favors acceptance of a causal relationship*—Evidence is strong and generally suggestive, although not firm enough to be described as convincing or established.
- *Evidence is inadequate to accept or reject a causal relationship*—The evidence is not reasonably convincing either in support of or against causality; evidence that is sparse, conflicting, of weak quality, or merely suggestive—whether toward or away from causality—falls into this category. Where there is no evidence meeting the standards described above, the committee also uses this causal conclusion.
- *Evidence favors rejection of a causal relationship*—The evidence is strong and generally convincing, and suggests there is no causal relationship.

The category of “establishes or convincingly supports *no* causal relationship” is not used because it is virtually impossible to prove the absence of a relationship with the same certainty that is possible in establishing the presence of one. Even in the presence of a convincing protective effect of a vaccine based on epidemiology, studies may not rule out the possibility that the reaction is caused by vaccine in a subset of individuals. Thus, the framework for this and previous IOM reports on vaccine safety is asymmetrical. The committee began not by assuming the causal relationship does *not* exist, but by requiring evidence to shift away from the neutral position that the evidence is “inadequate to accept or reject” a causal relationship.

The committee established a general framework by which the two streams of evidence (epidemiologic and mechanistic) influence the final causality conclusion (see Figure S-2). This framework needed to accommodate the reality that—for any given adverse event relationship reviewed—one or both of the types of evidence could be lacking, the two types of evidence could conflict, or neither type of evidence might definitively influence the causality conclusion. The framework does not accommodate any information regarding the benefit of the vaccine to either population or individual

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<sup>7</sup>Previous IOM committees used the term “establishes” instead of “convincingly supports.”



health. The focus of this particular committee is only on the question of what particular vaccines can cause particular adverse effects.

The framework also had to accommodate known strengths and limitations of both types of evidence. Mechanistic evidence can only support causation, but epidemiologic evidence can support a causal association or can support the absence of (“rejection of”) a causal association in the general population. Mechanistic evidence, particularly that emerging from case reports, occasionally provides compelling evidence of an association between exposure to a vaccine and an adverse event in the individual being studied, but it provides no meaningful information about the risk to the population. Epidemiologic analyses are usually unable to detect an increased or decreased risk that is small, unless the study population is very large or the between-group (e.g., vaccinated vs. unvaccinated) difference in risk is very high (e.g., smoking increases the risk of lung cancer by at least 10-fold). Epidemiologic analyses also cannot identify with certainty which individual in a population at risk will develop the condition.

The committee does not consider a single epidemiologic study—regardless of how well it is designed, the size of the estimated effect, or the narrowness of the confidence interval—sufficient to merit a weight of “high” or, in the absence of strong or intermediate mechanistic evidence, sufficient evidence to support a causality conclusion other than “inadequate to accept or reject a causal relationship.” This requirement might seem overly rigorous to some readers. However, the Agency for Healthcare Research and Quality advises the Evidence-based Practice Centers that it has funded to produce evidence reports on important issues in health care to view an evidence base of a single study with caution (Owens et al., 2010). It does so due to the inability to judge consistency of results, an important contributor to a strength of evidence, because one cannot “be certain that a single trial, no matter how large or well designed, presents the definitive picture of any particular clinical benefit or harm for a given treatment” (Owens et al., 2010). It is acknowledged by the committee and others (Owens et al., 2010) that policy makers must often make decisions based on only one study. However, the committee is not recommending policy, rather evaluating the evidence using a transparent and justifiable framework.

## CAUSALITY CONCLUSIONS

### Convincingly Supports

The framework allows for a causality conclusion of “convincingly supports” based on an epidemiologic weight-of-evidence assessment of high in the direction of increased risk (which requires at least two well-conducted epidemiologic studies). Strong mechanistic evidence, which requires at least

one case report in which compelling evidence exists that the vaccine indeed did cause the adverse event, always carries sufficient weight for the committee to conclude the evidence convincingly supports a causal relationship. The committee considered the detection of laboratory-confirmed, vaccine-strain virus compelling evidence to attribute the disease to the vaccine-strain virus and not other etiologies. This conclusion can be reached even if the epidemiologic evidence is rated high in the direction of no increased risk or even decreased risk.

The simplest explanation in this circumstance is that the adverse effect is real but also very rare. Stating this another way, if the vaccine *did* cause the adverse effect in one person, then it *can* cause the adverse effect in someone else; however, the isolated report of one convincing case provides no information about the risk of the adverse effect in the total population of vaccinated individuals compared with unvaccinated individuals.

The committee concluded the evidence convincingly supports 14 specific vaccine–adverse event relationships. In all but one of these relationships, the conclusion was based on strong mechanistic evidence with the epidemiologic evidence rated as either limited confidence or insufficient. The convincing evidence regarding varicella vaccine and disseminated Oka varicella zoster virus (VZV) and Oka VZV viral reactivation depended on identification of vaccine-strain virus as documented by polymerase chain reaction, as was the evidence regarding MMR vaccine and measles inclusion body encephalitis. Epidemiologic evidence, as well as mechanistic evidence, convincingly supported the causal relationship between MMR vaccine and febrile seizures. Clinical evidence from case reports and a well-identified mechanism of hypersensitivity reactions convincingly supported the conclusions regarding anaphylaxis and six vaccines (MMR, varicella, influenza, hepatitis B, meningococcal, and tetanus toxoid vaccine). Mechanistic evidence provided the convincing support for the conclusion that injection of vaccine, independent of the antigen involved, can lead to two adverse events: syncope and deltoid bursitis (see Table S-2).

### Favors Acceptance

A conclusion of “favors acceptance of a causal relationship” must be supported by either epidemiologic evidence of moderate certainty of an increased risk or by mechanistic evidence of intermediate weight. The committee concluded the evidence favors acceptance of four specific vaccine–adverse event relationships. These include HPV vaccine and anaphylaxis, MMR vaccine and transient arthralgia in female adults, MMR vaccine and transient arthralgia in children, and certain trivalent influenza vaccines used in Canada and a mild and temporary oculorespiratory syndrome. The conclusion regarding anaphylaxis was supported by only mechanistic evidence.

TABLE S-2 Summary of Causality Conclusions<sup>a</sup>

| Chapter | Vaccine   | Adverse Event   | Epidemiologic Assessment  | Studies Contributing to the Epidemiologic Assessment | Mechanistic Assessment                                       | Cases Contributing to the Mechanistic Assessment | Causality Conclusion               |
|---------|-----------|---|---|--|--|--|------------------------------------|
| 5       | Varicella | Disseminated Oka VZV without Other Organ Involvement  | Insufficient  | None   | Strong   | - <sup>b</sup>                                   | Convincingly Supports              |
| 5       | Varicella | Disseminated Oka VZV with Subsequent Infection Resulting in Pneumonia, Meningitis, or Hepatitis     | Limited (subsequent infection resulting in pneumonia)<br>Insufficient (subsequent infection resulting in meningitis or hepatitis) | 1  | Strong (in individuals with demonstrated immunodeficiencies) | 9  | Convincingly Supports <sup>c</sup> |
| 5       | Varicella | Vaccine Strain Viral Reactivation without Other Organ Involvement                                   | Insufficient  | None   | Strong   | - <sup>b</sup>                                   | Convincingly Supports              |
| 5       | Varicella | Vaccine Strain Viral Reactivation with Subsequent Infection Resulting in Meningitis or Encephalitis | Limited (subsequent infection resulting in encephalitis)<br>Insufficient (subsequent infection resulting in meningitis)           | 1  | Strong   | 6  | Convincingly Supports              |

*continued*



TABLE S-2 Continued

| Chapter | Vaccine        | Adverse Event                       | Epidemiologic Assessment | Studies Contributing to the Epidemiologic Assessment | Mechanistic Assessment  | Cases Contributing to the Mechanistic Assessment | Causality Conclusion                 |
|---------|----------------|-------------------------------------|--------------------------|--|---|--|--------------------------------------|
| 4       | MMR            | Measles Inclusion Body Encephalitis | Insufficient             | None   | Strong (measles; in individuals with demonstrated immunodeficiencies)<br>Lacking (mumps or rubella) | 1  | Convincingly Supports <sup>c,d</sup> |
| 4       | MMR            | Febrile Seizures                    | High (increase)          | 7  | Intermediate  | 12   | Convincingly Supports                |
| 4       | MMR            | Anaphylaxis                         | Insufficient             | None   | Strong  | 43 <sup>e</sup>                                  | Convincingly Supports                |
| 5       | Varicella      | Anaphylaxis                         | Limited                  | 1  | Strong  | 76 <sup>f</sup>                                  | Convincingly Supports                |
| 6       | Influenza      | Anaphylaxis                         | Limited                  | 1  | Strong  | 22   | Convincingly Supports                |
| 8       | Hepatitis B    | Anaphylaxis                         | Insufficient             | None   | Strong (in yeast-sensitive individuals)   | 10   | Convincingly Supports <sup>g</sup>   |
| 10      | Tetanus Toxoid | Anaphylaxis                         | Insufficient             | None   | Strong  | 6  | Convincingly Supports                |
| 11      | Meningococcal  | Anaphylaxis                         | Insufficient             | None   | Strong  | 1  | Convincingly Supports                |

|    |                         |  |                                 |      |                            |                 |                                |
|----|-------------------------|--|---------------------------------|------|----------------------------|-----------------|--------------------------------|
| 12 | Injection-Related Event | Deltoid Bursitis                               | Limited                         | 1    | Strong                     | 16              | Convincingly Supports          |
| 12 | Injection-Related Event | Syncope  | Insufficient                    | None | Strong                     | 35 <sup>b</sup> | Convincingly Supports          |
| 9  | HPV                     | Anaphylaxis                                    | Insufficient                    | None | Intermediate               | 36              | Favors Acceptance              |
| 4  | MMR                     | Transient Arthralgia in Women                  | Moderate (increase) (rubella)   | 4    | Intermediate (rubella)     | 13              | Favors Acceptance <sup>c</sup> |
|    |                         |  | Insufficient (measles or mumps) | None | Lacking (measles or mumps) | None            |                                |
| 4  | MMR                     | Transient Arthralgia in Children               | Moderate (increase)             | 7    | Weak (rubella)             | None            | Favors Acceptance              |
|    |                         |  | Insufficient (measles or mumps) | None | Lacking (measles or mumps) | None            |                                |
| 6  | Influenza               | Oculorespiratory Syndrome                      | Moderate (increase)             | 3    | Intermediate               | - <sup>i</sup>  | Favors Acceptance <sup>k</sup> |
| 4  | MMR                     | Autism   | High (null)                     | 4    | Lacking                    | None            | Favors Rejection               |
| 6  | Influenza               | Inactivated Influenza Vaccine and Bell's palsy | High (null)                     | 2    | Lacking                    | None            | Favors Rejection               |

*continued*

TABLE S-2 Continued

| Chapter | Vaccine                  | Adverse Event  | Epidemiologic Assessment | Studies Contributing to the Epidemiologic Assessment | Mechanistic Assessment | Cases Contributing to the Mechanistic Assessment | Causality Conclusion |
|---------|--------------------------|--|--------------------------|--|------------------------|--|----------------------|
| 6       | Influenza                | Inactivated Influenza Vaccine and Asthma Exacerbation or Reactive Airway Disease Episodes in Children and Adults | High (null)              | 9  | Weak                   | 6  | Favors Rejection     |
| 4       | MMR                      | Type 1 Diabetes  | High (null)              | 5  | Lacking                | None   | Favors Rejection     |
| 10      | DT, TT, or aP containing | Type 1 Diabetes  | High (null)              | 5  | Lacking                | None   | Favors Rejection     |

<sup>a</sup> All other causality conclusions are the evidence is inadequate to accept or reject a causal relationship.

<sup>b</sup> Due to the use of the same surveillance systems in some publications it is likely that some of the cases were presented more than once; thus, it is difficult to determine the number of unique cases.

<sup>c</sup> The committee attributes causation to individuals with demonstrated immunodeficiencies.

<sup>d</sup> The committee attributes causation to the measles component of the vaccine.

<sup>e</sup> Some cases were from passive surveillance systems; however, it is not possible to know how many represent unique cases or were reported elsewhere.

<sup>f</sup> In addition, at least 30 cases were reported to passive surveillance systems; however, it is not possible to know how many represent unique cases or were reported elsewhere.

<sup>g</sup> The committee attributes causation to yeast-sensitive individuals.

<sup>h</sup> In addition, hundreds of cases have been reported to passive surveillance systems; however, it is not possible to know how many represent unique cases or were reported elsewhere.

<sup>i</sup> The committee attributes causation to the rubella component of the vaccine.

<sup>j</sup> Due to the use of the same sample population in some studies it is likely that some of the cases were presented in more than one publication; thus, it is difficult to determine the number of unique cases.

<sup>k</sup> The committee attributes causation to two particular vaccines used in three particular years in Canada.

The other conclusions were supported by both epidemiologic evidence and by mechanistic evidence (see Table S-2).

### Favors Rejection

The framework allows the committee to “favor rejection” of a causal relationship only in the face of epidemiologic evidence rated as high or moderate in the direction of no effect (the null) or of decreased risk and in the absence of strong or intermediate mechanistic evidence in support of a causal relationship. The committee concluded the evidence favors rejection of five vaccine–adverse event relationships. These include MMR vaccine and type 1 diabetes, diphtheria, tetanus, and pertussis (DTaP) vaccine and type 1 diabetes, MMR vaccine and autism, inactivated influenza vaccine and asthma exacerbation or reactive airway disease episodes, and inactivated influenza vaccine and Bell’s palsy. The evidence base for these conclusions consisted of epidemiologic studies reporting no increased risk; this evidence was not countered by mechanistic evidence (see Table S-2).

### Inadequate to Accept or Reject

The committee identified two main pathways by which it concludes that the evidence is “inadequate to accept or reject” a causal relationship. The most common pathway to this conclusion occurs when the epidemiologic evidence was of limited certainty or insufficient and the mechanistic evidence was weak or lacking. Another pathway occurs when the epidemiologic evidence is of moderate certainty of no effect but the mechanistic evidence is intermediate in support of an association. The committee analyzed these sets of apparently contradictory evidence and ultimately depended upon their expert judgment in deciding if a conclusion to favor acceptance based on the intermediate mechanistic data was warranted, or if the conclusion remained as “inadequate to accept or reject” a causal relationship.

The vast majority of causality conclusions in the report are that the evidence was inadequate to accept or reject a causal relationship. Some might interpret that to mean either of the following statements:

- Because the committee did not find convincing evidence that the vaccine *does* cause the adverse event, the vaccine is safe.
- Because the committee did not find convincing evidence that the vaccine does *not* cause the adverse event, the vaccine is unsafe.

*Neither of these interpretations is correct.* “Inadequate to accept or reject” means just that—inadequate. If there is evidence in either direction that is suggestive but not sufficiently strong about the causal relationship, it

will be reflected in the weight-of-evidence assessments of the epidemiologic or the mechanistic data. However suggestive those assessments might be, in the end the committee concluded that the evidence was inadequate to accept or reject a causal association.

A list of all conclusions, including the weights of evidence for both the epidemiologic evidence and the mechanistic evidence, can be found in Appendix D.

## SUSCEPTIBILITY

The literature supporting several of the causality conclusions discussed in the previous section indicates that individuals with certain characteristics are more likely to suffer adverse effects from particular immunizations. Individuals with an acquired or genetic immunodeficiency are clearly recognized as at increased risk for specific adverse reactions to live viral vaccines such as MMR and varicella vaccine. Age is also a risk factor; seizures after immunization, for example, are more likely to occur in young children. Thus, the committee was able at times to reach more limited conclusions that did not generalize to the entire population.

## CONCLUDING COMMENT

Committee members spent an enormous amount of time reading thousands of articles. The committee makes 158 causality conclusions in this report. It tried to apply consistent standards when reviewing individual articles and when assessing the bodies of evidence. Some of the conclusions were easy to reach; the evidence was clear and consistent or, in the extreme, completely absent. Some conclusions required substantial discussion and debate. Inevitably, there are elements of expert clinical and scientific judgment involved.

The committee used the best evidence available at the time. The committee hopes that the report is sufficiently transparent such that when new information emerges from either the clinic or the laboratory, others will be able to assess the importance of that new information within the approach and set of conclusions presented in this report.

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## 1

## Introduction

Protecting health is a major priority of society, families, and individual parents. Over the past 100 years there has been a revolution in the ability to protect health in the developed world, where there are resources to enable this to happen. In 1900, among every 1,000 babies born in the United States, 100 would die before their first birthday, and five before 5 years of age (Guyer et al., 2000). By 2007, fewer than seven were expected to die before their first birthday, and only 0.29 per 1,000 before 5 years of age (HHS, 2010). Diseases severe enough to kill children and adults can also leave survivors disabled in some way, and as mortality has fallen, so has the chance of severe disability from these diseases.

Among the dangers for children and adults that have greatly diminished over the past century are infectious diseases. For bacterial diseases, antibiotics have been developed to treat infections before permanent harm can occur. For many viral and bacterial diseases, vaccines now exist.

In the early 20th century, smallpox (which has 30 percent mortality and a very high rate of disfigurement and other less common sequelae including blindness and encephalopathy) and rabies (virtually 100 percent fatal) could be prevented with immunization (CDC, 2001, 2008). With the fast growing understanding of microbes and immunity from 1920 onward, the development of immunizations became a race to “conquer” infectious disease. Beginning with the combination diphtheria, pertussis, and tetanus immunization during World War II and most recently with immunization to prevent cervical cancer (the human papillomavirus vaccine), immunizations have changed our expectations for child and adult health. Infections are less of a terror, and children are expected to survive to adulthood.



Vaccines function by stimulating the immune system and prompting a primary immune response to an infecting pathogen or to molecules derived from a particular pathogen. The immune response elicited by this primary exposure to vaccine pathogen creates immunological memory, which involves the generation of a pool of immune cells that will recognize the pathogen and mount a more robust or secondary response upon subsequent exposure to the virus or bacterium. In successful immunization, the secondary immune response is sufficient to prevent disease in the infected individual, as well as prevent the transmission of the pathogen to others. For communicable diseases, immunizations protect not only the individual who receives the immunization, but also others with whom he or she has contact. High levels of vaccination in a community increase the number of people who are less susceptible or resistant to illness and propagation of the infectious agent. Unvaccinated individuals or those who have not developed immunity to this pathogen are afforded an indirect measure of protection because those with immunity reduce the spread of the pathogen throughout the entire population. The larger the proportion of people with immunity, the greater the protection of those without immunity. This effect is called “herd immunity.” Herd immunity is an important phenomenon as immunization programs rarely achieve 100 percent immunization in a population; and in some cases, previously vaccinated persons may not exhibit effective immunity and disease may result from exposure to the pathogen. For protection, immunization of not only ourselves but also our neighbors is important.

The overwhelming safety and effectiveness of vaccines in current use in preventing serious disease has allowed them to gain their preeminent role in the routine protection of health. Before an immunization is introduced for population-wide use, it is tested for efficacy and safety. However, immunization is not without risks. For example, it is well established that the oral polio vaccine on rare occasion causes paralytic polio and that vaccines sometimes lead to anaphylactic shock. Given the widespread use of vaccines; state mandates requiring vaccination of children for entry into school, college, or day care; and the importance of ensuring that trust in immunization programs is justified, it is essential that safety concerns receive assiduous attention.

Congress passed the National Childhood Vaccine Injury Act (NCVIA, P.L. 99-660) in 1986. The legislation was intended to bolster vaccine research and development through federal coordination of the vaccine efforts in government and by providing relief to vaccine manufacturers who reported at the time that financial burdens from awards in the tort system threatened their financial viability. The legislation was also intended to address concerns about the safety of vaccines by instituting a compensation program financed by an excise tax on covered vaccines, setting up a passive surveillance system for vaccine adverse events, and by providing informa-

tion to consumers (CDC, 2010). Key provisions of the 1986 legislation include

- The establishment of the National Vaccine Program Office, which coordinates immunization-related activities between all Department of Health and Human Services (HHS) agencies including the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration, the National Institutes of Health, and the Health Resources and Services Administration (HRSA).
- The requirement that all health care providers who administer vaccines provide a vaccine information statement (VIS) to the vaccine recipient, or his or her parent or legal guardian, prior to each dose. Each VIS contains a brief description of the disease as well as the risks and benefits of the vaccine. The CDC develops VISs and distributes them to state and local health departments as well as individual providers.
- The requirement that health care providers must report certain and are encouraged to report other adverse events (health effects occurring after immunization that may or may not be related to the vaccine) following vaccination to the Vaccine Adverse Event Reporting System.
- The creation of the National Vaccine Injury Compensation Program (VICP) to compensate those injured by vaccines on a no-fault basis. Importantly, this compensation system has two parts:
  - The Secretary of Health and Human Services has created a Vaccine Injury Table (Table) that “lists and explains injuries/conditions that are presumed to be caused by vaccines. It also lists time periods in which the first symptom of these injuries/conditions must occur after receiving the vaccine. If the first symptom of these injuries/conditions occurs within the listed time periods, it is presumed that the vaccine was the cause of the injury or condition unless another cause is found” (<http://www.hrsa.gov/vaccinecompensation/table.htm>) and compensation is awarded.
  - Individuals who assert that they suffered an injury from a vaccine that is not on the Table (“off-Table” or “causation-in-fact”) must pursue their claim before Special Masters, who are appointed by the United States Court of Federal Claims, which hears any appeals. Claimants bear the burden of proving that the vaccine caused their injury, although the burden of proof is lower than that in the tort system.

A key component of the legislation, found in Sections 312 and 313, required the HHS secretary to consult with the Institute of Medicine (IOM)

to review the scientific literature on vaccine safety. Two reports were issued (IOM, 1991, 1994). These reports contain a framework for causality assessment of vaccine adverse events.<sup>1</sup> The reports addressed the vaccines covered by the VICP up to that point: diphtheria and tetanus toxoids and whole cell pertussis vaccine and other tetanus toxoid-containing vaccines; measles, mumps, and rubella (MMR) vaccines; *Haemophilus influenzae* type B vaccine; hepatitis B vaccine; and both inactivated and oral polio vaccines.<sup>2</sup> The reports informed the secretary's review of the Vaccine Injury Table. The reports have also been referenced extensively as a source of definitive scientific understanding of the evidence by Special Masters in decisions regarding injuries not listed on the Vaccine Injury Table.

The IOM was subsequently asked to review specific vaccine safety concerns in a series of reports requested by the CDC. These reports (IOM, 2001a,b, 2002a,b, 2003a,b, 2004a,b) included causality assessments similar to the previous IOM reports, but included other conclusions and recommendations regarding research, communications, and policy review.

### CHARGE TO THE COMMITTEE

In 2009 HRSA requested that the IOM convene a committee of experts to review the epidemiological, clinical, and biological evidence regarding adverse health events associated with specific vaccines covered by the VICP. The committee was charged with developing a consensus report with conclusions on the evidence bearing on causality and the evidence regarding the biological mechanisms that underlie specific theories for how a specific vaccine is related to a specific adverse event. The vaccines to be reviewed include varicella zoster vaccine, influenza vaccines (but not 2009 H1N1 vaccine), hepatitis B vaccine, human papillomavirus vaccine, tetanus-containing vaccines other than those containing the whole cell pertussis component, MMR vaccine, hepatitis A vaccine, and meningococcal vaccines. It is expected that the report will provide the scientific basis for review and adjudication of claims of vaccine injury by the VICP.

HRSA presented a list of specific adverse events for the committee to review (see Table 1-1). The selection criteria were described at the first committee meeting (Johann-Liang, 2009) as including the vast majority of adverse events in the claims for compensation. The committee added adverse events to the list if it identified epidemiologic studies or case reports

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<sup>1</sup>Adverse *events* are distinguished from adverse *effects* in that an event is something that occurs but may not be causally associated, whereas an adverse "effect" implies causation. All adverse effects are adverse events, but not all adverse events are adverse effects.

<sup>2</sup>Vaccines are included in the VICP if they are recommended by the CDC for routine administration in children and are subject to an excise tax. Adults who experience an adverse reaction to one of these "childhood" vaccines are also covered by the program.

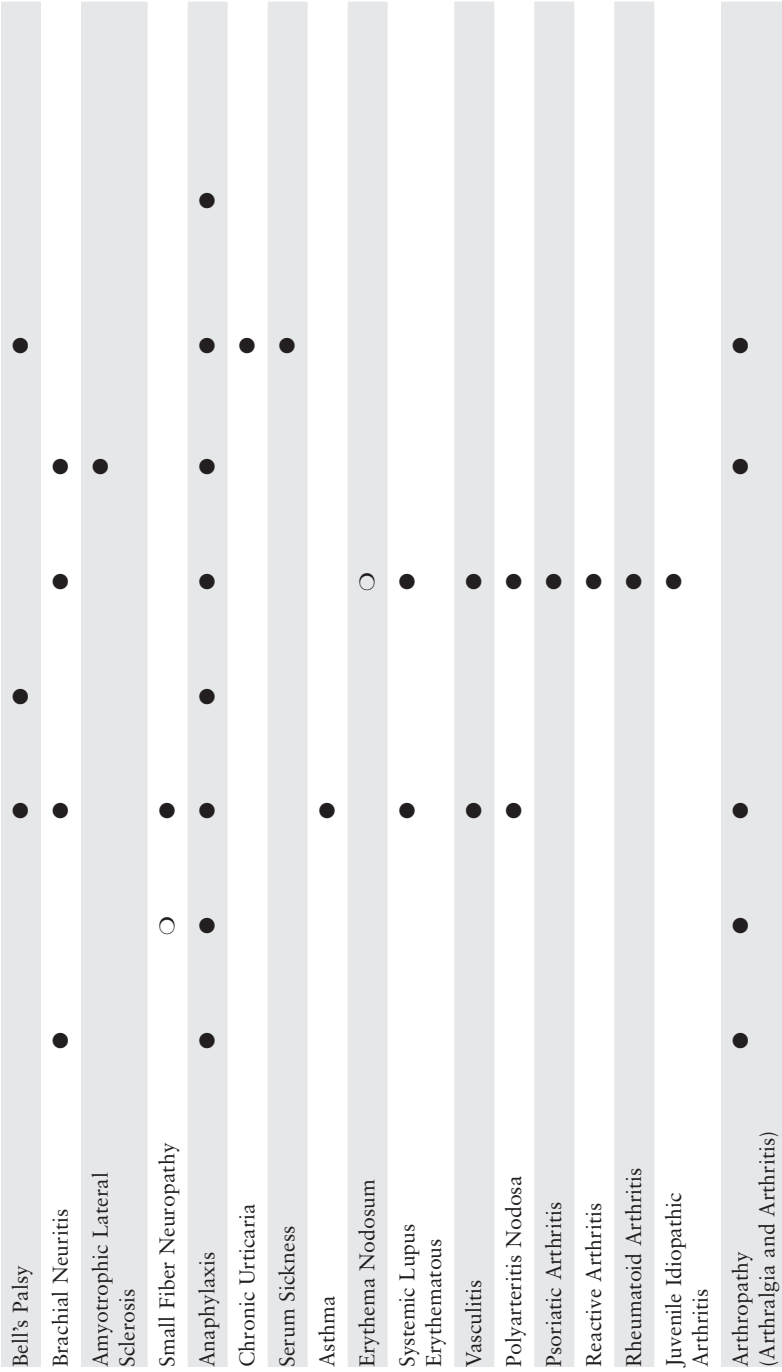
TABLE 1-1 Adverse Events Included in the Vaccine Chapters

| Adverse Event   | MMR Vaccine Chapter 4 | Varicella Vaccine Chapter 5 | Influenza Vaccine Chapter 6 | Hepatitis A Vaccine Chapter 7 | Hepatitis B Vaccine Chapter 8 | HPV Vaccine Chapter 9 | DT-, TT-, and aP-Containing Vaccines Chapter 10 | Meningococcal Vaccine Chapter 11 | Injected-Related Events Chapter 12 |
|---|-----------------------|-----------------------------|-----------------------------|-------------------------------|-------------------------------|-----------------------|---|----------------------------------|------------------------------------|
| Disseminated Oka VZV without Other Organ Involvement  |                       | ●                           |                             |                               |                               |                       |   |                                  |                                    |
| Disseminated Oka VZV with Subsequent Infection Resulting in Pneumonia, Meningitis, or Hepatitis     |                       | ●                           |                             |                               |                               |                       |   |                                  |                                    |
| Vaccine Strain Viral Reactivation without Other Organ Involvement                                   |                       | ●                           |                             |                               |                               |                       |   |                                  |                                    |
| Vaccine Strain Viral Reactivation with Subsequent Infection Resulting in Meningitis or Encephalitis |                       | ●                           |                             |                               |                               |                       |   |                                  |                                    |
| Measles Inclusion Body Encephalitis   | ●                     |                             |                             |                               |                               |                       |   |                                  |                                    |
| Encephalitis  | ●                     |                             | ●                           |                               | ●                             |                       | ●   |                                  | ●                                  |
| Encephalopathy  | ●                     |                             | ●                           |                               | ●                             |                       | ●   |                                  | ●                                  |
| Infantile Spasms  |                       |                             |                             |                               |                               |                       | ●   |                                  |                                    |

*continued*

TABLE 1-1 Continued

| Adverse Event                                    | MMR Vaccine Chapter 4 | Varicella Vaccine Chapter 5 | Influenza Vaccine Chapter 6 | Hepatitis A Vaccine Chapter 7 | Hepatitis B Vaccine Chapter 8 | HPV Vaccine Chapter 9 | DT-, TT-, and aP-   |                     | Meningococcal Vaccine Chapter 11 | Injected-Related Events Chapter 12 |
|--|-----------------------|-----------------------------|-----------------------------|-------------------------------|-------------------------------|-----------------------|---------------------|---------------------|----------------------------------|------------------------------------|
|  |                       |                             |                             |                               |                               |                       | Vaccines Chapter 10 | Vaccines Chapter 10 |                                  |                                    |
| Seizures   | ●                     | ●                           | ○                           |                               | ●                             |                       |                     | ●                   |                                  |                                    |
| Meningitis                                       | ○                     | ●                           |                             |                               |                               |                       |                     |                     |                                  |                                    |
| Cerebellar Ataxia                                |                       | ●                           |                             |                               |                               |                       |                     |                     |                                  |                                    |
| Ataxia   | ●                     |                             |                             |                               |                               |                       | ●                   |                     |                                  |                                    |
| Autism   | ●                     |                             |                             |                               |                               |                       | ●                   |                     |                                  |                                    |
| Acute Disseminated Encephalomyelitis             | ●                     | ●                           | ●                           | ●                             | ●                             | ●                     | ●                   | ●                   | ●                                |                                    |
| Transverse Myelitis                              | ●                     | ●                           | ●                           | ●                             | ●                             | ●                     | ●                   | ●                   | ●                                |                                    |
| Optic Neuritis                                   | ○                     |                             | ○                           |                               | ○                             |                       |                     | ○                   |                                  |                                    |
| Neuromyelitis Optica                             | ○                     |                             | ●                           |                               | ●                             |                       |                     |                     |                                  |                                    |
| Multiple Sclerosis                               | ●                     |                             | ●                           | ●                             | ●                             | ●                     | ●                   | ●                   | ●                                |                                    |
| First Demyelinating Event                        |                       |                             |                             |                               | ●                             |                       |                     |                     |                                  |                                    |
| Guillain-Barré Syndrome                          | ●                     | ●                           | ●                           | ●                             | ●                             | ●                     | ●                   | ●                   | ●                                | ●                                  |
| Chronic Inflammatory Disseminated Polyneuropathy | ●                     |                             | ●                           | ●                             | ●                             | ●                     | ●                   | ●                   | ●                                | ●                                  |
| Opsoclonus Myoclonus Syndrome                    | ●                     |                             |                             |                               |                               |                       |                     |                     |                                  | ●                                  |



*continued*

TABLE 1-1 Continued

| Adverse Event                | MMR Vaccine Chapter 4 | Varicella Vaccine Chapter 5 | Influenza Vaccine Chapter 6 | Hepatitis A Vaccine Chapter 7 | Hepatitis B Vaccine Chapter 8 | HPV Vaccine Chapter 9 | DT-, TT-, and aP- Vaccines Chapter 10 | Meningococcal Vaccine Chapter 11 | Injected-Related Events Chapter 12 |
|------------------------------|-----------------------|-----------------------------|-----------------------------|-------------------------------|-------------------------------|-----------------------|---------------------------------------|----------------------------------|------------------------------------|
| Type 1 Diabetes              | ●                     |                             |                             |                               | ●                             |                       | ●                                     |                                  |                                    |
| Hepatitis (Autoimmune)       |                       |                             | ●                           |                               |                               |                       |                                       |                                  |                                    |
| Myocarditis                  |                       |                             |                             |                               |                               |                       | ●                                     |                                  |                                    |
| Pancreatitis                 |                       |                             |                             |                               |                               | ●                     |                                       |                                  |                                    |
| Hepatitis                    | ●                     | ●                           |                             |                               |                               |                       |                                       |                                  |                                    |
| Thromboembolic Events        |                       |                             |                             |                               |                               | ●                     |                                       |                                  |                                    |
| Stroke                       |                       | ○                           | ●                           |                               |                               |                       |                                       |                                  |                                    |
| Hypercoagulable States       |                       |                             |                             |                               |                               | ●                     |                                       |                                  |                                    |
| Myocardial Infarction        |                       |                             | ●                           |                               |                               |                       |                                       |                                  |                                    |
| Chronic Fatigue Syndrome     | ●                     |                             |                             |                               |                               |                       |                                       |                                  |                                    |
| Chronic Headaches            |                       |                             |                             |                               |                               |                       |                                       | ●                                |                                    |
| Fibromyalgia                 | ●                     |                             | ●                           |                               | ●                             |                       | ●                                     |                                  |                                    |
| Sudden Infant Death Syndrome |                       |                             |                             |                               |                               |                       |                                       | ●                                |                                    |
| Hearing Loss                 | ●                     |                             |                             |                               |                               |                       |                                       |                                  |                                    |
| All-Cause Mortality          |                       |                             | ○                           |                               |                               |                       |                                       |                                  |                                    |
| Oculorespiratory Syndrome    |                       |                             | ●                           |                               |                               |                       |                                       |                                  |                                    |

|                                 |   |
|---------------------------------|---|
| Thrombocytopenia                | ● |
| Immune Thrombocytopenic Purpura | ● |
| Complex Regional Pain Syndrome  | ● |
| Deltoid Bursitis                | ● |
| Syncope                         | ● |

NOTE: Adverse events indicated by “O” were added to the list by the committee.



for an adverse event not originally assigned by HRSA. These additions were all-cause mortality and seizures following influenza vaccine; optic neuritis following MMR, influenza, hepatitis B, and diphtheria, tetanus, and pertussis (DTaP) vaccines; neuromyelitis optica and meningitis following MMR vaccine; erythema nodosum following hepatitis B vaccine; and stroke and small fiber neuropathy following varicella vaccine.

The committee was also tasked with addressing, as time and evidence allowed, general considerations. These included: underlying (susceptible) populations, “immune dysfunction,” vaccine administration issues, appropriate time intervals for anaphylaxis and autoimmune diseases, and sequential vaccination issues. The committee addressed some of these, as described in Chapters 4–12. It is important to note that the committee was *not* tasked with assessing the benefits (effectiveness) of vaccines or any policy issues related to vaccination. The task is clearly focused on an assessment only of the risk of vaccines.

### COMMITTEE PROCESS

The committee was composed of individuals with expertise in pediatrics, internal medicine, neurology, immunology, immunotoxicology, neurobiology, rheumatology, epidemiology, biostatistics, and law. Appendix F includes biographical sketches of the committee members. The committee met eight times between April 2009 and March 2011. The committee held open sessions at three of these meetings. Appendix G includes agendas of these open meetings. The committee’s methodology and approach to their task is described in Chapter 2.

### OUTLINE OF THE REPORT

Chapter 2 details the committee’s methodology. Chapter 3 discusses generally possible mechanisms of vaccine injury. Chapters 4–11 present the evidence reviewed by the committee for each of the eight vaccines covered and the conclusions it reaches. Chapter 12 presents causality assessments for adverse events that can occur with any injected vaccine regardless of the vaccine antigen and components. The committee discusses some special considerations of its work in Chapter 13.

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## 2

## Approach

Charged with assessing the epidemiologic, clinical, and biological evidence regarding the causal relationship between specific vaccines and specific adverse events, the committee drew upon previous reports by committees of the Institute of Medicine (IOM, 1991, 1994, 2001a,b, 2002a,b, 2003a,b, 2004a,b), other vaccine safety researchers (Halsey, 2002; Loke et al., 2008; WHO, 2001), general epidemiologic principles (Hill, 1965), and other systematic reviews in clinical medicine and public health (Liberati et al., 2009; Owens et al., 2010; Schunemann et al., 2011; Stroup et al., 2000; USPSTF, 2008). The committee adopted, with one exception,<sup>1</sup> the wording for the categories of causal conclusions used by the Institute of Medicine (IOM) committees in the past. The categories used previously were considered appropriate and the benefits of consistency were deemed compelling enough to extend the categories to this report.

Two streams of evidence from the peer-reviewed literature support the committee's causality conclusions: (1) epidemiologic evidence derived from studies of populations (most often based on observational designs but randomized trials when available), and (2) clinical and biological (mechanistic) evidence derived primarily from studies in animals and individual humans or small groups. Some studies provide evidence relevant to both epidemiologic and mechanistic questions. Drawing from both lines of evidence to support causal inference is well established in the literature. When confronted with epidemiologic and mechanistic evidence suggesting—however

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<sup>1</sup>As described in a subsequent section, previous IOM committees described the strongest evidence as *establishing* a causal relationship; this committee uses the term *convincingly supports*.

strongly or however weakly—that a vaccine is associated with an adverse event, one asks, “Does this make sense given what is known and generally accepted about the biological response to the natural infection, to the vaccine, and what is known about the pathophysiology of the adverse health outcome?”

### LITERATURE SEARCHING

As described in Chapter 1, the committee was tasked to assess the relationship between a specific adverse health outcome and a specific vaccine. A professional medical librarian conducted three waves of comprehensive literature searches of the published, peer-reviewed biomedical literature using MEDLINE (1950–present); EMBASE (1980–present); BIOSIS (1969–2005); Web of Science, consisting of the Science Citation Index (1900–present) and the Social Science Citation Index (1956–present); and search terms specific to each vaccine–adverse event relationship under study. Appendix C contains the search strategies used. The first wave of searches included the earliest date of the database to the date of the first search. Follow-up searches were conducted in August 2010 and late December 2010 to ensure that articles published after the initial search were not missed. On occasion, specialized searches were conducted to supplement the general searches. Also, review of the reference list of an article sometimes revealed studies not captured by the general search. These studies were retrieved.

Titles and abstracts, where available, were reviewed to screen out articles that did not address one of the potential vaccine adverse events to be reviewed or that were not primary research articles. See Figure 2-1. For example, the committee did not assess review articles. The committee restricted its review to those vaccines used in the United States, even if the study was conducted outside of the United States, with a few exceptions that will be discussed in the vaccine-specific chapters that follow. Articles were retrieved and reviewed again for relevance to the committee charge. Articles written in languages other than English were translated using Google Translate or a professional translation service. The committee did not include in its reviews data presented only in abstract form or in otherwise unpublished formats, with one exception described in Chapter 9, “Human Papillomavirus Vaccine.” An individual report from the Vaccine Adverse Event Reporting System was reviewed only if it had been described in a peer-reviewed research study and the committee wanted additional information. Decisions from the Vaccine Injury Compensation Program were not reviewed, because they are not published in the peer-reviewed medical literature. The committee did not review the conclusions contained in earlier IOM reports. The committee reviewed the data and made conclusions independently.

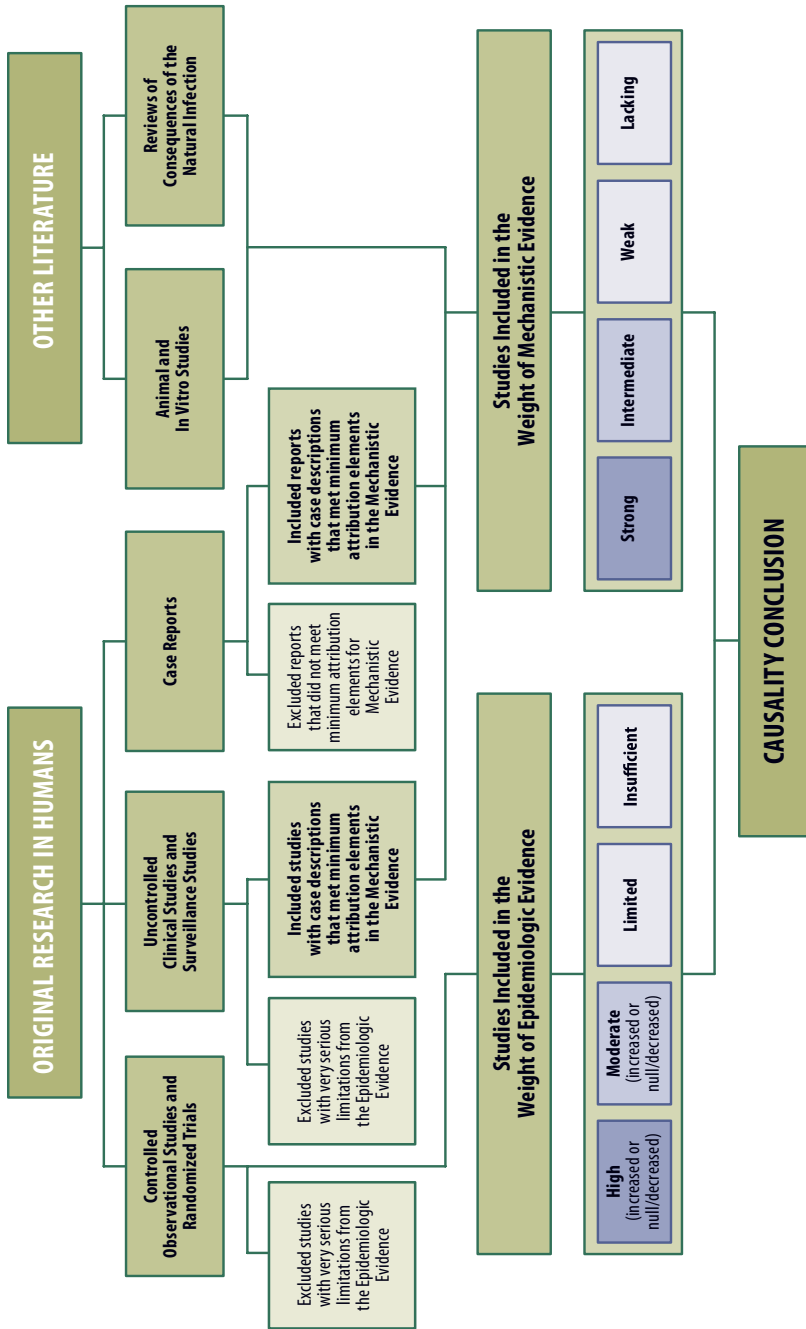


FIGURE 2-1 Epidemiologic and mechanistic evidence reviewed by the committee.

The committee's bibliographic retrieval was posted on the project website with a request for public comment regarding missing articles.<sup>2</sup> The committee received one submission, which was reviewed. The bibliography was separated into two sections. Section I contained those articles on which the committee focused its initial review. Section II contained those citations for articles that did not meet the committee's criteria (i.e., original research, vaccine used in the United States, adverse event within the committee's scope, animal or in vitro studies of relevance).

### WEIGHT OF EVIDENCE

The committee made three assessments for each relationship reviewed. The first assessment applies to the weight of evidence from the epidemiologic literature; the second applies to the weight of evidence from the biological and clinical (mechanistic) literature. The third assessment is the committee's conclusion about causality. In assessing the weights of evidence, each individual article (or findings within an article if more than one outcome or vaccine was studied) was evaluated for its strengths and weaknesses. The committee then synthesized the body of evidence of each type (epidemiologic or mechanistic) and assigned a "weight of evidence" for each. These weights of evidence are meant to summarize the assessment of the quality and quantity of evidence. The committee then reviewed the two weight-of-evidence assessments in order to make a conclusion about the causal relationship. The committee's approach to each of these three assessments will be discussed in the following sections.

#### Epidemiologic Evidence

Experimental studies (trials) are generally considered more rigorous than observational studies; controlled studies are generally considered more rigorous than uncontrolled studies. A brief description of major study designs and methodological considerations can be found in Appendix A. Surveillance studies were reviewed, but the absence of a control group limited their contribution to the weight of epidemiologic evidence; studies that included individual case descriptions were reviewed for their contribution to the evaluation of mechanistic evidence (discussed in subsequent sections). Small clinical studies that were not controlled for vaccine administration were generally reviewed for contributions to the mechanistic weight of evidence.

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<sup>2</sup>See <http://www.iom.edu/~media/Files/Bibliography.pdf>.

*Evaluation of Individual Studies*

Each epidemiologic study was evaluated for its methodological limitations (e.g., flawed measurement of either vaccine administration or adverse event, failure to adequately control confounding variables, incomplete or inadequate follow-up, failure to develop and apply appropriate eligibility criteria) and for the precision of the reported results (e.g., the width of the 95% confidence interval around an effect estimate, which also reflects the statistical power to detect a significantly increased risk of an adverse event). Studies that were deemed to be very seriously flawed did not contribute to the weight of evidence; they are identified in the text for completeness but are not discussed in depth.

It is important to note that a specific study could be well designed and well conducted but also have very serious limitations for the purposes of this committee's analysis. A specific study could have fewer limitations for some vaccines or some outcomes than for others. Small clinical studies can be well conducted but the number of subjects may be too small to detect most adverse events. Although most efficacy studies include a safety component, the results are often nonspecific (e.g., "no serious adverse events were detected"). Even some larger safety studies failed to detect an adverse event. Studies in which no cases of a specific adverse event were identified are uninformative for this review, because if the vaccinated cohort does not include enough cases to approximate background rates, the study is underpowered to inform an assessment. The upper limit of the 95% confidence interval will always overlap with the background rate unless the vaccine is protective. Some might use that information as means to approximate an upper limit on risk, but the committee did not see that as its charge (see Chapter 13). Studies such as these were considered to have very serious limitations for the purpose of the committee's assessment.

The committee was rigorous in assessing the strengths and weaknesses of each epidemiologic study. For many of the conditions and adverse events considered by the committee, the expected incidence and prevalence rates in the general unvaccinated population as well as in unvaccinated but potentially susceptible subgroups may be very low. Assembling a valid standard for comparison (e.g., an unvaccinated cohort of similar demographic composition and followed over a similar time period of risk, or a control group free of the adverse event but otherwise sufficiently similar to cases diagnosed with the adverse event) and objectively verifying the timing and type of vaccination and the details surrounding the onset and diagnosis of the adverse event are complex if not prohibitively expensive research endeavors. Although randomized clinical trials aiming to study vaccine efficacy may provide the most valid, controlled circumstances in which to also study vaccine safety, such trials inevitably enroll too few study par-



ticipants to be able to detect anything but extreme increases in the risks of relatively rare adverse events of potential concern. Some studies, as will be documented in chapters that follow, reviewed are likely the most methodologically sound that can be done given the nature of the exposure and the outcomes, even if the studies have some residual limitation due to the challenges that often attend such research. The reader will see in the summary paragraphs for the epidemiologic studies and, in some circumstances, the causality conclusion the committee's interpretation of the evidence more fully than can be captured with the formal and consistent wording of the conclusions used in this report.

### *Evaluation of the Body of Studies*

The committee reviewed methodological approaches of other systematic review efforts, but it was unable to identify one approach that incorporated all of the committee's needs and could be adopted for immediate use. Cochrane reviews, for example, focus on randomized controlled trials, which is an uncommon design in vaccine safety studies. Other efforts focused on evidence for or against a clinical practice or intervention (Guyatt et al., 2008; USPSTF, 2008).

Consequently, the committee adopted key components of these other approaches to develop a summary classification scheme that incorporates both the quality and quantity of the individual studies and the consistency of the group of studies in terms of direction of effect (i.e., is the effect of the vaccine to increase risk, decrease risk, or have no effect on risk). A key concept to these classifications is confidence, which refers to the confidence the committee has that the true effect lies close to that of the estimate of the average overall effect for the body of evidence (i.e., collection of reports) reviewed (Schunemann et al., 2011), and integrates committee evaluation of validity, precision, and consistency. Validity refers to the absence of confounding, selection bias and information or measurement bias (i.e., internal validity), and the generalizability (external validity) of the findings (Rothman et al., 2008b). Precision refers to the width of the confidence interval (e.g., a 95% confidence interval) around an effect estimate, which reflects the sample size of the study as well as the variability of the outcome measurement (Rothman et al., 2008a). The wider the 95% confidence intervals, the less statistical power to detect a difference as significant.

The four weight-of-evidence assessments for the epidemiologic literature are as follows:

- High: Two or more studies with negligible methodological limitations that are consistent in terms of the direction of the effect and taken together provide high confidence.

- Moderate: One study with negligible methodological limitations, or a collection of studies generally consistent in terms of the direction of the effect, provides moderate confidence.
- Limited: One study or a collection of studies lacking precision or consistency provides limited, or low, confidence.
- Insufficient: No epidemiologic studies of sufficient quality found.

Assessments of high and moderate include a direction of effect. These are to indicate increased risk of the adverse event, decreased risk of the adverse event, or no change (“null”) in the risk of the adverse event. Assessments of limited or insufficient include no direction of effect.

The committee does not consider a single study—regardless of how well it is designed, the size of the estimated effect, or the narrowness of the confidence interval—sufficient to merit a weight of “high” or, in the absence of strong or intermediate mechanistic evidence, sufficient to support a causality conclusion other than “inadequate to accept or reject a causal relationship.” This requirement might seem overly rigorous to some readers. However, the Agency for Healthcare Research and Quality advises the Evidence-based Practice Centers that it has funded to produce evidence reports on important issues in health care to view an evidence base of a single study with caution (Owens et al., 2010). It does so due to the inability to judge consistency of results, an important contributor to a strength of evidence, because one cannot “be certain that a single trial, no matter how large or well designed, presents the definitive picture of any particular clinical benefit or harm for a given treatment” (Owens et al., 2010). It is acknowledged by the committee and others (Owens et al., 2010) that policy makers must often make decisions based on only one study. However, the committee is not recommending policy, rather evaluating the evidence using a transparent and justifiable framework.

### Mechanistic Evidence

The committee assessed the mechanisms of vaccine adverse events by identifying and evaluating clinical and biological evidence. First, the committee looked for evidence in the peer-reviewed literature that a vaccine was or may be a cause of an adverse event in one or more persons (from case reports or clinical studies) in a reasonable time period after the vaccination. Then the committee looked for other information from the clinical and biological (human, animal, or in vitro studies) literature that would provide evidence of a pathophysiological process or mechanism that is reasonably likely to cause the adverse event or to occur in response to specific immunization. Chapter 3 contains a discussion of the major mechanisms the

committee invokes as possible explanations of how a given adverse event can occur after vaccination.

The committee identified many case reports in the literature describing adverse events following vaccination. For the purposes of this report, *case report* refers to a description of an individual patient; one publication could describe multiple case reports. The cases considered by the committee in weighing evidence of mechanisms were not derived from the large epidemiology studies considered above; there was no “double counting.” The committee evaluated each case report using a well-established set of criteria (“attribution elements”) for case evaluation (Miller et al., 2000). At a minimum, for a case to factor into the weight-of-evidence assessment, it had to include specific mention of the vaccine administered, evidence of clinician-diagnosed health outcome,<sup>3</sup> and a specified and reasonable time interval (i.e., temporality or latency) between vaccination and symptoms.<sup>4</sup> Case descriptions that did not have the three basic elements described above were not considered in the mechanistic weight-of-evidence determinations. As discussed in the next section, however, these three criteria were only necessary but not sufficient to affect the weight of mechanistic evidence. After identifying cases with the three basic elements, the committee looked for evidence in the case descriptions and in other clinical or biological literature of a possible operative mechanism(s) that would support a judgment that the vaccination was related to the adverse event. See Chapter 3 for a description of possible mechanisms identified by the committee.

Rechallenge cases, in which an adverse event occurred after more than one administration of a particular vaccine in the same individual, could influence the weight of evidence. Each rechallenge, however, must meet the same attributes of reasonable latency, documentation of vaccination receipt, and clinician diagnosis of the health outcome. It is possible that one or more of the “challenges” in an individual case patient reporting is related to a coincidental exposure; thus, the committee looked for other information, as described below, that would support a role for the vaccine in each challenge. The value for the committee of rechallenge cases is much greater for monophasic conditions (events that typically happen only once,

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<sup>3</sup>On occasion, the case report author describes clinical test results or observations but does not proffer a diagnosis. In these cases, the committee assigned the case report to the health outcome it felt appropriate. Some authors of older case reports use a diagnosis appropriate for the time, but by today’s understanding of clinical disease and pathophysiology, the committee offers a different diagnosis and the case report is described within that committee-directed assessment.

<sup>4</sup>What constitutes reasonable latency will vary across vaccines and across adverse events. For example, most adverse reactions from live virus vaccines would not be expected to occur within hours of vaccination; rather, time must elapse for viral replication.

e.g., vasculitis) than for relapsing-remitting conditions, such as multiple sclerosis or rheumatoid arthritis.

Another factor that affected the weight of evidence was information in the clinical workup that eliminated well-accepted alternative explanations for the condition, thus increasing the possibility that the vaccine could be associated with the adverse event. For example, Guillain-Barré syndrome (GBS) is known to be associated with specific infections (e.g., *Campylobacter*). Case reports of GBS following vaccination weighed more heavily in the committee's assessment if the authors reported that tests for those common infections were negative, thus eliminating some likely causes for the GBS other than vaccination. Another particularly strong piece of evidence in the case description that affected the weight of evidence is isolation of vaccine strain virus from the patient.

The committee follows the convention of previous IOM committees in considering the effects of the natural infection as one type, albeit minor, of clinical or biological evidence in support of mechanisms.<sup>5</sup> Other evidence, described above, provided much stronger evidence in support of the mechanistic assessment.

Evidence from animal studies is also informative if the model of the disease is well established as applicable to humans or if the basic immunology of the vaccine reaction is well understood. In vitro studies can also be informative, but such data must be eyed with skepticism regarding their relationship to the human experience. Specific examples of relevant clinical or biological information are discussed in Chapter 3 generally and in the vaccine-specific Chapters 4 through 11.

### *Evaluation of the Body of Clinical and Biological (Mechanistic) Evidence*

The committee reviewed the approach of previous IOM committees addressing vaccine safety (IOM, 1991, 1994, 2001a,b, 2002a,b, 2003a,b, 2004a,b) in evaluating the body of evidence of biological mechanisms. The committee also searched for other appropriate frameworks for evaluating biological evidence as support for causation analyses. The committee developed four categories for the weight-of-evidence assessment. Each category includes consideration of the clinical information from case reports and consideration of clinical and experimental evidence from other sources.

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<sup>5</sup>The committee relied on standard textbooks of infectious disease or internal medicine for this evaluation; the committee did not review original research to come to this determination. This is consistent with previous IOM committees tasked with reviewing evidence of causality for vaccine safety. Evidence consisting only of parallels with the natural infections is never sufficient to merit a conclusion other than the evidence is inadequate to accept or reject a causal relationship.

The following are the categories for the mechanistic weight-of-evidence assessments:

- **Strong:** One or more cases in the literature, for which the committee concludes the vaccine *was* a contributing cause of the adverse event, based on an overall assessment of attribution in the available cases and clinical, diagnostic, or experimental evidence consistent with relevant biological response to vaccine.
- **Intermediate:** At least two cases, taken together, for which the committee concludes the vaccine *may be* a contributing cause of the adverse event, based on an overall assessment of attribution in the available cases and clinical, diagnostic, or experimental evidence consistent with relevant biological response to vaccine. On occasion, the committee determined that at least two cases, taken together, while *suggestive*, are nonetheless insufficient for the committee to conclude the vaccine may be a contributing cause of the adverse event, based on an overall assessment of attribution in the available cases and clinical, diagnostic, or experimental evidence consistent with relevant biological response to vaccine. This evidence has been identified in the text as “low-intermediate.”
- **Weak:** Insufficient evidence from cases in the literature for the committee to conclude the vaccine may be a contributing cause of the adverse event, based on an overall assessment of attribution in the available cases and clinical, diagnostic, or experimental evidence consistent with relevant biological response to vaccine.
- **Lacking evidence of a biologic mechanism:** No clinical, diagnostic, or experimental evidence consistent with relevant biological response to vaccine,<sup>6</sup> regardless of the presence of individual cases in the literature.

### CAUSALITY ASSESSMENT

The committee adopted the categories of causation developed by previous IOM committees. Implicit in these categories is that “the absence of evidence is not evidence of absence.” That is, the committee began its assessment from the position of neutrality; until all evidence was reviewed, it presumed neither causation nor lack of causation. The committee then

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<sup>6</sup>The committee considered the clinical manifestations of the natural infection against which the vaccine is directed to be sufficient for a weight of evidence of weak, rather than lacking. As will be discussed in a subsequent section, a mechanism weight of evidence of weak alone is never sufficient to support a causality conclusion other than the evidence is inadequate to accept or reject a causal relationship.

moved from that position only when the combination of epidemiologic evidence and mechanistic evidence suggested a more definitive assessment regarding causation, either that vaccines might or might not pose an increased risk for an adverse event.

The following are the categories of causation used by the committee:

- *Evidence convincingly supports<sup>7</sup> a causal relationship*—This applies to relationships in which the causal link is convincing, as with the oral polio vaccine and vaccine-associated paralytic polio.
- *Evidence favors acceptance of a causal relationship*—Evidence is strong and generally suggestive, although not firm enough to be described as convincing or established.
- *Evidence is inadequate to accept or reject a causal relationship*—The evidence is not reasonably convincing either in support of or against causality; evidence that is sparse, conflicting, of weak quality, or merely suggestive—whether toward or away from causality—falls into this category.<sup>8</sup> Where there is no evidence meeting the standards described above, the committee also uses this causal conclusion.
- *Evidence favors rejection of a causal relationship*—The evidence is strong and generally convincing, and suggests there is no causal relationship.

The category of “establishes or convincingly supports *no* causal relationship” is not used because it is virtually impossible to prove the absence of a relationship with the same certainty that is possible in establishing the presence of one. Even in the presence of a convincing protective effect of vaccine in epidemiology, studies may not rule out the possibility that the reaction is caused by vaccine in a subset of individuals. Thus, the framework for this and previous IOM reports on vaccine safety is asymmetrical. The committee began not by assuming the causal relationship does *not* exist, but by requiring evidence to shift away from the neutral position that the evidence is “inadequate to accept or reject” a causal relationship.

The committee then established a general framework by which the two streams of evidence (epidemiologic and mechanistic) influence the final causality conclusion. It is important to note that mechanistic evidence can only support causation. Epidemiologic evidence, by contrast, can support (“favors acceptance of”) a causal association or can support the absence of (“favors rejection of”) a causal association in the general population and in various subgroups that can be identified and investigated, unless or

<sup>7</sup>Previous IOM committees used the term *establishes* instead of *convincingly supports*.

<sup>8</sup>See Chapter 13 for further discussion.

until supportive mechanistic evidence is discovered or a rare, susceptible subgroup can be identified and investigated. This framework needed to accommodate the reality that for any given causality conclusion one or both of the types of evidence could be lacking, the two types of evidence could conflict, or neither type of evidence might definitively influence the causality conclusion.

The framework also had to accommodate known limitations of both types of evidence. Epidemiologic analyses are usually unable to detect an increased or decreased risk that is small, unless the study population is very large or the difference between the groups (e.g., vaccinated vs. unvaccinated) at risk is very high (e.g., smoking increases the risk of lung cancer by at least 10-fold). Epidemiologic analyses also cannot identify with certainty which individual in a population at risk will develop a given condition. These studies also can fail to detect risks that affect a small subset of the population. Mechanistic evidence, particularly that emerging from case reports, occasionally can provide compelling evidence of an association between exposure to a vaccine and an adverse reaction in the individual being studied, but it provides no meaningful information about the degree of risk to the population or even to other individuals who have the same predisposing characteristics. The occurrence rate of the adverse event or condition in the general population cannot be estimated from case reports,<sup>9</sup> nor can one be certain that the risk is homogeneous across potentially vulnerable subgroups within the general population (e.g., the developing fetus and infants under 24 months, immunologically compromised individuals, or individuals with a rare genetic predisposition).

The framework does not accommodate any information regarding the benefit of the vaccine to either population or individual health. The focus of this particular committee is only on the question of what particular vaccines can cause particular adverse effects.

In general, the framework shown in Figure 2-2 illustrates how causality conclusions can be based primarily on epidemiologic evidence, primarily on mechanistic evidence, or on a combination of the two, and that on occasion expert judgment, such as that provided by the complement of expertise represented on the committee, is needed to weigh uncertain or competing evidence.

### **Evidence Convincingly Supports a Causal Relationship**

The framework allows for a causality conclusion of “convincingly supports” based on an epidemiologic weight-of-evidence assessment of high in

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<sup>9</sup>See Chapter 13 for further discussion.

| EPIDEMIOLOGIC ASSESSMENT |                                     |                           |  |         | MECHANISTIC ASSESSMENT |        |               |  | CAUSALITY CONCLUSION |         |                                |                  |                   |                       |
|--------------------------|-------------------------------------|---------------------------|--|---------|------------------------|--------|---------------|--|----------------------|---------|--------------------------------|------------------|-------------------|-----------------------|
| High (increased risk)    | High (decreased risk or no effect)  | Moderate (increased risk) | Moderate (decreased risk or no effect)                             | Limited | Insufficient           | Strong | Inter-mediate | Low-Inter-mediate                      | Weak                 | Lacking | Inadequate to Accept or Reject | Favors Rejection | Favors Acceptance | Convincingly Supports |
| High (increased risk)    |                                     |                           |  |         |                        |        |               |  |                      |         |                                |                  |                   | Convincingly Supports |
|                          |                                     |                           |  |         |                        | Strong |               |  |                      |         |                                |                  |                   |                       |
|                          |                                     | Moderate (increased risk) |  |         |                        |        |               |  |                      |         |                                |                  | Favors Acceptance |                       |
|                          |                                     |                           |  |         |                        |        | Inter-mediate |  |                      |         |                                |                  |                   |                       |
|                          | High (decreased risk or no effect)* |                           |  |         |                        |        |               |  |                      |         |                                | Favors Rejection |                   |                       |
|                          |                                     |                           | Moderate (decreased risk or no effect), Limited, or Insufficient** |         |                        |        |               |  |                      |         |                                |                  |                   |                       |
|                          |                                     |                           |  |         |                        |        |               |  |                      |         |                                |                  |                   |                       |
|                          |                                     |                           |  |         |                        |        |               | Low-Inter-mediate, Weak, or Lacking*** |                      |         |                                |                  |                   |                       |

\* Causality conclusion is favors rejection only if mechanistic assessment is **not** strong or intermediate.  
 \*\* Causality conclusion is inadequate to accept or reject only if mechanistic assessment is **not** strong or intermediate.  
 \*\*\* Causality conclusion is inadequate to accept or reject only if epidemiologic assessment is **not** high (increased risk), high (decreased risk or no effect), or moderate (increased risk).

FIGURE 2-2 Strength of evidence that determined the causality conclusions.



the direction of increased risk (which requires at least two well-conducted epidemiologic studies).

The framework also allows strong mechanistic evidence, which requires at least one case report in which compelling evidence exists that the vaccine indeed did cause the adverse event, to carry sufficient weight for the committee to conclude the evidence convincingly supports a causal relationship. The committee considered laboratory-confirmed, vaccine-strain virus isolation compelling evidence to attribute the disease to the vaccine-strain virus and not other etiologies. The committee recognizes that vaccine-strain virus can transiently appear in otherwise sterile spaces after vaccination; however, the committee determined that the accurate detection of vaccine-strain virus in symptomatic individuals to be strong evidence that the vaccine caused the symptoms. This conclusion can be reached even if the epidemiologic evidence is rated “high” in the direction of no increased risk or even decreased risk. The simplest explanation in this circumstance is that the adverse effect is real but also very rare. Another way of stating this is that if the vaccine *did* cause the adverse effect in one person, then it *can* cause the adverse effect in someone else (IOM, 1994). It might seem that the committee “overvalued” case reports in allowing one case to provide convincing evidence of causation; however, it is a rare case report that is so convincing. For most of the specific causality conclusions in this category, more than one compelling case report existed.

The isolated report of one convincing case provides no information about the risk of the adverse effect in the total population of vaccinated individuals compared with unvaccinated individuals. If the one convincing case has an underlying condition that may increase susceptibility to the adverse effect, it might have no relevance to the otherwise not-susceptible population.

As will be described in subsequent chapters of the report, the committee concluded the evidence convincingly supports 14 specific vaccine–adverse event relationships. In all but one of these relationships, the conclusion was based on strong mechanistic evidence with the epidemiologic evidence rated as either limited confidence or insufficient. When moderate or strong epidemiologic evidence is not available to support the committee’s conclusions favoring causality, it is difficult, if not impossible, to quantify the risk of the adverse event in either the entire population or the susceptible subgroup. See Chapter 13 for a discussion of this issue.

### Evidence Favors Acceptance of a Causal Relationship

A conclusion of “favors acceptance of a causal relationship” must be supported by either epidemiologic evidence of “moderate” certainty of an increased risk or by mechanistic evidence of intermediate weight. The

framework requires more than one epidemiologic study or more than one case report (with supporting but not conclusive mechanistic information) in support of this causality conclusion. A weight of mechanistic evidence of low-intermediate was not sufficient, without concurring epidemiologic evidence, to support a conclusion favoring acceptance of a causal relationship.

As will be described in subsequent chapters of the report, the committee concluded the evidence favors acceptance of four specific vaccine–adverse event relationships.

### **Evidence Favors Rejection of a Causal Relationship**

The framework allows the committee to “favor rejection” of a causal relationship only in the face of epidemiologic evidence rated as high or moderate in the direction of no effect (the null) or of decreased risk and the absence of strong or intermediate mechanistic evidence in support of a causal relationship. As described above, the committee requires more than one epidemiologic study to merit a conclusion that the evidence favors rejection of a causal relationship.

As will be described in subsequent chapters of the report, the committee concluded the evidence favors rejection of five specific vaccine–adverse event relationships.

### **Evidence Is Inadequate to Accept or Reject a Causal Relationship**

The committee identified two main pathways by which it concludes that the evidence is “inadequate to accept or reject” a causal relationship. The most common pathway to this conclusion occurs when the epidemiologic evidence was of limited certainty or insufficient and the mechanistic evidence was weak or lacking. Another pathway occurs when the epidemiologic evidence is of moderate certainty of no effect but the mechanistic evidence is intermediate in support of an association. The committee analyzed these sets of apparently contradictory evidence and ultimately depended upon its expert judgment in deciding if a conclusion to favor acceptance based on the intermediate mechanistic data was warranted or if the conclusion remained as “inadequate to accept or reject” a causal relationship. The committee required more than one epidemiologic study to conclude other than that the evidence is inadequate to accept or reject a causal relationship.

As will be described in subsequent chapters of the report, the committee concluded the evidence was inadequate to accept or reject the vast majority of specific vaccine–adverse event relationships. See Chapter 13 for a discussion of this conclusion.

## SPECIAL CONSIDERATIONS

As described in Chapter 3, the committee recognized that the risk of an adverse effect of a vaccine can be influenced by host factors, some known and others not yet understood. Where the committee thought the evidence—whether from epidemiologic analyses or from the clinical studies—regarding risks to subpopulations was informative, evidence-based, and biologically sound, it made separate conclusions. For example, the risk of invasive disease following varicella vaccine, a live virus vaccine, is likely much higher in immunocompromised persons than in persons who are immunocompetent. Other subpopulation analyses in the report include age and sex for some specific adverse events.

In their consideration of several adverse events, the committee concluded that the mechanism of injury was likely unrelated to the specific antigenic or other components of the vaccine. The committee concluded that the exposure of concern is not the injected vaccine, rather the injection of the vaccine. The adverse events include syncope, complex regional pain syndrome, and deltoid bursitis. These are covered in Chapter 12.

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## 3

## Evaluating Biological Mechanisms of Adverse Events

Charged with reporting on biological mechanisms, the committee reviewed evidence presented in case reports/clinical write-ups, laboratory tests, and animal models. Based on the array of adverse events and types of vaccines being reviewed, the committee compiled a list of mechanisms it deemed most likely to contribute to the development of adverse events after vaccination. The pathophysiologies and, at times, the evidence needed to identify a mechanism as operative were discussed. The mechanisms include immune-mediated reactions, viral activity, and injection-related reactions. The committee also discussed the coagulation cascade and its contribution to disease. In addition, the committee discussed the mechanisms that could lead to the development of adverse events in susceptible individuals, as well as the role vaccination could have in revealing an underlying immunodeficiency. The committee also discussed alterations in brain development that included a discussion of autism. Lastly, the advantages and disadvantages of applying evidence of a mechanism derived from an animal model to a human condition are discussed.

### LATENCY BETWEEN ANTIGEN EXPOSURE AND PEAK ADAPTIVE IMMUNE RESPONSE

Antigen exposure initiates an array of reactions involving the immune system, including the activation of white blood cells called *lymphocytes* that fight infection. After antigen exposure, two types of lymphocytes, B cells and T cells, differentiate into effector (e.g., antibody-producing B cells and cytotoxic and helper T cells) and memory cells. For both B and T cells in a

typical immune response to an antigen exposure, the latency between the first (primary) exposure and development of the primary response is characterized by a lag phase, logarithmic phase, and plateau phase. The lag phase is characterized by the initial activation of B and T cells upon encounter with the antigen for which they are specific, and this triggers the cells' differentiation into effector and memory cells. The lag phase between primary exposure to an antigen and the logarithmic phase is classically thought to be 4 to 7 days, but it varies depending on route of exposure and the antigen itself. For B cells, the logarithmic phase is characterized by an increase in serum antibody levels that classically is logarithmic. The plateau phase is characterized by the maintenance of peak antibody levels for a length of time that is followed by a decline in the serum antibody levels. For many antigens the latency (lag phase) between primary exposure and development of the primary antibody response is 7 to 10 days. Due to the development of memory B and T cells during the primary immune response, the latency between subsequent exposure to the antigen and development of the immune response will usually be shorter. The lag phase is generally 1 to 3 days; the logarithmic phase of the secondary antibody response occurs over the next 3 to 5 days. As mentioned for the primary immune response, these time periods will vary depending on the route of exposure, the timing of the subsequent exposure, the antigen itself, and the antigen dose. While this discussion is not specific to a particular antigen, it can be used as a reference point for the latency between antigen exposure and the initiation of some of the immune-mediated mechanisms described below.

Contributing to the activation of B and T cells and the initiation of the adaptive immune response are cells classically associated with the innate immune system (e.g., macrophages and dendritic cells). These cells play roles at each of the stages mentioned above and are usually the first cells of the immune system to be exposed to antigen. Upon antigen encounter, macrophages and dendritic cells engulf the antigen, a process that also activates these innate immune cells to become *antigen-presenting cells*. Antigen-presenting cells, as their name suggests, present the antigen to T cells (see "Effector Functions of T Cells" below) and release inflammatory mediators (e.g., cytokines and chemokines) that contribute to the recruitment, activation, and proliferation of B and T cells. Activated B and T cells in turn release inflammatory mediators leading to the recruitment and activation of additional immune cells that further amplify the immune response through the release of inflammatory mediators. Regulatory cells and soluble immunoregulatory mediators (not discussed in this report) play roles in suppressing the immune response. Chaplin (2010) provides a review of the immune response including discussion of the interplay between the innate and adaptive arms of the immune system, cells associated with the innate and adaptive immune systems, and inflammatory/immunoregulatory mediators.

Many vaccines, particularly subunit vaccines (e.g., recombinant hepatitis B and tetanus toxoid), contain adjuvants that help to increase the response rates to vaccines and facilitate the use of fewer and smaller doses (Coffman et al., 2010). Currently, two adjuvants (alum as aluminum phosphate or aluminum hydroxide, and ASO<sub>4</sub>, which is comprised of monophosphoryl lipid A and alum) are in vaccines licensed for use in the United States. Although the exact mechanism of action of many adjuvants is not completely understood, it is hypothesized that alum delays systemic absorption of injected antigens, resulting in antigen retention in particulate form and in high concentration at the site of local injection (Tritto et al., 2009). This in turn results in prolonged exposure of the cells of the innate immune system to antigen (Tritto et al., 2009). Furthermore, alum may directly activate cells of the innate immune system through its effect on local inflammasome complexes (Coffman et al., 2010) leading to the release of inflammatory mediators and enhancement of the immune response as described above. The review by Coffman et al. (2010) provides a detailed description of the mechanism(s) of action of clinically approved adjuvants including alum and ASO<sub>4</sub>.

## IMMUNE-MEDIATED MECHANISMS

Several immune-mediated mechanisms have been hypothesized to be involved in the pathogenesis of tissue damage or clinical disease related to natural infection or immunizations. A brief description of some of these mechanisms follows.

### Effector Functions of T Cells

T cells are the subset of lymphocytes that develop in the thymus. They are further delineated by the expression of cell surface markers and the production of inflammatory and immunoregulatory mediators. Two T cell subsets, CD8<sup>+</sup> and CD4<sup>+</sup> T cells, are activated via recognition of peptides derived from antigen. For activation of T cells to occur, the peptides are bound to major histocompatibility complexes (MHCs) expressed on the surface of specialized white blood cells called *antigen-presenting cells*. T cells have various functions in the immune response.

CD8<sup>+</sup> T cells are activated in response to antigens that gain access to the cytosol of cells. These antigens are broken down into peptides. The peptides are presented to CD8<sup>+</sup> T cells after being bound to class I MHC molecules. Class I MHC molecules are expressed on nearly all nucleated cells (Harty et al., 2000). CD8<sup>+</sup> T cells express a T cell receptor (TCR) that binds peptide-class I MHC complexes. CD8<sup>+</sup> T cells that express different TCRs allow for recognition of many different antigens. The binding of



the CD8<sup>+</sup> T cell TCR to the peptide-class I MHC complex on professional antigen-presenting cells (e.g., dendritic cells) activates the CD8<sup>+</sup> T cells which then respond against cytosolic infections such as viruses, intracytoplasmic bacteria, and protozoa (Harty et al., 2000). Activated CD8<sup>+</sup> T cells induce death of infected cells through mechanisms that include (1) release of granules containing the pore-forming molecular perforin or (2) engagement of Fas receptors on target cells (Harty et al., 2000). Both mechanisms induce apoptosis, or programmed cell death, in the target cell. In addition, activated CD8<sup>+</sup> T cells secrete cytokines, molecules critical to intercellular communication, that recruit and activate macrophages and neutrophils (Harty et al., 2000).

In contrast to CD8<sup>+</sup> T cells, CD4<sup>+</sup> T cells are predominantly activated in response to extracellular antigens that are endocytosed or phagocytosed, broken down into peptides, and bound to class II MHC molecules on the surface of professional antigen-presenting cells (Guermontprez et al., 2002). Class II MHC molecules are expressed on dendritic cells, macrophages, B cells, and activated T cells. The CD4<sup>+</sup> T cells express TCRs that bind peptide-class II MHC complexes. Recognition of peptide antigen-MHC complexes activates CD4<sup>+</sup> T cells against a variety of antigens including, but not limited to, bacteria, parasites, and proteins. Activated CD4<sup>+</sup> T cells direct aspects of the immune response via the secretion of immunoregulatory cytokines and other soluble mediators. These inflammatory mediators can induce B cells to undergo immunoglobulin (Ig) class switching (e.g., IgM to IgE); to support the activity of CD8<sup>+</sup> T cells; to recruit and activate eosinophils, basophils, neutrophils, mast cells, and macrophages; and to down-regulate immune responses (Koretzky, 2008; Wan and Flavell, 2009). Several lineages of CD4<sup>+</sup> T cells, with overlapping and competing effects based on those described above, have been identified (Wan and Flavell, 2009). One CD4<sup>+</sup> T cell lineage, referred to as regulatory T cells, functions to maintain self tolerance and immune homeostasis (Wan and Flavell, 2009). In addition, some CD4<sup>+</sup> T cells can induce cytolysis via the mechanisms described for CD8<sup>+</sup> T cells (Soghoian and Streeck, 2010).

In summary, T cells contribute to the establishment and maintenance of immune responses, the clearance of pathogens, and the maintenance of self-tolerance. T cells play roles in many disease processes including, but not limited to, rheumatoid arthritis, type 1 diabetes, and asthma (Wan and Flavell, 2009).

### Effector Functions of Antibodies and Autoantibodies

Antibodies are antigen-binding proteins produced by terminally differentiated effector B cells called *plasma cells*. Antibodies that bind antigens

derived from the host organism (i.e., self-antigens) are referred to as autoantibodies. Autoantibodies are considered one of the hallmarks of certain autoimmune diseases; however, the presence of autoantibodies does not correlate perfectly with disease. Autoantibodies have been detected in healthy individuals as well as those with autoimmune diseases (Elkon and Casali, 2008; Zelenay et al., 2007). The mechanisms whereby autoantibodies exert their effects in the disease process are the same used by antibodies against foreign antigens (i.e., non-self-antigens). These include, but are not limited to, opsonization, neutralization, complement activation, augmentation, and engagement of constant region (Fc) receptors.

Neutralization of an antigen or pathogen expressing the target antigen is one effector mechanism attributed to antibodies. For example, antibodies against influenza virus hemagglutinin neutralize the virus by blocking the interaction of the virus with the receptor on the target cell, thereby preventing infection (Han and Marasco, 2011). In addition, while not preventing influenza infection, antibodies against influenza neuraminidase restrict replication of the virus by preventing release of virus from infected cells (Han and Marasco, 2011). This is one of the ways vaccines, which induce pathogen-specific antibodies, elicit protection from diseases. However, neutralization of self-antigens by autoantibodies can also contribute to the pathogenesis of some autoimmune diseases. For example, neutralizing autoantibodies against the cytokine granulocyte/macrophage colony-stimulating factor (GM-CSF) are found in autoimmune pulmonary alveolar proteinosis, which is characterized by dysfunctional alveolar macrophages and functionally impaired neutrophils (Watanabe et al., 2010). Autoantibodies against GM-CSF block interaction of the cytokine with receptors on macrophages, inhibiting their maturation, and on neutrophils, leading to impairment of phagocytosis, adhesion, bacterial killing, and oxidative burst (Watanabe et al., 2010).

Antibodies against surface-bound antigens can lead to the opsonization (coating) of the pathogen or a cell expressing the antigen. For example, antibodies against the capsular polysaccharide of *Streptococcus pneumoniae* result in the opsonization of the bacteria and clearance of the bacteria by phagocytic cells (Bruyn et al., 1992). In a proinflammatory setting, such as antineutrophil cytoplasmic autoantibody-associated vasculitides, opsonization can lead to the perpetuation of inflammation (van Rossum et al., 2005). For example, opsonization of neutrophils by autoantibodies against proteinase 3 (PR3) and myeloperoxidase (MPO) contributes to the activation of neutrophils resulting in their degranulation, which in turn leads to vessel injury (van Rossum et al., 2005).

Antibody-antigen interactions can lead to complement activation (complement activation is discussed in a subsequent section). Antibodies against

bacteria lead to complement activation resulting in elimination of the bacteria (Bruyn et al., 1992). Similarly, engagement of aquaporin-4, expressed on the surface of astrocytes, by autoantibodies results in complement activation leading to disruption of the integrity of the plasma membrane and astrocyte injury (Cayrol et al., 2009).

Engagement of Fc receptors by antibodies bound to antigen can lead to clearance of the antigen or antigen-expressing pathogen or cell, or to activation of the receptor-expressing cell. The Fc receptors on macrophages, by binding to antibody-coated bacteria, allow the macrophages to engulf and then kill the bacteria. One example, discussed above, is the opsonization of *Streptococcus pneumoniae* by antibodies against the capsular polysaccharide that leads to the clearance of the bacteria by macrophages (Bruyn et al., 1992). Likewise, the clearance of apoptotic neutrophils opsonized by autoantibodies against PR3 and MPO, as discussed above, is facilitated by engagement of the Fc receptors expressed on the surface of the macrophages (van Rossum et al., 2005). In addition, as described above, opsonization of neutrophils by autoantibodies against PR3 and MPO contributes to the activation of neutrophils. Autoantibodies against PR3 and MPO contribute to neutrophil activation through engagement of Fc receptors by the constant region of the autoantibodies whose variable regions (Fab) are binding either PR3 or MPO on the same cell (van Rossum et al., 2005).

Autoantibodies also have the ability to augment the effects of the target antigen. For example, the autoantibody complex interleukin-8 (IL-8) has been shown to augment IL-8-induced neutrophil migration in acute respiratory distress syndrome (Watanabe et al., 2010). IL-8-induced neutrophil migration is more strongly induced by engagement of Fc receptors by IL-8-autoantibody complexes than by engagement of the IL-8 receptor alone (Watanabe et al., 2010).

As suggested above, autoantibodies use multiple mechanisms during a disease process. Antigen-bound autoantibodies can both (1) engage Fc receptors and (2) induce activation of the complement system. These processes lead to the activation of inflammatory cells such as neutrophils and macrophages, and to generation of proinflammatory mediators that play pathogenic roles in autoimmune diseases.

### Complement Activation

The complement system is comprised of more than 30 soluble or membrane-bound proteins. Complement activation, an outcome of a cascade of enzymatic reactions, leads to the generation of inflammatory mediators that play a role in host defense via three physiological processes (Dunkelberger and Song, 2010). First, complement activation leads to the targeted lysis of infectious agents through the generation of the mem-

brane attack complex (MAC), which forms membrane-penetrating pores in pathogens (Dunkelberger and Song, 2010). Second, complement activation leads to the opsonization of infectious agents by complement opsonins and the engagement of complement receptors on phagocytic cells resulting in the clearance of the infectious agent (Dunkelberger and Song, 2010). Lastly, complement activation leads to the generation of proinflammatory anaphylatoxins that act as vasodilators, cytokines, and inducers of smooth muscle contraction; oxidative bursts from neutrophils; and histamine release from mast cells (Sarma and Ward, 2011). In addition to the physiological processes described above, the complement system plays a role in the selection, maintenance, and differentiation of B cells into plasma and memory cells, and in the priming of CD4<sup>+</sup> and CD8<sup>+</sup> T cells (Dunkelberger and Song, 2010).

Three pathways—*classical*, *lectin*, and *alternative*—lead to complement activation and the generation of inflammatory mediators responsible for the physiological processes discussed above. These pathways converge where C3 convertases cleave the complement component C3 into the anaphylatoxin C3a and the opsonin C3b; from this point, further enzymatic reactions generate additional anaphylatoxins, opsonins, and the MAC (Gros et al., 2008). The pathways are discussed below.

The initiation of the *classical pathway* occurs when the complement component C1q, in complex with the complement components C1r and C1s, bind immune complexes (comprised of antigen bound by IgG or IgM antibodies) (Rus et al., 2005). C1q can also initiate the classical pathway by binding to C-reactive protein, serum amyloid P, gram-negative bacterial walls, and central nervous system myelin (Rus et al., 2005). Autocatalytic activation of C1r and C1s leads to an enzymatic reaction involving the complement components C4 and C2 and the generation of fragments that combine to form C3 convertase (Dunkelberger and Song, 2010).

The *lectin pathway* is initiated when pattern recognition receptors (PRRs), such as mannose-binding lectin, bind to highly conserved structures in microorganisms termed *pathogen-associated molecular patterns* (PAMPs) (Dunkelberger and Song, 2010). PAMPs can be found on the surfaces of yeast, bacteria, parasites, and viruses (Sarma and Ward, 2011). Similar to the classical pathway, recognition of PAMPs by PRRs leads to an enzymatic reaction involving the complement components C4 and C2 and the generation of fragments that combine to form C3 convertase (Dunkelberger and Song, 2010).

Initiation of the *alternative pathway* occurs when C3 undergoes spontaneous hydrolysis on the surface of pathogens or other targets that have neutral or positive charge characteristics and/or that support the binding of activated C3 (Holers, 2008). The altered form of C3, called C3<sub>i</sub> or C3(H<sub>2</sub>O), can bind factor B, which in turn is cleaved by factor D, leading

to the generation of C3 convertase (Holers, 2008). In addition to promoting the generation of the inflammatory mediators discussed above, the alternative pathway increases complement activation through an amplification loop (Holers, 2008). The amplification loop is engaged when C3b, generated by C3 convertase from any of the three complement activation pathways, binds factor B, which in turn is cleaved by factor D, leading to further C3 activation (Holers, 2008). Sites of local injury and decreased expression of complement regulatory proteins can promote engagement of the amplification loop (Holers, 2008).

### Hypersensitivity Reactions

Hypersensitivity reactions are immune-mediated reactions to substances, termed allergens, which do not generate adverse immune responses in the majority of the population. Individuals who are “atopic” develop immune responses to the allergens that lead to symptoms such as hay fever or wheezing in response to pollens, or vomiting and lip swelling in response to certain foods. These reactions develop after sensitizing exposure(s) and reexposure to an allergen, and are broadly classified as immediate or delayed hypersensitivity reactions. Described below are two mechanisms classified as immediate hypersensitivity reactions involved in allergic reactions, including the severe, potentially fatal, systemic allergic reactions that are rapid in onset and known as anaphylaxis.

#### *Immunoglobulin E–Mediated Hypersensitivity*

**Definition of immunoglobulin E–mediated hypersensitivity** By far the most common mechanism responsible for immediate hypersensitivity reactions involves immunoglobulin E (IgE) and is termed *immunoglobulin E–mediated hypersensitivity*, in which allergen-specific IgE antibodies undergo synthesis and binding to high-affinity IgE receptors on the surface of mast cells and basophils. Subsequent exposure of allergen to receptor-bound IgE leads to cross-linking of IgE, activation of mast cells and basophils, and release of inflammatory mediators (Simons, 2009).

**Evidence needed to conclude that IgE-mediated hypersensitivity is operative in anaphylaxis** Positive skin test results and/or the presence of allergen-specific IgE in serum indicate that a patient is sensitized to an allergen but alone are not conclusive of IgE-mediated reactions or anaphylaxis (Simons, 2009); similarly, negative tests do not conclusively exclude clinical reactivity to an allergen. Testing for mediators of allergic reactivity, such as histamine and tryptase, may be useful in confirming an episode of anaphylaxis (Simons, 2009). However, testing for these mediators is frequently not

available, so physicians must rely on the clinical history, and signs and symptoms of a reaction, to make the diagnosis (Sampson et al., 2006).

**Examples of allergen exposures thought to cause IgE-mediated anaphylaxis** Many allergens have been associated with the development of IgE-mediated anaphylaxis. These include food (e.g., milk, egg, peanuts, tree nuts, shellfish, gelatin), food additives (e.g., some colorants, spices, yeast), venoms (e.g., insect stings), latex, and inhalants (e.g., animal danders and grass pollen) (Simons, 2010).

**Adverse events on our list thought to be due to IgE-mediated hypersensitivity reactions** Antigen in the vaccines that the committee is charged with reviewing do not typically elicit an immediate hypersensitivity reaction (e.g., hepatitis B surface antigen, toxoids, gelatin, ovalbumin, casamino acids). However, as will be discussed in subsequent chapters, the above-mentioned antigens do occasionally induce IgE-mediated sensitization in some individuals and subsequent hypersensitivity reactions, including anaphylaxis.

### *Complement-Mediated Hypersensitivity*

**Definition of complement-mediated hypersensitivity** A much less frequent cause of immediate hypersensitivity is due to complement-mediated hypersensitivity, which involves the activation of the complement pathway by dialysis membranes, for example. Complement activation generates the anaphylatoxins C3a and C5a which bind to complement receptors on the surface of mast cells, leading to the release of inflammatory mediators (Noone and Osguthorpe, 2003).

**Evidence needed to conclude that complement-mediated hypersensitivity is operative in anaphylaxis** Although the clinical history and signs and symptoms of anaphylaxis are typically used to make the diagnosis of anaphylaxis, measurement of inflammatory mediators such as histamine, tryptase, kallikrein, and bradykinin, in addition to others, may be helpful in confirming an episode of anaphylaxis (Sampson et al., 2006; Simons, 2010). During or shortly after an episode of anaphylaxis, the demonstration of an acute elevation of C3a and C5a (both of which can increase vascular permeability and smooth muscle contraction) is useful in implicating complement-mediated hypersensitivity as the operative mechanism in the anaphylactic episode.

**Examples of exposures thought to cause complement-mediated anaphylaxis** A small number of substances have been associated with the development of complement-mediated anaphylaxis. These include dialysis

membranes, human proteins (e.g., transfusion or other blood product), immune complexes, and oversulfated chondroitin sulfate-contaminated heparin (Noone and Osguthorpe, 2003; Simons, 2010).

**Adverse events on our list thought to be due to complement-mediated hypersensitivity reactions** The antigens and potential antigens contained in the vaccines that the committee is charged with reviewing are not commonly associated with complement-mediated anaphylaxis.

### Immune Complexes

When present in adequate concentrations, antigen and antibody generate large complexes, termed *immune complexes*, which can lead to initiation of the inflammatory cascade through complement activation and engagement of Fc receptors, and to increased vascular permeability through the release of vasoactive factors upon activation of mast cells and neutrophils (Gao et al., 2006; Malbec and Daeron, 2007; Mayadas et al., 2009; Roubin and Benveniste, 1985; Volanakis, 1990). In addition, at cold temperatures, in vitro, some antibodies can precipitate from serum; they are called *cryoglobulins* (Tedeschi et al., 2007). The immune complexes may include IgM rheumatoid factor and antibodies against pathogens (Tedeschi et al., 2007). Immune complexes can cause pathologic damage and disease.

#### *Evidence Needed to Conclude That Immune Complexes Are Operative in a Clinical Case or an Animal Model*

The first requirement before attributing a symptom complex to the action of immune complexes is to demonstrate their presence. This can be done in plasma, using assays such as the Raji cell assay or the enzyme-linked immunosorbent assay to detect binding to plate-bound C1q, or to look for immune complexes on red cells that transport the complexes to the liver where they are ingested by Kupffer cells (Bellamy et al., 1997; Crockard et al., 1991; Kohro-Kawata et al., 2002; Zhong et al., 1997). It is also useful to demonstrate immune complexes in the affected tissue when tissue biopsy is available or needed for diagnostic purposes. Immunohistology showing co-localization of IgG and early components of the complement cascade serves to demonstrate the presence of immune complexes. To conclude that a particular antigen is responsible for immune complex formation, it is necessary to show that the antigen is present at the site of antibody deposition in tissue, or is within the circulating immune complexes in plasma. It is not necessary to show that the entire antigen is present, because serum and tissue proteases may digest much of the antigen that is not protected within the antibody-binding site (Durkin et al., 2009).

Therefore, negative studies for antigen may be considered inconclusive as only a small moiety of antigen may remain and may not be easily detectable (i.e., antibody to the antigen may be targeted to previously digested portions of the antigen).

*Examples of Natural Infection, Vaccine, or Drug Exposure Thought to Cause a Clinical Condition or Disease That Is Due to Immune Complexes*

There are several conditions in which immune complex–mediated tissue damage occurs.

- Hepatitis B infection is characterized by a number of accompanying comorbidities. Polyarteritis nodosa occurs in individuals with chronic hepatitis, and is thought to be mediated by immune complexes that include viral antigen and specific antibody (Cacoub and Terrier, 2009).
- Some drug allergies can cause serum sickness which is an immune complex disease with deposition of complexes in joints, pleura or pericardium, and glomeruli causing local, generally reversible, inflammation (Naguwa and Nelson, 1985).
- Systemic lupus is characterized by immune complexes in the circulation, skin, pleura, and pericardium. When the immune complexes are present in glomeruli, they cause glomerulonephritis, a serious manifestation of the disease. The target antigens in lupus appear to be apoptotic debris in circulating immune complexes, and both trapped and tissue antigen in the kidney (Munoz et al., 2010). In lupus, antibodies to the complement component C1q can bind to tissue-bound immune complexes, making it difficult to clear the complexes and increasing the consequent inflammation.
- Rheumatoid arthritis is a disease characterized by antibodies to IgG (rheumatoid factor) and cyclic citrullinated peptide. Both antibodies are thought to enhance inflammation in affected tissue, primarily joints (Conrad et al., 2010; Wegner et al., 2010). In mouse models, antibody-mediated enhancement of rheumatoid arthritis has been demonstrated; in the human disease, the model remains speculative.
- Streptococcal infections exhibit many antibody-mediated sequelae. In particular, arthritis and glomerulonephritis are considered to be the consequence of circulating immune complexes that deposit in joints and glomeruli, initiating an inflammatory cascade (Rodriguez-Iturbe and Batsford, 2007). These conditions are self-limited because the immune complexes cease to form once streptococcal antigen is eliminated.



- In many patients, hepatitis C is characterized by the presence of cryoglobulins that are thought to be rheumatoid factors bound to antibodies to the hepatitis C viral antigen (Sansonno et al., 2007). These cryoglobulins are notoriously difficult to treat, and they cause injury in multiple organs.

### *Adverse Events on Our List Thought to Be Due to Immune Complexes*

It is not clear that this mechanism is operative in any adverse event reported secondary to vaccine administration. It is important to note that the immune complexes and ensuing immune complex-mediated symptoms induced by vaccine usually should be short-lived. As vaccine antigen is eradicated by antibody or catabolism, specific antibody is no longer produced and the inflammatory process subsides. Only live vaccines have the potential for continued long-term production of antigen due to viral replication; antigen from nonreplicating vaccines is likely to disappear within a few weeks. The adverse events most suggestive of immune complex-mediated symptomatology are those associated with hepatitis B vaccine, as it is known that the antibodies raised to viral antigen in the course of the natural infection can form damage-inducing complexes. There are no data, however, documenting immune complexes containing hepatitis B surface antigen.

### **Tissue Responses (Fever and Seizures)**

The mechanisms leading to the development of febrile seizures include the induction of fever by inflammatory mediators and the effects of pyrexia, and of the inflammatory response on neuronal excitability. It is now recognized that febrile seizures have significant genetic susceptibility components.

### *Induction of Fever by Inflammatory Mediators*

Fever is a biologic response to a host of extrinsic and intrinsic pyrogenic stimuli (Avner, 2009). Extrinsic pyrogenic stimuli include bacterial toxins and other products of microbial metabolism (e.g., lipopolysaccharide released from the cell wall of gram-negative bacteria). Intrinsic pyrogenic stimuli include antigen-antibody complexes and activated components of the complement system, either of which may result from a microbial infection or immunization with microbial antigens.

These pyrogenic stimuli induce monocytes, macrophages, and other inflammatory cells to release pyrogenic cytokines (e.g., IL-1 alpha, IL-1 beta, TNF, interferon) into the circulation. Acting either directly or indirectly on the specialized neurons of the thermoregulatory center in the preoptic area

of the hypothalamus, these cytokines induce the production of E-series prostaglandins that raise the host's thermoregulatory set point, resulting in an increase in core body temperature.

### *Effects of Pyrexia and the Inflammatory Response on Neuronal Excitability*

The specific mechanism whereby fever might induce a seizure is not known. It is known that changes in temperature can alter certain ion channels in the brain and potentially cause abnormal or synchronized neuronal discharges and seizures (Shibasaki et al., 2007; Thomas et al., 2009). Moreover, fever-induced hyperventilation and the resulting alkalosis may also play a role in seizure induction (Schuchmann et al., 2006). Furthermore, animal data are emerging on the role of the inflammatory response in astroglial cells after a prolonged febrile seizure. It has been shown that IL-1 beta synthesis is induced after a febrile seizure, and that it has potent proconvulsant effects in both immature and adult rodents (Dube et al., 2010). The role inflammatory mediators play in epileptogenesis is not fully understood and is an area of intense research interest. Recently, Balosso et al. (2008) showed that IL-1 beta is overexpressed in glia and neurons in animal models with seizures. This inflammatory mechanism has a proconvulsant effect, and may influence changes in neuronal excitability (Balosso et al., 2008). Fever-induced factors (e.g., IL-1 beta) may precipitate seizures in the immature brain or in individuals who are genetically susceptible (Heida et al., 2009; Nakayama, 2009).

### *Genetics and Febrile Seizures*

Febrile seizures are the result of a combination of genetic and environmental factors, with polygenic inheritance the most common means of inheritance. Epidemiologic studies have shown that 13–37 percent of children with febrile seizures have a family history of febrile seizures and 4 percent have a family history of epilepsy (Offringa et al., 1994; Sadleir and Scheffer, 2007). In monozygotic twins, the concordance rate is higher (Corey et al., 1991; Tsuboi, 1987).

Although specific susceptibility genes have not been identified in most patients with febrile seizures, several susceptibility loci that are inherited in an autosomal dominant fashion in certain families have been identified (Audenaert et al., 2006; Hedera et al., 2006; Johnson et al., 1998; Kugler et al., 1998; Nabbout et al., 2002; Nakayama et al., 2000, 2002, 2004; Peiffer et al., 1999; Poduri et al., 2009; Wallace et al., 1996). Other genetic factors have been implicated as a link between fever and susceptibility to seizures. Mutations in sodium channels (e.g., splice site variant SCN1A) and gamma aminobutyric acid A receptor genes have been identified in

children with febrile seizures (Petrovski et al., 2009; Sadleir and Scheffer, 2007; Schlachter et al., 2009).

### Molecular Mimicry

Molecular mimicry is sequence and/or conformational homology between an exogenous agent (foreign antigen) and self-antigen leading to the development of tissue damage and clinical disease from antibodies and T cells directed initially against the exogenous agent that also react against self-antigen. Molecular mimicry as a mechanism that can cause pathologic damage and disease has been demonstrated in several animal models, most notably experimental allergic encephalomyelitis (EAE) in mice and rabbits (Oldstone, 2005).

#### *Evidence Needed to Conclude That Molecular Mimicry Is Operative in a Clinical Case or an Animal Model of Disease*

Essential to concluding molecular mimicry contributes to a clinical case or animal model of disease are the following: (1) a susceptible host whose genetic background and adaptive immune responses allows emergence of self-reactive immunity, (2) exposure to an exogenous agent which expresses antigens that are immunologically similar to self-antigen(s), and (3) a host immune response to the exogenous agent that cross-reacts with biologically relevant host tissue structures and causes tissue damage and clinical disease.

Proving that a particular human autoimmune disease is due to molecular mimicry is problematic (Albert and Inman, 1999; Rose and Mackay, 2000). A realistic and consistent temporal relationship between exposure to exogenous antigen and development of disease must be documented. This can be difficult in the case of a natural exposure to pathogen where infection may have been subclinical, making it impossible to define an exact temporal relationship.

Linear amino acid sequence homology or even similar conformational structure between an exogenous agent and a self-antigen alone are not sufficient to prove that molecular mimicry is the pathogenic mechanism for a disease. Many such homologies exist, and the vast majority of these are not associated with biologically relevant autoimmune phenomena or actual human disease (Albert and Inman, 1999).

Finding a tissue-specific antibody response following exposure to an exogenous agent is also, by itself, not proof of molecular mimicry as the pathologic mechanism of disease (Albert and Inman, 1999). Both naturally occurring and postinfectious cross-reactive antibodies and T cells are relatively common and most frequently not pathogenic (Fujinami et al., 2006). Cross-reacting antibodies can also be secondary to nonspecific tissue injury

(and to consequent expression of otherwise occult self-antigens) rather than primary to tissue injury itself. Moreover, in some circumstances, infection with viruses that express antigens having immunologic cross-reactivity with self-proteins can actually protect against autoimmune disease in certain animal models (Barnett et al., 1996; Fujinami et al., 2006).

Neither the *in vitro* demonstration of cross-reacting antibodies nor T cell activation by antigen-MHC complexes proves pathogenic mimicry. An *in vivo* pathogenic autoimmune attack would also require the demonstration of local binding of antibody with activation of the complement cascade, activation of the appropriate co-stimulatory T cell signals and cytokines, and/or involvement of other pathogenic effector mechanisms in a biologically relevant tissue site.

*Examples of a Natural Infection, Vaccine, or Drug Exposure Thought to Cause a Clinical Condition or Disease That Is Due to Molecular Mimicry*

While molecular mimicry is a well-established mechanism in selected animal models, its relevance to human autoimmune disease remains in most cases to be convincingly proven. Nevertheless, there is some experimental evidence (Albert and Inman, 1999; Fujinami et al., 2006; Rose and Mackay, 2000) that suggests or implicates this mechanism in certain human autoimmune diseases including (among others)

- Rheumatic fever associated with group A streptococcal infection;
- HLA B27-associated spondyloarthropathies and several antigens from *Shigella*, *Yersinia*, and *Klebsiella* bacteria;
- Multiple sclerosis and exposure to several different viruses;
- Insulin-dependent diabetes mellitus and Coxsackievirus B4; and
- Demyelinating diseases and hepatitis B:
  - Amino acid homology between myelin basic protein (MBP) and hepatitis B virus polymerase (HBVP) has been reported (Fujinami and Oldstone, 1985). In addition, injection of a HBVP immunologic epitope shared with MBP into rabbits resulted in an EAE-like disease, antibodies against MBP, and T cell reactivity (Fujinami and Oldstone, 1985). However, infection with hepatitis B is not associated with the development of demyelinating diseases. Furthermore, the recombinant vaccines contain hepatitis B surface antigen not hepatitis B virus polymerase.

One example of molecular mimicry as the likely mechanism causing clinical autoimmune disease is found in the subtype of Guillain-Barré syndrome (GBS) characterized by acute motor axonal neuropathy (AMAN).

Approximately one fourth of patients with GBS have had *Campylobacter jejuni* infection in the preceding few weeks, compared to only 1–2 percent of controls (Kuwabara et al., 2004; Rees et al., 1995b). *C. jejuni* infection is most highly correlated with AMAN, as opposed to the other subtypes of GBS (Griffin et al., 1996; Visser et al., 1995).

In patients who develop AMAN subsequent to *C. jejuni* enteritis, IgG autoantibodies and complement are found bound specifically to GM1 ganglioside in the axolemma membrane of peripheral nerves (Hafer-Macko et al., 1996; Solomon and Willison, 2003; Willison and Yuki, 2002). These patients often benefit from plasmapheresis, and their anti-GM1 autoantibody titers decrease as the clinical course improves (The Guillain-Barré Syndrome Study Group, 1985). By contrast, patients who develop *C. jejuni* enteritis not complicated by AMAN do not develop GM1 autoantibodies (Ogawara et al., 2000; Rees et al., 1995a).

GM1 ganglioside antigens in peripheral nerves are structurally identical to the terminal tetrasaccharides of the GM1-like lipo-oligosaccharide (LOS) structures expressed on the surface of certain strains of *C. jejuni* bacteria isolated from patients with AMAN (Aspinall et al., 1994a,b; Lee et al., 2004; Prendergast et al., 1998; Yuki et al., 1993, 2004). This suggests that autoantibodies bound to neuronal gangliosides in AMAN may result from immunologic cross-reactivity with antigens from *C. jejuni* lipo-oligosaccharides.

In the 1990s ganglioside preparations extracted from bovine brain tissue or isolated GM1 were occasionally used as therapeutic agents for various neurological disorders and some of these patients developed clinical AMAN with anti-GM1 IgG autoantibodies (Illa et al., 1995).

The association of *C. jejuni* infection leading to anti-GM1 autoantibody production and the cross-reactivity of those antibodies with nerve roots and clinical disease in vivo is further strengthened by development of a relevant animal model of the disease. Rabbits immunized with *C. jejuni* expressing GM1-like LOS surface structures develop high titers of anti-GM1 IgG antibody, flaccid limb weakness, and histopathologic features characteristic of AMAN (including IgG deposited on the axons of the ventral roots, internodal axolemmas, and nodes of Ranvier) (Moran et al., 2005; Susuki et al., 2003, 2004; Yuki, 2005; Yuki et al., 2004).

#### *Adverse Events (AEs) on Our List Thought to Be Due to Molecular Mimicry*

Some of the vaccine AEs under consideration by our committee share symptoms with human autoimmune diseases for which molecular mimicry has been hypothesized (i.e., arthritis, systemic lupus erythematosus, insulin-dependent diabetes mellitus, central and peripheral nervous system demyelinating diseases). However, the committee found little clinical evidence

(e.g., challenge/rechallenge), diagnostic evidence (e.g., presence of antigen or relevant immune complexes in affected tissue), or experimental evidence (e.g., in vitro evidence of cross-reactive T cells derived from a site of tissue injury) that could be consistent with the hypothesis of molecular mimicry in rare and selected case reports. For example, as will be discussed in subsequent chapters in more detail, Poirriez (2004) reported the absorption of antinuclear antibodies (ANAs), isolated from a single hepatitis B immunized patient who developed lupus, by highly concentrated vaccine antigen suggesting mimicry between vaccine antigen and self-antigen. There were no unimmunized ANA-positive or other controls tested in this study, and others have not reported this finding subsequently. Based on the literature reviewed, molecular mimicry was not confirmed to be a mechanism leading to the development of the adverse events postvaccination.

### Antigen Persistence

During a typical immune response, the offending antigen is effectively removed or neutralized, which reduces the immune stimulation and ultimately results in a down-regulation of the immune response. In contrast, ongoing immune responses to persisting antigens can result in continuing inflammation and tissue damage, which may result in the release of self-peptide, and/or activation of previously tolerant autoreactive T cells. The duration of antigen persistence depends on several variables: (1) whether the antigen or antigenic determinants that activate the immune system are derived from a replicating pathogen or are from a transient or intermittently present non-replicating source; (2) the life cycle of the pathogen, assuming it is the source of the antigen or antigenic determinants; and (3) the anatomical and cellular (intracellular or extracellular) location of the antigen source.

#### *Examples of Natural Infection, Vaccine, or Drug Exposure Thought to Cause a Clinical Condition or Disease That Is Due to Antigen Persistence*

The best understood reason for antigen persistence is pathogen replication. In many infections, the amount of pathogen-derived antigens often increases initially before decreasing as the pathogen is fully cleared by the immune system. In immunocompromised individuals, whether due to primary (genetic) or secondary (acquired; e.g., via chemotherapy) etiologies, it is possible that pathogens, and therefore pathogen-derived antigens, persist longer or achieve higher levels than they would in immunocompetent individuals. Regardless of the cause, the consequences of a reduced or delayed ability to eliminate a pathogen often, but not always, include more severe pathology at the target tissue or longer duration of illness. Some individuals may fail to eradicate the pathogen from their body.

Two other causes of antigen persistence are pathogen reactivation and persistent infection. Some pathogens persist within host cells without evoking immune responses, reemerging at a later time or creating a depot of antigen that may be released slowly over time. The mechanisms that control persistence, latency, and reactivation are the subject of active research at this time.

Examples of antigen persistence secondary to persistent infection or viral reactivation include hepatitis B and varicella zoster virus, which are discussed later under those topics. A third example of infectious disease associated with antigen persistence is immune reconstitution inflammatory syndrome which is an escalating immune response to chronically persisting antigen in patients with human immunodeficiency virus (HIV) who are co-infected with mycobacteria, cytomegalovirus, *Cryptococcus*, herpes simplex virus, and so on. Symptoms of inflammatory disease develop after patients begin highly active antiretroviral therapy, which allows reconstitution of the patient's T cell function and subsequent immune reaction to the co-infecting agent.

#### *Evidence Needed to Conclude That Antigen Persistence Is Operative in a Clinical Case or Animal Model of Viral Infection*

Vaccine-derived antigens persist longer when the vaccine is a live, attenuated virus. The vaccine virus, as an intact pathogen, is thought to persist in the host for several weeks, which is in contrast to the more transient presence of split product, recombinant, or killed whole vaccines, which persist for a much shorter period of time. For the discussion of antigen persistence herein, please refer to the persistent viral infection and viral reactivation sections beginning on page 77. In a handful of cases, there was experimental or clinical evidence (e.g., in vitro evidence of cross-reactive T cells derived from a site of tissue injury) that is consistent with the hypothesis of antigen persistence. Based on the literature reviewed, antigen persistence is a possible mechanism leading to the development of a handful of adverse events postvaccination, but only for live virus vaccines.

#### **Epitope Spreading**

Epitope spreading is a process in which a T cell response that is initially specific for one epitope spreads to unrelated epitopes. The initial immune response, such as a CD4 T cell response, is directed to one antigen. Chronic tissue destruction from the initial immune response results in production of additional epitopes that become targets for the immune response (Vanderlugt et al., 1998). The new targets are distinct from the original targets (Vanderlugt et al., 1998). Epitope spreading may result from

target antigens that complex with intracellular self-antigen. The result of this could be an autoimmune response that is initially triggered by the exogenous antigen, but then progresses to a sustained autoimmune response against self-antigen (Davies, 2000).

### Autoreactivity/Bystander Activation/Hyperresponsiveness

Autoreactivity can result from expression and immune recognition of self-antigens that have been modified by some extrinsic factor (e.g., binding of a reactive chemical or viral element) so that they appear foreign to the immune system. The response to such neo-antigens would cease when the transforming agent is removed. Examples include drug modifications of normal proteins, hapten-carrier complexes, and oxidative modification of normal cellular constituents.

In bystander activation, there is a robust or exaggerated immune response to an exogenous agent that induces local tissue inflammation and stimulation of otherwise normal unaffected cells. This inflammation can result in the release of normally sequestered self-antigens. The inflammation can result in nonspecific activation of previously dormant autoreactive Th1 cells that then react against the newly released self-antigens.

### Increased Cytokines

Cytokines are a group of molecules involved in intercellular communication. They are classed together as *lymphokines*, *interleukins*, and *chemokines*, based on their function, cell origin, and target of action. When the innate immune system, the adaptive immune system, or both are responding to a pathogen, cytokines activate immune cells to produce even more cytokines and alter function of resident cells in tissues.

The cytokine milieu contributes to the differentiation of T cells to one or another subset. Excessive differentiation of T cells to one or another subset may impair the homeostatic and regulatory mechanisms that limit autoreactivity.

### *Examples of Increased Cytokines*

Normally, the control of cytokine secretion is kept in check by regulatory mechanisms. However, in some instances, the regulatory mechanisms break down and too many immune cells (including those of both the innate immune system and the adaptive immune system) are activated, resulting in local tissue and organ damage, and systemic symptoms. This kind of profound systemic oversecretion of cytokines is called *cytokine storm*. It may follow infection or other types of massive immune activation includ-



ing bacterial sepsis, avian influenza, acute respiratory distress syndrome, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome (Sriskandan and Altmann, 2008; Szyper-Kravitz, 2009; Wong and Yuen, 2006; Yokoyama et al., 2010). Increased levels of proinflammatory cytokines, or decreased secretion of anti-inflammatory cytokines, are found in the active phase of many of the above-mentioned conditions.

Although the committee is not aware of reports of full-blown cytokine storm following administration of any of the vaccines reviewed, more subtle imbalances of proinflammatory and anti-inflammatory cytokines may occur following immunization against rubella, human papillomavirus, or hepatitis B (Albarran et al., 2005; Garcia-Pineres et al., 2007; Pukhalsky et al., 2003). Moreover, it is possible that the unique immunogenetic makeup of an individual might predispose that individual to an exaggerated cytokine imbalance following immune stimulation such as microbial infection or vaccine administration.

#### *Adverse Events on Our List Thought to Be Due to Increased Cytokines*

In review of the relevant literature related to the vaccine and AE combinations considered by the committee, no evidence that directly or indirectly supports the oversecretion of cytokines as an operative mechanism was found.

### **Superantigens**

Superantigens are determinants expressed by a microbe that can bypass T cell receptor signaling pathways and directly activate large numbers of T cells. An example would be TSS-A/B toxins in *Staphylococcal* and *Streptococcal* toxic shock syndromes. Superantigens can activate up to 20 percent of circulating T cells (Li et al., 1999). The committee found no evidence that supports superantigen stimulation of immune reactions as an operative mechanism in any of the vaccine adverse events under consideration.

## **VIRAL ACTIVITY**

Viral infections cause a host of symptoms in affected individuals. Some of these symptoms are attributable to direct or primary infection, persistent viral infection, and viral reactivation.

### **Direct or Primary Infection**

Primary infection with varicella, for example, results in varicella (chickenpox), manifesting as fever, malaise, listlessness, and a rash consist-

ing of vesicles, scabs, and maculopapules in varying stages of evolution (Whitley, 2010). Complications include secondary skin infections, myocarditis, nephritis, pneumonia, central nervous system involvement (acute cerebellar ataxia, encephalitis), and bleeding diatheses (Whitley, 2010).

Similarly, “[t]ransient polyarthralgia and polyarthritis [from rubella] rarely occur in children but are common in adolescents and adults, especially females. Encephalitis (1:5,000 cases) and thrombocytopenia (1:3,000 cases) are complications” (AAP, 2009c).

The acute complications of measles infection include otitis media, croup, and pneumonia (Gershon, 2010). Approximately 1 of every 1,000 individuals infected with measles virus develops acute encephalitis (AAP, 2009b). Furthermore, “[d]eath, predominantly resulting from respiratory and neurologic complications, occurs in 1 to 3 of every 1,000 cases reported in the United States” (AAP, 2009b).

### Persistent Viral Infection

Some viruses are capable of causing permanent, latent infection in nearly all individuals, the herpesviruses and retroviruses being the best-known examples. Reactivation, as discussed below, with production of new virus can occur with such latent viruses.

With other viruses, some infected individuals are unable to clear the viral infection. The classic example of persistent infection is hepatitis B virus (HBV). “More than 90 percent of infants infected perinatally will develop chronic HBV infection” (AAP, 2009a). Between 10 percent and 20 percent of children infected between 1 and 5 years of age become chronically infected, whereas approximately 5 percent of acutely infected adults develop chronic HBV infections (Koziel and Thio, 2010). Immunosuppressed patients or patients with an underlying chronic illness who develop an acute HBV infection are at an increased risk of developing a chronic infection (AAP, 2009a). It is important to note here, however, that the hepatitis B vaccine is not a live virus vaccine and so cannot infect recipients.

### Viral Reactivation

Reactivation of infection can occur when the virus, following the acute infection, remains in a dormant or latent state somewhere in the body, where it can subsequently reemerge. Varicella zoster virus (VZV) establishes latency in the dorsal root ganglia, cranial nerve ganglia, and enteric ganglia during primary infection (Gershon et al., 2008). Reactivation results in herpes zoster (shingles), characterized by a unilateral eruption of vesicles with a dermatomal distribution, sometimes accompanied by pain localized to the area (Whitley, 2010).

*Viral Activity Attributed to Vaccines Containing Live Attenuated Viruses*

Attenuated live viral vaccines such as the ones considered in this report (live attenuated influenza virus, cold-adapted influenza virus, VZV, MMR) can cause some of these same effects through the same mechanisms because the vaccines are live. As detailed further below, these effects occur most frequently in patients with impaired immunity. Varicella vaccine virus, which is distinct from the natural varicella virus, for example, has been recovered from the bronchoalveolar lavage fluid and lung biopsy of immunocompromised children who developed pneumonia and rash as a primary infection after receiving a varicella vaccine (Galea et al., 2008; Kramer et al., 2001; Levy et al., 2003; Sharrar et al., 2001; Waters et al., 2007). As examples of viral reactivation, children who had previously been vaccinated developed zoster and even encephalitis from which vaccine-strain virus was then recovered (Chan et al., 2007; Chouliaras et al., 2010; Iyer et al., 2009; Levin et al., 2003). Some, but not all, of these children were subsequently shown to be immunocompromised. The salient points in these examples are that the adverse effects observed are complications seen with natural infection and that the causal role of the vaccine virus was demonstrated by its isolation or identification by molecular techniques, typically from sites that are otherwise sterile.

**INJECTION-RELATED ADVERSE EVENTS**

One or more of the mechanisms described above could play a role in the development of many of the adverse events following vaccination reviewed by the committee. However, mechanisms leading to three adverse events (complex regional pain syndrome, frozen shoulder, and syncope) were considered by the committee to be a potential adverse event of direct trauma from the needle occurring with various injected vaccines and not necessarily attributable to the contents of the vaccine. Mechanisms for these adverse events are described below.

**Complex Regional Pain Syndrome**

Chronic severe and often burning pain affecting part or all of one or more extremities following an injury defines complex regional pain syndrome (CRPS). The pain is often accompanied by skin discoloration, local edema, fluctuation in skin temperature in the affected limb(s), allodynia (pain from stimuli that would not ordinarily be painful), and abnormal sweating (Bruehl, 2010). Mechanisms involving altered skin innervation, dysfunction of the sympathetic nervous system, local inflammation, and possible psychological factors have been purported to play a role in the development of CRPS.

### *Altered Skin Innervation*

The cascade of events leading to CRPS is widely considered to result from nerve trauma. Needle stick injuries to the distal nerves in rats resulted in reduction in sensory neuron density similar to findings in CRPS patients (Bruehl, 2010). In addition, lower densities of epidermal nerves and abnormal innervation around sweat glands and hair follicles have been reported in CRPS patients (Bruehl, 2010).

### *Dysfunction of the Sympathetic Nervous System*

Skin discoloration and fluctuation in skin temperature in the affected region suggests the involvement of the sympathetic nervous system in CRPS (Bruehl, 2010). In some CRPS patients, increased sympathetic nervous system activity is associated with increases in spontaneous pain and hyperalgesia (Bruehl, 2010). In addition, the expression of adrenergic receptors on pain fibers after trauma (in animal studies) provides a mechanism whereby sympathetic nervous system outflow could trigger a pain signal (Bruehl, 2010).

### *Inflammation*

Improvement of symptoms in CRPS patients treated with corticosteroids suggests inflammation as a contributing factor in the development of the acute phase of CRPS (Bruehl, 2010). Nerve injury could induce the release of proinflammatory cytokines and neuropeptides from nociceptive fibers (Bruehl, 2010). Increased levels of proinflammatory cytokines have been isolated from the serum, cerebrospinal fluid, and blister fluid of CRPS patients (Bruehl, 2010). Proinflammatory cytokines can contribute to the increased plasma loss, leading to localized edema (Bruehl, 2010). In addition, certain major histocompatibility complexes have been reported to be expressed at significantly higher frequencies in CRPS patients, further supporting inflammation as a mechanism (Bruehl, 2010).

### *Psychological Factors*

Initially CRPS, due to its poorly understood pathophysiology and unusual symptomatology, was thought to be purely psychogenic (Bruehl, 2010). While a purely psychogenic model is no longer considered, psychogenic factors could play a role in the development of CRPS. Greater CRPS pain intensity was predicted by increased depression levels in a patient self-study (Bruehl, 2010). In addition, psychological stress in CRPS patients has been associated with altered immune function (Bruehl, 2010). Psychological factors could impact all of the implicated mechanisms.

### *Comprehensive Mechanism*

While the mechanisms purported to contribute to the development of CRPS are studied and discussed in isolation, it has been hypothesized that the mechanisms are interconnected (Bruehl, 2010). Studies testing this hypothesis have yet to be performed.

### **Deltoid Bursitis**

Idiopathic- or injury-induced pain, stiffness, and restricted motion of the shoulder defines deltoid bursitis. The presentation of deltoid bursitis is comprised of shoulder pain and stiffness with restricted motion (Anton, 1993). Pathologic examination has revealed an inflammatory process in the affected shoulder. Increased deposition of growth factors, matrix metalloproteinases, and cytokines has been observed in capsular biopsy specimens from patients with deltoid bursitis (Brue et al., 2007; Dias et al., 2005). In addition, magnetic resonance imaging and arthrography have revealed abnormalities of the shoulder joint and synovial membrane, and thickening of the humeral ligament and joint capsule suggestive of inflammation (Brue et al., 2007). Although likely to be a rare event, direct trauma to the bursa from needle injury from the injected vaccine, independent of the contents of the needle, could lead to the activation and recruitment of inflammatory cells leading to the symptoms of deltoid bursitis.

### **Syncope**

Loss of consciousness resulting from decreased blood flow to the brain is termed *syncope*. The pathogenesis of syncope varies depending on the precipitating event. Syncope resulting from pain or emotional triggers, for example the sight of blood or administration of a vaccine or treatment via an injection, is termed *reflex syncope* and more specifically *vasovagal syncope* (van Dijk et al., 2009). The pathophysiology of vasovagal syncope has not been fully delineated; however, manipulation of the blood flow by the autonomic nervous system is involved. The injection of the vaccine leads to an initial increase in stimulation of the sympathetic nervous system (Arthur and Kaye, 2000). The increase in stimulation of the sympathetic nervous system results in an increased heart rate and arterial pressure (Grubb, 2005). The increased arterial pressure leads to the activation of baroreceptors and transmission of afferent signals from the aortic arch via the vagus nerve resulting in stimulation of the parasympathetic nervous system and the development of nausea, vertigo, facial pallor, dizziness, and epigastric discomfort commonly experienced 30 to 60 seconds prior to the loss of consciousness (Fenton et al., 2000; Wieling et al., 2009). Physiologically, the

stimulation of the parasympathetic nervous system results in a decreased heart rate and arterial pressure leading to decreased blood flow to the brain and the loss of consciousness (Grubb, 2005).

## COAGULATION AND HYPERCOAGULABLE STATES

Injury to the vessel wall, regardless of the type of injury, leads to the stimulation or activation of endothelial cells and platelets, and to the generation of a thrombus or blood clot. In response to injury, both cell types increase expression of the adhesion molecule P-selectin on the cell surface (Green, 2006). Through interaction with P-selectin, neutrophils, monocytes, and platelets form a thrombus at the site of injury (Green, 2006). The interaction of additional proteins secreted from the injured endothelial cells and platelets enhance platelet-to-platelet aggregation, leading to the formation of platelet-leukocyte aggregates that are favorable to fibrin formation (Green, 2006).

The generation of fibrin results from a cascade of enzymatic reactions initiated upon injury to the vessel wall. A key component of this cascade is tissue factor (TF), which exists in a soluble form and as a transmembrane protein (Shantsila and Lip, 2009). TF is activated upon vessel wall injury and exposure to the subendothelial tissues to blood (Shantsila and Lip, 2009). Monocytes are a major source of TF and can stimulate TF expression by endothelial cells, thus increasing the supply of tissues expressing the factor (Shantsila and Lip, 2009).

The aforementioned cascade is initiated upon the formation of complexes comprised of circulating factor VII and TF, leading to the activation of factor VII and the generation of factor VIIa (Sidhu and Soff, 2009). TF-factor VIIa complexes continue the cascade, culminating in the generation of the serine protease thrombin (Green, 2006). Thrombin activates integrins (these mediate platelet aggregation and other factors of the coagulation cascade), and it further activates platelets leading to the production of platelet activators (Sidhu and Soff, 2009). In addition, thrombin cleaves fibrinogen to produce fibrin monomers (Sidhu and Soff, 2009).

Monocytes, in addition to producing TF, contribute to prothrombotic effects via other mechanisms. Conjugation of monocytes with platelets induces the expression of integrins on monocytes, amplifying their interactions with platelets (Shantsila and Lip, 2009). During inflammation, stimulation of monocytes by T cells induces the expression of matrix metalloproteinases 1 and 3, which are elements of plaque destabilization (Shantsila and Lip, 2009). Monocytes can activate coagulation factor X, which is responsible for the generation of thrombin (Shantsila and Lip, 2009).

A few proteins facilitate regulation of the coagulation cascade. Protein C, which circulates in the plasma, is activated by the serine protease throm-

bin and its cofactor thrombin-thrombomodulin (Rezaie, 2010). Activated protein C functions as an anticoagulant by proteolytically degrading procoagulant cofactors essential for the generation of thrombin (Rezaie, 2010). The cofactor protein S enhances effects of activated protein C (Anderson and Weitz, 2010). In addition, the serine protease inhibitor antithrombin regulates the coagulation cascade by inactivating thrombin as well as other enzymes in the cascade (Rodgers, 2009).

In individuals with inherited (e.g., antithrombin deficiency, Factor V Leiden) or acquired (e.g., obesity, pregnancy) hypercoagulable states, the function of the enzymes involved in the aforementioned coagulation cascade and its regulation are altered or deficient, leading to excessive coagulability (Anderson and Weitz, 2010). Excessive coagulation can contribute to the development of thrombosis, myocardial infarction, and stroke (Anderson and Weitz, 2010).

### INCREASED SUSCEPTIBILITY

Both epidemiologic and mechanistic research suggest that most individuals who experience an adverse reaction to vaccines have a preexisting susceptibility. These predispositions can exist for a number of reasons—genetic variants (in human or microbiome DNA), environmental exposures, behaviors, intervening illness, or developmental stage, to name just a few—all of which can interact as suggested graphically in Figure 3-1.

Some of these adverse reactions are specific to the particular vaccine, while others may not be. Some of these predispositions may be detectable prior to the administration of vaccine; others, at least with current technology and practice, are not. Moreover, the occurrence of the adverse event is often the first sign of the underlying condition that confers susceptibility.

The best-understood vaccine-associated adverse effect is the occurrence of invasive disease (such as meningoencephalitis and arthritis) caused by the vaccine virus itself in individuals with an acquired or genetic immunodeficiency who receive live vaccines such as VZV, MMR, and oral polio vaccine. Although the incidence of such infections may decrease with the introduction of newborn screening for severe combined immunodeficiency, the occurrence of vaccine-related disease can be the trigger that leads to the recognition of immunodeficiency (Galea et al., 2008; Ghaffar et al., 2000; Kramer et al., 2001; Levy et al., 2003). Invasive disease may also occur by viral reactivation in individuals who previously received these vaccines while healthy, but who subsequently become immunocompromised, for example, as a result of chemotherapy should they later develop cancer or leukemia (Chan et al., 2007; Levin et al., 2003). Not all individuals who suffer invasive disease have demonstrated recognized immune deficiencies, even when vaccine virus is recovered from the patient (Iyer et al.,

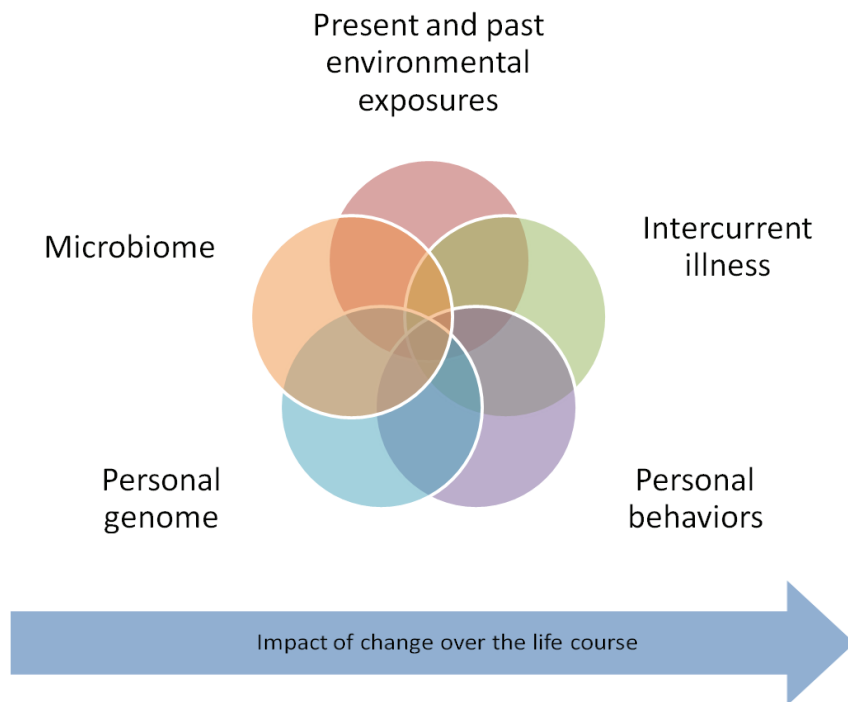


FIGURE 3-1 Present and past environmental exposures.

2009; Levin et al., 2008). This leads to two hypotheses: either immunocompetent individuals can acquire invasive disease from vaccine virus, or further evaluation of these patients would reveal previously unrecognized immunodeficiencies.

Many adverse events appear to be immune-mediated. Anaphylaxis is an obvious example of this. In some patients who experience anaphylaxis, the triggering antigen can be identified with follow-up testing. Known triggering antigens include egg and gelatin. But even when the triggering antigen such as egg or gelatin is known, it is not clear why some people develop anaphylaxis while the vast majority does not. Proposed mechanisms for other immune-mediated adverse responses are many, including molecular mimicry, development of immune complexes, inappropriate cytokine responses, antigen persistence, and epitope spreading, as described above. Here, evidence of predisposing factors to adverse effects from vaccines is beginning to emerge. Some genetic variants that affect immune response have been identified. Reif et al. (2009) demonstrated that genetic variants in ICAM-1, CSF-3, and IL-4 are associated with more severe adverse effects



from the highly reactogenic vaccine for smallpox. Finally, rechallenge cases (those in which a person suffered a particular adverse event after each administration of the same vaccine) also suggest a role for an altered immune response. As noted above, much work remains to be done to elucidate and to develop strategies to document the immunologic mechanisms that lead to adverse effects in individual patients.

Age can also affect susceptibility to adverse responses to vaccines because physiological development, particularly of the immune and nervous systems, continues throughout much or all of life. Some hypothesize so-called *critical periods* in which adverse reactions to a range of exposures are more likely to occur (IOM, 2006). Young children are more likely than are older children to develop febrile convulsions (Waruiru and Appleton, 2004). This type of rationale led the Japanese three decades ago to delay immunization with whole cell pertussis vaccine until children reached 2 years of age (Gangarosa et al., 1998). Gender can also be a factor. Females, for example, experience less local reactogenicity than males to smallpox vaccine (Talbot et al., 2004) but increased reactogenicity compared to males to anthrax vaccine (Pittman, 2002).

In some metabolically vulnerable children, receiving vaccines may be the largely nonspecific “last straw” that leads these children to reveal their underlying genotype. It was recently discovered that a large majority of children who developed encephalopathy after receiving whole cell pertussis vaccine have mutations in SCN1A, which are associated with Dravet syndrome or severe myoclonic epilepsy of childhood (Berkovic et al., 2006; McIntosh et al., 2010). While it seems likely that the vaccine triggered symptoms in these children by causing high fever, the particular vaccine antigens do not appear to alter the course of the disease. Rather, the ensuing phenotype could and probably would have been precipitated by multiple other fever-inducing triggers (McIntosh et al., 2010; Wiznitzer, 2010). Similarly, Yang et al. (2006) reported a series of seven cases in which children with undiagnosed or inadequately managed metabolic or endocrine disorders suffered acute metabolic crises within hours after administration of a variety of immunizations. Two of these children had adrenal hyperplasia and responded to administration of IV fluid and glucocorticoids.

This list of factors that are known to confer susceptibility is by no means definitive or exhaustive. Rather, we hypothesize that continued study of alleged vaccine-related injuries, the committee informed by epidemiologic studies that identify vulnerable populations and exploration of underlying mechanisms of susceptibility, will provide greater insight into these and other mechanisms and will identify more factors that contribute to vaccine susceptibility.

## ALTERATIONS IN BRAIN DEVELOPMENT

The committee was specifically tasked to assess the evidence that vaccines could alter neuronal development, resulting in “secondary autism” or “autistic features” arising from chronic encephalopathy, mitochondrial disorders, or other underlying disorders.<sup>1</sup> Some theorize that vaccines can alter the development of the nervous system through inflammatory responses or hyperarousal of the immune system. Most certainly, scientific advances have shown commonalities in the development of and the signaling between the immune and nervous systems.

Development of the human central nervous system is incompletely understood, but certain principles are well established. Development occurs in a predictable sequence, and the earlier in the sequence, the more reliably certain events can be timed. For example, closure of the neural tube is always complete before 28 days gestation. Nutritional factors such as folic acid deficiency or exposure to toxins such as valproic acid during this “critical period” predictably produce neural tube defects.

Nervous system development is under genetic control, and is incompletely understood, but it is clearly a highly complex process in which interactions with the environment beginning in the womb may modify the developmental process. Factors that may modify brain development include maternal, fetal, and infant nutrition; infection; toxins; vascular insults; direct trauma; and aspects of the social environment, in addition to mutations in critical genes regulating development.

Development of the nervous system involves formation of the neural plate and tube, followed by proliferation of neuronal precursors, which must then migrate to their final positions in the nervous system where they establish functional connections with other neurons and glial cells. The neuronal elements ultimately interact to form functional neural circuits. Essentially all of the nerve fiber tracts comprising these circuits are present at birth, but they are not functionally active because the rate of conduction in unmyelinated axons is slow. The process of myelination of fiber tracts occurs in an orderly sequence, most dramatically during the first few years of life, but continues on into the fourth decade. When a nerve fiber (axon) is ensheathed by myelin, the rate of impulse conduction accelerates dramatically, allowing neural circuits to become functionally active. In addition, synapses (the connections that form neural circuits) continue to form at a variable rate that peaks in various parts of the brain at different, but predictable times. These neural circuits exhibit plasticity, and they underlie much of human behavior. The essential stimuli for neural development

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<sup>1</sup>The list of adverse events the committee was asked to consider by the National Vaccine Injury Compensation Program can be found at: <http://www.iom.edu/--/media/Files/Activity%20Files/Research/VaccineAdvEffectReview/Working-List-of-AEs-January-10.pdf>.

need not be physical; social and emotional deprivation are well-recognized causes of impaired development.

It is apparent that interruption of circuits at many different or distinct points may produce similar phenotypes. The mechanisms could be structural, involving improper development or injury to axons, nerve bodies, or dendrites, or they could be functional, implying abnormalities of the neurotransmitters or their receptors through which neurons communicate with one another, or implying lack of appropriate stimulation of the otherwise normal circuits. The processes underlying such disruption may be genetic or acquired.

It is important to bear in mind that genetic disorders need not be expressed at birth. Gene expression is regulated throughout life and many genes are expressed selectively only at certain times in specific tissues. Certain developmental sequences appear to be more or less rigidly encoded by the genome, whereas others are more plastic and amenable to environmental influences. These variables are all relevant when considering patterns of both normal and abnormal brain development.

Animal models have been most helpful in understanding disease processes affecting the brain, particularly when these are expressed as structural or motor changes, or as seizures. Advances in molecular genetics have allowed genes to be knocked out completely, temporarily knocked down, or to create milder phenotypes (hypomorphs) by point mutations. Various manipulations of gene function have led to a better understanding of complex gene-gene and genotype-phenotype interactions. Transgenic models, usually generated in mice, permit the study of human gene function, albeit in a different species. However, no animal embodies the repertoire of behaviors seen in the human, and in particular, no animal has language equivalent to that of the human. Although certain behaviors in animals have been compared to human phenotypes, the analogies are always imperfect and may be misleading.

### Autism

The terms *autism*, *autism spectrum disorder*, and *pervasive developmental disorder not otherwise specified* embrace a diverse group of children with a common neurobehavioral phenotype, and the first term (*autism*) will be used to embrace all of these entities in the following discussion. The child psychiatrist Leo Kanner first coined this term in 1943; since that time, varying diagnostic criteria and concepts of autism have been proposed and accepted, and they continue to evolve. Currently, the *Diagnostic and Statistical Manual of Psychological Disorders*, fourth edition, text revision (DSM-IV-TR) defines the criteria most widely used to diagnose autism and autism spectrum disorders. The criteria require that children

show impairments in three domains: language, social interactions, and restricted interests or repetitive behaviors. Key features include the onset of the phenotype before the third year of life. In about one-third of cases, children who previously appeared to have been developing normally show evidence of regression. However, most of these children likely had not had prior expert evaluation. In the remaining majority of cases, development was never assessed as normal.

Autism is a complex behavioral phenotype, whose neuropathological underpinnings are beginning to be understood. Several lines of evidence, including functional and structural imaging studies (Anagnostou and Taylor, 2011) and neuropathology have pointed to abnormal patterns of neural connectivity as characteristic of autism spectrum disorders (Schipul et al., 2011; Wass, 2011). The autism phenotype can be defined by a trained clinical evaluator using a variety of instruments (Dover and Le Couteur, 2007), particularly the autism diagnostic observational schedule (ADOS) (Lord et al., 1989) and autism diagnostic index–revised, which are widely accepted as the standard for research studies. These instruments have been employed in many, but by no means all, studies of this syndrome. The specialized training required to administer ADOS testing is not universally available. The use of variable diagnostic criteria is a major challenge to interpretation of the burgeoning autism literature. This is particularly pertinent when considering longitudinal trends, since differing criteria have been employed over time. Changes in diagnostic criteria, accompanied by increased social acceptance of this diagnosis, have paralleled marked increases in the number of children receiving this diagnostic label in recent years. It is also important to recognize that autism is frequently accompanied by comorbidities, such as abdominal symptoms, sleep disorders, and seizures, mood disorders, and aggressive disorders.

Genetic variation accounts for many cases of autism; specific genes or genetic loci may be identified in up to 25 percent of patients with autism spectrum disorders (Eapen, 2011; Miles, 2011). Siblings of children with autism have a much higher rate of the disorder, with the highest rate seen in identical twins (Ronald and Hoekstra, 2011). Family members of children with autism have been found to have variants of expressive language suggesting some innate neurologic variant. Several single-gene disorders are associated with autism, including tuberous sclerosis complex, FMR-1 (fragile X), dystrophinopathies, phenylketonuria, Rett disorder (MECP2 mutations), Down syndrome, and oxidative phosphorylation defects (Miles, 2011). The last mentioned, often referred to as mitochondrial diseases, are highly variable multisystem disorders whose complex phenotypes often encompass the autism spectrum (Frye and Rossignol, 2011). In other cases, linkage has been established with genes known to be crucial in modulating neural connectivity, such as neuroligins and neurexins (Sudhof, 2008). It

also appears that the developing brain, particularly early in pregnancy, is subject to environmental insults, including valproic acid and maternal rubella infection, which can result in autism and other developmental disabilities in the offspring (Landrigan, 2010). Such in utero exposures may act by altering the expression of genes regulating development of the nervous system (Dufour-Rainfray et al., 2011). These exposures are less likely to cause autism if experienced later in pregnancy, thus supporting the concept of windows of vulnerability. Maternal antibodies against fetal brain proteins may also be implicated in some cases, raising questions about the possible role of other immune factors such as cytokines (Goines and Van de Water, 2010). There is a growing literature describing inflammatory changes in the autopsied brain in at least a portion of patients with autistic disorders (Pardo et al., 2005), although many of these signs of inflammation are also increased in many other neurodegenerative disorders. The etiology of most cases of autism spectrum disorders is still not understood.

Because the timing of diagnosis or recognition of autism coincides with the administration of many vaccines, questions have been raised regarding potential etiologic relationship(s) between the two. There are several challenges in interpreting existing data. Establishing a temporal relationship between a potential inciting event (such as vaccine administration) and the onset of autism is difficult because dating the onset of the syndrome in most cases is imprecise (although there is a subset of children with acute regression from reportedly normal development). Rechallenge data are not available, since most children do not rapidly (if ever) recover a normal developmental pattern following the onset of their symptoms.

Establishing a mechanistic link is also challenging because it is not understood how known causes of autism lead to this phenotype. Several murine models of genetic disorders have autistic features, and although such models can never reproduce the complete human phenotype, they have added further evidence that disruption of the function of genes participating in brain development may lead to autism spectrum disorders (Ey et al., 2011). Infection of neonatal Lewis rats with *Bornavirus* (Hornig et al., 2001) has produced a behavioral phenotype with features equated to human autism. One fact of note is that postnatal infections with the vaccine-targeted infectious agents, including measles, mumps, and rubella, are not known to cause autism, although autistic features have been reported in children with congenital rubella syndrome (Chess, 1971); one study reported the use of mathematical modeling and epidemiological data to conclude that MMR immunization had been associated with prevention of substantial numbers of cases of congenital rubella syndrome and associated autism in the period 2001–2010 in the United States (Berger et al., 2011). There are reports of autistic syndromes acquired in children with acute encephalopathic illnesses. DeLong et al. (1981) described three such children, one of

whom had evidence of herpes simplex infection. The two children in whom the etiology of the episode was not discovered made complete recoveries. Additional reports described an autistic syndrome following herpes simplex encephalitis in a 14-year-old girl (Gillberg, 1986) and an 11-year-old boy (Ghaziuddin et al., 2002). The preceding cases were atypical in that the age of onset of autism was between 5 and 14 years; two children with perinatal herpes simplex encephalitis experienced the onset of autism in early childhood (Ghaziuddin et al., 1992). Another series of 14 children with autism included three whose onset of symptoms closely followed episodes of malaria. However, given that malaria is common in Tanzania, where the series originated, this should not necessarily be regarded as evidence of a mechanistic relationship (Mankoski et al., 2006). A single report described a 9-year-old boy who exhibited changes of late-onset autism associated with anti-N-methyl-D-aspartate receptor antibody positive encephalitis; he recovered with monoclonal antibody therapy (Creten et al., 2011).

The foregoing literature suggests that infectious or inflammatory etiologies may underlie some cases of autism, although most of the cases described do not meet current diagnostic criteria for autistic disorder, owing to their late onset. Other studies have implicated dysfunction of the innate immune system in the genesis of some cases of autism. Vargas et al. (2005) described a unique pattern of inflammatory changes in brain tissue obtained at autopsy and in cerebrospinal fluid from living patients (Zimmerman et al., 2005) with established diagnoses of autism, using suitable controls and DSM-IV criteria. Herbert (2005) has suggested that the large brains often reported in children with autism in early life could be explained by inflammatory expansion of the white matter that could also contribute to abnormal central nervous system connectivity. The evidence supporting the concept of autism and a neuroimmune disorder has been reviewed recently (Theoharides et al., 2009).

At a minimum, prior to ascribing autism to vaccination, it would be important to rule out known associations with this phenotype. These include both macroscopic and microscopic structural abnormalities of the brain (Casanova, 2007), particularly minocolumnar architecture (Casanova and Trippe, 2009) as well as specific chromosomal and single-gene defects, including a variety of metabolic disorders and inflammatory or infectious antecedents.

### CONTRIBUTION OF ANIMAL MODELS

Laboratory animals have been studied for decades as a means to understand both normal physiology and pathogenesis of diseases. Throughout this time, it has become apparent that animal models can be very useful, or alternatively noninformative, depending on the question being addressed.

### Infections

When an infectious organism invades and replicates within a non-human host, there are likely to be many similarities between the human and nonhuman host. In particular, antibody responses appear to be quite similar, often targeting the same antigenic epitopes of the infectious agent. Likewise, tissue and cellular antigenicity is often similar, so the pathogenic or protective potential of human antibodies can be ascertained in animal models. Cellular mechanisms of microbial control and eradication are also often similar, as are mechanisms of microbial evasion of host defenses.

However, multiple differences in response to microbial infection between humans and laboratory animals exist. One major issue in animal models of infection is that not all infectious organisms will infect all hosts; this is particularly an issue for viruses and other intracellular pathogens whenever cellular entry is generally achieved through a particular receptor that may be present in one species and not another. A second issue affecting the response to microbes is the expression of histocompatibility molecules in the infected animal. Histocompatibility molecules vary among species and among individuals of that species; they are expressed on almost all tissues and immune cells. If the histocompatibility molecules can bind microbial antigens, an enhanced immune response to that microbe can develop. Laboratory studies usually focus on a particular strain of mouse or rat and therefore do not mimic the genetic diversity of the human population, either with respect to immune molecules such as histocompatibility molecules or with respect to other aspects of cellular metabolism.

Any observations made in an animal model of infection need to be confirmed in the human host because of the differences between man and animal models discussed above. Nonetheless, animal studies provide the opportunity to sample all body tissue and to ascertain the extent of microbial invasion and the cellular targets with likely correspondence to the human host. Studies of the immune response to microbial agents include vaccine studies that are also subject to the concerns discussed above. One frequent difference between vaccine studies in animals and humans is that vaccine studies in laboratory animals may include adjuvants that are not used in humans.

### Immune Response in a Host with a Preexisting Disease

It is well established that individuals with abnormalities in immune function, either genetic or acquired, respond differently to microbial infection and to vaccines compared to the responses of healthy individuals. Several rodent models exist with genetically derived immunodeficiencies or autoimmunity. Some of these models mimic the human condition either

with respect to genetic lesions or with respect to mechanisms and/or phenotypes of disease. It is possible, therefore, to ask whether the genetic lesion or the ensuing disease process renders the host more (or less) susceptible to a particular antigenic challenge. Such studies can provide important information, which must be confirmed in humans. Again, an advantage of an animal model is that one can explore all tissues in the body, including those that are inaccessible to study in living humans.

### Relevance to Adverse Events Following Vaccination

There are multiple uses of animal models in vaccine studies. It is possible to study each tissue of the body for microbial invasion and microbe-induced or immune-mediated damage. Fukuda et al. (1994) determined in a hamster model of measles that the measles virus can replicate in the labyrinth, providing a potential explanation of the deafness that occurs with measles infection and providing a biologic mechanism for deafness following vaccination with attenuated measles vaccine. The techniques used to show replication of measles virus in the labyrinth represent an advantage of animal models, as discussed above; techniques to show replication of measles virus in the labyrinth will not be performed on living human patients.

With animal models, it is possible to study whether particular genetic deficiencies or preexisting conditions attenuate, augment, or alter the immune response to infectious agents or microbial antigen, or whether the microbial or antigenic challenge exacerbates the preexisting condition or reveals otherwise unappreciated consequences of the genetic deficiency.

It is possible to look for molecular mimicry between vaccine antigen and self-antigen, although mimicry at the antibody level is more likely to translate to the human situation than molecular mimicry at the T cell level due to the diversity of histocompatibility molecules. Should molecular mimicry be found in an animal model, it still needs confirmation in humans.

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## 4

## Measles, Mumps, and Rubella Vaccine

## INTRODUCTION

## Measles

Measles is caused by a single-stranded, negative-sense nonsegmented RNA virus of the genus *Morbillivirus* and the family Paramyxoviridae that encodes at least eight structural proteins (Gershon, 2010a). The virus is easily inactivated by extremes of pH, heat, and sunlight (Strebel et al., 2008). As the only natural hosts for the wild virus, humans transmit measles through aerosolized respiratory fluids or droplet nuclei (Babbott and Gordon, 1954; de Jong, 1965).

The incubation period of the measles virus is 10 to 12 days (CDC, 1998). The prodromal stage, during which the infected individual is most contagious, lasts 2 to 4 days and manifests as conjunctivitis, fever, malaise, and tracheobronchitis (Strebel et al., 2008). This period is followed by 4 days of fever as high as 105°F (Strebel et al., 2008). Rash is preceded by Koplik's spots that appear on the lining of the cheeks and lips and may persist for 1 to 2 days after the onset of rash (Strebel et al., 2008). The rash, which occurs 14 days after exposure, starts on the head and spreads to the trunk and extremities over 3 to 4 days, before fading (Strebel et al., 2008). Individuals are infectious for as long as 4 days before and after the onset of rash (Strebel et al., 2008).

Serious complications of measles include pneumonia, postinfectious encephalitis, subacute sclerosing panencephalitis (SSPE), and death (Johnson et al., 1984; Miller, 1987; Strebel et al., 2008). These complications are

associated with a fever lasting more than 2 days after the onset of rash (Strebel et al., 2008). Measles-related mortality is highest for infants, young children, and adults with decreased risk in older children and adolescents (CDC, 1998). Other complications include acute otitis media, appendicitis, hepatitis, myocarditis, and thrombocytopenia (Kempe and Fulginiti, 1965).

Although recognized as a disease for approximately 2,000 years, the first major advance in the study of measles was in 1846 when Parnum observed measles cases in the Faroe Islands. Parnum confirmed the infectious nature of measles, defined the 2-week incubation period, and noted that individuals infected with measles did not become ill after subsequent exposure to the virus (Strebel et al., 2008). In 1954, Enders and Peebles propagated measles virus in human renal tissues (Enders and Peebles, 1954). Nine years later, in 1963, the first live, attenuated vaccine was licensed for use in the United States (Enders, 1962). The Edmonston B virus strain that was passaged at 35–36°C through primary renal cells, primary human amnion cells, and embryonic chicken cells a total of 59 times was used in many vaccines (Strebel et al., 2008). In 1965 and 1968, the Schwarz and Moraten (more attenuated strain derived from Ender's attenuated Edmonston measles virus) strains were also licensed in the United States. These strains were developed from the Edmonston B strain and were passaged at 32°C an additional 85 and 40 times, respectively (Strebel et al., 2008). The Schwarz and Moraten strains were shown to cause less severe and less frequent side effects (Andelman et al., 1963; Hilleman et al., 1968; Schwarz, 1964; Schwarz and Anderson, 1965; Schwarz et al., 1967; Strebel et al., 2008). Today, the only strain licensed in the United States is the more attenuated, live Ender's Edmonston strain (Moraten strain) (CDC, 1998).

Prior to the licensure of a measles vaccine, an average of 400,000 measles cases were reported each year, although the actual incidence was estimated to be 3.5 million based on the size of the annual birth cohort, and the fact that nearly 100 percent of the population was infected during childhood (CDC, 1998). With the licensure of the vaccine, the measles burden has been reduced by more than 99 percent, and in 1998, the Centers for Disease Control and Prevention (CDC) indicated that 95 and 98 percent of children vaccinated at age 12 and 15 months, respectively, developed measles antibodies (CDC, 1998).

### Mumps

Mumps is an acute viral infection caused by an enveloped, negative-sense RNA virus of the genus *Rubulavirus* (Litman and Baum, 2010). The virus is composed of 15,384 nucleotides that encode seven genes, one of which is the SH protein that has been used to identify at least 12 mumps virus strains (Jin et al., 2000; Plotkin and Rubin, 2008). Mumps is transmit-

ted by direct contact with infectious respiratory secretions, droplet nuclei, or fomites that are then transferred to the nose and mouth (Litman and Baum, 2010).

The average incubation period of the mumps virus is 16 to 18 days but can range from 2 to 4 weeks (Litman and Baum, 2010). Fifteen to 20 percent of mumps infections are asymptomatic; 50 percent of cases have nonspecific symptoms such as anorexia, headache, fever, and malaise, or present primarily as respiratory infections; and only 30 to 40 percent demonstrate the classic salivary gland tenderness and enlargement (parotitis) (CDC, 1998). Asymptomatic infection is more common in adults, while parotitis occurs most often in children age 2 to 9 years (CDC, 1998). Children younger than 5 years old more commonly manifest symptoms of lower respiratory disease (Plotkin and Rubin, 2008). Complications of mumps infection are possible without the presence of parotitis. In 1958, Philip et al. (1959) observed testicular and mammary inflammation in 5 percent of postpubertal men and 31 percent of women over 15 years of age. Pancreatitis occurs in 4 percent of cases, and although it has not been proven, evidence suggests an association between mumps infection and diabetes mellitus (Sultz et al., 1975). Neurological complications are more common in adults and occur three times more often in men than in women (Plotkin and Rubin, 2008). These complications include mumps meningitis, cerebellar ataxia, transverse myelitis and poliomyelitis-like disease, cranial nerve palsies, hydroencephalitis, and encephalitis, which occurs in less than 0.3 percent of cases, but is responsible for more than 50 percent of mumps-related fatalities (Bray, 1972; Cohen et al., 1992; Kilham et al., 1949; Lahat et al., 1993; Oldfelt, 1949; Oran et al., 1995; Plotkin and Rubin, 2008; Timmons and Johnson, 1970). Hearing loss due to infection of the endolymph is also a potential complication of mumps infection (Tanaka et al., 1988). Short-term, high-frequency deafness occurs in approximately 4 percent of mumps cases, and permanent hearing loss occurs in only 1 per 20,000 cases and is usually unilateral (Litman and Baum, 2010; Plotkin and Rubin, 2008). Mumps arthropathy, more common in men than women, occurs most often in young adults (Plotkin and Rubin, 2008). It may manifest as arthralgias, polyarticular migratory arthritis, and monoarticular arthritis (Gordon and Lauter, 1984; Harel et al., 1990). Myocarditis is rare and generally self-limited, although some fatal cases have been reported (Chaudary and Jaski, 1989; Roberts and Fox, 1965).

Johnson and Goodpasture (1934) identified the causative agent of mumps in 1934, and in 1945 Habel and Enders successfully cultivated the virus in chick embryos (Enders, 1946; Habel, 1945). The first inactivated mumps vaccine was developed in 1946 and tested in humans in 1951 (Habel, 1946, 1951). The first live, attenuated vaccine was developed in the 1960s in the United States and former Soviet Union (Plotkin and Rubin,

2008; Weibel et al., 1967). In the United States, mumps vaccines are manufactured using the Jeryl Lynn strain mumps virus that was isolated from the throat of Jeryl Lynn Hilleman in the 1960s (Plotkin and Rubin, 2008). The vaccine is currently licensed in the mono-, tri-, and tetravalent forms, although the monovalent, Mumpsvox (Merck and Co., Inc.), is no longer available in the United States.

Prior to the licensing of a live-attenuated mumps vaccine, mumps outbreaks occurred every 2 to 5 years, with peak incidence from January through May (Anderson and Seward, 2008; Litman and Baum, 2010). Since the introduction of the vaccine, the incidence of mumps infection has been reduced greatly, evidenced by a 99 percent decrease in mumps infection from 1968 to 1995 (CDC, 1998).

### Rubella

Rubella, also known as German measles, is caused by an enveloped, positive-sense RNA togavirus of the genus *Rubivirus* (Gershon, 2010b). The rubella virus genome consists of approximately 9,800 nucleotides, and the virus can be divided into two clades and at least seven genotypes (Zheng et al., 2003). Maturing by budding from the cell membrane (Murphy et al., 1968), rubella virus is relatively unstable and vulnerable to chemical inactivation, extremes of pH and heat, lipid solvents, and ultraviolet light (Gershon, 2010b).

Rubella is spread through contact with infectious respiratory secretions, and replication occurs in the nasopharynx of the infected individual (Plotkin and Reef, 2008). Rubella infections are subclinical in 25 to 50 percent of cases (CDC, 1998). In those cases in which clinical illness develops, the beginning of the 12- to 23-day incubation period is largely asymptomatic (CDC, 1998; Plotkin and Reef, 2008). By the end of the second week virus can be isolated from the blood and symptoms of conjunctivitis, low-grade fever, lymphadenopathy, and malaise are present (Plotkin and Reef, 2008). A rash follows spreading downwards from the face before fading within 1 to 3 days (Plotkin and Reef, 2008). Rubella illness in a child or adult is usually benign although arthritis and arthralgia has been observed in association with viral replication in the synovial cavity of the joints (Plotkin and Reef, 2008). Other complications of rubella include encephalitis, Guillain-Barré syndrome (GBS), progressive rubella panencephalitis, and thrombocytopenia (Gershon, 2010b; Plotkin and Reef, 2008).

Rubella virus infection during pregnancy can lead to congenital rubella infection in neonates. The disease outcome is directly correlated to the age of the fetus at the time of infection with younger fetuses experiencing more severe disease (Gershon, 2010b). Infections within the first 2 months of pregnancy can cause multiple congenital defects or spontaneous abortion in

65 to 85 percent of women (Gershon, 2010b). Infections in the third month and fourth month are associated with a single defect in 30 to 35 percent and 10 percent of cases, respectively (Gershon, 2010b). Commonly associated defects include transient thrombocytopenia purpura and meningoencephalitis, as well as permanent and developmental manifestations such as hearing loss, pulmonic stenosis, mental retardation, and behavioral disorders (Gershon, 2010b). Other less common manifestations include myocardial abnormalities, hepatitis, and seizure disorders (Gershon, 2010b). Studies have also shown that diabetes mellitus occurs 50 times more frequently in children with congenital rubella, and insulin-dependent diabetes has been reported in 40 percent of adults who were congenitally infected with rubella during the 1942 rubella epidemic (Gershon, 2010b).

Clinically described as early as the 1700s, rubella was considered a disease of children and young adults and was given little attention until 1941 when Gregg discovered an association between maternal rubella infection and congenital cataracts (Gregg, 1941). Parkman and colleagues and Weller and Neva isolated the causative agent of rubella in 1962 (Parkman et al., 1962; Weller and Neva, 1962). By 1970, three rubella virus strains were licensed for use in vaccines in the United States: Cendehill (grown in rabbit kidney), HPV-77 (grown in dog kidney), and HPV-77 (grown in duck embryo) (HPV-77DE) (Hilleman et al., 1969; Meyer et al., 1969; Prinzie et al., 1969). HPV-77DE was used as the rubella component of the first MMR vaccine, but was later replaced with RA 27/3 after studies showed RA 27/3 induced higher antibody levels, more persistent seropositivity, more resistance to reinfection, and greater herd immunity (Fogel et al., 1978; Gershon et al., 1980; Klock and Rachelefsky, 1973). Today, RA 27/3 is the only rubella virus strain available for use in vaccines in the United States.

### Measles-, Mumps-, and Rubella-Containing Vaccines

In the United States, measles, mumps, and rubella (MMR) vaccine is a live, attenuated virus vaccine and is manufactured by Merck & Co., Inc. Although Merck is licensed to produce monovalent measles, mumps, and rubella vaccines—Attenuvax, Meruvax, and Mumpsavax, respectively—currently, these vaccines are no longer available in the United States. The combination vaccine, M-M-R II (Merck), contains greater than 1,000 TCID<sub>50</sub> of a more attenuated line of measles virus derived from Ender's attenuated Edmonston strain, greater than 12,500 TCID<sub>50</sub> of Jeryl Lynn mumps virus, and greater than 1,000 TCID<sub>50</sub> of Wistar Institute RA 27/3 rubella virus, in addition to sorbitol, sodium phosphate, sucrose, sodium chloride, hydrolyzed gelatin, human albumin, fetal bovine serum, and neomycin (Merck & Co., Inc., 2007). The vaccine does not contain a preservative. In 2005 the Food and Drug Administration (FDA) licensed the tetravalent measles, mumps,



rubella, and varicella (MMRV) vaccine, ProQuad (Merck). ProQuad contains greater than  $3.0 \log_{10}$  TCID<sub>50</sub> of a more attenuated line of measles virus derived from Ender's attenuated Edmonston strain, greater than  $4.3 \log_{10}$  TCID<sub>50</sub> of Jeryl Lynn mumps virus, greater than  $3.0 \log_{10}$  TCID<sub>50</sub> of Wistar Institute RA 27/3 rubella virus, and greater than  $3.99 \log_{10}$  plaque-forming units (PFUs) of Oka/Merck varicella zoster virus (VZV)—the equivalent to that found in varicella virus vaccines (see Chapter 5) (Merck & Co., Inc., 2009). ProQuad also does not contain a preservative.

The Advisory Committee on Immunization Practices (ACIP) recommends that all children receive two subcutaneous doses of the MMR or MMRV vaccine without preference. The first dose is scheduled between 12 and 15 months of age and is followed by a second dose between 4 and 6 years of age prior to kindergarten or first grade. The ACIP also recommends that adults born after 1956 and all women of childbearing age who are not pregnant receive at least one dose of the MMR vaccine in the absence of prior immunity (CDC, 1998). The vaccine is contraindicated in those with hypersensitivity to any component of the vaccine including gelatin, pregnant women, those with allergies to neomycin, febrile respiratory illness or other active febrile infection, and the immunosuppressed. According to the National Immunization Survey, from 2005 to 2009 more than 90 percent of children aged 19 to 35 months had received at least one dose of the MMR vaccine (CDC, 2010).

The committee focused on virus strains used in licensed U.S. vaccines. On occasion, the committee reviewed other virus strains that were sufficiently similar to U.S. strains. This will be noted in the text. The committee was not charged with reviewing the MMRV vaccine.

## MEASLES INCLUSION BODY ENCEPHALITIS

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of measles inclusion body encephalitis after the administration of MMR vaccine.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between MMR vaccine and measles inclusion body encephalitis.*

### Mechanistic Evidence

The committee identified five publications reporting measles inclusion body encephalitis after the administration of measles or MMR vaccine. Freeman et al. (2004) and Kim et al. (1992) demonstrated wild-type measles virus in their patients. These cases did not contribute to the weight of mechanistic evidence.

Described below are three publications reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Bitnun et al. (1999) describe a 21-month-old boy presenting with status epilepticus, fever, irritability, and vomiting 9 months after receiving an MMR containing the Moraten strain of measles. Serology was positive for antimeasles IgM and IgG; the cerebrospinal fluid (CSF) was not positive for these antibodies. The patient died when ventilatory support was withdrawn 51 days after admission. Evaluation of the patient's immune system revealed depressed proliferative responses to mitogens and antigens and depressed CD8 cell numbers. Measles hemagglutinin and matrix proteins were observed by immunohistochemical staining performed on biopsied brain tissue. Furthermore, intracytoplasmic and intranuclear inclusions with the appearance of paramyxovirus nucleocapsids were revealed by electron microscopy. Reverse-transcription polymerase chain reaction (RT-PCR) amplified measles RNA from the patient's brain tissue. PCR analysis of the N gene and sequence analysis of the F gene from viral material isolated in the biopsied brain tissue was identical to the Moraten measles vaccine strain.

Baram et al. (1994) describe a 22-month-old girl who presented with focal and generalized myoclonic seizures, clumsiness, falling, head drop, and right arm jerk 4 months after receiving a measles, mumps, and rubella vaccine. The patient's history included a febrile illness with rash at the age of 5 weeks. The patient died of aspiration pneumonia at 25.5 months of age, 3.5 months after the onset of symptoms. Upon autopsy, inclusion bodies were identified and found to contain helical nucleocapsid tubules. Measles virus was amplified, by PCR, from the patient's brain.

Poon et al. (1998) described a 2-year-old boy, diagnosed with human immunodeficiency virus (HIV), presenting with generalized convulsive seizures lasting 40 minutes 9 months after receiving a measles, mumps, and rubella vaccine. Despite treatment the patient continued to develop partial and generalized seizures. The patient presented with a fever, lymphadenopathy, hepatosplenomegaly, and delayed language and motor skills upon physical and developmental examination. Tests were negative for herpes simplex virus, cytomegalovirus, respiratory syncytial virus, *Toxoplasma*, and cryptococcal organisms. The patient died 4 months after admission for pneumonia. Electron microscopic observation of a fine-needle aspiration

biopsy of the right temporal region showed intranuclear inclusions corresponding to the configuration and size of measles virus.

### *Weight of Mechanistic Evidence*

Measles inclusion body encephalitis is a complication of wild-type measles infection that develops months to years after the initial acute measles infection (Reuter and Schneider-Schaulies, 2010). Furthermore, measles inclusion body encephalitis is confined to immunodeficient patients and is inevitably fatal (Reuter and Schneider-Schaulies, 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

In addition, the three publications described above presented clinical evidence sufficient for the committee to conclude the vaccine was a contributing cause of measles inclusion body encephalitis after administration of a measles-containing vaccine. The publications reported either intranuclear inclusions corresponding to measles virus or the isolation of measles virus from the brain; vaccine strain measles virus was identified by PCR in one publication.

The latencies between vaccination and the development of measles inclusion body encephalitis in the publications described above were 4 and 9 months, suggesting persistent viral infection as the mechanism. Direct viral infection may also contribute to the symptoms of measles inclusion body encephalitis; however, the publications did not provide evidence linking this mechanism to MMR vaccine.

*The committee assesses the mechanistic evidence regarding an association between the measles vaccine and measles inclusion body encephalitis in individuals with demonstrated immunodeficiencies as strong based on one case presenting definitive clinical evidence.*

*The committee assesses the mechanistic evidence regarding an association between the mumps or rubella vaccine and measles inclusion body encephalitis as lacking.*

## Causality Conclusion

**Conclusion 4.1:** The evidence convincingly supports a causal relationship between MMR<sup>1</sup> vaccine and measles inclusion body encephalitis in individuals with demonstrated immunodeficiencies.

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<sup>1</sup>The committee attributes causation to the measles component of the vaccine.

## ENCEPHALITIS AND ENCEPHALOPATHY

### Epidemiologic Evidence

The committee reviewed 13 studies to evaluate the risk of encephalitis or encephalopathy after the administration of measles or MMR vaccine. Nine studies (Bino et al., 2003; D'Souza et al., 2000; Fescharek et al., 1990; Katz, 1969; Landrigan and Witte, 1973; Patja et al., 2000; Stetler et al., 1985; Vahdani et al., 2005; Weibel et al., 1998) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations. One controlled study (Griffin et al., 1991) had very serious methodological limitations that precluded its inclusion in this assessment. The study by Griffin et al. (1991) was unable to find any cases of encephalopathy following MMR immunization, so no conclusions could be drawn from this analysis.

The three remaining controlled studies (Makela et al., 2002; Ray et al., 2006; Ward et al., 2007) contributed to the weight of epidemiologic evidence and are described below.

Makela et al. (2002) conducted a retrospective cohort study in 535,544 children (1 to 7 years of age) who received an MMR vaccination in Finland from November 1982 to June 1986. Vaccination data were collected from a National Public Health Institute cohort that included the child's social security number, age at vaccination, and the year and month of vaccination. The nationwide hospital discharge register was linked to the vaccination data using the social security number of each child. The investigators reviewed the hospital discharge register for cases of encephalitis or encephalopathies (referred to as encephalitis) following vaccination; records with a defined cause unrelated to vaccination were excluded. Cases of encephalitis that occurred within 3 months of vaccination were validated with information from the patients' medical records and the exact dates of vaccination were verified. The number of events observed within the 3-month postvaccination risk period was compared to the events observed during the control period, which was defined as subsequent 3-month postvaccination intervals until 24 months was reached. A total of 199 children were hospitalized for encephalitis during the study period; 9 occurred within 3 months of MMR vaccination, 110 occurred after the 3 months following vaccination, and 80 occurred before MMR vaccination. The analysis did not find an increase of encephalitis hospitalizations within 3 months of vaccination ( $p = .28$ ). The authors concluded that MMR vaccination does not increase the risk of encephalitis in children.

Ray et al. (2006) conducted a case-control study in children (0 to 6 years of age) enrolled in four health maintenance organizations (HMOs) participating in the Vaccine Safety Datalink (VSD) from January 1981

through December 1995. The cases were defined as patients hospitalized with a primary or secondary diagnosis of encephalopathy, encephalitis, or Reye syndrome, and who were enrolled in the HMO at least 60 days before hospitalization (or since birth for patients under 60 days of age). The medical records of all cases were reviewed by a neurologist, who was blind to vaccination status, to confirm patients met the case definition. A total of 452 encephalopathy cases were identified and categorized according to whether the encephalopathy etiology was known, unknown, or suspected but unconfirmed. One to three controls were matched to each case on age (within 7 days), sex, HMO location, and length of enrollment in the HMO. Vaccination histories were obtained from the medical records and stratified into time windows; the cases and controls had similar vaccination rates. Odds ratios were calculated for MMR vaccination within the specified time windows and included all cases, cases with unknown or suspected but unconfirmed diagnoses, or cases with only suspected but unconfirmed diagnoses. None of the comparisons found a statistically significant increase in risk, meaning all 95% confidence intervals (CIs) for odds ratios included 1. In fact, most of the point estimates of the odds ratios in these comparisons were less than 1. The highest odds ratio point estimate was 1.23 (95% CI, 0.51–2.98) for cases of unknown or suspected encephalopathy within 90 days of MMR vaccination. The authors concluded that MMR vaccination is not associated with an increased risk of encephalopathy owing to the absence of a consistent time association between vaccination and encephalopathy onset.

Ward et al. (2007) conducted a self-controlled case series study in children (2 to 35 months of age) residing in the United Kingdom or Ireland between October 1998 and September 2001. MMR vaccines with the Jeryl Lynn or RIT 4385 mumps component, and Moraten or Schwarz measles component were in use during the study period. The British Pediatric Surveillance Unit distributed monthly surveillance surveys to pediatricians in order to identify children with encephalitis, or suspected severe illness with fever and seizures. The questionnaires were reviewed by a physician to confirm patients met the case definition of severe neurologic disease (encephalitis or febrile seizures). Vaccination histories of confirmed cases were obtained from the child's general practitioner by the Immunization Department, Health Protection Agency, Centre for Infections, London. The risk periods considered were 6–11 days and 15–35 days after MMR vaccination; each child was categorized as having been vaccinated or unvaccinated, and with disease or without disease based on dates of vaccine administration and disease episodes during these time periods. A total of 107 children (12 to 35 months of age) with confirmed severe neurologic disease were included in the analysis for MMR vaccine. The relative risk of severe neurologic disease within 6 to 11 days after MMR vaccination was

5.68 (95% CI, 2.31–13.97) and within 15 to 35 days after MMR vaccination was 1.34 (95% CI, 0.52–3.47). While a significant increased risk of disease was observed during the 6 to 11 day postvaccination period, three of the six cases received MMR and meningococcal C conjugate vaccine on the same day, and four of the six cases reported complex febrile seizures combined with encephalopathy. The authors concluded that administration of MMR vaccine is associated with an increased risk of severe neurologic disease within 6 to 11 days of vaccination, but attributed the risk to the inclusion of cases with complex febrile seizures. Furthermore, the study included two vaccine formulations, one of which is not available in the United States, and the association of these vaccines with encephalitis was not analyzed separately.

### *Weight of Epidemiologic Evidence*

Two of the three studies detailed above showed no significant increased risk of encephalopathy after MMR vaccination. Makela et al. (2002) found only 9 of the 199 cases were diagnosed within their defined risk period of 0–3 months, a rate no higher than during the control periods of this cohort study. All control periods were after vaccination, which weakens the results of this study. Of the three studies, the study by Ray et al. (2006) investigated the largest number of cases with 452 that were then matched to controls, and was the only study judged to have negligible limitations. The authors considered different risk intervals and different categories of diagnosis but did not find evidence of an increased risk. The last paper by Ward et al. (2007) showed a significant increase of neurologic disease—but the illnesses were predominantly complex febrile seizures with recovery except in one patient, not other forms of encephalopathy (the association of MMR vaccination and seizures is discussed in a subsequent section). The study also combined assessments for two vaccine formulations, one of which is not available in the United States. Thus, two of the three studies—of which only one had negligible limitations—found no association between MMR vaccine and encephalitis or encephalopathy. A third study did find an increase in risk, but the association was with febrile seizures, which are arbitrarily discussed in another section of the report. See Table 4-1 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has limited confidence in the epidemiologic evidence, based on three studies that lacked validity and precision to assess an association between MMR vaccine and encephalitis or encephalopathy.*

**TABLE 4-1** Studies Included in the Weight of Epidemiologic Evidence for MMR Vaccine and Encephalopathy or Encephalitis

| Citation             | Operationally Defined Outcome  | Study Setting   | Defined Study Population | Study Design  | Sample Size  | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)  | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|----------------------|--|---|--------------------------|---|--|---|---|--|
| Makela et al. (2002) | Encephalitis or encephalopathy identified in the nationwide hospital discharge register                | Finland from 11/1982 to 6/1986                                      | Ages 1–7 years           | Retrospective cohort<br><br>Risk period: 0–3 months after MMR vaccination<br><br>Control period: Subsequent 3-month intervals after the risk period until 24 months was reached | 535,544 children<br><br>199 children hospitalized for encephalitis<br><br>Nine encephalitis events occurred within 3 months of MMR vaccination | No increased risk of encephalitis within 3 months of MMR vaccination ( $p = .28$ )                                  | None described                                      | Serious  |
| Ray et al. (2006)    | Hospitalization for a primary or secondary diagnosis of encephalopathy, encephalitis, or Reye syndrome | Four HMOs participating in the VSD from 1/1/1981 through 12/31/1995 | Ages 0–6 years           | Case-control<br><br>Controls matched by age (within 7 days), sex, HMO location, and length of enrollment in the HMO   | 452 cases with encephalopathy<br><br>One to three controls were matched to each case   | OR for unknown or suspected encephalopathy within 90 days of MMR vaccination: 1.23 (95% CI, 0.51–2.98; $p = .647$ ) | None described                                      | Negligible                                       |

OR for encephalopathy among all cases and controls within 90 days of MMR vaccination: 0.98 (95% CI, 0.47–2.01;  $p = .951$ )

|                    |   |  |                  |   |   |  |   |            |
|--------------------|---|--|------------------|---|---|--|---|------------|
| Ward et al. (2007) | Diagnoses of severe neurologic disease (encephalitis or febrile seizures) obtained from monthly surveillance surveys to pediatricians | United Kingdom or Ireland between 10/1998 and 9/2001 | Ages 2–35 months | Self-controlled case series<br>Risk period: 6–11 days and 15–35 days after MMR vaccination<br>Control period: all time observed outside the risk period | 107 children (ages 12–35 months) with severe neurologic disease<br>Six events occurred within 6–11 days of vaccination<br>Five events occurred within 15–35 days of vaccination | RR of severe neurologic disease within 6–11 days of MMR vaccination: 5.68 (95% CI, 2.31–13.97)<br>RR of severe neurologic disease within 15–35 days of MMR vaccination: 1.34 (95% CI, 0.52–3.47) | Four of the six children who had severe neurologic disease within 6–11 days of MMR vaccination reported complex febrile seizures combined with encephalopathy | Negligible |
|--------------------|---|--|------------------|---|---|--|---|------------|

<sup>a</sup> The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup> The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup> Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.



### Mechanistic Evidence Regarding Encephalitis

The committee identified 18 publications reporting encephalitis or meningoencephalitis after the administration of vaccines containing measles, mumps, and rubella alone or in combination. Mustafa et al. (1993) described one case of encephalitis developing after administration of a MMR vaccine; however, wild-type measles virus was demonstrated in the patient. Fourteen publications did not provide evidence beyond temporality (Ehregut and Zastrow, 1989; Fescharek et al., 1990; Forster and Urbanek, 1982; Jagdis et al., 1975; Jorch et al., 1984; Kumar et al., 1982; Landrigan and Witte, 1973; Pollock and Morris, 1983; Ross and Yeager, 1977; Schneck, 1968; Schuil et al., 1998; Shuper, 2011; Wiersbitzky et al., 1992b, 1993a). In addition, five publications reported concomitant infections that could contribute to the development of symptoms (Ehregut and Zastrow, 1989; Forster and Urbanek, 1982; Jorch et al., 1984; Wiersbitzky et al., 1992b, 1993a). These publications did not contribute to the weight of mechanistic evidence.

Described below are three publications reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Bakshi et al. (1996) described a 16-month-old boy presenting with a focal seizure on the right side and left hemipareses and a left gaze preference 5 months after receiving a measles, mumps, and rubella vaccine and 3 days after undergoing bone marrow transplantation. The patient was administered the vaccine prior to being diagnosed with sickle cell trait and a severe combined immunodeficiency. Serum and CSF were negative for bacteria and fungi. Mumps virus was demonstrated in the urine, serum, and CSF. The patient was diagnosed with meningoencephalitis and died 2 months after the onset of symptoms. Pathological examination of the leptomeninges showed chronic and focally prominent meningitis.

Lacroix et al. (1995) describe a 5-year-old acquired immune deficiency syndrome (AIDS) patient presenting with fever, generalized seizures, and the inability to stand or walk approximately 2 years after vaccination against measles. The patient died months after presenting with neurological symptoms. Retrospective serum analysis showed measles antibody prior to vaccination. Viral cultures of brain samples were negative for measles virus. Frozen sections of basal ganglia, frontal cortex, and white matter were stained with antibodies against measles virus indicating the presence of measles virus in the brain.

Valmari et al. (1987) described a 7-year-old girl presenting with vomiting, headache, twitching of upper extremities, followed by coma lasting for several hours 54 days after receiving a measles, mumps, and rubella vaccine containing the Moraten measles strain and 5.5 years after receiving a

measles vaccine containing the Schwarz measles strain. On the day the measles, mumps, and rubella vaccine was administered the patient complained of back pains leading to a diagnosis of acute lymphoblastic leukemia 23 days after vaccination. The patient presented with the symptoms described above 1 day after the fourth methotrexate treatment. Treatment with acyclovir was started and the patient seemed to improve. Measles virus was demonstrated in the CSF. The patient experienced a recrudescence of the neurological symptoms 58 days postvaccination and fever, photophobia, conjunctival inflammation, and a maculopapular rash 63 days postvaccination. Measles virus was demonstrated in the CSF again.

### *Weight of Mechanistic Evidence*

Encephalitis is considered a complication of infection with wild-type measles, mumps, and rubella viruses (Gershon, 2010a,b; Litman and Baum, 2010). Encephalitis develops in 1:1,000 to 1:2,000 patients infected with measles virus (Gershon, 2010a). In addition many patients upon recovering suffer from neurologic sequelae (Gershon, 2010a). Encephalitis develops in 1:400 to 1:6,000 patients infected with mumps virus (Litman and Baum, 2010). In patients developing early-onset encephalitis upon infection with mumps virus, the damage to the neurons is by direct viral invasion (Litman and Baum, 2010). In patients infected with rubella virus, encephalitis develops in 1:5,000 patients (Gershon, 2010b). The committee considers the effects of natural infection one type of mechanistic evidence.

The three publications described above, when considered together, did not present evidence sufficient for the committee to conclude the vaccine may be a contributing cause of encephalitis after administration of a measles or MMR vaccine. The patients described in the cases above had demonstrated immunodeficiencies. The publications presented evidence of the detection of viral antigens on frozen sections or the isolation of mumps or measles virus from the patients. However, the authors did not identify the virus as vaccine strain.

The latency between vaccination and the development of encephalitis in the publications described above ranged from 5 months to 2 years, suggesting persistent viral infection as the mechanism. Direct viral infection and viral reactivation may contribute to encephalitis; however, the publications did not provide evidence linking these mechanisms to MMR vaccine.

*The committee assesses the mechanistic evidence regarding an association between MMR vaccine and encephalitis as weak based on knowledge about the natural infection and three cases.*

### Causality Conclusion

**Conclusion 4.2:** The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and encephalitis.

#### Mechanistic Evidence Regarding Encephalopathy

The committee identified 11 publications reporting encephalopathy after the administration of vaccines containing measles, mumps, and rubella alone or in combination. Nine publications did not provide evidence of causality beyond a temporal relationship between vaccination and the development of symptoms (Aydin et al., 2006; Ehrengut and Zastrow, 1989; Landrigan and Witte, 1973; Martinon-Torres, 1999; Shuper, 2011; Verity et al., 2010; Weibel et al., 1998; Wiersbitzky et al., 1991, 1993a). In addition, three publications reported concomitant infections that could contribute to the development of symptoms (Verity et al., 2010; Wiersbitzky et al., 1991, 1993a). Furthermore, the viral strains in the MMR vaccine administered to the patient described by Verity et al. (2010) are unknown. These publications did not contribute to the weight of mechanistic evidence.

Described below is one publication that merits greater discussion, although it does not contribute to the weight of mechanistic evidence.

Poling et al. (2006) reported the case of a 19-month-old girl who developed symptoms of encephalopathy and fever 48 hours after receiving a number of immunizations, one of which was a measles, mumps, and rubella vaccine. The only relationship reported for these symptoms is temporal, which the committee did not consider evidence of causality. The patient subsequently developed a number of neurologic and gastrointestinal symptoms, ultimately resulting in a diagnosis of autism. At approximately 2 years of age, the patient was also diagnosed with a mitochondrial disorder. The authors did not attribute the symptoms of encephalopathy to the vaccines.

Described below is one publication reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

As described in greater detail in the encephalitis section Valmari et al. (1987) reported the isolation of measles virus, on two occasions, from the CSF in a patient that developed symptoms of encephalopathy after administration of measles, mumps, and rubella vaccines.

#### *Weight of Mechanistic Evidence*

Neurological sequelae of encephalitis, including aphasia and psychomotor retardation, have been reported after infection with both wild-type measles virus and wild-type mumps virus (Gershon, 2010a; Litman and

Baum, 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

The publication described above did not present evidence sufficient for the committee to conclude the vaccine may be a contributing cause of encephalopathy after administration of MMR vaccine. Measles virus was demonstrated in the patient's CSF on two occasions. However, the authors did not identify the virus as vaccine strain. In addition, the patient underwent immunosuppressive therapy shortly after administration of the vaccine, which could have contributed to the development of symptoms.

The latency between vaccination and the development of encephalopathy in the publication described was 54 days suggesting persistent viral infection as the mechanism. Direct viral infection and viral reactivation may contribute to the symptoms of encephalopathy; however, the publications did not provide evidence linking these mechanisms to MMR vaccine.

*The committee assesses the mechanistic evidence regarding an association between MMR vaccine and encephalopathy as weak based on knowledge about the natural infection and one case.*

### Causality Conclusion

**Conclusion 4.3:** The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and encephalopathy.

### FEBRILE SEIZURES

#### Epidemiologic Evidence

The committee reviewed 19 studies to evaluate the risk of febrile seizures after the administration of vaccines containing measles, mumps, and rubella alone or in combination. Nine studies (Al Awaidy et al., 2010; Bino et al., 2003; D'Souza et al., 2000; Fescharek et al., 1990; Landrigan and Witte, 1973; Miller, 1982; Patja et al., 2000; Stetler et al., 1985; Vahdani et al., 2005) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations. Two controlled studies (Menniti-Ippolito et al., 2007; Morley et al., 1964) had very serious methodological limitations that precluded their inclusion in this assessment. The study by Menniti-Ippolito et al. (2007) provided inadequate information on the selection of controls and did not validate vaccination information provided in self-report questionnaires from the study participants. Morley et al. (1964) conducted a double-blind, randomized controlled trial in children living in Nigeria, but the sample size was too small to adequately

assess the risk of seizures following administration of the Edmonston B strain measles vaccine.

The eight remaining controlled studies (Andrews et al., 2007; Barlow et al., 2001; Chen et al., 1997; Farrington et al., 1995; Griffin et al., 1991; Miller et al., 2007; Vestergaard et al., 2004; Ward et al., 2007) contributed to the weight of epidemiologic evidence and are described below.

Griffin et al. (1991) conducted a retrospective cohort study in 18,364 children (12 to 36 months of age) enrolled in the Tennessee Medicaid program from 1974 through 1984. The study reviewed county health department records to identify children who received immunizations at public health clinics; 82 percent of these records were linked to Tennessee birth certificates for children born from 1974 through 1984. The study cohort included children enrolled in the Tennessee Medicaid program within 90 days of birth who received at least one diphtheria, tetanus, and pertussis (DTP) vaccination (during 29 to 365 days of birth) and one MMR or measles-rubella (MR) vaccination (during 12 to 36 months of age). The investigators screened Medicaid inpatient and outpatient claims files for diagnoses of febrile seizures, afebrile seizures, and symptomatic seizures following administration of MMR or MR vaccine. The claims files were verified with hospital-based records; events not leading to hospitalization were excluded from the analysis. Of the 18,222 MMR and 363 MR vaccines administered to the study participants, 77 cases of febrile seizures were reported following vaccination. The risk period and control period were defined as 7 to 14 days and 30 or more days after vaccination, respectively. The age-adjusted relative risk of febrile seizures 7 to 14 days after MMR or MR vaccination was 2.1 (95% CI, 0.7–6.4). Thus, the authors found a nonsignificant increased risk of febrile seizures within 7 to 14 days of MMR or MR vaccination.

Farrington et al. (1995) conducted a case-crossover study in children (12 to 24 months of age) who were enrolled from computerized hospital records in five districts in the United Kingdom between October 1988 and February 1993. A total of 1,057 cases of febrile seizures were identified using hospital diagnosis codes. MMR vaccination information was obtained from computerized child health and general practice records for 75 percent of the participants. The vaccine batch number was available in 78 percent of these records and was used to determine the mumps strain (Jeryl Lynn or Urabe) administered during vaccination. The risk periods for febrile seizures were defined as 6–11 days and 15–35 days after MMR vaccination based on when the authors might expect to observe neurological events attributable to the measles and mumps components of the vaccine. The control period was defined as any time not included in the risk period. The relative risk of febrile seizures within 6–11 days of MMR vaccination including the Jeryl Lynn mumps strain was 3.77 (95% CI, 1.95–7.30) and

within 15–35 days was 1.04 (95% CI, 0.56–1.93). The authors found a significantly increased risk of febrile seizures within 6 to 11 days of MMR vaccination.

Chen et al. (1997) conducted a self-controlled case-series study in more than 500,000 children (0 to 6 years of age) enrolled in four HMOs participating in the VSD from 1991 through 1996. Vaccination information and diagnostic codes for seizures were obtained from the HMO data systems without chart review. Children who experienced any type of seizure were included in the analysis (the number of cases was not provided). The relative rates of seizures observed during the risk periods (1–3 days, 4–7 days, 8–14 days, and 15–30 days following vaccination) were compared with prevaccination and more distant postvaccination control periods. The relative risk of seizures within 8–14 days of MMR vaccination (adjusted for concomitant *Haemophilus influenzae* type B [HiB] vaccination) was 2.42 (95% CI, 1.8–3.2). The authors did not provide relative risk information for the other defined risk periods.

Barlow et al. (2001) collected additional data on children enrolled in the study by Chen et al. (1997), which is described above. The authors conducted a retrospective cohort study in 679,942 children enrolled in four HMOs participating in the VSD from January 1991 to September 1993. A total of 2,281 children with possible first seizures were identified in the HMO data systems using diagnostic codes for seizures, seizures in a newborn, epilepsy, and myoclonus. The diagnostic codes were primarily limited to hospitalizations and emergency department visits. The investigators reviewed the medical records of 1,094 randomly selected children in order to validate and classify the events. Of the 716 validated diagnoses of first seizure, 487 were febrile seizures, 137 were afebrile seizures, 36 were infantile spasms, and 56 were from other causes. MMR immunization information was obtained from the HMO data systems but was not validated with medical record review. The risk intervals for febrile seizures were defined as 1–7 days, 8–14 days, and 15–30 days following MMR vaccination. The children in the exposed group were matched to the reference group on calendar time, age (within 1 day), and HMO. The reference group had not received an MMR vaccination within the preceding 30 days of the index date. The analysis was adjusted for age, sex, HMO, calendar time, and DTP administration. The adjusted relative risk of febrile seizures within 1–7 days of MMR vaccination was 1.73 (95% CI, 0.72–4.15), within 8–14 days was 2.83 (95% CI, 1.44–5.55), and within 15–30 days was 0.97 (95% CI, 0.49–1.95). The authors confirmed a significantly increased risk of febrile seizures within 8 to 14 days of MMR vaccination in a more detailed analysis of the population first reported in Chen et al. (1997).

Vestergaard et al. (2004) conducted a retrospective cohort study in children born in Denmark from January 1991 through December 1998. The

children were enrolled from the Danish Civil Registration System, which maintains personal identification information for all residents. These data were linked to records from other national registries. Diagnoses of febrile seizures were derived from diagnostic codes in the National Hospital Registry and MMR vaccination data were obtained from the National Board of Health. The MMR vaccine in use during the study period contained the same measles, mumps, and rubella strains as the U.S. vaccine. Children were classified as having a febrile seizure if they were 3 to 60 months of age at the time of hospital discharge and did not have a record of afebrile seizures or other exclusionary conditions (cerebral palsy, severe head trauma, intracranial tumors, meningitis, or encephalitis). Follow-up began at 3 months of age and continued until December 31, 1999, or the date of first diagnosis of febrile seizure, diagnosis of an exclusionary condition, 5 years of age, emigration, or death. A total of 537,171 children were followed for an average of 3.5 years; 17,986 children had at least one diagnosis of febrile seizures, of which 973 experienced the seizure within 2 weeks of MMR vaccination. Relative risks were calculated and adjusted for age (3-month categories) and calendar year. The adjusted relative risk of febrile seizures during the first week following MMR vaccination was 2.46 (95% CI, 2.22–2.73), during the second week following MMR vaccination was 3.17 (95% CI, 2.89–3.49), and within the combined 2 weeks following MMR vaccination was 2.75 (95% CI, 2.32–3.26). The authors concluded that MMR vaccination is associated with a significantly increased risk of febrile seizures within 2 weeks of vaccine administration.

Andrews et al. (2007) conducted a self-controlled case-series study in children (28 days to 17 years of age) diagnosed with seizures from November 1999 through September 2003 in the United Kingdom. MMR vaccines with the Jeryl Lynn or RIT 4385 mumps component (which is derived from the Jeryl Lynn strain), and Moraten or Schwarz measles component were in use during the study period. The cases were identified using diagnostic codes for seizures located in the hospital episode data from the London and South East regions. The hospital episode data was linked to vaccination information in the child-health databases from the same regions. The study participants were divided into three age groups: 28–365 days (infants), 1 year of age (toddlers), and 2–17 years of age (children). Cases were excluded from the analysis if they received a vaccination outside the recommended age range; MMR vaccine was not recommended in infants and these cases were excluded. Two risk periods were defined as 6–11 days and 15–35 days after MMR vaccination, and were compared to the background risk of seizures among the study participants (excluding the 7-day period before vaccination). A total of 342 participants from the 1-year age group reported 367 seizures (326 febrile seizures and 41 other or unspecified seizures) and 788 participants from the 2- to 17-year age group reported 863

seizures (500 febrile seizures and 363 other or unspecified seizures). The relative risk of seizures in the 1-year age group within 6–11 days of MMR vaccination was 2.07 (95% CI, 1.00–4.27) and within 15–35 days of MMR vaccination was 0.65 (95% CI, 0.36–1.19). The relative risk of seizures in the 2- to 17-year age group within 6–11 days of MMR vaccination was 1.74 (95% CI, 0.49–6.14) and within 15–35 days of MMR vaccination was 1.39 (95% CI, 0.71–2.74). The analyses were not separated by type of seizure. The authors found a significant increased risk of seizures in the 1-year age group within 6 to 11 days of MMR vaccination. However, the study included two vaccine formulations, one of which is not available in the United States, and the association of these vaccines with febrile seizures was not analyzed separately.

Miller et al. (2007) conducted a self-controlled case-series study in children (12 to 23 months of age) diagnosed with seizures from January 1998 through June 2002 in the United Kingdom. MMR vaccines with the Jeryl Lynn or RIT 4385 mumps component, and Moraten or Schwarz measles component were in use during the study period. The cases were identified using computerized hospital records listing admissions to the National Health Service hospitals, which were linked to MMR vaccination data from computerized immunization records in the North and South Thames regions. Cases with a diagnosis code for febrile seizures or unspecified seizures were included in the study. Two risk periods were defined as 6–11 days and 15–35 days after MMR vaccination, and were compared to the background risk of seizures among the participants (excluding the 2 weeks before vaccination). A total of 894 children were hospitalized with 988 seizure episodes during the study period and were included in the analysis; 73 received meningococcal C conjugate vaccine concurrently with MMR vaccine. The relative risk of febrile seizures within 6–11 days of MMR vaccination was 4.27 (95% CI, 3.17–5.76) and within 15–35 days of vaccination was 1.33 (95% CI, 1.00–1.77). The authors concluded that administration of MMR vaccine increases the risk of febrile seizures during the 6–11 days following vaccination. However, the study included two vaccine formulations, one of which is not available in the United States, and the association of these vaccines with febrile seizures was not analyzed separately.

The study by Ward et al. (2007) was described in detail in the section on encephalitis and encephalopathy. This self-controlled case-series study included 107 children (12 to 35 months of age) with confirmed severe neurologic disease, residing in the United Kingdom or Ireland between October 1998 and September 2001. The relative risk of severe neurologic disease within 6–11 days after MMR vaccination was 5.68 (95% CI, 2.31–13.97) and within 15–35 days after MMR vaccination was 1.34 (95% CI, 0.52–3.47). While a significant increased risk of disease was observed during the 6- to 11-day postvaccination period, three of the six cases received MMR



and meningococcal C conjugate vaccine on the same day, and four of the six cases reported complex febrile seizures combined with encephalopathy. The authors concluded that administration of MMR vaccine is associated with an increased risk of severe neurologic disease within 6 to 11 days of vaccination, and attributed the risk to the inclusion of cases with complex febrile seizures. Furthermore, the study included two vaccine formulations, one of which is not available in the United States, and the association of these vaccines with febrile seizures was not analyzed separately.

### *Weight of Epidemiologic Evidence*

Eight analyses of seven study groups contributed to the weight of evidence; Barlow et al. (2001) and Chen et al. (1997) examined the same population. Five studies assessed the risk of seizures using MMR formulations currently administered in the United States (Barlow et al., 2001; Chen et al., 1997; Farrington et al., 1995; Griffin et al., 1991; Vestergaard et al., 2004), while three studies combined assessments for two vaccine formulations, one of which is not available in the United States (Andrews et al., 2007; Miller et al., 2007; Ward et al., 2007). All found an increase in seizures within 7 to 14 days following MMR vaccination. Six of the studies noted these were febrile seizures; two studies (Andrews et al., 2007; Chen et al., 1997) did not mention whether the seizures were febrile or afebrile. In six studies the association was statistically significant. See Table 4-2 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has a high degree of confidence in the epidemiologic evidence based on seven studies with validity and precision to assess an association between MMR vaccine and febrile seizures; these studies consistently report an increased risk.*

### **Mechanistic Evidence**

The committee identified 15 publications reporting febrile seizures developing after the administration of vaccines containing measles, mumps, and rubella alone or in combination. One publication described multiple cases; some did not provide evidence beyond temporality (Ehregut and Zastrow, 1989). These cases did not contribute to the weight of mechanistic evidence. Eleven publications did not provide evidence beyond temporality (Forster and Urbanek, 1982; Hilleman et al., 1968; Konkell et al., 1993; Landrigan and Witte, 1973; Maspero et al., 1984; Miller, 1982; Miyake et al., 2001; Nader and Warren, 1968; Wiersbitzky et al., 1991, 1993b, 1995). In addition, five publications reported concomitant infections that could contribute to the development of symptoms (Forster and Urbanek,

TABLE 4-2 Studies Included in the Weight of Epidemiologic Evidence for MMR Vaccine and Febrile Seizures

| Citation                 | Operationally Defined Outcome  | Study Setting  | Defined Study Population   | Study Design   | Sample Size  | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)  | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|--------------------------|--|--|--|--|--|---|---|--|
| Griffin et al. (1991)    | Inpatient and outpatient diagnoses of febrile seizures                       | Tennessee Medicaid program from 1974–1984                                    | Ages 12–36 months born from 1974 through 1984 and enrolled in the Tennessee Medicaid program within 90 days of birth | Retrospective cohort<br><br>Risk periods: 7–14 days after vaccination<br><br>Control period: 30 or more days after vaccination                     | 18,364 children received a MMR or MR vaccination<br><br>Four children had febrile seizures 7–14 days after MMR or MR vaccination | Age-adjusted RR of febrile seizures 7–14 days after MMR or MR vaccination: 2.1 (95% CI, 0.7–6.4)  | None described                                      | Serious  |
| Farrington et al. (1995) | Hospital diagnosis for febrile seizures in the computerized hospital records | Hospitals in five districts in the United Kingdom between 10/1988 and 2/1993 | Ages 12–24 months who were hospitalized for febrile seizures   | Case-crossover<br><br>Risk periods: 6–11 days and 15–35 days after MMR vaccination<br><br>Control period: all time not included in the risk period | 1,057 cases of febrile seizures  | RR of febrile seizures within 6–11 days of MMR vaccination: 3.77 (95% CI, 1.95–7.30)<br><br>RR of febrile seizures within 15–35 days of MMR vaccination: 1.04 (95% CI, 0.56–1.93) | None described                                      | Serious  |

*continued*

TABLE 4-2 Continued

| Citation             | Operationally Defined Outcome   | Study Setting                                     | Defined Study Population | Study Design  | Sample Size  | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)                              |   | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|----------------------|---|---|--------------------------|---|--|---|---|---|--|
|                      |   |   |                          |   |  | RR of seizures within 8–14 days of MMR vaccination:<br>2.42 (95% CI, 1.8–3.2)                     | Adjusted RR of febrile seizures within 1–7 days of MMR vaccination:<br>1.73 (95% CI, 0.72–4.15) |   |  |
| Chen et al. (1997)   | Diagnostic codes for seizures obtained from the HMO data systems                              | Four HMOs participating in the VSD from 1991–1996 | Ages 0–6 years           | Retrospective cohort<br><br>Risk periods: 1–3 days, 4–7 days, 8–14 days, and 15–30 days after MMR vaccination | 500,000 children   |   | None described  | Serious   |  |
| Barlow et al. (2001) | Validated diagnoses of febrile seizures from medical records obtained in the HMO data systems | Four HMOs participating in the VSD from 1991–1993 | Ages 0–6 years           | Retrospective cohort<br><br>Risk periods: 1–7 days, 8–14 days, and 15–30 days after MMR vaccination           | 487 children with febrile seizures<br>32 febrile seizures occurred within 30 days of MMR vaccination | Adjusted RR of febrile seizures within 1–7 days of MMR vaccination:<br>1.73 (95% CI, 0.72–4.15)   | None described  | Serious   |  |
|                      |   |   |                          |   |  | Adjusted RR of febrile seizures within 15–30 days of MMR vaccination:<br>2.83 (95% CI, 1.44–5.55) |   |   |  |
|                      |   |   |                          |   |  | Adjusted RR of febrile seizures within 15–30 days of MMR vaccination:<br>0.97 (95% CI, 0.49–1.95) |   |   |  |

| Vestergaard et al. (2004) | Diagnoses of febrile seizures derived from diagnostic codes in the National Hospital Registry | Danish Civil Registration System and four other national registries | Children born in Denmark from 1/1/1991 through 12/31/1998 | Retrospective cohort | 537,171 children<br>17,986 had at least one diagnosis of febrile seizures | Adjusted RR of febrile seizures during the first week following MMR vaccination:<br>2.46 (95% CI, 2.22–2.73)<br>Adjusted RR of febrile seizures during the second week following MMR vaccination:<br>3.17 (95% CI, 2.89–3.49)<br>Adjusted RR of febrile seizures within the combined 2 weeks following MMR vaccination:<br>2.75 (95% CI, 2.32–3.26) | None described | Serious |
|---------------------------|---|---|---|----------------------|---|---|----------------|---------|
|                           |   |   |   |                      |   |   |                |         |

*continued*

TABLE 4-2 Continued

| Citation              | Operationally Defined Outcome   | Study Setting   | Defined Study Population  | Study Design   | Sample Size  | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)  | Heterogeneous Subgroups at Higher Risk <sup>b</sup>     | Limitations (Negligible or Serious) <sup>c</sup> |
|-----------------------|---------------------------------|---|---|--|--|---|---|--|
|                       |                                 |   |   |  |  |   |   |  |
| Andrews et al. (2007) | Hospital admission for seizures | Hospitals from the London and South East region of the United Kingdom | Ages 28 days to 17 years diagnosed with seizures from 11/1/1999 through 9/30/2003 | Self-controlled case series<br>Risk periods: 6–11 days and 15–35 days after MMR vaccination<br>Control period: all time not included in the risk period, excluding the 7 days before vaccination | 342 children in 1-year age group experienced a total of 367 seizures (326 febrile seizures and 41 other or unspecified seizures)         | RR of seizures in the 1-year age group within 6–11 days of MMR vaccination: 2.07 (95% CI, 1.00–4.27)<br>RR of seizures in the 1-year age group within 15–35 days of MMR vaccination: 0.65 (95% CI, 0.36–1.19)               | 1-year age group within 6 to 11 days of MMR vaccination | Serious  |
|                       |                                 |   |   |  | 788 children in 2- to 17-year age group experienced a total of 863 seizures (500 febrile seizures and 363 other or unspecified seizures) | RR of seizures in the 2- to 17-year age group within 6–11 days of MMR vaccination: 1.74 (95% CI, 0.49–6.14)<br>RR of seizures in the 2- to 17-year age group within 15–35 days of MMR vaccination: 1.39 (95% CI, 0.71–2.74) |   |  |

|                      |  |   |   |  |   |   |                |         |
|----------------------|--|---|---|--|---|---|----------------|---------|
| Miller et al. (2007) | Hospital admissions for febrile convulsions (includes all National Health Service hospitals) | North and South Thames region of the United Kingdom | Ages 12–23 months diagnosed with seizures from 1/1/1998 through 6/30/2002 | Self-controlled case series  | 894 children were hospitalized with 988 seizure episodes          | RR of febrile seizures within 6–11 days of MMR vaccination: 4.27 (95% CI, 3.17–5.76)<br>RR of febrile seizures within 15–35 days of MMR vaccination: 1.33 (95% CI, 1.00–1.77) | None described | Serious |
|                      |  |   |   | Risk periods: 6–11 days and 15–35 days after MMR vaccination                                       | 52 febrile seizures occurred within 6–11 days of MMR vaccination  |   |                |         |
|                      |  |   |   | Control period: all time not included in the risk period, excluding the 2 weeks before vaccination | 57 febrile seizures occurred within 15–35 days of MMR vaccination |   |                |         |

TABLE 4-2 Continued

| Citation           | Operationally Defined Outcome   | Study Setting             | Defined Study Population  | Study Design  | Sample Size   | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)   | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|--------------------|---|---------------------------|---|---|---|--|---|--|
| Ward et al. (2007) | Cases of severe neurologic disease (encephalitis or febrile seizures) obtained from monthly pediatrician surveillance surveys | United Kingdom or Ireland | Ages 2–35 months residing in United Kingdom or Ireland between 10/1998 and 9/2001 | Self-controlled case series<br>Risk periods: 6–11 days and 15–35 days after MMR vaccination | 107 children (ages 12–35 months) with severe neurologic disease | RR of severe neurologic disease within 6–11 days after MMR vaccination: 5.68 (95% CI, 2.31–13.97)<br><br>RR of severe neurologic disease within 15–35 days after MMR vaccination: 1.34 (95% CI, 0.52–3.47) | None described                                      | Serious  |

<sup>a</sup> The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup> The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup> Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.

1982; Konkel et al., 1993; Wiersbitzky et al., 1991, 1993b, 1995). These publications did not contribute to the weight of mechanistic evidence.

Described below are four publications reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Abe et al. (1985) described a 19-month-old boy presenting with fever and a generalized tonic-clonic seizure lasting 30 minutes 11 days after receiving a measles vaccine containing the Schwarz measles strain. The following day a morbilliform eruption and Koplik spots appeared. The patient experienced febrile seizures on three additional occasions 2 weeks, 5 weeks, and 7 months after the first seizure.

Ehregut and Zastrow (1989) reported 14 cases of febrile seizures developing after administration of a vaccine containing measles, mumps, and rubella alone or in combination. Case 1 (number 1 in the report) presented with a tonic-clonic seizure lasting 10 minutes while febrile and eye rolling to the right 8 days after administration of a measles, mumps, and rubella vaccine. Case 2 (number 4 in the report) presented with a tonic-clonic seizure lasting 5 minutes while febrile and meningismus 8 days after receiving a measles and mumps vaccine. Case 3 (number 7 in the report) presented with a febrile seizure and hemiplegia 14 days after administration of a measles and mumps vaccine. Case 4 (number 18 in the report) presented with a febrile seizure and exanthem 7 days after administration of a measles and mumps vaccine. Case 5 (number 25 in the report) presented with a maculopapular exanthema and febrile seizure 3 days and 9 days, respectively, after administration of a measles and mumps vaccine.

Fescharek et al. (1990) reported 6 of 34 cases of febrile seizures developing after vaccination against measles, mumps, and rubella alone or in combination in detail. One case (number 11 in the report) was previously published by Forster and Urbanek (1982). Case 1 (number 7 in the report) presented with a clonic seizure while febrile, ataxia, and general retardation 13 days after receiving a measles and mumps vaccine. Case 2 (number 10 in the report) presented with a tonic-clonic seizure with fever, hemiparesis, and nystagmus 9 days after administration of a measles and mumps vaccine. Case 3 (number 14 in the report) presented with a tonic-clonic seizure lasting 10 minutes with fever, exanthem, meningismus, and pharyngitis 10 days after receiving a measles and mumps vaccine. Case 4 (number 19 in the report) presented with a febrile tonic-clonic seizure lasting 10 minutes while febrile and right side hemiparesis with hyperreflexia 9 days after administration of a measles, mumps, and rubella vaccine. Case 5 (number 21 in the report) presented with a febrile seizure, exanthem, meningismus, and right side hemiparesis 10 days after receiving a measles, mumps, and rubella vaccine.



Parisi et al. (1991) described a 9-month-old patient (case 3 in the report) presenting with an exanthematic febrile reaction 11 days after administration of a measles vaccine. Physical examination showed hyperemic pharynx, rhinitis, conjunctivitis, and a maculopapular exanthem over the entire body. The symptoms disappeared after 4 to 5 days.

### *Weight of Mechanistic Evidence*

Fever is a prodromal symptom beginning after the 10- to 14-day incubation phase for wild-type measles virus and the 16- to 18-day incubation period for wild-type mumps virus (Gershon, 2010a; Litman and Baum, 2010). In addition, acute measles encephalitis is associated with fever and seizures (Gershon, 2010a). The committee considers the effects of natural infection one type of mechanistic evidence.

In addition, the four publications described above presented clinical evidence sufficient for the committee to conclude the vaccine may be a contributing cause of febrile seizures after administration of MMR vaccine. The publications presented a symptomology of fever with seizure developing within the incubation phases for measles and mumps viruses. In addition, some of the cases presented with exanthems and other neurologic symptoms consistent with measles infection. The failure to demonstrate vaccine-strain virus in the cases described above detracted from the weight of evidence.

The latency between vaccination and the development of the symptomology described above ranged from hours to 28 days after administration of a vaccine containing measles, mumps, and rubella alone or in combination; however, most of the cases discussed above presented between 7 and 14 days after vaccination. Fever, in some instances, may contribute to the development of seizures.

*The committee assesses the mechanistic evidence regarding an association between MMR vaccine and febrile seizures as intermediate based on 12 cases presenting clinical evidence.*

## Causality Conclusion

**Conclusion 4.4:** The evidence convincingly supports a causal relationship between MMR vaccine and febrile seizures.

## AFEBRILE SEIZURES

### Epidemiologic Evidence

The committee reviewed 11 studies to evaluate the risk of afebrile seizures after the administration of vaccines containing measles, mumps, and rubella alone or in combination. Seven studies (Al Awaidy et al., 2010; Bino et al., 2003; D'Souza et al., 2000; Fescharek et al., 1990; Patja et al., 2000; Stetler et al., 1985; Vahdani et al., 2005) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations. Two controlled studies (Griffin et al., 1991; Menniti-Ippolito et al., 2007) had very serious methodological limitations that precluded their inclusion in this assessment. The study by Menniti-Ippolito et al. (2007) used a self-report questionnaire but did not validate vaccination histories and provided inadequate information for the selection of controls. A study by Griffin et al. (1991) was described in detail in the section on febrile seizures following MMR vaccination. This retrospective cohort study did not observe an adequate number of children with afebrile seizures to estimate a relative risk; the authors only report that one child had afebrile seizures 1 and 3 days after vaccination.

The two remaining controlled studies (Barlow et al., 2001; Davis et al., 1997) contributed to the weight of epidemiologic evidence and are described below.

Davis et al. (1997) conducted a retrospective cohort study in children enrolled in the Group Health Cooperative (GHC) of Puget Sound and Northern California Kaiser (NCK) HMOs. The study included children who received MMR immunizations from March 1991 through December 1994, and were enrolled in the HMO at least 3 months before and 3 months after vaccination. Children in two age groups were examined: 4 to 6 years and 10 to 12 years. Based on routine practice in the GHC and NCK the authors assumed that an MMR immunization received in either of these two age groups was a second dose. History of a previous MMR vaccination was not validated. Other immunizations were given concurrently in some children: hepatitis B vaccine was most common in the 10- to 12-year age group, and DTaP (or DT or Td) and oral polio virus vaccines were mainly seen in the 4- to 6-year age group. The risk period began the day after immunization and continued for 30 days; the control period began 3 months before immunization and continued for 30 days, ending 2 months before immunization. A total of 18,036 children aged 10 to 12 years and 8,514 children aged 4 to 6 years were included in the analysis. Clinic, emergency department, and hospital visits for seizures were obtained from the medical records, and chart validation was performed to confirm the event. The

4- to 6-year-olds reported no chart-confirmed visits for seizure diagnoses during the risk period. The 10- to 12-year-olds reported more seizure diagnoses during the risk period (three cases) compared to the control period (no cases). The three seizures were described as one grand mal seizure, one syncopal seizure, and one partial complex seizure. Two of the children had similar seizure episodes that occurred before MMR vaccination and one was evaluated for a tic disorder prior to vaccination.

The study by Barlow et al. (2001) was described in detail in the section on febrile seizures following MMR vaccination. This retrospective cohort study assessed the risk of afebrile seizures within 0–7 days, 8–14 days, and 15–30 days of MMR vaccination. Of the 716 validated diagnoses of first seizure, 137 were afebrile seizures; seizures among children with diagnoses of epilepsy or residual seizure disorder were also classified as afebrile seizures. The relative risk of afebrile seizures within 8–14 days of MMR vaccination was 1.11 (95% CI, 0.11–11.28) and within 15–30 days was 0.48 (95% CI, 0.05–4.64); a relative risk was not calculated for afebrile seizures within 0–7 days of MMR vaccination. The authors found that MMR vaccination is not associated with an increased risk of afebrile seizures, but the confidence intervals were very wide.

### *Weight of Epidemiologic Evidence*

Two large studies (Barlow et al., 2001; Davis et al., 1997) failed to identify enough cases to adequately address whether MMR vaccination is associated with an increased risk of afebrile seizures. See Table 4-3 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has limited confidence in the epidemiologic evidence, based on two studies that lacked validity and precision to assess an association between MMR vaccine and afebrile seizures.*

### **Mechanistic Evidence**

The committee identified 10 publications reporting afebrile seizures developing after the administration of measles, mumps, and rubella alone or in combination. Popovic-Miocinovic et al. (1994) did not observe exacerbation of epilepsy after vaccination against measles in patients undergoing anticonvulsant therapy. One publication identified the development of status epilepticus in one patient after administration of a measles vaccine, but details including the time frame between vaccination and the development of symptoms were not provided (Scholtes et al., 1996). Eight publications did not provide evidence beyond temporality, some too short based on the

TABLE 4-3 Studies Included in the Weight of Epidemiologic Evidence for MMR Vaccine and Afebrile Seizures

| Citation            | Operationally Defined Outcome  | Study Setting                                | Defined Study Population       | Study Design  | Sample Size   | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)  | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|---------------------|--|--|--------------------------------|---|---|---|---|--|
| Davis et al. (1997) | Chart-confirmed clinic, emergency department, and hospital visits for seizures | GHC and NCK HMOs from 3/1991 through 12/1994 | Ages 4–6 years and 10–12 years | Retrospective cohort<br><br>Risk period: 1 month after MMR vaccination<br><br>Control period: Began 3 months before MMR vaccination and ended 2 months before vaccination | 18,036 children ages 10–12 years<br><br>8,514 children ages 4–6 years | 4- to 6-year-olds: No chart-confirmed visits for seizure diagnoses<br><br>10- to 12-year-olds: Three seizures diagnoses during the risk period compared to none during the control period | None described                                      | Serious  |

*continued*

TABLE 4-3 Continued

| Citation             | Operationally Defined Outcome   | Study Setting                                     | Defined Study Population | Study Design  | Sample Size   | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)   | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|----------------------|---|---|--------------------------|---|---|--|---|--|
| Barlow et al. (2001) | Validated diagnoses of afebrile seizures from medical records obtained in the HMO data systems                            | Four HMOs participating in the VSD from 1991–1993 | Ages 0–6 years           | Retrospective cohort<br>Risk periods: 0–7 days, 8–14 days, and 15–30 days after MMR vaccination | 137 children with afebrile seizures<br>Three afebrile seizures occurred within 30 days of MMR vaccination | Adjusted RR of afebrile seizures within 8–14 days of MMR vaccination: 1.11 (95% CI, 0.11–11.28)<br>Adjusted RR of afebrile seizures within 15–30 days of MMR vaccination: 0.48 (95% CI, 0.05–4.64) | None described                                      | Serious  |
|                      | Seizures among children with diagnoses of epilepsy or residual seizure disorder were also classified as afebrile seizures |   |                          |   |   | RR was not calculated for afebrile seizures within 0–7 days of MMR vaccination   |   |  |

<sup>a</sup> The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup> The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup> Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.

possible mechanisms involved (Ehregut and Zastrow, 1989; Fescharek et al., 1990; Konkel et al., 1993; Kumar et al., 1982; Nader and Warren, 1968; Schneck, 1968; Wiersbitzky et al., 1993b, 1995). The publications did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

*The committee assesses the mechanistic evidence regarding an association between MMR vaccine and afebrile seizures as lacking.*

### Causality Conclusion

**Conclusion 4.5: The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and afebrile seizures.**

## MENINGITIS

### Epidemiologic Evidence

The committee reviewed nine studies to evaluate the risk of meningitis after the administration of MMR vaccine. Three studies (Fescharek et al., 1990; Miller et al., 1993; Schlipkötter et al., 2002) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations. Three controlled studies (Davis et al., 1997; dos Santos et al., 2002; Miller et al., 2007) had very serious methodological limitations that precluded their inclusion in this assessment. The studies by Davis et al. (1997) and dos Santos et al. (2002) were unable to find any cases of meningitis following MMR immunization, so no conclusions could be drawn from these analyses. Miller et al. (2007) conducted a retrospective cohort study comparing the risk of meningitis after MMR vaccination with an RIT 4385 mumps component (derived from the Jeryl Lynn strain) to a historical control population. The historical comparison group also received MMR vaccine (Urabe mumps component) and was inadequate for assessing the risk of meningitis following the administration of RIT 4385 mumps component MMR vaccine.

The three remaining controlled studies (Black et al., 1997; Ki et al., 2003; Makela et al., 2002) contributed to the weight of epidemiologic evidence and are described below.

Black et al. (1997) conducted a case-control study in children (12 to 23 months of age) with meningitis enrolled at four HMOs participating in the VSD from 1984 to 1993. The cases were identified in the HMO hospitaliza-

tion records. The medical record of each case was reviewed to validate the meningitis diagnosis and ensure the absence of a prior underlying disease; the controls also had no evidence of underlying illness. Two controls were matched to each case on age (within 1 month), sex, HMO, and HMO membership status. A total of 59 cases and 118 matched controls were included in the analysis. The odds ratio for developing meningitis after the administration of MMR vaccine in combination with other vaccines was reported for three time intervals: within 14 days, 0.50 (95% CI, 0.1–4.5); within 30 days, 0.84 (95% CI, 0.2–3.5); and within 8 to 14 days, 1.00 (95% CI, 0.1–9.2). The authors concluded that MMR vaccination does not appear to increase the risk of hospitalization for aseptic meningitis in children, but the confidence intervals were very wide.

The study by Makela et al. (2002) was described in detail in the section on encephalitis and encephalopathy. This retrospective cohort study investigated the occurrence of aseptic meningitis following MMR vaccination in children (1 to 7 years of age) in Finland. Cases of aseptic meningitis identified in the nationwide hospital discharge register that occurred within 3 months of vaccination were validated with information from the patients' medical records, and the exact dates of vaccination were verified. The risk period was defined as 3 months after vaccination; the control period was defined as subsequent 3-month postvaccination intervals until 24 months was reached. A total of 161 children were hospitalized for aseptic meningitis during the study period, of which 10 occurred within 3 months of MMR vaccination, 54 occurred in the subsequent 21 months, and 41 occurred before MMR vaccination. The analysis did not find an increase of aseptic meningitis hospitalizations within 3 months of vaccination ( $p = .57$ ). The authors concluded that MMR vaccination does not appear to increase the risk of aseptic meningitis in children.

Ki et al. (2003) conducted a case-crossover study in children (8 to 36 months of age) with aseptic meningitis residing in Korea during 1998. The cases were identified using insurance claims data and included if they were hospitalized at the time of their diagnosis. A parental telephone survey was used to collect information on prior vaccinations; only patients that provided the vaccination date and place of vaccination from a vaccine record were included. Since information on the mumps strain used was not available, the authors assumed the MMR vaccines administered at public health centers would contain Urabe or Hoshino strains, and those administered at private clinics or hospitals would contain Jeryl Lynn or Rubini strains. A total of 67 children who received MMR vaccine within 1 year of aseptic meningitis onset were included in the analysis, of which 29 received Urabe or Hoshino mumps strain and 38 received Jeryl Lynn or Rubini mumps strain. Since neither Urabe nor Hoshino strain were used in the United States, the committee only looked at the results of the subset of patients

who received either Jeryl Lynn (U.S. mumps vaccine strain) or Rubini strain. The risk period was defined as 42 days before disease onset and the control period extended to 1 year before onset excluding the risk period (cases were self-matched). In the Jeryl Lynn or Rubini group ( $n = 38$ ), the relative risk of aseptic meningitis within 42 days of MMR vaccination was 0.6 (95% CI, 0.18–1.97). The authors concluded that MMR vaccination with Jeryl Lynn or Rubini mumps strain does not appear to be associated with an increased risk of aseptic meningitis in children.

### *Weight of Epidemiologic Evidence*

Three studies evaluating the risk of aseptic meningitis after MMR vaccination were included in the committee's review of the epidemiologic evidence (Black et al., 1997; Ki et al., 2003; Makela et al., 2002). None of these studies found a significant increased risk of aseptic meningitis after MMR vaccination with strains used in the United States. Although power was limited in all the studies, they were generally well done and results were consistent, supporting the committee's conclusion that the evidence overall reached a moderate level of confidence for a null association. See Table 4-4 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has a moderate degree of confidence in the epidemiologic evidence based on three studies with sufficient validity and precision to assess an association between MMR vaccine and meningitis; these studies consistently report a null association.*

### **Mechanistic Evidence**

The committee identified eight publications reporting meningitis after the administration of vaccines containing measles, mumps, and rubella alone or in combination. Usonis et al. (1999) reported one case of suspected meningitis or febrile seizure after MMR vaccination but did not provide clinical, diagnostic, or experimental evidence, including the time frame between vaccine administration and development of symptoms. Two publications described multiple cases, some of which did not provide evidence beyond temporality or attributed the symptoms to another etiology (Ehregut and Zastrow, 1989; Fescharek et al., 1990). These cases did not contribute to the weight of mechanistic evidence. Four publications did not provide evidence of causality beyond a temporal relationship between vaccination and the development of symptoms (Jorch et al., 1984; Riordan et al., 1995; Wiersbitzky et al., 1992a,b). In addition, two publications attributed the development of meningitis postvaccination to concomitant



TABLE 4-4 Studies Included in the Weight of Epidemiologic Evidence for MMR Vaccine and Meningitis

| Citation             | Operationally Defined Outcome                            | Study Setting                                     | Defined Study Population | Study Design  | Sample Size  | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)                      | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|----------------------|--|---|--------------------------|---|--|---|---|--|
| Black et al. (1997)  | Meningitis diagnosis identified in the medical record    | Four HMOs participating in the VSD from 1984–1993 | Ages 12–23 months        | Case-control<br>Controls matched by age (within 1 month), sex, HMO, and HMO membership status | 59 children with meningitis<br>118 matched controls          | OR for meningitis diagnosis within 14 days of MMR vaccination:<br>0.50 (95% CI 0.1–4.5)   | None described                                      | Negligible                                       |
| Makela et al. (2002) | Aseptic meningitis identified in the nationwide hospital | Finland from 11/1982 to 6/1986                    | Ages 1–7 years           | Retrospective cohort<br>Risk period: 0–3 months after MMR vaccination                         | 535,544 children<br>161 children hospitalized for meningitis | OR for meningitis diagnosis within 8–14 days of MMR vaccination:<br>1.00 (95% CI 0.1–9.2) | None described                                      | Serious  |

|                    |                  |  |                   |                  |  |   |  |                |         |
|--------------------|------------------|--|-------------------|------------------|--|---|--|----------------|---------|
| discharge register | Ki et al. (2003) | Aseptic meningitis identified in insurance claims data | Korea during 1998 | Ages 8–36 months | Control period: Subsequent 3-month intervals after the risk period until 24 months was reached | 10 meningitis events occurred within 3 months of MMR vaccination    | ( $p = .57$ )  | None described | Serious |
|                    |                  |  |                   |                  | Case-crossover   | 38 children received MMR  | Aseptic meningitis within 42 days of MMR                                 |                |         |
|                    |                  |  |                   |                  | Risk period: 42 days before the onset of meningitis  | vaccines with Jeryl Lynn or Rubini mumps strains                    | vaccination (Jeryl Lynn or Rubini mumps strain): 0.6 (95% CI, 0.18–1.97) |                |         |
|                    |                  |  |                   |                  | Control period: 1 year before the onset of meningitis excluding the risk period                | Three children had aseptic meningitis within 42 days of vaccination |  |                |         |

<sup>a</sup> The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup> The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup> Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.

infections (Jorch et al., 1984; Riordan et al., 1995). These cases did not contribute to the weight of mechanistic evidence.

Described below are three publications describing clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

The case reported by Bakshi et al. (1996) was described in detail in the section on encephalitis. The authors reported the isolation of mumps virus from the urine, serum, and CSF in a patient that developed symptoms of meningoencephalitis after administration of a MMR vaccine.

Ehrengut and Zastrow (1989) reported five cases of meningitis after vaccination against either mumps or measles and mumps. Case 3 described a 6-year-old boy presenting with vomiting, dizziness, and fever 21 days after receiving a mumps vaccine containing the Jeryl Lynn mumps strain. Mumps virus was demonstrated in pharyngeal smears. Cell culture examination showed that the isolated virus produced fewer syncytia, smaller inclusion bodies, and induced less cell damage to monkey kidney cells than wild-type mumps virus, suggesting vaccine-strain virus.

Fescharek et al. (1990) reported 14 cases of meningitis after vaccination against either mumps, measles and mumps, or measles, mumps, and rubella. Case 8 describes a 6-year-old boy presenting with diarrhea and vomiting 1 day after, and headache, fever, abdominal pain, and meningism 9 days after receiving a measles and mumps vaccine. Mumps virus was demonstrated in pharyngeal fluid. Case 12 describes an 8-year-old boy (whose friend's sister was suffering from mumps) presenting with fatigue, and malaise 9 days after, and vomiting and fever 12 days after receiving a mumps vaccine. ECHO virus type II was demonstrated in the stool, and mumps virus was demonstrated in the CSF.

### *Weight of Mechanistic Evidence*

Meningitis develops in 1–10 percent of persons infected with wild-type mumps virus (Litman and Baum, 2010). Furthermore, mumps meningitis can present before, during, or after parotitis (Litman and Baum, 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

The three publications described above did not present evidence sufficient for the committee to conclude the vaccine may be a contributing cause of meningitis after administration of a vaccine containing measles, mumps, and rubella alone or in combination. The publications reported the isolation of mumps virus from urine, blood, pharyngeal fluid and smears, and CSF, but while one publication reported the isolation of a mumps virus that acted similarly to vaccine strain mumps virus in cell culture studies, no publications definitively reported the isolation of vaccine strain mumps virus.

The latency between vaccination and the development of meningitis in the publications described above ranged from 9 days to 9 months, suggesting direct viral infection or persistent viral infection as the mechanism.

*The committee assesses the mechanistic evidence regarding an association between mumps vaccine and meningitis as weak based on knowledge about the natural infection and four cases.*

*The committee assesses the mechanistic evidence regarding an association between measles or rubella vaccine and meningitis as lacking.*

### Causality Conclusion

**Conclusion 4.6:** The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and meningitis.

## ATAXIA

### Epidemiologic Evidence

The committee reviewed four studies to evaluate the risk of ataxia after the administration of vaccines containing measles, mumps, and rubella alone or in combination. These four studies (Fescharek et al., 1990; Geier and Geier, 2003; Landrigan and Witte, 1973; Plesner et al., 2000) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between MMR vaccine and ataxia.*

### Mechanistic Evidence

The committee identified eight publications reporting ataxia after the administration of vaccines containing measles, mumps, and rubella alone or in combination. Seven publications did not provide evidence beyond temporality (Ehregut and Zastrow, 1989; Fescharek et al., 1990; Martinon-Torres, 1999; Nader and Warren, 1968; Peltola et al., 1998; Plesner et al., 2000; Trump and White, 1967). It was unclear what viral strains were

administered to the patient described by Martinon-Torres (1999). These publications did not contribute to the weight of mechanistic evidence.

Described below is one publication reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Landrigan and Witte (1973) retrospectively analyzed cases of neurological disorders developing within 1 month after administration of a measles vaccine from 1963 to 1971 reported to the Immunization Branch of the Center for Disease Control. The authors report three cases of ataxia developing after vaccination. Measles virus was demonstrated in the CSF of one patient that developed choreoathetosis and ataxia 7 days after vaccination. Laboratory analysis including infectivity titer, plaquing, and tissue culture sensitivity suggest the isolated virus to be vaccine-like.

### *Weight of Mechanistic Evidence*

While rare, infection with wild-type mumps is associated with cerebellar ataxia (Litman and Baum, 2010). In addition, invasion of the central nervous system by wild-type measles virus is common (Gershon, 2010a). The committee considers the effects of natural infection one type of mechanistic evidence.

The publication described above did not present evidence sufficient for the committee to conclude the vaccine may be a contributing cause of ataxia. The publication reported the demonstration of measles virus in the CSF and that the isolated virus acted similarly to vaccine-strain measles virus in cell culture studies. However, the publication did not definitively report the isolation of vaccine strain measles virus.

The latency between vaccination and the development of ataxia in the publication described above was 7 days, suggesting direct viral infection as the mechanism.

*The committee assesses the mechanistic evidence regarding an association between measles or mumps vaccine and ataxia as weak based on knowledge about the natural infection and one case.*

*The committee assesses the mechanistic evidence regarding an association between rubella vaccine and ataxia as lacking.*

## Causality Conclusion

**Conclusion 4.7:** The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and ataxia.

## AUTISM

### Epidemiologic Evidence

The committee reviewed 22 studies to evaluate the risk of autism after the administration of MMR vaccine. Twelve studies (Chen et al., 2004; Dales et al., 2001; Fombonne and Chakrabarti, 2001; Fombonne et al., 2006; Geier and Geier, 2004; Honda et al., 2005; Kaye et al., 2001; Makela et al., 2002; Mrozek-Budzyn and Kieltyka, 2008; Steffenburg et al., 2003; Takahashi et al., 2001, 2003) were not considered in the weight of epidemiologic evidence because they provided data from a passive surveillance system lacking an unvaccinated comparison population or an ecological comparison study lacking individual-level data. Five controlled studies (DeStefano et al., 2004; Richler et al., 2006; Schultz et al., 2008; Taylor et al., 2002; Uchiyama et al., 2007) had very serious methodological limitations that precluded their inclusion in this assessment. Taylor et al. (2002) inadequately described the data analysis used to compare autism compounded by serious bowel problems or regression (cases) with autism free of such problems (controls). DeStefano et al. (2004) and Uchiyama et al. (2007) did not provide sufficient data on whether autism onset or diagnosis preceded or followed MMR vaccination. The study by Richler et al. (2006) had the potential for recall bias since the age at autism onset was determined using parental interviews, and their data analysis appeared to ignore pair-matching of cases and controls, which could have biased their findings toward the null. Schultz et al. (2008) conducted an Internet-based case-control study and excluded many participants due to missing survey data, which increased the potential for selection and information bias.

The five remaining controlled studies (Farrington et al., 2001; Madsen et al., 2002; Mrozek-Budzyn et al., 2010; Smeeth et al., 2004; Taylor et al., 1999) contributed to the weight of epidemiologic evidence and are described below.

Taylor et al. (1999) conducted a self-controlled case-series study in children with autistic disorders residing in the North East Thames region of the United Kingdom. The children were identified from computerized special needs or disability registers. A total of 498 children who were born from 1979 through 1998 and had an autism diagnosis before 16 years of age were included in the analysis. After reviewing the clinical records, the investigators confirmed that the autism diagnoses met the criteria of the *International Classification of Diseases, 10th revision* (ICD-10) in 82 percent of typical autism cases and 31 percent of atypical autism cases (the authors used the term *core* to describe typical autism, as noted in the methods). The self-controlled analysis investigated the risk of typical or atypical autism diagnosis among 357 cases during two postvaccination periods (12 or 24

months after vaccination). The reference period consisted of time from birth through August 1998, not including the postvaccination risk periods. The relative risk of autism diagnosis within 12 months of MMR vaccination was 0.94 (95% CI, 0.60–1.47) and within 24 months of MMR vaccination was 1.09 (95% CI, 0.79–1.52). The relative risk of autism diagnosis within 12 months and 24 months of vaccination with MMR or single-antigen measles with mumps and rubella was 0.80 (95% CI, 0.53–1.22) and 1.05 (95% CI, 0.76–1.44), respectively. The authors noted the results were similar when the analyses were restricted to confirmed cases of typical or atypical autism. The authors concluded that MMR vaccination is not associated with autism.

Farrington et al. (2001) conducted a reanalysis of the study by Taylor et al. (1999). The two risk periods were changed to autism diagnosis within 59 months and any time after vaccination, and compared to a reference period that consisted of time from birth through 191 months of age or August 1998, whichever occurred first. The analysis was adjusted for both calendar year and age. The relative risk of autism diagnosis within 59 months of vaccination with MMR was 1.24 (95% CI, 0.67–2.27), and with MMR and any measles-containing vaccines was 0.96 (95% CI, 0.52–1.77). The relative risk of autism diagnosis any time after vaccination with MMR was 1.06 (95% CI, 0.49–2.30), and with MMR and any measles-containing vaccines was 2.03 (95% CI, 0.80–5.18). The authors concluded that there is no association between MMR or measles-containing vaccines and autism diagnosis any time after vaccination.

Madsen et al. (2002)<sup>2</sup> conducted a retrospective cohort study in children born in Denmark from January 1991 through December 1998. The children were enrolled from the Danish Civil Registration System, which stores personal identification information for all residents, and linked records to five other national registries. MMR vaccination data were obtained from the National Board of Health; autism diagnosis was derived from the Danish Psychiatric Central Register. The National Hospital Registry and Danish Medical Birth Registry provided birth weight and gestational age information, and data on socioeconomic status and mother's education came from Statistics Denmark. Autism diagnoses were based on criteria from the ICD-10; the diagnostic codes were separated into cases of autistic disorder or other autistic-spectrum disorders. Children with congenital rubella or an inherited genetic condition (fragile X syndrome, Angelman's syndrome, or tuberous sclerosis) were excluded from the analysis. A total of 537,303 children were included in the cohort, of which 316 had an autistic disorder diagnosis and 422 had an autistic-spectrum disorder diagnosis. Follow-up

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<sup>2</sup>One of the authors of this article, P. Thorsen, was indicted for embezzlement on April 13, 2011. The implications for the integrity of the study are unknown at this time.

began at 1 year of age and continued through December 31, 1999, or the date of autism diagnosis, diagnosis of other associated conditions, emigration, or death. Children who were vaccinated with MMR contributed 1,647,504 person-years of follow-up, and those not vaccinated contributed 482,360 person-years. Relative risks were calculated and adjusted for age, calendar period, sex, birth weight, gestation age, mother's education, and socioeconomic status. The adjusted relative risk of autism diagnosis after MMR vaccination was 0.92 (95% CI, 0.68–1.24) and of other autistic spectrum disorders after MMR vaccination was 0.83 (95% CI, 0.65–1.07). The authors concluded that MMR vaccination is not associated with an increased risk of autistic disorder or other autistic-spectrum disorders.

Smeech et al. (2004) conducted a case-control study in children (born between 1973 and 1999) enrolled in the General Practice Research Database (GPRD) from June 1987 through December 2001. The study included 991 cases with a recorded diagnosis of autism and 303 cases with other pervasive developmental disorder diagnosis. A total of 4,469 controls were individually matched to cases on year of birth (within 1 year), sex, and general practice. The study excluded cases and controls that were not enrolled in the database for at least 12 months before the diagnosis or index date (date that control was same age as matched case at time of diagnosis). MMR vaccination data were abstracted from the GPRD records, and the case or control status was concealed during the assessment. The unadjusted odds ratio for autism diagnosis after MMR vaccination was 0.77 (95% CI, 0.60–0.98). After adjustment for the age at which participants joined the GPRD, the odds ratio was 0.88 (95% CI, 0.67–1.15). The authors concluded that MMR vaccination is not associated with an increased risk of autism.

Mrozek-Budzyn et al. (2010) conducted a case-control study in children identified in the general practitioner records in the Malopolska Province of Poland. The study included 96 cases and 192 matched controls. The cases were diagnosed with childhood or atypical autism by a child psychiatrist according to the ICD-10 criteria. Two controls were matched to each case on year of birth, gender, and physician's practice. Vaccination histories and the date of autism diagnosis were extracted from the physician's records. Date of onset of symptoms was derived from parental interview. If MMR or single-antigen measles vaccination preceded the onset of symptoms, cases were classified as vaccinated. Controls were considered vaccinated if they received an MMR or single-antigen measles vaccine before the age of symptom onset observed in the matched case. The analysis adjusted for mother's age, medication during pregnancy, gestation time, perinatal injury, and 5-minute Apgar scale score. The adjusted odds ratio for autism diagnosis after MMR vaccination was 0.17 (95% CI, 0.06–0.52). The adjusted odds ratio for autism diagnosis after single-antigen measles or MMR vaccination



was 0.28 (95% CI, 0.10–0.76). The authors concluded that administration of MMR or single-antigen measles vaccine is not associated with an increased risk of autism in children.

### *Weight of Epidemiologic Evidence*

Three unique studies (Madsen et al., 2002; Smeeth et al., 2004; Taylor et al., 1999) were judged to have negligible limitations; all reported null associations (on average) between MMR vaccination and subsequent autism diagnosis (or onset) and the overall precision was high. A separate report (Farrington et al., 2001) using the same population and methods as Taylor et al. (1999) reported a null association (moderate precision) between MMR vaccination and subsequent onset or diagnosis of the regressive subtype of autism. The fifth study (Mrozek-Budzyn et al., 2010) also found no association between measles or MMR immunization using a hospital-based case-control design with appropriate methods for matching and analysis. This study was rated as having serious limitations because it did not provide information on medical conditions among the controls and relied on medical record abstraction for immunization dates and autism diagnosis dates. Overall, the studies were reasonably valid, and provided consistent and precise evidence supporting no increased risk. See Table 4-5 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has a high degree of confidence in the epidemiologic evidence based on four studies with validity and precision to assess an association between MMR vaccine and autism; these studies consistently report a null association.*

### **Mechanistic Evidence**

The committee identified four publications reporting autism developing after the administration of MMR vaccine. Three publications did not provide evidence beyond temporality, some too long (Frenkel et al., 1996; Spitzer et al., 2001; Wakefield et al., 1998).<sup>3</sup> Long latencies between vaccine administration and development of behavioral symptoms make it impossible to rule out other possible causes. In addition, the committee identified an editorial by Sharrard (2010) in which a temporal relationship between administration of a measles, mumps, and rubella vaccine and the development of autism was attributed to one patient reported in Verity et al. (2010). However, as reported in the original article and affirmed in a subsequent letter to the editor (Verity et al., 2011) the vaccinee did not

<sup>3</sup>During the committee's review the publisher issued a retraction of Wakefield et al. (1998).

TABLE 4-5 Studies Included in the Weight of Epidemiologic Evidence for MMR Vaccine and Autism

| Citation             | Operationally Defined Outcome   | Study Setting                              | Defined Study Population  | Study Design   | Sample Size                        | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)   | Heterogeneous Subgroups at Higher Risk <sup>b</sup>                                 | Limitations (Negligible or Serious) <sup>c</sup> |
|----------------------|---|--|---|--|------------------------------------|--|---|--|
| Taylor et al. (1999) | Autism diagnosis obtained from computerized special needs or disability registers | North East Thames Region of United Kingdom | Children born from 1979–1998, with autism diagnosis before age 16 | Self-controlled case series<br>Risk periods: 12 and 24 months after vaccination<br>Control period: time from birth through August 1998, not including the post-vaccination risk period | 357 children with autism diagnosis | RR of autism diagnosis within 12 months of MMR vaccination: 0.94 (95% CI, 0.60–1.47)<br>RR of autism diagnosis within 24 months of MMR vaccination: 1.09 (95% CI, 0.79–1.52) | RR of parental concern within 6 months of MMR vaccination: 1.48 (95% CI, 1.04–2.12) | Negligible                                       |

continued

TABLE 4-5 Continued

| Citation                           | Operationally Defined Outcome   | Study Setting                              | Defined Study Population  | Study Design  | Sample Size                        | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)                 | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|------------------------------------|---|--|---|---|------------------------------------|--|---|--|
| Farrington et al. (2001)           | Autism diagnosis obtained from computerized special needs or disability registers | North East Thames Region of United Kingdom | Children born from 1979–1998, with autism diagnosis before age 16 | Self-controlled case series                           | 357 children with autism diagnosis | RR of autism diagnosis within 59 months of MMR vaccination: 1.24 (95% CI, 0.67–2.27) | None described                                      | Negligible                                       |
| Reanalysis of Taylor et al. (1999) | 82% of typical autism cases and 31% of atypical autism cases met ICD-10 criteria  |  |   | Risk periods: 59 months and anytime after vaccination |                                    | RR of autism diagnosis anytime after MMR vaccination: 1.06 (95% CI, 0.49–2.30)       |   |  |

|                      |  |   |  |                      |  |  |                |            |
|----------------------|--|---|--|----------------------|--|--|----------------|------------|
| Madsen et al. (2002) | Autism diagnosis met the ICD-10 criteria and was obtained from Danish Psychiatric Central Register | Danish Civil Registration System and five other national registries | Children born in Denmark from 1/1/1991 through 12/31/1998                              | Retrospective cohort | 537,303 children<br>316 children with autism diagnosis<br>1,647,504 person-years of follow-up for exposed group<br>482,360 person-years of follow-up for unexposed group | Adjusted RR of autism diagnosis after MMR vaccination:<br>0.92 (95% CI, 0.68–1.24)<br>Adjusted RR of diagnosis of other autistic spectrum disorders following MMR vaccination:<br>0.83 (95% CI, 0.65–1.07) | None described | Negligible |
| Smeeth et al. (2004) | Autism diagnosis obtained from medical records   | GPRD  | Children born from 1973–1999 and enrolled in the GPRD from 6/1/1987 through 12/31/2001 | Case-control         | 991 children with autism diagnosis<br>4,469 controls   | Unadjusted OR for autism diagnosis after MMR vaccination:<br>0.77 (95% CI, 0.60–0.98)<br>Adjusted OR for autism diagnosis after MMR vaccination:<br>0.88 (95% CI, 0.67–1.15; $p = .35$ )                   | None described | Negligible |

*continued*

TABLE 4-5 Continued

| Citation                    | Operationally Defined Outcome   | Study Setting                 | Defined Study Population                               | Study Design  | Sample Size                                       | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)   | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|-----------------------------|---|-------------------------------|--|---|---|--|---|--|
| Mrozek-Budzyn et al. (2010) | Autism diagnosis met the ICD-10 criteria and was obtained from general practitioner records | Malopolska Province of Poland | Children ages 2–15 years with general practice records | Case-control<br>Controls matched by age, gender, and physician's practice | 96 children with autism diagnosis<br>192 controls | Adjusted OR for autism diagnosis after MMR vaccination:<br>0.17 (95% CI, 0.06–0.52)<br><br>Adjusted OR for autism diagnosis after single-antigen measles or MMR vaccination:<br>0.28 (95% CI, 0.10–0.76) | None described                                      | Serious  |

<sup>a</sup> The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup> The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup> Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.

develop autism, a fact that was misreported in the editorial by Sharrard. Two publications studied the association between MMR vaccination and autism with enteropathy (Hornig et al., 2008; Peltola et al., 1998). The authors reported a temporal relationship between vaccine administration and development of gastrointestinal disturbances but did not report autism after vaccination. The publications did not contribute to the weight of mechanistic evidence.<sup>4</sup>

#### *Weight of Mechanistic Evidence*

*The committee assesses the mechanistic evidence regarding an association between MMR vaccine and autism as lacking.*

### Causality Conclusion

**Conclusion 4.8: The evidence favors rejection of a causal relationship between MMR vaccine and autism.**

## ACUTE DISSEMINATED ENCEPHALOMYELITIS

### Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of acute disseminated encephalomyelitis (ADEM) after the administration of measles vaccine. This one study (Landrigan and Witte, 1973) was not considered in the weight of epidemiologic evidence because it provided data from a passive surveillance system and lacked an unvaccinated comparison population.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between MMR vaccine and ADEM.*

### Mechanistic Evidence

The committee identified three publications reporting the development of ADEM after the administration of vaccines containing measles, mumps, and rubella alone or in combination. The publications did not provide evidence beyond temporality (Gomez Sanchez et al., 2005; Landrigan and

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<sup>4</sup>The case report authored by Poling et al. (2006) is described in the section under encephalopathy.

Witte, 1973; Tenenbaum et al., 2002). The publications did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

While rare, wild-type measles, mumps, or rubella infections have been associated with the development of ADEM (Davis, 2008). The committee considers the effects of natural infection one type of mechanistic evidence.

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of ADEM. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of ADEM; however, the publications did not provide evidence linking these mechanisms to MMR vaccine.

*The committee assesses the mechanistic evidence regarding an association between MMR vaccine and ADEM as weak based on knowledge about the natural infection.*

#### **Causality Conclusion**

**Conclusion 4.9: The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and ADEM.**

### **TRANSVERSE MYELITIS**

#### **Epidemiologic Evidence**

The committee reviewed one study to evaluate the risk of transverse myelitis after the administration of measles vaccine. This one study (Landrigan and Witte, 1973) was not considered in the weight of epidemiologic evidence because it provided data from a passive surveillance system and lacked an unvaccinated comparison population.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between MMR vaccine and transverse myelitis.*

#### **Mechanistic Evidence**

The committee identified five publications reporting the development of transverse myelitis after the administration of vaccines containing measles, mumps, and rubella alone or in combination. Two publications did not provide evidence beyond temporality (Cizman et al., 2005; Landrigan and

Witte, 1973). In addition, Cizman et al. (2005) reported the concomitant administration of vaccines, making it difficult to determine which, if any, vaccine could have been the precipitating event. Furthermore, Cizman et al. (2005) reported serologic testing that showed an acute infection with Epstein-Barr virus that could have contributed to the development of transverse myelitis. This publication did not contribute to the weight of mechanistic evidence.

Described below are three publications describing clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Holt et al. (1976) described a 17-year-old girl presenting with sensory and motor impairment in the legs and transient paraesthesiae in the left arm 2 weeks after administration of a rubella vaccine containing the RA 27/3 strain. The vaccine was administered 1 week postpartum. Over the ensuing 3 days the patient developed anaesthesia below D4 dermatomal level, flaccid paraplegia with retention of urine, and fecal incontinence. The serum rubella haemagglutination inhibition titers increased from 1:20 prevaccination to 1:128 19 days postvaccination.

Lim et al. (2004) described a 9-year-old girl presenting with urinary incontinence 16 days after administration of a measles and rubella vaccine containing the Edmonston-Zagreb measles strain and RA 27/3 rubella strains. Lower limb weakness and back pain developed 4 days later. Serological testing was negative for *Mycoplasma*, herpes simplex virus, varicella zoster virus, and cytomegalovirus.

Joyce and Rees (1995) described a 20-year-old man presenting with malaise, fever, sore throat, and a transient rash over the upper torso 5 days after administration of a measles, mumps, and rubella vaccine. The symptoms fluctuated over the ensuing 2 weeks after which the patient developed urinary retention and ascending paraesthesia. Serologic testing showed a significant rise in titers of rubella antibodies postvaccination.

### *Weight of Mechanistic Evidence*

While rare, infection with wild-type mumps virus has been associated with the development of transverse myelitis (Litman and Baum, 2010). In addition, infection with wild-type measles and rubella viruses have been associated with the development of myelitis (Davis, 2008). The committee considers the effects of natural infection one type of mechanistic evidence.

The publications described above, when considered together, did not present evidence sufficient for the committee to conclude the vaccine may be a contributing cause of transverse myelitis. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of transverse myelitis; however, the publications did not provide evidence linking these mechanisms to MMR vaccine.



*The committee assesses the mechanistic evidence regarding an association between MMR vaccine and transverse myelitis as weak based on knowledge about the natural infection and three cases.*

### Causality Conclusion

**Conclusion 4.10: The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and transverse myelitis.**

## OPTIC NEURITIS

### Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of optic neuritis after the administration of MMR vaccine. This one controlled study (DeStefano et al., 2003) was included in the weight of epidemiologic evidence and is described below.

DeStefano et al. (2003) conducted a case-control study to evaluate the association between MMR vaccination and optic neuritis using data from three HMOs participating in the VSD. The optic neuritis analysis included 108 cases and 228 controls. The cases had a documented physician's diagnosis from January 1995 through December 1999, and were matched to controls from the HMO on date of birth (within 1 year) and sex. The authors evaluated the date of disease onset using data described in the medical record or reported in the telephone interview. The immunization status was obtained from vaccination records, medical records, and telephone interviews. The study had high rates of self-reported vaccinations from outside the HMO system (64 percent of cases and 65 percent of controls) that could not be verified, which may have biased the results. The odds ratio for ever vaccinated with MMR before optic neuritis diagnosis was 0.8 (95% CI, 0.3–2.2). The authors concluded that MMR vaccination does not appear to be associated with an increased risk of optic neuritis in adults.

### *Weight of Epidemiologic Evidence*

*The committee has limited confidence in the epidemiologic evidence, based on one study that lacked validity and precision to assess an association between MMR vaccine and optic neuritis.*

### Mechanistic Evidence

The committee identified three publications reporting optic neuritis developing after the administration of vaccines containing measles, mumps,

and rubella alone or in combination. Kazarian and Gager (1978) did not provide evidence beyond temporality. This publication did not contribute to the weight of mechanistic evidence.

Described below are two publications reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Stevenson et al. (1996) described two cases of optic neuritis developing after vaccination. Case one did not provide evidence of causality beyond a temporal relationship of 3 weeks between administration of a measles and rubella vaccine and development of symptoms after vaccination. Case two described a 13-year-old girl presenting with blurred vision and pain upon movement of the left eye 18 days after receiving a measles and rubella vaccine. Laboratory examination of the CSF revealed oligoclonal bands.

Riikonen (1995) described a 13-year-old girl presenting with acute pain and decreased visual acuity in the left eye 3 months after receiving a rubella vaccine. Laboratory examination of the CSF revealed oligoclonal antibodies and intrathecal antibody production against rubella 2 months after the onset of optic neuritis. Four months later antirubella antibody titers in the CSF were increased.

#### *Weight of Mechanistic Evidence*

While rare, infection with wild-type measles, mumps, or rubella viruses have been associated with optic neuritis (Davis, 2008). The committee considers the effects of natural infection one type of mechanistic evidence.

The publications described above, when considered together, did not present evidence sufficient for the committee to conclude the vaccine may be a contributing cause of optic neuritis after administration of rubella vaccine. Laboratory analysis of the CSF from both publications revealed oligoclonal antibodies, which are present in chronic rubella infections of the central nervous system. In addition, analysis of the CSF from one publication revealed intrathecal antirubella antibody production suggesting infection of the central nervous system. However, vaccine-strain rubella virus was not isolated.

Autoantibodies, T cells, immune complexes, direct viral infection, persistent viral infection, and molecular mimicry may contribute to the symptoms of optic neuritis; however, the publications did not provide evidence linking these mechanisms to MMR vaccine.

*The committee assesses the mechanistic evidence regarding an association between MMR vaccine and optic neuritis as weak based on knowledge about the natural infection and two cases.*

### Causality Conclusion

**Conclusion 4.11:** The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and optic neuritis.

## NEUROMYELITIS OPTICA

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of neuromyelitis optica (NMO) after the administration of MMR vaccine.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between MMR vaccine and NMO.*

### Mechanistic Evidence

The committee identified one publication reporting the development of NMO after the administration of rubella vaccine. Kline et al. (1982) described a 31-year-old woman presenting with left periorbital pain and a headache on the left side 5 days after vaccination. Over the next several days the patient reported pain upon left eye movement and a drop in visual acuity in the left eye. The patient developed soreness in the neck, shoulders, and lower part of the back; intermittent fever; lower extremity weakness; and sensory loss below the T-10 level. The patient's bladder function, visual acuity, and lower extremity weakness improved upon administration of prednisone. Two weeks after cessation of prednisone therapy the patient reported a burning sensation in both arms and legs, neck pain, generalized weakness, and bilateral deterioration of visual acuity. Laboratory examination of the CSF showed immune complexes, increased levels of myelin basic protein, and rubella antibodies (detected by enzyme-linked immunosorbent assay).

#### *Weight of Mechanistic Evidence*

While rare, infection with wild-type rubella virus has been associated with both optic neuritis and myelitis (Davis, 2008). Patients with neuromyelitis optica develop optic neuritis and transverse myelitis. The committee considers the effects of natural infection one type of mechanistic evidence.

The publication described above did not present evidence sufficient for the committee to conclude the vaccine may be a contributing cause of

NMO after administration of a rubella vaccine. The isolation of immune complexes and antirubella antibodies from the CSF are suggestive of their role in development of NMO after vaccination. However, the antigen and antibodies composing the immune complexes were not identified. Autoantibodies, T cells, complement activation, direct viral infection, and molecular mimicry may also contribute to the symptoms of NMO; however, the publication did not provide evidence linking these mechanisms to MMR vaccine.

*The committee assesses the mechanistic evidence regarding an association between rubella vaccine and neuromyelitis optica as weak based on knowledge about the natural infection and one case.*

*The committee assesses the mechanistic evidence regarding an association between measles or mumps vaccine and NMO as lacking.*

### Causality Conclusion

**Conclusion 4.12: The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and neuromyelitis optica.**

## MULTIPLE SCLEROSIS ONSET IN ADULTS

### Epidemiologic Evidence

The committee reviewed six studies to evaluate the risk of onset (date of first symptom) of multiple sclerosis (MS) in adults after the administration of measles or MMR vaccine. One study (Ahlgren et al., 2009a) was not considered in the weight of epidemiologic evidence because it lacked an unvaccinated comparison population. Three controlled studies (Pekmezovic et al., 2004; Ramagopalan et al., 2009; Zorzon et al., 2003) had very serious methodological limitations that precluded their inclusion in this assessment. The case-control study from Pekmezovic et al. (2004) used an inadequate control group that included patients diagnosed with other various neurological disorders. Ramagopalan et al. (2009) did not attempt to validate self-reported vaccination data or confirm the timing of vaccination, and the choice of spousal controls could have introduced selection bias. Zorzon et al. (2003) conducted a case-control study among MS patients and blood donor controls that could have introduced recall or selection bias. The study did not mention if the onset of MS was verified and did not adequately describe if vaccination occurred before disease onset.

The two remaining controlled studies (Ahlgren et al., 2009b; DeStefano et al., 2003) were included in the weight of epidemiologic evidence and are described below.

The study by DeStefano et al. (2003) was described in detail in the section on optic neuritis. This case-control study evaluated the association between MMR vaccination and MS or optic neuritis onset using data from three HMOs participating in the VSD. The MS analysis included 332 cases and 722 controls. Although there are a large number of cases and controls, the study had high rates of self-reported vaccinations from outside the HMO system (64 percent of cases and 65 percent of controls) that could not be verified, which may have biased the results. The odds ratio for ever vaccinated with MMR before MS onset was 0.9 (95% CI, 0.4–1.8). The authors concluded that MMR vaccination does not appear to be associated with an increased risk of MS onset in adults.

Ahlgren et al. (2009b) conducted a case-control study in children born in Gothenburg, Sweden, from 1959 through 1986. The MS cases were identified from administrative diagnosis registries at Sahlgrenska University Hospital and the National Patient Register of the National Board of Health and Welfare. The authors reviewed the records and confirmed the MS diagnosis, and enrolled patients who had disease onset at 10 years of age or older. The controls were randomly selected from the Gothenburg general population register and were born during the same years as the MS patients. The study included 206 cases and 888 controls. The immunization histories of the study participants were obtained from child health and school health records; the authors recorded monovalent and combined measles, mumps, and rubella vaccinations. The immunization was classified as “early” if the vaccine was given at or before 10 years of age and “late” if the vaccine was given after 10 years of age; however, the authors do not state the timing of MS onset relative to the vaccination. The odds ratio for MS onset with MMR vaccination compared to no MMR vaccination was 1.13 (95% CI, 0.62–2.05). The odds ratio for MS onset with “early” MMR vaccination compared to MMR vaccinations given at other ages was 4.92 (95% CI, 1.97–12.20). The odds ratio for MS onset with monovalent or combined measles, mumps, and rubella vaccinations compared to no vaccination was 1.22 (95% CI, 0.77–1.92). This final analysis included U.S. vaccine strains, as well as Schwarz measles strain found in the monovalent vaccine. The authors concluded that measles, mumps, and rubella vaccinations are not associated with MS onset, and noted that the increased odds ratio observed with early MMR vaccination relative to MMR vaccination given at other ages is considered weak evidence owing to the small number of subjects (only eight subjects in early vaccination group). A further weakness of this study is that the analysis was done combining all age groups, which makes it difficult to assess the true association of MMR vaccine and the onset of MS in adults.

*Weight of Epidemiologic Evidence*

Neither of the two case-control studies considered in the assessment of the epidemiologic evidence found an association between MMR vaccine and onset of MS in adults. However, there are some concerns about the study designs and analyses. DeStefano et al. (2003) did not define a specific exposure time and had no short-term assessment in their primary analysis. The authors performed secondary analyses considering the timing of the MMR vaccination (< 1 year, 1–5 years, and > 5 years) relative to the MS onset, which showed no significant association, but they did not state how they handled the timing of vaccination for those who had more than one MMR vaccine before the onset of MS or when MMR was given in combination with other vaccines. Ahlgren et al. (2009b) performed the analysis combining all age groups, which makes it difficult to assess the true association of MMR vaccine and the onset of MS in adults. Given these study limitations and the small number of studies, the committee has limited confidence in the overall evidence. See Table 4-6 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has limited confidence in the epidemiologic evidence, based on two studies that lacked validity and precision to assess an association between MMR vaccine and onset of MS in adults.*

**Mechanistic Evidence**

The committee identified one publication reporting the onset of MS in adults after the administration of rubella vaccine. Behan (1977) did not provide evidence beyond temporality. The publication did not contribute to the weight of mechanistic evidence.

*Weight of Mechanistic Evidence*

The symptoms described in the publication referenced above are consistent with MS. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of MS; however, the publication did not provide evidence linking these mechanisms to MMR vaccine.

*The committee assesses the mechanistic evidence regarding an association between MMR vaccine and onset of MS in adults as lacking.*

TABLE 4-6 Studies Included in the Weight of Epidemiologic Evidence for MMR Vaccine and MS Onset in Adults

| Citation                | Operationally Defined Outcome                                  | Study Setting  | Defined Study Population  | Study Design  | Sample Size                                  | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)  | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|-------------------------|--|--|---|---|--|---|---|--|
| DeStefano et al. (2003) | Date of MS onset from medical records or telephone interviews  | Three HMOs participating in the VSD  | Ages 18–49 years at MS diagnosis date<br>Cases had MS diagnosed by a physician from 1/1/1995 through 12/31/1999 | Case-control<br>Controls matched by date of birth (within 1 year) | 332 patients with MS<br>722 matched controls | Adjusted OR of MS onset anytime after MMR vaccination: 0.9 (95% CI, 0.4–1.8)  | None described                                      | Serious  |
| Ahlgren et al. (2009b)  | Date of MS onset from medical records and confirmed by authors | Administrative registries from Sahlgrenska University Hospital and the National Patient Register of Sweden | Born in Gothenburg, Sweden, from 1959–1986<br>Cases had MS onset at 10 years of age or older                    | Case-control  | 208 patients with MS<br>888 controls         | OR of MS onset with MMR vaccination compared to no MMR vaccination: 1.13 (95% CI, 0.62–2.05; <i>p</i> = .6849)<br>OR of MS onset with monovalent or combined measles, mumps, and rubella vaccination compared to no | None described                                      | Serious  |

vaccination:  
 1.22 (95% CI, 0.77–  
 1.92;  $p = .4101$ )  
 OR of MS onset  
 with “early”  
 MMR vaccination  
 compared to MMR  
 vaccinations given at  
 other ages:  
 4.92 (95% CI,  
 1.97–12.20;  $p =$   
 .0006)

<sup>a</sup> The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup> The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup> Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.



### Causality Conclusion

**Conclusion 4.13:** The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and the onset of MS in adults.

## MULTIPLE SCLEROSIS ONSET IN CHILDREN

### Epidemiologic Evidence

The committee reviewed two studies to evaluate the risk of onset of MS in children after the administration of MMR vaccine. One study (Ahlgren et al., 2009a) was not considered in the weight of epidemiologic evidence because it lacked an unvaccinated comparison population.

The one remaining controlled study (Ahlgren et al., 2009b) was included in the weight of epidemiologic evidence and is described below.

The study by Ahlgren et al. (2009b) was described in detail in the section on onset of MS in adults following MMR vaccination. This case-control study performed multiple analyses for monovalent and combined measles, mumps, and rubella vaccinations. The odds ratio for MS onset with MMR vaccination compared to no MMR vaccination was 1.13 (95% CI, 0.62–2.05). The odds ratio for MS onset with “early” MMR vaccination compared to MMR vaccinations given at other ages was 4.92 (95% CI, 1.97–12.20). The odds ratio for MS onset with monovalent or combined measles, mumps, and rubella vaccinations compared to no vaccination was 1.22 (95% CI, 0.77–1.92). This final analysis included U.S. vaccine strains, as well as Schwarz measles strain found in the monovalent vaccine. The authors concluded that measles, mumps, and rubella vaccinations are not associated with MS onset, and noted that the increased odds ratio observed with early MMR vaccination relative to MMR vaccination given at other ages is considered weak evidence owing to the small number of subjects (only eight subjects in early vaccination group). A further weakness of this study is that the analysis was done combining all age groups, which makes it difficult to assess the true association of MMR vaccine and the onset of MS in children.

### *Weight of Epidemiologic Evidence*

*The committee has limited confidence in the epidemiologic evidence, based on one study that lacked validity and precision to assess an association between MMR vaccine and onset of MS in children.*

### Mechanistic Evidence

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of the onset of MS in children after the administration of MMR vaccine.

#### *Weight of Mechanistic Evidence*

Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of MS; however, the committee did not identify literature reporting evidence of these mechanisms after administration of MMR vaccine.

*The committee assesses the mechanistic evidence regarding an association between MMR vaccine and onset of MS in children as lacking.*

### Causality Conclusion

**Conclusion 4.14:** The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and onset of MS in children.

## GUILLAIN-BARRÉ SYNDROME

### Epidemiologic Evidence

The committee reviewed five studies to evaluate the risk of GBS after the administration of measles or MMR vaccine. These five studies (Bino et al., 2003; Esteghamati et al., 2008; Patja et al., 2000, 2001b; Souayah et al., 2009) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between MMR vaccine and GBS.*

### Mechanistic Evidence

The committee identified seven publications reporting the development of GBS after the administration of vaccines containing measles, mumps, and rubella alone or in combination. Patja et al. (2001b) did not report

the development of GBS within 6 weeks after administration of MMR vaccine. Pritchard et al. (2002) did not report relapse in GBS patients after administration of measles, mumps, or rubella vaccines. Tonelli et al. (2005) reported the development of GBS after administration of a measles vaccine but did not provide clinical, diagnostic, or experimental evidence, including the time frame between vaccination and symptom development. Four publications did not provide evidence beyond temporality, some too short based on the possible mechanisms involved (Grose and Spigland, 1976; Koturoglu et al., 2008; Patja et al., 2000; Schessl et al., 2006). One publication also reported the concomitant administration of vaccines making it difficult to determine which, if any, vaccine could have been the precipitating event (Grose and Spigland, 1976). Furthermore, Schessl et al. (2006) reported serologic testing suggesting concomitant infections that could contribute to the development of GBS. The publications did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

While rare, infection with wild-type measles, mumps, or rubella viruses has been associated with the development of GBS (Davis, 2008). The committee considers the effects of natural infection one type of mechanistic evidence.

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of GBS. Autoantibodies, complement activation, immune complexes, T cells, and molecular mimicry may contribute to the symptoms of GBS; however, the publications did not provide evidence linking these mechanisms to MMR vaccine.

*The committee assesses the mechanistic evidence regarding an association between MMR vaccine and GBS as weak based on knowledge about the natural infection.*

#### **Causality Conclusion**

**Conclusion 4.15: The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and GBS.**

### **CHRONIC INFLAMMATORY DISSEMINATED POLYNEUROPATHY**

#### **Epidemiologic Evidence**

No studies were identified in the literature for the committee to evaluate the risk of chronic inflammatory disseminated polyneuropathy (CIDP) after the administration of MMR vaccine.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between MMR vaccine and CIDP.*

**Mechanistic Evidence**

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of CIDP after the administration of MMR vaccine.

*Weight of Mechanistic Evidence*

Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of CIDP; however, the committee did not identify literature reporting evidence of these mechanisms after administration of MMR vaccine.

*The committee assesses the mechanistic evidence regarding an association between MMR vaccine and CIDP as lacking.*

**Causality Conclusion**

**Conclusion 4.16:** The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and CIDP.

**OPSOCLONUS MYOCLONUS SYNDROME****Epidemiologic Evidence**

No studies were identified in the literature for the committee to evaluate the risk of opsoclonus myoclonus syndrome (OMS) after the administration of MMR vaccine.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between MMR vaccine and OMS.*

**Mechanistic Evidence**

The committee identified one publication reporting the development of OMS after the administration of rubella vaccine. Lapenna et al. (2000) did not provide evidence of causality beyond a temporal relationship of

15 days between vaccine administration and development of OMS after vaccination. The publication did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

The symptoms described in the publication referenced above are consistent with those leading to a diagnosis of OMS. Molecular mimicry may contribute to the symptoms of OMS; however, the publication did not provide evidence linking this mechanism to MMR vaccine.

*The committee assesses the mechanistic evidence regarding an association between MMR vaccine and OMS as lacking.*

### **Causality Conclusion**

**Conclusion 4.17: The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and OMS.**

## **BRACHIAL NEURITIS**

### **Epidemiologic Evidence**

No studies were identified in the literature for the committee to evaluate the risk of brachial neuritis after the administration of MMR vaccine.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between MMR vaccine and brachial neuritis.*

### **Mechanistic Evidence**

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of brachial neuritis developing after the administration of MMR vaccine.

#### *Weight of Mechanistic Evidence*

Autoantibodies, T cells, and complement activation may contribute to the symptoms of brachial neuritis; however, the committee did not identify literature reporting evidence of these mechanisms after administration of MMR vaccine.

*The committee assesses the mechanistic evidence regarding an association between MMR vaccine and brachial neuritis as lacking.*

### Causality Conclusion

**Conclusion 4.18: The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and brachial neuritis.**

## ANAPHYLAXIS

### Epidemiologic Evidence

The committee reviewed ten studies to evaluate the risk of anaphylaxis after the administration of MMR vaccine. These ten studies (Al Awaidy et al., 2010; Bino et al., 2003; Bohlke et al., 2003; D'Souza et al., 2000; DiMiceli et al., 2006; Khetsuriani et al., 2010; Nakayama et al., 1999; Patja et al., 2000; Peng and Jick, 2004; Planchamp et al., 2009) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems or lacked unvaccinated comparison populations.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between MMR vaccine and anaphylaxis.*

### Mechanistic Evidence

The committee identified 11 publications describing clinical, diagnostic, or experimental evidence of anaphylaxis after the administration of vaccines containing measles, mumps, and rubella alone or in combination that contributed to the weight of mechanistic evidence. These publications are described below.

Aukrust et al. (1980) reported six cases of anaphylaxis postvaccination against measles. Case 1 describes a 12-month-old girl presenting with cough, dyspnea, and cyanosis. Case 2 describes a 14-month-old boy presenting with stridor, urticaria, angioedema, dyspnea, and shock. Case 3 describes a 15-month-old boy presenting with dyspnea, stridor, shock, angioedema, urticaria, and cyanosis. Case 4 describes an 18-month-old girl presenting with urticaria, angioedema, cyanosis, and erythema, who was found to have a positive skin test to the vaccine. Case 5 describes a 16-month-old boy presenting with dyspnea, urticaria, erythema, and cya-

nosis. Case 6 describes a 14-month-old girl presenting with angioedema, stridor, dyspnea, vomiting, and erythema.

Baxter (1996) reported the vaccination of 200 egg-allergic children with either a measles or a measles, mumps, and rubella vaccine. Three vaccines were used in the study; two using different viral strains than those distributed in the United States. The remaining vaccine included the U.S. viral strains. One 15-month-old patient developed a positive wheal-and-flare response within 10 minutes of the skin prick test. The patient also developed a local reaction with urticarial lesions, hypotension, diarrhea, and irritability within 10 minutes of the intradermal test. The vaccine eliciting the response was not indicated.

Bohlke et al. (2003) studied anaphylaxis postvaccination using records from participants in the VSD from 1991 through 1997. The authors report three cases of anaphylaxis in patients receiving a measles, mumps, and rubella vaccine out of 848,945 doses administered. Case 1 (case 2 in the report) describes a 16-month-old presenting with wheezing, tachycardia, rash, and erythema within 1 hour after vaccination with MMR. The two other children (cases 3 and 5 in the report) presented with symptoms consistent with anaphylaxis but received vaccines in addition to MMR.

Erlewyn-Lajeunesse et al. (2008) reported two cases of anaphylaxis after administration of a rubella vaccine containing the RA 27/3 rubella strain and one case after administration of a measles vaccine containing the Schwarz strain. Case 1 describes a 15-month-old presenting with cyanosis, tachypnea, and angiodema less than 15 minutes after vaccination with the Schwarz-containing measles vaccine. Case 2 describes an 18-month-old presenting with stridor, erythema, and vomiting less than 5 minutes after vaccination with rubella vaccine. Case 3 describes a 20-month-old presenting with wheezing, cough, vomiting, and a flushed feeling less than 5 minutes after rubella vaccination.

Fasano et al. (1992) reported two cases of anaphylaxis after administration of a measles, mumps, and rubella vaccine in individuals with no history of allergy to egg or chicken meat. Case 1 describes an 8-year-old girl presenting with facial edema, throat tightening, hypotension, and wheezing 15 minutes after vaccination. Postvaccination the patient developed positive responses to intradermal tests against the MMR, measles, mumps, and rubella vaccines. The patient did not develop a response to either an intradermal test against neomycin or skin prick tests against the MMR, measles, mumps, and rubella vaccines and egg. Laboratory tests showed a serum IgE level of 57 IU/L. Case 2 describes a 10-year-old boy presenting with facial edema, wheezing, and generalized urticaria within 5 minutes after vaccination. Postvaccination the patient developed a positive response to skin prick tests against the MMR, measles, mumps, and rubella vaccines. The patient did not develop a response to skin prick tests against egg or

neomycin. Laboratory tests showed a serum IgE level of 583 IU/L and an anti-MMR IgE level of 0.088 ng/ml. In addition, the patient developed mild wheezing after vaccination against MMR at 15 months of age.

Giampietro et al. (1993) reported one case of anaphylaxis developing after administration of a measles vaccine containing the Edmonston-Zagreb strain. The patient was a 2-year-old boy presenting with severe dyspnea, lip cyanosis, and rhinoconjunctivitis within a few minutes after vaccination. The patient developed positive responses to skin prick tests against cow's milk and egg prior to vaccination.

Herman et al. (1983) reported two cases of anaphylaxis developing after administration of MMR vaccine. Case 1 describes a 15-month-old boy, with a history of egg sensitivity, presenting with angioedema, respiratory difficulty, and generalized urticaria within 1 minute after vaccination. Case 2 describes a 15-month-old boy, with a history of egg hypersensitivity, presenting with wheezing, angioedema, and generalized urticaria within 2 minutes after vaccination. Both patients were found to have IgE antibodies to ovalbumin, measles vaccine, and MMR vaccine.

Kelso et al. (1993) described a 17-year-old girl presenting with pruritus, hives, swelling of the hands and face, rhinorrhea, and the sensation of choking 10 minutes after vaccination against measles, mumps, and rubella. The patient was treated with epinephrine and diphenhydramine leading to some resolution of the hives and swelling. The patient complained of throat tightness 90 minutes later. The patient had positive responses to skin prick tests against the MMR vaccine and unflavored number one, lime, cherry, and orange gelatins. Furthermore, laboratory tests showed elevated levels of IgE antibodies to gelatin and the MMR vaccine.

Patja et al. (2001a) performed a prospective follow-up of adverse events reported to a passive surveillance system in Finland from November 1982 through December 1996. Out of 2.99 million doses of the MMR vaccine administered, 18 cases of anaphylaxis developing within 15 minutes after vaccination were identified. Eight cases of anaphylaxis developed after the first dose of vaccine while 10 developed after the second dose. Laboratory tests showed IgE antibodies to gelatin in two patients, IgE antibodies to egg in one patient, and IgE antibodies to chicken in one patient. These cases were also reported in a study by Patja et al. (2000), using data from the same passive surveillance system in Finland.

Pool et al. (2002) identified 57 patients in the Vaccine Adverse Event Reporting System (VAERS) database from 1991 through 1997 who developed anaphylaxis after MMR or measles vaccination. The authors reported that 34 individuals had a history of sensitivity to food, environmental allergens, or drugs. Twenty-two cases provided a serum sample for IgE testing. Of these, 2 received a measles single antigen vaccine alone, 11 received MMR vaccine alone, and 9 received MMR with one or two other



vaccines. Five individuals received the first dose of vaccine without incident. Six cases in which a measles vaccine or an MMR vaccine was administered alone were reported in detail. Case 1 described a 4-year-old boy, with a history of egg allergy, presenting with facial flushing, hypotension, cough without wheezing, and hives within 10 minutes after receiving an MMR vaccine. Laboratory tests on the patient's serum showed IgE antibodies to egg and gelatin. Case 2 described a 17-year-old girl presenting with wheezing, trouble swallowing, and swollen lips within 2 minutes after receiving an MMR vaccine. The patient's serum showed IgE antibodies to gelatin. Case 3 described a 12-year-old boy presenting with rhinorrhea, sneezing, hives, and tachycardia within 10 minutes after receiving an MMR vaccine. The patient's serum was positive for antigelatin IgE. Case 10 described a 15-year-old girl, with a history of allergies to pork and lamb, presenting with a rash on the neck and abdomen, edema, redness of the face, coughing, and an itchy throat 15 minutes after receiving an MMR vaccine. The patient's serum was positive for IgE antibodies to measles. Case 13 described a 15-month-old boy presenting with generalized flushing, facial edema, and upper body urticaria immediately after receiving an MMR vaccine and 5 minutes after receiving a HiB vaccine. The patient's serum showed antigelatin IgE. Case 14 described a 23-year-old man presenting with visual disturbances, numbness to the lips, flushing, and difficulty swallowing 30 minutes after receiving a measles vaccine. The patient's serum showed antigelatin IgE.

Puvvada et al. (1993) reported two cases of systemic reactions developing after intradermal testing with a measles, mumps, and rubella vaccine. Case 1 described an 11-month-old boy, with a history of sensitivity to egg, presenting with generalized urticaria and pruritus after undergoing an intradermal test using a 1:100 dilution of a measles, mumps, and rubella vaccine. Case 2 described a 22-month-old girl, with a history of egg allergy, presenting with dyspnea and wheezing within 30 minutes of undergoing an intradermal test using a 1:100 dilution of a measles, mumps, and rubella vaccine.

Additional publications reported humoral or cellular immune responses to gelatin in patients developing anaphylaxis after administration of a vaccine containing measles, mumps, and rubella alone or in combination; the vaccines contained viral strains not used in vaccines distributed in the United States (Kumagai et al., 1997; Sakaguchi et al., 1997, 1999a,b). Kumagai et al. (1997) reported the development of gelatin-specific humoral and cellular immune responses in six patients developing anaphylactic symptoms postvaccination. Laboratory tests showed all six patients developed positive IgE responses to gelatin and positive responses to a gelatin-specific IL-2 responsiveness assay.

Sakaguchi et al. (1997) reported that one patient (case 2 in the report) had antigelatin IgE when tested immediately after developing anaphylactic symptoms after a measles vaccination. The authors also report that a sec-

ond patient (case 3 in the report) had a high level of antigelatin IgE when tested 8 days after developing anaphylactic symptoms after a mumps vaccination. Furthermore, both patients were positive for IgE antibodies to egg white; however, the levels changed little during the observation period.

Sakaguchi et al. (1999b) reported on the reactivity of IgE to the  $\alpha 1$  and  $\alpha 2$  chains of bovine type I collagen. The authors reported that 10 patients who developed symptoms of anaphylaxis after a measles, mumps, or rubella vaccination were positive for IgE to gelatin and to type I collagen. Furthermore, IgE from all 10 patients reacted with the  $\alpha 2$  chain and not the  $\alpha 1$  chain.

Sakaguchi et al. (1999a) reported on the reactivity of IgE from 10 bovine-gelatin-sensitive children that developed anaphylaxis postvaccination. Most of the children had IgE specific to porcine gelatin as well as other mammals. Furthermore, sera from three children were used to sensitize mast cells. After sensitization the mast cells released histamine upon challenge with bovine gelatin.

Hori et al. (2002) used serum samples from 15 patients with systemic immediate type reactions, including anaphylaxis postvaccination, to analyze the binding sites of IgE to the  $\alpha 2$  chain in bovine type I collagen. The authors used IgE–enzyme-linked immunosorbent assay (ELISA) inhibition to delineate a 10–amino acid sequence in the  $\alpha 2$  chain as the minimum IgE epitope of gelatin allergen.

### *Weight of Mechanistic Evidence*

The publications described above presented clinical and experimental evidence sufficient for the committee to conclude the vaccine was a contributing cause of anaphylaxis after administration of vaccines containing measles, mumps, and rubella alone or in combination. The clinical descriptions provided in many of the publications establish a strong temporal relationship between administration of the vaccine and the anaphylactic reaction. In addition, several publications report evidence of allergy or IgE sensitivity to gelatin providing mechanistic evidence for the cause of the reaction in some patients. Gelatin in the MMR vaccine distributed in the United States is in a hydrolyzed form; the extent to which gelatin is hydrolyzed could vary from one vaccine lot to another and affect the development of anaphylaxis. Some patients are allergic to either bovine or porcine gelatin, but not both (Bogdanovic et al., 2009). Although there is considerable cross-reactivity between bovine and porcine gelatin, testing for antibody to one gelatin alone is not necessarily predictive of allergy to the other and may not be predictive of reactivity to the gelatin in MMR vaccine.

*The committee assesses the mechanistic evidence regarding an association between MMR vaccine and anaphylaxis as strong based on*

*43 cases<sup>5</sup> presenting temporality and clinical symptoms consistent with anaphylaxis.*

### Causality Conclusion

**Conclusion 4.19:** The evidence convincingly supports a causal relationship between MMR vaccine and anaphylaxis.

## TRANSIENT ARTHRALGIA IN WOMEN

### Epidemiologic Evidence

The committee reviewed five studies to evaluate the risk of transient arthralgia in women after the administration of rubella vaccine. One controlled study (Polk et al., 1982) had very serious methodological limitations that precluded its inclusion in this assessment. Polk et al. (1982) selected controls from a different population than the exposed group and provided limited detail on the selection criteria.

The four remaining controlled studies (Mitchell et al., 1998; Ray et al., 1997; Slater et al., 1995; Tingle et al., 1997) were included in the weight of epidemiologic evidence and are described below.

Slater et al. (1995) conducted a retrospective cohort study in women enrolled from 1985 through 1990 in the Ministry of Health Mother-Child Health (MHC) stations in Israel. The exposed group was composed of 485 women who received RA 27/3 strain rubella vaccine postpartum because of absent or nonprotective antibody titers. The control group included 493 women who were not vaccinated postpartum because of adequate antibody levels. The control group was selected from the same MHC stations and matched with vaccinated women for neighborhood of residence, date woman gave birth, and age. However, there were ethnic differences between the exposed and control groups. Telephone interviews were completed during 1992–1993 to evaluate the onset of joint symptoms within 4 months of vaccination; women reporting symptoms were invited to participate in personal interviews. Since interviews were conducted several years after vaccination, one limitation of this study was the dependence on subject recall to report symptoms. During the study period, four cases of arthralgia were reported among the exposed group (0.8 percent), compared to three cases in the control group (0.6 percent). The differences were not statistically significant. The authors concluded that no association was present

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<sup>5</sup>Some cases were from passive surveillance systems; however, it was not possible to know how many represented unique cases or were reported elsewhere.

between vaccination with RA 27/3 strain rubella and the development of arthralgia in postpartum women.

Ray et al. (1997) conducted a retrospective cohort study in women (aged 15 to 59 years) enrolled in the Northern California Kaiser Permanente Health Plan. Medical records were reviewed to identify women who had serological testing for rubella IgG antibody from 1990 through 1991, and received rubella vaccine within 1 year of testing. A total of 971 seronegative, vaccinated women were defined as the exposed group. The authors identified two control groups for comparison: 2,421 seropositive, unvaccinated women served as age-matched controls, and 924 seronegative, unvaccinated women were used as unmatched controls. Arthropathies or joint complaints (labeled as acute, chronic, or traumatic, but not defined in the study) were identified in inpatient and outpatient records, and confirmed by a rheumatologist. No significant differences in the prevalence of arthropathies were found between the exposed group and either comparison group. Of the five conditions reported in the vaccine group, four were labeled as acute arthralgia and one was indeterminate. Only one acute event was seen in the seropositive, unvaccinated control group. The authors concluded that vaccination with RA 27/3 strain rubella does not appear to increase the prevalence of acute arthropathies in women, but they noted the study's limitation to detect mild symptoms for which women are less likely to seek medical care.

Tingle et al. (1997) conducted a double-blind, randomized controlled trial in rubella-seronegative women living in Vancouver, Canada. A total of 546 postpartum women (0–12 weeks postpartum) were enrolled in the study from 1989 through 1992. The women were randomly assigned to receive live attenuated monovalent RA 27/3 strain rubella-virus vaccine (270 participants) or saline placebo (276 participants). The presence of arthropathy was evaluated 4 weeks and 12 months after vaccination with a home visit from a research nurse, and also by telephone at 3, 6, and 9 months after vaccination. The odds ratio for the frequency of acute arthralgia or arthritis among postpartum women receiving RA 27/3 strain rubella vaccine compared to placebo was 1.73 (95% CI, 1.17–2.57). Acute arthralgia was reported in 21 and 16 percent of women receiving rubella vaccine and placebo, respectively. The authors concluded that rubella vaccine was significantly associated with the development of acute arthralgia in postpartum women.

Mitchell et al. (1998) conducted a post-hoc analysis of the data provided in Tingle et al. (1997). The study explored the influences of immunogenetic background on the development of acute arthropathy (arthralgia and arthritis) in postpartum women receiving RA 27/3 strain rubella vaccine. Genetic typing for HLA-DR was performed for 283 of the original 313 white women that were enrolled in the vaccine and placebo groups.

This subgroup analysis revealed that higher frequencies of DR2 (OR, 4.8; 95% CI, 1.2–18.8) and DR5 (OR, 7.5; 95% CI, 1.5–37.5) were associated with an increased risk of women developing acute arthropathy after rubella vaccine during the postpartum period. The authors concluded that certain DR2 and DR5 alleles may influence the development of acute arthropathy in postpartum women receiving rubella vaccine.

### *Weight of Epidemiologic Evidence*

Of the four studies described above, Tingle et al. (1997) most influenced the committee's judgment. The randomized trial by Tingle et al. (1997) involved active monitoring of subjects in the month following the injection, and found a statistically significant increase in the rate of acute arthralgia among the immunized group. The studies by Ray et al. (1997) and Slater et al. (1995) did not find a significant increased risk of acute arthralgia in the immunized group, but since the studies did not conduct active monitoring of the subjects they could easily have failed to recognize the presence of this symptom. See Table 4-7 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has a moderate degree of confidence in the epidemiologic evidence based on four studies with sufficient validity and precision to assess an association between rubella vaccine and transient arthralgia in women; these studies generally report an increased risk.*

*The epidemiologic evidence is insufficient or absent to assess an association between measles or mumps vaccine and transient arthralgia in women.*

### **Mechanistic Evidence**

The committee identified 16 publications describing transient arthralgia in women after the administration of vaccines containing measles and rubella alone or in combination. Harcourt et al. (1979) did not find a correlation between the development of joint symptoms and human leukocyte antigens after rubella vaccination. Five publications did not provide evidence beyond temporality and therefore did not contribute to the weight of mechanistic evidence (Dudgeon et al., 1969; Grillner et al., 1973; Seager et al., 1994; Tingle et al., 1986, 1989). Two publications reported symptoms of arthralgia after vaccination but did not differentiate between men and women (Freestone et al., 1971; Simon et al., 2007). Three publications reported symptoms of arthralgia but did not indicate the duration

**TABLE 4-7** Studies Included in the Weight of Epidemiologic Evidence for MMR Vaccine and Transient Arthralgia in Women

| Citation             | Operationally Defined Outcome                       | Study Setting                             | Defined Study Population   | Study Design         | Sample Size                                    | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)  | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|----------------------|---|---|--|----------------------|--|---|---|--|
| Slater et al. (1995) | Joint symptoms reported during telephone interviews | Ministry of Health MHC Stations in Israel | Postpartum women enrolled from 1985–1990<br>Exposed group received rubella vaccine postpartum because of absent or nonprotective antibody titers | Retrospective cohort | 485 vaccinated women<br>493 unvaccinated women | Vaccinated: four cases of arthralgia (0.8%)<br>Unvaccinated: three cases of arthralgia (0.6%)<br>Differences were not statistically significant | None described                                      | Serious  |
|                      |   |   | Control group was not vaccinated postpartum because of adequate antibody levels  |                      |  |   |   |  |

*continued*

TABLE 4-7 Continued

| Citation             | Operationally Defined Outcome  | Study Setting                                     | Defined Study Population   | Study Design                              | Sample Size   | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)   | Heterogeneous Subgroups at Higher Risk <sup>b</sup>             | Limitations (Negligible or Serious) <sup>c</sup> |
|----------------------|--|---|--|---|---|--|---|--|
| Ray et al. (1997)    | Arthropathies or joint complaints (acute, chronic, and traumatic) identified in inpatient and outpatient records and confirmed by a rheumatologist | Northern California Kaiser Permanente Health Plan | Women whose serological testing was performed from 1990 through 1991<br>Exposed group received rubella vaccine within 1 year following testing | Retrospective cohort                      | 971 seronegative, vaccinated women<br>2,421 seropositive, unvaccinated aged-matched controls<br>924 seronegative, unvaccinated unmatched controls | Vaccinated: Four conditions labeled as acute arthralgias and one as indeterminate<br>Seropositive, unvaccinated controls:<br>One acute event | None described  | Negligible                                       |
| Tingle et al. (1997) | Acute and persistent arthropathy (arthralgia or arthritis) evaluated during home visit from a research nurse and by telephone                      | Participating hospitals in Vancouver, Canada      | Postpartum, rubella-seronegative women identified from 4/1/1989 through 4/30/1992  | Double-blind, randomized controlled trial | 268 vaccinated<br>275 received placebo  | OR of acute arthralgia or arthritis within 12 months of rubella vaccination:<br>1.73 (95% CI, 1.17-2.57)                                     | See analysis of HLA-DR genetic typing in Mitchell et al. (1998) | Negligible                                       |

|                        |  |  |  |   |  |  |                |         |
|------------------------|--|--|--|---|--|--|----------------|---------|
| Mitchell et al. (1998) | Genetic typing for HLA-DR was performed for 283 of the original 313 white women that were enrolled in the vaccine and placebo groups | Participating hospitals in Vancouver, Canada | Postpartum, rubella-seronegative, white women identified from 4/1/1989 through 4/30/1992 | Double-blind, randomized controlled trial | Presence of DR2: 41 vaccinated<br>38 received placebo<br>Presence of DR5: 32 vaccinated<br>27 received placebo | OR of acute arthralgia or arthritis within 12 months of rubella vaccination in women expressing DR2: 4.8 (95% CI, 1.2–18.8)<br>OR of acute arthralgia or arthritis within 12 months of rubella vaccination in women expressing DR5: 7.5 (95% CI, 1.5–37.5) | None described | Serious |
|------------------------|--|--|--|---|--|--|----------------|---------|

<sup>a</sup> The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup> The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup> Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.



of symptoms (Gershon et al., 1980; Simon et al., 2007; Zimmerman and Pellitieri, 1994). In addition, Zimmerman and Pellitieri (1994) reported the concomitant administration of vaccines making it difficult to determine which, if any, vaccine could have been the precipitating event. Valensin et al. (1987) was not included in the review because the mean age of the vaccinated individuals was 12 years, and the few patients aged 18 and above were not identified. These reports did not contribute to the weight of mechanistic evidence.

Described below are four publications describing clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Best et al. (1974) studied 36 women who were seronegative by hemagglutination inhibition (HAI) assay who received the RA 27/3 rubella vaccine. The authors reported the development of transient arthralgia in 9 of the 36 seronegative women after vaccination and transient arthritis in 6 of the 36 women. The joint symptoms usually commenced between days 13 and 21. The symptoms lasted as long as 8 days. Thirteen of the 36 subjects were tested for rubella viral excretion by culture of nasal and pharyngeal swabs. Seven of the 13 subjects tested were positive for rubella viral excretion between days 11 and 26.

The study by Mitchell et al. (1998) was described in detail in the epidemiologic evidence section on transient arthralgia in women. All 283 white vaccinees included in this study were seronegative by enzyme immunoassay (EIA) (Abbott) prior to vaccination. Patients developing arthralgia postvaccination expressed higher frequencies of the human leukocyte antigens, DR2, DR5, and DR7, but lower frequencies of DR4 and DR6 compared to the frequency of these alleles in women with arthralgia who had received a placebo, not the rubella vaccine. When examining the frequency of acute arthralgia, subjects with DR1, DR2, DR5, and DR7 had a higher rate of acute arthralgia after rubella vaccination than did subjects with these haplotypes after placebo.

Mitchell et al. (2000) reported the development of acute and chronic arthralgia and arthritis in a subset of 18- to 41-year-old women within 28 days after rubella vaccination, which contained RA 27/3. All the subjects were initially considered seronegative based on a result of  $< 0.999$  in the Rubazyme EIA assay (Abbott Laboratories). Additional testing of the prevaccine samples for the presence of antirubella antibodies found that several subjects had rubella-specific IgG suggesting prior exposure to rubella virus. Of the subjects, the ones who developed acute and chronic arthralgia and arthritis were those who had previously been exposed but had the lowest levels of prevaccine antibodies as measured by the additional techniques. This suggests that the inability to respond to wild-type rubella during previous exposures is associated with arthropathy after the vaccine.

Tingle et al. (1983) reported six cases of transient arthralgia postvaccination with rubella vaccine. None of the patients had been previously

immunized against rubella. All six were seronegative, based on an HAI assay, prior to vaccination but were later found to have had antibodies prevaccination based on an ELISA assay.

### *Weight of Mechanistic Evidence*

Arthritis and arthralgia have been reported to develop as complications in as many as one third of women with wild-type rubella infection (Gershon, 2010b). The committee considers the effects of natural infection one type of mechanistic evidence.

In addition, the four publications described above, when considered together, presented clinical evidence sufficient for the committee to conclude the vaccine may be a contributing cause of transient arthralgia in women. Evidence of direct rubella infection was presented in one case (Best et al., 1974). Furthermore, three publications suggest that host factors may be involved, particularly the inability to mount a robust immune response to rubella and the expression of certain HLA-DR haplotypes in cases of acute arthralgia after rubella vaccination (Mitchell et al., 1998, 2000; Tingle et al., 1983). The failure to differentiate between wild-type and vaccine strains of rubella, where virus was demonstrated, as well as the failure to demonstrate virus in joints, detracted from the weight of evidence.

The isolation of rubella virus, expression of certain HLA-DR haplotypes, and inadequate antibody response after vaccination suggests direct infection to be the mechanism for transient arthralgia in women after rubella vaccination. Autoantibodies, T cells, immune complexes, and complement activation may contribute to arthralgia as well; however, the publications did not provide evidence linking these mechanisms to MMR vaccine.

*The committee assesses the mechanistic evidence regarding an association between rubella vaccine and transient arthralgia in women as intermediate based on clinical evidence and 13 cases.*

*The committee assesses the mechanistic evidence regarding an association between measles or mumps vaccine and transient arthralgia in women as lacking.*

## Causality Conclusion

**Conclusion 4.20:** The evidence favors acceptance of a causal relationship between MMR<sup>6</sup> vaccine and transient arthralgia in women.

<sup>6</sup>The committee attributes causation to the rubella component of the vaccine.

## TRANSIENT ARTHRALGIA IN CHILDREN

### Epidemiologic Evidence

The committee reviewed 12 studies to evaluate the risk of transient arthralgia in children after the administration of vaccines containing measles, mumps, and rubella alone or in combination. Four studies (Bino et al., 2003; D'Souza et al., 2000; Ion-Nedelcu et al., 2001; Vahdani et al., 2005) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations. One controlled study (Black et al., 1976) had very serious methodological limitations that precluded its inclusion in this assessment. Black et al. (1976) conducted a small study (35 participants) that reported arthralgias in 26 percent of the vaccinated group, but only boys were vaccinated in this study and girls were the comparison group.

The seven remaining controlled studies (Benjamin et al., 1992; Davis et al., 1997; dos Santos et al., 2002; Heijstek et al., 2007; LeBaron et al., 2006; Peltola and Heinonen, 1986; Virtanen et al., 2000) contributed to the weight of epidemiologic evidence and are described below.

Peltola and Heinonen (1986) conducted a double-blind, controlled crossover study in 581 twin pairs who received MMR vaccine from November 1982 through October 1983 in Finland. The vaccines were color-coded and administered blind to the participants (aged 14 months to 6 years). One twin of each pair received vaccine at the first visit, then was given placebo 3 weeks later; similarly, one twin received placebo at the first visit and vaccine 3 weeks later. The participants were given color-coded questionnaires at both visits and asked to report any symptoms for 21 days following vaccine or placebo administration. The maximum difference in rate of arthropathy between the MMR vaccine and placebo groups was 0.8 percent (95% CI, 0.2–1.3%), with a peak frequency 7 to 9 days after vaccination. The authors noted the sample size was powered to detect low frequencies of adverse events, but rare reactions were difficult to study with this small sample.

Virtanen et al. (2000) conducted a reanalysis of the double-blind, controlled crossover study from Peltola and Heinonen (1986). In the reanalysis, adverse events from the questionnaires were reported in two age groups: group 1 included twins 14–18 months of age, and group 2 included twins 6 years of age. The adjusted odds ratio for arthralgia in the 14- to 18-month age group within 21 days following MMR vaccination was 3.66 (95% CI, 1.74–7.70). Arthralgia was also associated with MMR vaccination in the 6-year age group, but an odds ratio was not provided.

Benjamin et al. (1992) conducted a retrospective cohort study in children from the South Manchester Health District of the United Kingdom.

The exposed group included 1,588 children who received MMR vaccine during July 1989 through February 1990. The control group was composed of 1,242 children eligible for MMR vaccination during this same period but who remained unvaccinated. The parents of the vaccinated children were sent a self-report questionnaire 6 weeks after the vaccination date and were asked to describe any joint symptoms. The same questionnaire was sent to parents of the control group. If a parent reported one or more joint symptoms within the last 6 weeks, the child was visited at home by a clinician and the parent's responses were validated. The clinician was aware of the child's vaccination status, and the authors note this could have introduced bias in the diagnosis of arthralgia. The vaccinated group and control group achieved a 78 percent and 64 percent response rate, respectively; however, the authors did not compare the characteristics of the excluded children with the remaining study participants. The relative risk of children experiencing arthralgia within 6 weeks of MMR immunization was 4.2 (95% CI, 1.2–14.3). The authors concluded that MMR vaccination was associated with an increased risk of arthralgia in children, but noted the wide confidence interval.

The study by Davis et al. (1997) was described in detail in the section on afebrile seizures. This retrospective cohort study examined the occurrence of joint pain 30 days after MMR vaccination in children (4–6 and 10–12 years of age) enrolled in the GHC and NCK HMOs from March 1991 through December 1994. The 10- to 12-year-olds reported more chart-confirmed visits for joint pain during the risk period (13 cases) compared to the control period (6 cases). The majority of joint pain visits were for acute events. No joint pain visits were reported among the 4- to 6-year-olds in the risk period or control period. The authors concluded that MMR immunization is associated with an increased risk of joint pain in the 10- to 12-year age group.

dos Santos et al. (2002) conducted a double-blind, randomized controlled trial in schoolchildren (6 to 12 years old) selected from 70 public and private schools in Porto Alegre and Santa Maria, Brazil. The participants were randomly separated into four groups: (1) Tresivac was labeled vaccine A and administered to 2,226 children; (2) MMR II was labeled vaccine B and administered to 2,216 children; (3) Trimovax was labeled vaccine C and administered to 2,179 children; and (4) 3,521 children were assigned to a control group that did not receive an MMR vaccine. Vaccines were administered at the schools from August through September 1996. While the students and health professionals were blind to the type of vaccine, the control group was not blinded and was aware of the group assignment. Nurses visited the schools daily over 30 days and recorded any clinical events observed in the vaccinated or control groups. Home and hospital visits were also used when a student was absent from school. Over

the 30-day period, eight joint reactions were reported in the MMR II group, compared to none reported in the control group. Most of these reactions were transient arthralgia, and 65 percent were reported in women.

LeBaron et al. (2006) conducted a self-controlled case series (case-crossover) study in 1,800 children receiving care at the Marshfield Clinic in Wisconsin. The patients were enrolled prospectively over 2 years and were separated into three age groups: (1) children aged 12 to 24 months who received a first dose of MMR vaccine; (2) children aged 4 to 6 years who received a second dose of MMR vaccine; and (3) children aged 10 to 12 years who received a second dose of MMR vaccine. The family of each participant was given a prevaccination diary that was completed 2 weeks before vaccination, which served as the control period. The risk period was defined as 4 weeks after vaccination, and a postvaccination diary was given to the family to record any symptoms during this time. No significant increases in joint problems were reported in any of the three groups after MMR vaccination. Even though no significant change was reported, the small sample size was inadequate to detect a rare adverse event, and there were limitations in the use of patient diaries.

Heijstek et al. (2007) conducted a retrospective cohort study in patients with juvenile idiopathic arthritis (JIA) born from 1989 through 1996 in the Netherlands. The enrolled patients (8–9 years of age) provided their date of MMR vaccination, and missing dates were obtained from the National Vaccination Institute. Their disease activity was measured by counts of joints with active arthritis, the Physician's Global Assessment scale, and the erythrocyte sedimentation rate. A total of 108 patients received MMR vaccine; 86 patients were eligible but not vaccinated against MMR. The nonadjusted odds ratio for flares in JIA patients within 6 months of MMR vaccination was 1.7 (95% CI, 0.9–3.3). Adjusting for JIA type and medication use by propensity scoring, the adjusted odds ratio for flares within 6 months of MMR vaccination was 1.4 (95% CI, 0.7–2.9). The study also included a self-controlled case series analysis among 207 patients (unknown age range) who received MMR vaccine. The number of flares experienced 6 months before vaccination was compared to the disease activity 6 months after vaccination. Before MMR vaccination, 40 flares occurred in 36 patients, which was lower than the 56 flares reported in 50 patients after vaccination. The authors concluded that the risk of active disease was not significantly increased by MMR vaccination; however, they noted the limitations of a retrospective study design, the limited power to detect a significant association, and the likely presence of residual bias in the data set.

### *Weight of Epidemiologic Evidence*

Of the seven studies considered in this analysis, five had negligible limitations, and two of these (Peltola and Heinonen, 1986; Vertanen et al.,

2000) were analyses of the same controlled crossover study. The studies consistently report an increased risk of transient arthralgia following MMR vaccination in children, with some limitations. The evidence includes (a) the controlled crossover study of twins in Peltola and Heinonen (1986) and Virtanen et al. (2000) that noted an increased risk of arthralgia following vaccination; (b) the retrospective cohort study of Benjamin et al. (1992) with increased risk though wide confidence interval; (c) the retrospective cohort study of Davis et al. (1997) that observed an increased risk of arthralgia following MMR among those 10–12 years of age, but not among the smaller group of children 4–6 years of age studied; and (d) the randomized controlled trial of dos Santos et al. (2002) that observed rare arthralgias but only among the vaccinated group. Two studies that failed to observe an association had low power (Heijstek et al., 2007), limited generalizability (Heijstek—with a focus exclusively on patients with JIA), and limited control for confounding (LeBaron et al., 2006). See Table 4-8 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has a moderate degree of confidence in the epidemiologic evidence based on seven studies with sufficient validity and precision to assess an association between MMR vaccine and transient arthralgia in children; these studies consistently report an increased risk.*

### Mechanistic Evidence

The committee identified seven publications of transient arthralgia in children after the administration of rubella or MMR vaccine. The publications did not provide evidence beyond temporality (Balfour et al., 1976; Bottiger et al., 1974; Cassidy et al., 2005; Poyner et al., 1986; Valensin et al., 1987; Weibel et al., 1980a,b). In addition, Cassidy et al. (2005) reported the concomitant administration of vaccines making it difficult to determine which, if any, vaccine could have been the precipitating event. The publications did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

While rare, arthritis and arthralgia have been reported as a complication of wild-type rubella infection in children (Gershon, 2010b). The committee considers the effects of natural infection one type of mechanistic evidence.

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of arthralgia. Autoantibodies, T cells, immune complexes, direct viral infection, and complement activation may contribute to arthralgia; however, the publications did not provide evidence linking these mechanisms to MMR vaccine.

**TABLE 4-8** Studies Included in the Weight of Epidemiologic Evidence for MMR Vaccine and Transient Arthralgia in Children

| Citation  | Operationally Defined Outcome                            | Study Setting | Defined Study Population  | Study Design                             | Sample Size  | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)   | Heterogeneous Subgroups at Higher Risk <sup>b</sup>                 | Limitations (Negligible or Serious) <sup>c</sup> |
|---|--|---------------|---|--|--|--|---|--|
| Peltola and Heinonen (1986)                         | Self-report of arthropathy symptoms using questionnaires | Finland       | Twin pairs aged 14 months to 6 years who received MMR vaccine from 11/1/1982 through 10/31/1983 | Double-blind, controlled crossover study | 581 twin pairs   | Maximum difference rate of arthropathy between MMR vaccine and placebo groups at 7–9 days after vaccination: 0.8% (95% CI, 0.2–1.3%) | See analysis of the 14–18 month age group in Virtanen et al. (2000) | Negligible                                       |
| Virtanen et al. (2000)                              | Self-report of arthropathy symptoms using questionnaires | Finland       | Twin pairs aged 14 months to 6 years who received MMR vaccine from 11/1/1982 through 10/31/1983 | Double-blind, controlled crossover study | 581 twin pairs, separated into two age groups: 14–18 months and 6 years of age | Adjusted OR of arthralgia in the 14–18 month age group within 21 days of MMR vaccination: 3.66 (95% CI, 1.74–7.70)                   | None described  | Negligible                                       |
| Reanalysis of data from Peltola and Heinonen (1986) |  |               |   |  |  | OR was not provided for 6 year age group   |   |  |

|                        |   |  |  |   |   |   |                |            |
|------------------------|---|--|--|---|---|---|----------------|------------|
| Benjamin et al. (1992) | Joint symptoms identified with self-report questionnaire and confirmed by clinician at a home visit | South Manchester Health District, United Kingdom | Children residing in South Manchester Health District from 7/1989 through 2/1990 | Retrospective cohort  | 1,588 vaccinated<br>1,242 unvaccinated                            | RR of arthralgia within 6 weeks of MMR vaccination: 4.2 (95% CI, 1.2–14.3)  | None described | Negligible |
| Davis et al. (1997)    | Chart-confirmed clinic, emergency department, and hospital visits for joint pain                    | GHC and NCK HMOs from 3/1991 through 12/1994     | Children aged 4–6 years and 10–12 years  | Retrospective cohort<br>Risk period: 1 month after MMR vaccination<br>Control period: began 3 months before MMR vaccination and ended 2 months before vaccination | 18,036 children ages 10–12 years<br>8,514 children ages 4–6 years | 10–12-year-olds: 13 visits for joint pain 1 month after MMR vaccination<br>Six visits for joint pain 3 months before MMR vaccination<br>4–6-year-olds: No visits for joint pain | None described | Negligible |

*continued*



TABLE 4-8 Continued

| Citation                 | Operationally Defined Outcome                                    | Study Setting                        | Defined Study Population   | Study Design   | Sample Size  | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)  | Heterogeneous Subgroups at Higher Risk <sup>b</sup>      | Limitations (Negligible or Serious) <sup>c</sup> |
|--------------------------|--|--------------------------------------|--|--|--|---|--|--|
| dos Santos et al. (2002) | Clinical events observed by nurses who visited the schools daily | Porto Alegre and Santa Maria, Brazil | Schoolchildren aged 6–12 years selected from 70 public and private schools                     | Double-blind, randomized control trial   | 2,216 vaccinated with MMR II<br><br>3,521 unvaccinated | MMR II group:<br>8 joint reactions (primarily transient arthralgia) within 30 days of vaccination<br><br>Control group:<br>No joint reactions | 65 percent of the joint reactions were reported in women | Negligible                                       |
| LeBaron et al. (2006)    | Prospective self-report of joint problems using diaries          | Marshfield Clinic, Wisconsin         | Children aged 12–24 months, 4–6 years, and 10–12 years receiving care at the Marshfield Clinic | Case-crossover<br><br>Risk period: 4 weeks after MMR vaccination<br><br>Control period: 2 weeks before MMR vaccination | 1,800 children   | No significant increases in joint problems were reported in any of the three age groups after MMR vaccination                                 | None described   | Serious  |

|                              |  |             |   |                         |   |  |                   |         |
|------------------------------|--|-------------|---|-------------------------|---|--|-------------------|---------|
| Heijstek<br>et al.<br>(2007) | Disease<br>activity<br>measured by<br>joint counts,<br>Physician's<br>Global<br>Assessment,<br>and<br>erythrocyte<br>sedimentation<br>rate | Netherlands | JJA patients<br>aged 8–9<br>years born<br>from 1989<br>through 1996 | Retrospective<br>cohort | 108<br>vaccinated<br>86<br>unvaccinated | Unadjusted OR<br>of flares within 6<br>months of MMR<br>vaccination:<br><b>1.7 (95% CI,<br/>0.9–3.3)</b> | None<br>described | Serious |
|                              |  |             |   |                         |   | Adjusted OR of<br>flares within 6<br>months of MMR<br>vaccination:<br><b>1.4 (95% CI,<br/>0.7–2.9)</b>   |                   |         |

<sup>a</sup> The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup> The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup> Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.

*The committee assesses the mechanistic evidence regarding an association between rubella vaccine and transient arthralgia in children as weak based on knowledge about the natural infection.*

*The committee assesses the mechanistic evidence regarding an association between measles or mumps vaccine and transient arthralgia in children as lacking.*

### Causality Conclusion

**Conclusion 4.21:** The evidence favors acceptance of a causal relationship between MMR vaccine and transient arthralgia in children.

## CHRONIC ARTHRALGIA IN WOMEN

### Epidemiologic Evidence

The committee reviewed two studies to evaluate the risk of chronic arthralgia in women after the administration of rubella vaccine. These two controlled studies (Ray et al., 1997; Tingle et al., 1997) contributed to the weight of epidemiologic evidence and are described below.

Ray et al. (1997) conducted a retrospective cohort study that is described in detail in the section on transient arthralgia in women. None of the seronegative, vaccinated women were diagnosed with chronic arthropathy during the study period. The authors concluded that vaccination with the RA 27/3 strain of rubella does not appear to increase the prevalence of persistent joint symptoms in women, but noted the sample size limited the ability to assess an association.

The study by Tingle et al. (1997) was described in detail in the section on transient arthralgia in women. The authors defined persistent arthropathy as the “occurrence of arthralgia or arthritis at any time during the 12 months after vaccination in women who experienced acute arthropathy and for whom joint complaints could not be attributed to other causes” (Tingle et al., 1997). This randomized controlled trial reported an odds ratio of 1.59 (95% CI, 1.01–2.45) for the frequency of persistent arthralgia or arthritis among postpartum women receiving rubella vaccine compared to placebo. This comparison included 268 vaccine participants and 275 placebo participants that completed 1 month to 12 months of follow-up. The authors concluded that marginally significant differences of persistent arthralgia or arthritis occurred after rubella vaccination, and a study with more participants would be necessary to establish an association.

*Weight of Epidemiologic Evidence*

The two studies described above had negligible limitations but inconsistent results; one study had limited generalizability. A large retrospective cohort study (Ray et al., 1997) with appropriately defined exposed and control groups found no evidence of an association between immunization and chronic arthropathy. A randomized controlled trial (Tingle et al., 1997) involving a moderate number of postpartum women with careful follow-up by both history and physical examination, and appropriate adjustment for confounders, did find higher rates of persistent arthralgia or arthritis among the immunized group, but the difference was of marginal statistical significance. Additionally, this trial was restricted to one subgroup of women (postpartum period) when the physiologic milieu is quite different from other times in a woman's life. See Table 4-9 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has limited confidence in the epidemiologic evidence, based on two studies that lacked validity and precision to assess an association between rubella vaccine and chronic arthralgia in women.*

*The epidemiologic evidence is insufficient or absent to assess an association between measles or mumps vaccine and chronic arthralgia in women.*

**Mechanistic Evidence**

The committee identified eight publications describing chronic arthralgia in women after the administration of rubella or MMR vaccine. Five publications did not provide evidence beyond temporality and therefore did not contribute to the weight of mechanistic evidence (Boling, 1980; Frenkel et al., 1996; Tingle et al., 1986, 1989; Weibel and Benor, 1996).

Described below are three reports describing clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Mitchell et al. (1993) reported two cases of chronic arthralgia developing after vaccination with rubella strain RA 27/3. Significant in these cases is the finding of rubella virus RNA in the peripheral blood long after vaccination. Case 1 describes a 22-year-old postpartum woman presenting with aching in the wrists that worsened as the day progressed 5–6 weeks after receiving a rubella vaccine. Over the next 3 months the arthralgias evolved to include the neck, elbows, wrists, and knees. Four months postvaccination the patient was hospitalized for fever, diffuse rashes, and worsening joint pain. Serologic studies were negative for cytomegalovirus

**TABLE 4-9 Studies Included in the Weight of Epidemiologic Evidence for MMR Vaccine and Chronic Arthralgia in Women**

| Citation             | Operationally Defined Outcome  | Study Setting                                     | Defined Study Population   | Study Design                           | Sample Size  | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)                                       | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|----------------------|--|---|--|--|--|--|---|--|
| Ray et al. (1997)    | Arthropathies or joint complaints (acute, chronic, and traumatic) identified in inpatient and outpatient records and confirmed by a rheumatologist | Northern California Kaiser Permanente Health Plan | Women whose serological testing was performed from 1990 through 1991   | Retrospective cohort                   | 971 seronegative, vaccinated women<br>2,421 seropositive, unvaccinated aged-matched controls | None of the seronegative, vaccinated women were diagnosed with chronic arthralgia during the study period  | None described                                      | Negligible                                       |
| Tingle et al. (1997) | Acute and persistent arthropathy (arthralgia or arthritis) evaluated during home visit from a research nurse and by telephone                      | Participating hospitals in Vancouver, Canada      | Exposed group received rubella vaccine within 1 year following testing | Double-blind, randomized control trial | 268 vaccinated<br>275 received placebo   | OR of persistent arthralgia or arthritis within 12 months of rubella vaccination: 1.59 (95% CI, 1.01-2.45) | None described                                      | Negligible                                       |

<sup>a</sup> The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup> The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup> Studies designated as serious had more methodologic limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.

and hepatitis B virus, positive for Epstein-Barr virus, and weakly positive for parvovirus B19. The patient did not produce antirubella neutralizing antibodies. Rubella virus RNA was detected by PCR in peripheral blood mononuclear cells 10 months postvaccination. The patient began treatment with prednisone 6 months postvaccination and was asymptomatic 20 months postvaccination. Case 2 describes a 26-year-old woman presenting with an erythematous maculopapular rash on the trunk and extremities followed by fatigue, myalgia, and arthralgias involving the large joints 4 weeks after receiving a rubella vaccine. Serologic tests were negative for hepatitis B virus, cytomegalovirus, and *Borrelia burgdorferi* and showed past infections of Epstein-Barr virus and parvovirus. Rubella virus RNA was detected by PCR in peripheral blood mononuclear cells 8 months postvaccination. The patient began treatment with prednisone 13 months postvaccination; however, the patient was still symptomatic 30 months postvaccination. In neither case was the strain of rubella delineated from the RNA isolated.

Tingle et al. (1985) reported two cases of chronic arthralgia developing postvaccination with rubella strain RA 27/3. Case 1 (number 5 in the article) describes a woman in the postpartum period presenting with polyarthritis 3 weeks after vaccination. Subsequently the patient developed arthralgia involving the shoulders, elbows, wrists, hips, and knees. The patient was followed for 2 years, 9 months. Rubella virus was demonstrated in peripheral blood mononuclear cells 15 months postvaccination. Case 2 (number 6 in the article) describes a woman in the postpartum period presenting with polyarthritis 3 weeks after vaccination. Subsequently the patient developed a continuing arthritis and arthralgia. The patient was followed for 2 years, 2 months. Rubella virus was demonstrated in peripheral blood mononuclear cells and breast milk mononuclear cells 7 and 9 months postvaccination, respectively. Both patients had titers of HAI antirubella antibodies of  $< 1:8$ , but significantly elevated levels of antirubella IgG antibodies prior to vaccination. Furthermore, both patients showed a delayed time course and lower peak hemagglutination inhibition titers than women immunized with the rubella strain HPV-77 DE/5. Two years or more after vaccination the patients' antirubella antibody levels declined to those detected prevaccination. In neither case was the strain of rubella delineated from the virus isolated.

Mitchell et al. (2000) was described in detail in the section on transient arthralgia in women. The authors reported the development of acute and chronic arthralgia and arthritis in a subset of 18- to 41-year-old women within 28 days after rubella vaccination, which contained RA 27/3. The subjects who developed acute and chronic arthralgia and arthritis were those who had previously been exposed but had the lowest levels of prevaccine antibodies as measured by the additional techniques. This suggests that

the inability to respond to wild-type rubella during previous exposures is associated with arthropathy after the vaccine.

### *Weight of Mechanistic Evidence*

It has been reported that as many as one-third of women with a wild-type rubella infection develop arthralgia (Gershon, 2010b). The committee considers the effects of natural infection one type of mechanistic evidence.

The three publications described above, when considered together, presented clinical evidence suggestive but not sufficient for the committee to conclude the vaccine may be a contributing cause of chronic arthralgia in women after vaccination against rubella. Lower peak hemagglutination inhibition titers or the lack of production of antirubella-neutralizing antibodies after vaccination were reported in three cases (Mitchell et al., 1993; Tingle et al., 1985). Furthermore, two publications reported the development of arthralgia postvaccination in women initially thought to be seronegative prior to administration of the vaccine; further tests showed the women had not mounted a robust antibody response to a prior exposure to rubella (Mitchell et al., 2000; Tingle et al., 1985). The isolation of rubella virus or viral RNA > 7 months postvaccination suggests the development of a persistent rubella infection (Mitchell et al., 1993; Tingle et al., 1985). The association of persistent viremia and inadequate antibody formation suggests persistent viral infection to be the mechanism for chronic arthralgia in women after rubella vaccination. The latency between vaccination and the development of arthralgia symptoms in the cases described above ranged from 12 days to 6 weeks.

The failure to differentiate between wild-type and vaccine strains of rubella, where virus was demonstrated, detracted from the weight of evidence. In addition, the publications described above were produced by one group; the results of these studies have not been reported by another group.

Autoantibodies, T cells, immune complexes, and complement activation may contribute to arthralgia as well; however, the publications did not provide evidence linking these mechanisms to MMR vaccine.

*The committee assesses the mechanistic evidence regarding an association between rubella vaccine and chronic arthralgia in women as low-intermediate based on clinical evidence in four cases.*

*The committee assesses the mechanistic evidence regarding an association between measles or mumps vaccine and chronic arthralgia in women as lacking.*

### Causality Conclusion

**Conclusion 4.22:** The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and chronic arthralgia in women.

## CHRONIC ARTHRITIS IN WOMEN

### Epidemiologic Evidence

The committee reviewed two studies to evaluate the risk of chronic arthritis in women after the administration of rubella vaccine. These two controlled studies (Ray et al., 1997; Tingle et al., 1997) contributed to the weight of epidemiologic evidence and are described below.

Ray et al. (1997) conducted a retrospective cohort study that is described in detail in the section on transient arthralgia in women. No cases of chronic arthropathy were diagnosed in the exposed group of seronegative, vaccinated women. Only one case of rheumatoid arthritis was diagnosed in the study population; this case was reported in the seropositive, unimmunized control group. The authors concluded that vaccination with RA 27/3 strain rubella does not appear to increase the prevalence of persistent joint symptoms in women, but noted the sample size may limit the ability to assess an association.

The study by Tingle et al. (1997) was described in detail in the section on transient arthralgia in women. This randomized controlled trial reported an odds ratio of 1.58 (95% CI, 1.01–2.45) for the frequency of persistent arthralgia or arthritis among postpartum women receiving rubella vaccine compared to placebo. The authors concluded that marginally significant differences of persistent arthralgia or arthritis occurred after rubella vaccination, and a study with more participants may be necessary to establish an association.

### *Weight of Epidemiologic Evidence*

The two studies described above had negligible limitations but inconsistent results; one study had limited generalizability. A large retrospective cohort study (Ray et al., 1997) with appropriately defined exposed and control groups found no evidence of an association between immunization and chronic arthropathy. A randomized controlled trial (Tingle et al., 1997) involving a moderate number of postpartum women with careful follow-up by both history and physical examination, and appropriate adjustment for confounders, did find higher rates of persistent arthralgia or arthritis among the immunized group, but the difference was of marginal statisti-



cal significance. Additionally, this trial was restricted to one subgroup of women (postpartum period) when the physiologic milieu is quite different from other times in a woman's life. See Table 4-10 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has limited confidence in the epidemiologic evidence, based on two studies that lacked validity and precision to assess an association between rubella vaccine and chronic arthritis in women.*

*The epidemiologic evidence is insufficient or absent to assess an association between measles or mumps vaccine and chronic arthritis in women.*

### Mechanistic Evidence

The committee identified seven publications describing chronic arthritis in women after the administration of rubella or MMR vaccine. In two publications, chronic arthropathy was not distinguished from chronic arthritis; these publications did not contribute to the weight of mechanistic evidence (Mitchell et al., 2000; Tingle et al., 1989). Three publications did not provide evidence beyond temporality and therefore did not contribute to the weight of mechanistic evidence (Tingle et al., 1986; von Wehren and von Torklus, 1983; Weibel and Benor, 1996).

Described below are two publications describing clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Tingle et al. (1983) reported the development of arthritis involving the metacarpophalangeal joints, wrists, and knees in four women after vaccination with rubella strain RA 27/3. None of the patients had been previously immunized against rubella. All four were seronegative, based on an HAI assay, prior to vaccination but were later found, based on an ELISA assay, to have had antibodies prevaccination. The patients had recurrent episodes of arthritis involving the same joints over a 6-month period after vaccination. The authors pointed out that the patients who developed arthritis had more acute symptoms of infection (posterior cervical lymphadenitis and pharyngitis) than patients who did not develop arthritis.

The case reported by Tingle et al. (1985) was described in detail in the section on chronic arthralgia in women. The authors reported one case of a woman in the postpartum period who developed continuing arthralgia and arthritis after rubella vaccination. The patient was followed for 2 years and 2 months. Rubella virus was demonstrated in peripheral blood mononuclear cells and breast milk mononuclear cells at 7 and 9 months postvac-

**TABLE 4-10** Studies Included in the Weight of Epidemiologic Evidence for MMR Vaccine and Chronic Arthritis in Women

| Citation             | Operationally Defined Outcome  | Study Setting                                     | Defined Study Population   | Study Design                           | Sample Size  | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)  | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|----------------------|--|---|--|--|--|---|---|--|
| Ray et al. (1997)    | Arthropathies or joint complaints (acute, chronic, and traumatic) identified in inpatient and outpatient records and confirmed by a rheumatologist | Northern California Kaiser Permanente Health Plan | Women whose serological testing was performed from 1990 through 1991<br>Exposed group received rubella vaccine within 1 year following testing | Retrospective cohort                   | 971 seronegative, vaccinated women<br>2,421 seropositive, unvaccinated aged-matched controls | None of the seronegative, vaccinated women were diagnosed with chronic arthritis during the study period      | None described                                      | Negligible                                       |
| Tingle et al. (1997) | Acute and persistent arthropathy (arthralgia or arthritis) evaluated during home visit from a research nurse and by telephone                      | Participating hospitals in Vancouver, Canada      | Postpartum, rubella-seronegative women identified from 4/1/1989 through 4/30/1992  | Double-blind, randomized control trial | 268 vaccinated<br>275 received placebo   | OR of persistent arthralgia or arthritis within 12 months of rubella vaccination:<br>1.58 (95% CI, 1.01–2.45) | None described                                      | Negligible                                       |

<sup>a</sup>The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup>The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup>Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.

ination, respectively. Similar to other reports, this patient was determined to be seronegative by HAI prior to vaccination, but further tests showed the patient had prevaccination antibodies to rubella. The patient showed a delayed time course and lower peak hemagglutination inhibition titers after vaccination as compared to other patients receiving the HPV-77 DE/5 rubella vaccine. Two years or more after vaccination the patient's antirubella antibody levels declined to those detected prevaccination.

### *Weight of Mechanistic Evidence*

While rare, chronic arthritis has been associated with wild-type rubella infection (Gershon, 2010b). Rubella has been demonstrated in the joint in cases of acute or recurrent arthritis, as well as from peripheral blood mononuclear cells in cases of chronic arthritis, suggesting persistent rubella infection (Gershon, 2010b). The committee considers the effects of natural infection one type of mechanistic evidence.

The two publications described above, when considered together, presented clinical evidence suggestive but not sufficient for the committee to conclude the vaccine may be a contributing cause of chronic arthritis in women after vaccination against rubella. Evidence of persistent rubella infection in monocytes was presented in one case (Tingle et al., 1985). Furthermore, the cases suggest that a host factor may be involved, particularly, the inability to mount a robust immune response to rubella in six cases. The association of persistent viremia and inadequate antibody response suggests persistent viral infection may be a mechanism for chronic arthritis in women after rubella vaccination. The latency between vaccination and the development of arthritis symptoms in the cases described above ranged from 18 days to 3 weeks.

The failure to differentiate between wild-type and vaccine strains of rubella, where virus was demonstrated, as well as the failure to demonstrate virus in joints, detracted from the weight of evidence. In addition, the publications described above were produced by one group; the results of these studies have not been reproduced by another group.

Autoantibodies, T cells, immune complexes, and complement activation may contribute to arthritis as well; however, the publications did not provide evidence linking these mechanisms to MMR vaccine.

*The committee assesses the mechanistic evidence regarding an association between rubella vaccine and chronic arthritis in women as low-intermediate based on clinical evidence in five cases.*

*The committee assesses the mechanistic evidence regarding an association between measles or mumps vaccine and chronic arthritis in women as lacking.*

### Causality Conclusion

**Conclusion 4.23:** The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and chronic arthritis in women.

## CHRONIC ARTHROPATHY IN CHILDREN

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of chronic arthropathy (arthralgia or arthritis) in children after the administration of MMR vaccine.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between MMR vaccine and chronic arthropathy in children.*

### Mechanistic Evidence

The committee identified five publications describing chronic arthropathy in children after the administration of vaccines containing measles, mumps, and rubella alone or in combination. Two publications did not provide evidence beyond temporality (Balfour et al., 1980; Bottiger et al., 1974). In addition, the patient described in Bottiger et al. (1974) developed symptoms following strep throat. Since it is well appreciated that streptococcal infection can cause joint symptoms, it is not possible to solely attribute the symptoms in this individual to the rubella vaccine. Borte et al. (2009) did not observe exacerbation of juvenile idiopathic arthritis after MMR vaccination. These publications did not contribute to the weight of mechanistic evidence.

Described below are two publications reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Peters and Horowitz (1984) report one case of a 10-year-old girl presenting with lower extremity pain 1 week after receiving a measles and rubella vaccine. Subsequently, the patient developed bilateral thigh pain, fever, and a macular rash over the anterior trunk. Eight months postvaccination laboratory tests showed hemagglutination titers of 1:32 and 1:8 for rubella and measles, respectively, and an IgM specific rubella antibody titer of < 1:4. The patient had recurrent symptoms over 4 years leading to a diagnosis of pauciarticular juvenile rheumatoid arthritis.

Geiger et al. (1995) reported the case of a 16-year-old boy, diagnosed

with acute lymphoblastic leukemia, who was undergoing maintenance treatment with methotrexate and 6-mercaptopurine when he was inadvertently given the rubella vaccine. This patient had been seronegative prior to chemotherapy 15 months earlier. Fifty-one days after vaccination, the patient presented with arthritis of the wrist, metacarpophalangeal, carpal, proximal, and distal interphalangeal joints. The arthritis resolved over 8 weeks with therapy. Nucleic acid specific for rubella was detected in whole blood and in stimulated and unstimulated mononuclear cells obtained 8 months after vaccination. The test for rubella nucleic acid involved reverse transcription followed by nested PCR. Sequence analysis was not performed to determine if the nucleic acid was from wild-type or vaccine virus.

### *Weight of Mechanistic Evidence*

While rare, arthritis and arthralgia have been reported as a complication of wild-type rubella infection in children (Gershon, 2010b). The committee considers the effects of natural infection one type of mechanistic evidence.

The publications, described above, did not present clinical evidence sufficient for the committee to conclude the vaccine may be a contributing cause of chronic arthropathy in children. The failure to differentiate between wild-type and vaccine strains of rubella, where virus was demonstrated, as well as the failure to demonstrate virus in the joints, detracted from the weight of evidence.

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of chronic arthropathy. Autoantibodies, T cells, immune complexes, persistent viral infection, and complement activation may contribute to chronic arthropathy; however, the publications did not provide evidence linking these mechanisms to MMR vaccine.

*The committee assesses the mechanistic evidence regarding an association between rubella vaccine and chronic arthropathy in children as weak based on knowledge about the natural infection and two cases.*

*The committee assesses the mechanistic evidence regarding an association between measles or mumps vaccine and chronic arthropathy in children as lacking.*

### Causality Conclusion

**Conclusion 4.24:** The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and chronic arthropathy in children.

## ARTHROPATHY IN MEN

### Epidemiologic Evidence

The committee reviewed four studies to evaluate the risk of arthropathy in men after the administration of rubella or MMR vaccine. Two studies (Geier and Geier, 2001; Stetler et al., 1985) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

Two controlled studies (Chen et al., 1991; Pattison et al., 2008) were included in the weight of epidemiologic evidence and are described below.

Chen et al. (1991) conducted a retrospective cohort study of undergraduate students living in dormitories at Boston University (BU) and Massachusetts Institute of Technology (MIT) in March 1985. As a result of a measles outbreak, an increased number of students were vaccinated with MMR from February through March 1985. Self-administered questionnaires were used to determine the incidence of adverse events after MMR vaccination at BU and MIT. Only students vaccinated at BU or MIT were included in the exposed group (401 and 133, respectively); those vaccinated by a private physician, with a history of measles disease, or unknown vaccination status were excluded. The remaining students not vaccinated during the measles outbreak served as the control group at BU (391 students) and MIT (352 students). The study had multiple limitations including a low survey response rate (62 percent of BU students and 31 percent of MIT students), inadequate definition of exposed and control groups, and reliance on self-reported data. The authors concluded that the incidence of joint swelling, or joint ache or pain, was not increased among students vaccinated with MMR or measles, compared to respective controls.

Pattison et al. (2008) conducted a case-control study in 125 patients with psoriatic arthritis and 163 psoriasis controls in the United Kingdom. The cases were identified through a nationwide campaign and confirmed by local consultant rheumatologists, whereas controls were recruited from the Psoriasis Clinic at the Dermatology Centre, Hope Hospital, Salford. The psoriatic arthritis patients experienced their first joint swelling within 5 years of the start of the study. A self-report questionnaire was sent to the cases and controls to assess exposures in the 10 years before disease onset; 82.7 percent of the cases and 50.0 percent of the controls responded to the questionnaire. The authors reported an increased risk of psoriatic arthritis after rubella vaccination (OR, 12.4; 95% CI, 1.20–122.14); however, these results were not generalizable to men.

*Weight of Epidemiologic Evidence*

The two studies described above had serious limitations and low precision. One study by Pattison et al. (2008) found an association but studied men with psoriasis, and thus the results could not be generalized to all men. The study by Chen et al. (1991) found no association. See Table 4-11 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has limited confidence in the epidemiologic evidence, based on two studies that lacked validity and precision, to assess an association between MMR vaccine and arthropathy in men.*

**Mechanistic Evidence**

The committee identified four publications of chronic or transient arthropathy in men after the administration of vaccines containing measles, mumps, and rubella alone or in combination. Two publications did not provide evidence beyond temporality (Seager et al., 1994; Weibel and Benor, 1996). Two publications reported symptoms of arthralgia after vaccination but did not differentiate between men and women (Freestone et al., 1971; Simon et al., 2007). These publications did not contribute to the weight of mechanistic evidence.

*Weight of Mechanistic Evidence*

While rare, arthritis and arthralgia have been reported as complications of wild-type rubella infection in men (Gershon, 2010b). The committee considers the effects of natural infection one type of mechanistic evidence.

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of arthropathy. Autoantibodies, T cells, immune complexes, direct viral infection, persistent viral infection, and complement activation may contribute to arthropathy; however, the publications did not provide evidence linking these mechanisms to MMR vaccine.

*The committee assesses the mechanistic evidence regarding an association between rubella vaccine and arthropathy in men as weak based on knowledge about the natural infection.*

*The committee assesses the mechanistic evidence regarding an association between measles or mumps vaccine and arthropathy in men as lacking.*

TABLE 4-11 Studies Included in the Weight of Epidemiologic Evidence for MMR Vaccine and Arthropathy in Men

| Citation               | Operationally Defined Outcome  | Study Setting            | Defined Study Population   | Study Design | Sample Size   | Primary Effect  |  |
|------------------------|--|--------------------------|--|--------------|---|---|--|
|                        |  |                          |  |              |   | Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)                                       | Limitations (Negligible or Serious) <sup>c</sup> |
| Chen et al. (1991)     | Joint swelling or joint ache/pain identified with self-administered questionnaires | BU and MIT during 3/1985 | Undergraduate students living in dormitories at BU or MIT<br>Exposed group included students who received MMR or measles vaccine on their college campus                                   | Cohort       | BU:<br>401 vaccinated<br>391 unvaccinated<br>MIT:<br>133 vaccinated<br>352 unvaccinated | No increased risk of joint swelling or joint ache/pain following MMR or measles vaccination | None described<br>None described<br>Serious      |
| Pattison et al. (2008) | Psoriatic arthritis confirmed by local consultant rheumatologists                  | United Kingdom           | Cases: Psoriatic arthritis patients identified by nationwide campaign<br>Controls: Psoriasis patients identified at the Psoriasis Clinic at the Dermatology Centre, Hope Hospital, Salford | Case-control | 125 patients with psoriatic arthritis<br>163 patients with psoriasis                    | OR for psoriatic arthritis after rubella vaccination:<br>12.4 (95% CI, 1.20–122.14)         | None described<br>Serious                        |

<sup>a</sup> The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup> The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup> Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.



### Causality Conclusion

**Conclusion 4.25:** The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and arthropathy in men.

### TYPE 1 DIABETES

#### Epidemiologic Evidence

The committee reviewed eight studies to evaluate the risk of type 1 diabetes after the administration of MMR vaccine. One study (Fescharek et al., 1990) was not considered in the weight of epidemiologic evidence because it provided data from a passive surveillance system and lacked an unvaccinated comparison population. Two controlled studies (Karavanaki et al., 2008; Telahun et al., 1994) had very serious methodological limitations that precluded their inclusion in this assessment. Karavanaki et al. (2008) and Telahun et al. (1994) conducted case-control studies in diabetic children and hospital controls using a self-report questionnaire, but did not validate vaccination histories with medical records or adequately adjust for age or date of diagnosis.

The five remaining controlled studies (Altobelli et al., 2003; Blom et al., 1991; DeStefano et al., 2001; Hviid et al., 2004; Patterson, 2000) contributed to the weight of epidemiologic evidence and are described below.

Blom et al. (1991) conducted a case-control study in diabetic children (0 to 14 years of age) enrolled in the Swedish Childhood Diabetes Register from September 1985 through August 1986. A total of 393 children with type 1 diabetes were matched to 786 controls (two controls for each case matched on age, sex, and county) from the official Swedish population register. The dates of vaccination were ascertained from questionnaires that were sent to the parents of cases and their matched controls within 4 weeks of disease diagnosis. Questionnaires were returned for 86 percent of the cases and 67 percent of the controls. There were no systematic differences in the age, sex, and county categories of those that returned the questionnaire compared to those that did not, but other factors that were not reported in the study could suggest selection bias. Self-report vaccination data were compared to vaccination records from the local child health care centers and school health units. The authors were able to validate the vaccination status of 88.5 percent and 82.1 percent of the cases and controls, respectively. Since the relative risk ratio of matched and unmatched data remained close to 1, the case and control matching was removed to avoid losing information during the analysis. The odds ratio for diabetes diagnosis any time after vaccination was assessed for MMR vaccine, 0.95 (95% CI, 0.71–1.28); measles vaccine, 0.74 (95% CI, 0.55–1.00); mumps

vaccine, 1.75 (95% CI, 0.54–5.70); and rubella vaccine, 1.24 (95% CI, 0.41–3.73). The authors concluded that MMR vaccine does not increase the risk of type 1 diabetes in children, and measles vaccine may have a protective effect that should be investigated.

Patterson (2000) conducted a case-control study in children (under 15 years of age) with type 1 diabetes enrolled at seven centers participating in the EURODIAB ACE Group from 1989 to 1995. Controls were selected at each center from population registers, general practitioners' lists, or school rolls, and matched to cases by age. Of the 1,028 cases and 3,044 controls invited to participate in the study, 900 (87.5 percent) and 2,302 (75.6) responded, respectively. The authors did not provide any information on the nonresponders. Vaccination data were obtained from parent interviews or questionnaires depending on the center, and were validated with official records or child health care booklets in 74 percent of the cases and 78 percent of the controls. A diagnosis date was assigned to each control based on the midpoint of the recruitment period for the corresponding diabetic child. The Mantel Haenszel approach was used to stratify the analysis by center, and the odds ratio for diabetes diagnosis any time after rubella vaccination was 1.18 (95% CI, 0.91–1.53). A logistic regression analysis was used to adjust for confounding variables, and the odds ratio for diabetes diagnosis any time after rubella vaccination was 1.27 (95% CI, 0.93–1.72). The authors concluded that administration of rubella vaccine does not increase the risk of type 1 diabetes in children.

DeStefano et al. (2001) conducted a case-control study in children (10 months to 10 years of age) enrolled in four HMOs participating in the VSD. A total of 252 type 1 diabetes cases and 768 matched controls were included in the analysis. The study required participants to be born from 1988 through 1997, enrolled in the HMO since birth, and continuously enrolled for the first 6 months of life. Additionally, cases had to be enrolled at least 12 months before the diabetes diagnosis except when diagnosis occurred before 12 months of age. The case index date was defined as the first date of type 1 diabetes diagnosis in the medical record; controls were assigned the same index date as their matched case. At least three controls were matched to each case on sex, date of birth (within 7 days), HMO, and length of enrollment in the HMO (up to the index date). Trained chart abstractors obtained complete vaccination histories from the medical records of the cases and controls. Vaccination histories were similar for the cases and controls with 92.1 percent and 90.6 percent exposed to MMR vaccine, respectively. The results of two conditional logistic regression models were provided: Model 1 stratified by the matching variables; Model 2 stratified by the matching variables and race, ethnicity, and family history of type 1 diabetes (additional variables also obtained from medical records). The odds ratio for diabetes diagnosis any time after MMR vaccination using

Model 1 was 1.36 (95% CI, 0.70–2.63) and using Model 2 was 1.43 (95% CI, 0.71–2.86). The authors concluded that vaccination with MMR does not increase the risk of type 1 diabetes in children.

Altobelli et al. (2003) conducted a case-control study in children (under 15 years of age) with type 1 diabetes enrolled in the diabetes register of the Abruzzo region of Italy from 1990 through 1996. A total of 136 cases (52.9 percent men and 47.1 percent women) and 272 controls (50.7 percent men and 49.3 percent women) participated in the study. The controls were identified in the National Health System records and were matched to cases on age (within 1 year) and registration with the same family pediatrician. The pediatricians certified that all controls were free of diabetes and none were diagnosed with diabetes during the study period. Trained physicians collected immunization information from the parents of diabetic cases and controls using a questionnaire at the first diabetologic examination or pediatric examination, respectively. The vaccination data were verified with records from the National Health System. A larger proportion of the controls were exposed to MMR vaccine and measles vaccine when compared to the cases: MMR vaccination in 8.1 percent of cases and 18.7 percent of controls; measles vaccination in 10.3 percent of cases and 12.9 percent of controls. The odds ratio for diabetes diagnosis any time after MMR vaccination was 0.382 (95% CI, 0.201–0.798) and measles vaccination was 0.777 (95% CI 0.403–1.498). The authors concluded that administration of MMR vaccine or measles vaccine does not increase the risk of type 1 diabetes in children.

Hviid et al. (2004) conducted a retrospective cohort study in children born from January 1990 through December 2000 and who resided in Denmark through December 2001 (end of study period). The participants were identified in the Danish Civil Registration System, and linked to information on type 1 diabetes diagnosis in the Danish National Hospital Register and vaccination data from the National Board of Health. The children were followed from birth and removed from the study at the first occurrence of an outcome of interest. The study outcomes included diagnosis of type 1 diabetes, loss to follow-up or emigration, reaching 12 years of age, and death. Vaccination status was considered a time-varying variable and was classified according to the number of doses administered (zero, one, two, or three doses of each vaccine). A total of 739,694 children were included in the study, of whom 16,421 were prematurely removed from the analysis because of loss to follow-up, emigration, or death. The rate ratio for diabetes diagnosis any time after one dose of MMR vaccine (compared to the unvaccinated) was 1.14 (95% CI, 0.90–1.45). The study also evaluated the rate ratios of diabetes diagnosis 1, 2, 3, 4, and > 4 years after MMR vaccination and found no significant differences. The authors

concluded that MMR vaccination does not increase the risk of type 1 diabetes in children.

### *Weight of Epidemiologic Evidence*

The five observational studies consistently reported no increased risks of type 1 diabetes following MMR vaccination, and two had negligible methodological limitations (Hviid et al., 2004; Patterson, 2000). The five studies had relatively large sample sizes and were representative of European and U.S. populations of children across a broad range of ages and varying time periods at risk of type 1 diabetes following vaccination. See Table 4-12 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has a high degree of confidence in the epidemiologic evidence based on five studies with validity and precision to assess an association between MMR vaccine and type 1 diabetes; these studies consistently report a null association.*

### **Mechanistic Evidence**

The committee identified five publications reporting type 1 diabetes developing after the administration of vaccines containing measles and mumps alone or in combination. The publications did not provide evidence beyond temporality, some too long or too short based on the possible mechanisms involved (Ehregut and Zastrow, 1989; Fescharek et al., 1990; Helmke et al., 1986; Otten et al., 1984; Sinaniotis et al., 1975). Long latencies between vaccine administration and development of symptoms make it impossible to rule out other possible causes. In addition, Otten et al. (1984) reported that one patient contracted mumps 2 years after vaccination and 4 years before development of type 1 diabetes making it impossible to attribute the development of type 1 diabetes to vaccination. Two publications studied antibodies to mumps in patients developing type 1 diabetes or autoantibodies associated with the development of type 1 diabetes in patients after mumps infection or vaccination. Vaandrager et al. (1986) tested sera from patients after mumps infection or vaccination for the presence of autoantibodies associated with type 1 diabetes. The authors isolated autoantibodies from patients after mumps infection or vaccination but reported that the patients did not develop type 1 diabetes. Hyoty et al. (1993) tested sera collected from patients before and after receiving an MMR vaccination. The authors reported a decline of mumps antibodies in type 1 diabetes patients. The publications did not contribute to the weight of mechanistic evidence.

TABLE 4-12 Studies Included in the Weight of Epidemiologic Evidence for MMR Vaccine and Type 1 Diabetes

| Citation           | Operationally Defined Outcome                                       | Study Setting | Defined Study Population   | Study Design | Sample Size  | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)   | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|--------------------|---|---------------|--|--------------|--|--|---|--|
| Blom et al. (1991) | Type 1 diabetes reported to the Swedish Childhood Diabetes Register | Sweden        | Children aged 0–14 years<br>Cases were enrolled in the Swedish Childhood Diabetes Register from 9/1/1985 through 8/31/1986<br>Controls were identified in the official Swedish population register | Case-control | 393 children with type 1 diabetes<br>786 controls<br>matched on age, sex, and county | OR for type 1 diabetes diagnosis any time after MMR vaccination: 0.95 (95% CI, 0.71–1.28)<br>OR for type 1 diabetes diagnosis any time after measles vaccination: 0.74 (95% CI, 0.55–1.00)<br>OR for type 1 diabetes diagnosis any time after mumps vaccination: 1.75 (95% CI, 0.54–5.70)<br>OR for type 1 diabetes diagnosis any time after rubella vaccination: 1.24 (95% CI, 0.41–3.73) | None described                                      | Serious  |

|                         |   |  | Case-control  |   |  |                |            |  |  |
|-------------------------|---|--|---|---|--|----------------|------------|--|--|
| Patterson (2000)        | Type 1 diabetes diagnosed by the EURODIAB ACE Group           | Europe (Austria, Latvia, Lithuania, Luxembourg, Romania, United Kingdom) | Children under 15 years of age enrolled at seven centers participating in the EURODIAB ACE Group from 1989 through 1995<br>Controls were selected at each center from population registers, general practitioners' lists, or school rolls | 900 children with type 1 diabetes<br>2,302 controls matched on age  | OR for type 1 diabetes diagnosis any time after rubella vaccination using the Mantel Haenszel approach: 1.18 (95% CI, 0.91–1.53; $p = .21$ )<br>OR for type 1 diabetes diagnosis any time after rubella vaccination using a logistic regression analysis: 1.27 (95% CI, 0.93–1.72; $p = .13$ ) | None described | Negligible |  |  |
| DeStefano et al. (2001) | First date of type 1 diabetes diagnosis in the medical record | Four HMOs participating in the VSD                                       | Children born from 1988 through 1997, ages 10 months to 10 years  | 252 children with type 1 diabetes<br>768 controls matched on sex, date of birth, HMO, and length of enrollment in the HMO | OR for type 1 diabetes diagnosis any time after MMR vaccination using Model 1: 1.36 (95% CI, 0.70–2.63)<br>OR for type 1 diabetes diagnosis any time after MMR vaccination using Model 2: 1.43 (95% CI, 0.71–2.86)   | None described | Serious    |  |  |

*continued*

TABLE 4-12 Continued

| Citation                | Operationally Defined Outcome                                      | Study Setting           | Defined Study Population  | Study Design         | Sample Size  | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)  | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|-------------------------|--|-------------------------|---|----------------------|--|---|---|--|
| Altobelli et al. (2003) | Type 1 diabetes diagnosis in the diabetes register                 | Abruzzo region of Italy | Children under 15 years of age with type 1 diabetes in the diabetes register of the Abruzzo region from 1990 to 1996                                      | Case-control         | 136 children with type 1 diabetes  | OR for type 1 diabetes diagnosis any time after MMR vaccination: 0.382 (95% CI, 0.201–0.798)  | None described                                      | Serious  |
| Hviid et al. (2004)     | Type 1 diabetes diagnosis in the Danish National Hospital Register | Denmark                 | Controls identified in the National Health System records of Italy<br>Children born from 1/1/1990 through 12/31/2000, residing in Denmark through 12/2001 | Retrospective cohort | 272 controls matched on age and registration with the same family pediatrician<br>739,694 children | OR for type 1 diabetes diagnosis any time after measles vaccination: 0.777 (95% CI, 0.403–1.498)<br>Rate ratio for type 1 diabetes diagnosis any time after one dose of MMR vaccine compared to the unexposed: 1.14 (95% CI, 0.90–1.45) | None described                                      | Negligible                                       |

<sup>a</sup> The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup> The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup> Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.

*Weight of Mechanistic Evidence*

The association of type 1 diabetes with wild-type mumps infection is controversial. Several publications have reported cases of type 1 diabetes developing after mumps infection (Litman and Baum, 2010). Epidemiologic studies report a 3- to 4-year lag time between mumps infection and type 1 diabetes (Litman and Baum, 2010), which would be consistent with a slow loss of islet cells not clinically apparent for several years; however, it would also be consistent with numerous other triggers. In addition, a decrease in the frequency of type 1 diabetes has not been associated with a decrease in the frequency of mumps infection after implementation of mumps vaccines (Litman and Baum, 2010). Owing to the uncertainty the committee did not consider mumps infection when determining the weight of mechanistic evidence.

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of type 1 diabetes. Autoantibodies, T cells, molecular mimicry, and complement activation may contribute to type 1 diabetes; however, the publications did not provide evidence linking these mechanisms to MMR vaccine.

*The committee assesses the mechanistic evidence regarding an association between MMR vaccine and type 1 diabetes as lacking.*

**Causality Conclusion**

**Conclusion 4.26:** The evidence favors rejection of a causal relationship between MMR vaccine and type 1 diabetes.

**HEPATITIS****Epidemiologic Evidence**

No studies were identified in the literature for the committee to evaluate the risk of hepatitis after the administration of MMR vaccine.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between MMR vaccine and hepatitis.*



### Mechanistic Evidence

The committee identified two publications reporting the development of hepatitis after the administration of vaccines containing measles, mumps, and rubella alone or in combination. Saliba and Elias (2005) did not provide evidence beyond temporality. Jorch et al. (1984) described a 2-year-old presenting with meningoencephalitis 7 days after administration of a measles and mumps vaccine and 3 days prior to brain death and cardiac arrest. Hepatitis was not reported as a symptom after vaccination and the liver was not enlarged, but a liver biopsy showed paramyxovirus-like intranuclear filaments suggesting the presence of measles virus or mumps virus or both. There was no attempt to identify virus in the liver either by culture or PCR, although vaccine-strain viremia is likely to be present at 7 days postvaccination. The publications did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

On rare occasions, infection with wild-type measles, mumps, and rubella viruses has been associated with hepatitis (Gershon, 2010a,b; Litman and Baum, 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

The symptoms described above are consistent with those leading to a diagnosis of hepatitis. Autoantibodies, T cells, direct viral infection, and complement activation may contribute to the symptoms of hepatitis; however, the publications did not provide evidence linking these mechanisms to MMR vaccine.

*The committee assesses the mechanistic evidence regarding an association between MMR vaccine and hepatitis as weak based on knowledge about the natural infection.*

### Causality Conclusion

**Conclusion 4.27:** The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and hepatitis.

## CHRONIC FATIGUE SYNDROME

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of chronic fatigue syndrome after the administration of MMR vaccine.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between MMR vaccine and chronic fatigue syndrome.*

**Mechanistic Evidence**

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of chronic fatigue syndrome after the administration of MMR vaccine.

*Weight of Mechanistic Evidence*

*The committee assesses the mechanistic evidence regarding an association between MMR vaccine and chronic fatigue syndrome as lacking.*

**Causality Conclusion**

**Conclusion 4.28:** The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and chronic fatigue syndrome.

**FIBROMYALGIA****Epidemiologic Evidence**

No studies were identified in the literature for the committee to evaluate the risk of fibromyalgia after the administration of MMR vaccine.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between MMR vaccine and fibromyalgia.*

**Mechanistic Evidence**

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of fibromyalgia after the administration of MMR vaccine.

*Weight of Mechanistic Evidence*

*The committee assesses the mechanistic evidence regarding an association between MMR vaccine and fibromyalgia as lacking.*

### Causality Conclusion

**Conclusion 4.29:** The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and fibromyalgia.

## HEARING LOSS

### Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of hearing loss after the administration of MMR vaccine. This one study (Asatryan et al., 2008) was not considered in the weight of epidemiologic evidence because it provided data from a passive surveillance system and lacked an unvaccinated comparison population.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between MMR vaccine and hearing loss.*

### Mechanistic Evidence

The committee identified 11 publications reporting hearing loss after the administration of vaccines containing measles, mumps, and rubella alone or in combination. Two publications described multiple cases, some did not provide a time frame between vaccination and development of hearing loss while others did not provide evidence beyond temporality, some too long or too short based on the possible mechanisms involved (Asatryan et al., 2008; Jayarajan and Sedler, 1995). Long latencies between vaccine administration and development of symptoms make it impossible to rule out other possible causes. These cases did not contribute to the weight of mechanistic evidence. Four publications did not provide evidence beyond a temporal relationship between administration of either a mumps vaccine or MMR vaccine and development of hearing loss (Garcia Callejo et al., 2005; Healy, 1972; Nabe-Nielsen and Walter, 1988a,b). These publications did not contribute to the weight of mechanistic evidence.

Described below are eight publications reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence. In most of the cases, fever develops between days 5 and 12 after vaccination, a time frame consistent with studies researching fevers after immunization. The committee included some cases in which fever developed outside this time frame when in association with other symptoms suggestive of involvement of the ear, such as tinnitus and gait disturbance.

Angerstein (1995) described a 24-month-old patient presenting with horizontal spontaneous nystagmus to the right, a sudden tendency to fall to the left, and left caloric excitability of the labyrinth 7 days after administration of a measles and mumps vaccine. Four years after vaccination laboratory evaluation detected complete failure of the caloric labyrinth on the left with good excitability on the right.

Asatryan et al. (2008) identified 202 reports, received by VAERS from January 1990 through December 2003, of hearing loss developing after vaccination against measles, mumps, and rubella. Of these 158 met the exclusion criteria or were duplicate submissions. Of the remaining 44 reports the authors summarized the 14 cases providing the most detailed clinical information. The following cases provided clinical evidence in addition to a temporal relationship between vaccination and the development of hearing loss that contributed to the weight of mechanistic evidence. Case 1 (number 6 in the report) describes a 1-year-old girl presenting with a fever within 1 month, and possibly as early as 1 week, after administration of measles, mumps, and rubella and *Haemophilus influenzae* type B (HiB) vaccines. The patient was diagnosed with bilateral hearing loss 3 years after vaccination. Case 2 (number 7 in the report) describes a 4-year-old boy presenting with fever and decreased hearing 2 weeks after simultaneous administration of measles, mumps, and rubella, diphtheria-tetanus-acellular pertussis (DTaP), HiB, and oral polio vaccines. Case 3 (number 8 in the report) describes a 1.5-year-old girl presenting with fever and exanthem subitum 2 weeks after administration of a measles, mumps, and rubella vaccine. Ataxia and bilateral hearing loss were reported 1 month and 4 months after vaccination, respectively.

Brodsky and Stanievich (1985) describe a 3-year-old presenting with fever, ataxia, irritability, headache, nausea, vomiting, and nystagmus 10 days after administration of a measles, mumps, and rubella vaccine at 15 months of age. Decreased hearing became a concern of the parents soon thereafter. A diagnosis of persistent otitis media led to the insertion of tympanostomy tubes at 2.5 years of age. No change in hearing was noted after the insertion of the tubes, and the patient was subsequently diagnosed as having bilateral hearing loss. The patient's father had sensorineural hearing loss in the left ear thought to be caused by a mumps infection in childhood.

Hulbert et al. (1991) describe a 27-year-old woman presenting with generalized arthralgia, fever, headache, tinnitus, vomiting, dizziness, and gait disturbance 3 days after receiving a measles and rubella vaccine. The patient experienced progressive hearing loss 22 days after vaccination. Serologic tests were negative for Epstein-Barr virus, St. Louis encephalitis virus, western equine and eastern equine encephalomyelitis viruses, systemic lupus, and syphilis.

Landrigan (1972) responded to a question presented by C. Herbert

Crane regarding hearing loss after vaccination. The patient presented with a febrile illness lasting 2.5 days 10 days after administration of a measles vaccine at 1 year of age. Hearing loss in the high-frequency range was observed at 30 months.

Watson (1990) described a 14-month-old girl presenting with a generalized pink blotchy rash starting on the neck 12 days after administration of a measles vaccine. The rash became a dull pink the following day and disappeared in 2 days. While afflicted with the rash, the patient repeatedly pulled at both ears. Two weeks later the mother noticed the patient would not respond to commands leading to the realization that the patient was unable to hear. A hearing assessment performed at 11 months of age had been normal.

Two publications provided experimental evidence for an association between the development of hearing loss and vaccination against measles or mumps. Fukuda et al. (2001) examined antimumps IgG and IgM in the sera of 69 cases of idiopathic sudden sensorineural hearing loss diagnosed at the Otolaryngology Department, Hokkaido University Hospital, from February 1992 through December 1999. The etiologies leading to hearing loss were not known. The authors were studying the association of silent mumps infection with idiopathic sudden sensorineural hearing loss. The authors demonstrated antimumps IgM in seven patients. Of these seven patients antimumps IgG were demonstrated in six. Antimumps IgG were demonstrated in an additional 36 patients.

Fukuda et al. (1994) used a hamster model to study acute measles infection of the cochlea. The authors used a hamster-adapted neurotropic strain of measles to inoculate the perilymphatic compartment of the ipsilateral cochlea in Syrian gold hamsters. Four to five days after virus inoculation the temporal bones were removed and subjected to indirect immunofluorescence using antimeasles virus antisera. Positive immunofluorescence was observed in the inflammatory cell infiltrates in the cochlear ducts and the lining of the perilymphatic structure.

### *Weight of Mechanistic Evidence*

Wild-type mumps virus infection has been associated with transient high-frequency-range deafness in 4.4 percent of mumps cases in the military (Litman and Baum, 2010). Permanent unilateral deafness has been reported to occur in 1 in 20,000 cases of mumps virus infection (Litman and Baum, 2010). Similarly, infection with wild-type measles virus has been associated with bilateral sensorineural hearing loss in 5–10 percent of measles cases (McKenna, 1997). The committee considers the effects of natural infection one type of mechanistic evidence.

In addition, the eight publications described above presented clinical

and experimental evidence suggestive but not sufficient for the committee to conclude the vaccine may be a contributing cause of hearing loss after administration of vaccines containing measles, mumps, and rubella alone or in combination. The publications presented a symptomology of fever, rash, and nystagmus consistent with direct infection of the measles or mumps viruses leading to hearing loss. The diagnosis of hearing loss after vaccination ranged from 6 days to 4 years after vaccination. Furthermore, the demonstration of antimumps antibodies in patients with idiopathic sudden sensorineural hearing loss and detection of measles antigen in the cochlear ducts in a hamster model of measles infection suggest the involvement of measles and mumps viruses in the pathogenesis of hearing loss. The animal model suggests the measles virus may replicate in the perilymph. However, the committee recognizes the limitations of this model.

The latency between vaccination and the development of the symptomology described above ranged from hours to 12 days after administration of a vaccine containing measles, mumps, and rubella alone or in combination, suggesting direct viral infection as the mechanism.

*The committee assesses the mechanistic evidence regarding an association between measles or mumps vaccine and hearing loss as low-intermediate based on knowledge about the natural infection, experimental evidence, and eight cases.*

*The committee assesses the mechanistic evidence regarding an association between rubella vaccine and hearing loss as lacking.*

### Causality Conclusion

**Conclusion 4.30:** The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and hearing loss.

### CONCLUDING SECTION

Table 4-13 provides a summary of the epidemiologic assessments, mechanistic assessments, and causality conclusions for MMR vaccine.

**TABLE 4-13** Summary of Epidemiologic Assessments, Mechanistic Assessments, and Causality Conclusions for Measles, Mumps, and Rubella Vaccine

| Vaccine | Adverse Event                       | Inclusion Body  | Epidemiologic Assessment | Studies Contributing to the Epidemiologic Assessment | Mechanistic Assessment  | Cases Contributing to the Mechanistic Assessment | Causality Conclusion   |
|---------|-------------------------------------|-----------------|--------------------------|--|---|--|--|
| MMR     | Measles Inclusion Body Encephalitis |                 | Insufficient             | None   | Strong (measles; in individuals with demonstrated immunodeficiencies)<br>Lacking (mumps or rubella) | 1<br>None  | Convincingly Supports <sup>a</sup> (in individuals with demonstrated immunodeficiencies) |
| MMR     | Encephalitis                        | Limited         | Limited                  | 3  | Weak  | 3  | Inadequate   |
| MMR     | Encephalopathy                      | Limited         | Limited                  | 3  | Weak  | 1  | Inadequate   |
| MMR     | Febrile Seizures                    | High (increase) | High (increase)          | 7  | Intermediate  | 12   | Convincingly Supports  |
| MMR     | Afebrile Seizures                   | Limited         | Limited                  | 2  | Lacking   | None   | Inadequate   |
| MMR     | Meningitis <sup>b</sup>             | Moderate (null) | Moderate (null)          | 3  | Weak (mumps)<br>Lacking (measles or rubella)  | 4<br>None  | Inadequate   |
| MMR     | Ataxia                              | Insufficient    | Insufficient             | None   | Weak (measles or mumps)<br>Lacking (rubella)  | 1<br>None  | Inadequate   |
| MMR     | Autism                              | High (null)     | High (null)              | 4  | Lacking   | None   | Favors Rejection   |

|     |  |                                 |      |                            |                 |                                |
|-----|--|---------------------------------|------|----------------------------|-----------------|--------------------------------|
| MMR | Acute Disseminated Encephalomyelitis             | Insufficient                    | None | Weak                       | None            | Inadequate                     |
| MMR | Transverse Myelitis                              | Insufficient                    | None | Weak                       | 3               | Inadequate                     |
| MMR | Optic Neuritis <sup>b</sup>                      | Limited                         | 1    | Weak                       | 2               | Inadequate                     |
| MMR | Neuromyelitis Optica <sup>b</sup>                | Insufficient                    | None | Weak (rubella)             | 1               | Inadequate                     |
|     |  |                                 |      | Lacking (measles or mumps) | None            |                                |
| MMR | Multiple Sclerosis Onset in Adults               | Limited                         | 2    | Lacking                    | None            | Inadequate                     |
| MMR | Multiple Sclerosis Onset in Children             | Limited                         | 1    | Lacking                    | None            | Inadequate                     |
| MMR | Guillain-Barré Syndrome                          | Insufficient                    | None | Weak                       | None            | Inadequate                     |
| MMR | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient                    | None | Lacking                    | None            | Inadequate                     |
| MMR | Opsoclonus Myoclonus Syndrome                    | Insufficient                    | None | Lacking                    | None            | Inadequate                     |
| MMR | Brachial Neuritis                                | Insufficient                    | None | Lacking                    | None            | Inadequate                     |
| MMR | Anaphylaxis                                      | Insufficient                    | None | Strong                     | 43 <sup>c</sup> | Convincingly Supports          |
| MMR | Transient Arthralgia in Women                    | Moderate (increase) (rubella)   | 4    | Intermediate (rubella)     | 13              | Favors Acceptance <sup>d</sup> |
|     |  | Insufficient (measles or mumps) | None | Lacking (measles or mumps) | None            |                                |

*continued*



TABLE 4-13 Continued

| Vaccine | Adverse Event                    | Epidemiologic Assessment                             | Studies Contributing to the Epidemiologic Assessment | Mechanistic Assessment                                   | Cases Contributing to the Mechanistic Assessment | Causality Conclusion |
|---------|----------------------------------|--|--|--|--|----------------------|
| MMR     | Transient Arthralgia in Children | Moderate (increase)                                  | 7  | Weak (rubella)<br>Lacking (measles or mumps)             | None<br>None                                     | Favors Acceptance    |
| MMR     | Chronic Arthralgia in Women      | Limited (rubella)<br>Insufficient (measles or mumps) | 2<br>None  | Low-Intermediate (rubella)<br>Lacking (measles or mumps) | 4<br>None  | Inadequate           |
| MMR     | Chronic Arthritis in Women       | Limited (rubella)<br>Insufficient (measles or mumps) | 2<br>None  | Low-Intermediate (rubella)<br>Lacking (measles or mumps) | 5<br>None  | Inadequate           |
| MMR     | Chronic Arthropathy in Children  | Insufficient   | None   | Weak (rubella)<br>Lacking (measles or mumps)             | 2<br>None  | Inadequate           |
| MMR     | Arthropathy in Men               | Limited  | 2  | Weak (rubella)<br>Lacking (measles or mumps)             | None<br>None                                     | Inadequate           |
| MMR     | Type 1 Diabetes                  | High (null)  | 5  | Lacking  | None   | Favors Rejection     |

|     |                          |              |      |  |      |            |
|-----|--------------------------|--------------|------|--|------|------------|
| MMR | Hepatitis                | Insufficient | None | Weak                                   | None | Inadequate |
| MMR | Chronic Fatigue Syndrome | Insufficient | None | Lacking                                | None | Inadequate |
| MMR | Fibromyalgia             | Insufficient | None | Lacking                                | None | Inadequate |
| MMR | Hearing Loss             | Insufficient | None | Low-Intermediate<br>(measles or mumps) | 8    | Inadequate |
|     |                          |              |      | Lacking<br>(rubella)                   | None |            |

<sup>a</sup> The committee attributes causation to the measles component of the vaccine.

<sup>b</sup> Although not originally charged to the committee by the sponsor, the committee considered this adverse event in its review of the literature.

<sup>c</sup> Some cases were from passive surveillance systems; however, it was not possible to know how many represented unique cases or were reported elsewhere.

<sup>d</sup> The committee attributes causation to the rubella component of the vaccine.

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## 5

## Varicella Virus Vaccine

## INTRODUCTION

Varicella, more commonly known as chickenpox, is caused by the human alpha herpesvirus varicella zoster virus (VZV). Transmitted through direct contact with or inhalation of infectious fluid, VZV is highly contagious and infects approximately 90 percent of susceptible household contacts and 10 to 35 percent of individuals with limited exposure (Arvin, 1996; Ross et al., 1962).

The incubation period of VZV from exposure to illness is 10–21 days (Arvin, 1996). During most of this time, the individual is asymptomatic. About 50 percent of cases will experience fever, headache, abdominal pain, or general malaise within 24–48 hours prior to the onset of typical chickenpox rash (Arvin, 1996). The varicella rash is characterized by pruritic, erythematous papules which develop into small, fluid-filled vesicles usually beginning on the scalp, face, or torso before spreading to proximal limbs and mucosal areas such as the conjunctivae (eye), oropharynx (back of the throat), and vagina (Arvin, 1996). In uncomplicated VZV infection, new lesions may form for up to 7 days (Arvin, 1996). The infected individual is considered contagious from 1–2 days prior to the appearance of the first lesion until all lesions have crusted, approximately 24–48 hours after the appearance of the last lesion, and generally within 4–7 days of symptom onset (AAP, 2009; Arvin, 1996).

Possible complications from varicella infection include pneumonia and secondary bacterial infections typically due to *Staphylococcus aureus* and streptococcus; transient hepatitis; thrombocytopenia; and various neu-

rologic complications including cerebellar ataxia, encephalitis, Guillain-Barré syndrome (GBS), meningitis, and transverse myelitis (Ey et al., 1981; Fleisher et al., 1981; Guess et al., 1986; Jackson et al., 1992; Liu and Urion, 1992; Preblud, 1986). Immunocompromised individuals such as those treated for cancer or with congenital defects in cellular immunity often experience more severe varicella infection and are at greater risk of fatal infection (Whitley, 2010).

Following the acute phase of the infection, the primary VZV infection is resolved, and the virus begins a dormant phase in the sensory nerve ganglia of the individual. The individual usually has lifetime immunity against reinfection, and will not again have an illness that resembles primary chickenpox; however, the latent VZV may be reactivated and cause shingles (also called *herpes zoster* [HZ]). Shingles (or HZ) is a painful, unilateral, pruritic rash appearing on dermatomal areas of one or more sensory-nerve roots (Arvin, 1996). Risk factors for shingles include aging, immunosuppression, and VZV infection prior to 12 months of age (Arvin, 1996). An estimated 15 to 30 percent of the population develops shingles, a percentage that is expected to increase with increasing life expectancies (CDC, 2007). Postherpetic neuralgia (PHN) is the most common complication of herpes zoster, especially in older individuals (CDC, 2007). The pain of PHN can last from 4 weeks to 10 years, and in one study, it lasted more than 1 year in 22 percent of study participants (Arvin, 1996; Ragozzino et al., 1982). Additional complications of herpes zoster include herpes ophthalmicus, dissemination, and central nervous system, pulmonary, and hepatic disease (CDC, 2007).

Prior to the development and dissemination of the varicella vaccine in 1995, varicella was a common childhood disease in the United States. The Centers for Disease Control and Prevention (CDC) estimates that from 1980 through 1990, 4 million cases of varicella occurred annually with approximately 77 percent of cases in children 9 years old and younger, and more than 90 percent in children less than 15 years of age (CDC, 2007). Furthermore, national seroprevalence data from 1988–1994 showed that 95.5 percent of adults aged 20–29 years, 98.9 percent of adults aged 30–39 years, and 99.6 percent of adults aged 40 years and older were immune to varicella (Kilgore et al., 2003).

From 1988 through 1995, hospitalizations due to varicella ranged from 2.3 to 7.0 per 100,000 cases (CDC, 2007). Among those most often hospitalized were adults 20 years of age and older, and children 4 years and younger, respectively representing 31.9 and 44.4 percent of varicella-related hospitalizations (Galil et al., 2002). Despite adults being less likely to require hospitalization due to varicella infection, from 1990 to 1994 adults were 25 times more likely to experience fatal varicella infections than children between the ages of 1 and 4 years (Meyer et al., 2000). Secondary

infections, central nervous system complications including encephalitis, and pneumonia were among the most common causes of hospitalization and death, and these instances occurred most often in healthy individuals who were not severely immunocompromised or undergoing immunocompromising treatments (Meyer et al., 2000).

Since the 1980s, VZV infections in immunocompromised individuals have been treated with acyclovir, a synthetic nucleoside analog that inhibits the replication of human herpes viruses including VZV. In 1992, acyclovir was approved for the treatment of VZV infection in healthy children (CDC, 2007). Used within 24 hours of initial presentation, intravenous acyclovir effectively lessens illness severity and fatality in immunocompromised individuals (Nyerges et al., 1988; Prober et al., 1982). In 1992, oral acyclovir was approved for treatment of varicella in healthy children based on study data indicating favorable clinical outcomes, for example shortening of disease and contagious state, and severity of symptoms, if administered within 24 hours of rash onset (CDC, 2007). However, in 1993, the American Academy of Pediatrics Committee on Infectious Disease issued a statement that the benefit of acyclovir was not sufficient to justify routine administration in healthy children (CDC, 2007). Instead, they recommended that the oral treatment be reserved for otherwise healthy individuals at increased risk for moderate to severe varicella such as individuals 13 years or older and persons with chronic skin or pulmonary disorders (Hall et al., 1993).

The first live attenuated varicella vaccine was developed and tested in Japan by Takahashi and colleagues in the 1970s. The virus, designated *Oka strain*, was isolated from vesicular fluid of a healthy 3-year-old boy infected with VZV (Takahashi et al., 1975). The virus was attenuated through serial passaging through human embryonic lung cells, guinea-pig cells, and human diploid cells (WI-38 and MRC-5) (Arvin and Gershon, 1996). Takahashi et al. inoculated 51 healthy children who subsequently experienced a 92 percent VZV antibody formation rate (Takahashi et al., 1975). Following this study, Takahashi and his associates studied the impact of the vaccine on the VZV seroconversion in children with underlying diseases such as nephritis, asthma, and hepatitis. This study showed that the VZV vaccine was safe for children receiving low to moderate doses of steroids (Takahashi et al., 1974, 1975).

Reports of varicella vaccination in immunocompromised children showed that with suspended chemotherapy, children with leukemia could be vaccinated successfully against VZV (Arvin and Gershon, 1996). These studies spurred similar studies in the United States and Canada. In 1979, the National Institute of Allergy and Infectious Diseases sponsored the Varicella Vaccine Collaborative Study that looked at the effectiveness of the vaccine on children whose leukemia was in remission. The Collaborative Study showed seroconversion in 88 percent of leukemic children after

the first dose and a 98 percent conversion after the second dose (Gershon and Steinberg, 1989).

In 1995, the live, attenuated virus vaccine, Varivax (Merck & Co., Inc.) was licensed in the United States for use in healthy individuals greater than 12 months of age (CDC, 2007). The vaccine contains 1,350 plaque-forming units (PFUs) of Oka/Merck VZV; 25 mg of sucrose; 12.5 mg of hydrolyzed gelatin; and trace amounts of neomycin, fetal bovine serum, and residual components of MRC-5 (CDC, 2007). In 2005, Merck received licensure from the Food and Drug Administration to release the combination measles, mumps, rubella, and varicella (MMRV) vaccine ProQuad (Merck) for use among healthy children aged 12 months through 12 years (CDC, 2007). Each dose of ProQuad contains at least  $3.0 \log_{10}$  TCID<sub>50</sub> of measles virus,  $4.3 \log_{10}$  TCID<sub>50</sub> of mumps virus, and  $3.0 \log_{10}$  TCID<sub>50</sub> of rubella virus in addition to  $3.99 \log_{10}$  PFUs of the attenuated varicella virus (Merck & Co., Inc., 2009).

Currently, two 0.5-mL doses of varicella vaccine are recommended for children older than 12 months, adolescents, and adults who show no evidence of prior immunity (CDC, 2007). For children aged 12 months to 12 years, the recommended minimum interval between the two doses is 3 months (CDC, 2007). For persons greater than 13 years of age, the recommended minimum interval is 4 weeks (CDC, 2007). Because of greater association with fevers and febrile seizures after MMRV vaccine as compared to the MMR and monovalent varicella vaccines as separate injections, the Advisory Committee on Immunization Practices recommends that individuals between 12 and 47 months of age receive the MMR and monovalent varicella vaccines as separate injections or MMRV for the first dose of the vaccines at the discretion of the administering physician and the parents (CDC, 2010b). The combination MMRV vaccine is preferred as a second dose for individuals aged between 12 months and 12 years, and as a first dose for individuals greater than 4 years of age when all four vaccines are needed and none are contraindicated (CDC, 2006, 2010b). Since 2005, about 90 percent of U.S. children aged 19–35 months have received at least one dose of varicella vaccine (CDC, 2010a).

#### DISSEMINATED OKA VZV WITHOUT OTHER ORGAN INVOLVEMENT

This review of adverse events related to disseminated Oka VZV or vaccine-strain viral reactivation is divided into four sections. Two sections deal with initial adverse events (1) limited to the skin or (2) involving dissemination to other organs. The other two sections report cases of VZV reactivation as zoster either (1) involving dissemination limited to the skin or (2) involving dissemination to other organs. In the cases limited to the

skin, the committee reports cases in which the rash appeared in more than one dermatome and, hence, had disseminated beyond the site of the initial vaccination. Not all cases could easily be assigned to one or another section. The committee arbitrarily placed all cases reporting herpes zoster in the viral reactivation sections even when these rashes appeared early after administration of the vaccine.

“Disseminated” in this section refers to the spreading of the rash beyond the dermatome involved in the vaccination. Reports in which there were a few vesicles at the site of the injection were not included. The cases that were used to definitively show the association were those in which (i) the patient received the varicella vaccine currently in use in the United States or one similar, (ii) the rash extended to dermatomes beyond that of the initial injection, and (iii) vaccine virus was demonstrated in skin lesions.

### Epidemiologic Evidence

The committee reviewed three studies to evaluate the risk of disseminated Oka VZV without other organ involvement after the administration of varicella vaccine. These three studies (Chaves et al., 2008; Sharrar et al., 2001; Wise et al., 2000) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between varicella vaccine and disseminated Oka VZV without other organ involvement.*

### Mechanistic Evidence

The committee identified 54 publications reporting disseminated Oka VZV without other organ involvement after vaccination against varicella. Thirty-three publications either did not provide evidence beyond temporality or demonstrated wild-type varicella virus in the vesicles (Alpay et al., 2002; Austgulen, 1985; Barton et al., 2009; Barzaga et al., 2002; Brunell et al., 1982; Chaves et al., 2005; Diaz et al., 1991; Donati et al., 2000; Haas et al., 1985a,b; Hadinegoro et al., 2009; Heath and Malpas, 1985; Heller et al., 1985; Kamiya et al., 1984; Katsushima et al., 1982; Konno et al., 1984; Kreth and Hoeger, 2006; Lassker et al., 2002; Leung et al., 2004; Lydick et al., 1989; Minamitani et al., 1982; Nunoue, 1984; Oka et al., 1984; Quinlivan et al., 2009; Shah et al., 2007; Shiow et al., 2009; Slordahl et al., 1984, 1985; Sorensen et al., 2009; Sugino et al., 1984; Takahashi



et al., 1985; Ueda et al., 1977; Zamora et al., 1994). These publications did not contribute to the weight of mechanistic evidence.

Described below are 21 publications reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence. The studies are grouped to indicate the certainty that the vaccine was sufficiently similar to that used currently in the United States and that there was primary dermal dissemination of vaccine virus. The vaccine which has been in use in the United States since 1995 contains a minimum of 1,350 PFUs of Oka VZV virus. Studies from prior to general use of the vaccine report many rashes and other adverse events associated with wild-type varicella virus because of the high prevalence of wild-type disease.

### *Cases of Primary Dermal Dissemination of Vaccine Virus*

Jean-Philippe et al. (2007) describe an 18-month-old girl, subsequently diagnosed with a T cell dysfunction, presenting with fever and papulo-vesicular/pustular skin lesions beginning on the trunk and spreading to cover the patient's entire body including the soles, palms, and scalp five weeks after receiving a varicella vaccine. New lesions continued to appear for more than 14 days after the appearance of the initial lesions. Vaccine-strain varicella was demonstrated, by polymerase chain reaction (PCR), in a biopsy of the skin lesions.

Angelini et al. (2009) describe a 17-month-old girl presenting with fever and vesicular-hemorrhagic lesions on the entire body 23 days after receiving a varicella vaccine. Laboratory tests showed pancytopenia reflecting macrocytic-normochromic-hyporegenerative anemia. Vaccine-strain varicella virus was demonstrated, by PCR, in skin lesions.

Kraft and Shaw (2006) described a 36-year-old man presenting with pruritic lesions on the face, limbs, and trunk 24 days after receiving a varicella vaccine and 2 years after undergoing a heart transplant. The patient was taking mycophenylate mofetil and cyclosporine twice daily. New lesions developed 3 days later. Vaccine-strain varicella virus was demonstrated, by PCR, in the lesions.

### *Other Cases*

There were five publications describing reports submitted to passive surveillance systems regarding rash associated with vaccine virus without other organ involvement in the first 42 days after vaccination. The limitation of these publications is that the distribution of the rash is not reported, so the committee cannot conclude that the rash disseminated beyond the site of the initial injection. Chaves et al. (2008), Galea et al. (2008), Sharrar et al. (2001), and Wise et al. (2000) described the development of rashes after administration of a varicella vaccine reported to either the Vaccine

Adverse Event Reporting System (VAERS) or Merck's Worldwide Adverse Experience System (WAES). Sharrar et al. (2001) report that all of the reports submitted to WAES are submitted to VAERS. Due to the use of the same databases, it is likely that many of the cases overlap in the four publications.

Chaves et al. (2008) identified 8,262 reports of rash submitted to VAERS from May 1995 through December 2005. The authors reported that of 209 specimens, submitted to the National VZV Laboratory at the CDC, 55 were wild-type varicella virus and 37 were vaccine-strain varicella virus. The remaining specimens either tested negative for varicella virus or were inadequate for testing.

Galea et al. (2008) identified 3,192 reports of rash developing within 42 days of vaccination submitted to WAES in the first 10 years of the licensure of the varicella vaccine in the United States. The authors report that of 130 specimens submitted to the Varicella Zoster Virus Identification Program (VZVIP), 42 were wild-type varicella virus and 37 were vaccine-strain varicella virus. The remaining specimens were negative for varicella virus, positive for varicella virus but untypable, or inadequate samples.

Sharrar et al. (2001) identified 1,349 reports of rash developing within 42 days of vaccination submitted to VAERS and WAES during the first 4 years of marketing the varicella vaccine licensed in the United States. Ninety-seven specimens were available for analysis by PCR. Of these, 38 were wild-type varicella virus, 24 were vaccine-strain varicella virus, 19 were inadequate, 8 were negative for varicella virus, and 8 were positive for varicella virus but the strain was not identified.

Wise et al. (2000) identified 3,640 reports of rash submitted to VAERS from March 1995 through July 1998. Varicella virus was demonstrated, by PCR, in 70 rash specimens. Of these, the strain was not identified in 5, 43 were wild-type varicella virus, and 22 were vaccine-strain varicella virus.

Goulleret and colleagues (2010) used data from the European VZVIP to study adverse events reported after vaccination against varicella after introduction of the varicella vaccine, licensed for use in the United States, in Europe. The authors identified 259 reports of rash developing within 42 days after vaccination. Specimens were collected from 44 of these cases and analyzed by PCR. Of these, 3 were inadequate samples, 4 were negative for varicella virus, 32 were wild-type varicella virus, and 5 were vaccine-strain varicella virus.

Described below are 13 publications in which vaccine-strain varicella was demonstrated in the skin in individuals after vaccination. However, the vaccine was either not that used in the United States, it is unclear which vaccine was used, or it is unclear that the rash was disseminated beyond the dermatome in which the vaccine was administered.

Bancillon et al. (1991) administered a varicella vaccine to 33 acute lymphoblastic leukemia (ALL) and 4 acute myeloblastic leukemia children.

Maintenance therapy consisting of 6-mercaptopurine, methotrexate, vincristine, and prednisolone for ALL patients and 6-mercaptopurine and cytosine arabinoside for acute myeloid leukemia patients was suspended 8 days before and 8 days after vaccination. Eight of the children experienced varicella developing 21 to 87 days postvaccination. Vaccine-strain varicella virus was demonstrated in one patient. This report is included in the “primary infection” section despite the length of days (up to 87) in which the rashes appeared because these children were immunosuppressed. It is likely that primary infection could manifest itself with a different time course than that of normal healthy children.

Brunell et al. (1987) administered a varicella vaccine (from three sources) to 52 children with acute lymphocytic leukemia. In children receiving chemotherapy the treatment was suspended 1 week prior to vaccination and 1 week after vaccination. The authors reported fever, lymphadenopathy, malaise, back and joint pain, and vesicular rashes after vaccination. Vesicular lesions developed between 18 and 36 days after vaccination in 5 of the 52 children immunized. Vaccine-strain varicella virus was demonstrated, by restriction endonuclease analysis, in vesicular fluid isolated from two of the five children presenting with vesicular rashes. In the three remaining children either no virus was demonstrated in vesicular fluid or specimens were not obtained.

Christensen et al. (1999) describe a girl 3 years, 6 months old with acute lymphocytic leukemia presenting with typical varicella 32 days after vaccination and 29 days after receiving a bolus of vincristine. Maintenance chemotherapy consisting of 6-mercaptopurine and methotrexate was suspended before and after vaccination. Vaccine-strain varicella virus was demonstrated in vesicular fluid by restriction endonuclease analysis.

Gelb et al. (1987) administered a varicella vaccine (“research” and “consistency” lots) to 350 children with acute lymphocytic leukemia in remission for at least 1 year and 117 normal adults. The authors report that rashes were more common in children receiving chemotherapy than in those who completed chemotherapy. The rashes developed between 1 and 6 weeks after vaccination. Varicella virus demonstrated in eight children was determined to be vaccine-strain varicella virus in three children and wild-type varicella virus in three children by restriction endonuclease analysis. In two children the type of varicella virus was not determined.

Gershon et al. (1984a) administered a varicella vaccine to 191 children with acute leukemia in remission for 1 year or more. Of the children, 53 were no longer receiving chemotherapy while chemotherapy was suspended in 138. Two of the 53 children no longer receiving chemotherapy and 49 of the 138 children whose chemotherapy was suspended developed rashes after vaccination. Vaccine-strain varicella virus was demonstrated in two of these children by restriction endonuclease analysis. A follow-up publi-

cation on the same group of children had similar results (Gershon et al., 1984b). Gershon et al. (1985) presented data from this collaborative study after the total enrollment had increased to 240 children. They reported that vaccine-strain varicella virus was demonstrated by restriction endonuclease analysis in rashes in four children undergoing maintenance chemotherapy. After the enrollment had increased to 307 children with acute lymphocytic leukemia, Gershon et al. (1986) published updated follow-up results. At this time point, the children had been in remission from 9 to 52 months. The authors reported maculopapular or papulovesicular rashes developing about 1 month after vaccination in three children not receiving maintenance chemotherapy and 100 children receiving maintenance chemotherapy. Vaccine-strain varicella virus was demonstrated, by restriction endonuclease analysis, in eight children. When enrollment had reached 437 children with leukemia in remission for 1 year or more, Gershon et al. (1989) published another follow-up report. As reported in the previous publications, for those patients receiving maintenance chemotherapy, therapy was suspended 1 week before and after vaccination. Seven of the 65 patients no longer receiving chemotherapy and 149 of the 372 patients whose chemotherapy was stopped for the vaccination developed rashes. Vaccine-strain varicella virus was demonstrated in 17 of these children by restriction endonuclease analysis. In this report, Gershon et al. (1989) reported that the source of vaccine for the entire study to that time included multiple lots from two different companies.

Ninane et al. (1985) administered a varicella vaccine to 45 children with either acute leukemia or solid malignant tumors. In leukemia patients maintenance therapy was suspended 1 week before and 1 week after vaccination. In patients with solid tumors the vaccine was administered in the middle of a 4-week interval in their therapy. Clinical varicella developed in 8 of the 45 children. Vaccine-strain varicella virus was demonstrated in a vesicle in one of the eight children. In the remaining seven children, wild-type varicella virus was demonstrated in four and no virus was demonstrated in three.

White et al. (1991) reviewed data from a multicenter trial of five production lots of vaccine in 3,303 children and adolescents. Three of the five lots had fewer than the current minimum 1,350 PFUs per dose. The authors reported cases of injection site complaints and rashes developing after vaccination. Specimens were collected from 32 patients for analysis. Of these, 11 were varicella virus. Nine of these samples were further analyzed by restriction endonuclease analysis. Of these nine specimens, eight were wild-type varicella virus and one was vaccine-strain varicella virus.

Hughes et al. (1994) describe a 5-year-old boy, diagnosed with ALL, presenting with maculopapular lesions on the right cheek and right leg 8 days after receiving a varicella vaccine and 2 years after remission was

achieved. He was given the varicella vaccine as part of the vaccine study described by Gershon et al. (1984a,b, 1985, 1989). The source of the vaccine was not listed in the report. Maintenance chemotherapy was suspended for the week before and week after vaccination. New skin lesions continued to appear over the next 10 days. The patient had more than 200 skin lesions 32 days after vaccination. The 3-year-old sister of the vaccinee developed vesicles on her face and trunk 14 days after the vaccinee was hospitalized. Furthermore, 16 days after the vaccinee's hospitalization the 22-month-old brother of the vaccinee developed vesicles on his scalp and trunk. Vaccine-strain varicella was demonstrated, by PCR, in the lesions developing on the vaccinee's siblings. Although vaccine virus was not demonstrated in the vaccine recipient, this report is included because the siblings developed a rash associated with vaccine virus.

One case describes primary dissemination of vaccine virus, but it is not proven that vaccine virus was involved. Levitsky et al. (2002) described a 60-year-old woman who received a varicella vaccine 11 months after undergoing an orthotopic liver transplant. At the time of vaccination she was taking tacrolimus, sirolimus, and prednisone daily. Three weeks after vaccination she presented with small blisters on her abdomen, back, and shoulders. The blisters resolved after undergoing treatment with acyclovir. Two days after completing the acyclovir treatment a pruritic erythematous rash developed on her legs and abdomen followed by the eruption of clear vesicles in a multidermatomal distribution. The vesicles resolved after undergoing treatment with acyclovir. Varicella virus was detected, by a direct fluorescent antibody test and rapid shell vial test, in scrapings of the vesicles. The virus was unable to be cultured and was not typed. Given the age of this subject, even though she did not remember having had varicella, it is possible that the rash was wild type, not vaccine related.

### *Weight of Mechanistic Evidence*

Infection with varicella zoster virus manifests as a rash, malaise, and low-grade fever (Whitley, 2010). The rash, which is a hallmark of infection, consists of vesicles, maculopapules, and scabs in varying stages (Whitley, 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

In addition, the 21 publications described above presented clinical evidence sufficient for the committee to conclude the vaccine was a contributing cause of disseminated Oka VZV without other organ involvement. There were three cases that unequivocally showed that vaccination with the current vaccine caused a rash that spread beyond the injection dermatome without involvement of other organs. These rashes occurred in immunodeficient patients. In five publications describing reports submitted to passive

surveillance systems it was unclear if the rash extended beyond the dermatome in which the vaccine was administered, but vaccine virus was demonstrated in the rash from some of the subjects. In nine case reports and five publications from a large study of children with leukemia it was not clear that the vaccine administered was equivalent to that currently used in the United States. In one case of dermal dissemination in an immunosuppressed adult, it was not proven that vaccine virus was involved in the rash. In all publications described above the vaccine administered contained the Oka varicella strain described in the introduction to the chapter. Rashes were reported in individuals with and without demonstrated immunodeficiencies (e.g., genetic or acquired). Vaccine-strain varicella was demonstrated in skin biopsy and vesicular fluid in 20 of the publications described above although it should be noted that five publications represent reports over time of the same multicenter study.

The latency between vaccination and development of rash in the publications described above ranged from 8 to 87 days suggesting direct viral infection as the mechanism responsible for disseminated Oka VZV without other organ involvement. It should be noted that the publications did not provide evidence linking autoantibodies, T cells, or complement activation to disseminated rash after varicella vaccination.

*The committee assesses the mechanistic evidence regarding an association between varicella vaccine and disseminated Oka VZV without other organ involvement in individuals with or without demonstrated immunodeficiencies as strong based on cases<sup>1</sup> presenting definitive clinical evidence.*

### Causality Conclusion

**Conclusion 5.1: The evidence convincingly supports a causal relationship between varicella vaccine and disseminated Oka VZV without other organ involvement.**

### DISSEMINATED OKA VZV WITH OTHER ORGAN INVOLVEMENT

“Disseminated” in this section refers to disease present in organs in addition to the skin in a time frame associated with acute infection. The cases that were used to definitively show the association were those in which (1) the patient received the vaccine currently in use in the United States,

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<sup>1</sup>Due to the use of the same surveillance systems in some publications it is likely that some of the cases were presented more than once, thus it is difficult to determine the number of unique cases.

(2) the disease, not mildly abnormal laboratory values, was found in organs with or without skin involvement, and (3) vaccine virus was demonstrated in the organ.

## Epidemiologic Evidence

### *Pneumonia*

The committee reviewed five studies to evaluate the risk of pneumonia after the administration of varicella vaccine. Four studies (Chaves et al., 2008; Goulleret et al., 2010; Sharrar et al., 2001; Wise et al., 2000) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

The one remaining controlled study (Black et al., 1999) contributed to the weight of epidemiologic evidence and is described below.

Black et al. (1999) conducted a retrospective cohort study in 89,753 patients (12 to 18 months of age, older children, and adults) enrolled at the Northern California Kaiser Permanente Medical Care Program (KPMCP) from April 1995 through December 1996. Eligible patients were identified in the clinical database, and received at least one dose of varicella vaccine during the study period. Potential adverse events were obtained from the database; diagnoses from hospitalizations, emergency room (ER) visits, and outpatient clinic visits were included in the analysis. The risk periods for diagnoses recorded at outpatient clinic visits, ER visits, and hospitalizations were defined as 1–30 days, 0–30 days, and 0–60 days after vaccination, respectively. Three control periods were used in the analysis. A historical cohort was available for the ER visit and hospitalization analysis; children who were 1–2 years of age 1 year before the study began were matched to the exposed group on birth date, sex, and date of MMR vaccination. Events following routine pediatric vaccinations within the equivalent 30- or 60-day risk period were recorded for the historical cohort. Prevacination and postvaccination control periods were included in the analysis. The prevaccination periods were defined as 31–60 days before outpatient clinic visits or ER visits, and 31–90 days before hospitalizations. The postvaccination periods were defined as 91–120 days after outpatient clinic visits or ER visits, and 91–150 days after hospitalizations. The relative risk of pneumonia in the 1-year age group recorded during clinic visits within 30 days of varicella vaccination (81 cases), compared to the 31–60 prevaccination control period (59 cases), was 1.42 (95% CI, 1.02–1.99). Only statistically significant increased risks were reported in the study; analyses were not

available for other age groups or comparison groups. The large number of comparisons conducted in the study increased the potential for type I error.

### *Meningitis*

The committee reviewed three studies to evaluate the risk of meningitis after the administration of varicella vaccine. These three studies (Chaves et al., 2008; Goulleret et al., 2010; Wise et al., 2000) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

### *Hepatitis*

The committee reviewed two studies to evaluate the risk of hepatitis after the administration of varicella vaccine. These two studies (Chaves et al., 2008; Wise et al., 2000) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

### *Weight of Epidemiologic Evidence*

*The committee has limited confidence in the epidemiologic evidence, based on one study that lacked validity and precision, to assess an association between varicella vaccine and disseminated Oka VZV with subsequent infection resulting in pneumonia.*

*The epidemiologic evidence is insufficient or absent to assess an association between varicella vaccine and disseminated Oka VZV with subsequent infection resulting in meningitis or hepatitis.*

## **Mechanistic Evidence**

### *Pneumonia*

The committee identified 11 publications reporting disseminated VZV with pneumonia after administration of a varicella vaccine. Four publications did not provide evidence beyond temporality (Chaves et al., 2008; Goulleret et al., 2010; LaRussa et al., 1996; Lohiya et al., 2004). One case reported in publications by Ghaffar et al. (2000), Galea et al. (2008), Sharrar et al. (2001), and Wise et al. (2000) did not contribute to the weight of mechanistic evidence owing to the failure to isolate vaccine-strain varicella from the bronchial lavage fluid. In this case, rhinovirus, enterovirus,



and parainfluenza type III were isolated from the bronchoalveolar fluid suggesting the presence of concomitant infections (Ghaffar et al., 2000).

Described below are five cases reported in six publications reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

One case, a 5-year-old boy with a history of cerebral palsy, quadriplegia, seizure disorder, and reactive airway disease treated with clonazepam, carbamazepine, albuterol, budesonide, and intermittent steroid therapy, was described in two publications (Galea et al., 2008; Sharrar et al., 2001). The patient presented with a rash and pneumonia 10 and 17 days, respectively, after receiving a varicella vaccine. The vaccine was administered 7 days after the patient finished a steroid taper. Vaccine-strain varicella virus was demonstrated, by PCR, in endotracheal secretions.

One case, a 16-month-old boy who presented with fever, respiratory distress, and lower extremity weakness was described in four publications (Galea et al., 2008; Kramer et al., 2001; Sharrar et al., 2001; Wise et al., 2000). The patient had developed a rash 1 month earlier. The patient had oral thrush; the patient's history revealed recurrent thrush from 11 months of age. The patient received MMR and varicella vaccines at 13 months of age. The patient was found to have a total CD4 count of 8 cell/mm<sup>3</sup> and was diagnosed with human immunodeficiency virus (HIV)-1 infection. An open-lung biopsy revealed multinucleated giant cells. Vaccine-strain varicella virus was demonstrated via PCR in the lung biopsy and bronchoalveolar lavage fluid. The patient recovered after treatment with acyclovir and antiretrovirals.

One case, a 13-month-old boy who had previously been diagnosed with DiGeorge syndrome and found to have low T cell numbers (396 CD3 T cells; normal range 2,400–6,900/mm<sup>3</sup>) at 8 months of age was described in two publications (Galea et al., 2008; Waters et al., 2007). The patient underwent heart surgery for congenital heart disease at 10 months of age. At 12 months of age the patient received the measles, mumps, and rubella (MMR) vaccine together with the varicella vaccine. The patient presented 1 month later with lethargy, vomiting, decreased oral intake, and an episode of hematemesis. Respiratory examination revealed tachypnea and bilateral inspiratory crackles. Evaluation of bronchoscopy specimens demonstrated multinucleated giant cells with nuclear inclusions. Vaccine-strain varicella virus was demonstrated via PCR in tracheal aspirates and vesicular lesions obtained 7 weeks postvaccination. Measles virus was not detected by PCR. The patient remained intubated, and died 6 months later of pulmonary hemorrhage.

One case, an 11-year-old girl who developed an erythematous rash over the trunk and scalp, cough, labored breathing, increased respiratory

secretions, lethargy, hypothermia, and hypoxemia 5 weeks after varicella vaccination was described in two publications (Galea et al., 2008; Levy et al., 2003). The patient had congenital cytomegalovirus and a history of recurrent, presumably viral infections. Varicella virus was demonstrated via PCR in endotracheal fluid. Subsequent restriction fragment length polymorphisms analysis revealed the virus to be vaccine-strain varicella. The patient was treated with acyclovir, and recovered. A comprehensive immunologic evaluation of the patient revealed a deficiency of natural killer (NK) cells.

Galea et al. (2008) described a 48-year-old man with Down syndrome who developed pneumonitis 13 days after varicella vaccination. The patient developed a generalized rash 2 weeks later. Vaccine-strain varicella virus was demonstrated via PCR in lesions and sputum specimens. Although Down syndrome is not a primary immunodeficiency, adults with Down syndrome often have immunoglobulin subclass abnormalities. It is unknown if the humoral immunity of this subject was tested.

### *Meningitis*

The committee identified two publications reporting disseminated VZV with meningitis after administration of a varicella vaccine. Wise et al. (2000) either did not provide evidence beyond temporality or attributed the disseminated VZV with meningitis to wild-type varicella virus. This publication did not contribute to the weight of mechanistic evidence.

Described below is one publication reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Bryan et al. (2008) described a 21-month-old girl subsequently diagnosed with stage IV neuroblastoma, presenting with two erythematous, umbilicated papules on the right finger and lower right abdomen 5 weeks after receiving a varicella vaccine, and 4 weeks into a chemotherapy regimen consisting of cyclophosphamide, adriamycin, vincristine, cisplatin, and etoposide. The lesions evolved into vesicular patches. The lesions were positive for varicella virus by PCR. Acyclovir was initially administered followed by foscarnet therapy. The patient developed conjunctivitis, lethargy, fatigue, and photophobia 8 weeks after beginning foscarnet therapy. Varicella virus was demonstrated by PCR in lesion scrapings and the cerebrospinal fluid (CSF). Varicella virus demonstrated in lesion scrapings was identified as vaccine-strain virus upon restriction endonuclease analysis. The strain of varicella virus in the CSF was not determined. Although vaccine-strain virus was not demonstrated in the CSF of this child, it is probable that vaccine virus was involved because of its presence in the skin and because this case likely presented well after the initiation of widespread varicella vaccination in the United States.

### Hepatitis

The committee identified eight publications reporting the development of hepatitis or hepatic pathology after administration of a varicella vaccine. Two case reports did not contribute to the weight of mechanistic evidence. Suvatte et al. (1985) did not provide evidence beyond temporality. Italiano et al. (2009) reported the isolation of vaccine-strain varicella from serum, but not from the liver, making it difficult to determine the etiology of liver pathology. In addition, Italiano et al. (2009) reported the development of toxic shock syndrome resulting from a concomitant *Streptococcus pyogenes* infection. Two publications describing reports submitted to passive surveillance systems, Chaves et al. (2008) and Wise et al. (2000), did not provide clinical, diagnostic, or experimental evidence of causality, including the time frame between vaccination and development of hepatic pathology beyond the additional data reported in case reports described below and thus did not separately contribute to the weight of mechanistic evidence.

Described below are three cases reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

One case, a 13-month-old boy who was subsequently diagnosed with adenosine deaminase deficiency, a severe combined immunodeficiency, was described in four publications (Galea et al., 2008; Ghaffar et al., 2000; Sharrar et al., 2001; Wise et al., 2000). The patient presented with diarrhea and respiratory distress requiring ventilation 2 weeks after receiving a varicella vaccine. Rhinovirus, enterovirus, and parainfluenza type III were demonstrated in a bronchoalveolar lavage specimen. The patient's coagulation studies were abnormal; the serum transaminase values were elevated. A liver biopsy revealed multifocal areas of necrosis. Standard cultures were negative. The patient developed maculopapular and vesicular lesions on the extremities and trunk 4 weeks postvaccination. Varicella virus DNA was demonstrated via PCR in the skin lesions and in supernatant of a viral culture of a homogenate of the liver biopsy. The identity of the virus as vaccine strain was confirmed by restriction fragment length polymorphisms.

Ihara et al. (1992) reported one case of a 5-year-old girl with a history of acute lymphocytic leukemia. The patient was vaccinated 6 months after complete remission while receiving consolidation chemotherapy consisting of vincristine, adriamycin, and dexamethasone every 3 months. The patient presented with fever and vesicles 20 days after receiving a varicella vaccine (13 days after receiving the third course of consolidation therapy), and 5 days later the patient was still febrile, in addition to having developed jaundice. The patient's lactate dehydrogenase, aspartate aminotransferase, and alanine aminotransferase levels were 2,700 IU/L, 1,060 IU/L, and 1,690 IU/L, respectively. Varicella virus was demonstrated in vesicular fluids and

peripheral blood mononuclear cells, and was determined to be vaccine strain using restriction endonucleases. Analyses of serum immunoglobulins were normal; lymphocyte phenotyping, and proliferation in response to mitogens, were not performed. The weakness of this case is that a liver biopsy was not done demonstrating vaccine virus in the liver. The jaundice and very elevated liver enzymes directly reflect liver disease not normally seen after vaccination. Since vaccine virus was demonstrated in the skin lesions and since the child was immune suppressed, it is likely that the vaccine virus caused this adverse event.

One case, reported in detail in the publication by Galea et al. (2008), was a 14-month-old boy who presented with a vesicular rash 19 days after vaccination. The boy was hospitalized with a disseminated rash, elevated aspartate aminotransferase and alanine aminotransferase levels, and fever. Multinucleated giant cells consistent with varicella virus infection were revealed by a liver biopsy. However, vaccine-strain varicella virus was only demonstrated, by PCR, in a lesion. We include this case because of the pathology (giant cells) seen in the liver. The boy was subsequently diagnosed with a severe combined immunodeficiency making it likely that the vaccine virus seen in a skin lesion was also in the liver.

#### *Weight of Mechanistic Evidence*

Infection with varicella zoster virus manifests as a rash, malaise, and low-grade fever (Whitley, 2010). The rash, which is a hallmark of infection, consists of vesicles, maculopapules, and scabs in varying stages (Whitley, 2010). Varicella pneumonitis is associated with varicella zoster infection, and occurs more commonly in adults and immunocompromised individuals (Whitley, 2010). Furthermore, varicella pneumonitis can develop in the absence of clinical symptoms (Whitley, 2010). In addition, meningitis has been reported as a nervous system manifestation of wild-type varicella infection (Whitley, 2010). Furthermore, while rare, hepatitis has been associated with wild-type varicella zoster virus infection (Whitley, 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

The nine cases described above presented clinical evidence sufficient for the committee to conclude the vaccine was a contributing cause of disseminated Oka VZV with subsequent infection resulting in pneumonia, meningitis, or hepatitis. All of the cases described above report patients with either a genetic or acquired immunodeficiency with the possible exception of one adult with Down syndrome discussed above. Vaccine-strain varicella virus was demonstrated in the vesicular fluid, peripheral blood mononuclear cells, liver biopsy supernatant, endotracheal fluid, tracheal aspirates, lung biopsy, and bronchoalveolar lavage fluid in the cases described above. In most cases vaccine-strain varicella virus was demonstrated in a speci-

men from the liver or lung. The one exception was Bryan et al. (2008) as the authors demonstrated varicella virus in the CSF of an immunodeficient patient but did not identify the strain. The committee felt that vaccine strain virus was likely the etiology of the meningitis as it would be unusual to have dermal dissemination of vaccine virus in an immunodeficient patient who had wild-type virus in the CSF.

The latency between vaccination and disseminated Oka VZV with subsequent infection resulting in pneumonia, meningitis, or hepatitis in the publications described above ranged from 10 days to 2 months suggesting direct viral infection as the mechanism. Autoantibodies, T cells, and complement activation may also contribute to hepatitis; however, the publications did not provide evidence linking these mechanisms to varicella vaccine.

*The committee assesses the mechanistic evidence regarding an association between varicella vaccine and disseminated Oka VZV with subsequent infection resulting in pneumonia, meningitis, or hepatitis in individuals with demonstrated immunodeficiencies as strong based on nine cases presenting definitive clinical evidence.*

### Causality Conclusion

**Conclusion 5.2:** The evidence convincingly supports a causal relationship between varicella vaccine and disseminated Oka VZV with subsequent infection resulting in pneumonia, meningitis, or hepatitis in individuals with demonstrated immunodeficiencies.

### VACCINE-STRAIN VIRAL REACTIVATION WITHOUT OTHER ORGAN INVOLVEMENT

Vaccine-strain viral reactivation and dissemination as zoster limited to the skin is defined as appearance of zoster in more than the dermatome that was the site of the initial vaccination.

### Epidemiologic Evidence

The committee reviewed three studies to evaluate the risk of vaccine-strain viral reactivation without other organ involvement after the administration of varicella vaccine. These three studies (Chaves et al., 2008; Sharrar et al., 2001; Wise et al., 2000) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between varicella vaccine and vaccine-strain viral reactivation without other organ involvement.*

**Mechanistic Evidence**

The committee identified 27 publications reporting viral reactivation without other organ involvement after vaccination against varicella. Eight publications did not provide evidence beyond temporality (Broyer and Boudailliez, 1985; Diaz et al., 1991; Emir et al., 2006; Katsushima et al., 1982; Lin et al., 2009; Minamitani et al., 1982; Naseri et al., 2003; Takahashi et al., 1985). These publications did not contribute to the weight of mechanistic evidence.

Described below are 19 publications reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence. The zoster in some cases seemed to involve more than the initial site of vaccination but that was only explicitly stated in two cases, one reported in two publications describing reports submitted to passive surveillance systems, Chaves et al. (2008) and Galea et al. (2008), and one reported by Chan et al. (2007).

Chaves et al. (2008), Galea et al. (2008), Sharrar et al. (2001), and Wise et al. (2000) described the development of rashes after administration of a varicella vaccine reported to either the VAERS or WAES. Sharrar et al. (2001) report that all of the reports submitted to WAES are submitted to VAERS. Due to the use of the same databases, it is likely that many of the cases overlap in the four publications.

Chaves et al. (2008) identified 981 reports of herpes zoster after vaccination submitted to VAERS from May 1995 through December 2005. Of the 981 reports, 1 was due to herpes simplex virus, 1 was due to an allergic reaction, 11 were due to varicella virus but genotyping was not performed, 10 were due to wild-type varicella virus, and 8 were due to vaccine-strain varicella virus. In addition, the authors report that of 118 specimens submitted to the National VZV Laboratory at the CDC, 24 were wild-type varicella virus, and 47 were vaccine-strain varicella virus. The latency between vaccination and presentation of herpes zoster in patients where vaccine-strain varicella virus was demonstrated ranged from 1 to 11 years. One case, reported in detail, was a 5-year-old girl who presented with a zoster-like rash on the right side of the face and right eye 25 days after receiving a varicella vaccine, diphtheria-tetanus-acellular pertussis (DTaP) vaccine, and oral polio virus vaccine. The vaccine strain of VZV was demonstrated. This section was arbitrarily assigned to the reactivation

section despite the early onset because of the description of the virus as “zoster-like.” This case was also reported by Galea et al. (2008).

Galea et al. (2008) identified 697 reports of herpes zoster after vaccination submitted to WAES in the first 10 years of the licensure of the varicella vaccine in the United States. Of the 697 reports, 38 were due to wild-type varicella virus and 57 were due to vaccine-strain varicella virus (some of these cases also reported meningitis). In one case a child was diagnosed with acute lymphocytic leukemia 10 days after administration of a varicella vaccine. The child developed herpes zoster 23 days, 47 days, and 116 days after vaccination. Vaccine-strain varicella virus was demonstrated by PCR. The latency between vaccination and presentation of herpes zoster in patients where vaccine-strain varicella virus was demonstrated ranged from 23 days to 7.7 years.

Sharrar et al. (2001) identified 205 reports of herpes zoster after vaccination submitted to VAERS and WAES during the first 4 years of marketing the varicella vaccine licensed in the United States. From these 205 reports 56 specimens were analyzed by PCR. Of the 56 specimens, 4 were negative, 18 were inadequate, 2 were not typed, 10 were wild-type varicella virus, and 22 were vaccine-strain varicella virus. The latency between vaccination and presentation of herpes zoster in patients where vaccine-strain varicella virus was demonstrated ranged from 47 to 1,249 days.

Wise et al. (2000) identified 251 reports of herpes zoster after vaccination submitted to VAERS from March 1995 through July 1998. Varicella virus was demonstrated via PCR in 26 of the 251 reports. Of the 26 specimens, 12 were wild-type varicella virus and 14 were vaccine-strain varicella virus. The latency between vaccination and presentation of herpes zoster in patients where vaccine-strain varicella virus was demonstrated was a median of 19 weeks.

Goulleret et al. (2010) used data from the European VZVIP to study adverse events reported after vaccination against varicella after introduction of the varicella vaccine, licensed for use in the United States, in Europe. The authors identified 44 reports of herpes zoster after vaccination. Specimens were collected from 17 of the 44 cases. Of these 17 specimens, seven were negative for varicella virus, one was positive for varicella virus but the strain was not determined, one was wild-type varicella virus, and eight were vaccine-strain varicella virus. The latency between vaccination and presentation of herpes zoster in patients where vaccine-strain varicella virus was demonstrated ranged from 89 days to 30 months. The location of the zoster was not reported.

Chan et al. (2007) reported the case of a 9-year-old boy with chronic granulomatous disease with multiple complications from the disease who was administered a varicella vaccine at age 7 years, and who subsequently underwent bone marrow transplantation at age 8 years. He was placed

on long-term therapy consisting of prednisolone 5 mg and azithromycin 250 mg daily. At age 9 years (approximately 2 years after vaccination) the patient developed herpes zoster over his back and left arm. Varicella virus was demonstrated via PCR in vesicular lesions. Subsequent restriction enzyme analysis revealed the virus to be vaccine-strain varicella.

Ota et al. (2008) reported a 28-month-old boy presenting with vesicles on the anterior thorax, left forearm, left wrist, and left hand. The patient received a varicella vaccine 15 months before the development of symptoms. The patient received a dual hepatitis A and hepatitis B vaccine 2 days prior to developing herpes zoster. Similar lesions appeared in the same areas 3 months later. The patient experienced a third episode with lesions in the same areas 2 months later. Vaccine-strain varicella virus was demonstrated via PCR in vesicular fluid obtained during the first outbreak of herpes zoster. The patient's history did not suggest an underlying immunodeficiency. Evaluation of immunoglobulin levels; antibody titers; T, B, and NK cell numbers; and proliferative responses to mitogens and antigens including VZV were found to be normal. In addition, the patient tested negative for HIV-1.

### *Other Cases*

Described below are publications in which vaccine-strain varicella was demonstrated in individuals with viral reactivation; however, the vaccine was not that used in the United States.

Christensen et al. (1999) reported the case of a 4-year-old boy who began treatment for acute lymphocytic leukemia, received a varicella vaccine, and then developed a rash and fever 30 days after vaccination. At the time of vaccination, the patient was undergoing treatment with methotrexate and mercaptopurine, and this therapy was continued postvaccination. The patient developed herpes zoster over the left chest 70 days postvaccination. Varicella virus DNA was demonstrated via PCR in vesicle fluid, and was found to be vaccine strain by restriction endonuclease analysis.

One case, a 27-month-old girl presenting with a herpes zoster rash in a C6–C8 dermatomal distribution 16 months after receiving a varicella vaccine, was described in three publications (Sauerbrei et al., 2003, 2004; Uebe et al., 2002). The patient was vaccinated 2 days after her sister developed varicella. Vaccine-strain varicella was demonstrated via PCR in vesicular fluid. The child had a history suspicious for immunocompromise with two hospital admissions (one for fever, the other for diarrhea), molluscum contagiosum beginning at 18 months, and monthly upper respiratory infections since 21 months of age. Evaluation of the immune system did not reveal immunodeficiency. There were normal T, B, and NK cell numbers but an inverted CD4:CD8 ratio with slightly elevated CD8 T cells. Serum IgG, IgA,



and IgM were normal, and the patient had specific antibodies to viral antigens. Tests excluded purine nucleoside phosphorylase deficiency and HIV.

In the following three cases the vaccine was likely not that used in the United States and the distribution of zoster may have been the inoculation site. For these two reasons, these cases do not contribute to the weight of evidence.

One case, a 4-year-old boy with acute lymphocytic leukemia who developed herpes zoster in the right deltoid 22 months after administration of a varicella vaccine (source not given), was described in seven publications (Gelb et al., 1987; Gershon et al., 1984b, 1985, 1986; Hardy et al., 1991; Lawrence et al., 1988; Williams et al., 1985). The vaccine was administered 18 months after initiation of chemotherapy. Chemotherapy was suspended 1 week prior to and after administration of the vaccine. Varicella virus was cultured from vesicular fluid. Subsequent restriction endonuclease analysis demonstrated the virus to be vaccine-strain varicella. In addition to the case described above, Hardy et al. (1991) reported a 5-year-old boy with leukemia who developed herpes zoster in the right arm (possibly the vaccination site) 19 months after vaccination (source not given) and 3 months after undergoing bone marrow transplantation. Varicella virus was cultured from vesicular fluid; subsequent restriction endonuclease analysis demonstrated the virus to be vaccine-strain varicella. The patient was considered immunocompromised due to the short duration since bone marrow transplantation.

Otsuka et al. (2009) described a 3-year-old girl who presented with herpes zoster 2 years after receiving a varicella vaccine. The distribution of the zoster was not provided. The patient's 2-year-old brother developed a fever and rash consisting of papulovesicles on the day that the patient recovered. Varicella virus DNA was demonstrated in the patient's brother's vesicular fluid and crust specimens; the virus was identified as vaccine-strain varicella by restriction fragment length polymorphism.

### *Weight of Mechanistic Evidence*

Herpes zoster is characterized by vesicular lesions erupting in a dermatomal distribution upon the reactivation of latent wild-type varicella virus (Whitley, 2010). Herpes zoster afflicts approximately 20 percent of the population (Whitley, 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

Cases showing definite dermal dissemination of zoster from the vaccine needed to meet three criteria, namely, (1) the zoster distribution was reported to extend beyond the dermatome of the initial injection, (2) the zoster was shown to be vaccine type, and (3) the vaccine given was that currently given in the United States. Only two cases meet these criteria, one reported by Chan et al. (2007) and one reported by both Chaves et al.

(2008) and Galea et al. (2008). This second case is somewhat less convincing because the zoster-like rash in that case developed only 25 days after the initial vaccination. The other cases reviewed, however, increased the committee's confidence, because of the large number of zoster cases reported in the four publications describing reports submitted to passive surveillance systems. It seems certain that some of these had disseminated beyond the initial injection site. In addition, the vaccines that were not clearly that used in the United States led to disseminated zoster limited to the skin in several cases. Thus, the 18 publications described above presented clinical evidence sufficient for the committee to conclude that the vaccine was a contributing cause of viral reactivation with dermal dissemination without other organ involvement. In 13 of the publications described above it was unclear if the vaccine administered was equivalent to that currently used in the United States. In all publications described above the vaccine administered contained the Oka varicella strain described in the introduction to the chapter. Herpes zoster was reported in individuals with and without demonstrated immunodeficiencies (e.g., genetic or acquired). Vaccine-strain varicella was demonstrated in vesicular fluid in the cases described above.

The latency between vaccination and development of herpes zoster in the publications described above ranged from 23 days to 11 years suggesting viral reactivation as the mechanism.

*The committee assesses the mechanistic evidence regarding an association between varicella vaccine and vaccine-strain viral reactivation without other organ involvement as strong based on cases<sup>2</sup> presenting clinical evidence.*

### Causality Conclusion

**Conclusion 5.3: The evidence convincingly supports a causal relationship between varicella vaccine and vaccine-strain viral reactivation without other organ involvement.**

### VACCINE-STRAIN VIRAL REACTIVATION WITH OTHER ORGAN INVOLVEMENT

The definition of vaccine-strain viral reactivation with organ involvement involves the finding of vaccine virus in sites other than the skin after 42 days after the initial vaccination. Vaccine virus should be found in the

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<sup>2</sup>Due to the use of the same surveillance systems in some publications it is likely that some of the cases were presented more than once, thus it is difficult to determine the number of unique cases.

organ that is involved and the findings in the organ should support the presence of disease not merely minor laboratory abnormalities.

### Epidemiologic Evidence

#### *Meningitis*

The committee reviewed three studies to evaluate the risk of meningitis after the administration of varicella vaccine. These three studies (Chaves et al., 2008; Goulleret et al., 2010; Wise et al., 2000) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

#### *Encephalitis*

The committee reviewed six studies to evaluate the risk of encephalitis after the administration of varicella vaccine. Five studies (Chaves et al., 2008; Galea et al., 2008; Goulleret et al., 2010; Sharrar et al., 2001; Wise et al., 2000) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

The one remaining controlled study (Donahue et al., 2009) contributed to the weight of epidemiologic evidence and is described below.

Donahue et al. (2009) conducted a retrospective cohort study in 3.25 million children (11 months to 17 years of age) enrolled at eight medical care organizations (MCOs) participating in the Vaccine Safety Datalink (VSD) from January 1991 through December 2004. The study investigated the occurrence of ischemic stroke or encephalitis (reported in hospitalizations) within 12 months of varicella vaccination. The unexposed period included all other time observed outside the 12-month risk window. Children were eligible to participate if they were enrolled in the MCO for at least 12 months (or since birth). Patients with diagnoses of infantile cerebral palsy, stroke, or hemiplegia/hemiparesis at or before 11 months of age were excluded. The participants were disenrolled from the study once they experienced one of the primary outcomes, reached 18 years of age, left their MCO, or received one of the exclusionary diagnoses (leukemia/lymphoma, HIV/AIDS, primary immune system and bone marrow disorders, leucopenia, myeloproliferative diseases, and other syndromes associated with immunodeficiency). The analyses were adjusted for MCO site, months after exposure, calendar time, and gender. The vaccination and diagnosis information were obtained from electronic databases; the authors did not review the medical charts. Approximately 1.14 million children were vaccinated and 2.09 million children were not vaccinated during the

study. A total of 243 children were diagnosed with encephalitis, of whom 11 were diagnosed within 12 months, and 1 was diagnosed within 90 days of receiving a varicella vaccination. None of the adjusted hazard ratios for encephalitis observed at any time within 12 months of vaccination were significantly elevated. Only one hazard ratio was listed in the study for encephalitis within 30–90 days of varicella vaccination (HR, 0.7; 95% CI, 0.1–5.2). The authors found no association between the administration of varicella vaccine and encephalitis within 12 months following vaccination.

### *Weight of Epidemiologic Evidence*

*The committee has limited confidence in the epidemiologic evidence, based on one study that lacked validity and precision, to assess an association between varicella vaccine and vaccine-strain viral reactivation with subsequent infection resulting in encephalitis.*

*The epidemiologic evidence is insufficient or absent to assess an association between varicella vaccine and vaccine-strain viral reactivation with subsequent infection resulting in meningitis.*

## Mechanistic Evidence

### *Meningitis*

The committee identified nine publications reporting viral reactivation with subsequent infection resulting in meningitis after administration of a varicella vaccine. Wise et al. (2000) reported the isolation of wild-type varicella virus in one girl that developed herpes zoster and meningitis 21 months after administration of a varicella vaccine. This publication did not contribute to the weight of mechanistic evidence.

Described below are eight publications reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence. Seven case reports were strong in that vaccine virus was detected in the CSF associated with meningitis months to years after the initial vaccination.

Chaves et al. (2008) and Galea et al. (2008) described the development of herpes zoster with subsequent infection resulting in meningitis after administration of a varicella vaccine reported to VAERS and WAES. Sharrar et al. (2001) report that all of the reports submitted to WAES are submitted to VAERS. Due to the use of the same material it is likely that many of the cases overlap in Chaves et al. (2008) and Galea et al. (2008).

There were two cases in the publications describing reports submitted

to passive surveillance systems with meningitis and vaccine virus demonstrated in the CSF. The other cases were not associated with vaccine virus in the CSF and thus did not contribute to the weight of mechanistic evidence. One case was a 4-year-old child undergoing chemotherapy for acute lymphocytic leukemia who presented with herpes zoster followed by meningitis (Chaves et al., 2008; Galea et al., 2008). The child had been given the varicella vaccine while healthy, 19 months before presentation of symptoms of meningitis. Vaccine-strain varicella was demonstrated in the CSF and herpes zoster lesions. The patient's immune system was suppressed by the chemotherapy. Chaves et al. (2008) reported a second case. A 4-year-old previously healthy child presented with herpes zoster rash followed by meningitis. The patient had received a varicella vaccine 32 months earlier. Vaccine-strain varicella was demonstrated in the CSF.

Chaves et al. (2008) identified an additional eight cases of herpes zoster with subsequent infection resulting in meningitis after administration of a varicella vaccine. Two demonstrated vaccine-strain varicella in skin lesions but did not detect varicella virus in the CSF. Galea et al. (2008) identified an additional five cases of herpes zoster with subsequent infection resulting in meningitis after administration of a varicella vaccine. CSF specimens from these cases were negative for varicella virus. Vaccine-strain varicella virus was demonstrated in the herpes zoster lesions in two of the five cases. Wild-type varicella virus was demonstrated in the herpes zoster lesion in one of the five cases. Also, in one of the five cases enterovirus was demonstrated in the CSF. These cases did not contribute to the weight of evidence.

Iyer et al. (2009) reported a 9-year-old boy presenting with a zoster rash followed 4 days later by headache and then fatigue, as well as neck and back pain. The previously healthy child had received a varicella vaccine 8 years before development of symptoms. The CSF was negative for bacteria, enterovirus, and herpes simplex virus. DNA was amplified via PCR from vesicle fluid and the CSF, and demonstrated to be vaccine-strain varicella by identification of single-nucleotide polymorphisms. The patient was screened for immunodeficiency; a lymphocyte subset analysis was performed and was normal.

Levin et al. (2008) reported an 8-year-old boy who developed pruritic vesicles on the left shoulder followed 4 days later by headache, meningismus, photophobia, vomiting, and fever. The patient was diagnosed with herpes zoster and meningitis. The patient had received a varicella vaccine 7 years before presentation of symptoms. Vaccine-strain varicella was demonstrated via PCR in vesicular lesions and the CSF. The patient was screened for immunodeficiency; the patient's immunoglobulin levels, and T cell and B cell subsets, were found to be normal and the HIV-1 test was negative.

Levin et al. (2003) describe a 1-year-old boy, subsequently diagnosed with a neuroblastoma, presenting with herpes zoster lesions on the right

thigh, the site of vaccination, 3 months after receiving a varicella vaccine and the start of chemotherapy. The lesions increased in number and area of involvement 4 months after the onset of herpes zoster. The patient became irritable and developed fever and erythematous papules on the scalp, face, and trunk 1 month after stem-cell infusion. Varicella virus isolated from a skin biopsy and the CSF was determined to be vaccine strain by PCR.

Three cases of meningitis were reported in which varicella was detected in the CSF but the virus was not typed. These cases follow but did not contribute to the weight of evidence. Schwab and Ryan (2004) described a 5-year-old girl who presented with headache, fever, and a pruritic rash with raised lesions that began on the face and spread to the trunk 18 months after receiving a varicella vaccine. A positive Brudzinski sign was elicited. Varicella virus was demonstrated in skin lesions by direct immunofluorescence antibody and in the CSF by PCR; the strain of virus was not identified.

Chilek et al. (2010) described a 10-year-old boy who presented with a bilateral photophobia, headache, left eye pain, and a nondermatomal vesicular rash involving the upper extremities, neck, and left eye after administration of catch up of two varicella vaccines 9 and 3 months earlier. Varicella virus was demonstrated by direct fluorescent antibody and viral culture. Testing was not done to determine if the virus was wild type or vaccine type. The patient tested positive for HIV.

Naruse et al. (1993) described a 45-month-old boy who presented with a vesicular rash, not limited to any dermatomal distribution, originating on the face and chest and spreading to the extremities 21 months after administration of a varicella vaccine. Two days later the patient developed headache and frequent vomiting. Bacterial cultures of the blood, throat swab, and CSF were negative. Varicella virus was demonstrated in the CSF by PCR; the strain of virus was not identified.

### *Encephalitis*

The committee identified three publications reporting the development of encephalitis after administration of a varicella vaccine. One publication reported multiple cases but did not provide evidence beyond temporality (Sharrar et al., 2001). In addition, the development of encephalitis in some of the cases was attributed to other etiologies. This publication did not contribute to the weight of mechanistic evidence.

Described below is one case described in two publications reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

The single case was a 3-year-old girl who presented with a herpetiform rash on the right side of her face, dizziness, vomiting, somnolence, fever, and conjunctivitis 20 months after receiving a varicella vaccine (Chouliaras

et al., 2010; Goulleret et al., 2010). An electroencephalogram showed slow waves consistent with encephalitis. Analysis of the CSF revealed normal levels of protein and glucose, and no white blood cells. In addition, the CSF was negative for herpes simplex virus 1 and 2. The patient was diagnosed with mild encephalitis and herpes zoster ophthalmicus. Vaccine-strain varicella was demonstrated via PCR in the CSF. Analysis of serum immunoglobulins and quantification of T cell and B cell subpopulations did not reveal abnormalities of the patient's immune system.

### *Weight of Mechanistic Evidence*

Herpes zoster is characterized by vesicular lesions erupting in a dermatomal distribution upon the reactivation of latent wild-type varicella virus (Whitley, 2010). Herpes zoster afflicts approximately 20 percent of the population, and can be associated with central nervous system complications (Whitley, 2010). Meningitis and encephalitis have been reported as nervous system manifestations of wild-type varicella infection (Whitley, 2010). Encephalitis has been reported as a nervous system manifestation in 0.1–0.2 percent of individuals infected with wild-type varicella zoster virus (Whitley, 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

In addition, six cases described above presented clinical evidence sufficient for the committee to conclude the vaccine was a contributing cause of vaccine-strain viral reactivation with subsequent infection resulting in meningitis or encephalitis (Chaves et al., 2008; Chouliaras et al., 2010; Galea et al., 2008; Goulleret et al., 2010; Iyer et al., 2009; Levin et al., 2003, 2008). Vaccine-strain varicella virus was demonstrated in the CSF in six cases described above (Chaves et al., 2008; Chouliaras et al., 2010; Galea et al., 2008; Goulleret et al., 2010; Iyer et al., 2009; Levin et al., 2003, 2008). In addition, vaccine-strain varicella virus was demonstrated in vesicular lesions in four of the cases described above (Chaves et al., 2008; Galea et al., 2008; Iyer et al., 2009; Levin et al., 2003, 2008).

The variation in the latency between vaccination and development of symptoms of either meningitis or encephalitis was considerable. The latency between vaccination and the development of either meningitis or encephalitis ranged from 19 months to 8 years suggesting viral reactivation as the mechanism in the cases described above.

*The committee concludes the clinical and biological evidence is strong in support of an association between varicella vaccine and vaccine-strain viral reactivation with subsequent infection resulting in meningitis or encephalitis based on six cases presenting definitive clinical evidence.*

### Causality Conclusion

**Conclusion 5.4:** The evidence convincingly supports a causal relationship between varicella vaccine and vaccine-strain viral reactivation with subsequent infection resulting in meningitis or encephalitis.

## ENCEPHALOPATHY

### Epidemiologic Evidence

The committee reviewed three studies to evaluate the risk of encephalitis after the administration of varicella vaccine. These three studies (Chaves et al., 2008; Goulleret et al., 2010; Wise et al., 2000) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between varicella vaccine and encephalopathy.*

### Mechanistic Evidence

The committee identified three publications reporting the development of encephalopathy after administration of a varicella vaccine. Two publications did not provide clinical, diagnostic, or experimental evidence, including the time frame between vaccination and development of symptoms (Chaves et al., 2008; Goulleret et al., 2010). One publication reported multiple cases, but did not provide evidence beyond temporality (Wise et al., 2000). In addition, the development of symptoms in some of the cases described by Wise et al. (2000) was attributed to other etiologies. The publications did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of encephalopathy. Viral infection and viral reactivation may contribute to the symptoms of encephalopathy; however, the publications did not provide evidence linking these mechanisms to varicella vaccine.

*The committee assesses the mechanistic evidence regarding an association between varicella vaccine and encephalopathy as lacking.*



### Causality Conclusion

**Conclusion 5.5:** The evidence is inadequate to accept or reject a causal relationship between varicella vaccine and encephalopathy.

## SEIZURES

### Epidemiologic Evidence

The committee reviewed four studies to evaluate the risk of seizures after the administration of varicella vaccine. Three studies (Chaves et al., 2008; Klein et al., 2010; Wise et al., 2000) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

The one remaining controlled study (Black et al., 1999) contributed to the weight of epidemiologic evidence and is described below.

The study by Black et al. (1999) was described in detail in the section on disseminated Oka VZV with subsequent infection resulting in pneumonia. This retrospective cohort study reported potential adverse events following varicella vaccination, obtained from the KPMCP database. The relative risk of febrile seizures in the 1-year age group recorded during hospitalizations within 60 days of varicella vaccination (21 cases), compared to the 91–150 postvaccination control period (8 cases), was 2.27 (95% CI, 1.03–5.45;  $p = .04$ ). When this analysis was adjusted for patients who received MMR vaccine in combination with varicella vaccine, the association was no longer statistically significant (relative risk [RR], 0.58; 95% CI, 0.07–3.92;  $p = .586$ ).<sup>3</sup> The relative risk of seizures in the 1-year age group recorded during clinic visits within 30 days of varicella vaccination (52 cases), compared to the 91–120 postvaccination control period (30 cases), was 1.36 (95% CI, 1.02–2.52); however, this analysis was not adjusted for combined MMR vaccination. Only statistically significant increased risks were reported in the study; analyses were not available for other age groups or comparison groups. The authors concluded that varicella vaccination is not associated with an increased risk of seizures when the results are adjusted for combined administration of MMR vaccine.

### *Weight of Epidemiologic Evidence*

*The committee has limited confidence in the epidemiologic evidence, based on one study that lacked validity and precision, to assess an association between varicella vaccine and seizures.*

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<sup>3</sup>P. M. Ray, Kaiser Permanente Vaccine Study Center, personal communication, April 22, 2010.

### Mechanistic Evidence

The committee identified three publications reporting seizures developing after administration of a varicella vaccine. One publication did not provide clinical, diagnostic, or experimental evidence, including the time frame between vaccine administration and development of seizure (Chaves et al., 2008). Two publications did not provide evidence beyond temporality (Klein et al., 2010; Wise et al., 2000). In addition, Klein et al. (2010) reported the concomitant administration of vaccines, making it difficult to determine which, if any, vaccine could have been the precipitating event. The publications did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

Varicella infection is associated with seizures indirectly. Seizures can develop after wild-type varicella infection secondary to encephalitis and stroke (Whitley, 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

The symptoms described in the publications described above are consistent with those leading to a diagnosis of seizure. In some instances fever may contribute to the development of seizures; however, the publications did not provide evidence linking this mechanism to varicella vaccine.

*The committee assesses the mechanistic evidence regarding an association between varicella vaccine and seizures as weak based on knowledge about the natural infection.*

### Causality Conclusion

**Conclusion 5.6:** The evidence is inadequate to accept or reject a causal relationship between varicella vaccine and seizures.

## CEREBELLAR ATAXIA

### Epidemiologic Evidence

The committee reviewed six studies to evaluate the risk of cerebellar ataxia after the administration of varicella vaccine. Five studies (Chaves et al., 2008; Goulleret et al., 2010; Sharrar et al., 2001; van der Maas et al., 2009; Wise et al., 2000) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations. One controlled study (Black et al., 1999) had very serious methodological limitations that precluded its inclusion in this assessment. The study by Black et al. (1999) was unable

to find any cases of cerebellar ataxia following varicella vaccination, so no conclusions could be drawn from this analysis.

### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between varicella vaccine and cerebellar ataxia.*

### **Mechanistic Evidence**

The committee identified five publications reporting cerebellar ataxia developing after administration of a varicella vaccine. Two publications did not provide clinical, diagnostic, or experimental evidence, including the time frame between vaccination and development of ataxia (Chaves et al., 2008; Goulleret et al., 2010). Three publications did not provide evidence beyond temporality (Sharrar et al., 2001; Sunaga et al., 1995; Wise et al., 2000). The publications did not contribute to the weight of mechanistic evidence.

### *Weight of Mechanistic Evidence*

Cerebellar ataxia is associated with wild-type varicella infection with an incidence of approximately 1 in 4,000 cases among children younger than 15 years of age (Whitley, 2010). Cerebellar ataxia has been reported to present as late as 21 days after rash onset, while acute cerebellar ataxia has been reported to present within 1 week of rash onset (Whitley, 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of cerebellar ataxia. Viral infection may contribute to the symptoms of cerebellar ataxia; however, evidence of this mechanism was not reported in the publications referenced above.

*The committee assesses the mechanistic evidence regarding an association between varicella vaccine and cerebellar ataxia as weak based on knowledge about the natural infection.*

### **Causality Conclusion**

**Conclusion 5.7:** The evidence is inadequate to accept or reject a causal relationship between varicella vaccine and cerebellar ataxia.

## ACUTE DISSEMINATED ENCEPHALOMYELITIS

### Epidemiologic Evidence

The committee reviewed two studies to evaluate the risk of acute disseminated encephalomyelitis (ADEM) after the administration of varicella vaccine. These two studies (Goulleret et al., 2010; Wise et al., 2000) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between varicella vaccine and ADEM.*

### Mechanistic Evidence

The committee identified one publication reporting development of ADEM after administration of a varicella vaccine. The publication reported several cases but did not provide evidence beyond temporality (Wise et al., 2000). The publication did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

Infection with wild-type varicella zoster is associated with ADEM with an incidence of approximately 1 per 10,000 cases (Davis, 2008). The committee considers the effects of natural infection one type of mechanistic evidence.

The symptoms described in the publication referenced above are consistent with those leading to a diagnosis of ADEM. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of ADEM; however, the publication did not provide evidence linking these mechanisms to varicella vaccine.

*The committee assesses the mechanistic evidence regarding an association between varicella vaccine and ADEM as weak based on knowledge about the natural infection.*

### Causality Conclusion

**Conclusion 5.8:** The evidence is inadequate to accept or reject a causal relationship between varicella vaccine and ADEM.

## TRANSVERSE MYELITIS

### Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of transverse myelitis after the administration of varicella vaccine. This one study (Wise et al., 2000) was not considered in the weight of epidemiologic evidence because it provided data from a passive surveillance system and lacked an unvaccinated comparison population.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between varicella vaccine and transverse myelitis.*

### Mechanistic Evidence

The committee identified two publications reporting transverse myelitis after administration of a varicella vaccine. One publication did not provide evidence beyond temporality (Wise et al., 2000). The publication did not contribute to the weight of mechanistic evidence.

Described below is one publication reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

LaRovere et al. (2008) described a 14-year-old boy presenting with a papulovesicular rash 8 years after receiving a varicella vaccine. The patient presented with mid-scapular pain 6 days after resolution of the rash, followed 2 days later by bilateral leg paresthesias and weakness, urinary retention, and unsteady gait leading to a diagnosis of acute transverse myelitis. Antivaricella antibodies, but not varicella virus, were demonstrated in the CSF. The patient was treated with intravenous methylprednisolone and was asymptomatic 2 months after development of the symptoms.

#### *Weight of Mechanistic Evidence*

On rare occasions transverse myelitis has been associated with herpes zoster and reactivation of latent wild-type varicella viruses (Whitley, 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

The publication described above did not present evidence sufficient for the committee to conclude the vaccine may be a contributing cause of transverse myelitis. The development of a papulovesicular rash 8 years after administration of the vaccine, and isolation of antivaricella antibodies

from the CSF, suggests viral reactivation as a mechanism. However, vaccine-strain varicella was not isolated, detracting from the weight of mechanistic evidence.

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of transverse myelitis. Autoantibodies, T cells, viral reactivation, infection, and molecular mimicry may contribute to the development of transverse myelitis; however, the publications did not provide evidence linking these mechanisms to varicella vaccine.

*The committee assesses the mechanistic evidence regarding an association between varicella vaccine and transverse myelitis as weak based on knowledge about the natural infection and one publication.*

### Causality Conclusion

**Conclusion 5.9:** The evidence is inadequate to accept or reject a causal relationship between varicella vaccine and transverse myelitis.

## GUILLAIN-BARRÉ SYNDROME

### Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of GBS after the administration of varicella vaccine. This one study (Wise et al., 2000) was not considered in the weight of epidemiologic evidence because it provided data from a passive surveillance system and lacked an unvaccinated comparison population.

### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between varicella vaccine and GBS.*

### Mechanistic Evidence

The committee identified one publication reporting development of GBS after administration of a varicella vaccine. The publication reported several cases but did not provide evidence beyond temporality (Wise et al., 2000). The publication did not contribute to the weight of mechanistic evidence.

*Weight of Mechanistic Evidence*

On rare occasions GBS has been associated with herpes zoster and reactivation of latent wild-type varicella viruses (Whitley, 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

The symptoms described in the publication referenced above are consistent with those leading to a diagnosis of GBS. Autoantibodies, complement activation, immune complexes, T cells, and molecular mimicry may contribute to the symptoms of GBS; however, the publication did not provide evidence linking these mechanisms to varicella vaccine.

*The committee assesses the mechanistic evidence regarding an association between varicella vaccine and GBS as weak based on knowledge about the natural infection.*

**Causality Conclusion**

**Conclusion 5.10:** The evidence is inadequate to accept or reject a causal relationship between varicella vaccine and GBS.

**SMALL FIBER NEUROPATHY****Epidemiologic Evidence**

No studies were identified in the literature for the committee to evaluate the risk of small fiber neuropathy after the administration of varicella vaccine.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between varicella vaccine and small fiber neuropathy.*

**Mechanistic Evidence**

The committee identified one publication reporting small fiber neuropathy after administration of a varicella vaccine. The publication did not provide evidence beyond temporality (Souayah et al., 2009). The publication did not contribute to the weight of mechanistic evidence.

*Weight of Mechanistic Evidence*

The symptoms described in the publication referenced above are consistent with those leading to a diagnosis of small fiber neuropathy. Autoanti-

bodies, T cells, and molecular mimicry may contribute to the symptoms of small fiber neuropathy; however, the publication did not provide evidence linking these mechanisms to varicella vaccine.

*The committee assesses the mechanistic evidence regarding an association between varicella vaccine and small fiber neuropathy as lacking.*

### Causality Conclusion

**Conclusion 5.11:** The evidence is inadequate to accept or reject a causal relationship between varicella vaccine and small fiber neuropathy.

## ANAPHYLAXIS

### Epidemiologic Evidence

The committee reviewed seven studies to evaluate the risk of anaphylaxis after the administration of varicella vaccine. Six studies (Chaves et al., 2008; DiMiceli et al., 2006; Ozaki et al., 2005; Sakaguchi et al., 2000b; Sharrar et al., 2001; Wise et al., 2000) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

The one remaining controlled study (Black et al., 1999) contributed to the weight of epidemiologic evidence and is described below.

The study by Black et al. (1999) was described in detail in the section on disseminated Oka VZV with subsequent infection resulting in pneumonia. This retrospective cohort study reported potential adverse events following varicella vaccination, obtained from the KPMCP database. The relative risk of allergic reactions with or without hives in the 1-year age group recorded during clinic visits within 30 days of varicella vaccination (180 cases), compared to the 91–120-day postvaccination control period (130 cases), was 1.27 (95% CI, 1.02–1.60). Only statistically significant increased risks were reported in the study; analyses were not available for other age groups or comparison groups.

### *Weight of Epidemiologic Evidence*

*The committee has limited confidence in the epidemiologic evidence, based on one study that lacked validity and precision, to assess an association between varicella vaccine and anaphylaxis.*



### Mechanistic Evidence

The committee identified eight publications describing clinical, diagnostic, or experimental evidence of anaphylaxis postvaccination against varicella vaccines that contributed to the weight of mechanistic evidence. These publications are described below.

DiMiceli et al. (2006) identified cases of anaphylaxis postvaccination in patients with a history of yeast allergy reported to VAERS from July 1990 through July 2004. One case (case 15 in the report) describes a 35-year-old woman presenting with urticaria, pruritus, oropharyngeal edema, nasal congestion, dyspnea, and tachycardia 1 hour after receiving a varicella vaccine.

Kumagai et al. (1997) identified two cases of anaphylaxis (cases 3 and 4 in the report) developing in men, ages 22 and 23, after vaccination with a varicella vaccine. One patient presented with wheezing and dyspnea, and the other presented with wheezing, urticaria, and dyspnea. In both cases the symptoms developed within 15 minutes after receipt of the vaccine. Furthermore, laboratory tests showed that both patients were positive for antigelatin IgE.

Ozaki et al. (2005) identified anaphylaxis and allergic reactions, after administration of varicella vaccines, reported to the Post-Marketing Surveillance Center of the Research Foundation for Microbial Diseases of Osaka University. The authors defined anaphylaxis as cardiovascular and/or respiratory symptoms with an allergic reaction developing within 1 hour after receipt of the vaccine. Thirty-two cases of anaphylaxis developed and serum samples were isolated from nine patients. All nine samples were positive for antigelatin IgE.

Sakaguchi et al. (1997) reported three cases of anaphylaxis postvaccination with varicella vaccines. Case 1 describes a 4-year-old boy presenting with vomiting, urticaria, and airway obstructions with wheezing 40 minutes after vaccination. Case 2 describes a 16-month-old boy presenting with angioedema, urticaria, and airway obstruction with wheezing 20 minutes after vaccination. Case 3 describes a 22-month-old boy presenting with cough, urticaria, and wheezing 1 hour after vaccination. Laboratory tests showed all three patients were positive for antigelatin IgE.

Sakaguchi et al. (2000a) studied the relationship between antigelatin IgE and IgG and non-immediate-type reactions to gelatin-containing varicella vaccines. The authors examined sera from 33 patients that experienced immediate-type reactions after administration of a varicella vaccine as a positive control. Within 1 hour after vaccination, 18 of the patients serving as positive controls developed respiratory and cutaneous symptoms. All 18 of the patients produced antigelatin IgE and IgG antibodies.

Sakaguchi et al. (2000b) reported the incidence of anaphylaxis after

live viral vaccines containing gelatin. The authors subdivided systemic immediate-type reactions into three groups. Two groups, severe anaphylaxis and mild anaphylaxis, consisted of respiratory and cutaneous symptoms developing within 1 hour after vaccination. The third group consisted of cutaneous symptoms alone developing within 1 hour after vaccination. A total of 16 cases of anaphylaxis and 14 cases of systemic cutaneous symptoms developing after vaccination against varicella were identified. Of the above described cases, 27 had antigelatin IgE antibodies.

Sharrar et al. (2001) identified seven cases of anaphylaxis postvaricella vaccination reported to WAES or VAERS during the first 4 years of marketing of a gelatin-containing varicella vaccine. The four boys and three girls ranged in age from 3 to 8 years. The patients developed symptoms of urticaria, hypotension, coughing, wheezing, stridor, swollen lips, and/or itching shortly after vaccination.

Wise et al. (2000) identified 30 cases of anaphylaxis postvaricella vaccination reported to VAERS from March 1995 through July 1998. Each case presented with skin and respiratory symptoms within 4 hours after vaccination; in 11 cases, patients presented symptoms within 15 minutes after vaccination. One patient had a history of egg allergy, and presented with similar symptoms after receiving an MMR vaccine. Three patients had a history of allergies to antibiotics, atropine, or ophthalmic solution.

### *Weight of Mechanistic Evidence*

The publications described above presented clinical evidence sufficient for the committee to conclude the vaccine was a contributing cause of anaphylaxis after administration of a gelatin-containing varicella vaccine. Four publications from investigators in Japan described well-documented cases of anaphylaxis occurring in individuals with documented IgE antibodies to gelatin (Ozaki et al., 2005; Sakaguchi et al., 1997, 2000a,b). Gelatin, both whole bovine and hydrolyzed gelatin, was used as a stabilizer in a number of vaccines in Japan, and it is likely that children experiencing anaphylactic reactions to the gelatin-containing varicella vaccine had developed IgE sensitization to gelatin from the administration of previous vaccines. The varicella vaccine distributed in the United States contains only hydrolyzed gelatin; the extent to which gelatin is hydrolyzed could vary from one vaccine lot to another and affect the development of anaphylaxis. Some patients are allergic to either bovine or porcine gelatin, but not both (Bogdanovic et al., 2009). Although there is considerable cross-reactivity between bovine and porcine gelatin, testing for antibody to one gelatin alone is not necessarily predictive of allergy to the other and may not be predictive of reactivity to the gelatin in varicella vaccine.

*The committee assesses the mechanistic evidence regarding an association between varicella vaccine and anaphylaxis as strong based on 76 cases<sup>4</sup> presenting temporality and clinical symptoms consistent with anaphylaxis.*

### Causality Conclusion

**Conclusion 5.12: The evidence convincingly supports a causal relationship between varicella vaccine and anaphylaxis.**

## ONSET OR EXACERBATION OF ARTHROPATHY

### Epidemiologic Evidence

The committee reviewed two studies to evaluate the risk of arthropathy (arthralgia and arthritis) after the administration of varicella vaccine. These two studies (Chaves et al., 2008; Wise et al., 2000) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between varicella vaccine and onset or exacerbation of arthropathy.*

### Mechanistic Evidence

The committee identified three publications reporting onset or exacerbation of arthropathy (arthritis and arthralgia) after administration of a varicella vaccine. Two publications reported multiple cases but either did not provide evidence beyond temporality or did not provide clinical, diagnostic, or experimental evidence, including the time frame between vaccination and development of symptoms (Chaves et al., 2008; Wise et al., 2000). Pileggi et al. (2010) did not observe the worsening of symptoms in patients previously diagnosed with juvenile rheumatic diseases after administration of a varicella vaccine. The publications did not contribute to the weight of mechanistic evidence.

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<sup>4</sup>In addition, at least 30 cases were reported to passive surveillance systems; however, it was not possible to know how many were represented unique cases or were reported elsewhere.

*Weight of Mechanistic Evidence*

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of arthropathy. Autoantibodies, T cells, complement activation, immune complexes, infection, viral reactivation, and viral persistence may contribute to the symptoms of arthropathy; however, the publications did not provide evidence linking these mechanisms to varicella vaccine.

*The committee assesses the mechanistic evidence regarding an association between varicella vaccine and onset or exacerbation of arthropathy as lacking.*

**Causality Conclusion**

**Conclusion 5.13:** The evidence is inadequate to accept or reject a causal relationship between varicella vaccine and onset or exacerbation of arthropathy.

**STROKE****Epidemiologic Evidence**

The committee reviewed one study to evaluate the risk of ischemic stroke after the administration of varicella vaccine. This one controlled study (Donahue et al., 2009) contributed to the weight of epidemiologic evidence and is described below.

The study by Donahue et al. (2009) was described in detail in the section on vaccine strain viral reactivation with subsequent infection resulting in encephalitis. This retrospective cohort study investigated the occurrence of ischemic stroke or encephalitis (reported in hospitalizations obtained from the VSD) within 12 months of varicella vaccination. A total of 203 children were diagnosed with ischemic stroke, of whom one received a varicella vaccination within 3 months of diagnosis, and eight did so within 12 months. Adjusted hazard ratios (HRs) were reported for stroke within 1 month of vaccination (HR, 1.1; 95% CI, 0.1–9.2), 1–3 months of vaccination (HR, 0.7; 95% CI, 0.1–5.7), 3–6 months of vaccination (HR, 1.3; 95% CI, 0.3–5.6), 6–9 months of vaccination (HR, 1.3; 95% CI, 0.4–4.9), and 9–12 months of vaccination (HR, 0.4; 95% CI, 0.0–3.2). The authors concluded that varicella vaccination is not associated with ischemic stroke in children.

*Weight of Epidemiologic Evidence*

*The committee has limited confidence in the epidemiologic evidence, based on one study that lacked validity and precision, to assess an association between varicella vaccine and ischemic stroke.*

**Mechanistic Evidence**

The committee identified two publications reporting stroke after administration of a varicella vaccine. The publications did not provide evidence beyond temporality and therefore did not contribute to the weight of mechanistic evidence (Donahue et al., 2009; Wirrell et al., 2004).

*Weight of Mechanistic Evidence*

Infection with varicella virus has been associated with stroke with an incidence of approximately 1 in 15,000 cases (Nagel et al., 2010). Varicella virus has been shown to produce vasculopathy via direct invasion of cerebral arteries (Nagel et al., 2010). In adults, stroke associated with varicella presents after herpes zoster ophthalmicus, which is followed weeks to months later by acute contralateral hemiplegia (Nagel et al., 2010). In children, stroke follows acute hemiplegia following varicella infection (Nagel et al., 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of stroke. Direct viral infection, viral reactivation, and alterations in the coagulation cascade can lead to a hypercoagulable state that may contribute to the symptoms of stroke; however, the publications did not provide evidence linking these mechanisms to varicella vaccine.

*The committee assesses the mechanistic evidence regarding an association between varicella vaccine and stroke as weak based on knowledge about the natural infection.*

**Causality Conclusion**

**Conclusion 5.14:** The evidence is inadequate to accept or reject a causal relationship between varicella vaccine and stroke.

## THROMBOCYTOPENIA

### Epidemiologic Evidence

The committee reviewed three studies to evaluate the risk of thrombocytopenia after the administration of varicella vaccine. These three studies (Chaves et al., 2008; Sharrar et al., 2001; Wise et al., 2000) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between varicella vaccine and thrombocytopenia.*

### Mechanistic Evidence

The committee identified six publications reporting thrombocytopenia or idiopathic thrombocytopenic purpura after administration of a varicella vaccine. Chaves et al. (2008) did not provide clinical, diagnostic, or experimental evidence, including the time frame between vaccine administration and development of thrombocytopenia. Three publications did not provide evidence beyond temporality (Ferrera et al., 2009; Lee et al., 1986; Sharrar et al., 2001). One publication reported decreased platelet counts without development of unexplained bleeding, clotting, or bruising after vaccination but did not issue a diagnosis (Weibel et al., 1985). These publications did not contribute to the weight of mechanistic evidence.

Described below is one publication reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Wise et al. (2000) identified 31 reports, submitted to VAERS from March 1995 through July 1998, of thrombocytopenia developing after administration of a varicella vaccine. The authors did not provide evidence of causality beyond a temporal relationship of 4 to 28 days between vaccine administration and development of thrombocytopenia after vaccination for most reports. One VAERS report, identified in Wise et al. (2000), was obtained via a Freedom of Information Act request (FDA, 2010). The report describes a 14-year-old boy presenting with petechiae on the legs 1 week after administration of the first dose of a varicella vaccine. The patient experienced excessive bruising and was admitted to the hospital 9 days after administration of the second dose, and after being pinched. Laboratory

tests during hospitalization revealed a platelet count of 29,000 on day 1 and 62,000 on day 3. The patient's platelet count was 198,000 on day 6.

### *Weight of Mechanistic Evidence*

While rare, infection with wild-type varicella virus has been associated with bleeding diathesis (Whitley, 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

The publication described above did not present evidence sufficient for the committee to conclude the vaccine may be a contributing cause of thrombocytopenia. The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of thrombocytopenia, but the only evidence that could be attributed to the vaccine was recurrence of symptoms upon vaccine rechallenge. Autoantibodies and complement activation may contribute to the symptoms of thrombocytopenia; however, the publications did not provide evidence linking these mechanisms to varicella vaccine.

*The committee assesses the mechanistic evidence regarding an association between varicella vaccine and thrombocytopenia as weak based on knowledge about the natural infection and one case.*

### **Causality Conclusion**

**Conclusion 5.15: The evidence is inadequate to accept or reject a causal relationship between varicella vaccine and thrombocytopenia.**

### **CONCLUDING SECTION**

Table 5-1 provides a summary of the epidemiologic assessments, mechanistic assessments, and causality conclusions for varicella vaccine.

**TABLE 5-1** Summary of Epidemiologic Assessments, Mechanistic Assessments, and Causality Conclusions for Varicella Vaccine

| Vaccine   | Adverse Event   | Epidemiologic Assessment  | Studies Contributing to the Epidemiologic Assessment | Mechanistic Assessment                                       | Cases Contributing to the Mechanistic Assessment | Causality Conclusion  |
|-----------|---|---|--|--|--|---|
| Varicella | Disseminated Oka VZV without Other Organ Involvement  | Insufficient  | None   | Strong   | – <sup>a</sup>                                   | Convincingly Supports   |
| Varicella | Disseminated Oka VZV with Subsequent Infection Resulting in Pneumonia, Meningitis, or Hepatitis     | Limited (subsequent infection resulting in pneumonia)<br>Insufficient (subsequent infection resulting in meningitis or hepatitis) | 1<br>None  | Strong (in individuals with demonstrated immunodeficiencies) | 9  | Convincingly Supports (in individuals with demonstrated immunodeficiencies) |
| Varicella | Vaccine-Strain Viral Reactivation without Other Organ Involvement                                   | Insufficient  | None   | Strong   | – <sup>a</sup>                                   | Convincingly Supports   |
| Varicella | Vaccine-Strain Viral Reactivation with Subsequent Infection Resulting in Meningitis or Encephalitis | Limited (subsequent infection resulting in encephalitis)<br>Insufficient (subsequent infection resulting in meningitis)           | 1<br>None  | Strong   | 6  | Convincingly Supports   |
| Varicella | Encephalopathy  | Insufficient  | None   | Lacking  | None   | Inadequate  |
| Varicella | Seizures  | Limited   | 1  | Weak   | None   | Inadequate  |

*continued*



TABLE 5-1 Continued

| Vaccine   | Adverse Event                        | Studies                  |  |                        | Cases                                      |                       |
|-----------|--------------------------------------|--------------------------|--|------------------------|--|-----------------------|
|           |                                      | Epidemiologic Assessment | Contributing to the Epidemiologic Assessment | Mechanistic Assessment | Contributing to the Mechanistic Assessment | Causality Conclusion  |
| Varicella | Cerebellar Ataxia                    | Insufficient             | None   | Weak                   | None                                       | Inadequate            |
| Varicella | Acute Disseminated Encephalomyelitis | Insufficient             | None   | Weak                   | None                                       | Inadequate            |
| Varicella | Transverse Myelitis                  | Insufficient             | None   | Weak                   | 1  | Inadequate            |
| Varicella | Guillain-Barré Syndrome              | Insufficient             | None   | Weak                   | None                                       | Inadequate            |
| Varicella | Small Fiber Neuropathy <sup>b</sup>  | Insufficient             | None   | Lacking                | None                                       | Inadequate            |
| Varicella | Anaphylaxis                          | Limited                  | 1  | Strong                 | 76 <sup>c</sup>                            | Convincingly Supports |
| Varicella | Onset or Exacerbation of Arthropathy | Insufficient             | None   | Lacking                | None                                       | Inadequate            |
| Varicella | Stroke <sup>b</sup>                  | Limited                  | 1  | Weak                   | None                                       | Inadequate            |
| Varicella | Thrombocytopenia                     | Insufficient             | None   | Weak                   | 1  | Inadequate            |

<sup>a</sup>Due to the use of the same surveillance systems in some publications it is likely that some of the cases were presented more than once; thus, it is difficult to determine the number of unique cases.

<sup>b</sup>Although not originally charged to the committee by the sponsor, the committee considered this adverse event in its review of the literature.

<sup>c</sup>In addition, at least 30 cases were reported to passive surveillance systems; however, it was not possible to know how many represented unique cases or were reported elsewhere.

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## 6

## Influenza Vaccine

## INTRODUCTION

Influenza viruses are 80–120 nm enveloped viruses of the family Orthomyxoviridae (Treanor, 2010). Divided into three types—A, B, and C—these viruses can infect a range of hosts from humans only (influenza B) to humans and swine (influenza C) to multiple host organisms including humans, swine, equine, avian, and marine mammals (influenza A) (Treanor, 2010). Influenza viruses are highly changeable viruses. Small antigenic changes, known as “antigenic drift,” occur regularly, usually as point mutations in the virus genome or through exchange of small gene segments with another strain of influenza virus (Han and Marasco, 2011; Treanor, 2010). Occasionally, influenza viruses undergo an abrupt and dramatic change in genome. This change, known as “antigenic shift,” results in a new virus that is so different from previous viruses that no immunity exists in the population and can lead to pandemic influenza (Treanor, 2010). Antigenic shift is usually caused by genetic recombination between two strains of influenza virus; one from a strain that can infect humans and one that, prior to the genetic exchange, could not (Han and Marasco, 2011). The impact of these changes depends on the extent of the change, but because viral epitopes from the variant strains that result from antigenic shifts and drifts may not be recognized by the immune system, vaccines must be altered regularly to combat the infection.

Influenza viruses are named based on the type of influenza, the location of initial isolation, strain designation number, and the year of isolation (e.g., A/Brisbane/59/2007). Influenza A viruses are further divided into subtypes

based on the characteristics of the hemagglutinin (H or HA) and neuraminidase (N or NA) surface proteins (Treanor, 2010). This subtyping is the basis of the H#N# designations of the influenza A viruses. At least 16 distinct HA and 9 distinct NA surface proteins have been identified (Treanor, 2010). Influenza B viruses are subdivided as Yamagata or Victoria based on genetic lineage (Xu et al., 2004). Of the three distinct types of influenza viruses, influenza A viruses are the only viruses proven to cause pandemic disease and are capable of interspecies transmission, as demonstrated with the 1997 outbreak of avian (H5N1) influenza from poultry to humans (de Jong et al., 1997; Subbarao et al., 1998; Yuen et al., 1998).

Influenza viruses have caused epidemics every 1 to 3 years during the past four centuries, and four major pandemics have occurred including the great pandemic of 1918 (Treanor, 2010). These pandemics were caused by influenza A viruses H1N1 (1918 and 2009), H2N2 (1957), and H3N2 (1968) (Treanor, 2010). In any given year, two influenza A strains considered to be most likely to contribute to widespread (epidemic or pandemic) illness are included in the trivalent vaccine. Because of its ability to produce epidemic disease, an influenza B virus strain is also included in all current vaccines.

In the United States, a nearly annual influenza epidemic usually begins in late fall and peaks in mid to late winter. Influenza viruses are transmitted by contact with aerosol secretions containing the virus, and this occurs generally through coughing and sneezing (Belshe et al., 2008; Treanor, 2010). Following an average incubation period of 2 days but ranging from 1 to 4 days, adults and children remain infectious for approximately 5 days after the onset of the illness (CDC, 2002). Children, who generally have the highest attack rate and serve as the major source of transmission within communities (Glezen and Couch, 1978; Monto and Kioumeh, 1975), can be infectious for longer periods both before and after the onset of illness (Belshe et al., 2008). Uncomplicated influenza often begins abruptly with systemic symptoms of fever, chills, headaches, myalgia, malaise, anorexia, and fatigue. These symptoms persist for the duration of the fever—typically for 3 days (Treanor, 2010). Respiratory symptoms such as dry cough, sore throat, and nonproductive cough may also occur and usually persist for 2 weeks or more (Belshe et al., 2008; Treanor, 2010). Fevers tend to be higher in children and can lead to febrile seizures, while elderly individuals may experience afebrile disease with lassitude or confusion (Babcock et al., 2006; Bridges et al., 2008; Neuzil et al., 2003). The risk of complications from influenza is higher in children and the elderly and those with certain underlying conditions (Barker, 1986; Bridges et al., 2008; Simonsen et al., 2000; Thompson et al., 2004). The most common complications include primary influenza viral pneumonia, secondary bacterial pneumonia, and the

exacerbation of chronic pulmonary and cardiopulmonary diseases such as asthma and congestive heart failure (Bridges et al., 2008).

The influenza viruses were first isolated in the early 1900s by Smith and his associates (influenza A, 1933), Francis (influenza B, 1939), and Taylor (influenza C, 1950) (Francis, 1940; Smith et al., 1933; Taylor, 1951). In 1936, Burnet discovered that the virus could be grown in embryonated hen eggs, and in the 1950s animal cell culture systems were developed (Burnet, 1936; Mogabgab et al., 1954; Treanor, 2010). In 1943, the first commercial influenza vaccines were approved for use in the United States, and consisted of inactivated virus grown in chicken eggs (Treanor, 2010). With a few adaptations, propagation of influenza viruses in chicken eggs remains the primary means for growing virus for vaccine production and biomedical research (Treanor, 2010).

Currently, two types of vaccines are available in the United States—the trivalent, inactivated influenza virus (TIV) vaccine, and the live, attenuated, cold-adapted influenza virus (LAIV) vaccine (also trivalent). TIV vaccines, which were first licensed for use in the United States in 1943, are inactivated (killed) virus vaccines that provide immunity against the viruses without causing any signs or symptoms of the infection (Treanor, 2010). The LAIV vaccine is a live but attenuated virus vaccine that is capable of causing mild signs and symptoms of vaccine virus infection (Treanor, 2010). Approved in 2003, LAIV is a live virus vaccine that is cold-adapted (attenuated) so that it does not replicate in the warmer body temperature of the lower airways (CDC, 2003; Treanor, 2010). It is capable of causing mild signs and symptoms of wild-type influenza infection (Treanor, 2010). TIV is administered through an intramuscular injection, while LAIV is administered intranasally via an aerosol sprayer. Both vaccines contain two influenza A and one influenza B subtypes which are recommended by the World Health Organization (WHO) Global Influenza Programme—for example A/California/7/2009 (H1N1)-like,<sup>1</sup> A/Perth/16/2009 (H3N2)-like, and B/Brisbane/60-2008-like for the 2010–2011 season (WHO, 2010).

The Advisory Committee on Immunization Practices (ACIP) recommends that all persons 6 months or older receive an annual influenza virus vaccine (CDC, 2010b). For healthy, nonpregnant persons aged 2 to 49 years either TIV or LAIV vaccine is recommended without preference (CDC, 2010b). LAIV is not recommended for children under 2 years of

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<sup>1</sup>A/California/7/2009 (H1N1)-like is derived from the 2009 pandemic influenza A (H1N1) virus. This strain was included in the trivalent vaccine in 2010. The monovalent vaccine developed for the pandemic is not covered under the National Vaccine Injury Compensation Program (VICP); it is covered under the Countermeasures Injury Compensation Program and is therefore beyond the scope of this report.

age, pregnant women, adults over 50 years of age, and persons with a history of hypersensitivity to eggs or LAIV vaccine components (CDC, 2010b). It is also not recommended for persons with asthma and children between 2 and 4 years of age with a history of asthma or wheezing episodes in the 12 months prior to vaccination (CDC, 2010b). For these individuals and individuals with chronic conditions such as hematologic, hepatic, metabolic, neurologic or neuromuscular, pulmonary, or renal disorders; the immunosuppressed; and those between the ages of 6 months and 18 years receiving aspirin or other salicylates; ACIP recommends use of the age-appropriate TIV vaccine (Table 6-1) (CDC, 2010b).

In the 2008–2009 season, influenza vaccination was received by 29.1 percent of all persons aged 6 months to 18 years (CDC, 2010a). Thirty-three percent of individuals aged 19 to 49 years, who were considered high-risk for this age group, were vaccinated in comparison to 19.7 percent of individuals who were not considered high-risk for influenza (CDC, 2010a). The vaccine was administered to 51.5 percent of high-risk adults aged 50 to 64 years and 34.2 percent of non-high-risk adults in this age group (CDC, 2010a).

## ENCEPHALITIS AND ENCEPHALOPATHY

### Epidemiologic Evidence

The committee reviewed four studies to evaluate the risk of encephalitis or encephalopathy after the administration of influenza vaccine. One study (Nakayama and Onoda, 2007) was not considered in the weight of epidemiologic evidence because it provided data from a passive surveillance system and lacked an unvaccinated comparison population. Three controlled studies (France et al., 2004; Goodman et al., 2006; Hambidge et al., 2006) had very serious methodological limitations that precluded their inclusion in this assessment. The studies by France et al. (2004), Goodman et al. (2006), and Hambidge et al. (2006) were unable to find any cases of encephalopathy or encephalitis following influenza vaccination using a case-crossover or case-control design, so no conclusions could be drawn from these analyses.

### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between influenza vaccine and encephalitis or encephalopathy.*

TABLE 6-1 Influenza Vaccines Licensed and Available in the United States

| Vaccine          | Trade Name                     | Manufacturer                              | Presentation                           | Mercury Content (mcg Hg/0.5 mL dose) | Age Group         | Number of Doses     | Route                      |
|------------------|--------------------------------|---|--|--------------------------------------|-------------------|---------------------|----------------------------|
| TIV <sup>a</sup> | Fluzone                        | Sanofi Pasteur, Inc.                      | 0.25 mL prefilled syringe              | 0.0                                  | 6–35 months       | 1 or 2 <sup>b</sup> | Intramuscular <sup>c</sup> |
|                  |                                |   | 0.5 mL prefilled syringe               | 0.0                                  | 36 months–8 years | 1 or 2 <sup>b</sup> | Intramuscular <sup>c</sup> |
|                  |                                |   | 0.5 mL single-dose vial                | 0.0                                  | ≥ 36 months       | 1 or 2 <sup>b</sup> | Intramuscular <sup>c</sup> |
|                  |                                |   | 5.0 mL multidose vial                  | 25.0                                 | ≥ 6 months        | 1 or 2 <sup>b</sup> | Intramuscular <sup>c</sup> |
| TIV              | Fluzone Intradermal            | Sanofi Pasteur, Inc.                      | 0.1 mL prefilled microinjection system | 0.0                                  | 18–64 years       | 1                   | Intradermal                |
| TIV              | Fluzone High-Dose <sup>d</sup> | Sanofi Pasteur, Inc.                      | 0.5 mL prefilled syringe               | 0.0                                  | ≥ 65 years        | 1                   | Intramuscular <sup>c</sup> |
| TIV              | Fluvirin                       | Novartis Vaccines and Diagnostics Limited | 5.0 mL multidose vial                  | 25.0                                 | ≥ 4 years         | 1 or 2 <sup>b</sup> | Intramuscular <sup>c</sup> |
|                  |                                |   | 0.5 mL prefilled syringe               | 0.0                                  | ≥ 4 years         | 1 or 2 <sup>b</sup> | Intramuscular <sup>c</sup> |
| TIV              | Fluarix                        | GlaxoSmithKline                           | 0.5 mL prefilled syringe               | 0.0                                  | ≥ 3 years         | 1 or 2 <sup>b</sup> | Intramuscular <sup>c</sup> |
| TIV              | FluLaval                       | ID Biomedical Corporation of Quebec       | 5.0 mL multidose vial                  | 25.0                                 | ≥ 18 years        | 1                   | Intramuscular <sup>c</sup> |
| TIV              | Afluria                        | CSL Limited                               | 0.5 mL prefilled syringe               | 0.0                                  | ≥ 5 years         | 1 or 2 <sup>b</sup> | Intramuscular <sup>c</sup> |
|                  |                                |   | 5.0 mL multidose vial                  | 24.5                                 | ≥ 5 years         | 1 or 2 <sup>b</sup> | Intramuscular <sup>c</sup> |

*continued*

TABLE 6-1 Continued

| Vaccine           | Trade Name           | Manufacturer                            | Presentation                 | Mercury Content (mcg Hg/0.5 mL dose) | Age Group  | Number of Doses     | Route                      |
|-------------------|----------------------|---|------------------------------|--------------------------------------|------------|---------------------|----------------------------|
| TIV               | Agriflu              | Novartis Vaccines and Diagnostics, Inc. | 0.5 mL prefilled syringe     | 0.0                                  | ≥ 18 years | 1                   | Intramuscular <sup>c</sup> |
| LAIV <sup>e</sup> | FluMist <sup>f</sup> | MedImmune, LLC                          | 0.2 mL sprayer, divided dose | 0.0                                  | 2–49 years | 1 or 2 <sup>b</sup> | Intranasal                 |

<sup>a</sup> Trivalent inactivated vaccine.

<sup>b</sup> Children less than 9 years of age not previously vaccinated with an influenza vaccine or vaccinated for the first time in the last season with only one dose should receive two doses, spaced more than 4 weeks apart. Children less than 9 years of age given two doses in the previous season and individuals greater than 9 years of age should receive only one dose of the vaccine.

<sup>c</sup> For adults and older children, the recommended site of vaccination is the deltoid muscle. If applicable, the preferred site for infants and young children is the anterolateral aspect of the thigh.

<sup>d</sup> Trivalent inactivated vaccine high dose. A 0.5-mL dose contains 60 mcg each of A/California/7/2009 (H1N1)-like, A/Perth/16/2009 (H3N2)-like, and B/Brisbane/60/2008-like antigens.

<sup>e</sup> Live attenuated influenza vaccine.

<sup>f</sup> FluMist is shipped refrigerated and should be stored in the refrigerator between 36°F and 46°F (2°C to 8°C) after arrival in the vaccination clinic. The dose is 0.2 mL, divided equally between each nostril.

SOURCES: CSL Limited, 2011; GlaxoSmithKline, 2011a,b; MedImmune, LLC, 2011; Novartis Vaccines and Diagnostics, Inc., 2010, 2011; Sanofi Pasteur, 2011.

### Mechanistic Evidence Regarding Encephalitis

The committee identified 11 publications reporting meningoencephalitis or encephalitis after administration of an influenza vaccine. Ten publications did not provide evidence beyond temporality (Blanco et al., 1999; Buchner et al., 1988; Chhor et al., 2008; Drouet et al., 2002; Ehrengut and Allerdist, 1977; Gross et al., 1978; Rosenberg, 1970; Saito and Yanagisawa, 1989; Turkoglu and Tuzun, 2009; Utumi et al., 2010). One publication attributed the development of encephalitis after vaccination to a concomitant infection with herpes simplex virus (Utumi et al., 2010). These publications did not contribute to the weight of mechanistic evidence.

Described below is one publication reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Froissart et al. (1978) described a 29-year-old woman presenting with vomiting, fever, and a stiff neck leading to a diagnosis of meningoencephalitis 2 days after administration of an influenza vaccine. The previous year the patient presented with similar symptoms 2 days after receiving an influenza vaccine.

#### *Weight of Mechanistic Evidence*

While rare, infection with influenza has been associated with encephalitis (Treanor, 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

The publication, described above, did not present evidence sufficient for the committee to conclude the vaccine may be a contributing cause of encephalitis after administration of an influenza vaccine. The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of encephalitis, but the only evidence that could be attributed to the vaccine was recurrence of symptoms upon vaccine rechallenge. Viral infection and viral reactivation may contribute to the symptoms of encephalitis; however, the publications did not provide evidence linking these mechanisms to influenza vaccine.

*The committee assesses the mechanistic evidence regarding an association between influenza vaccine and encephalitis as weak based on knowledge about the natural infection and one case.*

### Causality Conclusion

**Conclusion 6.1:** The evidence is inadequate to accept or reject a causal relationship between influenza vaccine and encephalitis.



### Mechanistic Evidence Regarding Encephalopathy

The committee identified five publications reporting encephalopathy after administration of an influenza vaccine. Three publications did not provide evidence beyond temporality and therefore did not contribute to the weight of mechanistic evidence (Ehregut and Allerdist, 1977; Morimoto et al., 1985; Woods and Ellison, 1964).

Described below are two publications reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Boutros and Keck (1993) described a 75-year-old woman presenting with confusion 12 days after receiving an influenza vaccine. Physical examination showed anorexia, insomnia, hallucinations, and delirium. High signal lesions in the white matter were revealed upon magnetic resonance imaging. The symptoms resolved upon treatment with thiothixene. One year prior to the current episode the patient developed similar symptoms 21 days after receiving an influenza vaccine.

Warren (1956) described a 19-year-old man presenting with profuse rhinorrhea, wheezing, feverishness, soreness behind the eyes, shaking chills, and aching of the arms, back, and head hours after receiving an influenza vaccine. Two hours later the patient was weak, dizzy, unable to sit upright, and began to black out. Physical examination revealed the patient to be semicomatose and delirious. One year prior to the current episode the patient had presented with severe malaise 2 days after receiving an influenza vaccine.

#### *Weight of Mechanistic Evidence*

The publications described above did not present evidence sufficient for the committee to conclude the vaccine may be a contributing cause of encephalopathy after administration of an influenza vaccine. The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of encephalopathy, but the only evidence that could be attributed to the vaccine was recurrence of symptoms upon vaccine rechallenge. Viral infection and viral reactivation may contribute to the symptoms of encephalopathy; however, the publications did not provide evidence linking these mechanisms to influenza vaccine.

*The committee assesses the mechanistic evidence regarding an association between influenza vaccine and encephalopathy as weak based on two cases.*

### Causality Conclusion

**Conclusion 6.2:** The evidence is inadequate to accept or reject a causal relationship between influenza vaccine and encephalopathy.

## SEIZURES

### Epidemiologic Evidence

The committee reviewed eight studies to evaluate the risk of seizures after the administration of influenza vaccine. Four studies (D'Heilly et al., 2006; Izurieta et al., 2005; McMahon et al., 2005; Rosenberg et al., 2009) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

The four remaining controlled studies (France et al., 2004; Goodman et al., 2006; Greene et al., 2010; Hambidge et al., 2006) were included in the weight of epidemiologic evidence and are described below.

France et al. (2004) conducted a case-crossover study in 251,600 children (younger than 18 years of age) enrolled in five health maintenance organizations (HMOs) participating in the Vaccine Safety Datalink (VSD). The study investigated the occurrence of adverse events (reported as outpatient, inpatient, and emergency department visits) within 14 days of TIV administration from January 1993 through December 1999. Two control periods were defined as 15 to 28 days before vaccination (control period 1) and 15 to 28 days after vaccination (control period 2). The inclusion criteria required participants to be enrolled in the HMO 28 days before and 28 days after receiving TIV, and have a record of an adverse event in either the risk period or one of the two control periods. Study participants were excluded from the analysis if they experienced an event during both the risk period and one of the control periods, which limited the analysis to discordant pairs. Multiple vaccinations in an individual were treated as independent in the analysis and the pre- and postvaccination control periods in the same individual were analyzed independently, which would tend to increase the number of associations found to be significant by chance alone (type I error). Seizures were observed in 81 children, but no significant associations were reported for outpatient, inpatient, and emergency department visits for seizures during the 14-day risk period when compared to the prevaccination control period or postvaccination control period. Additional analyses with liberalized significance criterion ( $.05 < p \leq .20$ ) were used to identify potentially overlooked associations, but seizures remained nonsignificant.

Hambidge et al. (2006) conducted case-crossover analysis to examine

the risk of seizures after influenza vaccination in 45,356 children (6 to 23 months of age) enrolled in eight medical care organizations (MCOs) participating in the VSD. The study investigated the occurrence of adverse events (reported as outpatient, inpatient, and emergency department visits) within 14 days (primary analysis) of TIV administration from 1991 through 2003. Two control periods were defined as 15 to 28 days before vaccination (control period 1) and 15 to 28 days after vaccination (control period 2). Only discordant pairs were analyzed, and participants that experienced an event during both the risk period and one of the control periods were excluded. Half of the study population overlapped the patients observed in the study by France et al. (2004), but separate analyses for the unique subgroups presented in this paper (1991–1992 and 2000–2003) were not performed. A total of 24 seizures were observed in the 14-day risk window; 22 were found to be febrile seizures, and 17 were reported during the same period that has been associated with febrile seizures following measles, mumps, and rubella (MMR) immunization (7–14 days postvaccination). Children who received MMR vaccine on the same day as TIV were excluded from the analysis (nine cases and one control). The matched odds ratio for seizures within 14 days of TIV administration was 1.36 (95% CI, 0.63–2.97). The authors concluded that after excluding children who received MMR vaccine on the same day, TIV administration was not associated with an increased risk in febrile seizures. They also noted that no signal of seizures within 3 days of TIV administration was observed.

Goodman et al. (2006) conducted a nested case-control study in children (6 to 23 months of age) enrolled in the HealthPartners Medical Group (HPMG) during the 2002–2003 and 2003–2004 influenza seasons. Vaccination histories were obtained from the HPMG vaccine registry and the investigators coded whether the TIV injection was a first or second dose during the given influenza season. Seizure diagnoses were verified by reviewing the medical charts. The risk window was defined as 0–42 days following vaccination, but the investigators also analyzed 0–3-day, 4–14-day, and 14–42-day windows. The cohort included 13,383 children, of whom 3,697 received TIV during the study period. Cases were matched to three controls (children who did not have the outcome of interest) on date of birth and gender; the index date for the controls was the date the event was observed in the matched case. The authors did not report how many cases and controls were included in the seizure analysis or list characteristics of these two groups. The hazard ratio for seizures within 42 days of a first dose of TIV was 1.17 (95% CI, 0.36–3.86), and within 42 days of a second dose of TIV the hazard ratio was 1.026 (95% CI, 0.19–5.56). Shorter time windows did not have the power to assess the hazard ratio for seizures following TIV and were not listed in the study.

The authors concluded that TIV administration is not associated with an increased rate of seizures.

Greene et al. (2010) conducted a retrospective cohort study in children (6 months to 17 years of age) and adults ( $\geq 18$  years of age) enrolled in eight MCOs participating in the VSD. The study investigated the occurrence of adverse events (reported as inpatient and emergency department visits) after receipt of influenza vaccine from September through April of the 2005–2006, 2006–2007, and 2007–2008 influenza seasons. The risk period for the seizures analysis (0 to 7 days after vaccination) of the given season was compared to the control period (8 to 15 days after vaccination) of the same season. The number of vaccine doses administered to children during the 2005–2006 season was 317,108; during the 2006–2007 season was 415,446; and during the 2007–2008 season was 462,998. The relative risk of seizures in children within 7 days of influenza vaccination was 1.35, 0.80, and 0.98 for the 2005–2006, 2006–2007, and 2007–2008 influenza seasons, respectively. The number of vaccine doses administered to adults during the 2005–2006 season was 1,429,974; during the 2006–2007 season it was 1,598,880; and during the 2007–2008 season it was 1,742,858. The relative risk of seizures in adults within 7 days of influenza vaccination was 0.99, 0.96, and 1.09 for the 2005–2006, 2006–2007, and 2007–2008 influenza seasons, respectively. None of the associations reached the critical value of the log-likelihood ratio, and none of the relative risks achieved statistical significance. This paper also included an analysis comparing rate ratios in the current year with the cumulative ratios in prior comparison years. All of these comparisons also found no increase in seizures in the risk period.

### *Weight of Epidemiologic Evidence*

Analyses from four studies (one retrospective cohort, one case-control, and two case-crossover designs) were included in the epidemiologic evidence. France et al. (2004) did not find a statistically significant association between seizures and TIV, even with liberalized significance criterion ( $.05 < p \leq .20$ ). The study by Hambidge et al. (2006) observed a null association in seizures within 14 days of TIV administration when children who received MMR simultaneously with TIV were removed from the case-crossover analysis. The case-control study by Goodman et al. (2006) found no association between seizures and TIV, but the precision was low. Greene et al. (2010) did not find a statistically significant association among the analyses for children and adults; however, the control period was within the risk period of the other papers. Although power was limited in all the studies, they were generally well done and results were consistent, supporting the

committee's conclusion that the evidence overall reached a moderate level of confidence for a null association. See Table 6-2 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has a moderate degree of confidence in the epidemiologic evidence based on four studies with sufficient validity and precision to assess an association between influenza vaccine and seizures; these studies consistently report a null association.*

### Mechanistic Evidence

The committee identified five publications reporting the development of seizures after administration of an influenza vaccine. The publications did not provide evidence beyond temporality (Chhor et al., 2008; Hirtz et al., 1983; Kennedy et al., 2002; Marine and Stuart-Harris, 1976; Wright et al., 1976). In addition, Kennedy et al. (2002) attributed seizure development to the corticosteroid therapy used to treat respiratory problems in the patient. One publication reported a cell culture study using an influenza vaccine. Takahashi et al. (2006) reported the isolation of lymphocytes reactive to both the neuronal molecule GluR $\epsilon$ 2 and influenza vaccine from a patient diagnosed with Rasmussen syndrome who had developed a febrile seizure upon infection with influenza A. The publications did not contribute to the weight of mechanistic evidence.

### *Weight of Mechanistic Evidence*

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of seizure. In some instances fever may contribute to the development of seizures; however, the publications did not provide evidence linking this mechanism to influenza vaccine.

*The committee assesses the mechanistic evidence regarding an association between influenza vaccine and seizures as lacking.*

### Causality Conclusion

**Conclusion 6.3:** The evidence is inadequate to accept or reject a causal relationship between influenza vaccine and seizures.

TABLE 6-2 Studies Included in the Weight of Epidemiologic Evidence for Influenza Vaccine and Seizures

| Citation             | Operationally Defined Outcome                                       | Study Setting  | Defined Study Population | Study Design  | Sample Size   | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)   | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|----------------------|---|--|--------------------------|---|---------------|--|---|--|
| France et al. (2004) | Outpatient, inpatient, and emergency department visits for seizures | Five HMOs participating in the VSD from 1/1993 through 12/1999 | Ages under 18 years      | Case-crossover<br>Risk period: 14 days after influenza vaccination<br>Control period 1: 15 to 28 days before vaccination<br>Control period 2: 15 to 28 days after vaccination | 251,600 cases | No significant associations of outpatient, inpatient, and emergency department visits for seizures within 14 days of influenza vaccination | None described                                      | Serious  |

*continued*

TABLE 6-2 Continued

| Citation               | Operationally Defined Outcome                                       | Study Setting   | Defined Study Population | Study Design  | Sample Size  | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)   | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|------------------------|---|---|--------------------------|---|--|--|---|--|
| Hambidge et al. (2006) | Outpatient, inpatient, and emergency department visits for seizures | Eight MCOs participating in the VSD from 1991 through 2003                    | Ages 6 to 23 months      | Case-crossover<br>Risk period:<br>14 days after TIV administration<br>Control period 1:<br>15 to 28 days before vaccination<br>Control period 2:<br>15 to 28 days after vaccination | 45,356 cases   | OR of seizures within 14 days of influenza vaccination:<br>1.36 (95% CI, 0.63–2.97)  | None described                                      | Serious  |
| Goodman et al. (2006)  | Seizure diagnoses obtained from medical charts                      | HealthPartners Medical Group during 2002–2003 and 2003–2004 influenza seasons | Ages 6 to 23 months      | Nested case-control<br>Risk period:<br>0–42 days after TIV administration   | 13,383 cases<br>3,697 received TIV during study period | HR for seizures within 42 days of first TIV dose:<br>1.17 (95% CI, 0.36–3.86)<br>HR for seizures within 42 days of second TIV dose:<br>1.026 (95% CI, 0.19–5.56) | None described                                      | Serious  |

|                      |  |  |                                     |  |   |  |                |            |
|----------------------|--|--|-------------------------------------|--|---|--|----------------|------------|
| Greene et al. (2010) | Inpatient and emergency department visits for seizures | Eight MCOs participating in the VSD during 2005–2006, 2006–2007, and 2007–2008 influenza seasons | Ages 6–17 years and $\geq 18$ years | Retrospective cohort<br>Risk period: 0–7 days after TIV administration for a given season<br>Control period: 8–15 days after vaccination for the same season | 2005–2006: 317,108 doses administered to children; 1,429,974 doses administered to adults<br>2006–2007: 415,446 doses administered to children; 1,598,880 doses administered to adults<br>2007–2008: 462,998 doses administered to children; 1,742,858 doses administered to adults | RR of seizures in children within 7 days of influenza vaccination was 1.35 for 2005–2006, 0.80 for 2006–2007, and 0.98 for 2007–2008 influenza seasons<br>RR of seizures in adults within 7 days of influenza vaccination was 0.99 for 2005–2006, 0.96 for 2006–2007, and 1.09 for 2007–2008 influenza seasons | None described | Negligible |
|----------------------|--|--|-------------------------------------|--|---|--|----------------|------------|

<sup>a</sup> The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup> The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup> Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.



## ACUTE DISSEMINATED ENCEPHALOMYELITIS

### Epidemiologic Evidence

The committee reviewed two studies to evaluate the risk of acute disseminated encephalomyelitis (ADEM) after the administration of influenza vaccine. These two studies (Izurieta et al., 2005; Nakayama and Onoda, 2007) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between influenza vaccine and ADEM.*

### Mechanistic Evidence

The committee identified 15 publications reporting the development of ADEM after administration of an influenza vaccine. The publications did not provide evidence beyond temporality, some too short based on the possible mechanisms involved (Antony et al., 1995; Buchner et al., 1988; Garea Garcia-Malvar et al., 2004; Huynh et al., 2008; Iyoda et al., 2004; Kavadas et al., 2008; Kepes, 1993; Nagano et al., 1988; Nakamura et al., 2003; Ravaglia et al., 2004; Rosenberg, 1970; Saito et al., 1980; Selvaraj et al., 1998; Vilain et al., 2000; Yahr and Lobo-Antunes, 1972). In addition, two publications reported concomitant infections making it difficult to determine the precipitating event (Kavadas et al., 2008; Nagano et al., 1988). The publications did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

While rare, influenza infection has been associated with the development of ADEM (Yiu and Kornberg, 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of ADEM. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of ADEM; however, the publications did not provide evidence linking these mechanisms to influenza vaccine.

*The committee assesses the mechanistic evidence regarding an association between influenza vaccine and ADEM as weak based on knowledge about the natural infection.*

### Causality Conclusion

**Conclusion 6.4:** The evidence is inadequate to accept or reject a causal relationship between influenza vaccine and ADEM.

## TRANSVERSE MYELITIS

### Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of transverse myelitis after the administration of influenza vaccine. This study (Vellozzi et al., 2009) was not considered in the weight of epidemiologic evidence because it provided data from a passive surveillance system and lacked an unvaccinated comparison population.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between influenza vaccine and transverse myelitis.*

### Mechanistic Evidence

The committee identified six publications reporting the development of transverse myelitis after administration of an influenza vaccine. The publications did not provide evidence beyond temporality, some too short based on the possible mechanisms involved (Bakshi and Mazziotta, 1996; Buchner et al., 1988; Lerner and Farmer, 2000; Nakamura et al., 2003; Sugimoto et al., 1968; Wells, 1971). The publications did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

Influenza infection has, rarely, been associated with the development of transverse myelitis (Treanor, 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of transverse myelitis. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of transverse myelitis; however, the publications did not provide evidence linking these mechanisms to influenza vaccine.

*The committee assesses the mechanistic evidence regarding an association between influenza vaccine and transverse myelitis as weak based on knowledge about the natural infection.*

### Causality Conclusion

**Conclusion 6.4:** The evidence is inadequate to accept or reject a causal relationship between influenza vaccine and transverse myelitis.

## OPTIC NEURITIS

### Epidemiologic Evidence

The committee reviewed two studies to evaluate the risk of optic neuritis (ON) after the administration of influenza vaccine. The two controlled studies (DeStefano et al., 2003; Payne et al., 2006) contributed to the weight of epidemiologic evidence and are described below.

DeStefano et al. (2003) conducted a case-control study to evaluate the association between influenza vaccination and optic neuritis using data from three HMOs participating in the VSD. The optic neuritis analysis included 108 cases and 228 controls. The cases had a documented physician's diagnosis from 1995 through 1999, and were matched to controls from the HMO on date of birth (within 1 year) and sex. The authors evaluated the date of disease onset using data described in the medical record or reported in the telephone interview. The immunization status was obtained from vaccination records, medical records, and telephone interviews. The study had high rates of self-reported vaccinations from outside the HMO system (32 percent of cases and 39 percent of controls) that could not be verified, which may have biased the results. The odds ratio for ever vaccinated with influenza before optic neuritis diagnosis was 1.2 (95% CI, 0.6–2.3). The authors concluded that influenza vaccination did not appear to be associated with an increased risk of optic neuritis in adults.

Payne et al. (2006) used the Defense Medical Surveillance System (DMSS) to conduct a case-control study among U.S. military personnel. The study included 1,131 cases with a first diagnosis of optic neuritis from 1998 through 2003, and 3,393 controls. The cases and controls were matched on sex, military service (e.g., active or reserve), and deployment within 18 weeks of diagnosis date. The vaccination status and date of first symptom of optic neuritis were obtained from the DMSS and reviewed by a neuro-ophthalmologist. About 15 percent of the cases (173 patients) and controls (510 patients) received influenza vaccine within the 18-week risk period, which suggested that possible confounders related to the decision to vaccinate were present. Although the authors considered three exposure times—6, 12, and 18 weeks after vaccination—only the odds ratio for optic neuritis diagnosis within 18 weeks of influenza vaccination was given (OR, 1.01; 95% CI, 0.79–1.29). The authors noted without presenting results

that similar conclusions were obtained using 6- and 12-month exposure times. The authors concluded that vaccination against influenza does not appear to increase the risk of optic neuritis in adults.

### *Weight of Epidemiologic Evidence*

Neither of the two case-control studies included in the evidence assessment found evidence of an association between influenza vaccine and the onset of ON in adults even after adjustment for potential confounders. However, DeStefano et al. (2003) did not define a specific exposure time and had no short-term assessment in their primary analysis. The authors performed secondary analyses considering the timing of the influenza vaccination (< 1 year, 1–5 years, and > 5 years) relative to the ON onset, which also showed no significant association, but they did not state how they handled the timing of vaccination for those who had more than one influenza vaccine before the onset of ON or when influenza was given in combination with other vaccines. In both studies (DeStefano et al., 2003; Payne et al., 2006), the proportion of cases and controls who had influenza vaccination was around 15–16 percent, which suggests possible confounders related to the decision to vaccinate may be present. Payne et al. (2006) is a study with a better design and analysis. The authors mentioned adjusting for other vaccines in their analysis of anthrax vaccine, but it is not clearly stated that they adjusted for other vaccines in their analysis of the safety of the influenza vaccine, which is the interest in this review. The confidence intervals for the odds ratio from DeStefano et al. (2003) were wide while those from Payne et al. (2006) were relatively narrow around 1. Considering the limitations of the studies, the small number of studies, and the width of the confidence intervals, the committee has limited confidence in the epidemiologic evidence. See Table 6-3 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has limited confidence in the epidemiologic evidence, based on two studies that lacked validity and precision, to assess an association between influenza vaccine and optic neuritis.*

### **Mechanistic Evidence**

The committee identified six publications reporting the development of optic neuritis after administration of an influenza vaccine. Four publications did not provide evidence beyond temporality (Huynh et al., 2008; Ray and Dreizin, 1996; Tan et al., 2010; Vilain et al., 2000). These publications did not contribute to the weight of mechanistic evidence.

TABLE 6-3 Studies Included in the Weight of Epidemiologic Evidence for Influenza Vaccine and Optic Neuritis

| Citation                | Operationally Defined Outcome  | Study Setting                       | Defined Study Population                | Study Design | Sample Size  | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)                                     | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|-------------------------|--|-------------------------------------|---|--------------|--|--|---|--|
| DeStefano et al. (2003) | Date of optic neuritis onset from medical records or telephone interviews                      | Three HMOs participating in the VSD | Ages < 18, 18–40, > 40 years            | Case control | 108 patients with optic neuritis<br>228 controls     | OR for optic neuritis onset any time after influenza vaccination:<br><b>1.2 (95% CI, 0.6–2.3)</b>        | None described                                      | Serious  |
| Payne et al. (2006)     | Date of first symptom of optic neuritis listed in system and reviewed by neuro-ophthalmologist | Defense Medical Surveillance System | U.S. military personnel ages ≥ 18 years | Case control | 1,131 patients with optic neuritis<br>3,393 controls | OR for optic neuritis onset within 18 weeks of influenza vaccination:<br><b>1.01 (95% CI, 0.79–1.29)</b> | None described                                      | Serious  |

<sup>a</sup> The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup> The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup> Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.

Described below are publications reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

A Vaccine Adverse Event Reporting System (VAERS) report, identified in Vellozzi et al. (2009), describing the development of optic neuritis after administration of influenza vaccines in back-to-back years, was obtained via a Freedom of Information Act (FOIA) request (FDA, 2010). The patient was a 61-year-old woman presenting with transient blindness 20 and 17 days after receiving influenza vaccines in 1992 and 1993, respectively. Evidence of causality beyond a temporal relationship between administration of the vaccines and development of transient blindness was not provided.

Hull and Bates (1997) described a 59-year-old woman presenting with decreased visual acuity. Physical examination showed light perception in the right eye, the ability to count fingers at one foot in the left eye, and bilateral disk edema 2 weeks after administration of an influenza vaccine. The patient's visual acuity recovered with intravenous corticosteroid treatment. One year later the patient presented with deterioration of vision to light perception in both eyes 17 days after receiving an influenza vaccine. After intravenous corticosteroid treatment visual acuity improved in the patient's right eye but remained unchanged in the left eye.

#### *Weight of Mechanistic Evidence*

The publications, described above, did not present evidence sufficient for the committee to conclude the vaccine may be a contributing cause of optic neuritis after administration of an influenza vaccine. The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of optic neuritis, but the only evidence that could be attributed to the vaccine was recurrence of symptoms upon vaccine rechallenge. Autoantibodies, T cells, immune complexes, and molecular mimicry may contribute to the symptoms of optic neuritis; however, the publications did not provide evidence linking these mechanisms to influenza vaccine.

*The committee assesses the mechanistic evidence regarding an association between influenza vaccine and optic neuritis as weak based on two cases.*

#### **Causality Conclusion**

**Conclusion 6.6:** The evidence is inadequate to accept or reject a causal relationship between influenza vaccine and optic neuritis.

## NEUROMYELITIS OPTICA

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of neuromyelitis optica (NMO) after the administration of influenza vaccine.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between influenza vaccine and NMO.*

### Mechanistic Evidence

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of NMO developing after administration of an influenza vaccine.

#### *Weight of Mechanistic Evidence*

Autoantibodies, T cells, complement activation, and molecular mimicry may contribute to the symptoms of NMO; however, the committee did not identify literature reporting evidence of these mechanisms after administration of influenza vaccine.

*The committee assesses the mechanistic evidence regarding an association between influenza vaccine and NMO as lacking.*

### Causality Conclusion

**Conclusion 6.7:** The evidence is inadequate to accept or reject a causal relationship between influenza vaccine and NMO.

## MULTIPLE SCLEROSIS ONSET IN ADULTS

### Epidemiologic Evidence

The committee reviewed four studies to evaluate the risk of onset (date of first symptom) of multiple sclerosis (MS) in adults after the administration of influenza vaccine. Two controlled studies (Lauer and Firnhaber, 1990; Ramagopalan et al., 2009) had very serious methodological limitations that precluded their inclusion in this assessment. The control group

used in the study by Lauer et al. (1990) was flawed, and the authors may have selected a group at greater or lesser likelihood to receive the vaccine. Ramagopalan et al. (2009) did not attempt to validate self-report vaccination data or confirm the timing of vaccination, and the choice of spousal controls could have introduced selection bias.

The two remaining controlled studies (DeStefano et al., 2003; Hernan et al., 2004) contributed to the weight of epidemiologic evidence and are described below.

The study by DeStefano et al. (2003) was described in detail in the section on optic neuritis. This case-control study evaluated the association between influenza vaccination and MS or optic neuritis onset using data from three HMOs participating in the VSD. The MS analysis included 332 cases and 722 controls. Although there is a large number of cases and controls, the study had high rates of self-reported vaccinations from outside the HMO system (32 percent of cases and 39 percent of controls) that could not be verified, which may have biased the results. The odds ratio for ever versus never vaccinated with influenza before MS onset was 0.7 (95% CI, 0.5–1.1). The authors concluded that influenza vaccination does not appear to be associated with an increased risk of MS onset in adults.

Hernan et al. (2004) used the General Practice Research Database (GPRD) to perform a nested case-control study. Cases with a confirmed MS diagnosis from 1993 through 2000, and a minimum of 3 years follow-up in the database, were selected and matched with controls. The study included 163 cases and 1,604 controls; all participants were over 18 years of age, except for one unvaccinated control that was 16 years of age. The date of first symptom of MS and influenza vaccination status were identified in the medical record. The rates of vaccination were very low among the cases and controls (6.1 percent and 6.0 percent, respectively), which raised the possibility that subjects selected for vaccination were different in relevant ways. The odds ratio for MS onset within 3 years of influenza immunization compared to never vaccinated was 1.0 (95% CI, 0.5–2.0). The authors concluded that influenza immunization did not appear to be associated with an increased risk of MS onset in adults, but the confidence intervals in the study were quite broad, including a potential doubling of risk with vaccination.

### *Weight of Epidemiologic Evidence*

Neither of the two case-control studies considered in the assessment of epidemiologic evidence found an association between influenza vaccine and onset of MS in adults. However, there are some concerns about the study designs and analyses. DeStefano et al. (2003) did not define a specific exposure time and had no short-term assessment in their primary analysis.



The authors performed secondary analyses considering the timing of the influenza vaccination (< 1 year, 1–5 years, and > 5 years) relative to the MS onset, which showed no significant association, but they did not state how they handled the timing of vaccination for those who had more than one influenza vaccine before the onset of MS or when influenza was given in combination with other vaccines. Hernan et al. (2004) considered a fixed exposure time of 3 years within the onset of MS but did not present results on any subanalysis considering the timing of the influenza vaccination. In addition, the rates of vaccination were very low among the cases and controls (around 6 percent). Finally, the confidence intervals of the study were fairly broad and a clinically relevant association could not be ruled out. Given these study limitations and the small number of studies, the committee has limited confidence in the overall evidence. See Table 6-4 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has limited confidence in the epidemiologic evidence based on two studies that lacked validity and precision to assess an association between influenza vaccine and onset of MS in adults.*

### Mechanistic Evidence

The committee identified three publications reporting the onset of MS in adults after administration of an influenza vaccine. Rabin (1973) reported the development of MS after administration of an influenza vaccine in one patient but did not provide clinical, diagnostic, or experimental evidence, including the time frame between administration of the vaccine and development of symptoms. Two publications did not provide evidence beyond temporality (Nakajima et al., 2003; Yahr and Lobo-Antunes, 1972). The publications did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

The symptoms described in the publications referenced above are consistent with those leading to the onset of MS in adults. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of MS; however, the publications did not provide evidence linking these mechanisms to influenza vaccine.

*The committee assesses the mechanistic evidence regarding an association between influenza vaccine and onset of MS in adults as lacking.*

TABLE 6-4 Studies Included in the Weight of Epidemiologic Evidence for Influenza Vaccine and MS Onset in Adults

| Citation                | Operationally Defined Outcome                                | Study Setting                       | Defined Study Population  | Study Design | Sample Size                 | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)              | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|-------------------------|--|-------------------------------------|---|--------------|-----------------------------|---|---|--|
| DeStefano et al. (2003) | MS onset reported in medical records or telephone interviews | Three HMOs participating in the VSD | Ages < 18, 18–40, > 40 years<br>Cases had MS diagnosed by a physician     | Case control | 332 cases<br>722 controls   | OR for MS onset any time after influenza vaccination:<br>0.7 (95% CI, 0.5–1.1)    | None described                                      | Serious  |
| Hernan et al. (2004)    | MS onset reported in medical records                         | GPRD                                | Ages < 30, 30–49, > 50 years<br>Cases had MS diagnosis in medical records | Case control | 163 cases<br>1,604 controls | OR for MS onset within 3 years of influenza vaccination:<br>1.0 (95% CI, 0.5–2.0) | None described                                      | Serious  |

<sup>a</sup> The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup> The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup> Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.

### Causality Conclusion

**Conclusion 6.8:** The evidence is inadequate to accept or reject a causal relationship between influenza vaccine and onset of MS in adults.

## MULTIPLE SCLEROSIS RELAPSE IN ADULTS

### Epidemiologic Evidence

The committee reviewed three studies to evaluate the risk of relapse of MS in adults after the administration of influenza vaccine. One controlled study (Mokhtarian, 1997) had very serious methodological limitations that precluded its inclusion in this assessment. Mokhtarian (1997) conducted a placebo-controlled trial with 19 MS patients, but the study was too small to be informative, and the author did not state if the treatment was assigned randomly.

The two remaining controlled studies (Confavreux et al., 2001; Miller et al., 1997) contributed to the weight of epidemiologic evidence and are described below.

Miller et al. (1997) conducted a double-blind, randomized controlled trial in 104 patients with relapsing-remitting MS identified at five MS centers in the United States. The participants were randomized at each center to receive influenza vaccination (49 patients) or placebo injection (54 patients). Injections took place during the autumn of 1993, and then patients were followed for 6 months for evidence of MS relapse. At 4 weeks and 6 months, patients were examined by a blinded neurologist, and at 1 week and 3 months a blinded nurse conducted a telephone assessment. Comparisons of MS relapse were performed at 28 days after and 6 months after vaccine or placebo injection. During the 28-day period, MS exacerbations were reported in three vaccine patients and two placebo patients. Over the 6-month period, 11 vaccine patients and 6 placebo patients experienced MS exacerbations. The difference in MS relapse was not statistically significant for either risk period. The authors concluded that influenza vaccination did not appear to be associated with an increased risk of relapse in MS patients.

Confavreux et al. (2001) conducted a case-crossover study in adults attending neurology centers affiliated with the European Database for Multiple Sclerosis. The study included 643 adults with definite or probable MS diagnoses and at least one relapse of symptoms that occurred from 1993 through 1997. The relapse was confirmed during outpatient visits or during hospitalizations at the neurology centers. For each patient, information on immunizations received was obtained from telephone questionnaires and confirmed with vaccination records or written confirmation from the physi-

cian. Vaccinations were confirmed for 260 participants, not confirmed for 57, and 326 reported receiving no vaccinations during the study period. The risk period was defined as any time within 2 months before the relapse, and the four control periods were outlined as 2-month intervals prior to the risk period (2–10 months before the relapse). The relative risk of relapse of MS within 2 months of influenza vaccination was 1.08 (95% CI, 0.37–3.10). The authors concluded that vaccination against influenza does not appear to increase the risk of MS relapse in adults.

### *Weight of Epidemiologic Evidence*

The two studies considered in the assessment of the epidemiologic evidence did not find evidence of an association between influenza vaccine and relapse of MS. However, both studies had methodological issues. Neither of the studies were adequately powered to rule out a clinically relevant association. Furthermore, the study by Confavreux et al. (2001) could not adequately control for a potential association between influenza infection and MS relapse, which could have been affected by vaccination and would tend to mask a causative influence of vaccination in a subset of patients. See Table 6-5 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has limited confidence in the epidemiologic evidence, based on two studies that lacked validity and precision, to assess an association between influenza vaccine and relapse of MS in adults.*

### **Mechanistic Evidence**

The committee identified three publications reporting the administration of an influenza vaccine to patients with MS. Moriabadi et al. (2001) did not report MS relapse after vaccination. Salvetti et al. (1995) reported fewer MS relapses in the year after vaccination than during the year preceding vaccination. The authors did not report the latency between administration of the vaccine and MS relapse after vaccination. Kepes (1993) did not provide evidence beyond temporality. The publications did not contribute to the weight of mechanistic evidence.

### *Weight of Mechanistic Evidence*

There is strong evidence that several viral infections trigger flare-ups in patients with MS. Whether influenza virus triggers these flare-ups is less certain. Given that vaccination triggers inflammatory responses, and inflam-

**TABLE 6-5 Studies Included in the Weight of Epidemiologic Evidence for Influenza Vaccine and MS Relapse in Adults**

| Citation                 | Operationally Defined Outcome  | Study Setting                            | Defined Study Population                       | Study Design  | Sample Size   | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)                        | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|--------------------------|--|--|--|---|---|---|---|--|
| Miller et al. (1997)     | MS relapse confirmed by a neurologist  | Five MS centers in the United States     | Patients with relapsing-remitting MS diagnoses | Double-blind, randomized controlled trial   | 49 vaccinated<br>54 received placebo                | No significant difference in MS relapse within 28 days or 6 months of influenza vaccination | None described                                      | Serious  |
| Confavreux et al. (2001) | MS relapse confirmed during outpatient visits or hospitalizations at neurology centers | European Database for Multiple Sclerosis |  | Case-crossover<br>Risk period: within 2 months before MS relapse<br>Control period: 3–10 months before MS relapse | 643 patients with definite or probable MS diagnoses | RR of MS relapse within 2 months of influenza vaccination:<br>1.08 (95% CI, 0.37–3.10)      | None described                                      | Serious  |

<sup>a</sup> The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup> The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup> Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.

mation is associated with exacerbations of MS, it is possible that vaccination could exacerbate clinical symptoms in MS patients. However, clinical studies with cohorts of MS patients generally do not support a causal relationship between TIV and exacerbations of MS. Case reports are few, but generally time is the only connection between MS flare-up and vaccination. Thus, there is no mechanistic evidence to support an association between influenza vaccines and MS relapse in adults.

The symptoms described in the publications referenced above are consistent with those leading to the relapse of MS in adults. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of MS; however, the publications did not provide evidence linking these mechanisms to influenza vaccine.

*The committee assesses the mechanistic evidence regarding an association between influenza vaccine and relapse of MS in adults as lacking.*

### Causality Conclusion

**Conclusion 6.9:** The evidence is inadequate to accept or reject a causal relationship between influenza vaccine and relapse of MS in adults.

## GUILLAIN-BARRÉ SYNDROME

### Epidemiologic Evidence

The committee reviewed 21 studies to evaluate the risk of Guillain-Barré syndrome (GBS) after the administration of influenza vaccine.<sup>2</sup> Nine studies (Geier et al., 2003; Haber et al., 2004; Izurieta et al., 2005; Johnson, 1982; Muhammad et al., 2011; Nakayama and Onoda, 2007; Souayah et al., 2007, 2009; Vellozzi et al., 2009) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations. Three controlled studies (Hambidge et al., 2006; Lasky et al., 1998; Wu et al., 1999) had very serious methodological limitations that precluded their inclusion in this assessment. The study by Hambidge et al. (2006) was unable to find any cases of GBS within the defined risk period following influenza vaccination using a case-crossover design, so no conclusions could be drawn from

<sup>2</sup>The committee does not include in this review any of the studies of the 1976–1977 swine influenza vaccine and its relationship to GBS. This association is accepted as causal by most analysts and a previous IOM committee (Institute of Medicine, 2004).

this analysis. The random-digit-dialing telephone survey used by Lasky et al. (1998) to define the population rates of vaccination was problematic, and the results suggested confounding by age may be present. Wu et al. (1999) conducted a case-control study, but provided inadequate information on how the controls and exposure were classified.

The nine remaining controlled studies (Burwen et al., 2010; Greene et al., 2010; Hughes et al., 2006; Hurwitz et al., 1981; Juurlink et al., 2006; Kaplan et al., 1982; Roscelli et al., 1991; Stowe et al., 2009; Tam et al., 2007) contributed to the weight of epidemiologic evidence and are described below.

Hurwitz et al. (1981) conducted a cohort study in GBS patients based on data from a voluntary surveillance system that analyzed disease onset from September 1978 through March 1979. During the study period, 1,813 neurologists (37 percent of the American Academy of Neurology members) submitted surveillance forms reporting new cases of GBS. The surveillance form listed the patient's date of birth, race, sex, county of residence, date of GBS onset, and date and type of any vaccinations received within 8 weeks of disease onset. Cases of GBS that did not receive an influenza vaccination within 8 weeks of onset were classified as unvaccinated, whereas those that received influenza vaccine during this period were listed as vaccinated. Since only neurologists participated, cases reported or seen in other settings were missed in this analysis. The vaccinated patients tended to be older than the unvaccinated (median age of 55 years compared to 35 years of age, respectively) and included a higher percentage of women (69 percent compared to 44 percent). The analysis was restricted to adults ( $\geq 18$  years of age) and included 12 vaccinated and 393 unvaccinated cases. U.S. population estimates were used from the Bureau of the Census, and an estimate of the number of vaccinated adults was obtained from a national immunization survey conducted by the Opinion Research Corporation. Incidence rates were calculated for the vaccinated and unvaccinated groups, and expressed as 0.52 and 0.38 cases per million persons per month, respectively. The relative risk of onset of GBS within 8 weeks of influenza vaccination was 1.4 (95% CI, 0.7–2.7). The authors concluded that there was no increased risk of GBS onset within 8 weeks of immunization during the 1978–1979 influenza season.

Kaplan et al. (1982) conducted a cohort study in GBS patients and used the same methods as Hurwitz et al. (1981) to analyze the onset of disease from September through March of the 1979–1980 and 1980–1981 influenza seasons. A total of 1,648 neurologists submitted surveillance forms in 1979–1980, and 1,557 participated in 1980–1981. Cases not reported or seen by neurologists were missed in this study. The analysis included 7 vaccinated and 412 unvaccinated adults ( $\geq 18$  years of age) with GBS onset during 1979–1980, and 12 vaccinated and 347 unvaccinated during

1980–1981. The relative risk of GBS onset within 8 weeks of vaccination during the 1979–1980 influenza season was 0.6 (95% CI, 0.45–1.32), and during the 1980–1981 season it was 1.4 (95% CI, 0.80–1.76). The authors concluded that there was no increased risk of GBS onset within 8 weeks of immunization during the 1979–1980 or 1980–1981 influenza season.

Roscelli et al. (1991) conducted a retrospective cohort study in active duty soldiers with health statistics from the U.S. Army Health Services Command database and vaccination information from the office of the Surgeon General of the U.S. Army. A total of 289 patients were hospitalized for onset of GBS at U.S. Army Medical Treatment Facilities from 1980 through 1988. The risk period was defined as cases of GBS occurring during November of 1980 to 1988, and the control period included cases reported in non-November months during these years. By looking at diagnoses in November, the onset of GBS was assumed to occur 1 month after vaccination (the U.S. Army requires annual immunization during the last week of October). A total of 23 cases occurred in November, and a mean of 24.18 cases were reported for non-November months. The monthly incidence of GBS was calculated by estimating the annual number of active duty army soldiers eligible for influenza vaccination (780,000 soldiers) and the number that received vaccine (624,000 based on an 80 percent compliance rate). For the month of November, the monthly incidence of GBS was 3.3 per million (95% CI, 2.0–4.6); during the non-November months, the incidence was 3.4 per million (95% CI, 3.0–3.8). No significant difference was observed between the risk and control periods. The authors concluded that influenza vaccination during 1980 through 1988 was not associated with an increased incidence in GBS in active duty U.S. Army soldiers. GBS is generally more frequent in winter months and has been associated with influenza infection itself, and these confounders could mask an association between vaccination and GBS. However, there was no evidence of seasonal differences in rates in the non-November months in this study.

Hughes et al. (2006) conducted a self-controlled case-series study in patients (0 to 100 years of age) registered in the GPRD from January 1992 through December 2000. A total of 228 new cases of GBS were identified from medical diagnostic codes in the medical records. If multiple diagnostic codes were present for one patient, the first recorded code was considered the date of disease onset. The immunization status was also found in the medical record. Cases of GBS occurring within 42 days of vaccination (risk period) were compared to diagnoses occurring at any other time during the study period (control period). Three cases occurred in the risk period and 225 cases occurred in the control period. The adjusted relative risk of GBS onset within 42 days of influenza vaccination was 0.99 (95% CI, 0.32–3.12). The authors concluded that vaccination against influenza does not increase the risk of GBS incidence within 42 days of immunization,



but noted the study was underpowered to assess a small increase in the background incidence.

Juurlink et al. (2006) conducted a self-controlled case-series study in adults ( $\geq 18$  years of age) from April 1993 through March 2004. Vaccination records were obtained from the Ontario Health Insurance Plan database and linked to hospital admissions information from the Canadian Institute for Health Information Discharge Abstract Database. To identify new cases of GBS and avoid misclassification of patients with chronic inflammatory demyelinating polyneuropathy, the authors excluded cases that had any previous admission for GBS. Any general vaccination that was provided to adults during October and November of each season was classified as an influenza immunization (the authors noted that influenza vaccinations rarely received specific codes). The analysis was restricted to patients who received a vaccination and were hospitalized for GBS onset during the 43 weeks of follow-up. The primary risk and control periods were defined as 2 to 7 weeks and 26 to 43 weeks after vaccination, respectively. A total of 51 cases were observed in the risk period and 141 cases were observed in the control period. The relative risk of a hospitalization for GBS onset during the 2 to 7 weeks after influenza immunization was 1.45 (95% CI, 1.05–1.99). Three additional sensitivity analyses using a longer risk period, shorter control period, or longer control period were conducted to evaluate the seasonal variations in GBS incidence and the results were consistent. The authors also performed an ecological analysis at the population level using a time series in the period between June 1, 1991, and March 31, 2004, to determine if there was an increase in GBS hospitalizations after introduction of universal influenza immunization program. The authors found no significant increase in hospitalization for GBS onset in adults after the mass influenza vaccination program; however, the analysis failed to adequately control for confounding by influenza season.

Tam et al. (2007) used the GPRD to perform a nested case-control study in 553 GBS patients with onset from 1990 through 2001, and 5,445 randomly selected, matched controls. The enrolled cases had a consultation for GBS in their medical record (repeat consultations were excluded) and at least 1 year of follow-up in the GPRD. Any cases with consultations within 4 months of joining a new clinic or less than 2 months of follow-up from the date of GBS onset were excluded from the analysis. A total of 10 controls were matched to each case on general practice clinic, sex, birth year, and an assigned date of GBS consultation. The controls also had to meet the same inclusion criteria that were described above for the GBS cases. The date of influenza immunization was obtained from the medical record and the risk period was defined as 60 days prior to the GBS consultation (or assigned date in controls). The odds ratio for GBS onset within 60 days of immunization against influenza was 0.16 (95% CI, 0.02–1.25). The authors

concluded that influenza vaccination is not associated with an increased risk of GBS in adults; however, they noted that this association was not the primary goal of the study. Also, differences between those selected for vaccination and others could have contributed to the association reported.

Stowe et al. (2009) conducted a self-controlled case-series study in GBS patients (all ages) registered in the GPRD from 1990 through 2005. Patients with a first or new consultation for GBS in their medical records were identified, and the date of influenza immunization was recorded. Cases that received at least one influenza vaccination had to complete a two-stage validation process to verify the date of diagnosis and to assess if an earlier date of onset was present in the medical record. The study controlled for season by using the calendar month of vaccination and controlled for age by using 12 age periods in the analysis. A total of 775 episodes occurred in 690 enrolled patients, of which 169 had at least one influenza vaccination. The primary risk period was defined as 0–90 days after vaccination, and 12 and 157 cases occurred within the risk and control periods, respectively (the control period was not defined). The relative risk of GBS onset within 90 days of influenza vaccination was 0.76 (95% CI, 0.41–1.40). The authors concluded that vaccination against influenza does not increase the risk of GBS incidence, and suggested that an association with influenza-like illness may explain the increase of GBS cases often observed during the influenza season.

Burwen et al. (2010) conducted a retrospective cohort study in 22.2 million adults (< 65 and ≥ 65 years of age) who received an influenza vaccination from September through December of 2000 and 2001 according to Medicare claims data. Cases of GBS were identified using hospital claims data from Medicare files, and diagnoses that occurred within 18 weeks of vaccination were reviewed by a physician. The cases were classified as definite, probable, or possible GBS, or not a case. Definite or probable case definitions required exclusion of other diagnoses in the information available. The date of GBS onset was obtained from the medical record. The authors compared the incidence rate of GBS during the risk period (0 to 6 weeks after vaccination) to the incidence rate during the control period (9 to 14 weeks after vaccination). The authors excluded weeks 7 and 8 from the analysis to avoid misclassification of cases in the control period if the risk of GBS extended beyond week 6. In 2000, a total of 33 cases and 10,206,581 person-periods were reported in the risk period, and 38 cases and 10,137,566 person-periods were reported in the control period. In 2001, a total of 51 cases and 11,972,259 person-periods were reported in the risk period, and 42 cases and 11,895,891 person-periods were reported in the control period. The relative risk of onset of GBS (definite or probable) within 6 weeks of influenza vaccination during the 2000 study period was 0.86 (95% CI, 0.52–1.41), and during the 2001 study period it

was 1.21 (95% CI, 0.79–1.86). The authors concluded that influenza vaccine was not associated with GBS in adults ( $\geq 65$  years of age) during the 2000–2001 or 2001–2002 influenza season. However, the study was unable to control for the seasonal variation in influenza, a potential confounder.

The study by Greene et al. (2010) was described in detail in the section on seizures. This retrospective cohort study investigated the occurrence of adverse events after influenza vaccination in children and adults enrolled in eight MCOs participating in the VSD. The authors used a Poisson-based approach (applying a maximized sequential probability ratio test [MaxSPRT]) to assess the risk of GBS after influenza vaccination. The study included cases of GBS reported during outpatient, inpatient, and emergency department visits after receipt of influenza vaccine from September through April of the 2005–2006, 2006–2007, and 2007–2008 influenza seasons. The analysis was restricted to new cases of GBS (the first event of its type) that occurred in the year of interest. The risk period for the GBS analysis (1 to 42 days after vaccination) of the current season was compared to the risk period of the previous seasons (historical risk period). The relative risk of GBS (in all ages) reported 1 to 42 days after influenza vaccination was 0.83 during the 2005–2006 season, 1.13 during the 2006–2007 season, and 1.37 during the 2007–2008 season; none of the associations was significant. The authors concluded that the risk of GBS after influenza vaccination was not significantly elevated compared to no vaccine during the 2005–2006, 2006–2007, and 2007–2008 seasons. However, annual variations in timing and severity of influenza may have affected GBS rates and confounded these associations.

### *Weight of Epidemiologic Evidence*

Of the nine epidemiologic studies reviewed, none were from a randomized clinical trial. GBS has a known seasonal variation, and some studies (see for instance Juurlink et al., 2006; Stowe et al., 2009) have demonstrated an association between GBS and influenza infection, so the risk of confounding by seasonal variation is very high. Only one paper (Juurlink et al., 2006) found a significantly increased risk of GBS associated with influenza vaccine, but results are limited by possible seasonality confounding. Furthermore, the authors noted that the absolute risk is very low. A recently published cohort study (Burwen et al., 2010) using a larger data set for analysis from two influenza seasons did not find a significant increased risk in GBS. One study (Hughes et al., 2006), which also showed no significant association, had a good study design, but the source data used for this analysis did not have enough power to assess an association. Taken together, the nine controlled studies did not support that influenza vaccination is associated with GBS. There are a relatively large number

of studies showing lack of evidence of an association between influenza vaccine and GBS, and they were generally well done. All the studies were potentially limited by confounding by seasonality and by the association between influenza itself and GBS, which could mask an association between vaccine and GBS. In addition, strains of influenza targeted by the vaccine vary each year and associations with GBS also may vary. See Table 6-6 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has a moderate degree of confidence in the epidemiologic evidence based on nine studies with sufficient validity and precision to assess an association between influenza vaccine and GBS; these studies generally report a null association, but the findings are variable across these studies.*

### Mechanistic Evidence

The committee identified 16 publications reporting the development of GBS after administration of an influenza vaccine. Fifteen publications did not provide evidence beyond temporality, some too long or too short based on the possible mechanisms involved (Blanco-Marchite et al., 2008; Brooks and Reznik, 1980; Eckert et al., 2005; Haber et al., 2004; Hajiabdolbaghi et al., 2009; Kao et al., 2004; Kavadas et al., 2008; Kuitwaard et al., 2009; Liu et al., 2006; Moon and Souayah, 2006; Muhammad et al., 2011; Nakashima et al., 1982; Pelosio et al., 1990; Pritchard et al., 2002; Thaler, 2008). Long latencies between vaccine administration and development of symptoms make it impossible to rule out other possible causes. One publication also reported the concomitant administration of vaccines making it difficult to determine which, if any, vaccine could have been the precipitating event (Thaler, 2008). In addition, two publications reported preceding illnesses that could have contributed to the symptoms (Haber et al., 2004; Muhammad et al., 2011). These publications did not contribute to the weight of mechanistic evidence.

Described below are two publications, reporting clinical or experimental evidence that contributed to the weight of mechanistic evidence.

Bedard Marrero et al. (2010) described in case number 1 a 68-year-old man, with a history of hypertension, who presented with tingling sensation of the hands and feet 2 weeks after receiving an influenza vaccine. The patient later developed respiratory difficulties, the inability to void, flaccid paralysis in all four extremities, and decreased sensation in cranial nerve V with decreased corneal and gag reflexes leading to a diagnosis of GBS. Immunoglobulin (Ig) G anti-GM1 ganglioside antibodies were demonstrated in the patient.

TABLE 6-6 Studies Included in the Weight of Epidemiologic Evidence for Influenza Vaccine and GBS

| Citation              | Operationally Defined Outcome                         | Study Setting                                  | Defined Study Population  | Study Design | Sample Size   | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)   | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|-----------------------|---|--|---|--------------|---|--|---|--|
| Hurwitz et al. (1981) | GBS onset within 8 weeks of vaccination or index date | Reports from neurologists across United States | Ages ≥ 18 years with GBS onset from 9/1978 through 3/1979                                 | Cohort       | 12 vaccinated<br>393 unvaccinated   | RR of GBS onset within 8 weeks of influenza vaccination: 1.4 (95% CI, 0.7–2.1)   | None described                                      | Serious  |
| Kaplan et al. (1982)  | GBS onset within 8 weeks of vaccination or index date | Reports from neurologists across United States | Ages ≥ 18 years with GBS onset from 9/1979 through 3/1980, and from 9/1980 through 3/1981 | Cohort       | 1979–1980 season:<br>7 vaccinated<br>412 unvaccinated<br>1980–1981 season:<br>12 vaccinated<br>347 unvaccinated | RR of GBS onset within 8 weeks of vaccination during 1979–1980 season: 0.6 (95% CI, 0.45–1.32)<br>RR of GBS onset within 8 weeks of vaccination during 1980–1981 season: 1.4 (95% CI, 0.80–1.76) | None described                                      | Serious  |

|                        |  |  |   |   |  |                |            |
|------------------------|--|--|---|---|--|----------------|------------|
| Roscelli et al. (1991) | U.S. Army Medical Treatment Facilities | Active duty soldiers with GBS onset from 1980 through 1988<br>Estimates of the annual number of active duty army soldiers who were eligible for and received influenza vaccination | Retrospective cohort<br>Risk period: November of 1980 through 1988<br>Control period: non-November months of 1980 through 1988  | 3.3 cases/million vaccinated in November<br>3.4 cases/million vaccinated in non-November months<br>23 GBS cases occurred in November<br>Mean of 24.18 cases occurred in non-November months | No significant difference was observed between the risk and control periods ( $p = .90$ )              | None described | Serious    |
| Hughes et al. (2006)   | GPRD                                   | Ages 0 to 100 years with GBS onset from 1/1992 through 12/2000   | Self-controlled case series<br>Risk period: 42 days after vaccination<br>Control period: all other time during the study period | Three GBS cases in risk period<br>225 GBS cases in control period   | Adjusted RR of GBS onset within 42 days of influenza vaccination: 0.99 (95% CI, 0.32–3.12; $p = .99$ ) | None described | Negligible |

*continued*

TABLE 6-6 Continued

| Citation               | Operationally Defined Outcome                         | Study Setting                 | Defined Study Population  | Study Design   | Sample Size  | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)   | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|------------------------|---|-------------------------------|---|--|--|--|---|--|
| Juurlink et al. (2006) | GBS onset within 2 to 7 weeks of vaccination          | Ontario Health Insurance Plan | Ages ≥ 18 years with vaccination records from 4/1993 through 2/2004 | Self-controlled case series<br>Risk period: 2–7 weeks after vaccination  | 51 GBS cases in risk period<br>141 GBS cases in control period | RR of hospitalization for GBS onset during the 2–7 weeks after influenza vaccination: 1.45 (95% CI, 1.05–1.99) | None described                                      | Serious  |
| Tam et al. (2007)      | GBS onset within 60 days of vaccination or index date | GPRD                          | Patients with vaccination records from 1990 through 2001            | Nested case control  | 553 patients with GBS<br>5,445 controls                        | OR for GBS onset within 60 days of influenza vaccination: 0.16 (95% CI, 0.02–1.25; <i>p</i> = .081)            | None described                                      | Serious  |
| Stowe et al. (2009)    | GBS onset within 90 days of vaccination               | GPRD                          | All ages with GBS and medical records from 1990 through 2005        | Self-controlled case series<br>Risk period: 90 days after influenza vaccination<br>Control period: not defined | 12 GBS cases in risk period<br>157 GBS cases in control period | RR of GBS onset within 90 days of influenza vaccination: 0.76 (95% CI, 0.41–1.40)                              | None described                                      | Serious  |

| Burwen et al. (2010) | GBS onset (definite or probable) within 6 weeks of vaccination | Medicare claims data | Ages < 65 years and ≥ 65 years with vaccination claims from 9/2000 through 12/2000, and from 9/2001 through 12/2001 | Retrospective cohort                         | 2000 season: 33 GBS cases and 10,206,581 person-periods in risk period | RR of GBS onset within 6 weeks of influenza vaccination during the 2000 season: 0.86 (95% CI, 0.52–1.41) | None described | Serious |
|----------------------|--|----------------------|---|--|--|--|----------------|---------|
|                      |  |                      |   | Risk period: 0–6 weeks after vaccination     | 38 GBS cases and 10,137,566 person-periods in control period           | RR of GBS onset within 6 weeks of influenza vaccination during the 2001 season: 1.21 (95% CI, 0.79–1.86) |                |         |
|                      |  |                      |   | Control period: 9–14 weeks after vaccination | 42 GBS cases and 11,972,259 person-periods in risk period              |  |                |         |
|                      |  |                      |   |  | 11,895,891 person-periods in control period                            |  |                |         |



TABLE 6-6 Continued

| Citation             | Operationally Defined Outcome           | Study Setting  | Defined Study Population   | Study Design   | Sample Size  | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)   | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|----------------------|---|--|--|--|--|--|---|--|
| Greene et al. (2010) | GBS onset within 42 days of vaccination | Eight MCOs participating in the VSD during the 2005–2006, 2006–2007, and 2007–2008 influenza seasons | Ages 6 months to 17 years and ≥ 18 years with GBS onset from 9/2005 through 4/2006, from 9/2006 through 4/2007, and from 9/2007 through 4/2008 | Retrospective cohort with Poisson-based MaxSPRT approach<br>Risk period: 1–42 days after vaccination in current season<br>Control period: 1–42 days after vaccination in previous seasons (historical risk period) | 2005–2006: 12 events in risk period; 14.4 events in control period<br>2006–2007: 17 events in risk period; 15.1 events in control period<br>2007–2008: 23 events in risk period; 16.7 events in control period | RR of GBS onset (all ages) 1–42 days after influenza vaccination during the 2005–2006 season: 0.83<br>RR of GBS onset (all ages) 1–42 days after influenza vaccination during the 2006–2007 season: 1.13<br>RR of GBS onset (all ages) 1–42 days after influenza vaccination during the 2007–2008 season: 1.37<br>(none was statistically significant) | None described<br>Serious                           |  |

<sup>a</sup> The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup> The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup> Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.

Nachamkin et al. (2008) immunized mice with influenza vaccines to determine if *Campylobacter jejuni* (*C. jejuni*) contamination of influenza vaccine induced GBS by eliciting antiganglioside antibodies. Mice were immunized twice with *C. jejuni* (positive control), *C. jejuni* waaF knock-out mutant (negative control), A/NJ/1976 influenza vaccine (1976 swine influenza vaccine), 1991–1992 influenza vaccine, or the 2004–2005 influenza vaccine; the immunizations were separated by 21 days. Antibodies to hemagglutinin were demonstrated in mice immunized with influenza vaccine but neither the positive nor negative controls. To determine if the vaccine preparations were contaminated with *C. jejuni*, the authors tested the serum samples from influenza-vaccine-immunized mice for antibodies to *C. jejuni* and performed polymerase chain reaction (PCR) on the vaccine preparations to amplify prokaryotic ribosomal ribonucleic acid. The serum tests and PCR were negative suggesting the vaccine preparations were not contaminated with *C. jejuni*. However, IgM and IgG anti-GM1 ganglioside antibodies were demonstrated in mice immunized with an influenza vaccine or the positive control. Furthermore, the concentration of anti-GM1 IgM and IgG antibodies demonstrated in mice immunized with the A/NJ/1976 influenza vaccine were statistically significant on days 7, 21, and 35 after immunization compared to the day of immunization. The antiganglioside antibody-positive mice did not present with clinical disease.

#### *Weight of Mechanistic Evidence*

While rare, infection with influenza viruses A and B have been associated with the development of GBS (Davis, 2008). The committee considers the effects of natural infection one type of mechanistic evidence.

The publications described above did not present evidence sufficient for the committee to conclude the vaccine may be a contributing cause of GBS after administration of an influenza vaccine. The presence of antiganglioside antibodies has been associated with many cases of GBS that were not precipitated by *C. jejuni* infections (Willison, 2005). The mechanism appears to be a cross-reaction to viruses. The presence of antibodies in the case described in Bedard Marrero et al. (2010) is consistent with GBS but does not provide an etiologic connection with the vaccine. Furthermore, Bedard Marrero et al. (2010) did not rule out other possible etiologies of the GBS. Nachamkin et al. (2008) ruled out *C. jejuni* contamination of the 1976 influenza vaccine. In addition, Nachamkin et al. (2008) reported antiganglioside antibodies in mice immunized against the 1976 influenza vaccine and non-GBS-associated influenza vaccines. However, the mice with antiganglioside antibodies did not have clinical disease and the vaccine dose was higher by body weight than the human vaccine dose (Nachamkin et al.,

2008). Furthermore, Nachamkin et al. (2008) did not include a negative influenza control virus that does not induce anti-GM1 antibodies in the study.

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of GBS. Autoantibodies, complement activation, immune complexes, T cells, and molecular mimicry may contribute to the symptoms of GBS; however, the publications did not provide evidence linking these mechanisms to influenza vaccine.

*The committee assesses the mechanistic evidence regarding an association between influenza vaccine and GBS as weak based on knowledge about the natural infection, one case, and experimental evidence.*

### Causality Conclusion

**Conclusion 6.10: The evidence is inadequate to accept or reject a causal relationship between influenza vaccine and GBS.**

Although the epidemiologic evidence is graded moderate-null, the committee does not feel the evidence is adequate to favor rejection of an association because of the potential for confounding by season and influenza infection and because of the yearly differences in influenza strains included in the vaccine. While the weight of epidemiologic evidence does not support a causal link between influenza vaccinations evaluated over the last 30 years, an association cannot be confidently ruled out, particularly for future vaccine strains.

## CHRONIC INFLAMMATORY DISSEMINATED POLYNEUROPATHY

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of chronic inflammatory disseminated polyneuropathy (CIDP) after the administration of influenza vaccine.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between influenza vaccine and CIDP.*

### Mechanistic Evidence

The committee identified five publications reporting CIDP after administration of an influenza vaccine. Four publications did not provide evidence

beyond temporality, some too short based on the possible mechanisms involved (Brostoff et al., 2008; Kelkar, 2006; Pritchard et al., 2002; Wells, 1971). The publications did not contribute to the weight of mechanistic evidence.

Described below is one publication that contributed to the weight of mechanistic evidence.

Three VAERS reports, identified in Vellozzi et al. (2009) describing the development of CIPD after administration of influenza vaccines were obtained via a FOIA request (FDA, 2010). In two reports the patients developed CIPD after administration of influenza vaccines in two different years. Symptoms developed between 1 and 10 days after administration of the influenza vaccines. In a third report an influenza vaccine was administered to a patient with a history of CIPD. Evidence beyond a temporal relationship between administration of the vaccine and development of CIPD after vaccination was not provided in any of the reports.

#### *Weight of Mechanistic Evidence*

The publication described above did not provide evidence sufficient for the committee to conclude the vaccine may be a contributing cause of CIPD. The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of CIPD, but the only evidence that could be attributed to the vaccine was recurrence of symptoms upon vaccine rechallenge. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of CIPD; however, the publications did not provide evidence linking these mechanisms to the vaccine.

*The committee assesses the mechanistic evidence regarding an association between influenza vaccine and CIPD as weak based on two cases.*

#### **Causality Conclusion**

**Conclusion 6.11: The evidence is inadequate to accept or reject a causal relationship between influenza vaccine and CIPD.**

#### **BELL'S PALSY**

##### **Epidemiologic Evidence**

The committee reviewed five studies to evaluate the risk of Bell's palsy after the administration of influenza vaccine. Two studies (Izurieta et al., 2005; Zhou et al., 2004) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems

and lacked unvaccinated comparison populations. One controlled study (Mutsch et al., 2004) investigated the association of a vaccine product that is no longer in use and was not included in the epidemiologic evidence.

The two remaining controlled studies (Greene et al., 2010; Stowe et al., 2006) contributed to the epidemiologic weight of evidence and are described below.

Stowe et al. (2006) conducted a self-controlled case-series study in patients (2 to 95 years of age) enrolled in the GPRD. Eligible patients received at least one inactivated influenza vaccine and had a consultation for Bell's palsy from July 1992 through June 2005. Multiple consultations were counted as a single episode if the second consultation occurred within 6 months of the first visit. Follow-up ended on the date the patient left the practice, the date data were last obtained from the practice, date of death, or June 30, 2005, whichever occurred first. The risk period was defined as 1–91 days after vaccination, with separate analyses for 1–30 days, 31–60 days, and 61–91 days. The authors expected a reduced number of events 14 days prior to vaccination and an increased number of events on the day of vaccination because of increased opportunity to record cases, so these were analyzed as separate risk periods. The control period included all other time not attributed to the risk periods. Analyses were adjusted for age (5-year categories), influenza season (defined as July through June), and calendar time (by quarter). A total of 2,128 patients were included in the analysis; they experienced 2,263 Bell's palsy episodes, and received 8,376 doses of influenza vaccine. The relative risk of Bell's palsy within 1–91 days of influenza vaccination was 0.92 (95% CI, 0.78–1.08). Additionally, no significant increased risk was observed when the risk period was separated into 30-day intervals or when the analyses were separated into three age groups (0–44 years, 45–64 years,  $\geq 65$  years). The authors concluded that influenza vaccine is not associated with an increased risk of Bell's palsy within 3 months of vaccination.

The study by Greene et al. (2010) was described in detail in the section on seizures. This retrospective cohort study investigated the occurrence of adverse events after influenza vaccination in children and adults enrolled in eight MCOs participating in the VSD. The study included cases of Bell's palsy reported during outpatient, inpatient, and emergency department visits after receipt of influenza vaccine from September through April of the 2005–2006, 2006–2007, and 2007–2008 influenza seasons. The risk period for the Bell's palsy analysis (1 to 42 days after vaccination) of the given season was compared to the control period (15 to 74 days before vaccination) of the same season. Because the prevaccination period tended to always be in the earliest part of the season, residual confounding owing to the lack of adjustment for different seasonal risks of infection was present. The relative risk of Bell's palsy in children within 1–42 days of influenza

vaccination was 0.67, 1.81, and 1.27 for the 2005–2006, 2006–2007, and 2007–2008 influenza seasons, respectively. The relative risk of Bell’s palsy in adults within 1–42 days of influenza vaccination was 1.06, 1.07, and 0.99 for the 2005–2006, 2006–2007, and 2007–2008 influenza seasons, respectively. None of the associations was significant. This paper also included an analysis comparing rate ratios in the current year with the cumulative ratios in prior comparison years. All of these comparisons also found no increase in Bell’s palsy in the risk period.

### *Weight of Epidemiologic Evidence*

Analyses from one retrospective cohort study and one self-controlled case-series study were included in the epidemiologic evidence. Neither of these studies (Greene et al., 2010; Stowe et al., 2006) found a significantly increased risk of Bell’s palsy after influenza vaccination. The studies were generally well done and the results were consistent, supporting the committee’s conclusion that the evidence overall reached a high level of confidence for a null association. See Table 6-7 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has a high degree of confidence in the epidemiologic evidence based on two studies with validity and precision to assess an association between inactivated influenza vaccine and Bell’s palsy; these studies consistently report a null association.*

### **Mechanistic Evidence**

The committee identified two publications reporting Bell’s palsy after administration of an influenza vaccine. The publications did not provide evidence beyond temporality, some too short based on the possible mechanisms involved (Chou et al., 2007; Philippin et al., 2002). The publications did not contribute to the weight of mechanistic evidence.

### *Weight of Mechanistic Evidence*

*The committee assesses the mechanistic evidence regarding an association between influenza vaccine and Bell’s palsy as lacking.*

### **Causality Conclusion**

**Conclusion 6.12:** The evidence favors rejection of a causal relationship between inactivated influenza vaccine and Bell’s palsy.

TABLE 6-7 Studies Included in the Weight of Epidemiologic Evidence for Influenza Vaccine and Bell's Palsy

| Citation            | Operationally Defined Outcome  | Study Setting | Defined Study Population | Study Design  | Sample Size                      | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)                      | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|---------------------|--------------------------------|---------------|--------------------------|---|----------------------------------|---|---|--|
| Stowe et al. (2006) | Consultations for Bell's palsy | GPRD          | Ages 2 to 95 years       | Self-controlled case series<br>Risk period: 1–91 days after influenza vaccination<br>Control period: all time not attributed to a risk period excluding 14 days prior to vaccination and day of vaccination | 2,128 patients with Bell's palsy | RR of Bell's palsy within 1–91 days of influenza vaccination:<br>0.92 (95% CI, 0.78–1.08) | None described                                      | Negligible                                       |

| Greene et al. (2010) | Outpatient, inpatient, and emergency department visits for Bell's palsy | Eight MCOs participating in the VSD during the 2005–2006, 2006–2007, and 2007–2008 influenza seasons | Ages 6–17 years and ≥ 18 years | Retrospective cohort  | 2005–2006: 317,108 doses administered to children; 1,432,218 doses administered to adults | 2006–2007: 415,446 doses administered to children; 1,598,880 doses administered to adults | 2007–2008: 462,998 doses administered to children; 1,742,858 doses administered to adults | RR of Bell's palsy in children within 1–42 days of influenza vaccination was 0.67 for 2005–2006, 1.81 for 2006–2007, and 1.27 for 2007–2008 influenza seasons | RR of Bell's palsy in adults within 1–42 days of influenza vaccination was 1.06 for 2005–2006, 1.07 for 2006–2007, and 0.99 for 2007–2008 influenza seasons | None described | Negligible |
|----------------------|---|--|--------------------------------|---|---|---|---|---|---|----------------|------------|
|                      |   |  |                                | Risk period: 1–42 days after influenza vaccination for a given influenza season |   | Control period: 15–74 days before vaccination for the same influenza season               |   |   |   |                |            |

<sup>a</sup> The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup> The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup> Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.



## BRACHIAL NEURITIS

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of brachial neuritis after the administration of influenza vaccine.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between influenza vaccine and brachial neuritis.*

### Mechanistic Evidence

The committee identified two publications reporting brachial neuritis after administration of an influenza vaccine. The publications did not provide evidence beyond temporality and therefore did not contribute to the weight of mechanistic evidence (Hansen, 2005; Wells, 1971).

#### *Weight of Mechanistic Evidence*

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of brachial neuritis. Autoantibodies, T cells, and complement activation may contribute to the symptoms of brachial neuritis; however, the publications did not provide evidence linking these mechanisms to influenza vaccine.

*The committee assesses the mechanistic evidence regarding an association between influenza vaccine and brachial neuritis as lacking.*

### Causality Conclusion

**Conclusion 6.13:** The evidence is inadequate to accept or reject a causal relationship between influenza vaccine and brachial neuritis.

## SMALL FIBER NEUROPATHY

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of small fiber neuropathy after the administration of influenza vaccine.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between influenza vaccine and small fiber neuropathy.*

**Mechanistic Evidence**

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of small fiber neuropathy developing after administration of an influenza vaccine.

*Weight of Mechanistic Evidence*

Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of small fiber neuropathy; however, the committee did not identify literature reporting evidence of these mechanisms after administration of influenza vaccine.

*The committee assesses the mechanistic evidence regarding an association between influenza vaccine and small fiber neuropathy as lacking.*

**Causality Conclusion**

**Conclusion 6.14:** The evidence is inadequate to accept or reject a causal relationship between influenza vaccine and small fiber neuropathy.

**ANAPHYLAXIS****Epidemiologic Evidence**

The committee reviewed eight studies to evaluate the risk of anaphylaxis after the administration of influenza vaccine. Seven studies (Bohlke et al., 2003; D’Heilly et al., 2006; DiMiceli et al., 2006; Izurieta et al., 2005; Muhammad et al., 2011; Nakayama and Onoda, 2007; Peng and Jick, 2004) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

The one remaining controlled study (Greene et al., 2010) contributed to the weight of epidemiologic evidence and is described below.

The study by Greene et al. (2010) was described in detail in the section on seizures. This retrospective cohort study investigated the occurrence of

adverse events after influenza vaccination in children and adults enrolled in eight MCOs participating in the VSD. The study included cases of anaphylaxis reported during inpatient and emergency department visits after receipt of influenza vaccine from September through April of the 2005–2006, 2006–2007, and 2007–2008 influenza seasons. The risk period for the anaphylaxis analysis (0 to 2 days after vaccination) of the given season was compared to the control period (7 to 9 days after vaccination) of the same season. The relative risk of anaphylaxis in individuals of all ages within 2 days of influenza vaccination was 3.00, 4.00, and 1.00 for the 2005–2006, 2006–2007, and 2007–2008 influenza seasons, respectively. None of the associations was significant.

### *Weight of Epidemiologic Evidence*

*The committee has limited confidence in the epidemiologic evidence, based on one study that lacked validity and precision, to assess an association between influenza vaccine and anaphylaxis.*

### **Mechanistic Evidence**

The committee identified 10 publications reporting anaphylaxis after the administration of an influenza vaccine. One publication reported the concomitant administration of vaccines, making it difficult to determine which, if any, vaccine could have been the precipitating event (Ball et al., 2001). This publication did not contribute to the weight of mechanistic evidence.

Described below are nine publications reporting clinical, diagnostic, or experiment evidence that contributed to the weight of mechanistic evidence.

Coop et al. (2008) describe a 37-year-old man presenting with a warm sensation over the entire body, face tingling and redness, postnasal drip, pruritus, and lip numbness 15 minutes after receiving an influenza vaccine. Lip swelling, heart burn, and worsening facial flushing developed over the next 15 minutes. The patient was treated with epinephrine and ranitidine. Subsequent skin prick testing showed positive responses to influenza vaccine and gelatin, and a minimal response to egg. Bands corresponding to the molecular weights of gelatin, hemagglutinin from the influenza vaccine, and ovalbumin from chicken egg were observed on the patient's IgE immunoblot.

Chung et al. (2010) performed a retrospective chart review of egg allergic children (6 months to 18 years) receiving an influenza vaccine during the influenza seasons 2002–2003 through 2008–2009. Patients receiving an influenza vaccine skin test, the two-dose graded administration of the vaccine, or both were identified in each of the influenza seasons. Between

the 2002–2003 and 2006–2007 influenza seasons 91 of 146 patients developed a positive response to an influenza vaccine skin test. Between the 2006–2007 and 2008–2009 influenza seasons 24 of 115 patients developed localized or systemic reactions after receiving the two-dose graded influenza vaccine. In addition, 12 of the 56 patients vaccinated, after skin testing, with the influenza vaccine developed localized or systemic reactions. Six systemic reactions involved the development of wheezing, eczema exacerbation, or hives on the face or chest 30 minutes after vaccination.

James et al. (1998) conducted a multicenter clinical trial to investigate the two-dose administration of influenza vaccines to egg allergic individuals. Eighty-three of the 207 subjects recruited into the investigation had a history of egg allergy. All 83 egg allergic subjects developed a positive response to skin prick testing with egg, and four of the 83 subjects developed positive responses to skin prick testing with the influenza vaccine. All 83 egg allergic subjects were administered the influenza vaccine using the two-dose protocol without developing serious immediate or delayed reactions.

DiMiceli et al. (2006) searched the VAERS database from July 1990 to July 2004 for reports mentioning a history of yeast allergy present prior to vaccination. The authors identified 107 reports mentioning a history of yeast allergy. Of the 107 reports, two reported anaphylaxis after vaccination against influenza. Case 1 (13 in the report) describes a 64-year-old woman presenting with oral edema and itchy watery eyes 15–45 minutes after vaccination against influenza. Case 2 (14 in the report) describes a 29-year-old woman presenting with numbness, tachycardia, and difficulty breathing 20 minutes after administration of an influenza vaccine.

Izurieta et al. (2005) reviewed adverse events, reported to VAERS, after administration of a live attenuated influenza vaccine during the 2003–2004 and 2004–2005 influenza seasons. The authors identified seven cases of possible anaphylaxis. Throat swelling developed in four individuals, and periorbital swelling developed in one individual. In all seven reports symptoms developed less than 3 hours after vaccination, and in five reports the symptoms developed in 20 minutes or less.

Lasley (2007) describes a 2.5-year-old boy presenting with hives scattered on the body shortly after receiving his first dose of an influenza vaccine. One month later the patient presented with hives scattered on the body, wheezing, and coughing 10 minutes after receiving a booster dose of influenza vaccine. The patient was treated with diphenhydramine and albuterol. The mother recalls the patient developing perioral hives after eating gummy candy fruit snacks. The patient developed positive responses to skin prick testing with Knox gelatin and liquefied gummy fruit snack. Furthermore, serum testing showed antiovine gelatin IgE.

Muhammad et al. (2011) reviewed reports of adverse events after administration of a trivalent influenza vaccine submitted to VAERS from

January 1990 through June 2006, of 2- to 17-year-old children and from July 2008 through June 2009, of 5- to 17-year-old children. The authors identified six cases of anaphylaxis developing after administration of an influenza vaccine from 1990 through 2006. Two of the six did not receive other vaccines and developed chest tightness or wheezing and erythema or hives on the day of vaccination. The remaining four developed symptoms either after the day of vaccination or after administration of multiple vaccines.

Peng and Jick (2004) conducted a population-based study of anaphylaxis using computer records from the GPRD for the period of January 1994 through December 1999. The authors identified two cases of anaphylaxis developing after administration of influenza vaccines. One patient was resuscitated in the emergency department immediately after vaccination.

Zheng et al. (2007) describes a 31-year-old woman with a history of seasonal allergic rhinitis and irritable bowel syndrome who developed conjunctival erythema and pain after using a thimerosal-containing contact lens solution. A booster dose of tetanus toxoid and a thimerosal-free pediatric influenza vaccine were administered without incident. The patient developed a positive response to skin prick testing with a full strength adult influenza vaccine. Generalized pruritus, throat tightness, and a dry cough developed 20 minutes after the skin prick test. The patient was treated with epinephrine.

### *Weight of Mechanistic Evidence*

The publications, described above, presented clinical evidence sufficient for the committee to conclude the vaccine was a contributing cause of anaphylaxis after administration of influenza vaccines. The clinical descriptions provided in many of the publications establish a strong temporal relationship between administration of the vaccine and anaphylactic reactions. In addition, two publications reported the isolation of antigelatin IgE, and two reported positive reactions upon prick skin testing with gelatin. In addition, one publication reported the development of symptoms to vaccination against influenza on two occasions. The vast majority of anaphylactic reactions with evidence of IgE antibodies to constituents within the vaccine have occurred in egg allergic individuals. However, in recent years, vaccine manufacturers have markedly reduced the egg protein content of vaccines and a few recent studies have demonstrated the safety of these vaccines in egg allergic patients.

*The committee assesses the mechanistic evidence regarding an association between influenza vaccine and anaphylaxis as strong based on 22 cases presenting temporality and clinical symptoms consistent with anaphylaxis.*

### Causality Conclusion

**Conclusion 6.15:** The evidence convincingly supports a causal relationship between influenza vaccine and anaphylaxis.

### INACTIVATED INFLUENZA VACCINE AND ASTHMA EXACERBATION OR REACTIVE AIRWAY DISEASE EPISODES IN CHILDREN AND ADULTS

#### Epidemiologic Evidence

The committee reviewed eight studies to evaluate the risk of asthma or reactive airway disease episodes after TIV administration in children and adults with a prior diagnosis of asthma. One controlled study (Kramarz et al., 2000) had very serious methodological limitations that precluded its inclusion in the assessment. Kramarz et al. (2000) inadequately defined the control group and comparison time periods used in their retrospective cohort study.

The seven remaining controlled studies (Bueving et al., 2004; Castro et al., 2001; Kmiecik et al., 2007; Nicholson et al., 1998; Pedroza et al., 2009; Stenius-Aarniala et al., 1986; Tata et al., 2003) were included in the weight of epidemiologic evidence and are described below.

Stenius-Aarniala et al. (1986) conducted a double-blind, randomized controlled trial in 318 patients aged 15 to 73 years, with moderate to severe asthma recruited at nine centers in Finland. The patients were randomly assigned to TIV or placebo groups, and asked to record their peak expiratory flow (PEF) values, medications, and symptom scores throughout the study. A total of 27 patients were lost to follow-up, and it was not clear whether they were balanced across the vaccine and placebo groups. No difference was observed between the PEF values reported among the vaccine and placebo groups during the 7 days after injection. Additionally, there was no difference between the severity of asthma (PEF values, symptom scores, changes in medication, or hospitalization due to asthma) observed in the groups during the 8-month follow-up period from September 1981 through April 1982. The authors concluded that TIV administration does not induce asthma exacerbations in adults with moderate to severe asthma.

Nicholson et al. (1998) conducted a double-blind, randomized controlled crossover trial in patients (18 to 75 years of age) with a history of asthma, recruited from nine respiratory centers and two asthma clinics in the United Kingdom. A total of 255 participants were included in a paired data analysis. These patients received TIV and placebo injections (vaccine then placebo or placebo then vaccine, separated by 2 weeks) and completed symptom diaries postinjection. The authors did not provide information on the characteristics of patients lost to follow-up or the results from appropri-

ate intention-to-treat analysis. The primary outcome was exacerbation of asthma within 72 hours of injection (defined as a decrease in PEF values). Asthma exacerbations were observed in 11 patients after TIV (4.3 percent; 95% CI, 2.2 percent to 7.6 percent) compared to 3 patients after placebo (1.2 percent; 95% CI, 0.2 percent to 3.3 percent). Moderate or severe exacerbations were more common after first-time vaccinations compared to repeat vaccinations (1 in 16 and 1 in 83, respectively), which suggests that an initial TIV exposure is more likely to exacerbate asthma or that patients who experience an exacerbation after TIV are more likely to avoid further doses. The authors concluded that TIV may increase the risk of pulmonary complications in asthmatic patients, although this risk is very small.

Castro et al. (2001) conducted a double-blind, randomized controlled crossover trial in asthmatic patients (3 to 64 years of age) recruited from 19 American Lung Association Asthma Clinical Research Centers from September through November 2000. A total of 1,952 patients received TIV and placebo injections (vaccine followed by placebo or placebo followed by vaccine) and completed symptom diaries for the 14 days following each injection. The mean time between injections was 22 days. The rates of asthma exacerbations in the vaccine group (28.8 percent) were equivalent to the placebo group (27.7 percent) for the 14 days after injection (absolute difference, 1.1 percent; 95% CI, -1.4 percent to 3.6 percent). The authors concluded that TIV does not increase the rate of exacerbations in asthmatic patients.

Tata et al. (2003) conducted a self-controlled case-series study in 6,000 patients with asthma and 6,000 patients with chronic obstructive pulmonary disease (65 to 79 years of age) who were randomly selected from the GPRD. The study used patient records to assess the association between TIV and disease exacerbations for the 1991–1992, 1992–1993, and 1993–1994 influenza seasons. Only patients who experienced at least one event during one of the three risk periods (the day of vaccination, 1 to 2 days after, and 3 to 14 days after vaccination) were included in the analysis. The frequency of diagnostic codes for asthma exacerbation, any asthma diagnosis, and asthma drug prescription use during the risk periods was compared to corresponding rates during the remaining influenza season (defined as October 1 through April 30). In observation of multiple outcomes (asthma exacerbation, asthma diagnosis, and increased medication use) over three influenza seasons and three risk periods, no rate ratio showed an increased risk of the outcome following influenza vaccination. The authors concluded that vaccination with TIV does not increase the risk of asthma exacerbations in patients with asthma. However, the statistical power of the study was reduced by lower than expected vaccination rates (40 percent were vaccinated) and low reporting rates of asthma exacerbation (less than 5 percent of all asthma diagnosis codes).

Bueving et al. (2004) conducted a double-blind, randomized controlled trial in 696 children (6 to 18 years of age) with asthma who were enrolled from general practices in the Netherlands during the 1999–2000 and 2000–2001 influenza seasons. The study participants were randomly assigned to TIV (347 children) or placebo groups (349 children); the groups had similar baseline characteristics. The patients recorded any asthma symptoms during the 7 days after injection, and each child only participated in one influenza season. No differences in asthma symptoms were reported between the TIV and placebo groups within 7 days of injection. Additionally, the two groups did not differ in the use of medication and number of physician consultations, school absenteeism, and work absenteeism after injection. The authors concluded that asthmatic children have no severe local or general adverse reactions to TIV administration in general practice.

Kmiecik et al. (2007) conducted a double-blind, randomized controlled crossover trial in patients (18 to 65 years of age) with a history of asthma, enrolled at four centers in Poland from October 2004 through January 2005. The study participants were randomized to receive TIV at visit one and placebo at visit two (group A), or placebo at visit one and TIV at visit two (group B). The visits were separated by 14-day intervals. During the 14 days after each injection, patients recorded any asthma exacerbations on diary cards. A total of 286 patients (144 from group A and 142 from group B) were included in the analysis; they received the TIV and placebo injections and completed both 14-day observation periods. The difference in the asthma exacerbation rates after TIV compared to placebo was 2.8 percent (95% CI, 1.9 percent to 4.2 percent) for any exacerbation and 1.7 percent (95% CI, 1.0 percent to 2.7 percent) for severe exacerbations. These small differences were less than the 5 percent difference that the authors considered clinically significant, as well as being less than the study was designed to be able to detect with adequate statistical power. The authors reported that significantly more asthma exacerbations were observed in groups A and B during the first 14-day interval compared to the second 14-day interval; however, results from appropriate repeated measures analyses (required for crossover study designs) were not provided, making the finding somewhat difficult to interpret.

Pedroza et al. (2009) conducted a double-blind, randomized controlled trial in 163 children (5 to 9 years of age) with a diagnosis of mild intermittent or moderate persistent asthma. The study participants were enrolled from the outpatient clinics of the Instituto Nacional de Pediatría, Mexico, and randomized to receive two doses of TIV (132 children) or placebo (31 children) during the 2001–2002 influenza season. The injections were separated by 28-day intervals. Evaluation of adverse events and measurement of the forced expiratory volumes (FEVs) at 1, 2, and 3 seconds (FEV1, FEV2, and FEV3, respectively) were assessed at baseline (visit one), 3 to



5 days after the first injection (visit two), and 3 to 5 days after the second injection (visit four). The authors did not adjust for differences in baseline FEV values between the vaccine and placebo groups; the placebo group had higher FEV values at visit one. There were no significant differences in changes in FEV1, FEV2, or FEV3 among the TIV and placebo groups between visits one and two, or visits one and four. The authors concluded that TIV administration in children with asthma is not associated with a significant change in pulmonary function tests.

The committee reviewed four studies evaluating the risk of asthma or reactive airway disease episodes after TIV administration in children without regard to any prior diagnosis of asthma. One study (Rosenberg et al., 2009) was not considered in the weight of epidemiologic evidence because it provided data from a passive surveillance system and lacked an unvaccinated comparison population. One controlled study (Benke et al., 2004) had very serious methodological limitations that precluded its inclusion in the assessment. The study by Benke et al. (2004) was a cross-sectional survey that could not establish the temporal sequence between influenza vaccination and asthma episodes, and since the survey was based on self-reported recall of past events, vaccinations were not validated.

The two remaining controlled studies included in the weight of epidemiologic evidence (France et al., 2004; Hambidge et al., 2006) had overlapping study populations and are described below.

The study by France et al. (2004) was described in detail in the section on seizures. This case-crossover study investigated the occurrence of adverse events within 14 days of TIV administration in children enrolled in five HMOs participating in the VSD from January 1993 through December 1999. Information regarding any prior diagnosis of asthma was not ascertained. Significant negative associations were reported for outpatient, inpatient, and emergency department visits for asthma during the 14-day risk period when compared to the prevaccination control period (OR, 0.72; 95% CI, 0.68–0.76) and postvaccination control period (OR, 0.87; 95% CI, 0.82–0.93). When children aged 6 to 23 months were analyzed separately, a negative association was observed for outpatient and emergency department asthma visits 14 days after vaccination compared to the prevaccination control period (OR, 0.73; 95% CI, 0.63–0.85) and postvaccination control period (OR, 0.84; 95% CI, 0.72–0.99). Separate analyses were not provided for asthma episodes among children with a prior diagnosis of asthma or without a prior diagnosis. The authors concluded that TIV does not increase the risk of asthma in children during the 14 days after vaccination.

The study by Hambidge et al. (2006) was described in detail in the section on seizures. This case-crossover analysis examined the occurrence of adverse events within 14 days of TIV administration in children enrolled

in eight MCOs participating in the VSD from 1991 through 2003. Half of the study population overlapped the patients observed in the study by France et al. (2004), but separate analyses for the additional time periods presented in this paper (1991–1992 and 2000–2003) were not performed. Significantly fewer outpatient visits for asthma occurred in children aged 6 to 23 months within 14 days of vaccination compared to pre- and postvaccination periods (control period 1 OR, 0.69; 95% CI, 0.63–0.76; control period 2 OR, 0.80; 95% CI 0.73–0.87). Separate analyses were not provided to distinguish asthma episodes among children with a prior diagnosis of asthma or without a prior diagnosis. The authors concluded that the lower risk of asthma observed within 14 days of TIV administration may be due to the healthy vaccine effect or reflect a change in asthma therapy during the vaccination visit.

### *Weight of Epidemiologic Evidence*

The seven studies reviewed (of which six were randomized controlled trials and four had negligible limitations in research methodology) for asthma or reactive airway disease episodes after TIV administration in children and adults with a prior diagnosis of asthma reported consistent findings across a broad age range of children and adults. The studies suggest no clinically or statistically significant increase in asthma exacerbation episodes occurs after TIV administration, regardless of whether episodes were measured by objective pulmonary function tests, prescription drug use, clinic visits, hospitalizations, absence from school or work, or subjective symptom diaries. In one randomized trial with serious losses to follow-up and other methodological limitations (Nicholson et al., 1998), a significant but relatively small reduction in PEF was reported, but only among first-time vaccinated asthma patients. The two overlapping studies (France et al., 2004; Hambidge et al., 2006) that followed large samples of children without regard to any prior diagnosis of asthma both reported consistently negative (protective) associations across a broad age range of children, suggesting no clinically or statistically significant increase in asthma episodes following TIV administration. Both studies were potentially confounded by the healthy vaccine effect and neither differentiated between asthma episodes in children with a prior asthma diagnosis or without a prior diagnosis. Under the assumption that a prior asthma diagnosis has no modifying effect (i.e., the influence of inactivated influenza vaccination on a child's risk of an asthma-like episode is the same regardless of any prior diagnosis of asthma), these reports add to the evidence described in the paragraphs above for asthma episodes in individuals with a prior asthma diagnosis. However, these two reports are unable to shed any light on whether inactivated influenza vaccine may have a differential effect

on asthma or wheezing episodes in children depending on the presence or absence of a prior diagnosis of asthma. See Table 6-8 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has a high degree of confidence in the epidemiologic evidence based on nine studies with validity and precision to assess an association between inactivated influenza vaccine and asthma exacerbation or reactive airway disease episodes in children and adults; these studies consistently report a null association.*

### Mechanistic Evidence

The committee identified 17 publications studying or reporting asthma or reactive airway disease episodes after the administration of an inactivated influenza vaccine. Reizis et al. (1987) did not provide evidence beyond temporality between vaccination and the development, not exacerbation, of asthma. Fischer et al. (1982) reported no change in theophylline levels and did not report disease activity in asthmatic patients after administration of an inactivated influenza vaccine. Hanania et al. (2004) reported that the humoral immune response to an inactivated influenza vaccine was not adversely affected by corticosteroid treatment in asthmatics. The authors did not report disease activity following vaccination. Ouellette et al. (1965) reported changes in airway hyperreactivity after methacholine challenge in asthmatics administered an inactivated influenza vaccine. The authors did not observe changes in airway hyperreactivity after administration of the vaccine in the absence of methacholine challenge. Ahmed et al. (1997) reported that pre- and postsymptom scores were not significantly different in asthmatics administered an inactivated influenza vaccine. Three publications did not report asthma exacerbation after administration of an inactivated influenza vaccine (Albazzaz et al., 1987; Chiu et al., 2003; Sener et al., 1999). Eight publications did not provide evidence beyond temporality between vaccine administration and dyspnea, bronchial reactivity, decreased peak expiratory flow rates, bronchospasm, increased use of an inhaler, asthma attacks, wheezing, and asthma exacerbation (Bell et al., 1978; Esposito et al., 2008; Innes et al., 2000; Kava and Laitinen, 1985; Kava et al., 1987; Miguères et al., 1987; Murphy and Strunk, 1985; Nicholson et al., 1998). These publications did not contribute to the weight of mechanistic evidence.

Described below is one publication reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

De Jongste et al. (1984) reported significant differences in histamine-induced bronchial hyperreactivity pre- and postvaccination in nine of nine asthmatic patients receiving LAIV and six of nine asthmatic patients re-

**TABLE 6-8 Studies Included in the Weight of Epidemiologic Evidence for Inactivated Influenza Vaccine and Asthma Exacerbation or Reactive Airway Disease Episodes in Children and Adults**

| Citation                       | Operationally Defined Outcome   | Study Setting   | Defined Study Population                           | Study Design  | Sample Size                                      | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)  | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|--------------------------------|---|---|--|---|--|---|---|--|
| Stenius-Aarniala et al. (1986) | PEF values, symptom scores, changes in medication, hospitalization due to asthma exacerbation | Nine asthma centers in Finland from 9/1981 through 4/1982             | Ages 15 to 73 years with moderate to severe asthma | Double-blind, randomized controlled trial   | 161 received TIV<br>157 received placebo         | No difference in outcome measures within 8 months of TIV administration   | None described                                      | Negligible                                       |
| Nicholson et al. (1998)        | Exacerbation of asthma within 72 hours of vaccination, defined as a decrease in PEF values    | Nine respiratory centers and two asthma clinics in the United Kingdom | Ages 18 to 73 years with a history of asthma       | Double-blind, randomized controlled crossover trial<br>Injections separated by 2 week intervals | 255 patients received TIV and placebo injections | Asthma exacerbations observed in 11 patients after TIV (4.3 percent; 95% CI, 2.2 to 7.6 percent)<br>Asthma exacerbations observed in 3 patients after placebo (1.2 percent; 95% CI, 0.2 to 3.3 percent) | None described                                      | Serious  |

*continued*

TABLE 6-8 Continued

| Citation             | Operationally Defined Outcome   | Study Setting   | Defined Study Population   | Study Design   | Sample Size  | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)  | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|----------------------|---|---|--|--|--|---|---|--|
| Castro et al. (2001) | Asthma exacerbations  | 19 American Lung Association Asthma Clinical Research Centers from 9/2000 through 11/2000 | Ages 3 to 64 years with asthma   | Double-blind, randomized controlled crossover trial<br>Mean time between injections was 22 days  | 1,952 patients received TIV and placebo injections | Rate of asthma exacerbation in TIV group: <b>28.8 percent</b><br>Rate of asthma exacerbation in placebo group: <b>27.7 percent</b><br>Absolute difference: <b>1.1 percent (95% CI, -1.4 to 3.6 percent)</b> | None described                                      | Negligible                                       |
| Tata et al. (2003)   | Diagnostic codes for asthma exacerbation, asthma diagnosis, and asthma prescription use | GPRD during the 1991–1992, 1992–1993, and 1993–1994 influenza seasons                     | Ages 65 to 79 years with asthma or chronic obstructive pulmonary disease | Self-controlled case series<br>Three risk periods: day of vaccination, 1–2 days postvaccination, and 3–14 days postvaccination<br>Control period: remaining influenza season from October 1 through April 30 | 12,000 patients                                    | No rate ratio showed an increased risk of a defined outcome following influenza vaccination   | None described                                      | Negligible                                       |

|                       |  |   |  |   |  |   |                |            |
|-----------------------|--|---|--|---|--|---|----------------|------------|
| Bueving et al. (2004) | Any asthma symptoms                          | General practices in the Netherlands during the 1999–2000 and 2000–2001 influenza seasons | Ages 6 to 18 years with asthma               | Double-blind, randomized controlled trial   | 347 received TIV<br>349 received placebo           | No differences in asthma symptoms were reported between the TIV and placebo groups  | None described | Negligible |
| Kmiecik et al. (2007) | Asthma exacerbations recorded on diary cards | Four centers in Poland from 10/2004 through 1/2005  | Ages 18 to 65 years with a history of asthma | Double-blind, randomized controlled crossover trial<br>Injections separated by 14 day intervals | 144 patients in group A<br>142 patients in group B | Difference in asthma exacerbation rates after TIV compared to placebo:<br><b>2.8 percent (95% CI, 1.9 to 4.2 percent)</b><br>Difference in severe asthma exacerbation rates after TIV compared to placebo:<br><b>1.7 percent (95% CI, 1.0 to 2.7 percent)</b> | None described | Serious    |

*continued*

TABLE 6-8 Continued

| Citation              | Operationally Defined Outcome                                     | Study Setting   | Defined Study Population   | Study Design   | Sample Size                             | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)   | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|-----------------------|---|---|--|--|---|--|---|--|
| Pedroza et al. (2009) | FEV measurements 3–5 days after injection                         | Outpatient clinics of the Instituto Nacional de Pediatría, Mexico during the 2001–2002 influenza season | Ages 5 to 9 years with mild intermittent or moderate persistent asthma | Double-blind, randomized controlled trial  | 132 received TIV<br>31 received placebo | No significant differences in changes in FEV <sub>1</sub> , FEV <sub>2</sub> , or FEV <sub>3</sub> among the TIV and placebo groups  | None described                                      | Serious  |
| France et al. (2004)  | Outpatient, inpatient, and emergency department visits for asthma | Five HMOs participating in the VSD from 1/1993 through 12/1999  | Ages under 18 years (without regard to any prior diagnosis of asthma)  | Case-crossover<br>Risk period: 14 days after TIV administration<br>Control period 1: 15 to 28 days before vaccination<br>Control period 2: 15 to 28 days after vaccination | 251,600 cases                           | Visits for asthma within 14 days of TIV administration compared to control period 1: 0.72 (95% CI, 0.68–0.76)<br>Visits for asthma within 14 days of TIV administration compared to control period 2: 0.87 (95% CI, 0.82–0.93) | None described                                      | Serious  |

| Hambidge et al. (2006) | Outpatient, inpatient, and emergency department visits for asthma | Eight MCOs participating in the VSD from 1991 through 2003 | Ages 6 to 23 months (without regard to any prior diagnosis of asthma) | Case-crossover<br>Risk period: 14 days after TIV administration<br>Control period 1: 15 to 28 days before vaccination<br>Control period 2: 15 to 28 days after vaccination | 45,356 cases | Visits for asthma within 14 days of TIV administration compared to control period 1: 0.69 (95% CI, 0.63–0.76)<br>Visits for asthma within 14 days of TIV administration compared to control period 2: 0.80 (95% CI, 0.73–0.87) | None described | Serious |
|------------------------|---|--|---|--|--------------|--|----------------|---------|
|                        |   |  |   |  |              |  |                |         |

<sup>a</sup> The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup> The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup> Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.



ceiving the inactivated influenza vaccine. The change in bronchial hyper-reactivity occurred in individuals receiving killed virus as well as live virus; therefore, this was not considered to reflect the same mechanism for asthma exacerbation that occurs with natural infection.

### *Weight of Mechanistic Evidence*

Infection with influenza viruses is associated with exacerbation of asthma (Treanor, 2010). Furthermore, morbidity and mortality rates associated with influenza virus infection are high in individuals with asthma (Treanor, 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

The publication described above did not present evidence sufficient for the committee to conclude the vaccine may be a contributing cause of asthma exacerbation or reactive airway disease episodes in children and adults after administration of an inactivated influenza vaccine. The symptoms described in the publications referenced above are consistent with those of asthma exacerbation. Viral infection and IgE-mediated hypersensitivity may contribute to asthma exacerbation; however, the publications did not provide evidence linking these mechanisms to influenza vaccine.

*The committee assesses the mechanistic evidence regarding an association between inactivated influenza vaccine and asthma exacerbation or reactive airway disease episodes in children and adults as weak based on six cases.*

## Causality Conclusion

**Conclusion 6.16:** The evidence favors rejection of a causal relationship between inactivated influenza vaccine and asthma exacerbation or reactive airway disease episodes in children and adults.

## LIVE ATTENUATED INFLUENZA VACCINE AND ASTHMA EXACERBATION OR REACTIVE AIRWAY DISEASE EPISODES IN CHILDREN YOUNGER THAN 5 YEARS OF AGE

### Epidemiologic Evidence

The committee reviewed six studies to evaluate the risk of asthma or reactive airway disease episodes in children younger than 5 years of age with and without a prior diagnosis of asthma after LAIV or CAIV administration. Four papers that reported analyses from two separate controlled studies (Belshe et al., 2004; Bergen et al., 2004; Gaglani et al., 2008; Piedra

et al., 2005) and two additional controlled studies that compared LAIV to TIV (Ashkenazi et al., 2006; Belshe et al., 2007) contributed to the weight of epidemiologic evidence and are described below. Concern for a possibly greater risk of asthma episodes following LAIV or CAIV in the subgroup of children younger than 5 years of age arose from age-specific (i.e., stratified) analyses that were reported in two published papers based on the same study population of children between 1 and 18 years of age (Belshe et al., 2004; Bergen et al., 2004).

Bergen et al. (2004) conducted a double-blind, randomized controlled trial in healthy children and adolescents (1 to 18 years of age) selected from the Kaiser Permanente (KP) health plan. A total of 9,689 participants were enrolled from October through December 2000 and randomized (2:1 ratio) to receive cold-adapted, trivalent intranasal influenza virus vaccine (CAIV) or placebo. Among the children aged 1 to 8 years, 3,769 were immunized with CAIV and 1,868 received placebo; this age group also received a second dose of the assigned agent 28 to 42 days after the first dose. Of the children aged 9 to 18 years, 2,704 received CAIV and 1,348 received placebo. The investigators reviewed the KP database to assess any hospitalizations, emergency visits, or clinic visits among the cases and controls within 42 days of vaccine or placebo administration. Serious adverse events required additional review of the medical record or contact with the patient's physician or parents. Elevated risk ratios for asthma episodes were observed in children aged 18 to 35 months: the relative risk of asthma episodes (all settings combined) within 42 days after CAIV (all doses combined) was 4.06 (90% CI, 1.29–17.86). Although history of asthma or possible asthma (by parent report) was an exclusion criterion, the authors noted that upon review of the study participants' medical records, 8.8 percent had previous visits for asthma/reactive airway disease. The authors also reported that among the 18- to 35-month age group, 7 of the 16 children experiencing asthma after CAIV had a prior visit for asthma listed in their medical record. In an analysis restricted to participants with prior asthma/reactive airway visits, the relative risk of asthma diagnosis within 42 days of CAIV vaccination was 1.11 (90% CI, 0.59–2.14); however, the analysis was not simultaneously separated or adjusted by age (e.g., 18 to 35 months).

Belshe et al. (2004) conducted a post hoc analysis of the study by Bergen et al. (2004). In the post hoc analysis, the risk of medically attended events for asthma or reactive airway disease within 42 days of CAIV administration was assessed for different age groups. The relative risk of asthma or reactive airway disease episodes within 42 days of administration of dose one of CAIV in children aged 12 to 59 months was 3.5 (90% CI, 1.09–15.54); however, no statistically significant increased risk was observed for children aged 36 to 59 months. There is a concern for the lack of simultaneous adjustment for age and history of asthma or reactive

airway disease visits, which was discussed above in Bergen et al. (2004). The authors note the lack of temporal clustering of asthma or reactive airway disease episodes within 42 days of vaccination for any age group suggests the observed increased risk of asthma may not be a result of vaccine administration.

It is important to note that the increased rates of asthma or reactive airway disease episodes following CAIV administration reported by Bergen et al. (2004) and Belshe et al. (2004) for children younger than 5 years of age were based on analyses of the same study population (albeit stratified by slightly different age cut-points); the subgroup was small and the observed increases in relative risk (4.06 and 3.5, respectively) did not achieve statistical significance at the conventional 0.05 level. The authors chose to report 90 percent rather than conventional 95 percent confidence limits, which may have heightened concern for the potential medical or public health significance of the increased relative risks computed for these small subgroups despite their instability and lack of statistical significance. Several subsequent papers examined different study populations for asthma exacerbation following LAIV or CAIV administration in children younger than 5 years of age.

Piedra et al. (2005) conducted a retrospective cohort study of children (18 months to 18 years of age) from the Scott & White Health Plan (SWHP) in Texas. The study included healthy children and children with a history of wheezing or mild intermittent asthma. It excluded children who had a previous hospital or emergency room visit for asthma, reactive airway disease, or wheezing within 6 to 12 months of enrollment. All study participants received one LAIV each year they were enrolled from 1998 through 2002. Two risk periods (defined as 0 to 14 days and 15 to 42 days after vaccination) were compared to a prevaccination reference period (defined as start date of vaccination program to date of vaccination). Adverse events during visits to clinics, emergency departments, and hospitals were ascertained by searching the SWHP administrative database. While the authors adjusted for the activity of respiratory viruses during each enrollment year, the prevaccination period tended to always be in the earliest part of the season and residual confounding owing to the lack of adjustment for different seasonal risks of infection was still present. No significant increased risk of asthma was reported 0 to 14 days after LAIV administration in children aged 18 months to 4 years. One significant increased risk was observed in this age group 15 to 42 days after vaccination in year 1 (RR, 2.85; 95% CI, 1.01–8.03), but not in the other 3 vaccine years. The authors concluded that the observed increased risk of asthma in the 18-month to 4-year age group during the 15 to 42 days after LAIV administration was most likely due to chance effect because of the large number of comparisons made without adjustment.

Gaglani et al. (2008) conducted a reanalysis of the study from Piedra et al. (2005). The reanalysis focused on exacerbation of existing mild intermittent asthma, reactive airway disease, or wheezing among study participants and new onset of asthma in those without a history of wheezing, reactive airways disease, or asthma. Two risk periods (defined as 0 to 14 days and 0 to 42 days after LAIV vaccination) were compared to a reference period that included events observed before vaccination and after the defined risk periods. One main concern with the analysis is the possibility for confounding due to residual seasonal differences in the risk period comparisons (postvaccination risk period compared to the combination of a pre- and postvaccination reference period). The authors did not find an increased risk of asthma exacerbation or new onset asthma during the 0-to-14-day or 0-to-42-day risk period after LAIV administration in the 18-month to 4-year age group during any of the 4 study years. The authors concluded that LAIV administration does not increase the risk of health care utilization for new-onset asthma or asthma exacerbation in children aged 18 months to 4 years.

Ashkenazi et al. (2006) conducted a randomized controlled trial in children (6 to 71 months of age) to assess the safety of CAIV in comparison to TIV in 10 countries (Belgium, Czech Republic, Finland, Germany, Israel, Italy, Poland, Spain, Switzerland, and the United Kingdom). The study participants were randomly assigned in a 1:1 ratio to receive two doses of CAIV-T or TIV; the doses were administered approximately 35 days apart. A total of 1,107 and 1,080 children received dose 1 CAIV-T and TIV, respectively; 1,068 and 1,046 children received dose 2 of CAIV-T and TIV, respectively. The two treatment groups had similar characteristics; a history of wheezing was reported among 47.1 percent of the CAIV-T group and 44.5 percent of the TIV group, and a history of asthma diagnosis was observed in 22.5 percent of the CAIV-T group and 22.8 percent of the TIV group. Wheezing was recorded after vaccination by parental use of diary cards (0 to 10 days); active surveillance consisting of telephone calls, clinic visits, or home visits (11 to 41 days); and reports by medical practitioners (11 to 41 days). The incidence of wheezing within 41 days of vaccination was similar in both treatment groups for dose 1 (incidence difference,  $-0.8$ ; 90% CI,  $-3.1$ – $1.6$ ) and for dose 2 (incidence difference,  $1.4$ ; 90% CI,  $-1.0$ – $3.8$ ).

Belshe et al. (2007) conducted a randomized controlled trial in children (6 to 59 months of age) to assess the safety of LAIV in comparison to TIV in 16 countries (the United States, 12 countries in Europe and the Middle East, and 3 countries in Asia). The study participants were randomly assigned to LAIV (4,179 children) or TIV (4,173 children) based on a 1:1 ratio, and an intramuscular or intranasal placebo was administered with the corresponding vaccine. The study participants and the clinical, biostatisti-

cal, and data-management staff did not know the treatment assignments. Children with wheezing recorded more than 42 days before enrollment or mild asthma were included in the study, whereas children with recent wheezing (less than 42 days before enrollment) or severe asthma were excluded. The subjects' parents recorded adverse events during the 42 days after vaccination. The authors only included in the analysis those subjects who completed the study and did not provide any data on the characteristics of the study withdrawals that would enable assessment of bias due to differential withdrawal across study groups. No significant difference in medically significant wheezing was observed between the LAIV and TIV groups for children aged 6 to 59 months, less than 24 months, or greater than or equal to 24 months. When children with or without a history of recurrent wheezing were analyzed separately, no significant difference was observed. The only observed difference in medically significant wheezing (within 42 days of vaccination) was in children less than 12 months of age, where 12 additional episodes of wheezing were reported after LAIV compared to TIV (3.8 percent and 2.1 percent, respectively).

#### *Weight of Epidemiologic Evidence*

In examining evidence for an association of asthma with TIV or LAIV immunization, the committee addressed asthma or wheezing episodes in study populations with and without a prior diagnosis of asthma. The majority of the studies enrolled persons with prior histories of asthma episodes. The diagnosis of asthma in a child usually involves a clinical judgment following repeated episodes of wheezing. Most children with asthma are atopic, having demonstrable IgE antibodies to specific antigens. The age at which wheezing is first diagnosed is variable and often accompanies a viral illness or antigen exposure, which are not causative, but rather stimulate a pathway that already existed, as described in the weight of mechanistic evidence below.

Four of the papers described above, representing two discrete cohorts in which LAIV is compared to a control population or a control time period, reported what may appear to be inconsistent findings for children younger than 5 years of age owing largely to the choice and emphasis in the first two papers on 90 percent rather than the conventional 95 percent confidence intervals. Bergen et al. (2004) and Belshe et al. (2004) analyzed age-stratified data from a large double-blind randomized controlled trial (RCT) with serious limitations. The study protocol excluded children with known asthma diagnosis, but when the study was analyzed it was found that 8.8 percent of the participants in fact had an asthma diagnosis or symptoms in the past. In the Bergen et al. (2004) analysis, there was an increased risk of wheezing in the 42 days after LAIV administration among

children 18–35 months of age (including seven children with prior asthma and nine children without prior asthma); and in the Belshe et al. (2004) analysis, increased wheezing was observed in the 12- to 59-month age group in the 42 days after LAIV administration. The relative risk estimates for the youngest subgroups of children in the original study (Bergen et al., 2004) and the reanalysis (Belshe et al., 2004) were very unstable and were not significantly increased at the conventional 0.05 level. For example, for the 3.5-fold increased relative risk reported in Belshe et al. (2004), the 95% CI would be 0.59–20.61; and for the 4.06-fold increased relative risk reported in Bergen et al. (2004), the 95% CI would be 0.36–23.72. Neither of these are statistically significant at the conventional 0.05 level. The lack of temporal clustering of asthma within the 42 days following vaccination decreases confidence that there is a causal association. In the second set of papers from Piedra et al. (2005) and Gagliani et al. (2008) the prevaccination season was used as the comparison period in the analysis. If wheezing rate is different in different seasons, this could obscure the effect of vaccine (e.g., if wheezing is expected to be higher in the winter, the lack of increased wheezing would suggest a protective effect of vaccine). Although the papers did not account for possible seasonal variation in wheezing, it is noteworthy that wheezing episodes did not increase following vaccination.

Two papers comparing TIV and LAIV found no difference in likelihood of wheezing or asthma episodes after immunization in children with a prior history of wheezing or asthma (Ashkenazi et al., 2006; Belshe et al., 2007). Since TIV vaccination compared to no vaccination showed a consistent null association with asthma episodes in children younger than 5 years of age (France et al., 2004; Hambidge et al., 2006) (see prior section on inactivated influenza vaccine and asthma or reactive airway disease episodes in children and adults), the two LAIV versus TIV studies provide further support for a null association. See Table 6-9 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has a moderate degree of confidence in the epidemiologic evidence based on six studies with sufficient validity and precision to assess an association between LAIV and asthma exacerbation or reactive airway disease episodes in children younger than 5 years of age; these studies generally report a null association.*

### Mechanistic Evidence

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of asthma or reactive airway disease episodes in children younger than 5 years of age with and without a prior diagnosis of asthma after LAIV or CAIV administration.

**TABLE 6-9** Studies Included in the Weight of Epidemiologic Evidence for Live Attenuated Influenza Vaccine and Asthma Exacerbation or Reactive Airway Disease Episodes in Children Younger Than 5 Years of Age

| Citation             | Operationally Defined Outcome                                    | Study Setting  | Defined Study Population | Study Design                              | Sample Size   | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)  | Heterogeneous Subgroups at Higher Risk <sup>b</sup>                              | Limitations (Negligible or Serious) <sup>c</sup> |
|----------------------|--|--|--------------------------|---|---|---|--|--|
| Bergen et al. (2004) | Hospitalizations, emergency visits, and clinic visits for asthma | Kaiser Permanente health plan from 10/2000 through 12/2000 | Ages 1–18 years          | Double-blind, randomized controlled trial | Ages 1–8 years:<br>3,769 received CAIV<br>1,868 received placebo    | Asthma episodes within 42 days of CAIV administration among ages 18–35 months:<br>4.06 (90% CI, 1.29–17.86)                           | No   | Serious  |
| Belshe et al. (2004) | Hospitalizations, emergency visits, and clinic visits for asthma | Kaiser Permanente health plan from 10/2000 through 12/2000 | Ages 1–17 years          | Double-blind, randomized controlled trial | Ages 12–59 months:<br>2,021 received CAIV<br>1,011 received placebo | Asthma or reactive airway disease episodes within 42 days of CAIV administration among ages 12–59 months:<br>3.5 (90% CI, 1.09–15.54) | statistically significant increased risk observed for children aged 36–59 months | Serious  |

|                      |  |   |                            |  |   |   |         |
|----------------------|--|---|----------------------------|--|---|---|---------|
| Piedra et al. (2005) | Clinic, emergency department, and hospital visits for asthma | Scott & White Health Plan in Texas from 1998 through 2002 | Ages 18 months to 18 years | Retrospective cohort<br>Risk period 1: 0–14 days after vaccination<br>Risk period 2: 15–42 days after vaccination<br>Control period: prevaccination period from start date of program to date of vaccination | No significant increased risk of asthma within 0–14 days of LAIV administration among ages 18 months to 4 years during all four study periods<br>No significant increased risk of asthma within 15–42 days of LAIV administration among ages 18 months to 4 years during the last three study periods | One significant increased risk of asthma within 15–42 days of LAIV administration among ages 18 months to 4 years during the first study period | Serious |
|----------------------|--|---|----------------------------|--|---|---|---------|

*continued*



TABLE 6-9 Continued

| Citation                           | Operationally Defined Outcome   | Study Setting                      | Defined Study Population  | Study Design  | Sample Size | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)                                      | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|------------------------------------|---|------------------------------------|---------------------------|---|-------------|---|---|--|
| Gaglani et al. (2008)              | Clinic, emergency department, and hospital visits for asthma exacerbation | Scott & White Health Plan in Texas | Ages 18 months to 4 years | Retrospective cohort  |             | No increased risk of asthma exacerbation  | None described                                      | Serious  |
| Reanalysis of Piedra et al. (2005) | visits for asthma exacerbation or new onset asthma                        | from 1998 through 2002             |                           | Risk period 1: 0–14 days after vaccination<br>Risk period 2: 0–42 days after vaccination  |             | during the 0–14 day or 0–42 day risk period among ages 18 months to 4 years during all four study periods |   |  |
|                                    |   |                                    |                           | Control period: prevaccination period from start date of program to date of vaccination and postvaccination period after defined risk periods |             |   |   |  |

|                         |  |              |                  |                             |  |  |                |         |
|-------------------------|--|--------------|------------------|-----------------------------|--|--|----------------|---------|
| Ashkenazi et al. (2006) | Wheezing recorded with diary cards, active surveillance and reports by medical practitioners | 10 countries | Ages 6–71 months | Randomized controlled trial | Dose 1: 1,107 received CAIV-T<br>1,080 received TIV<br>Dose 2: 1,068 received CAIV-T<br>1,046 received TIV | Incidence of wheezing within 41 days of vaccination was similar for dose 1 (incidence difference, $-0.8$ ; 90% CI, $-3.1$ – $1.6$ ) and dose 2 (incidence difference, $1.4$ ; 90% CI, $-1.0$ – $3.8$ ) | None described | Serious |
| Belshe et al. (2007)    | Wheezing recorded by parents   | 16 countries | Ages 6–59 months | Randomized controlled trial | 4,179 received LAIV<br>4,173 received TIV  | No significant difference in medically significant wheezing was observed between the LAIV or TIV groups for children aged 6–59 months, < 24 months, or $\geq$ 24 months                                | None described | Serious |

<sup>a</sup> The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup> The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup> Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.

*Weight of Mechanistic Evidence*

Infection with influenza is associated with exacerbations of asthma (Treanor, 2010). Furthermore, morbidity and mortality rates associated with influenza infection are high in individuals with asthma (Treanor, 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

Viral infections, IgE-mediated hypersensitivity reactions to allergens, and response to environmental pollutants may contribute to exacerbations of asthma in individuals predisposed to developing airway hyperresponsiveness. Both viral infections and environmental allergens and pollutants result in inflammation in the airway leading to the recruitment of immunomodulatory cells that release inflammatory mediators resulting in airway hyperresponsiveness and remodeling. Reviews by Holgate (2008) and Jackson and Johnston (2010) provide detailed descriptions of the cells and mechanisms involved in the pathogenesis of asthma, including abnormal responses of airway epithelial cells and the innate immune system, which promote inflammation and remodeling. The committee did not identify literature reporting evidence of these mechanisms after administration of LAIV.

*The committee assesses the mechanistic evidence regarding an association between LAIV and asthma exacerbation or reactive airway disease episodes in children younger than 5 years of age as weak based on knowledge about the natural infection.*

**Causality Conclusion**

**Conclusion 6.17:** The evidence is inadequate to accept or reject a causal relationship between LAIV and asthma exacerbation or reactive airway disease episodes in children younger than 5 years of age.

**LIVE ATTENUATED INFLUENZA VACCINE AND ASTHMA EXACERBATION OR REACTIVE AIRWAY DISEASE EPISODES IN PERSONS 5 YEARS OF AGE OR OLDER****Epidemiologic Evidence**

The committee reviewed six studies to evaluate the risk of asthma or reactive airway disease episodes in persons 5 years of age or older after LAIV or CAIV administration. One study (Izurietta et al., 2005) was not considered in the weight of epidemiologic evidence because it provided data

from a passive surveillance system and lacked an unvaccinated comparison population.

Four papers that reported analyses from two separate controlled studies (Belshe et al., 2004; Bergen et al., 2004; Gaglani et al., 2008; Piedra et al., 2005) and one additional controlled study that compared LAIV to TIV (Fleming et al., 2006) contributed to the weight of epidemiologic evidence and are described below.

The study by Bergen et al. (2004) was described in detail in the section on LAIV and asthma exacerbation or reactive airway disease episodes in children younger than 5 years of age. This randomized controlled trial did not observe an increased risk of asthma episodes in the 1- to 8-year or 9- to 17-year age group within 42 days of CAIV administration. Since the authors only reported relative risks for positive associations, specific risk ratios were not available for these subgroup analyses.

Belshe et al. (2004) conducted a post hoc analysis of the study by Bergen et al. (2004). This study is described in detail in the section on LAIV and asthma exacerbation or reactive airway disease episodes in children younger than 5 years of age. The authors report relative risks of asthma or reactive airway disease episodes within 42 days of CAIV administration in children aged 5 to 17 years after dose one (RR, 0.74; 90% CI, 0.42–1.33) and after dose two (RR, 0.33; 90% CI, 0.10–0.96). The authors concluded that the administration of CAIV in children 5 to 17 years of age does not increase the risk of asthma.

The study by Piedra et al. (2005) was described in detail in the section on LAIV and asthma exacerbation or reactive airway disease episodes in children younger than 5 years of age. This retrospective cohort study did not observe an increased risk of asthma 0 to 14 days or 15 to 42 days after LAIV administration in children aged 5 to 9 years or 10 to 18 years during any of the four study periods.

Gaglani et al. (2008) conducted a reanalysis of the study from Piedra et al. (2005). This reanalysis is described in detail in the section on LAIV and asthma exacerbation or reactive airway disease episodes in children younger than 5 years of age. The authors did not find an increased risk of asthma exacerbation or new-onset wheezing during the 0- to 14-day or 0- to 42-day risk period after LAIV administration in the 5- to 9-year or 10- to 18-year age group during any of the 4 study years.

Fleming et al. (2006) conducted a randomized controlled trial in children (6 to 17 years of age) with a clinical diagnosis of asthma. The study took place in 13 countries (Belgium, Finland, Germany, Greece, Israel, Italy, the Netherlands, Norway, Poland, Portugal, Spain, Switzerland, and the United Kingdom) from October 2002 through May 2003. The study participants were randomized 1:1 to receive CAIV (1,114 children) or TIV (1,115 children), and daily asthma symptoms were recorded by their par-

ents for 15 days postvaccination. Asthma events were also recorded during a surveillance phase (from day 14 through May 2003) that consisted of telephone calls, home visits, and clinic visits. No significant differences in the incidence of asthma exacerbations were observed between the CAIV and TIV groups after vaccination. The percentage point difference of incidence of asthma exacerbation within 42 days of CAIV administration compared to TIV was  $-0.1$  (90% CI,  $-2.4$ – $-2.2$ ; 95% CI,  $-2.8$ – $-2.6$ ). The authors noted the majority of subjects that received CAIV and TIV reported no asthma symptoms within 15 days postvaccination.

### *Weight of Epidemiologic Evidence*

In examining evidence for an association of asthma with TIV or LAIV immunization, the committee addressed asthma episodes in study populations with varying asthma histories. The majority of the studies enrolled persons with prior histories of asthma episodes. The diagnosis of asthma in a child usually involves a clinical judgment following repeated episodes of wheezing. Most children with asthma are atopic, having demonstrable IgE antibodies to specific antigens. The age at which wheezing is first diagnosed is variable and often accompanies a viral illness or antigen exposure, which are not causative, but rather stimulate a pathway that already existed, as described in the weight of mechanistic evidence below.

The five studies that reported observations from three different data sets showed consistent results. Belshe et al. (2004) and Bergen et al. (2004) report on a large retrospective cohort with appropriately defined control periods and found no association between LAIV and wheezing in children over 5 years of age. Although preexisting asthma was an exclusion criterion, 8.8 percent of the participants had a record of prior asthma diagnosis or symptoms. In these children receipt of CAIV was not associated with an increased risk of an asthma or reactive airway disease episode in the 42 days after vaccination (RR, 1.11; 90% CI, 0.59–2.14). The retrospective cohort analyzed in Piedra et al. (2005) and Gaglani et al. (2008) included children with prior asthma, and no increase in wheezing was seen in children over 5 years in either group. Interpretation of this study is limited by the fact that the control period was consistently earlier in the year, when asthma and wheezing risk may be different. However, if wheezing rates vary across different seasons and wheezing is expected to be higher in the winter, the lack of increased wheezing could suggest a protective effect of vaccination. The study comparing CAIV and TIV groups (Fleming et al., 2006) has the advantage of observing children during the same season, and finds no difference in asthma exacerbation or wheezing. Since TIV has been shown to not be associated with asthma episodes (see prior section on inactivated influenza vaccine and asthma or reactive airway episodes in

children or adults), this finding of no difference provides support for our weight of evidence of no association of LAIV or CAIV and asthma. See Table 6-10 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has a moderate degree of confidence in the epidemiologic evidence based on five studies with sufficient validity and precision to assess an association between LAIV and asthma exacerbation or reactive airway disease episodes in persons 5 years of age or older; these studies consistently report a null association.*

### Mechanistic Evidence

The committee identified five publications studying LAIV and asthma or reactive airway disease episodes in persons 5 years of age or older. Two publications did not observe exacerbation of asthma after administration of LAIV (Atmar et al., 1990; Storms et al., 1976). Two publications did not provide evidence beyond temporality (Kava and Laitinen, 1985; Redding et al., 2002). These publications did not contribute to the weight of mechanistic evidence.

Described below is one publication reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

De Jongste et al. (1984) reported significant differences in histamine-induced bronchial hyperreactivity pre- and postvaccination in all nine asthmatic patients receiving LAIV and six of nine asthmatic patients receiving the inactivated influenza vaccine. The change in bronchial hyperreactivity occurred in individuals receiving killed virus as well as live virus; therefore, this was not considered to reflect the same mechanism for asthma exacerbation that occurs with natural infection.

### *Weight of Mechanistic Evidence*

Infection with influenza viruses is associated with exacerbation of asthma (Treanor, 2010). Furthermore, morbidity and mortality rates associated with influenza virus infection are high in individuals with asthma (Treanor, 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

The publication described above did not present evidence sufficient for the committee to conclude the vaccine may be a contributing cause of asthma exacerbation or reactive airway disease episodes in persons 5 years of age or older after administration of LAIV. The symptoms described in the publications referenced above are consistent with those of asthma exacerbation. Viral infections, IgE-mediated hypersensitivity reactions to

**TABLE 6-10** Studies Included in the Weight of Epidemiologic Evidence for Live Attenuated Influenza Vaccine and Asthma Exacerbation or Reactive Airway Disease Episodes in Persons 5 Years of Age or Older

| Citation             | Operationally Defined Outcome                                    | Study Setting  | Defined Study Population | Study Design                              | Sample Size   | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)  | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|----------------------|--|--|--------------------------|---|---|---|---|--|
| Bergen et al. (2004) | Hospitalizations, emergency visits, and clinic visits for asthma | Kaiser Permanente health plan from 10/2000 through 12/2000 | Ages 1–18 years          | Double-blind, randomized controlled trial | Ages 1–8 years: 3,769 received CAIV<br>1,868 received placebo<br>Ages 9–18 years: 2,704 received CAIV<br>1,348 received placebo | No increased risk of asthma episodes within 42 days of CAIV administration among ages 1–8 years and 9–17 years (no data provided) | None described                                      | Serious  |

|  |  |  |                            |  |  |   |                |         |
|--|--|--|----------------------------|--|--|---|----------------|---------|
| Belshe et al. (2004)<br>Reanalysis of Bergen et al. (2004) | Hospitalizations, emergency visits, and clinic visits for asthma | Kaiser Permanente health plan from 10/2000 through 12/2000 | Ages 1–17 years            | Double-blind, randomized controlled trial  | Ages 5–17 years: 4,452 received CAIV<br>2,205 received placebo   | Asthma episodes within 42 days of CAIV dose 1 among ages 5–17 years: 0.74 (90% CI, 0.42–1.33)<br>Asthma diagnoses within 42 days of CAIV dose 2 among ages 5–17 years: 0.33 (90% CI, 0.10–0.96) | None described | Serious |
| Piedra et al. (2005)                                       | Clinic, emergency department, and hospital visits for asthma     | Scott & White Health Plan in Texas during 1998 to 2002     | Ages 18 months to 18 years | Case-crossover study<br>Risk period 1: 0–14 days after vaccination<br>Risk period 2: 15–42 days after vaccination<br>Control period: prevaccination period from start date of program to date of vaccination | No increased risk of asthma within 0–14 days or 15–42 of LAIV administration among ages 5–9 years or 10–18 years during all four study periods |   |                | Serious |

*continued*



TABLE 6-10 Continued

| Citation              | Operationally Defined Outcome   | Study Setting  | Defined Study Population                 | Study Design  | Sample Size                               | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)  | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|-----------------------|---|--|--|---|---|---|---|--|
| Gaglani et al. (2008) | Clinic, emergency department, and hospital visits for asthma exacerbation or new onset asthma | Scott & White Health Plan in Texas during 1998 to 2002 | Ages 18 months to 4 years                | Case-crossover study<br>Risk period 1: 0–14 days after vaccination<br>Risk period 2: 0–42 days after vaccination<br>Control period: prevaccination period from start date of program to date of vaccination and postvaccination period after defined risk periods |   | No increased risk of asthma exacerbation or new onset asthma within 0–14 days or 0–42 days of LAIV administration among ages 5–9 years or 10–18 years during all four study periods | None described                                      | Serious  |
| Fleming et al. (2006) | Asthma symptoms recorded by parents and active surveillance                                   | 13 countries during October 2002 through May 2003      | Ages 6–17 years with an asthma diagnosis | Randomized controlled trial   | 1,114 received CAIV<br>1,115 received TIV | Percentage point difference of asthma exacerbation within 42 days of CAIV compared to TIV: -0.1 (95% CI, -2.8–2.6)  | None described                                      | Serious  |

<sup>a</sup>The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup>The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup>Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.

allergens, and response to environmental pollutants may contribute to exacerbations of asthma in individuals predisposed to developing airway hyperresponsiveness. Both viral infections and environmental allergens and pollutants result in inflammation in the airway leading to the recruitment of immunomodulatory cells that release inflammatory mediators resulting in airway hyperresponsiveness and remodeling. Reviews by Holgate (2008) and Jackson and Johnston (2010) provide detailed descriptions of the cells and mechanisms involved in the pathogenesis of asthma, including abnormal responses of airway epithelial cells and the innate immune system, which promote inflammation and remodeling. The committee did not identify literature reporting evidence of these mechanisms after administration of LAIV.

*The committee assesses the mechanistic evidence regarding an association between LAIV and asthma exacerbation or reactive airway disease episodes in persons 5 years of age or older as weak based on knowledge about the natural infection and nine cases.*

### Causality Conclusion

**Conclusion 6.18:** The evidence is inadequate to accept or reject a causal relationship between LAIV and asthma exacerbation or reactive airway disease episodes in persons 5 years of age or older.

## ONSET OR EXACERBATION OF SYSTEMIC LUPUS ERYTHEMATOSUS

### Epidemiologic Evidence

The committee reviewed four studies to evaluate the risk of systemic lupus erythematosus (SLE) after the administration of influenza vaccine; the studies assessed the risk of SLE exacerbation in patients with preexisting disease. These four controlled studies (Abu-Shakra et al., 2000; Del Porto et al., 2006; Stojanovich, 2006; Williams et al., 1978) contributed to the weight of epidemiologic evidence and are described below.

Williams et al. (1978) conducted a double-blind, randomized controlled trial in patients with SLE to investigate changes in disease activity following influenza immunization. A total of 40 patients who met the American Rheumatism Association diagnosis criteria for SLE were randomized to receive a bivalent whole influenza vaccine or saline injection. The authors noted that the two groups were balanced for age, sex, treatment, clinical manifestations, and prevaccination disease activity. Clinical evaluations were conducted at 1, 2, 4, and 6 weeks following injection, and then

monthly through 20 weeks of follow-up. Between weeks 15 and 20, one patient from the vaccinated group and one patient from the placebo group required hospitalization for disease flare-ups. The authors concluded that influenza vaccination does not increase the disease activity of SLE patients, but noted they had limited information to adequately assess this risk.

Abu-Shakra et al. (2000) conducted a cohort study (presumably retrospective, however the cohort design was not further described) in patients with SLE who were enrolled from October through November 1998. A total of 48 consecutive patients who met the American College of Rheumatology diagnosis criteria for SLE were included in the study; 24 patients received influenza vaccine, and 24 patients were not vaccinated during the study period. The exposed and unexposed groups had similar characteristics (age, sex, ethnic origin, disease duration, and disease activity at diagnosis), but the authors failed to describe the exclusion criteria (especially for unvaccinated patients). SLE activity was evaluated using the SLE Disease Activity Index (SLEDAI) at vaccination and during follow-up assessments at 6 and 12 weeks postvaccination. Multivariate analysis of variance was performed to compare the repeated SLEDAI measurements. Changes in SLEDAI score for the vaccinated and unvaccinated patients were not statistically different after the three assessments ( $p = .29$ ). There was a significant decrease in the SLEDAI score within each group at 6 and 12 weeks postvaccination compared to the time of vaccination ( $p = .02$ ). The authors concluded that influenza vaccine does not adversely influence the disease activity of SLE patients.

Del Porto et al. (2006) conducted a prospective cohort study in SLE and rheumatoid arthritis (RA) patients enrolled at an outpatient clinic from 2003 through 2004. The exposed group included 14 SLE patients and 10 RA patients who met the American College of Rheumatology diagnostic criteria and agreed to receive influenza vaccine during the study period. The unexposed group included 14 SLE patients and 10 RA patients who were randomly selected from the patients that did not consent to vaccine administration. Disease activity of the 28 SLE patients was evaluated before vaccination and at 1, 3, and 6 months after vaccination. The investigators assessed the SLEDAI scores, number and severity of flare-ups, and local or systemic clinical adverse events for the exposed and unexposed groups. No systemic clinical adverse events were observed in the vaccinated patients. The SLEDAI scores did not significantly increase among the vaccinated and unvaccinated SLE patients during the 6 months of follow-up. Additionally, the number and severity of flare-ups were not significantly different among the two groups (OR, 2.17; 95% CI, 0.1–137.49), and were observed in two vaccinated patients and one unvaccinated patient. The authors concluded that influenza vaccination does not adversely influence the disease activity of SLE patients.

Stojanovich (2006) conducted a cohort study in 69 SLE patients. A total of 23 patients received influenza vaccine in November 2003, and 46 patients remained unvaccinated. The exposed and unexposed groups had comparable characteristics (age, gender, disease activity, manifestations of main disease, and immunoserological parameters) at time of vaccination. The investigators assessed the disease activity (SLEDAI scores) and occurrence of viral and bacterial infections for 1 year following vaccination. The authors noted that the disease activity did not worsen in vaccinated SLE patients, but measures of disease activity were not provided. The unvaccinated SLE patients experienced more viral and bacterial infections and worsening of disease activity, which was attributed to changes in the medical management of SLE necessitated by treatment (e.g., antibiotics) for the infections. The authors concluded that influenza vaccination does not adversely influence the disease activity of SLE patients, and noted that unvaccinated patients are at higher risk of disease exacerbation resulting from viral and bacterial infections.

#### *Weight of Epidemiologic Evidence*

The studies considered in the epidemiologic evidence consist of one small RCT comparing influenza vaccine and no vaccine in SLE patients (Williams et al., 1978) and three observational studies that include unvaccinated patients (Abu-Shakra et al., 2000; Del Porto et al., 2006; Stojanovich, 2006). The observational studies are variably limited by size and adjustment for confounding. Changes in disease activity pre- and postvaccination are reported based on SLE symptom scales (SLEDAI scores). The results in each of the four studies are consistent with no change in disease activity or a negative association with disease activity (Stojanovich, 2006) following influenza vaccination. See Table 6-11 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has limited confidence in the epidemiologic evidence, based on four studies that lacked validity and precision, to assess an association between influenza vaccine and exacerbation of SLE.*

*The epidemiologic evidence is insufficient or absent to assess an association between influenza vaccine and onset of SLE.*

#### **Mechanistic Evidence**

The committee identified nine publications reporting or studying the onset or exacerbation of SLE after administration of an influenza vaccine.

**TABLE 6-11** Studies Included in the Weight of Epidemiologic Evidence for Influenza Vaccine and Exacerbation of SLE

| Citation                 | Operationally Defined Outcome   | Study Setting | Defined Study Population  | Study Design                              | Sample Size  | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)  | Heterogeneous Subgroups at Higher Risk <sup>b</sup>  | Limitations (Negligible or Serious) <sup>c</sup> |
|--------------------------|---------------------------------|---------------|---|---|--|---|--|--|
| Williams et al. (1978)   | Disease flare-ups               |               | Patients with SLE that met the American Rheumatism Association diagnostic criteria  | Double-blind, randomized controlled trial | 20 received a bivalent whole influenza vaccine<br>20 received saline injection | No significant differences in the vaccinated and placebo groups   | None described   | Serious  |
| Abu-Shakra et al. (2000) | SLEDAI score                    |               | Patients with SLE that met the American College of Rheumatology diagnostic criteria | Cohort                                    | 24 vaccinated<br>24 unvaccinated   | SLEDAI scores for the vaccinated and unvaccinated patients were not statistically different at 0, 6, and 12 weeks postvaccination ( <i>p</i> = .29) | Significant decrease in SLEDAI scores of both groups at 6 and 12 weeks after influenza vaccination ( <i>p</i> = .02) | Serious  |
| Del Porto et al. (2006)  | SLEDAI score and disease flares |               | Patients with SLE that met the American College of Rheumatology diagnostic criteria | Prospective cohort                        | 14 vaccinated<br>14 unvaccinated   | OR for disease flares at 6 months after influenza vaccination: 2.17 (95% CI, 0.1–137.49)  | None described   | Serious  |

|                    |  |                   |        |                                  |  |                |         |
|--------------------|--|-------------------|--------|----------------------------------|--|----------------|---------|
| Stojanovich (2006) | SLEDAI score, and occurrence of viral and bacterial infections | Patients with SLE | Cohort | 23 vaccinated<br>46 unvaccinated | Disease activity did not worsen in exposed group, but measures not provided in article | None described | Serious |
|--------------------|--|-------------------|--------|----------------------------------|--|----------------|---------|

<sup>a</sup> The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup> The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup> Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.

Five publications either did not observe exacerbation of SLE after administration of an influenza vaccine or did not provide evidence beyond temporality between vaccine administration and exacerbation of SLE (Brodman et al., 1978; Holvast et al., 2009b; Ichikawa et al., 1983; Wallin et al., 2009; Wiesik-Szewczyk et al., 2010). Four publications did not provide evidence beyond temporality between administration of influenza vaccine and diagnosis of SLE (Brown et al., 1994; Ichikawa et al., 1983; Older et al., 1999; Vainer-Mossel et al., 2009). In addition, Older et al. (1999) reported the concomitant administration of vaccines, making it difficult to determine which, if any, vaccine could have been the precipitating event. These publications did not contribute to the weight of mechanistic evidence.

Described below is one publication reporting clinical, diagnostic, or experimental evidence that merits greater discussion.

Augey et al. (2003) described a 65-year-old woman, with a history of hypertension and thrombosis of the retina, presenting with nonpruritic bubbles on the chest and arms 7 days after receiving an influenza vaccine. The rash spontaneously resolved within 6 months. One year later, the patient presented with similar symptoms, except the bubbles were more numerous and larger, 4 days after receiving an influenza vaccine. A biopsy of a bubble showed granulocytes, neutrophils, and eosinophils. The biopsy also showed inflammation of the dermis with a primarily lymphocytic infiltrate in the perivascular nodules. Deposits of IgA, IgG, IgM, and C3 were revealed by direct immunofluorescence. SLE was diagnosed based on the histology. There were no data linking the diagnosis of SLE to the vaccine, and there was no proposed mechanism.

### *Weight of Mechanistic Evidence*

There are data suggesting that natural infections, but not influenza viruses per se, can exacerbate symptoms in patients with SLE (Doria et al., 2008). Vaccination, like natural infection, triggers an inflammatory response, and inflammation is present during exacerbations of SLE. It is important to note, however, that not all inflammation is infectious so lupus flare-ups may also be associated with sterile inflammation as would be the case with an inactivated influenza vaccine. Autoantibodies, T cells, complement activation, and immune complexes may contribute to the onset or exacerbation of SLE; however, the publications did not provide evidence linking these mechanisms to influenza vaccine. Notably, the time for progression to SLE is thought to be many years. Therefore, a person with no history of SLE who presents with SLE symptoms shortly after receiving an influenza vaccine would not have had a vaccine-induced initiation of the disease process. The committee finds temporality, which is insufficient to conclude a causal relationship, the only association between SLE and influenza vaccine.

*The committee assesses the mechanistic evidence regarding an association between influenza vaccine and onset or exacerbation of SLE as lacking.*

### Causality Conclusion

**Conclusion 6.19:** The evidence is inadequate to accept or reject a causal relationship between influenza vaccine and onset or exacerbation of SLE.

## ONSET OR EXACERBATION OF VASCULITIS

### Epidemiologic Evidence

The committee reviewed two studies to evaluate the risk of exacerbation of vasculitis after the administration of influenza vaccine. These two controlled studies (Holvast et al., 2009a; Stassen et al., 2008) contributed to the weight of epidemiologic evidence and are described below.

Stassen et al. (2008) conducted a retrospective cohort study in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Consecutive AAV patients (mainly with Wegener's granulomatosis) with at least 1 year of medical record follow-up between 1999 and 2004 were enrolled in the study. Influenza vaccination histories were obtained from interviews conducted in 2004 using a standardized questionnaire and supplemented with additional data from the patients' general practitioners. Disease relapse was assessed by reviewing the medical charts for new or increased disease activity and was attributed to influenza vaccination if the vaccine was administered within 1 year of the relapse. The analysis provided relapse rates each year for the vaccinated and unvaccinated groups. A total of 230 AAV patients with at least 1 year of follow-up were included in the study; 156 were vaccinated at least once and 74 were never vaccinated. The exposed group was significantly older, had longer disease duration before enrollment, and used a lower dosage of immunosuppressive medication than the unexposed group. The relapse rate per 100 patients at risk during 1999–2004 was 3.4 and 6.3 for the vaccinated and unvaccinated groups, respectively (RR, 0.54). The authors concluded that influenza vaccination does not increase the occurrence of disease relapse in AAV patients.

Holvast et al. (2009a) conducted a randomized controlled trial in Wegener's granulomatosis patients with quiescent disease from October through December 1995. Patients with active disease were excluded from the study. A total of 72 patients were randomized in a 2:1 ratio to receive influenza vaccine (49 patients) or serve as controls (23 patients). Disease activity was assessed at entry, 1 month postvaccination, and 3–4 months post-



vaccination. At each visit, the Birmingham vasculitis activity score (BVAS), visual analogue score (VAS), and ANCA titers were measured. The patients completed standardized questionnaires to record any adverse effects from influenza vaccination, and both groups reported comparable events. One vaccinated and one unvaccinated patient developed active disease within 1 month of follow-up; no vaccinated and two unvaccinated patients developed active disease within 4 months of follow-up. The ANCA titers, fourfold increase in ANCA titers, and VAS did not differ among the vaccinated and control groups during the 4 months of follow-up. The authors concluded that influenza vaccination does not increase the occurrence of disease relapse in Wegener's granulomatosis patients with quiescent disease; however, they noted the study was underpowered to adequately detect this effect.

### *Weight of Epidemiologic Evidence*

Two studies are considered in the epidemiologic evidence. One is a larger observational study of consecutive AAV patients with 1 year of follow-up. The results show a negative association with moderate precision; however, the exposure was not randomly allocated and the analysis did not adjust for potential confounders. The second study is a smaller RCT with 3–4 months of follow-up (Wegener's patients randomized to vaccine or no vaccine). The pre- and postvaccination disease scores are the same or lower in the vaccine group, but the study may be underpowered to adequately assess this outcome. See Table 6-12 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has limited confidence in the epidemiologic evidence, based on two studies that lacked validity and precision, to assess an association between influenza vaccine and exacerbation of vasculitis.*

*The epidemiologic evidence is insufficient or absent to assess an association between influenza vaccine and onset of vasculitis.*

### **Mechanistic Evidence**

The committee identified 48 publications reporting or studying onset or exacerbation of vasculitis after administration of an influenza vaccine. Holvast et al. (2010) did not report differences in cell-mediated immune responses between Wegener's granulomatosis patients undergoing treatment with immunosuppressants, those not undergoing treatment with immunosuppressants, and healthy controls. Three publications did not provide clinical, diagnostic, or experimental evidence, including the time frame

**TABLE 6-12** Studies Included in the Weight of Epidemiologic Evidence for Influenza Vaccine and Exacerbation of Vasculitis

| Citation               | Operationally Defined Outcome     | Study Setting | Defined Study Population               | Study Design                | Sample Size                                  | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)   | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|------------------------|-----------------------------------|---------------|--|-----------------------------|--|--|---|--|
| Stassen et al. (2008)  | New or increased disease activity |               | Patients with AAV                      | Retrospective cohort        | 156 vaccinated<br>74 unvaccinated            | RR of disease relapse within 1 year of influenza vaccination: 0.54   | None described                                      | Serious  |
| Holvast et al. (2009a) | BVAS, VAS, and ANCA titers        |               | Patients with Wegener's granulomatosis | Randomized controlled trial | 49 received influenza vaccine<br>23 controls | No difference in ANCA titers or VAS among vaccinated and control groups within 4 months of influenza vaccination | None described                                      | Serious  |

<sup>a</sup> The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup> The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup> Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.

between vaccination and development of symptoms (Gburek and Gozdzik, 2002; Gerth, 1992; Spaetgens et al., 2009). Forty-three publications did not provide evidence beyond temporality, some too long or too short based on the possible mechanisms involved (Bedard and Gascon, 1999; Begier et al., 2004; Bellut et al., 2001; Birck et al., 2009; Blumberg et al., 1980; Cannata et al., 1981; Famularo et al., 2006; Finsterer et al., 2001; Garcia Robledo et al., 2010; Gavaghan and Webber, 1993; Ghose et al., 1976; Guillevin and Levy, 1983; Herron et al., 1979; Houston, 1983; Hu et al., 2009; Hyla-Klekot et al., 2005; Iyngkaran et al., 2003; Jover-Saenz et al., 2008; Kasper et al., 2004; Kelsall et al., 1997; Liozon et al., 2000; Lohse et al., 1999; Mader et al., 1993; Molina et al., 1990; Mormile et al., 2004; Patel et al., 1988; Perez et al., 2000; Pou et al., 2008; Reizis et al., 1987; Ritter et al., 2003; Shuster, 2006; Tavadia et al., 2003; Uji et al., 2005; Ulm et al., 2006; Vaglio et al., 2009; Verschuren and Blockmans, 1998; Vial et al., 1990; Wada et al., 2008; Walker et al., 2004; Watanabe and Onda, 2001; Wattiaux et al., 1988; Wharton and Pietroni, 1974; Yanai-Berar et al., 2002). Long latencies between vaccine administration and development of symptoms make it impossible to rule out other possible causes. One publication also reported the concomitant administration of vaccines, making it difficult to determine which, if any, vaccine could have been the precipitating event (Houston, 1983). Furthermore, four publications reported concomitant infections, making it difficult to determine which could have been the precipitating event (Finsterer et al., 2001; Liozon et al., 2000; Verschuren and Blockmans, 1998; Wada et al., 2008). These publications did not contribute to the weight of mechanistic evidence.

Described below is one publication reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Two VAERS reports, identified in Vellozzi et al. (2009), describing the development of vasculitis after administration of influenza vaccines were obtained via a FOIA request (FDA, 2010). One patient reported the development of vasculitis 8 days after administration of influenza vaccines on two occasions. One patient reported the development of leukocytoclastic vasculitis on the day of vaccination on two occasions. These reports potentially represent cases of rechallenge. Evidence of causality beyond a temporal relationship between administration of the vaccines and development of transient blindness was not provided. The influenza vaccine changes yearly, but generally includes some strains from the previous year.

### *Weight of Mechanistic Evidence*

The publication described above did not provide evidence sufficient for the committee to conclude the vaccine may be a contributing cause of vasculitis. The symptoms described in the publications referenced above are

consistent with those leading to a diagnosis of vasculitis, but the only evidence that could be attributed to the vaccine was recurrence of symptoms upon vaccine rechallenge. Autoantibodies, T cells, complement activation, and immune complexes may contribute to the symptoms of vasculitis; however, the publications did not provide evidence linking these mechanisms to influenza vaccine.

*The committee assesses the mechanistic evidence regarding an association between influenza vaccine and exacerbation of vasculitis as weak based on two cases.*

*The committee assesses the mechanistic evidence regarding an association between influenza vaccine and onset of vasculitis as lacking.*

### Causality Conclusion

**Conclusion 6.20:** The evidence is inadequate to accept or reject a causal relationship between influenza vaccine and vasculitis.

## POLYARTERITIS NODOSA

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of polyarteritis nodosa (PAN) after the administration of influenza vaccine.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between influenza vaccine and PAN.*

### Mechanistic Evidence

The committee identified one publication reporting the development of PAN after administration of an influenza vaccine. The publication did not provide evidence beyond temporality and therefore did not contribute to the weight of mechanistic evidence (Wharton and Pietroni, 1974).

#### *Weight of Mechanistic Evidence*

The symptoms described in the publication referenced above are consistent with those leading to a diagnosis of PAN. Autoantibodies, T cells,

complement activation, and immune complexes may contribute to the symptoms of PAN; however, the publication did not provide evidence linking these mechanisms to influenza vaccine.

*The committee assesses the mechanistic evidence regarding an association between influenza vaccine and PAN as lacking.*

### Causality Conclusion

**Conclusion 6.21: The evidence is inadequate to accept or reject a causal relationship between influenza vaccine and PAN.**

## ONSET OR EXACERBATION OF ARTHROPATHY

### Epidemiologic Evidence

The committee reviewed two studies to evaluate the risk of onset or exacerbation of arthropathy after the administration of influenza vaccine. These two studies (Chalmers et al., 1994; Harrison et al., 1997) had very serious methodological limitations that precluded their inclusion in this assessment. The study by Chalmers et al. (1994) assessed the association between influenza vaccine and disease flare-ups in RA patients, but the authors did not use a clear measure for the outcome of interest, and the results were difficult to compare across groups. Harrison et al. (1997) conducted a case-control study in patients with inflammatory polyarthritis, but the methods for selecting controls were not well described, and differential assessment of the cases could have led to biased ascertainment of the exposure.

### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between influenza vaccine and onset or exacerbation of arthropathy.*

### Mechanistic Evidence

The committee identified 12 publications either reporting or studying the onset or exacerbation of arthropathy after administration of an influenza vaccine. Three publications did not report exacerbation of rheumatoid arthritis after administration of an influenza vaccine to patients receiving treatment (Elkayam et al., 2010; Salemi et al., 2010; Van Assen et al., 2010). Eight publications did not provide evidence beyond temporality between vaccine administration and the development or exacerbation of

arthropathies (Asakawa et al., 2005; Biasi et al., 1994; Brown et al., 1994; Harrison et al., 1997; Kato et al., 2006; Malleson et al., 1993; Pou et al., 2008; Yoo, 2010). In addition, Pou et al. (2008) reported the concomitant administration of vaccines, making it difficult to determine which, if any, vaccine could have been the precipitating event. Furthermore, Brown et al. (1994) reported the development of a flu-like illness in the same time frame, making it difficult to determine the precipitating event. These publications did not contribute to the weight of mechanistic evidence.

Described below is one publication reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Thurairajan et al. (1997) reported a 78-year-old man, with a history of chronic obstructive airway disease and ischemic heart disease, presenting with malaise, swollen joints, stiffness of the hands, ankles, and knees, and pyrexia leading to a diagnosis of polyarthropathy 2 hours after receiving an inactivated influenza vaccine. The symptoms spontaneously resolved within 1 week. One year prior the patient developed similar symptoms 2 hours after administration of an influenza vaccine with spontaneous resolution of symptoms within 1 day.

#### *Weight of Mechanistic Evidence*

Arthralgia is commonly observed during infection with influenza (Treanor, 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

The publication described above did not present clinical evidence sufficient for the committee to conclude the vaccine may be a contributing cause of arthropathy after vaccination against influenza. The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of arthropathy, but the only evidence that could be attributed to the vaccine was recurrence of symptoms upon vaccine rechallenge. Autoantibodies, T cells, complement activation, immune complexes, and infection may contribute to the symptoms of arthropathy; however, the publications did not provide evidence linking these mechanisms to the vaccine.

*The committee assesses the mechanistic evidence regarding an association between influenza vaccine and onset or exacerbation of arthropathy as weak based on one case and knowledge about the natural infection.*

#### Causality Conclusion

**Conclusion 6.22:** The evidence is inadequate to accept or reject a causal relationship between influenza vaccine and onset or exacerbation of arthropathy.

## STROKE

### Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of stroke after the administration of influenza vaccine. This one controlled study (Smeeth et al., 2004) contributed to the weight of epidemiologic evidence and is described below.

The study by Smeeth et al. (2004) was described in detail in the section on influenza vaccine and myocardial infarction. This self-controlled case-series study included patients who were enrolled in the GPRD for at least 1 year and had a stroke diagnosis at least 6 months after enrollment; patients were excluded if vascular events listed in their medical records appeared to be recorded retrospectively. A total of 19,063 patients with a validated date of a first stroke and influenza vaccination were included in the analysis. Age-adjusted incidence ratios (IRs) were calculated for a first stroke occurring within 1–3 days (IR, 0.77; 95% CI, 0.61–0.96), 4–7 days (IR, 0.72; 95% CI, 0.59–0.88), 8–14 days (IR, 0.84; 95% CI, 0.73–0.96), 15–28 days (IR 0.88; 95% CI, 0.80–0.97), and 29–91 days (IR, 1.01; 95% CI, 0.96–1.06) following vaccination. The authors concluded that influenza vaccination is not associated with an increased risk of stroke.

#### *Weight of Epidemiologic Evidence*

*The committee has a moderate degree of confidence in the epidemiologic evidence based on a single study with sufficient validity and precision to assess an association between influenza vaccine and stroke; this study reports a decreased risk within 1 month following vaccination.*

### Mechanistic Evidence

The committee identified one publication reporting ischemic stroke after administration of an influenza vaccine. The publication did not provide evidence beyond temporality and therefore did not contribute to the weight of mechanistic evidence (Vainer-Mossel et al., 2009).

#### *Weight of Mechanistic Evidence*

The symptoms described in the publication referenced above are consistent with those leading to a diagnosis of ischemic stroke. Alterations in the coagulation cascade may contribute to the symptoms of ischemic stroke;

however, the publication did not provide evidence linking this mechanism to influenza vaccine.

*The committee assesses the mechanistic evidence regarding an association between inactivated influenza vaccine and ischemic stroke as lacking.*

### Causality Conclusion

**Conclusion 6.23:** The evidence is inadequate to accept or reject a causal relationship between influenza vaccine and stroke.<sup>3</sup>

## MYOCARDIAL INFARCTION

### Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of myocardial infarction after the administration of influenza vaccine. This one controlled study (Smeeth et al., 2004) contributed to the weight of epidemiologic evidence and is described below.

Smeeth et al. (2004) conducted a self-controlled case-series study in patients ( $\geq 18$  years of age) enrolled in the GPRD from 1987 through 2001. Eligible patients were enrolled in the GPRD for at least 1 year and had a myocardial infarction at least 6 months after enrollment; patients were excluded if vascular events listed in their medical records appeared to be recorded retrospectively. Vaccination histories were obtained from the GPRD, and participants were classified as vaccinated if they received an influenza vaccine from September through March of a given influenza season. The risk period included the 1–91 days following vaccination and was subdivided into five smaller periods (1–3 days, 4–7 days, 8–14 days, 15–28 days, and 29–91 days after vaccination). The control period consisted of all other time outside the risk period not including the time before a participant's first influenza vaccination, since influenza vaccine is indicated for patients with preexisting cardiovascular disease. Participants who received multiple influenza vaccinations during the study period were followed for 91 days after each exposure. A total of 20,486 patients with

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<sup>3</sup>In order for the evidence to favor rejection of a causal relationship, the committee's framework requires two or more epidemiologic studies with negligible limitations (indicating a null association or decreased risk) to reach a high degree of confidence in the epidemiologic evidence. Only one epidemiologic study with negligible methodological limitations that reports a decreased risk is included in the weight of evidence for this causality conclusion.



a validated date of a first myocardial infarction and influenza vaccination were included in the analysis. Age-adjusted incidence ratios were calculated for a first myocardial infarction occurring within 1–3 days (IR, 0.75; 95% CI, 0.60–0.94), 4–7 days (IR, 0.68; 95% CI, 0.56–0.84), 8–14 days (IR, 0.73; 95% CI, 0.63–0.85), 15–28 days (IR 0.87; 95% CI, 0.79–0.96), and 29–91 days (IR, 1.03; 95% CI, 0.98–1.08) following vaccination. The authors concluded that influenza vaccination is not associated with an increased risk of a first myocardial infarction.

### *Weight of Epidemiologic Evidence*

*The committee has a moderate degree of confidence in the epidemiologic evidence based on a single study with sufficient validity and precision to assess an association between influenza vaccine and myocardial infarction; this study reports a decreased risk within 1 month following vaccination.*

### **Mechanistic Evidence**

The committee identified one publication reporting myocardial infarction after administration of an influenza vaccine. The publication did not provide evidence beyond temporality and therefore did not contribute to the weight of mechanistic evidence (Ritter et al., 2003).

### *Weight of Mechanistic Evidence*

While rare, influenza infection has been associated with myocardial infarction (Treanor, 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

The symptoms described in the publication referenced above are consistent with those leading to a diagnosis of myocardial infarction. Viral infection and alterations in the coagulation cascade may contribute to the symptoms of myocardial infarction; however, the publication did not provide evidence linking these mechanisms to influenza vaccine.

*The committee assesses the mechanistic evidence regarding an association between LAIV and myocardial infarctions as weak based on knowledge about the natural infection.*

*The committee assesses the mechanistic evidence regarding an association between inactivated influenza vaccine and myocardial infarction as lacking.*

### Causality Conclusion

**Conclusion 6.24:** The evidence is inadequate to accept or reject a causal relationship between influenza vaccine and myocardial infarction.<sup>4</sup>

## FIBROMYALGIA

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of fibromyalgia after the administration of influenza vaccine.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between influenza vaccine and fibromyalgia.*

### Mechanistic Evidence

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of fibromyalgia after administration of an influenza vaccine.

#### *Weight of Mechanistic Evidence*

*The committee assesses the mechanistic evidence regarding an association between influenza vaccine and fibromyalgia as lacking.*

### Causality Conclusion

**Conclusion 6.25:** The evidence is inadequate to accept or reject a causal relationship between influenza vaccine and fibromyalgia.

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<sup>4</sup>In order for the evidence to favor rejection of a causal relationship, the committee's framework requires two or more epidemiologic studies with negligible limitations (indicating a null association or decreased risk) to reach a high degree of confidence in the epidemiologic evidence. Only one epidemiologic study with negligible methodological limitations that reports a decreased risk is included in the weight of evidence for this causality conclusion.

## ALL-CAUSE MORTALITY

### Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of all-cause mortality following the administration of influenza vaccine. This one controlled study (Kokia et al., 2007) contributed to the weight of epidemiologic evidence and is described below.

Kokia et al. (2007) conducted a retrospective cohort study in adults (55 years of age and older) enrolled in the Maccabi Healthcare Services HMO in Israel during the 2006–2007 influenza season. The influenza vaccination date was obtained from computerized physician and nurse treatment files; 3,064 cases were excluded because the exact date of vaccine administration could not be determined from the files. The outcome was defined as death due to any cause. The National Insurance Institute provided the date of death, which was included in the HMO membership files. One case was excluded because of a reporting error that listed the date of death before the vaccination date. The vaccinated group included patients who received an influenza vaccine during October 2006. The nonvaccinated group included patients who did not receive an influenza vaccine during October 2006 (some of whom were vaccinated later in the 2006–2007 influenza season). Follow-up began after the index date (date of vaccination for exposed and October 1 for unexposed) and ended after 14 days. A total of 259,781 patients were included in the survival analysis; 31,043 were vaccinated and 228,738 did not receive influenza vaccine in October 2006. The hazard ratio model was adjusted for factors associated with higher mortality risk (age, history of diabetes or cardiovascular disease, and homebound status). The adjusted hazard ratio for all-cause mortality within 14 days of administration of influenza vaccine was 0.33 (95% CI, 0.18–0.61). The authors concluded that influenza vaccination is not associated with an increased risk of death in the short term.

### *Weight of Epidemiologic Evidence*

*The committee has a moderate degree of confidence in the epidemiologic evidence based on a single study with sufficient validity and precision to assess an association between influenza vaccine and all-cause mortality; this study reports a decreased risk.*

### Mechanistic Evidence

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of all-cause mortality after administration of an influenza vaccine.

*Weight of Mechanistic Evidence*

Infection with wild-type influenza viruses is associated with excess mortality (Treanor, 2010). Increases in all-cause excess mortality are observed during epidemics of influenza (Treanor, 2010).

*The committee assesses the mechanistic evidence regarding an association between LAIV and all-cause mortality as weak based on knowledge about the natural infection.*

*The committee assesses the mechanistic evidence regarding an association between inactivated influenza vaccine and all-cause mortality as lacking.*

**Causality Conclusion**

**Conclusion 6.26:** The evidence is inadequate to accept or reject a causal relationship between influenza vaccine and all-cause mortality.<sup>5</sup>

**OCULORESPIRATORY SYNDROME****Epidemiologic Evidence**

The committee reviewed seven studies to evaluate the risk of oculo-respiratory syndrome (ORS) after the administration of influenza vaccine. Two studies (De Serres et al., 2003, 2005) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations. One controlled study (Skowronski et al., 2006) had very serious methodological limitations that precluded its inclusion in this assessment. Skowronski et al. (2006) conducted a retrospective cohort study based on a household telephone survey that did not validate self-reported vaccination data, and the choice of household controls could have introduced selection bias.

The four remaining controlled studies (De Serres et al., 2004; Hambidge et al., 2006; Scheifele et al., 2003; Skowronski et al., 2003a) contributed to the weight of epidemiologic evidence and are described below. Scheifele et al. (2003) and Skowronski et al. (2003a) conducted concurrent studies; patients who had not previously experienced ORS were enrolled in Scheifele

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<sup>5</sup>In order for the evidence to favor rejection of a causal relationship, the committee's framework requires two or more epidemiologic studies with negligible limitations (indicating a null association or decreased risk) to reach a high degree of confidence in the epidemiologic evidence. Only one epidemiologic study with negligible methodological limitations that reports a decreased risk is included in the weight of evidence for this causality conclusion.

et al. (2003), and patients who had ORS following influenza vaccination during the 2000–2001 season were included in Skowronski et al. (2003a).

Scheifele et al. (2003) conducted a randomized controlled crossover trial in adults (30–59 years of age) residing in provinces of Canada where Fluviral S/F influenza vaccine was exclusively supplied during the 2000–2001 influenza season. Patients were excluded if they experienced ORS symptoms after a previous influenza vaccination. The participants were randomly assigned to receive Fluviral S/F vaccine then placebo, or placebo then Fluviral S/F vaccine. The injections were given 5 to 7 days apart during September 2001. The nurse or pharmacist administering the injection and the patient were blinded to the treatment assignments. Patients were contacted by telephone 24 hours and 6 days after each injection, and a team member collected data on ORS symptoms (bilateral conjunctival redness, facial swelling, sore throat, hoarseness, difficulty swallowing, coughing, wheezing, difficulty breathing, and chest discomfort) and duration of illness. Of the 622 doses of vaccine and 626 doses of placebo administered, 620 and 624 patients completed the telephone interview, respectively. The vaccine-attributable risk of ORS symptoms within 24 hours of injection (with resolution of symptoms within 48 hours of onset) was 2.9 percent (95% CI, 0.6–5.2). The ORS symptoms observed in the study were mild and generally short lived.

Skowronski et al. (2003a) conducted a randomized controlled crossover trial in adults ( $\geq 19$  years of age) enrolled from Quebec, Manitoba, Alberta, and British Columbia provinces of Canada. Patients were eligible if they had ORS following the administration of Fluviral S/F vaccine during the 2000–2001 influenza season. The participants were randomly assigned to receive Fluviral S/F vaccine then placebo, or placebo then Fluviral S/F vaccine. The injections were given 5 to 7 days apart during September 2001. The nurse or pharmacist administering the injection and the patient were blinded to the treatment assignments. Patients were contacted by telephone the evening of the injection day, and 24 hours and 6 days after each injection. A team member collected data on ORS symptoms (bilateral conjunctival redness, coughing, wheezing, chest discomfort, difficulty breathing, difficulty swallowing, hoarseness, sore throat, and facial swelling) and duration of illness. The study was stopped early because the vaccine-attributable ORS recurrence rate exceeded 10 percent. A total of 61 patients received a first injection and completed a follow-up interview when the study ended; 34 patients received vaccine and 27 patients received placebo. The vaccine-attributable risk of ORS symptoms within 24 hours of injection with no time limit for resolution of symptoms was 33 percent (95% CI, 10–53 percent), and with resolution of symptoms within 48 hours of onset it was 27 percent (95% CI, 5–47 percent). Odds ratios were also calculated for the occurrence of ORS symptoms within 24 hours

of injection with no time limit for resolution of symptoms (OR, 4.0; 95% CI, 1.4–37.8) and with resolution of symptoms within 48 hours of onset (OR, 5.0; 95% CI, 1.1–30.0). Most ORS symptoms were considered mild and easily tolerated.

De Serres et al. (2004) conducted a randomized controlled crossover trial in adults ( $\geq 18$  years of age) enrolled from Vancouver, Quebec City, and the Montérégie area in Canada during the 2002–2003 influenza season. Patients were eligible if they had ORS after receiving the 2000–2001 influenza vaccine and were not revaccinated (group A), had ORS after receiving the 2000–2001 influenza vaccine and were revaccinated in 2001–2002 (group B), or had a first occurrence of ORS after receiving the 2001–2002 influenza vaccine (group C). A total of 281 patients were eligible, of whom 150 (53 percent) agreed to participate; 146 were included in the analysis (46 in group A, 50 in group B, and 50 in group C). The patients in each group were randomly assigned to receive Fluviral S/F vaccine then placebo, Vaxigrip vaccine then placebo, placebo then Fluviral S/F vaccine, or placebo then Vaxigrip vaccine. The two injections were given 7 days apart, and the immunizing nurse and patient were blinded to the content of the injections. Patients were contacted by telephone 24 hours and 7 days after each injection, and a trained nurse collected data on ORS symptoms (bilateral red eyes, sore throat, difficulty swallowing, cough, breathing difficulty, chest tightness, wheezing, and facial or palpebral edema) and duration of illness. The vaccine-attributable risk of ORS symptoms in the first 24 hours of injection (with no time limit for resolution of symptoms) was 34 percent (95% CI, 21–47 percent) in patients receiving Fluviral S/F vaccine and 15 percent (95% CI, 2–28 percent) in patients receiving Vaxigrip vaccine. Only the association between ORS and Fluviral S/F vaccine remained statistically significant when the case definition was restricted to include at least one edema or ocular symptom and at least one respiratory symptom. After the 2002–2003 influenza vaccination, the highest risk of ORS was observed in group A patients (41 percent) compared to patients in groups B and C (16 percent and 18 percent, respectively). Overall, 86 percent of the patients described their ORS symptoms as mild.

The study by Hambidge et al. (2006) was described in detail in the section on seizures. This case-crossover analysis examined the occurrence of adverse events after TIV administration in children enrolled in eight MCOs participating in the VSD from 1991 through 2003. The investigators looked for episodes of ORS symptoms (red eyes, respiratory symptoms, or facial swelling) during four risk periods (0–2 or 1–3 days, 1–14 days, 15–42 days, and 1–42 days) after influenza vaccination, but were limited to predefined codes in the MCO databases. The authors state that “no increased signal” of conjunctivitis (individual code or part of aggregate code for eye symptoms) was observed in any cohort or medical setting after administration

of a U.S. influenza vaccine, but they do not provide data as to the actual number of cases of conjunctivitis in the risk windows or the control periods. The weakness of the study is that since ORS symptoms are mild, subjects may not have sought medical attention; thus, in the absence of the active surveillance conducted in the three Canadian studies above, no conclusions can be drawn about the incidence of ORS symptoms following this U.S. immunization program.

### *Weight of Epidemiologic Evidence*

Of the four papers described above, three are well-designed randomized controlled crossover clinical studies. One randomized study (Scheifele et al., 2003) examining ORS occurrence after Fluviral S/F vaccine compared to placebo showed significant evidence of an increased risk of ORS after influenza vaccine. Two randomized trials (De Serres et al., 2004; Skowronski, et al., 2003a) examined the recurrence of ORS following repeat influenza vaccination in people who had experienced ORS following prior vaccination in Canada, and showed highly significant increased risk of recurrence of ORS. Although De Serres et al. (2004) included Vaxigrip in their trial, the risk of ORS did not remain statistically significant when a more narrow case definition (ocular symptoms or edema plus respiratory symptoms) was employed. Scheifele, Skowronski, and De Serres indicated that the ORS symptoms were mild and easily resolved—an important consideration in weighing the risk versus the benefit of these influenza vaccines. One case-crossover study by Hambidge et al. (2006) did not observe an increased frequency of conjunctivitis symptoms following influenza vaccine in the United States. However, this study did not conduct active surveillance of ORS symptoms, relying instead on evidence from predefined diagnosis codes from medical records. Since ORS symptoms reported by other studies were mild, and often did not lead subjects to seek medical care, the study by Hambidge et al. (2006) only allows the conclusion that ORS symptoms severe or persistent enough to lead subjects to seek medical care did not occur more frequently following influenza immunization. Thus, the evidence is limited to observations following the administration of two particular vaccines used in Canada in the first 3 years of the 21st century, and does not offer useful information as to the risk of ORS following influenza vaccination in the United States. See Table 6-13 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has a moderate degree of confidence in the epidemiologic evidence based on three studies with sufficient validity and precision to assess an association between ORS and two*

**TABLE 6-13** Studies Included in the Weight of Epidemiologic Evidence for Influenza Vaccine and Oculorespiratory Syndrome

| Citation                | Operationally Defined Outcome  | Study Setting  | Defined Study Population  | Study Design  | Sample Size  | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)   | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|-------------------------|--|--|---|---|--|--|---|--|
| Scheifele et al. (2003) | ORS symptoms recorded by a team member by telephone 24 hours and 6 days after each injection | Canada (Vancouver, Calgary, Winnipeg, and Quebec City) | Adults aged 30–59 years residing in provinces where Fluviral S/F influenza vaccine was exclusively supplied during the 2000–2001 influenza season | Randomized controlled crossover trial<br>Injections were given 5–7 days apart during September 2001 | 620 received Fluviral S/F influenza vaccine for the 2001–2002 season<br>624 received placebo | The vaccine-attributable risk of ORS symptoms within 24 hours of injection with resolution of symptoms within 48 hours of onset:<br>2.9% (95% CI, 0.6%–5.2%) | None described                                      | Negligible                                       |

*continued*



TABLE 6-13 Continued

| Citation                 | Operationally Defined Outcome  | Study Setting  | Defined Study Population   | Study Design  | Sample Size   | Primary Effect   |   |
|--------------------------|--|--|--|---|---|--|---|
|                          |  |  |  |   |   | Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)  | Limitations (Negligible or Serious) <sup>c</sup>                                    |
| Skowronski et al. (2003) | ORS symptoms recorded by a team member by telephone 24 hours and 6 days after each injection | Canada (Quebec, Manitoba, Alberta, and British Columbia) | Adults aged $\geq 19$ years who had ORS following Fluviral S/F vaccination during the 2000–2001 influenza season | Randomized controlled crossover trial<br>Injections were given 5–7 days apart during September 2001 | 34 received Fluviral S/F influenza vaccine for the 2001–2002 season | OR for occurrence of ORS symptoms within 24 hours of injection with no time limit for resolution of symptoms:<br>4.0 (95% CI, 1.4–37.8)        | Heterogeneous Subgroups at Higher Risk <sup>b</sup><br>None described<br>Negligible |
|                          |  |  |  |   | 27 received placebo   | OR for occurrence of ORS symptoms within 24 hours of injection with resolution of symptoms within 48 hours of onset:<br>5.0 (95% CI, 1.1–30.0) |   |

| De Serres et al. (2004) | ORS symptoms recorded by a trained nurse by telephone 24 hours and 7 days after each injection | Canada (Vancouver, Quebec City, and the Montérégie area) | Adults ≥ 18 years of age<br>Group A: patients who had ORS after receiving the 2000–2001 influenza vaccine and were not revaccinated<br>Group B: patients who had ORS after receiving the 2000–2001 influenza vaccine and were revaccinated during the 2001–2002 influenza season<br>Group C: patients who had a first occurrence of ORS after receiving the 2001–2002 influenza vaccine | Randomized controlled crossover trial<br>Injections were given 7 days apart | 73 received Fluoral S/F influenza vaccines for the 2002–2003 season<br>73 received Vaxigrip influenza vaccines for the 2002–2003 season<br>146 received placebo | The vaccine-attributable risk of ORS symptoms within 24 hours of Fluoral S/F vaccination with no time limit for resolution of symptoms:<br><b>34 percent (95% CI, 21–47 percent)</b><br>The vaccine-attributable risk of ORS symptoms within 24 hours of Vaxigrip vaccination with no time limit for resolution of symptoms:<br><b>15 percent (95% CI, 2–28 percent)</b> | None described | Negligible |
|-------------------------|--|--|---|---|---|--|----------------|------------|
|-------------------------|--|--|---|---|---|--|----------------|------------|

*continued*

TABLE 6-13 Continued

| Citation               | Operationally Defined Outcome  | Study Setting  | Defined Study Population     | Study Design  | Sample Size  | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)   | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|------------------------|--|--|------------------------------|---|--------------|--|---|--|
| Hambidge et al. (2006) | Outpatient, inpatient, and emergency department visits for conjunctivitis as an individual code or part of aggregate code for eye symptoms | Eight MCOs participating in the VSD from 1991 through 2003 | Children ages 6 to 23 months | Case-crossover<br>Risk periods: 1–3 days, 1–14 days, 15–42 days, and 1–42 days after TIV administration<br>Control period: 15 to 28 days before vaccination and 15 to 28 days after vaccination | 45,356 cases | No increased signal of conjunctivitis (individual code or part of aggregate code for eye symptoms) was observed in any cohort or medical setting | None described                                      | Serious  |

<sup>a</sup>The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup>The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup>Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.

*particular vaccines used in three particular years in Canada; these studies consistently report an increased risk.*

### Mechanistic Evidence

The committee identified eight publications of ORS postvaccination against influenza. Two publications did not provide evidence beyond temporality and therefore did not contribute to the weight of mechanistic evidence (Skowronski et al., 2003b,c).

Described below are six publications reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

De Serres et al. (2004) performed a placebo controlled clinical trial in which patients were divided into three groups. In two groups patients developed ORS postinfluenza vaccination in 2000–2001; one group was revaccinated in 2001–2002 while the other was not. The third group consisted of patients that developed ORS, for the first time, postinfluenza vaccination in 2001–2002. Each patient received the placebo and the 2002–2003 vaccine, either Fluviral S/F or Vaxigrip, 7 days apart. Fifty-two of the 146 patients participating in the study developed a recurrence of ORS symptoms after receiving the 2002–2003 vaccine. Of the patients who developed ORS symptoms after vaccination in 2000–2001, 12 patients experienced a recurrence of symptoms after receiving the 2001–2002 vaccine, and 13 patients experienced a recurrence of symptoms after receiving the 2002–2003 vaccine. ORS symptoms were more frequent in patients receiving Fluviral S/F than in those receiving Vaxigrip.

De Serres et al. (2005) produced a report on the development of ORS postvaccination during four influenza seasons (2000–2003) using vaccine-associated adverse event data reported to public health units in Quebec, Canada. The Fluviral vaccine was the only influenza vaccine distributed in 2000 and made up 99 percent of the doses administered in 2003. Fluviral and Vaxigrip were distributed in 2001 and 2002. The authors identified 1,488 cases of ORS. Recurrent ORS symptoms were reported by 17, 43, and 11 patients in 2001, 2002, and 2003, respectively. Five patients developed symptoms of ORS after each of three vaccinations while three patients developed symptoms after each of four vaccinations.

Fredette et al. (2003) described six patients presenting with symptoms of ORS developing 1.5 to 12 hours postinfluenza vaccination. All of the patients reported red eyes, three reported a sensation of palpebral fullness, and three reported ocular pruritus. Five patients complained of ocular secretions and two reported photophobia and blurred vision. Four patients complained of a sore throat. Levels of total hemolytic complement (CH50) were at or lower than the low reference point for the normal range in

four patients. Likewise, C3 and C4 levels were at or lower than the low reference points for the normal ranges in four patients and three patients, respectively.

Skowronski et al. (2002) conducted a survey of British Columbia residents that reported an adverse event postinfluenza vaccination during the 2000–2001 season. Of the survey participants, 398 developed ORS after vaccination during the 2000–2001 season. One hundred twenty-two participants that developed ORS during the 2000–2001 season were vaccinated against influenza during the 2001–2002 season; approximately 5 percent experienced a recurrence of symptoms.

Skowronski et al. (2003a) conducted a randomized, double-blind, placebo-controlled trial to determine the risk of recurrence of ORS. Seventy-three participants, of whom 61 met the inclusion and exclusion criteria, were enrolled in the study when it was halted because the early stopping rule was exceeded. Forty-four percent of the 34 individuals who received the Fluviral S/F influenza vaccine experienced a recurrence of ORS symptoms.

Skowronski et al. (2005) conducted a survey of children in British Columbia, Canada, to assess the development of adverse events postinfluenza vaccination in 2000–2001. A total of 1,074 children were vaccinated during the 2000–2001 influenza season. Of the 39 children who received two doses of influenza vaccine, 10 experienced ORS. The symptoms were described as being worse or the same after the first dose compared to the second dose by 8 of the 10 children.

### *Weight of Mechanistic Evidence*

The six publications described above, when considered together, presented clinical evidence sufficient for the committee to conclude the vaccine may be a contributing cause of ORS after vaccination against influenza. Evidence from these publications include latency of  $\leq 24$  hours between vaccination and the development of symptoms, complement activation, and importantly, recurrence of symptoms after vaccine rechallenge in six publications. In addition, the activation of the complement cascade by influenza viruses directly through binding of its matrix (M1) protein (Zhang et al., 2009) or through immune complex formation with preformed nonprotective antibodies leading to tissue pathology has been reported (Monsalvo et al., 2011).

The mechanistic evidence, described above, suggests that complement activation may be a mechanism for ORS after influenza vaccination.

*The committee assesses the mechanistic evidence regarding an association between ORS and two particular vaccines used in three*

*particular years in Canada as intermediate based on experimental evidence and cases<sup>6</sup> presenting clinical evidence.*

### Causality Conclusion

**Conclusion 6.27:** The evidence favors acceptance of a causal relationship between ORS and two particular vaccines used in 3 particular years in Canada.

### CONCLUDING SECTION

Table 6-14 provides a summary of the epidemiologic assessments, mechanistic assessments, and causality conclusions for influenza vaccine.

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<sup>6</sup>Due to the use of the same sample population in some studies it is likely that some of the cases were presented in more than one publication; thus, it is difficult to determine the number of unique cases.

**TABLE 6-14** Summary of Epidemiologic Assessments, Mechanistic Assessments, and Causality Conclusions for Influenza Vaccine

| Vaccine   | Adverse Event                                    | Studies                  |  |                        | Cases Contributing to the Mechanistic Assessment | Causality Conclusion |
|-----------|--|--------------------------|--|------------------------|--|----------------------|
|           |  | Epidemiologic Assessment | Contributing to the Epidemiologic Assessment | Mechanistic Assessment |  |                      |
| Influenza | Encephalitis                                     | Insufficient             | None   | Weak                   | 1  | Inadequate           |
| Influenza | Encephalopathy                                   | Insufficient             | None   | Weak                   | 2  | Inadequate           |
| Influenza | Seizures <sup>a</sup>                            | Moderate (null)          | 4  | Lacking                | None   | Inadequate           |
| Influenza | Acute Disseminated Encephalomyelitis             | Insufficient             | None   | Weak                   | None   | Inadequate           |
| Influenza | Transverse Myelitis                              | Insufficient             | None   | Weak                   | None   | Inadequate           |
| Influenza | Optic Neuritis <sup>a</sup>                      | Limited                  | 2  | Weak                   | 2  | Inadequate           |
| Influenza | Neuromyelitis Optica                             | Insufficient             | None   | Lacking                | None   | Inadequate           |
| Influenza | Multiple Sclerosis Onset in Adults               | Limited                  | 2  | Lacking                | None   | Inadequate           |
| Influenza | Multiple Sclerosis Relapse in Adults             | Limited                  | 2  | Lacking                | None   | Inadequate           |
| Influenza | Guillain-Barré Syndrome                          | Moderate (null)          | 9  | Weak                   | 1  | Inadequate           |
| Influenza | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient             | None   | Weak                   | 2  | Inadequate           |
| Influenza | Inactivated Influenza Vaccine and Bell's Palsy   | High (null)              | 2  | Lacking                | None   | Favors Rejection     |
| Influenza | Brachial Neuritis                                | Insufficient             | None   | Lacking                | None   | Inadequate           |
| Influenza | Small Fiber Neuropathy                           | Insufficient             | None   | Lacking                | None   | Inadequate           |

| Influenza | Anaphylaxis   | Limited  | 1         | Strong                                 | 22        | Convincingly Supports |
|-----------|---|--|-----------|--|-----------|-----------------------|
| Influenza | Inactivated Influenza Vaccine and Asthma Exacerbation or Reactive Airway Disease Episodes in Children and Adults                      | High (null)                                    | 9         | Weak                                   | 6         | Favors Rejection      |
| Influenza | Live Attenuated Influenza Vaccine and Asthma Exacerbation or Reactive Airway Disease Episodes in Children Younger Than 5 Years of Age | Moderate (null)                                | 6         | Weak                                   | None      | Inadequate            |
| Influenza | Live Attenuated Influenza Vaccine and Asthma Exacerbation or Reactive Airway Disease Episodes in Persons 5 Years of Age or Older      | Moderate (null)                                | 5         | Weak                                   | 9         | Inadequate            |
| Influenza | Onset or Exacerbation of Systemic Lupus Erythematosus   | Limited (exacerbation)<br>Insufficient (onset) | 4<br>None | Lacking                                | None      | Inadequate            |
| Influenza | Onset or Exacerbation of Vasculitis   | Limited (exacerbation)<br>Insufficient (onset) | 2<br>None | Weak (exacerbation)<br>Lacking (onset) | 2<br>None | Inadequate            |
| Influenza | Polyarteritis Nodosa  | Insufficient                                   | None      | Lacking                                | None      | Inadequate            |
| Influenza | Onset or Exacerbation of Arthropathy  | Insufficient                                   | None      | Weak                                   | 1         | Inadequate            |
| Influenza | Stroke  | Moderate (decrease)                            | 1         | Lacking                                | None      | Inadequate            |

*continued*



TABLE 6-14 Continued

| Vaccine   | Adverse Event                    | Epidemiologic Assessment         | Studies Contributing to the Epidemiologic Assessment | Mechanistic Assessment                   | Cases Contributing to the Mechanistic Assessment | Causality Conclusion           |
|-----------|----------------------------------|----------------------------------|--|--|--|--------------------------------|
| Influenza | Myocardial Infarction            | Moderate (decrease)              | 1  | Weak (live attenuated influenza vaccine) | None   | Inadequate                     |
| Influenza | Fibromyalgia                     | Insufficient                     | None   | Lacking                                  | None   | Inadequate                     |
| Influenza | All-Cause Mortality <sup>a</sup> | Moderate (decrease)              | 1  | Weak (live attenuated influenza vaccine) | None   | Inadequate                     |
| Influenza | Oculorespiratory Syndrome        | Moderate (increase) <sup>b</sup> | 3  | Lacking (inactivated influenza vaccine)  | None   | Favors Acceptance <sup>b</sup> |
|           |                                  |                                  |  | Intermediate <sup>b</sup>                | – <sup>c</sup>                                   |                                |

<sup>a</sup> Although not originally charged to the committee by the sponsor, the committee considered this adverse event in its review of the literature.

<sup>b</sup> The committee attributes causation to two particular vaccines used in three particular years in Canada.

<sup>c</sup> Due to the use of the same sample population in some studies it is likely that some of the cases were presented in more than one publication, thus it is difficult to determine the number of unique cases.

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## Hepatitis A Vaccine

### INTRODUCTION

Hepatitis A virus (HAV) is a 27-nm spherical RNA virus that replicates in the liver of the infected individual (Fiore et al., 2008). HAV incubates for an average of 28 days, but this period can range from 15 to 50 days (CDC, 2006; Fiore et al., 2008). Prior to the onset of typical hepatitis symptoms such as darkening urine, pale stools, and jaundice, individuals may experience less specific symptoms including abdominal pain, anorexia, fatigue, fever, malaise, myalgia, nausea, or vomiting (Lemon, 1985; Tong et al., 1995). The illness lasts several weeks before the virus is eliminated from the body; recovery is virtually 100 percent (Fiore et al., 2008; Tong et al., 1995).

The severity of illness with HAV infection is directly correlated to the age of the individual at the time of infection. Fifty to 90 percent of infections in persons less than 5 years of age are asymptomatic, while 70–95 percent of adults experience some symptoms (Fiore et al., 2008). Although 11–22 percent of cases require hospitalization (CDC, 2006), serious or permanent complications from HAV infection are rare (Fiore et al., 2008). Atypical manifestations, which may occur in 7–11 percent of patients, include relapse, a prolonged cholestatic phase that occurs with itching and jaundice, and rash (Fiore et al., 2008; Tong et al., 1995). Itching and arthralgia are not uncommon during the prodromal phase before jaundice appears (Tong et al., 1995). A very rare occurrence is type I autoimmune chronic hepatitis (Tong et al., 1995). It is not known whether this is caused by hepatitis A infection, or whether the infection triggers a condition al-

ready present (Tong et al., 1995). This condition resolves with prednisone treatment (Tong et al., 1995). Very rarely fulminant hepatitis associated with coma and occasionally death may occur (Wasley et al., 2010). In most cases of hepatitis A infection, all symptoms and the infection resolve completely (Gordon et al., 1984; Tong et al., 1995).

The fecal-oral route is the most common mode of transmission for hepatitis A. An individual with HAV is most infectious, with highest stool HAV concentrations, during the 2 weeks prior to appearance of jaundice (Fiore et al., 2008). Transmission from a person with active infection may occur through food preparation, household contact, and sexual contact (Fiore et al., 2008). Because children with HAV are frequently asymptomatic, they may serve as reservoirs of disease in households and close-contact environments such as day care (Smith et al., 1997; Staes et al., 2000). HAV has been transmitted through blood transfusion; however, screening has greatly reduced this risk (Soucie et al., 1998). Finally, HAV is resistant to most organic solvents, detergents, and heat, and can survive in the environment (Fiore et al., 2008; Murphy et al., 1993; Peterson et al., 1983). As a result, HAV can be transmitted by food and water contamination, as well as through contact with infected soil and marine sediment (Fiore et al., 2008). Food and waterborne hepatitis is generally associated with contamination by HAV-infected workers, sewage contamination, and inadequate water treatment (Bergeisen et al., 1985; Bloch et al., 1990; Dalton et al., 1996; De Serres et al., 1999; Fiore, 2004).

From 1980 through 1995, reports of hepatitis A to the Centers for Disease Control and Prevention (CDC) numbered between 22 and 36 thousand cases per year (CDC, 2006). Approximately 33 percent of reported cases were in children less than 15 years old (CDC, 2008), and outbreaks of hepatitis A were reported among injection and noninjection drug users and men who have sex with men (Cotter et al., 2003; Harkess et al., 1989; Hutin et al., 1999; Schade and Komorwska, 1988).

Prior to the development and licensure of a vaccine, immune globulin, a sterile solution of antibodies collected and purified from a large group of donors, was used to prevent hepatitis A in those likely to be exposed or recently exposed to the virus (Fiore et al., 2008). In 1995–1996, inactivated vaccines for hepatitis A became available, and since 1999 the CDC has reported a significant decrease in HAV infection in the United States—markedly a 76 percent decrease in 2003 when compared to 1990–1997 (Wasley et al., 2005). Currently, three inactivated vaccines—Havrix (GlaxoSmithKline Biologicals), VAQTA (Merck & Co., Inc.), and Twinrix (GlaxoSmithKline)—are available in the United States. In these vaccines, the virus is grown in MRC-5 cell cultures and harvested by cell lysis (Fiore et al., 2008). From there, the virus is inactivated and purified through various methods before being packaged with (Havrix and Twinrix) or without (VAQTA) a preservative (Fiore et al., 2008).

Havrix and VAQTA are single-antigen vaccines and are available in two formulations for individuals between 12 months and 18 years of age, and those who are 18 years of age and older (Fiore et al., 2008). The child formulations of both vaccines are prepared with half the concentration of the adult dose (Fiore et al., 2008). Havrix and VAQTA are given on a two-dose schedule at least 6 months apart (Fiore et al., 2008). Twinrix is approved for adults and contains antigens for HAV and hepatitis B virus (HBV). Twinrix is given on the same schedule commonly used for single-antigen HBV vaccine and includes three doses of the vaccine given at 0, 1, and 6 months after the initial inoculation (CDC, 2006). By 2009 46.6 percent of children aged 19 to 35 months were vaccinated against HAV (CDC, 2010).

## ACUTE DISSEMINATED ENCEPHALOMYELITIS

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of acute disseminated encephalomyelitis (ADEM) after the administration of hepatitis A vaccine.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between hepatitis A vaccine and ADEM.*

### Mechanistic Evidence

The committee identified two publications reporting the development of ADEM after administration of hepatitis A vaccine. The publications did not provide evidence beyond temporality, one too short based on the possible mechanisms involved (Huber et al., 1999; Rogalewski et al., 2007). Rogalewski et al. (2007) reported the concomitant administration of vaccines, making it difficult to determine which, if any, vaccine could have been the precipitating event. In addition, the patient described in Huber et al. (1999) had a concomitant *Campylobacter jejuni* infection. The publications did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

While rare, hepatitis A infection has been associated with the development of ADEM (Yiu and Kornberg, 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of ADEM. Autoantibodies, T cells,

and molecular mimicry may contribute to the symptoms of ADEM; however, the publications did not provide evidence linking these mechanisms to hepatitis A vaccine.

*The committee assesses the mechanistic evidence regarding an association between hepatitis A vaccine and ADEM as weak based on knowledge about the natural infection.*

### Causality Conclusion

**Conclusion 7.1:** The evidence is inadequate to accept or reject a causal relationship between hepatitis A vaccine and ADEM.

## TRANSVERSE MYELITIS

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of transverse myelitis after the administration of hepatitis A vaccine.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between hepatitis A vaccine and transverse myelitis.*

### Mechanistic Evidence

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of transverse myelitis after the administration of hepatitis A vaccine.

#### *Weight of Mechanistic Evidence*

While rare, hepatitis A infection has been associated with the development of transverse myelitis (Wasley et al., 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of transverse myelitis; however, the committee did not identify literature reporting evidence of these mechanisms after administration of hepatitis A vaccine.

*The committee assesses the mechanistic evidence regarding an association between hepatitis A vaccine and transverse myelitis as weak based on knowledge about the natural infection.*

### Causality Conclusion

**Conclusion 7.2:** The evidence is inadequate to accept or reject a causal relationship between hepatitis A vaccine and transverse myelitis.

## MULTIPLE SCLEROSIS

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of multiple sclerosis (MS) after the administration of hepatitis A vaccine.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between hepatitis A vaccine and MS.*

### Mechanistic Evidence

The committee identified one publication reporting symptoms of MS after administration of hepatitis A vaccine. Rogalewski et al. (2007) did not provide evidence beyond a temporal relationship between vaccination against hepatitis B, diphtheria and tetanus toxoids, poliovirus, and hepatitis A and development of symptoms. The concomitant administration of vaccines make it difficult to determine which vaccine, if any, could have been the precipitating event. The publication did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

The symptoms described above are consistent with those leading to a diagnosis of MS. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of MS; however, the publication did not provide evidence linking these mechanisms to hepatitis A vaccine.

*The committee assesses the mechanistic evidence regarding an association between hepatitis A vaccines and MS as lacking.*

### Causality Conclusion

**Conclusion 7.3:** The evidence is inadequate to accept or reject a causal relationship between hepatitis A vaccine and MS.

## GUILLAIN-BARRÉ SYNDROME

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of Guillain-Barré syndrome (GBS) after the administration of hepatitis A vaccine.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between hepatitis A vaccine and GBS.*

### Mechanistic Evidence

The committee identified four publications reporting the development of GBS after the administration of hepatitis A vaccine. The publications did not provide evidence beyond temporality, some too short based on the possible mechanisms involved (Blumenthal et al., 2004; Huber et al., 1999; Pritchard et al., 2002; Uriondo San Juan et al., 2004). One publication also reported the concomitant administration of vaccines, making it difficult to determine which, if any, vaccine could have been the precipitating event (Uriondo San Juan et al., 2004). In addition, the patient described in Huber et al. (1999) had a concomitant *Campylobacter jejuni* infection. These publications did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

While rare, hepatitis A infection has been associated with the development of GBS (Wasley et al., 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of GBS. Autoantibodies, complement activation, immune complexes, T cells, and molecular mimicry may contribute to the symptoms of GBS; however, the publications did not provide evidence linking these mechanisms to hepatitis A vaccine.

*The committee assesses the mechanistic evidence regarding an association between hepatitis A vaccine and GBS as weak based on knowledge about the natural infection.*

### Causality Conclusion

**Conclusion 7.4:** The evidence is inadequate to accept or reject a causal relationship between hepatitis A vaccine and GBS.

**CHRONIC INFLAMMATORY DISSEMINATED POLYNEUROPATHY****Epidemiologic Evidence**

No studies were identified in the literature for the committee to evaluate the risk of chronic inflammatory disseminated polyneuropathy (CIDP) after the administration of hepatitis A vaccine.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between hepatitis A vaccine and CIDP.*

**Mechanistic Evidence**

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of CIDP after the administration of hepatitis A vaccine.

*Weight of Mechanistic Evidence*

Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of CIDP; however, the committee did not identify literature reporting evidence of these mechanisms after administration of hepatitis A vaccine.

*The committee assesses the mechanistic evidence regarding an association between hepatitis A vaccine and CIDP as lacking.*

**Causality Conclusion**

**Conclusion 7.5:** The evidence is inadequate to accept or reject a causal relationship between hepatitis A vaccine and CIDP.

**BELL'S PALSY****Epidemiologic Evidence**

No studies were identified in the literature for the committee to evaluate the risk of Bell's palsy after the administration of hepatitis A vaccine.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between hepatitis A vaccine and Bell's palsy.*



### Mechanistic Evidence

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of Bell's palsy after the administration of hepatitis A vaccine.

#### *Weight of Mechanistic Evidence*

*The committee assesses the mechanistic evidence regarding an association between hepatitis A vaccine and Bell's palsy as lacking.*

### Causality Conclusion

**Conclusion 7.6:** The evidence is inadequate to accept or reject a causal relationship between hepatitis A vaccine and Bell's palsy.

## ANAPHYLAXIS

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of anaphylaxis after the administration of hepatitis A vaccine.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between hepatitis A vaccine and anaphylaxis.*

### Mechanistic Evidence

The committee identified two publications identifying the development of anaphylaxis posthepatitis A vaccination (Bohlke et al., 2003; Peng and Jick, 2004). Bohlke et al. (2003) used records from participants in the Vaccine Safety Datalink to study the development of anaphylaxis postvaccination. The authors did not observe a single case of anaphylaxis postvaccination out of 23,185 doses of hepatitis A vaccine administered. Peng and Jick (2004) used computer records from general practitioners in the United Kingdom to study the incidence, cause, and severity of anaphylaxis. The authors reviewed 120 cases, out of 897, in detail. One report of anaphylaxis developing after vaccination against hepatitis A was identified.

*Weight of Mechanistic Evidence*

The publications described above did not present evidence sufficient for the committee to conclude the vaccine may be a contributing cause of anaphylaxis after the administration of hepatitis A vaccine. A temporal relationship was established between the administration of a hepatitis A vaccine and the development of anaphylaxis in one case; however, clinical details were not presented. Also, while it was presumed the patient had experienced an IgE-mediated reaction, no data were reported to establish the mechanism of action.

*The committee assesses the mechanistic evidence regarding an association between hepatitis A vaccine and anaphylaxis as weak based on one case presenting temporality consistent with anaphylaxis.*

**Causality Conclusion**

**Conclusion 7.7:** The evidence is inadequate to accept or reject a causal relationship between hepatitis A vaccine and anaphylaxis.

**AUTOIMMUNE HEPATITIS****Epidemiologic Evidence**

No studies were identified in the literature for the committee to evaluate the risk of autoimmune hepatitis after the administration of hepatitis A vaccine.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between hepatitis A vaccine and autoimmune hepatitis.*

**Mechanistic Evidence**

The committee identified two publications reporting the development of autoimmune hepatitis after the administration of hepatitis A vaccine. The publications did not provide evidence beyond temporality, one too short based on the possible mechanisms involved (Berry and Smith-Laing, 2007; Veerappan et al., 2005). One publication reported the concomitant administration of vaccines making it difficult to determine which, if any, vaccine could have been the precipitating event (Veerappan et al., 2005). In addition, the patient described by Berry and Smith-Laing (2007) presented

with acute hepatitis 5 months before vaccination. The publications did not contribute to the weight of mechanistic evidence.

### *Weight of Mechanistic Evidence*

Active autoimmune hepatitis is a recognized complication of infection with hepatitis A (Wasley et al., 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of autoimmune hepatitis. Autoantibodies, T cells, and complement activation may contribute to the symptoms of autoimmune hepatitis; however, the publications did not provide evidence linking these mechanisms to hepatitis A vaccine.

*The committee assesses the mechanistic evidence regarding an association between hepatitis A vaccine and autoimmune hepatitis as weak based on knowledge about the natural infection.*

### Causality Conclusion

**Conclusion 7.8:** The evidence is inadequate to accept or reject a causal relationship between hepatitis A vaccine and autoimmune hepatitis.

### CONCLUDING SECTION

Table 7-1 provides a summary of the epidemiologic assessments, mechanistic assessments, and causality conclusions for hepatitis A vaccine.

**TABLE 7-1** Summary of Epidemiologic Assessments, Mechanistic Assessments, and Causality Conclusions for Hepatitis A Vaccine

| Vaccine     | Adverse Event                                    | Epidemiologic Assessment | Studies Contributing to the Epidemiologic Assessment | Mechanistic Assessment | Cases Contributing to the Mechanistic Assessment | Causality Conclusion |
|-------------|--|--------------------------|--|------------------------|--|----------------------|
| Hepatitis A | Acute Disseminated Encephalomyelitis             | Insufficient             | None   | Weak                   | None   | Inadequate           |
| Hepatitis A | Transverse Myelitis                              | Insufficient             | None   | Weak                   | None   | Inadequate           |
| Hepatitis A | Multiple Sclerosis                               | Insufficient             | None   | Lacking                | None   | Inadequate           |
| Hepatitis A | Guillain-Barré Syndrome                          | Insufficient             | None   | Weak                   | None   | Inadequate           |
| Hepatitis A | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient             | None   | Lacking                | None   | Inadequate           |
| Hepatitis A | Bell's Palsy                                     | Insufficient             | None   | Lacking                | None   | Inadequate           |
| Hepatitis A | Anaphylaxis                                      | Insufficient             | None   | Weak                   | 1  | Inadequate           |
| Hepatitis A | Autoimmune Hepatitis                             | Insufficient             | None   | Weak                   | None   | Inadequate           |

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## 8

## Hepatitis B Vaccine

## INTRODUCTION

Hepatitis B virus (HBV) is a 42-nm spherical particle that replicates primarily in the liver of infected individuals (Mast and Ward, 2008). In infected persons, the virus can be found in most bodily fluids, with the highest infectious concentration in the serum and with transmittable levels also found in semen and saliva (Alter et al., 1977; Bancroft et al., 1977; CDC, 2006; Scott et al., 1980). The virus is very hardy and can live on surfaces for more than 7 days (CDC, 2006). Among adults, the primary modes of transmission are sexual intercourse with persons with chronic lifelong infection (carriers) and percutaneous exposure to the virus due to intravenous drug usage or occupational exposures to needles and other sharp objects (CDC, 2006). In the United States, exposure in children 5 years old and under is generally limited (Shapiro, 1993). Infection is associated with perinatal exposure to maternal blood or exposure to infected blood or saliva within the immediate environment (Shapiro, 1993).

HBV-infected individuals are often asymptomatic. Clinical symptoms of acute HBV infection are more likely in older individuals than in younger individuals (McMahon et al., 1985). When manifested, symptoms may include fever, fatigue, nausea, vomiting, and abdominal pain before progressing to clay-colored stools, dark urine, and jaundice indicating increased liver involvement and cholestasis—the accumulation of bile in the liver (CDC, 2006; Mast and Ward, 2008). Extrahepatic manifestations of hepatitis B can include arthritis, urticaria, vasculitis, and glomerulonephritis (Mast and Ward, 2008). Symptomatic infection generally presents within



the first 6 months of exposure averaging 90 days from exposure to jaundice and 60 days to abnormal serum alanine aminotransferase (ALT) levels indicating liver injury (Krugman et al., 1979).

Approximately 95 percent of all hepatitis B infections among otherwise healthy adults resolve without sequelae, and the recovered individual possesses lifelong immunity to HBV infection (CDC, 2006). In the other 5 percent, chronic infection develops (CDC, 2006). Chronic HBV infection may lead to liver cirrhosis, liver failure, hepatocellular carcinoma, or death (Mast and Ward, 2008). These outcomes are thought to be the result of the constant activity of the immune system and not a direct consequence of damage caused by the virus itself (Ganem and Prince, 2004). The likelihood of chronic hepatitis B disease is inversely related to the age of the individual at the time of HBV infection (Beasley et al., 1983; Edmunds et al., 1993). Among infants perinatally infected with HBV, 80–90 percent develop chronic disease; among children infected postnatally through 5 years of age, 30 percent; and among adults, fewer than 5 percent (Hyams, 1995). The risk of chronic disease may be higher in the immunocompromised and diabetics dependent on finger-stick monitoring devices (CDC, 2006; Polish et al., 1992).

HBV transmission through blood and blood products was first evidenced in 1883 after an outbreak of hepatitis among shipyard workers following smallpox vaccination in Bremen, Germany (Mast and Ward, 2008). In 1965, Blumberg and Alter (Blumberg and Alter, 1965) discovered the Australia antigen (Au), which was later determined to be hepatitis B surface antigen (HBsAg) (Prince, 1968). Research performed in the early 1970s showed that HBV could be heat-inactivated and that inoculation with inactivated serum provided resistance to or modification of the virus (Krugman, 1974; Krugman and Giles, 1973).

In the early 1980s, several groups developed preliminary HBV vaccines (Coutinho et al., 1983; McLean et al., 1983; Purcell and Gerin, 1975). The vaccines consisted of inactivated, alum-adsorbed, 22-nm HBsAg particles recovered and purified from individuals with chronic hepatitis B infection (Coutinho et al., 1983; McLean et al., 1983; Purcell and Gerin, 1975). With the development of DNA recombinant technologies and the ability to obtain HBsAg from other sources such as *Saccharomyces cerevisiae* (baker's yeast), DNA recombinant vaccines replaced plasma-derived vaccines in the United States (Mast and Ward, 2008). In 1991, the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics recommended HBV vaccination for all infants and adults (CDC, 1991).

Currently, hepatitis B vaccines are available in single- and multiantigen formulations (CDC, 2005). The two single-antigen vaccines are Recombivax HB (Merck & Co., Inc.) and Engerix-B (GlaxoSmithKline Biologicals) (CDC, 2005). Of the three licensed combination vaccines, Comvax (Merck) and Pediarix (GlaxoSmithKline) are used for infant and child

vaccination, while Twinrix (GlaxoSmithKline) is used for adult vaccination (CDC, 2005). Comvax is a bivalent vaccine designed to prevent *Haemophilus influenzae* type B infection in addition to hepatitis B and contains *Haemophilus influenzae* type B capsular polysaccharide polyribosylribitol phosphate affixed to *Neisseria meningitidis* outer-membrane protein complex and HBsAg from recombinant yeast cultures (CDC, 2005). Pediarix contains recombinant HBsAg, diphtheria and tetanus toxoids and acellular pertussis adsorbed (DTaP), and inactivated poliovirus (CDC, 2005). Twinrix is designed to prevent hepatitis A and B, and contains recombinant HBsAg and inactivated hepatitis A virus (CDC, 2005).

The Advisory Committee on Immunization Practices, the American Academy of Pediatrics, and the American Academy of Family Physicians recommend the HBV vaccine in a series of three doses: at birth, between 1 and 2 months, and between 6 and 18 months (CDC, 1991; Mast and Ward, 2008). In unvaccinated adolescents and adults, the CDC recommends three doses of the vaccine with the first and second dose 1 month apart and the third dose 6 months after the initial dose (CDC, 1991). The three-dose series results in protective concentrations of HBsAg antibodies in more than 95 percent of healthy infants, children, and adolescents and in greater than 90 percent of healthy adults aged up to 40 years (Mast and Ward, 2008). In adults older than 40 years, immunogenicity drops below 90 percent (Mast and Ward, 2008). The hepatitis B vaccine has a preexposure efficacy of 80–100 percent, and if given in conjunction with hepatitis B immune globulin, the vaccine is 85–95 percent effective in preventing chronic infection post-HBV exposure (Mast and Ward, 2008). Following vaccination, HBV immunity appears to be lifelong, and booster doses of the vaccine are not routinely recommended (Mast and Ward, 2008). In 2009, 92 percent of U.S. children aged 19–35 months completed all three recommended doses of hepatitis B vaccine (CDC, 2010).

## ENCEPHALITIS AND ENCEPHALOPATHY

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of encephalitis or encephalopathy after the administration of hepatitis B vaccine.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between hepatitis B vaccine and encephalitis or encephalopathy.*

### Mechanistic Evidence

The committee identified three publications reporting encephalitis or encephalopathy after administration of a hepatitis B vaccine. The publications did not provide evidence beyond temporality (Deisenhammer et al., 1994; Manna et al., 1996; Yang et al., 2006). The publications did not contribute to the weight of mechanistic of evidence.

#### *Weight of Mechanistic Evidence*

*The committee assesses the mechanistic evidence regarding an association between hepatitis B vaccine and encephalitis or encephalopathy as lacking.*

### Causality Conclusion

**Conclusion 8.1:** The evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and encephalitis.

**Conclusion 8.2:** The evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and encephalopathy.

## SEIZURES

### Epidemiologic Evidence

The committee reviewed four studies to evaluate the risk of seizures after the administration of hepatitis B vaccine. Two studies (Dobson et al., 1995; Niu et al., 1996) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations. One controlled study (Zipp et al., 1999) had very serious methodological limitations that precluded its inclusion in this assessment. The study by Zipp et al. (1999) was a letter to the editor judged by the committee to have insufficient methodological detail.

The one remaining controlled study (Lewis et al., 2001) contributed to the weight of epidemiologic evidence and is described below.

Lewis et al. (2001) conducted a cohort study in children enrolled in the San Francisco Medical Center of Northern California Kaiser Permanente. Patients born from November 1991 through April 1994 were included in the study; premature and low-birth-weight infants, and infants with diagnoses (e.g., sepsis, congenital infection, hematologic disorder, cardiac disease, neurologic disease, and lung disease) that made vaccination less likely in the opinion of the authors were excluded. A total of 5,655 patients met the in-

clusion criteria and were included in the analysis. Computerized databases provided information on hepatitis B vaccinations and hospital, outpatient, or emergency department visits for seizures. An event was considered a seizure if one of the following diagnoses were listed in the medical record: seizure or infantile spasm, seizure, seizure in newborn, and epilepsy. In the primary analysis, patients who received hepatitis B vaccine within 21 days of birth were classified as vaccinated (3,302 cases). In the secondary analysis, patients who received hepatitis B vaccine on the day of birth or the day after birth were classified as vaccinated (2,718 cases). The study did not specify the timing from vaccination to seizure. The relative risk of seizure following administration of hepatitis B within 21 days of birth was 0.18 (95% CI, 0.02–1.6) and following administration of hepatitis B on the day of birth or day after birth was 0.22 (95% CI, 0.02–2.19). The authors concluded that hepatitis B vaccination does not increase the risk of seizure in children, but noted the analysis had limited power to assess this association.

#### *Weight of Epidemiologic Evidence*

*The committee has limited confidence in the epidemiologic evidence based on one study that lacked validity and precision to assess an association between hepatitis B vaccine and seizures.*

#### **Mechanistic Evidence**

The committee identified six publications reporting seizures after administration of a hepatitis B vaccine. The publications did not provide evidence beyond temporality, some too long or too short based on the possible mechanisms involved (Battaglia and Valiani, 1992; de Carvalho and Shoenfeld, 2008; Hartman, 1990; Kaygusuz et al., 2002; Planchamp et al., 2009; Yang et al., 2006). In addition, Planchamp et al. (2009) reported the concomitant administration of vaccines, making it difficult to determine which, if any, vaccine could have been the precipitating event. The publications did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of seizure. In some instances fever may contribute to the development of seizures; however, the publications did not provide evidence linking this mechanism to hepatitis B vaccine.

*The committee assesses the mechanistic evidence regarding an association between hepatitis B vaccine and seizures as lacking.*

### Causality Conclusion

**Conclusion 8.3:** The evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and seizures.

## ACUTE DISSEMINATED ENCEPHALOMYELITIS

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of acute disseminated encephalomyelitis (ADEM) after the administration of hepatitis B vaccine.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between hepatitis B vaccine and ADEM.*

### Mechanistic Evidence

The committee identified eight publications describing the development of ADEM after the administration of hepatitis B vaccine. Six publications did not report evidence of causality beyond a temporal relationship between vaccination and the development of ADEM (Brinar and Poser, 2008; Cabrera-Gomez et al., 2002; Geier and Geier, 2004; Herroelen et al., 1991; Rogalewski et al., 2007; Voigt et al., 2001). In addition, Rogalewski et al. (2007) reported the concomitant administration of vaccines making it difficult to determine which vaccine, if any, could have been the precipitating event. These publications did not contribute to the weight of mechanistic evidence.

Described below are two publications reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Konstantinou et al. (2001) reported a 39-year-old woman presenting with complete right homonymous hemianopia and severe dyslexia 4 weeks after receiving the second dose of hepatitis B vaccine. Brain MRI revealed a lesion occupying the left occipital lobe and extending into the splenium of corpus callosum. T1-weighted sequences of the lesion displayed hypointense signal while T2-weighted sequences displayed hyperintense signal. The lesion was enhanced on postgadolinium T1-weighted sequences and demonstrated mass effect and obliteration of adjacent sulci. Histological examination and immunoperoxidase staining of a biopsy of the lesion were consistent with demyelinating disease. Improvement in the condition was noted after surgery. Eleven days after the third dose of hepatitis B vaccine the patient developed left hemiparesis and acute progressive deterioration

of vision. Brain MRIs after the second and third vaccine doses revealed large lesions occupying the left occipital lobe and right parieto-occipital region, respectively. The lesions displayed hypointense signals on T2-weighted MRIs. Histologic examination and immunoperoxidase staining were consistent with demyelinating disease. Testing for oligoclonal IgG bands in the cerebrospinal fluid (CSF) and examination for intrathecal hepatitis B surface antibodies were not performed after the third dose of vaccine. Improvement of the condition was noted after treatment with dexamethasone. Brain MRIs performed at follow-up visits 1 year and 2.5 years after the onset of the initial episode showed almost complete resolution of the previous findings.

Tourbah et al. (1999) reported a 31-year-old man (patient 5 in the article) with vertigo and paresthesia in hands and legs 2 weeks after the first injection of hepatitis B vaccine. The symptoms resolved in 10 days. The patient presented with asthenia, vertigo, paresthesia, and left hemihypoesthesia after the second dose of a hepatitis B vaccine. The symptoms resolved in 10 days. The symptoms reappeared 7 days after receiving a booster dose of hepatitis B vaccine. A brain MRI after the first dose showed multiple T2-weighted high-intensity signals. An MRI after the third dose showed high signal lesions T2-weighted images involving arcuate fibers of both hemispheres, periventricular and subcortical white matter, corpus callosum and cerebellar white matter, and cortex.

#### *Weight of Mechanistic Evidence*

The two publications described above, when considered together, presented clinical evidence suggestive but not sufficient for the committee to conclude the vaccine may be a contributing cause of ADEM after vaccination against hepatitis B. The mechanistic evidence contributing to the analysis includes a clinical picture consistent with ADEM, and recurrence of symptoms after revaccination with hepatitis B vaccine where new white matter disease was associated with each revaccination. In the publications described above all of the patients recovered with steroids. In addition, a brain biopsy performed by Konstantinou et al. (2001) showed demyelination. Furthermore, Konstantinou et al. (2001) did not observe oligoclonal bands in the CSF. Neither publication reported the development of antibodies to HBsAg.

Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of ADEM; however, the publications did not provide evidence linking these mechanisms to hepatitis B vaccine.

*The committee assesses the mechanistic evidence regarding an association between hepatitis B vaccine and ADEM as low-intermediate based on two cases.*

### Causality Conclusion

**Conclusion 8.4:** The evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and ADEM.

## TRANSVERSE MYELITIS

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of transverse myelitis after the administration of hepatitis B vaccine.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between hepatitis B vaccine and transverse myelitis.*

### Mechanistic Evidence

The committee identified seven publications reporting transverse myelitis after the administration of hepatitis B vaccine. Six publications did not provide evidence beyond temporality, some too long or too short based on the possible mechanisms involved (Fonseca et al., 2003; Iniguez et al., 2000; Karaali-Savrun et al., 2001; Mahassin et al., 1993; Renard et al., 1999; Senejoux et al., 1996). Long latencies between vaccine administration and development of symptoms make it impossible to rule out other possible causes. These publications did not contribute to the weight of mechanistic evidence.

Described below is one publication that reported clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Tartaglino and colleagues (1995) described a 40-year-old man presenting with lower extremity numbness and difficulty walking 2 weeks after receiving the first dose of hepatitis B vaccine. One month after receiving the second dose of hepatitis B vaccine the patient had difficulty walking, and the sensory disturbance ascended to the nipple level. A swollen edematous cord extending from C-3 to T-9 was revealed via T1-weighted and T2-weighted spin-echo pulse sequences.

#### *Weight of Mechanistic Evidence*

The publication described above did not present evidence sufficient for the committee to conclude the vaccine may be a contributing cause of

transverse myelitis after vaccination against hepatitis B. The timing of the rechallenge appears to be a second episode, but the 1-month time frame between the two episodes is not sufficient to determine if the symptoms represent one or two episodes. A patient must return to baseline or be stable for at least 6 weeks before a new episode is recorded. Furthermore, no immunology indicating an enhancement of a proinflammatory response linked to the vaccine is presented.

Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of transverse myelitis; however, the publications did not provide evidence linking these mechanisms to hepatitis B vaccine.

*The committee assesses the mechanistic evidence regarding an association between hepatitis B vaccine and transverse myelitis as weak based on one case.*

### Causality Conclusion

**Conclusion 8.5: The evidence is inadequate to accept or reject a causal relation between hepatitis B vaccine and transverse myelitis.**

## OPTIC NEURITIS

### Epidemiologic Evidence

The committee reviewed three studies to evaluate the risk of optic neuritis in adults after the administration of hepatitis B vaccine. One study (Geier and Geier, 2005) was not considered in the weight of epidemiologic evidence because it provided data from a passive surveillance system and lacked an unvaccinated comparison population.

The two remaining controlled studies (DeStefano et al., 2003; Payne et al., 2006) were included in the weight of epidemiologic evidence and are described below.

DeStefano et al. (2003) conducted a case-control study to evaluate the association between hepatitis B vaccination and optic neuritis using data from three health maintenance organizations (HMOs) participating in the Vaccine Safety Datalink (VSD). The optic neuritis analysis included 108 cases and 228 controls. The cases had a documented physician's diagnosis from 1995 through 1999, and were matched to controls from the HMO on date of birth (within 1 year) and sex. The authors evaluated the date of disease onset using data described in the medical record or reported in the telephone interview. The immunization status was obtained from vaccination records, medical records, and telephone interviews. The study had high rates of self-reported vaccinations from outside the HMO system (51 percent of cases and 50 percent of controls) that could not be verified,



which may have biased the results. The odds ratio for ever vaccinated with hepatitis B before optic neuritis diagnosis was 1.2 (95% CI, 0.5–3.1). The authors concluded that hepatitis B vaccination does not appear to be associated with an increased risk of optic neuritis in adults.

Payne et al. (2006) used the Defense Medical Surveillance System (DMSS) to conduct a case-control study among U.S. military personnel. The study included 1,131 cases with a first diagnosis of optic neuritis from 1998 through 2003, and 3,393 controls. The cases and controls were matched on sex, military service (e.g., active or reserve), and deployment within 18 weeks of diagnosis date. The vaccination status and date of first symptom of optic neuritis were obtained from the DMSS and reviewed by a neuro-ophthalmologist. About 3 percent of the cases (37 patients) and controls (118 patients) received hepatitis B vaccine within the 18-week risk period, which suggested that possible confounders related to the decision to vaccinate were present. Although the authors considered three exposure times—6, 12, and 18 weeks after vaccination—only the odds ratio for optic neuritis diagnosis within 18 weeks of hepatitis B vaccination was given (OR, 1.02; 95% CI, 0.68–1.54). The authors noted without presenting results that similar conclusions were obtained using 6- and 12-month exposure times. The authors concluded that vaccination against hepatitis B does not appear to increase the risk of optic neuritis in adults.

### *Weight of Epidemiologic Evidence*

Two case-control studies evaluating the risk of optic neuritis in adults after hepatitis B vaccination were included in the committee's review of the epidemiologic evidence. Neither of these studies found a significantly increased risk of optic neuritis after hepatitis B vaccination. Hepatitis B vaccination was infrequent in both cases and controls, raising the possibility that selection bias could affect reported associations. See Table 8-1 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has limited confidence in the epidemiologic evidence, based on two studies that lacked validity and precision to assess an association between hepatitis B vaccine and optic neuritis in adults.*

### **Mechanistic Evidence**

The committee identified six publications reporting optic neuritis after the administration of hepatitis B vaccine. The publications did not provide evidence beyond temporality (Albitar et al., 1997; Erguven et al., 2009;

TABLE 8-1 Studies Included in the Weight of Epidemiologic Evidence for Hepatitis B Vaccine and Optic Neuritis

| Citation                | Operationally Defined Outcome  | Study Setting                       | Defined Study Population  | Study Design | Sample Size  | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)                             | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|-------------------------|--|-------------------------------------|---|--------------|--|--|---|--|
| DeStefano et al. (2003) | Date of optic neuritis onset from medical records or telephone interviews                      | Three HMOs participating in the VSD | Ages < 18, 18–40, > 40 years<br>Cases had optic neuritis diagnosed by a physician from 1995 through 1999            | Case control | 108 patients with optic neuritis<br>228 controls     | OR for optic neuritis onset any time after hepatitis B vaccination: 1.2 (95% CI, 0.5–3.1)        | None described                                      | Serious  |
| Payne et al. (2006)     | Date of first symptom of optic neuritis listed in system and reviewed by neuro-ophthalmologist | Defense Medical Surveillance System | U.S. military personnel ages ≥ 18 years<br>Cases had optic neuritis diagnosed by a physician from 1998 through 2003 | Case control | 1,131 patients with optic neuritis<br>3,393 controls | OR for optic neuritis onset within 18 weeks of hepatitis B vaccination: 1.02 (95% CI, 0.68–1.54) | None described                                      | Serious  |

<sup>a</sup> The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup> The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup> Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.

Hamard et al., 2000; Roussat et al., 2001; Stewart et al., 1999; Voigt et al., 2001). Two publications also reported the concomitant administration of vaccines making it difficult to determine which, if any, vaccine could have been the precipitating event (Stewart et al., 1999; Voigt et al., 2001). In addition, serological testing reported in Roussat et al. (2001) revealed a concomitant infection that could contribute to the development of symptoms in one case described in the publication. These publications did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of optic neuritis. Autoantibodies, T cells, immune complexes, and molecular mimicry may contribute to the symptoms of optic neuritis; however, the publications did not provide evidence linking these mechanisms to hepatitis B vaccine.

*The committee assesses the mechanistic evidence regarding an association between hepatitis B vaccine and optic neuritis as lacking.*

#### **Causality Conclusion**

**Conclusion 8.6: The evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and optic neuritis.**

### **NEUROMYELITIS OPTICA**

#### **Epidemiologic Evidence**

No studies were identified in the literature for the committee to evaluate the risk of neuromyelitis optica (NMO) after the administration of hepatitis B vaccine.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between hepatitis B vaccine and NMO.*

#### **Mechanistic Evidence**

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of NMO after the administration of hepatitis B vaccine.

*Weight of Mechanistic Evidence*

Autoantibodies, T cells, complement activation, and molecular mimicry may contribute to the symptoms of NMO; however, the committee did not identify literature reporting evidence of these mechanisms after administration of hepatitis B vaccine.

*The committee assesses the mechanistic evidence regarding an association between hepatitis B vaccine and NMO as lacking.*

**Causality Conclusion**

**Conclusion 8.7:** The evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and NMO.

**MULTIPLE SCLEROSIS ONSET IN ADULTS****Epidemiologic Evidence**

The committee reviewed eight studies to evaluate the risk of onset (date of first symptom) of multiple sclerosis (MS) in adults after the administration of hepatitis B vaccine. One study (Geier and Geier, 2005) was not considered in the weight of epidemiologic evidence because it provided data from a passive surveillance system and lacked an unvaccinated comparison population. Two controlled studies (Ramagopalan et al., 2009; Touze et al., 2002) had very serious methodological limitations that precluded their inclusion in this assessment. Ramagopalan et al. (2009) did not attempt to validate self-reported vaccination data or confirm the timing of vaccination, and the choice of spousal controls could have introduced selection bias. The hospital controls in Touze et al. (2002) also were problematic, and the high exclusion rates among cases and controls invited to participate in the study raised the potential for serious bias and confounding.

The four remaining controlled studies (Ascherio et al., 2001; DeStefano et al., 2003; Hernan et al., 2004; Hocine et al., 2007) were included in the weight of epidemiologic evidence and are described below. One additional study is listed below (DeStefano et al., 2005), but it is not included in the assessment since the cases overlap data already described (DeStefano, 2003).

Ascherio et al. (2001) conducted a nested case-control study in women enrolled in the Nurses' Health Study and the Nurses' Health Study II. A total of 190 women with a probable or definite MS diagnosis from 1976 through 1998 were compared to 534 randomly selected healthy controls and 111 matched breast cancer controls (to test for recall bias among

women with a serious disease). The date of MS onset was reported by the physicians and study participants, and the earliest date was used in the analysis. The immunization status was obtained through a self-report questionnaire, and vaccination records were only reviewed when participants reported receiving hepatitis B vaccine. This study had high exclusion rates among the self-reported vaccinated cases and controls, for whom vaccination certificates were not available. The age-adjusted relative risk of MS onset any time after hepatitis B vaccination compared to unvaccinated controls was 0.9 (95% CI, 0.5–1.6). Additionally, the relative risk of MS onset within 2 years of vaccination was 0.7 (95% CI, 0.3–1.7). The authors concluded that vaccination against hepatitis B does not appear to increase the risk of the onset of MS in adults, but confidence intervals were broad.

The study by DeStefano et al. (2003) was described in detail in the section on optic neuritis. This case-control study evaluated the association between hepatitis B vaccination and MS or optic neuritis onset using data from three HMOs participating in the VSD. The MS analysis included 332 cases and 722 controls. Although there is a large number of cases and controls, the study had high rates of self-reported vaccinations from outside the HMO system (51 percent of cases and 50 percent of controls) that could not be verified, which may have biased the results. The odds ratio for ever vaccinated with hepatitis B before MS onset was 0.8 (95% CI, 0.5–1.4). The authors concluded that hepatitis B vaccination does not appear to be associated with an increased risk of MS onset in adults.

DeStefano et al. (2005) provided a reanalysis of the VSD data in a peer-reviewed letter to the editor based on the methods used by Hernan et al. (2004). The reanalysis restricted the assessment of MS onset and hepatitis B vaccination to diagnoses and immunizations reported in the medical record, and included 119 cases in the study. The authors provided relative risk data for 1 year after vaccination, greater than 5 years after, and ever vaccinated. The odds ratio for the reanalysis of ever vaccinated with hepatitis B before MS onset was 0.4 (95% CI, 0.1–1.5), and no significant association or protective effect was demonstrated in analyses evaluating several different time delays from vaccination. The authors concluded that hepatitis B vaccination does not appear to increase the risk of MS onset in adults. Since the participants included in this study completely overlapped those described in DeStefano et al. (2003), the results of this reanalysis were not independently considered in weighing the totality of evidence.

Hernan et al. (2004) used the General Practice Research Database (GPRD) to perform a nested case-control study. Cases with a confirmed MS diagnosis from 1993 through 2000 and a minimum of 3 years follow-up in the database were selected and matched with controls on age (within 1 year), sex, general practice, and date of joining the practice (within 1 year). The study included 163 cases and 1,604 controls. The date of first

symptom of MS and hepatitis B vaccination status were identified in the medical record. There were a number of methodological concerns for this study including possible differences in the completeness of hepatitis B vaccination ascertainment and a lack of adjustment for potential differences in socioeconomic status and past medical history. For example, prior to the index date, controls had more medical encounters on average than cases. The rates of vaccination were very low among the cases and controls, which raised the possibility that subjects selected for vaccination were importantly different. The odds ratio for MS onset within 3 years of immunization against hepatitis B was 3.1 (95% CI, 1.5–6.3). The authors concluded that hepatitis B immunization is associated with a threefold increase risk of MS onset in adults.

Hocine et al. (2007) conducted a self-controlled case-series study based on data from a case-control study by Touze et al. (2002). The committee determined Touze et al. (2002) had methodological limitations and did not include the results in the epidemiologic assessment. The dataset used by Hocine et al. included cases of central nervous system (CNS) demyelinating disease identified at 18 departments of neurology in France from 1994 through 1995. Patients were followed to identify cases that went on to have a definite or probable MS diagnosis. The immunization status was obtained during telephone interviews, during which participants referred to their vaccination records. The analysis included 192 cases with definite or probable MS. Two risk periods for MS diagnosis, 0–60 days and 61–365 days after hepatitis B vaccination, were used. A third risk period (indefinite postvaccination risk period) was also employed to compare results to the 3-year period described in Hernan et al. (2004). The relative risk of probable or definite MS diagnosis within 0–60 days of hepatitis B vaccination was 1.59 (95% CI, 0.66–3.81), within 61–365 days was 1.04 (95% CI, 0.46–2.34), and indefinitely (maximum of 2.29 years) after hepatitis B vaccination was 1.55 (95% CI, 0.64–3.75). The authors concluded that vaccination against hepatitis B was not strongly associated with a diagnosis of MS in adults.

### *Weight of Epidemiologic Evidence*

Four epidemiologic studies independently evaluating the risk of MS onset in adults after hepatitis B vaccination were included in the committee's overview of the evidence. Three of these were case-control studies, and one was a self-controlled case-series study. Only one study (a case-control study) found a significant association between MS and administration of hepatitis B within 3 years (Hernan et al., 2004). Two case-control studies found nonsignificant trends toward protection with vaccine (Ascherio et al., 2001; DeStefano et al., 2003), and the self-controlled case-series study found nonsignificant increases in risk of MS after hepatitis B vaccination. Rates

of hepatitis B vaccination were low in all studies, raising the possibilities that those selected for the vaccine were different from controls for factors that could predict risk of a later MS diagnosis, such as by manifesting early symptoms of MS that prompted a physician visit but did not result in an immediate diagnosis. Given the inconsistency of findings in the studies and the potential for selection bias, the committee graded the overall epidemiologic evidence as limited. See Table 8-2 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has limited confidence in the epidemiologic evidence, based on four studies that lacked validity and precision, to assess an association between hepatitis B vaccine and onset of MS in adults.*

### Mechanistic Evidence

The committee identified one publication reporting the onset of MS in an adult after administration of a hepatitis B vaccine. The publication did not provide evidence beyond temporality (Rogalewski et al., 2007). In addition, Rogalewski et al. (2007) reported the concomitant administration of vaccines, making it difficult to determine which, if any, vaccine could have been the precipitating event. The publication did not contribute to the weight of mechanistic evidence.

### *Weight of Mechanistic Evidence*

The symptoms described in the publication above are consistent with those leading to a diagnosis of MS. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of MS; however, the publication did not provide evidence linking these mechanisms to hepatitis B vaccine.

*The committee assesses the mechanistic evidence regarding an association between hepatitis B vaccine and onset of MS in adults as lacking.*

### Causality Conclusion

**Conclusion 8.8:** The evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and onset of MS in adults.

**TABLE 8-2** Studies Included in the Weight of Epidemiologic Evidence for Hepatitis B Vaccine and MS Onset in Adults

| Citation               | Operationally Defined Outcome                | Study Setting                                    | Defined Study Population   | Study Design        | Sample Size                                  | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)  | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|------------------------|--|--|--|---------------------|--|---|---|--|
| Ascherio et al. (2001) | MS onset reported by physicians and patients | Nurses' Health Study and Nurses' Health Study II | Women Ages 25–55 years<br>Cases had probable or definite MS diagnoses from 1976 through 1998 | Nested case control | 190 patients with MS<br>534 healthy controls | Age-adjusted RR of MS onset any time after hepatitis B vaccination compared to healthy controls:<br><b>0.9 (95% CI, 0.5–1.6)</b>          | None described                                      | Serious  |
|                        |  |  |  |                     | 111 breast cancer controls                   | Age-adjusted RR of MS onset within 2 years of hepatitis B vaccination compared to healthy controls:<br><b>0.7 (95% CI, 0.3–1.7)</b>       |   |  |
|                        |  |  |  |                     |  | Age-adjusted RR of MS onset any time after hepatitis B vaccination compared to breast cancer controls:<br><b>1.2 (95% CI, 0.5–2.9)</b>    |   |  |
|                        |  |  |  |                     |  | Age-adjusted RR of MS onset within 2 years of hepatitis B vaccination compared to breast cancer controls:<br><b>1.0 (95% CI, 0.3–4.2)</b> |   |  |

*continued*



TABLE 8-2 Continued

| Citation   | Operationally Defined Outcome                                | Study Setting                       | Defined Study Population   | Study Design | Sample Size  | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)   | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|--|--|-------------------------------------|--|--------------|--|--|---|--|
| DeStefano et al. (2003)  | MS onset reported in medical records or telephone interviews | Three HMOs participating in the VSD | Ages < 18, 18–40, > 40 years<br>Cases had MS diagnosed by a physician from 1995 through 1999     | Case control | 332 patients with MS<br>722 controls                     | OR for MS onset any time after hepatitis B vaccination:<br>0.8 (95% CI, 0.5–1.4)   | None described                                      | Serious  |
| DeStefano et al. (2005)<br>Reanalysis of DeStefano et al. (2003) | MS onset reported in medical records                         | Three HMOs participating in the VSD | Restricted to MS diagnoses and vaccinations reported in medical records                          | Case control | 119 patients with MS<br>Number of controls not described | OR for MS onset any time after hepatitis B vaccination:<br>0.4 (95% CI, 0.1–1.5)<br>OR for MS onset 0–1 year after hepatitis B vaccination:<br>1.4 (95% CI, 0.1–23.6)<br>OR for MS onset > 5 years after hepatitis B vaccination:<br>0.8 (95% CI, 0.1–8.9) | None described                                      | Serious  |
| Hernan et al. (2004)   | MS onset reported in medical records                         | GPRD                                | Ages < 30, 30–49, > 50 years<br>Cases had MS diagnoses in medical records from 1993 through 2000 | Case control | 163 patients with MS<br>1,604 controls                   | OR for MS onset within 3 years of hepatitis B vaccination:<br>3.1 (95% CI, 1.5–6.3)  | None described                                      | Serious  |

|                      |                                      |                                       |  |  |           |  |                |         |
|----------------------|--------------------------------------|---------------------------------------|--|--|-----------|--|----------------|---------|
| Hocine et al. (2007) | MS onset reported in medical records | 18 departments of neurology in France | Ages 13–60 years<br>Cases had probable or definite MS diagnosed by a physician | Self-controlled case series<br>Risk periods:<br>0–60 days, 61–365 days, and indefinitely after vaccination | 192 cases | RR of MS onset 0–60 days after hepatitis B vaccination:<br>1.59 (95% CI, 0.66–3.81)<br>RR of MS onset 61–365 days after hepatitis B vaccination:<br>1.04 (95% CI, 0.46–2.34)<br>RR of MS onset indefinitely (maximum of 2.29 years) after hepatitis B vaccination:<br>1.55 (95% CI, 0.64–3.75) | None described | Serious |
|----------------------|--------------------------------------|---------------------------------------|--|--|-----------|--|----------------|---------|

<sup>a</sup> The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup> The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup> Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.

## MULTIPLE SCLEROSIS ONSET IN CHILDREN

### Epidemiologic Evidence

The committee reviewed two studies to evaluate the risk of onset (date of first symptom) of MS in children after the administration of hepatitis B vaccine. One study (Sadovnick and Scheifele, 2000) was not considered in the weight of epidemiologic evidence because it provided data from a surveillance system and lacked an unvaccinated comparison population.

The one remaining controlled study (Mikaeloff et al., 2007b) contributed to the weight of epidemiologic evidence and is described below.

Mikaeloff et al. (2007b) conducted a case-control study in children (younger than 16 years of age) enrolled in the French Kid Sclérose en Plaques (KIDSEP) neuropediatric MS data set. The analysis included 143 children with a confirmed MS diagnosis and first episode that occurred from 1994 through 2003, and 1,122 matched controls from the French general population. The controls were selected through random-digit dialing from a telephone directory. The date of first symptom of MS was obtained from the medical record, and telephone calls and written questionnaires were used to gather more data on the description of symptoms. The immunization status was obtained from vaccination certificates, and telephone interviews were used for 30 controls that did not provide certificates. One limitation of this study was the use of random-digit dialing for the selection of controls, with responder bias a known threat to validity. Additionally, 583 of the initial 1,705 recruited controls were excluded because vaccination information was not available, and the authors did not compare the characteristics of the excluded and retained controls, so controls may not have been representative of the general underlying population. The adjusted odds ratio for the onset of MS within 3 years of hepatitis B vaccination was 1.03 (95% CI, 0.62–1.69).<sup>1</sup> The authors concluded that vaccination against hepatitis B does not appear to increase the risk of MS onset in children.

### *Weight of Epidemiologic Evidence*

*The committee has limited confidence in the epidemiologic evidence, based on one study that lacked validity and precision, to assess an association between hepatitis B vaccine and onset of MS in children.*

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<sup>1</sup>Mikaeloff et al. (2009) provided a subgroup analysis for specific brands of hepatitis B vaccine last used before MS onset in children compliant with vaccinations as outlined by the authors. The authors observed one increased odds ratio for MS onset > 3 years after Engerix vaccination (OR, 2.77; 95% CI, 1.23–6.24).

### Mechanistic Evidence

The committee identified one publication reporting the onset of MS in children after the administration of hepatitis B vaccine. The publication did not provide evidence beyond temporality, which was determined to be too long (Terney et al., 2006). Long latencies between vaccine administration and development of symptoms make it impossible to rule out other possible causes. This publication did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

The symptoms described in the publication referenced above are consistent with those leading to a diagnosis of MS. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of MS; however, the publication did not provide evidence linking these mechanisms to hepatitis B vaccine.

*The committee assesses the mechanistic evidence regarding an association between hepatitis B vaccine and onset of MS in children as lacking.*

### Causality Conclusion

**Conclusion 8.9:** The evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and onset of MS in children.

## MULTIPLE SCLEROSIS RELAPSE IN ADULTS

### Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of relapse of MS (date of third demyelinating episode) in adults after the administration of hepatitis B vaccine. This one controlled study (Confavreux et al., 2001) contributed to the weight of epidemiologic evidence and is described below.

Confavreux et al. (2001) conducted a case-crossover study in adults attending neurology centers affiliated with the European Database for Multiple Sclerosis. The study included 643 adults with definite or probable MS diagnosis and at least one relapse of symptoms that occurred from 1993 through 1997. The relapse was confirmed during outpatient visits or during hospitalizations at the neurology centers. The immunization status was obtained from telephone questionnaires and confirmed with vaccina-

tion records or written confirmation from the physician. Vaccinations were confirmed for 260 participants, not confirmed for 57, and 326 reported receiving no vaccinations during the study period. The risk period was defined as any time within 2 months before the relapse, and the four control periods were outlined as 2-month intervals prior to the risk period (2–10 months before the relapse). The relative risk of relapse of MS within 2 months of hepatitis B vaccination was 0.67 (95% CI, 0.2–2.17). The authors concluded that vaccination against hepatitis B does not appear to increase the risk of MS relapse in adults, but confidence intervals were broad and could include a clinically significant association.

#### *Weight of Epidemiologic Evidence*

*The committee has limited confidence in the epidemiologic evidence, based on one study that lacked validity and precision to assess an association between hepatitis B vaccine and relapse of MS in adults.*

#### **Mechanistic Evidence**

The committee identified one publication reporting relapse of MS in adults after the administration of hepatitis B vaccine. The publication did not provide evidence beyond temporality (Herroelen et al., 1991). The publication did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

The symptoms described in the publication referenced above are consistent with those leading to a relapse of MS. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of MS; however, the publication did not provide evidence linking these mechanisms to hepatitis B vaccine.

*The committee assesses the mechanistic evidence regarding an association between hepatitis B vaccine and relapse of MS in adults as lacking.*

#### **Causality Conclusion**

**Conclusion 8.10:** The evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and relapse of MS in adults.

## MULTIPLE SCLEROSIS RELAPSE IN CHILDREN

### Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of relapse of MS (date of second episode) in children after the administration of hepatitis B vaccine. This one controlled study (Mikaeloff et al., 2007a) contributed to the weight of epidemiologic evidence and is described below.

Mikaeloff et al. (2007a) conducted a retrospective cohort study with children (younger than 16 years of age) enrolled in the KIDSEP neuro-pediatric data set. The study included 356 children with a first episode of acute CNS inflammatory demyelination that occurred from 1994 through 2003, of which 33 received hepatitis B vaccine and 323 were not vaccinated after the first episode. The outcome reported was a second episode of neurological symptoms. The first episode was confirmed in the medical record, and the second episode was reported through routine clinical visits and telephone interviews until the end of 2005. The immunization status was obtained from vaccination certificates; telephone interviews were used for six participants that did not provide certificates. The participants exposed to hepatitis B vaccine significantly differed from those without the vaccination. In particular, those who were vaccinated were more likely to have had a first episode before 1997, more likely to have transverse myelitis during a first episode, less likely to be treated with high-dose steroids after a first episode, and in most the hepatitis B vaccination was their first dose. The adjusted hazard ratio for relapse of MS within 3 years of hepatitis B vaccination was 0.78 (95% CI, 0.32–1.89). The authors concluded that vaccination against hepatitis B does not appear to increase the risk of a second episode of MS in children.

### *Weight of Epidemiologic Evidence*

*The committee has limited confidence in the epidemiologic evidence, based on one study that lacked validity and precision to assess an association between hepatitis B vaccine and relapse of MS in children.*

### Mechanistic Evidence

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of relapse of MS in children after the administration of hepatitis B vaccine.

*Weight of Mechanistic Evidence*

Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of MS; however, the committee did not identify literature reporting evidence of these mechanisms after administration of hepatitis B vaccine.

*The committee assesses the mechanistic evidence regarding an association between hepatitis B vaccine relapse of MS in children as lacking.*

**Causality Conclusion**

**Conclusion 8.11: The evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and relapse of MS in children.**

**FIRST DEMYELINATING EVENT IN ADULTS****Epidemiologic Evidence**

The committee reviewed eight studies to evaluate the risk of a first demyelinating event (first episode with or without relapse) in adults after the administration of hepatitis B vaccine. Two studies (Fourrier et al., 2001; Soubeyrand et al., 2000) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations. Three controlled studies (Touze et al., 2000, 2002; Zipp et al., 1999) had very serious methodological limitations that precluded their inclusion in this assessment. There were high exclusion rates and a lack of validation for self-reported vaccinations among the participants in two studies (Touze et al., 2000, 2002) that raised the potential for serious bias and confounding. The third study (Zipp et al., 1999) was a letter to the editor judged by the committee to have insufficient methodological detail.

The three remaining controlled studies (DeStefano et al., 2003; Hocine et al., 2007; Payne et al., 2006) were included in the weight of epidemiologic evidence and are described below.

The study by DeStefano et al. (2003) was described in detail in the section on optic neuritis. This case-control study evaluated the association between hepatitis B vaccination and MS or optic neuritis onset using data from three HMOs participating in the VSD. The first demyelinating event analysis included 440 cases (documented diagnosis of MS or optic neuritis) and 950 controls. Although there is a large number of cases and controls,

the study had high rates of self-reported vaccinations from outside the HMO system (51 percent of cases and 50 percent of controls) that could not be verified, which may have biased the results. The odds ratio for ever vaccinated with hepatitis B before demyelinating disease onset was 0.9 (95% CI, 0.6–1.5). The authors concluded that hepatitis B vaccination does not appear to be associated with an increased risk of demyelinating disease in adults.

The study by Payne et al. (2006) was described in detail in the section on optic neuritis. This case-control study investigated the occurrence of optic neuritis after hepatitis B vaccination in U.S. military personnel. About 3 percent of the cases (37 patients) and controls (118 patients) received hepatitis B vaccine within the 18-week risk period, which suggested that possible confounders related to the decision to vaccinate were present. Although the authors considered three exposure times—6, 12, and 18 weeks after vaccination—only the odds ratio for optic neuritis diagnosis within 18 weeks of hepatitis B vaccination was given (OR, 1.02; 95% CI, 0.68–1.54). The authors noted without presenting results that similar conclusions were obtained using 6- and 12-month exposure times. The authors concluded that vaccination against hepatitis B does not appear to increase the risk of optic neuritis in adults.

Hocine et al. (2007) conducted a self-controlled case-series study. The data set included cases of CNS demyelinating disease identified at 18 departments of neurology in France from 1994 through 1995. The immunization status was obtained during telephone interviews and participants were asked to reference their vaccination certificates. The analysis included 234 cases with a first CNS demyelinating event, of which 64 percent referred to vaccination certificates. The primary risk period was 0–60 days postvaccination, but the authors also reported relative risks for 61–365 days and indefinitely after hepatitis B vaccination. The relative risk of a first demyelinating event within 0–60 days was 1.68 (95% CI, 0.76–3.68), within 61–365 days was 1.33 (95% CI, 0.65–2.69), and indefinitely (maximum of 2.29 years) after hepatitis B vaccination was 1.35 (95% CI, 0.61–3.01). The authors concluded that vaccination against hepatitis B was not associated with a first CNS demyelinating event in adults.

### *Weight of Epidemiologic Evidence*

Two case-control studies and one self-controlled case-series study evaluating the risk of first demyelinating events in adults after hepatitis B vaccination were included in the committee's review of the epidemiologic evidence. None of these studies found a significantly increased risk of first demyelinating events after hepatitis B vaccination. The types of demyelinating events were distinct in the studies, with one including only cases of optic



neuritis (Payne et al., 2006), one including cases of MS and optic neuritis (DeStefano et al., 2003), and another including only CNS demyelinating events (Hocine et al., 2007). The studies were generally well done and results were consistent. See Table 8-3 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has a moderate degree of confidence in the epidemiologic evidence based on three studies of sufficient validity and precision to assess an association between hepatitis B vaccine and a first demyelinating event in adults; these studies consistently report a null association.*

### Mechanistic Evidence

The committee identified 15 publications reporting the development of a first demyelinating event (with or without relapse) in adults after the administration of hepatitis B vaccine. Eleven publications did not present evidence beyond temporality, some too short based on the possible mechanisms involved (Albitar et al., 1997; Brinar and Poser, 2008; Cabrera-Gomez et al., 2002; Herroelen et al., 1991; Karaali-Savrun et al., 2001; Mahassin et al., 1993; Pirmohamed and Winstanley, 1997; Rogalewski et al., 2007; Senejoux et al., 1996; Stewart et al., 1999; Voigt et al., 2001). In addition, serological testing reported in Roussat et al. (2001) revealed a concomitant infection that could contribute to the development of symptoms in one case described in the publication. Furthermore, Rogalewski et al. (2007) reported the concomitant administration of vaccines, making it difficult to determine which, if any, vaccine could have been the precipitating event. Tartaglino and colleagues (1995) reported what appeared to be a vaccine rechallenge case of transverse myelitis developing after the first and second doses of hepatitis B vaccine. However, the patient did not return to baseline prior to presentation with symptoms after the second dose of vaccine indicating that the patient was suffering from a single demyelinating event. The authors did not report evidence beyond temporality. These publications did not contribute to the weight of mechanistic evidence.

Described below are two publications reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

The case reported by Konstantinou et al. (2001) was described in detail in the section on ADEM. The authors reported a vaccine rechallenge case in which the patient developed symptoms consistent with ADEM after administration of the second and third doses of hepatitis B vaccine. Brain MRIs revealed new white matter disease associated with each vaccination.

The case reported by Tourbah et al. (1999) was described in detail in

**TABLE 8-3** Studies Included in the Weight of Epidemiologic Evidence for Hepatitis B Vaccine and First Demyelinating Event in Adults

| Citation                | Operationally Defined Outcome  | Study Setting                       | Defined Study Population  | Study Design | Sample Size   | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)                                | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|-------------------------|--|-------------------------------------|---|--------------|---|---|---|--|
| DeStefano et al. (2003) | Date of demyelinating disease onset from medical records or telephone interviews of patients with optic neuritis or MS diagnosis | Three HMOs participating in the VSD | Ages < 18, 18–40, > 40 years<br>Cases had optic neuritis or MS diagnosed by a physician from 1995 through 1999      | Case control | 440 patients with demyelinating disease<br>950 controls | OR for demyelinating disease onset any time after hepatitis B vaccination:<br>0.9 (95% CI, 0.6–1.5) | None described                                      | Serious  |
| Payne et al. (2006)     | Date of first symptom of optic neuritis listed in system and reviewed by neuro-ophthalmologist                                   | Defense Medical Surveillance System | U.S. military personnel ages ≥ 18 years<br>Cases had optic neuritis diagnosed by a physician from 1998 through 2003 | Case control | 1,131 patients with optic neuritis<br>3,393 controls    | OR for optic neuritis onset within 18 weeks of hepatitis B vaccination:<br>1.02 (95% CI, 0.68–1.54) | None described                                      | Serious  |

*continued*



the section on ADEM. The authors reported a vaccine rechallenge case in which the patient developed symptoms consistent with ADEM after administration of the first, second, and third doses of hepatitis B vaccine. Brain MRIs revealed new white matter disease after the first and third doses of vaccine.

### *Weight of Mechanistic Evidence*

The two publications described above, when considered together, presented clinical evidence suggestive but not sufficient for the committee to conclude the vaccine may be a contributing cause of a first demyelinating event in adults after vaccination against hepatitis B. The mechanistic evidence contributing to the analysis includes a clinical picture consistent with ADEM, and recurrence of symptoms after revaccination with hepatitis B where new white matter disease was associated with each revaccination. In the publications described above all of the patients recovered with steroids. In addition, a brain biopsy performed by Konstantinou et al. (2001) showed demyelination. Furthermore, Konstantinou et al. (2001) did not observe oligoclonal bands in the CSF. Neither publication reported the development of antibodies to HBsAg.

The symptoms described in the publications referenced above are consistent with those leading to the diagnosis reported in the publications. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms reported in the publications; however, the publications did not provide evidence linking these mechanisms to hepatitis B vaccine.

*The committee assesses the mechanistic evidence regarding an association between hepatitis B vaccine and a first demyelinating event in adults as low-intermediate based on two cases.*

### Causality Conclusion

**Conclusion 8.12: The evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and a first demyelinating event in adults.**

Although the epidemiologic evidence is graded moderate-null, the committee considered the overall data inadequate to favor rejection of an association. The first demyelinating event category included different clinical entities (optic neuritis alone, CNS demyelinating events alone, or the two together), so considering the studies confirmations of each other may not be fully justified. Also, a first demyelinating event is required for an ultimate diagnosis of MS, and the data on the association of hepatitis B vaccine

with a diagnosis of MS were heterogeneous. In addition, the committee's assessment of the mechanistic evidence (low-intermediate) was limited to diagnoses of ADEM and countered the null assessment of the epidemiologic evidence. The uncertainties in the epidemiologic evidence combined with the uncertainties in the mechanistic evidence impacted the committee's final interpretation as applied to the causality conclusion.

## FIRST DEMYELINATING EVENT IN CHILDREN

### Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of a first demyelinating event (first episode with or without relapse) in children after the administration of hepatitis B vaccine. This one controlled study (Mikaeloff et al., 2009) contributed to the weight of epidemiologic evidence and is described below.

Mikaeloff et al. (2009) conducted a case-control study in children (younger than 16 years of age) enrolled in the KIDSEP data set. The analysis included 349 children with a first episode of acute CNS inflammatory demyelination that occurred from 1994 through 2003. This study included 143 MS cases who were also analyzed in the 2007 study by Mikaeloff and colleagues discussed above under MS onset in children. The cases included patients with a single episode without relapse and those who later relapsed and were diagnosed with MS. The study enrolled 2,941 matched controls from the French general population who were selected through random-digit dialing from a telephone directory. The date of first episode of CNS demyelination was obtained from the medical record. The immunization status was verified with vaccination certificates, and telephone interviews were used for 68 controls who did not provide certificates. One limitation of this study was the use of random-digit dialing for the selection of controls, with responder bias a known risk to validity. Additionally, 1,231 of the initial 4,172 recruited controls were excluded because vaccination information was not available, and the authors did not compare the characteristics of the excluded and retained controls so it is unclear whether controls were representative of the general population. The adjusted odds ratio for a first episode of CNS inflammatory demyelination within 3 years of hepatitis B vaccination was 0.74 (95% CI, 0.54–1.02). The authors concluded that hepatitis B vaccination generally does not increase the risk of a CNS inflammatory demyelination in children.

### *Weight of Epidemiologic Evidence*

*The committee has limited confidence in the epidemiologic evidence, based on one study that lacked validity and precision, to*

*assess an association between hepatitis B vaccine and a first demyelinating event in children.*

### Mechanistic Evidence

The committee identified six publications reporting the development of a first demyelinating event (first episode with or without relapse) in children after the administration of hepatitis B vaccine. The publications did not provide evidence beyond temporality (Erguven et al., 2009; Fonseca et al., 2003; Hamard et al., 2000; Iniguez et al., 2000; Renard et al., 1999; Roussat et al., 2001). The publications did not contribute to the weight of mechanistic evidence.

### *Weight of Mechanistic Evidence*

The symptoms described in the publications referenced above are consistent with those leading to the diagnoses reported in the publications. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms reported in the publications; however, the publications did not provide evidence linking these mechanisms to hepatitis B vaccine.

*The committee assesses the mechanistic evidence regarding an association between hepatitis B vaccine and a first demyelinating event in children as lacking.*

### Causality Conclusion

**Conclusion 8.13:** The evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and a first demyelinating event in children.

## GUILLAIN-BARRÉ SYNDROME

### Epidemiologic Evidence

The committee reviewed five studies to evaluate the risk of Guillain-Barré syndrome (GBS) after the administration of hepatitis B vaccine. Four studies (Geier and Geier, 2002c, 2004; Souayah et al., 2007, 2009) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations. One controlled study (Wu et al., 1999) had very serious methodological limitations that precluded its inclusion in this assessment. Wu et al. (1999) conducted a case-control study, but provided inadequate information on how the controls and exposure were classified.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between hepatitis B vaccine and GBS.*

**Mechanistic Evidence**

The committee identified eight publications describing the development of GBS after administration of a recombinant hepatitis B vaccine. The publications did not provide evidence beyond temporality, some too long or too short based on the possible mechanisms involved (Creange et al., 1999; Kakar and Sethi, 1997; Khamaisi et al., 2004; Pritchard et al., 2002; Schessl et al., 2006; Seti et al., 2002; Sinsawaiwong and Thampanitchawong, 2000; Tuohy, 1989). Long latencies between vaccine administration and development of symptoms make it impossible to rule out other possible causes. In addition, Schessl et al. (2006) reported that serologic tests revealed concomitant infections that could contribute to the development of GBS in four of five cases described in the publication. These publications did not contribute to the weight of mechanistic evidence.

*Weight of Mechanistic Evidence*

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of GBS. Autoantibodies, complement activation, immune complexes, T cells, and molecular mimicry may contribute to the symptoms of GBS; however, the publications did not provide evidence linking these mechanisms to hepatitis B vaccine.

*The committee assesses the mechanistic evidence regarding an association between hepatitis B vaccine and GBS as lacking.*

**Causality Conclusion**

**Conclusion 8.14:** The evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and GBS.

**CHRONIC INFLAMMATORY DISSEMINATED POLYNEUROPATHY****Epidemiologic Evidence**

No studies were identified in the literature for the committee to evaluate the risk of chronic inflammatory disseminated polyneuropathy (CIDP) after the administration of hepatitis B vaccine.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between hepatitis B vaccine and CIDP.*

**Mechanistic Evidence**

The committee identified one publication reporting two cases of the development of CIDP after the administration of hepatitis B vaccine (Vital et al., 2002). The cases did not provide evidence beyond temporality and did not contribute to the weight of mechanistic evidence.

*Weight of Mechanistic Evidence*

The symptoms described in the publication referenced above are consistent with those leading to a diagnosis of CIDP. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of CIDP; however, the publication did not provide evidence linking these mechanisms to hepatitis B vaccine.

*The committee assesses the mechanistic evidence regarding an association between hepatitis B vaccine and CIDP as lacking.*

**Causality Conclusion**

**Conclusion 8.15:** The evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and CIDP.

**BRACHIAL NEURITIS****Epidemiologic Evidence**

No studies were identified in the literature for the committee to evaluate the risk of brachial neuritis after the administration of hepatitis B vaccine.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between hepatitis B vaccine and brachial neuritis.*

**Mechanistic Evidence**

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of brachial neuritis after administration of a hepatitis B vaccine.



*Weight of Mechanistic Evidence*

Autoantibodies, T cells, and complement activation may contribute to the symptoms of brachial neuritis; however, the committee did not identify literature reporting evidence of these mechanisms after administration of hepatitis B vaccine.

*The committee assesses the mechanistic evidence regarding an association between hepatitis B vaccine and brachial neuritis as lacking.*

**Causality Conclusion**

**Conclusion 8.16:** The evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and brachial neuritis.

**ANAPHYLAXIS****Epidemiologic Evidence**

The committee reviewed four studies to evaluate the risk of anaphylaxis after the administration of hepatitis B vaccine. These four studies (Bohlke et al., 2003; DiMiceli et al., 2006; Duclos, 1992; Peng and Jick, 2004) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between hepatitis B vaccine and anaphylaxis.*

**Mechanistic Evidence**

The committee identified two publications reporting anaphylaxis after the administration of hepatitis B vaccine. One publication reported the concomitant administration of vaccines, making it difficult to determine which, if any, vaccine could have been the precipitating event (Ball et al., 2001). This publication did not contribute to the weight of mechanistic evidence.

Described below is one publication reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

DiMiceli et al. (2006) reported 11 cases of anaphylaxis in yeast-sensitive individuals after the administration of hepatitis B vaccine. The

authors identified 107 reports mentioning a history of yeast allergy submitted to the Vaccine Adverse Event Reporting System (VAERS). Of the 107 reports, 82 received a hepatitis B vaccine, and 11 of these reported the development of anaphylaxis after vaccination. The latency between administration of the vaccine and development of symptoms ranged from immediately after vaccination to 3 hours after vaccination in 10 cases. One case reported a latency of 5 hours between vaccination and the development of anaphylaxis. The committee determined the latency in this case to be too long.

#### *Weight of Mechanistic Evidence*

The publication described above presented clinical evidence sufficient for the committee to conclude the vaccine was a contributing cause of anaphylaxis in yeast-sensitive individuals after administration of a hepatitis B vaccine. The clinical descriptions establish a strong temporal relationship between administration of the vaccine and the anaphylactic reaction. The publication did not report evidence supporting a mechanism; however, the vaccines may contain yeast protein.

*The committee assesses the mechanistic evidence regarding an association between hepatitis B vaccine and anaphylaxis in yeast-sensitive individuals as strong based on ten cases presenting temporality and clinical symptoms consistent with anaphylaxis.*

### Causality Conclusion

**Conclusion 8.17:** The evidence convincingly supports a causal relationship between hepatitis B vaccine and anaphylaxis in yeast-sensitive individuals.

## ERYTHEMA NODOSUM

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of erythema nodosum after the administration of hepatitis B vaccine.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between hepatitis B vaccine and erythema nodosum.*

### Mechanistic Evidence

The committee identified four publications reporting erythema nodosum after administration of a hepatitis B vaccine. Three publications did not provide evidence beyond temporality, some too short based on the possible mechanisms involved (Llobat Estelles et al., 1995; Rogerson and Nye, 1990; Verstraeten et al., 2008). In addition, Llobat Estelles et al. (1995) reported that the lesions of erythema nodosum that developed 10 days after the first dose of the vaccine and resolved over the next 8 weeks did not recur when the patient was subsequently rechallenged with a second dose of the vaccine. These publications did not contribute to the weight of mechanistic evidence.

Described below is one publication reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Goolsby (1989) described a 43-year-old woman with known asthma, pulmonary interstitial fibrosis, and eczema who presented with painful nodules on each leg 4 days after administration of the first dose of a hepatitis B vaccine. Physical examination and punch biopsy of a lesion led to a diagnosis of erythema nodosum. A chest X-ray showed interstitial reticulonodular densities, and laboratory tests showed decreased forced vital capacity and forced expiratory volume, elevation of serum IgE concentration, positive aspergillus skin test, and serum aspergillus antibody titer of less than 1:8. The patient was treated with prednisone for pulmonary interstitial fibrosis. The skin lesions resolved over several weeks. Three weeks after beginning the course of steroids a second dose of the vaccine was administered, and 3 days after the second vaccine dose the erythema nodosum recurred.

#### *Weight of Mechanistic Evidence*

The publication, described above, did not present evidence sufficient for the committee to conclude the vaccine may be a contributing cause of erythema nodosum after administration of a hepatitis B vaccine. The publication reported a temporal association and recurrence of symptoms after vaccine rechallenge. Autoantibodies, T cells, complement activation, and immune complexes may contribute to the symptoms of erythema nodosum; however, the publications did not provide evidence linking these mechanisms to hepatitis B vaccine.

*The committee assesses the mechanistic evidence regarding an association between hepatitis B vaccine and erythema nodosum as weak based on one case.*

### Causality Conclusion

**Conclusion 8.18:** The evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and erythema nodosum.

## ONSET OR EXACERBATION OF SYSTEMIC LUPUS ERYTHEMATOSUS

### Epidemiologic Evidence

The committee reviewed two studies to evaluate the risk of onset of systemic lupus erythematosus (SLE) after the administration of hepatitis B vaccine. One study (Geier and Geier, 2005) was not considered in the weight of epidemiologic evidence because it provided data from a passive surveillance system and lacked an unvaccinated comparison population.

The one remaining controlled study (Cooper et al., 2002) contributed to the weight of epidemiologic evidence and is described below.

Cooper et al. (2002) conducted a case-control study in individuals (15 to 81 years of age) residing in 60 counties in eastern North Carolina and eastern South Carolina. SLE patients were referred by rheumatologists at university practices, public health clinics, and community-based practices in the area. The authors reviewed the patients' medical records and enrolled individuals who met the 1997 revised American College of Rheumatology SLE criteria, received a diagnosis from January 1995 through July 1999, lived in the area at least 6 months before diagnosis, were at least 18 years of age at enrollment, and spoke English. Controls were identified with driver's license records and were required to meet separate eligibility criteria (at least 18 years of age, speak English, and never diagnosed with any type of lupus). Vaccination histories were obtained from structured, in-person interviews and were not confirmed with medical records. A total of 265 cases and 355 controls were included in the analysis. Hepatitis B vaccination was low among the cases (18.7 percent) and the controls (16.5 percent), and the timing of vaccination was not clearly described relative to the onset of lupus. The controls were frequency matched to the cases on age (5-year age groups), sex, and state, and were randomly assigned index dates that corresponded to the onset dates of cases. The analyses were adjusted for matched variables, race, and education. The odds ratio for SLE diagnosis after hepatitis B vaccination was 1.3 (95% CI, 0.8–2.1). The authors concluded that hepatitis B vaccination does not appear to be associated with development of SLE.

*Weight of Epidemiologic Evidence*

*The committee has limited confidence in the epidemiologic evidence, based on one study that lacked validity and precision to assess an association between hepatitis B vaccine and onset of SLE.*

*The epidemiologic evidence is insufficient or absent to assess an association between hepatitis B vaccine and exacerbation of SLE.*

**Mechanistic Evidence**

The committee identified 13 publications reporting the onset or exacerbation of SLE after the administration of hepatitis B vaccine. Twelve publications did not provide evidence beyond temporality, some too long or too short based on the possible mechanisms involved (Agmon-Levin et al., 2009; Delbrel et al., 1998; Finielz et al., 1998; Geier and Geier, 2005; Grezard et al., 1996; Guiserix, 1996; Maillefert et al., 1999, 2000; Mamoux and Dumont, 1994; Santoro et al., 2007; Senecal et al., 1999; Tudela et al., 1992). Long latencies between vaccine administration and development of symptoms make it impossible to rule out other possible causes. These publications did not contribute to the weight of mechanistic evidence.

Described below is one publication reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Poirriez (2004) described a 12-year-old girl that presented with symptoms leading to a diagnosis of neurologic lupus 2 months after administration of a booster dose of a hepatitis B vaccine. Laboratory examinations revealed increased levels of antinuclear antibodies, anticardiolipin antibodies, and decreased concentrations of complement. Furthermore, the authors report that the patient's serum antinuclear antibodies were completely absorbed by mixing the serum with 4,950  $\mu\text{L}$  of the vaccine containing 200  $\mu\text{g}$  of HBsAg, partially absorbed by 2,450  $\mu\text{L}$  of the vaccine containing 100  $\mu\text{g}$  of HBsAg, but not removed at all by 450  $\mu\text{L}$  of the vaccine containing 20  $\mu\text{g}$  of HBsAg.

*Weight of Mechanistic Evidence*

The publication, described above, did not present clinical and experimental evidence sufficient for the committee to conclude the vaccine may be a contributing cause of SLE after the administration of hepatitis B vaccine. The publication provided preliminary evidence suggesting cross-reactivity between a patient's antinuclear antibodies (ANAs) and some component of the vaccine (Poirriez, 2004). However, the significance of this finding is

uncertain in that control sera from other ANA-positive patients (both vaccinated and unvaccinated) were not tested. Moreover, other reports in the literature confirming this finding were not identified.

In addition to autoantibodies, T cells, complement activation, and immune complexes may contribute to the symptoms of SLE; however, the publications did not provide evidence linking these mechanisms to hepatitis B vaccine. Furthermore, symptoms leading to a diagnosis of SLE are thought to develop over many years, making it impossible to determine the inciting event.

*The committee assesses the mechanistic evidence regarding an association between hepatitis B vaccine and onset or exacerbation of SLE as weak based on experimental evidence and one case.*

### Causality Conclusion

**Conclusion 8.19:** The evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and onset or exacerbation of SLE.

## ONSET OR EXACERBATION OF VASCULITIS

### Epidemiologic Evidence

The committee reviewed two studies to evaluate the risk of vasculitis after the administration of hepatitis B vaccine. These two studies (Geier and Geier, 2002c, 2005) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between hepatitis B vaccine and onset or exacerbation of vasculitis.*

### Mechanistic Evidence

The committee identified 17 publications describing onset or exacerbation of vasculitis after the administration of hepatitis B vaccine. Nine publications did not provide evidence beyond temporality, some too long or too short based on the possible mechanisms involved (Allen et al., 1993; Bellut et al., 2001; Beretta et al., 2001; Cockwell et al., 1990; Jacobi et al., 2005;

Masse and Descoffres, 1998; Miron et al., 2003; Vanoli et al., 1998; Zaas et al., 2001). Long latencies between vaccine administration and development of symptoms make it impossible to rule out other possible causes. These publications did not contribute to the weight of mechanistic evidence.

Described below are eight publications reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Begier et al. (2004) note that 2 of 25 cases reported to VAERS as polyarteritis nodosa were more likely to be microscopic polyangiitis. Case 2 describes a 33-year-old woman with symptoms arising 2 weeks after the third dose of a hepatitis B vaccine. The patient had kidney and liver aneurysms, presumably detected on angiogram. The presence of renal pathology supports the diagnosis of microscopic polyangiitis. The patient remained symptomatic for at least 6 years: the duration of disease suggests that immune complexes involving HBsAg are unlikely to be the etiologic agent. Case 4 describes a 56-year-old woman who developed biopsy-proven vasculitis and hematuria 2 weeks after the third dose of a hepatitis B vaccine. Renal involvement suggests microscopic polyangiitis. Symptoms lasted 4 months with therapy. There is no statement regarding immune complexes in blood or biopsy and no information on antibodies to HBsAg.

Bui-Quang et al. (1998) described a 51-year-old woman presenting with erysipelas of the ankle days after receiving the second dose of a hepatitis B vaccine. Three days after the third dose the patient developed a fever and cutaneous vasculitis. The patient was negative for hepatitis C, parvovirus B19, Lyme disease, and cytomegalovirus. The patient presented with ANA at 1/80 and circulating immune complexes to 6 mg/L. A skin biopsy performed 5 days after the third dose showed significant infiltration of lymphocytes and neutrophils. Immunofluorescence showed granular deposits of IgA, IgM, and C3. The symptoms spontaneously resolved after 2 weeks. Two months later the patient was negative for ANA but positive for circulating immune complexes. No effort was made to find anti-HBsAg antibodies in lesions, but serum antibodies were present.

Chave et al. (2003) described a 28-year-old woman presenting with a purpuric rash over the limbs and trunk and symmetrical arthralgia affecting the elbows and knees 19 days after receiving a booster dose of a hepatitis B vaccine. Microscopic hematuria and proteinuria were revealed by urine dipstick, and vasculitis was revealed by sigmoidoscopy. Serological tests showed increased IgA levels. A skin biopsy confirmed vasculitis and immunofluorescence showed deposition of granular IgA, granular C3, and fibrin in blood vessel walls. Most symptoms resolved rapidly on steroids but hematuria and proteinuria persisted for 1 year, making these symptoms unlikely to be vaccine related.

Drucker et al. (1997) described a 26-year-old woman presenting with

rectal bleeding, bilateral leg pain, and ill-defined abdominal discomfort 10 days after receiving the second dose of hepatitis B vaccine. Serological findings were negative for parasites; Lyme disease; hepatitis A, B, and C; human immunodeficiency virus (HIV); human T-lymphotropic virus (HTLV) 1 and 2; and compatible with remote infection with parvovirus. Biopsy of the vastus lateralis showed a predominantly CD4<sup>+</sup> T cell infiltration of the small vessel walls and a rare nonnecrotizing granuloma. With no antibody response to HBsAg and no evidence of clonality in the vessel infiltrating T cells, it is difficult to find more than temporality relating the vaccine to the symptoms.

Journe et al. (1995) described a 44-year-old diabetic man presenting with an erythematous rash, maculopapular and purpuric in areas on the trunk, abdomen, and lower limb and the appearance of nodular lesions on the hands and elbows 4 weeks after receiving the second dose of a hepatitis B vaccine. Examination showed the patient was positive for polyclonal cryoglobulins (155 mg/L) and that CH50 was low. Histology of skin lesions confirmed leukocytoclastic vasculitis. Immunofluorescence showed granular deposits of C3 on capillary walls. The symptoms resolved within 3 weeks.

Le Hello et al. (1999) reported three cases of vasculitis developing after the administration of hepatitis B vaccine. The first two cases did not provide evidence beyond a temporal relationship between vaccination and development of symptoms. These cases did not contribute to the weight of mechanistic evidence. Case 3 described a 19-year-old woman presenting with transient weakness of the left leg 3 months after receiving the second dose of a hepatitis B vaccine. Seven days after the third dose of a hepatitis B vaccine, the patient presented with arthralgias, left side hemihypesthesia, and an unstable gait. MRI showed right occipital, lenticular, and thalamic signals. Narrowing of the right anterior cerebral artery, right middle cerebral artery, right posterior cerebral artery, left anterior cerebral artery, left middle cerebral artery, and basilar artery were detected by cerebral angiographic studies. There was no evidence of infection or of an autoimmune disease. The patient was positive for HBsAb. Symptoms resolved within months.

Maillefert et al. (1999) reported one case of proven vasculitis and two of presumed vasculitis, in women aged 17, 20, and 49 years, presenting 1 week, 2 weeks, and 2 months after administration of a hepatitis B vaccine. Laboratory results showed circulating immune complexes in one patient, cryoglobulins in two patients, and rheumatoid factor in one patient. All had rapid resolution of symptoms. It is neither stated if any were HBsAb positive nor if other etiologies were ruled out.

Mathieu et al. (1996) reported two cases of cryoglobulinemia postvaccination. Case one described an 18-year-old woman presenting with painful necrotic and bullous purpura of the legs 10 days after receiving the second



dose of a hepatitis B vaccine. Examination showed complement activation with a low level of C4b. Cryoglobulinemia was confirmed by cytocrit, but the cryoglobulins were not typed. Serology was negative for HIV, hepatitis C, and cytomegalovirus, but positive for HBsAb. Case 2 described a 36-year-old patient presenting with fever, pain, and bilateral purpura of the legs 30 days after receiving a booster dose of a hepatitis B vaccine. Serological testing was positive for HBsAb. The patient had received three prior doses without adverse events. Skin biopsy showed evidence of leukocytoclastic vasculitis. The patient had type II mixed cryoglobulinemia, IgG-IgM with a monoclonal IgM component. The symptoms and cryoglobulins spontaneously resolved within 20 days.

### *Weight of Mechanistic Evidence*

While rare, vasculitis, particularly polyarteritis nodosa, is associated with hepatitis B infections (Koziel and Thio, 2010). The pathogenesis leading to vasculitis after hepatitis B infection is thought to be mediated by immune complexes containing HBsAg (Cacoub and Terrier, 2009). The committee considers the effects of natural infection one type of mechanistic evidence.

In addition, the eight publications described above, when considered together, presented clinical evidence suggestive but not sufficient for the committee to conclude the vaccine may be a contributing cause of vasculitis after vaccination against hepatitis B. The evidence contributing to the weight of mechanistic evidence includes the latency of several days to 4 weeks between vaccination and development of symptoms, the resolution of symptoms after vaccination, positive tests for circulating immune complexes or cryoglobulins, and recurrence or exacerbation of symptoms after revaccination against hepatitis B in two publications. The lack of evidence of HBsAg in the circulating immune complexes detracted from the weight of mechanistic evidence.

The latency between administration of the second, third, or fourth doses of a hepatitis B vaccine and development of vasculitis in the publications described above ranged from several days to 4 weeks. The isolation of circulating immune complexes or cryoglobulins in several publications suggests immune complexes as the mechanism. In addition, autoantibodies, T cells, and complement activation may contribute to the symptoms of vasculitis; however, the publications did not provide evidence linking these mechanisms to hepatitis B vaccine.

*The committee assesses the mechanistic evidence regarding an association between hepatitis B vaccine and onset or exacerbation of vasculitis as low-intermediate based on knowledge about the natural infection and twelve cases.*

### Causality Conclusion

**Conclusion 8.20:** The evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and onset or exacerbation of vasculitis.

### ONSET OR EXACERBATION OF POLYARTERITIS NODOSA

#### Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of onset or exacerbation of polyarteritis nodosa (PAN) after the administration of hepatitis B vaccine. This study (Begier et al., 2004) was not considered in the weight of epidemiologic evidence because it provided data from a passive surveillance system and lacked an unvaccinated comparison population.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between hepatitis B vaccine and onset or exacerbation of PAN.*

#### Mechanistic Evidence

The committee identified nine publications of onset or exacerbation of PAN after administration of a hepatitis B vaccine. Five publications did not provide evidence beyond temporality (de Carvalho et al., 2008; Kerleau et al., 1997; Le Goff et al., 1988, 1991; Saadoun et al., 2001). In addition, Saadoun and colleagues (2001) reported development of PAN, in a previously undiagnosed carrier of hepatitis B, after administration of hepatitis B vaccine and attributed the development of PAN to the hepatitis B infection. These publications did not contribute to the weight of mechanistic evidence.

Described below are four publications reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Begier et al. (2004) identified 25 cases of PAN developing after administration of a vaccine reported to VAERS from 1990 through 2001. Nine cases of PAN reported after administration of a hepatitis B vaccine with no other etiologies were described in detail. Two cases described microscopic polyangiitis and are discussed in the section on vasculitis. Two cases were previously reported by De Keyser et al. (2000) and are discussed below. Two cases did not provide evidence of causality beyond a temporal relationship between administration of a vaccine and development of PAN. Two cases reported latencies of between 4 and 8 months between the

administration of a vaccine and development of PAN, which the committee considered to be too long. One case reported a temporal relationship between administration of a vaccine and development of symptoms, but the symptoms persisted beyond the time vaccine antigen would be present.

Bourgeois et al. (2003) reported one case of a 37-year-old woman presenting with livedo extending from the legs to the abdomen after receiving the first dose of a hepatitis B vaccine. The patient was positive for antinuclear antibodies at 1:500. The symptoms lasted several years. A skin biopsy showed necrotizing vasculitis, but no antibodies to HBsAg were detected in the biopsy. Tests for infectious agents were negative.

De Keyser et al. (2000) reported two cases of PAN developing after vaccination against hepatitis B. Case 1 describes a 45-year-old man presenting with myalgia, joint pain, and morning stiffness 2 weeks after receiving the first dose of a hepatitis B vaccine. After the second dose the patient presented with arthralgia, increased myalgia, an ulcer over the left lower limb, ischemic lesions over the fingertips, and ischemic discoloration distal to the second and third digits of the left hand. The patient was positive for antinuclear antibodies, antineutrophil cytoplasmic antibodies (cANCA), and a raised concentration of immune complexes. The patient did not have antibodies to HBsAg. A skin biopsy of the lower left limb ulcer showed granulation tissue composed of fibroblasts with inflammatory cells. A medium-sized vessel under the granulation tissue presented with fibrosis of the muscle wall with infiltrating inflammatory cells. The disease lasted for 3 years at least, long after the HBsAg should have been eradicated; thus a diagnosis of PAN based on immune complexes of HBsAg and HBsAg is unlikely. Case 2 did not provide evidence of causality beyond a temporal relationship between administration of a hepatitis B vaccine and development of PAN.

Ventura et al. (2009) described the case of an 11-year-old boy who presented with livedo and constitutional symptoms 1 week after the third dose of a hepatitis B vaccine. A skin biopsy revealed PAN. The patient had circulating immune complexes; no HBsAg was detected in the biopsy. Livedo persisted for at least 2 years. The timing of onset suggests a relationship to the vaccine, but the duration of symptoms is inconsistent with an immune complex disease of HBsAg and anti-HBsAg antibodies.

### *Weight of Mechanistic Evidence*

While rare, PAN has been reported as a complication of natural hepatitis B infection (Koziel and Thio, 2010). Furthermore, circulating immune complexes containing hepatitis B surface antigen (HBsAg) are thought to be the pathogenic antigen in extrahepatic manifestations, such as PAN, of hepatitis B infection (Cacoub and Terrier, 2009). However, HBsAg-

containing circulating immune complexes are also found in patients that do not develop vasculitis as a complication of hepatitis B infection (Tsai et al., 1998). The committee considers the effects of natural infection one type of mechanistic evidence.

The four publications described above, when considered together, did not present evidence sufficient for the committee to conclude the vaccine may be a contributing cause of PAN after vaccination against hepatitis B. The cases of PAN diagnosed after vaccination against hepatitis B are similar to PAN following the natural infection with regards to the clinical manifestations, biopsy findings, and seropositivity for antinuclear antibodies. However, the cases do not report HBsAg-containing circulating immune complexes. Furthermore, there is large variability in the latency between vaccination and the development of symptoms (1–32 weeks) and only one case of exacerbation of symptoms upon rechallenge with the vaccine. In addition, several of the publications report the persistence of symptoms beyond the time vaccine antigen would be present. Hepatitis B surface antigenemia has been documented to persist for up to 18 days following administration of a vaccine containing 20 µg of HBsAg; it is not clear antigen routinely persists beyond that time (Lunn et al., 2000).

The laboratory observations, described above, suggest the formation of immune complexes as a mechanism for PAN after hepatitis B vaccination. In addition, autoantibodies, T cells, and complement activation may contribute to the symptoms of vasculitis; however, the publications did not provide evidence linking these mechanisms to hepatitis B vaccine.

*The committee assesses the mechanistic evidence regarding an association between hepatitis B vaccine and onset or exacerbation of PAN as weak based on knowledge about the natural infection and three cases.*

### Causality Conclusion

**Conclusion 8.21:** The evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and onset or exacerbation of PAN.

## ONSET OR EXACERBATION OF PSORIATIC ARTHRITIS

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of onset or exacerbation of psoriatic arthritis after the administration of hepatitis B vaccine.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between hepatitis B vaccine and onset or exacerbation of psoriatic arthritis.*

**Mechanistic Evidence**

The committee identified one report describing two cases of onset or exacerbation of psoriatic arthritis postvaccination against hepatitis B. Aherne and Collins (1995) did not provide evidence beyond temporality in the two cases and did not contribute to the weight of mechanistic evidence.

*Weight of Mechanistic Evidence*

*The committee assesses the mechanistic evidence regarding an association between hepatitis B vaccine and onset or exacerbation of psoriatic arthritis as lacking.*

**Causality Conclusion**

**Conclusion 8.22:** The evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and onset or exacerbation of psoriatic arthritis.

**ONSET OR EXACERBATION OF REACTIVE ARTHRITIS****Epidemiologic Evidence**

No studies were identified in the literature for the committee to evaluate the risk of onset or exacerbation of reactive arthritis after the administration of hepatitis B vaccine.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between hepatitis B vaccine and onset or exacerbation of reactive arthritis.*

**Mechanistic Evidence**

The committee identified 10 publications reporting onset or exacerbation of reactive arthritis postvaccination against hepatitis B. Eight publica-

tions did not provide evidence beyond temporality and did not contribute to the weight of mechanistic evidence (Biasi et al., 1994; Casals and Vasquez, 1999; Cathebras et al., 1996; Christau and Helin, 1987; Ferrazzi et al., 1997; Gross et al., 1995; Hassan and Oldham, 1994; Maillefert et al., 1997).

Described below are two publications reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Biasi et al. (1993) reported one case of a 41-year-old man, expressing the HLA-B27 haplotype, presenting with increasing pain, swelling, mobility limitation of the knees, right shoulder, right wrist, and right metacarpal and metatarsophalangeal joints 15 days after the second dose of a hepatitis B vaccine. The patient also complained of pain in the lumbar and cervical column, functional distress, fever, and malaise. Six weeks or more postvaccination the patient presented with arthritis and pain at the same sites. The patient was positive for circulating immune complexes and for antibodies to HBsAg. The patient was negative for *Borrelia*, *Yersinia*, and *Chlamydia*.

Maillefert et al. (1999) reported five cases of reactive arthritis developing postvaccination against hepatitis B in women ranging from 15–27 years of age. Symptoms developed after 2 and 12 days, and less than 1 month, 1 month, and 2 months postvaccination. The symptoms worsened in three patients after an additional vaccination. One patient was positive for rheumatoid factor. Two patients were positive for antinuclear antibodies. Two patients expressed the HLA-B27 haplotype.

### *Weight of Mechanistic Evidence*

Reactive arthritis is a clinical condition classified among the group of spondyloarthropathies in which it is thought that infection triggers the development of symptoms that persist after the infection itself is eradicated. The onset of arthritis typically occurs several days to several weeks following either gastroenteritis or urethritis caused by certain specific organisms (*Chlamydia trachomatis*, *Yersinia*, *Salmonella*, *Shigella*, *Campylobacter*, and possibly *Clostridium difficile* and *Chlamydia pneumoniae*) (Toivanen and Toivanen, 2000). Approximately, 50 percent to 80 percent of reactive arthritis patients express HLA-B27 (Sieper, 2001). From experimentation in animal models, persistence of bacterial antigen or molecular mimicry in a susceptible host who expresses HLA-B27 have been hypothesized as mechanisms inducing autoreactive T cells against host articular structures (Sahlberg et al., 2009).

The two publications described above, when considered together, did not present evidence sufficient for the committee to conclude the vaccine may be a contributing cause of reactive arthritis after vaccination against

hepatitis B. The publications provide very little information that would support any particular mechanism for the development of reactive arthritis after vaccination against hepatitis B. The vaccine rechallenge cases described above are compelling. There are, however, no studies of T cell reactivity to HBsAg. Furthermore, the latency between vaccination and the presentation of symptoms varied considerably from 2 days to 2 months. Two days is short for the development of reactive arthritis based on the possible mechanisms involved. In one patient antibody to HBsAg was detected; no information is provided on the other five. One patient was shown to have immune complexes; however, reactive arthritis is not considered to be an immune complex-mediated disease. In addition, molecular mimicry may contribute to the symptoms of reactive arthritis; however, the publications did not provide evidence linking this mechanism to hepatitis B vaccine.

*The committee assesses the mechanistic evidence regarding an association between hepatitis B vaccine and onset or exacerbation of reactive arthritis as weak based on four cases.*

### Causality Conclusion

**Conclusion 8.23:** The evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and onset or exacerbation of reactive arthritis.

## ONSET OR EXACERBATION OF RHEUMATOID ARTHRITIS

### Epidemiologic Evidence

The committee reviewed 10 studies to evaluate the risk of onset or exacerbation of rheumatoid arthritis after the administration of hepatitis B vaccine. Eight studies (Adverse Drug Reactions Advisory Committee, 1996; Caillard et al., 1985; Duclos, 1992; Geier and Geier, 2000, 2002a,b,c, 2005) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations. One controlled study (Fisher et al., 2001) had very serious methodological limitations that precluded its inclusion in this assessment. Fisher et al. (2001) conducted a retrospective cohort study using data from the National Health Interview Survey, but did not provide a definition of the outcome and relied on self-reported diagnoses that could have biased the results.

The one remaining controlled study (Elkayam et al., 2002) contributed to the weight of epidemiologic evidence and is described below.

Elkayam et al. (2002) conducted a prospective cohort study in patients

with rheumatoid arthritis (RA) as defined by the American College of Rheumatology criteria. Exclusion criteria included pregnancy, past vaccination allergy, and positive screening for hepatitis B surface antigen, antihepatitis B surface, or antihepatitis B core antibodies above the normal ranges. Patients who declined vaccination were assigned to the unexposed group, and patients who accepted vaccination were assigned to the exposed group. A total of 44 RA patients were enrolled in the study, 22 were vaccinated and 22 were not vaccinated. The vaccinated group received three doses of hepatitis vaccine at 0, 1, and 6 months. Clinical assessments and routine laboratory tests were performed before vaccination, and 2 and 7 months after vaccination. The different measurements of disease activity (daytime pain, morning stiffness, number of tender joints, number of swollen joints, Westergren erythrocyte sedimentation rate, and C reactive protein levels) were not statistically different among the vaccinated and unvaccinated groups at 0 weeks, 1 month, or 7 months. The authors concluded the hepatitis B vaccination is not associated with exacerbation of RA disease.

#### *Weight of Epidemiologic Evidence*

*The committee has limited confidence in the epidemiologic evidence, based on one study that lacked validity and precision, to assess an association between hepatitis B vaccine and exacerbation of rheumatoid arthritis.*

*The epidemiologic evidence is insufficient or absent to assess an association between hepatitis B vaccine and onset of rheumatoid arthritis.*

#### **Mechanistic Evidence**

The committee identified eight publications reporting the onset of rheumatoid arthritis postvaccination against hepatitis B. Geier and Geier (2004) did not provide evidence beyond temporality and did not contribute to the weight of mechanistic evidence.

Described below are seven publications reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Biasi et al. (1994) reported one case of an 18-year-old girl, expressing the HLA-B27 haplotype, presenting with fever and fatigue 1 month after receiving the second dose of hepatitis B vaccine. One month after receiving the third dose the patient presented with malaise, arthralgia, and heart rhythm disturbances. Waaler rose and rheumatoid tests were positive.

Gross et al. (1995) reported one case of a 20-year-old woman, express-



ing the HLA-DR4 haplotype, presenting with swelling of the right wrist and two interphalangeal joints 4 days after receiving a hepatitis B vaccine. The patient developed the same symptoms after a second dose.

Maillefert et al. (1999) reported six cases of rheumatoid arthritis developing postvaccination against hepatitis B in women ranging from 25 to 45 years of age. Symptoms developed 1, 2, 3, 10, 18, and 20 days postvaccination. The symptoms worsened in four patients following subsequent vaccination; three after the second and third doses, one after the second dose. Four patients were positive for rheumatoid factor. Four patients were positive for antinuclear antibodies. Three patients expressed the HLA-DR4 haplotype.

Pope et al. (1998) reported 10 cases of rheumatoid arthritis developing postvaccination against hepatitis B. Four cases were men and six were women. Nine cases were HLA DR1 or DR4 positive. Two cases did not develop antibodies to hepatitis B; four were not tested; four were positive for antibodies. Six cases were positive for rheumatoid factor. Two cases developed symptoms after the first and second doses of hepatitis B vaccines.

Soubrier and colleagues (1997) describe a 37-year-old patient presenting with hives days after administration of the first dose of hepatitis B vaccine. Days after receiving the third dose the patient presented with inflammatory arthralgia of the hands, ankles, and feet progressing to erosive arthritis of the digits.

Treves and colleagues (1997) describe a 43-year-old woman presenting with arthritis of the ankle 3 days after administration of the second dose of hepatitis B vaccine. Four days after administration of the third dose the patient presented with polyarthritis involving the wrists, fingers, knees, and ankles, and morning stiffness. The patient was negative for rheumatoid factor.

Vautier and Carty (1994) describe one case of a 49-year-old woman presenting with oligoarthritis of the hands 24 hours after receiving the first dose of a hepatitis B vaccine. The symptoms developed into a symmetrical arthritis with stiffness of the metacarpophalangeal joints, wrists, hands, and ankles. The patient was positive for rheumatoid factor and HLA-DR4.

### *Weight of Mechanistic Evidence*

Extrahepatic manifestations, including the development of arthralgia and polyarthritis, develop in 10–20 percent of patients with acute hepatitis and are thought to be mediated by circulating immune complexes (Koziel and Thio, 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

The seven publications described above, when considered together, did not present evidence sufficient for the committee to conclude the vaccine may be a contributing cause of rheumatoid arthritis after vaccination

against hepatitis B. Two publications described latencies between administration of vaccine and development of symptoms the committee determined to be short based on the possible mechanisms involved (Soubrier et al., 1997; Treves et al., 1997). While initially reported as such it is not clear that the patient described by Biasi et al. (1994) had arthritis. Furthermore, the case does not meet the definition for rheumatoid arthritis (Aletaha et al., 2010). Elements from these publications that are consistent with an immune complex mechanism as a cause of rheumatoid arthritis include latency of 2–4 weeks between vaccination and clinical disease, positive tests for rheumatoid factor, and recurrence or exacerbation of symptoms after vaccine rechallenge. The finding of certain HLA-DR4 extended haplotypes that are known to be associated with rheumatoid arthritis is difficult to interpret as it would characterize rheumatoid arthritis arising unrelated to prior vaccine. In no cases were immune complexes identified. In addition, it is not plausible to invoke immune complex–mediated disease from the vaccine as an etiology for rheumatoid arthritis in cases where symptoms persist over many years, after vaccine antigen would no longer be present. It would be necessary to posit that both immune complexes and molecular mimicry leading to autoantibodies and autoreactive T cells were operative, and no evidence for molecular mimicry was presented in any case. In addition to immune complexes and molecular mimicry, autoantibodies, T cells, and complement activation may contribute to the symptoms of rheumatoid arthritis; however, the publications did not provide evidence linking these mechanisms to hepatitis B vaccine.

*The committee assesses the mechanistic evidence regarding an association between hepatitis B vaccine and onset or exacerbation of rheumatoid arthritis as weak based on knowledge about the natural infection and 19 cases.*

### Causality Conclusion

**Conclusion 8.24:** The evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and onset or exacerbation of rheumatoid arthritis.

## ONSET OR EXACERBATION OF JUVENILE IDIOPATHIC ARTHRITIS

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of onset or exacerbation of juvenile idiopathic arthritis after the administration of hepatitis B vaccine.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between hepatitis B vaccine and onset or exacerbation of juvenile idiopathic arthritis.*

**Mechanistic Evidence**

The committee identified four publications describing eight cases of onset or exacerbation of juvenile idiopathic arthritis following vaccination against hepatitis B. These publications contributed to the weight of mechanistic evidence and are described below.

Bracci and Zoppini (1997) reported one case of a 9-year-old boy presenting with fever, fatigue, and polyarthritis involving the ankles, hands, feet, wrists, shoulders, and hips 3 weeks after receiving the second dose of a hepatitis B vaccine. Laboratory tests showed increased IgA, IgG, and IgM levels. The patient was negative for antinuclear antibodies and antistreptolysin O. Treatment with nonsteroidal anti-inflammatory drugs led to the resolution of symptoms within 3 months.

Grasland et al. (1998) reported one case of adult onset Still's disease in a 38-year-old woman presenting with fever, sore throat, maculopapular rash, and arthritis of the knees 10 days after the first dose of hepatitis B and hepatitis A vaccines. Serology was negative for *Mycoplasma*, *Yersinia*, *Legionella*, *Chlamydia*, Lyme disease, leptospirosis, hepatitis B and C, HIV, treponema pallidum haemagglutination (TPHA)–venereal disease research laboratory (VDRL), and parvovirus B19; no circulating immune complexes were detected.

Sebag et al. (1998) reported one case of a 15-year-old child with a history of relapsing-remitting juvenile idiopathic arthritis. At 4 years of age the patient presented with arthritis of the left ankle. The patient was positive for antinuclear antibodies at 1/200. The patient developed ocular manifestations in January 1992 and arthritis of the right knee in 1995. In July 1997 with the disease in remission, antinuclear antibodies at 1/50, the patient received one dose of a hepatitis B vaccine. In August the patient presented with uveitis in the right eye. In September the patient developed an acute arthritis of the right knee after the second dose. The patient's antinuclear antibody levels were 1/160. The authors did not report whether the patient developed antibodies to HBsAg.

Sikora et al. (2000) reported five cases of disease exacerbation in patients receiving a hepatitis B vaccine. Case one describes a 14-year-old girl with an 11-year history of polyarthritis. The patient received the first and second doses without incident. Two months after the third dose the patient presented with clinical exacerbation of the disease. Case 2 describes

a 10-year-old child with a 7-year history of polyarthritis. Two days before vaccination the patient had a mild flare. Five days after receiving the first dose the patient presented with swelling in the left ankle and a left metatarsal joint. The patient received the second and third doses without incident. Antinuclear antibody levels were 1/80 before vaccination, 1/160 after the second dose, and 1/320 after the third dose. Case 3 describes a 15-year-old child with oligoarthritis since 7 years of age. Four weeks after the second dose the patient presented with swelling of the left knee. Antinuclear antibody levels were 1/160. Four months after the third dose the acute phase indicators were still high and swelling of the knees was visible. Case 4 describes a 9-year-old child with a history of systemic disease. Five months after the second dose the patient experienced a respiratory tract infection with fever. Case 5 describes a 15-year-old child with a history of polyarthritis. Acute phase indicators were low prior to vaccination. Six months after receiving the second dose the patient experienced a respiratory tract infection and swelling of the ankles, wrists, and joints of the hands.

#### *Weight of Mechanistic Evidence*

In 10–20 percent of patients, acute hepatitis B infection may manifest as a polyarthritis (Koziel and Thio, 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

The four publications described above, when considered together, did not present evidence sufficient for the committee to conclude the vaccine may be a contributing cause of juvenile idiopathic arthritis after vaccination against hepatitis B. Bracci and Zoppini (1997) and Grasland et al. (1998) present cases of new onset polyarticular juvenile idiopathic arthritis and new onset adult Still's disease (systemic juvenile idiopathic arthritis) after administration of the first dose of a hepatitis B vaccine, respectively. The remaining cases present exacerbations of clinical signs and symptoms in patients with prior diagnoses of juvenile idiopathic arthritis.

Juvenile idiopathic arthritis is a chronic relapsing and remitting condition in which clinical flare-ups are known to occur following intercurrent viral infections, psychological stress, and physical stress. As such, the exacerbations reported in these case reports are not unique. Autoantibodies such as antinuclear antibodies and rheumatoid factor are sometimes, but not universally, found in patients with juvenile idiopathic arthritis. The latency between the development of symptoms after vaccination is quite variable, ranging from 5 days to 6 months. In addition, some of the juvenile idiopathic arthritis patients tolerated one or more doses of the vaccine without disease exacerbation only to develop symptoms after the third dose. In contrast, disease exacerbation was reported in some of the juvenile idiopathic arthritis patients after the first dose of vaccine, but subsequent

doses were administered without incident. Furthermore, variable titers of antinuclear antibodies were reported after vaccination.

Autoantibodies, T cells, complement activation, and bystander activation may contribute to the symptoms of juvenile idiopathic arthritis; however, the publications did not provide evidence linking these mechanisms to hepatitis B vaccine.

*The committee assesses the mechanistic evidence regarding an association between hepatitis B vaccine and onset or exacerbation of juvenile idiopathic arthritis as weak based on knowledge about the natural infection and eight cases.*

### Causality Conclusion

**Conclusion 8.25: The evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and onset or exacerbation of juvenile idiopathic arthritis.**

## TYPE 1 DIABETES

### Epidemiologic Evidence

The committee reviewed two studies to evaluate the risk of type 1 diabetes after the administration of hepatitis B vaccine. One study (Cherian et al., 2010) was not considered in the weight of epidemiologic evidence because it lacked an unvaccinated comparison population.

The one remaining controlled study (DeStefano et al., 2001) contributed to the weight of epidemiologic evidence and is described below.

DeStefano et al. (2001) conducted a case-control study in children (10 months to 10 years of age) enrolled in four HMOs participating in the VSD. A total of 252 type 1 diabetes cases and 768 matched controls were included in the analysis. The study required participants to be born in 1988 through 1997, enrolled in the HMO since birth, and continuously enrolled for the first 6 months of life. Additionally, cases had to be enrolled at least 12 months before diabetes diagnosis unless diagnosis occurred before 12 months of age. The case index date was defined as the first date of type 1 diabetes diagnosis in the medical record; controls were assigned the same index date as their matched case. At least three controls were matched to each case on sex, date of birth (within 7 days), HMO, and length of enrollment in the HMO (up to the index date). Trained chart abstractors obtained complete vaccination histories from the medical records. Vaccina-

tion histories were similar for the cases and controls with 44.0 percent and 46.4 percent exposed to hepatitis B vaccine, respectively. The results of two conditional logistic regression models were provided: Model 1 stratified by the matching variables; Model 2 stratified by the matching variables and race, ethnicity, and family history of type 1 diabetes (additional variables obtained from medical records). The odds ratio for diabetes diagnosis any time after hepatitis B vaccination using Model 1 was 0.81 (95% CI, 0.52–1.27), and using Model 2 it was 0.73 (95% CI, 0.45–1.19). Odds ratios were also provided for hepatitis B vaccination 0–14 days, 15–55 days, and  $\geq 56$  days before diabetes diagnosis; the odds ratios indicated no association between diabetes and the timing of vaccination. The authors concluded that vaccination with hepatitis B does not increase the risk of type 1 diabetes in children.

#### *Weight of Epidemiologic Evidence*

*The committee has a moderate degree of confidence in the epidemiologic evidence based on a single study with sufficient validity and precision to assess an association between hepatitis B vaccine and type 1 diabetes; this study reports a null association.*

#### **Mechanistic Evidence**

The committee identified one surveillance study reporting 28 cases of type 1 diabetes in persons who previously received hepatitis B vaccination (Thivolet et al., 1999). The authors did not provide evidence beyond temporality, some too long or too short based on the possible mechanisms involved. Long latencies between vaccine administration and development of symptoms make it impossible to rule out other possible causes. The publication did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

Autoantibodies, T cells, complement activation, and molecular mimicry may contribute to the symptoms of type 1 diabetes; however, the publication did not provide evidence linking these mechanisms to hepatitis B vaccine.

*The committee assesses the mechanistic evidence regarding an association between hepatitis B vaccine and type 1 diabetes as lacking.*

### Causality Conclusion

**Conclusion 8.26:** The evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and type 1 diabetes.<sup>2</sup>

## FIBROMYALGIA

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of fibromyalgia after the administration of hepatitis B vaccine.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between hepatitis B vaccine and fibromyalgia.*

### Mechanistic Evidence

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of fibromyalgia after administration of a hepatitis B vaccine.

#### *Weight of Mechanistic Evidence*

*The committee assesses the mechanistic evidence regarding an association between hepatitis B vaccine and fibromyalgia as lacking.*

### Causality Conclusion

**Conclusion 8.27:** The evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and fibromyalgia.

## CONCLUDING SECTION

Table 8-4 provides a summary of the epidemiologic assessments, mechanistic assessments, and causality conclusions for hepatitis B vaccine.

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<sup>2</sup>In order for the evidence to favor rejection of a causal relationship, the committee's framework requires two or more epidemiologic studies with negligible limitations (indicating a null association or decreased risk) to reach a high degree of confidence in the epidemiologic evidence. Only one epidemiologic study with negligible methodological limitations that reports a null association is included in the weight of evidence for this causality conclusion.

**TABLE 8-4** Summary of Epidemiologic Assessments, Mechanistic Assessments, and Causality Conclusions for Hepatitis B Vaccine

| Vaccine     | Adverse Event                          | Epidemiologic Assessment | Studies Contributing to the Epidemiologic Assessment | Mechanistic Assessment | Cases Contributing to the Mechanistic Assessment | Causality Conclusion |
|-------------|--|--------------------------|--|------------------------|--|----------------------|
| Hepatitis B | Encephalitis                           | Insufficient             | None   | Lacking                | None   | Inadequate           |
| Hepatitis B | Encephalopathy                         | Insufficient             | None   | Lacking                | None   | Inadequate           |
| Hepatitis B | Seizures                               | Limited                  | 1  | Lacking                | None   | Inadequate           |
| Hepatitis B | Acute Disseminated Encephalomyelitis   | Insufficient             | None   | Low-Intermediate       | 2  | Inadequate           |
| Hepatitis B | Transverse Myelitis                    | Insufficient             | None   | Weak                   | 1  | Inadequate           |
| Hepatitis B | Optic Neuritis*                        | Limited                  | 2  | Lacking                | None   | Inadequate           |
| Hepatitis B | Neuromyelitis Optica                   | Insufficient             | None   | Lacking                | None   | Inadequate           |
| Hepatitis B | Multiple Sclerosis Onset in Adults     | Limited                  | 4  | Lacking                | None   | Inadequate           |
| Hepatitis B | Multiple Sclerosis Onset in Children   | Limited                  | 1  | Lacking                | None   | Inadequate           |
| Hepatitis B | Multiple Sclerosis Relapse in Adults   | Limited                  | 1  | Lacking                | None   | Inadequate           |
| Hepatitis B | Multiple Sclerosis Relapse in Children | Limited                  | 1  | Lacking                | None   | Inadequate           |
| Hepatitis B | First Demyelinating Event in Adults    | Moderate (null)          | 3  | Low-Intermediate       | 2  | Inadequate           |

*continued*



TABLE 8-4 Continued

| Vaccine     | Adverse Event   | Epidemiologic Assessment | Studies Contributing to the Epidemiologic Assessment | Mechanistic Assessment                  | Cases Contributing to the Mechanistic Assessment | Causality Conclusion                                   |
|-------------|---|--------------------------|--|---|--|--|
| Hepatitis B | First Demyelinating Event in Children                 | Limited                  | 1  | Lacking                                 | None   | Inadequate   |
| Hepatitis B | Guillain-Barré Syndrome                               | Insufficient             | None   | Lacking                                 | None   | Inadequate   |
| Hepatitis B | Chronic Inflammatory Disseminated Polyneuropathy      | Insufficient             | None   | Lacking                                 | None   | Inadequate   |
| Hepatitis B | Brachial Neuritis                                     | Insufficient             | None   | Lacking                                 | None   | Inadequate   |
| Hepatitis B | Anaphylaxis   | Insufficient             | None   | Strong (in yeast-sensitive individuals) | 10   | Convincingly Supports (in yeast-sensitive individuals) |
| Hepatitis B | Erythema Nodosum*                                     | Insufficient             | None   | Weak                                    | 1  | Inadequate   |
| Hepatitis B | Onset or Exacerbation of Systemic Lupus Erythematosus | Limited (onset)          | 1  | Weak                                    | 1  | Inadequate   |
| Hepatitis B | Onset or Exacerbation of Vasculitis                   | Insufficient             | None   | Low-Intermediate                        | 12   | Inadequate   |
| Hepatitis B | Onset or Exacerbation Polyarteritis Nodosa            | Insufficient             | None   | Weak                                    | 3  | Inadequate   |
| Hepatitis B | Onset or Exacerbation of Psoriatic Arthritis          | Insufficient             | None   | Lacking                                 | None   | Inadequate   |

|             |  |                        |      |         |      |            |
|-------------|--|------------------------|------|---------|------|------------|
| Hepatitis B | Onset or Exacerbation of Reactive Arthritis            | Insufficient           | None | Weak    | 4    | Inadequate |
| Hepatitis B | Onset or Exacerbation of Rheumatoid Arthritis          | Limited (exacerbation) | 1    | Weak    | 19   | Inadequate |
|             |  | Insufficient (onset)   | None |         |      |            |
| Hepatitis B | Onset or Exacerbation of Juvenile Idiopathic Arthritis | Insufficient           | None | Weak    | 8    | Inadequate |
| Hepatitis B | Type 1 Diabetes  | Moderate (null)        | 1    | Lacking | None | Inadequate |
| Hepatitis B | Fibromyalgia   | Insufficient           | None | Lacking | None | Inadequate |

\*Although not originally charged to the committee by the sponsor, the committee considered this adverse event in its review of the literature.

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# Human Papillomavirus Vaccine

## INTRODUCTION

Human papillomaviruses (HPVs) represent a family of more than 100 nonenveloped, double-stranded DNA viruses uniquely targeted to the human epithelial cells (de Villiers et al., 2004; Schiller et al., 2008). HPVs are numbered in order of discovery and can be classified into groups according to the anatomic areas they infect (de Villiers et al., 2004; Schiller et al., 2008). Common, plantar, and juvenile or flat warts are caused by HPV1 and HPV2 (Bonnez and Reichman, 2010). These warts are common among the general population and are most common in children (Bonnez and Reichman, 2010). Genital warts and high-risk genital HPV infections, caused by HPV6 and 11 and HPV16, 18, 33, and 65 respectively, occur in an estimated 6.2 million people every year in persons aged 14 to 44 years, 74 percent among individuals between 15 and 24 years (Schiller et al., 2008; Weinstock et al., 2004).

HPV is transmitted through direct contact with the lesions or warts that develop as a result of HPV infection (Bonnez and Reichman, 2010). Genital HPV infections may be spread by penetrative intercourse and non-penetrative encounters such as oral-genital, manual-genital, and genital-genital interaction (Marrazzo et al., 2000; Winer et al., 2003). According to Schiller et al. (2008), up to 70 percent of sexually active young women will be infected with at least one HPV within the first 5 years of initial sexual encounter. The risk of infection increases with instances of sexual activity and the number of lifetime sexual partners. Manhart et al. (2006) indicated that among women 18 to 25, 14.3 percent with one lifetime sexual partner,

22.3 percent with two lifetime sexual partners, and 31.5 percent with three or more lifetime sexual partners experience at least one HPV infection.

HPV infection is often asymptomatic, but it may lead to the presence of cervical lesions or warts in some individuals. HPV infection is considered transient and usually lasts between 4 and 20 months in healthy individuals (Trottier and Franco, 2006). High-risk types of HPV such as HPV16 and HPV18 carrying the greatest risk of persistent infection constitute the most important risk factor for cervical cell abnormalities and invasive cervical cancer (Molano et al., 2003). Various approaches such as cryotherapy, electrocautery, surgical excision, and topical therapies have been used to treat HPV-associated lesions and warts (CDC, 2002).

Research and development of an HPV vaccine was spurred by evidence that inactivated bovine papillomavirus (BPV) could immunize cattle against BPV infection in the 1980s (Jarrett et al., 1990). However, owing to the oncogenic nature of HPV, live attenuated or inactivated vaccines could not be safely developed for humans (Schiller et al., 2008). In the 1990s, researchers found that inoculation with virus-like particles (VLPs) developed from the L1 protein of specific papillomaviruses (PVs) could protect against PV infection, but the protection is not universal for all HPVs (Schiller and Lowy, 1996).

Currently, two vaccines are licensed in the United States to prevent diseases caused by HPV infection. The quadrivalent vaccine, Gardasil (Merck & Co., Inc.) (HPV4), was licensed in 2006 by the Food and Drug Administration (FDA) to protect girls and women age 9 through 26 against anogenital warts and cancers (vulvar, vaginal, cervical, and anal) caused by HPV6, 11, 16, and 18 (CDC, 2007). Each 0.5 mL dose contains 20  $\mu$ g each of HPV 6 and HPV 18 L1 protein and 40  $\mu$ g each of HPV 11 and HPV 16 L1 protein (CDC, 2007). It also contains 225  $\mu$ g of amorphous aluminum hydroxyphosphate sulfate (adjuvant), sodium chloride, L-histidine, polysorbate 80, sodium borate, and water (CDC, 2007). In 2009, Gardasil was also approved for use in males aged 9–26 years for the prevention of anal cancer and genital warts; however, although it is licensed for use in the same schedule and composition, as of May 2010, the Advisory Committee on Immunization Practices did not recommend routine vaccination in this population (CDC, 2010b). The bivalent vaccine, Cervarix (GlaxoSmithKline Biologicals) (HPV2), was also licensed in 2009 by the FDA to protect girls and women age 10 through 25 against HPV 16 and 18 (CDC, 2010a). Each dose of Cervarix is 0.5 mL and contains 20  $\mu$ g each of HPV 16 and HPV 18 as well as 500  $\mu$ g of aluminum hydroxide, 50  $\mu$ g of 3-O-desacyl-4'-monophosphoryl lipid A (adjuvant), sodium chloride, sodium dihydrogen phosphate dehydrate, and water (CDC, 2010a). Both vaccines are recommended in a three-dose series of intramuscular

inoculations with the second and third dose administered 2 and 6 months after the first dose (CDC, 2010a). Both vaccines protect against 70 percent of HPV16 and 18 associated cancers, with Gardasil providing additional protection against 80 to 90 percent of genital wart-causing HPV infections (Bonnez and Reichman, 2010; CDC, 2010a). In 2009, 44.3 percent of girls in the United States aged 13 to 17 had received at least an initial dose of either the HPV4 or HPV2 vaccine (CDC, 2010c).

## ACUTE DISSEMINATED ENCEPHALOMYELITIS

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of acute disseminated encephalomyelitis (ADEM) after the administration of HPV vaccine.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between HPV vaccine and ADEM.*

### Mechanistic Evidence

The committee identified four publications reporting ADEM after administration of HPV vaccine. The publications did not provide evidence beyond temporality (Borja-Hart et al., 2009; Mendoza Plasencia et al., 2010; Schaffer et al., 2008; Wildemann et al., 2009). In addition, Borja-Hart et al. (2009) intimated that in some cases multiple vaccines were administered concomitantly, making it difficult to determine which, if any, vaccine could have been the precipitating event. The publications did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of ADEM. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of ADEM; however, the publications did not provide evidence linking these mechanisms to HPV vaccine.

*The committee assesses the mechanistic evidence regarding an association between HPV vaccine and ADEM as lacking.*



### Causality Conclusion

**Conclusion 9.1:** The evidence is inadequate to accept or reject a causal relationship between HPV vaccine and ADEM.

## TRANSVERSE MYELITIS

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of transverse myelitis after the administration of HPV vaccine.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between HPV vaccine and transverse myelitis.*

### Mechanistic Evidence

The committee identified two publications reporting the development of transverse myelitis after administration of HPV vaccine. The publications did not provide evidence beyond temporality (Borja-Hart et al., 2009; Slade et al., 2009). In addition, Borja-Hart et al. (2009) intimated that in some cases multiple vaccines were administered concomitantly, making it difficult to determine which, if any, vaccine could have been the precipitating event. The publications did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of transverse myelitis. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of transverse myelitis; however, the publications did not provide evidence linking these mechanisms to HPV vaccine.

*The committee assesses the mechanistic evidence regarding an association between HPV vaccine and transverse myelitis as lacking.*

### Causality Conclusion

**Conclusion 9.2:** The evidence is inadequate to accept or reject a causal relationship between HPV vaccine and transverse myelitis.

## NEUROMYELITIS OPTICA

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of neuromyelitis optica (NMO) after the administration of HPV vaccine.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between HPV vaccine and NMO.*

### Mechanistic Evidence

The committee identified one publication reporting the development of neuromyelitis optica after administration of HPV vaccine. Borja-Hart et al. (2009) do not provide evidence beyond temporality. In addition, the authors intimate that in some cases multiple vaccines were administered concomitantly, making it difficult to determine which, if any, vaccine could have been the precipitating event. The publication did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

The symptoms described in the publication described above are consistent with those leading to a diagnosis of NMO. Autoantibodies, T cells, complement activation, and molecular mimicry may contribute to the symptoms of NMO; however, the publication did not provide evidence linking these mechanisms to HPV vaccine.

*The committee assesses the mechanistic evidence regarding an association between HPV vaccine and NMO as lacking.*

### Causality Conclusion

**Conclusion 9.3:** The evidence is inadequate to accept or reject a causal relationship between HPV vaccine and NMO.

## MULTIPLE SCLEROSIS

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of multiple sclerosis (MS) after the administration of HPV vaccine.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between HPV vaccine and MS.*

### Mechanistic Evidence

The committee identified two publications reporting MS developing after administration of HPV vaccine. One publication did not provide clinical, diagnostic, or experimental evidence, including the time frame between administration of HPV vaccine and development of symptoms (Verstraeten et al., 2008). Sutton et al. (2009) did not provide evidence beyond temporality that for some cases was too short based on the possible mechanisms involved. The publications did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of MS. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of MS; however, the publications did not provide evidence linking these mechanisms to HPV vaccine.

*The committee assesses the mechanistic evidence regarding an association between HPV vaccine and MS as lacking.*

### Causality Conclusion

**Conclusion 9.4:** The evidence is inadequate to accept or reject a causal relationship between HPV vaccine and MS.

## GUILLAIN-BARRÉ SYNDROME

### Epidemiologic Evidence

The committee reviewed three studies to evaluate the risk of Guillain-Barré syndrome (GBS) after the administration of HPV vaccine. These three studies (Borja-Hart et al., 2009; Slade et al., 2009; Souayah et al., 2010) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between HPV vaccine and GBS.*

### Mechanistic Evidence

The committee identified three publications reporting GBS after administration of HPV vaccine. One publication did not provide clinical, diagnostic, or experimental evidence, including the time frame between administration of HPV vaccine and development of symptoms (Verstraeten et al., 2008). Two publications did not provide evidence beyond temporality (Borja-Hart et al., 2009; Slade et al., 2009). In addition, two publications reported the concomitant administration of vaccines, in some cases making it difficult to determine which, if any, vaccine could have been the precipitating event (Borja-Hart et al., 2009; Slade et al., 2009). The publications did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of GBS. Autoantibodies, complement activation, immune complexes, T cells, and molecular mimicry may contribute to the symptoms of GBS; however, the publications did not provide evidence linking these mechanisms to HPV vaccine.

*The committee assesses the mechanistic evidence regarding an association between HPV vaccine and GBS as lacking.*

### Causality Conclusion

**Conclusion 9.5:** The evidence is inadequate to accept or reject a causal relationship between HPV vaccine and GBS.

## CHRONIC INFLAMMATORY DISSEMINATED POLYNEUROPATHY

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of chronic inflammatory disseminated polyneuropathy (CIDP) after the administration of HPV vaccine.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between HPV vaccine and CIDP.*

### Mechanistic Evidence

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of CIDP after administration of HPV vaccine.

#### *Weight of Mechanistic Evidence*

Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of CIDP; however, the committee did not identify literature reporting evidence of these mechanisms after administration of HPV vaccine.

*The committee assesses the mechanistic evidence regarding an association between HPV vaccine and CIDP as lacking.*

### Causality Conclusion

**Conclusion 9.6:** The evidence is inadequate to accept or reject a causal relationship between HPV vaccine and CIDP.

## BRACHIAL NEURITIS

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of brachial neuritis after the administration of HPV vaccine.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between HPV vaccine and brachial neuritis.*

**Mechanistic Evidence**

The committee identified two publications reporting brachial neuritis after administration of HPV vaccine. The publications did not provide evidence beyond temporality, some too long (Gardasil—Brachial plexus neuritis, 2009; Debeer et al., 2008). Long latencies between vaccine administration and development of symptoms make it impossible to rule out other possible causes. The publications did not contribute to the weight of mechanistic evidence.

*Weight of Mechanistic Evidence*

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of brachial neuritis. Autoantibodies, T cells, and complement activation may contribute to the symptoms of brachial neuritis; however, the publications did not provide evidence linking these mechanisms to HPV vaccine.

*The committee assesses the mechanistic evidence regarding an association between HPV vaccine and brachial neuritis as lacking.*

**Causality Conclusion**

**Conclusion 9.7:** The evidence is inadequate to accept or reject a causal relationship between HPV vaccine and brachial neuritis.

**AMYOTROPHIC LATERAL SCLEROSIS****Epidemiologic Evidence**

No studies were identified in the literature for the committee to evaluate the risk of amyotrophic lateral sclerosis (ALS) after the administration of HPV vaccine.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between HPV vaccine and ALS.*

### Mechanistic Evidence

The committee identified one publication and one abstract reporting the development of ALS after administration of HPV vaccine. Slade et al. (2009) did not provide clinical, diagnostic, or experimental evidence including the time frame between administration of vaccine and development of symptoms. This publication did not contribute to the weight of mechanistic evidence.

Huang et al. (2009), in an abstract, described a 14-year-old girl presenting with a rapidly progressing motor neuron disease 2 months after administration of the third dose of the HPV vaccine Gardasil. Despite treatment the patient's weakness progressed leading to her death from respiratory failure 23 months after vaccination. Laboratory examinations revealed infiltrates of macrophages and T lymphocytes in the grey and white matter of the spinal cord and demyelination and loss of motor neurons. The patient was diagnosed with a rapidly progressive form of juvenile ALS.

Further investigation revealed that the patient expressed a point mutation in the fused in sarcoma/translocated in liposarcoma (FUS/TLS) gene leading to an amino acid substitution in a highly evolutionarily conserved region of the protein (Huang et al., 2010). Immunohistochemistry staining of motor neurons from the spinal cord revealed strongly FUS-positive basophilic inclusions in the patient. In contrast, patients with late-onset ALS showed no FUS-positive inclusions in motor neurons from the spinal cord. Similar basophilic inclusions were observed in the reticular formation in the medulla oblongata, red nucleus, nucleus ambiguus, sensorimotor cortex, and frontal cortex in the patient.

Based on the genetic analysis and neuropathology, the authors did not attribute the rapidly progressive form of juvenile ALS in the patient to vaccination against HPV using the quadrivalent vaccine Gardasil.<sup>1</sup>

#### *Weight of Mechanistic Evidence*

The symptoms described in the publication referenced above are consistent with those leading to a diagnosis of ALS. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of ALS; however, the publications did not provide evidence linking these mechanisms to HPV vaccine.

*The committee assesses the mechanistic evidence regarding an association between HPV vaccine and ALS as lacking.*

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<sup>1</sup>C. Lomen-Hoerth, ALS Center, University of California San Francisco, personal communication, November 11, 2010.

### Causality Conclusion

**Conclusion 9.8:** The evidence is inadequate to accept or reject a causal relationship between HPV vaccine and ALS.

## ANAPHYLAXIS

### Epidemiologic Evidence

The committee reviewed three studies to evaluate the risk of anaphylaxis after the administration of HPV vaccine. These three studies (Brotherton et al., 2008; Kang et al., 2008; Slade et al., 2009) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between HPV vaccine and anaphylaxis.*

### Mechanistic Evidence

The committee identified three publications describing clinical, diagnostic, or experimental evidence of anaphylaxis after administration of HPV vaccine. Kang et al. (2008) identified individuals suspected of developing a hypersensitivity reaction after administration of HPV vaccine; however, hypersensitivity reactions were not observed upon the subsequent administration of additional doses of HPV vaccine. This publication did not contribute to the weight of mechanistic evidence.

Described below are two publications reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Brotherton et al. (2008) conducted telephone interviews with patients, the patients' guardians, and witnesses of adverse reactions to the HPV vaccine Gardasil in Australian school children. The authors reported eight cases of anaphylaxis in detail. Anaphylaxis developed in less than 5 minutes in four cases, 5–10 minutes in three cases, and 10–15 minutes in one case.

Slade et al. (2009) analyzed reports on the HPV vaccine Gardasil received by the Vaccine Adverse Event Reporting System (VAERS) from June 2006 through December 2008. The authors identified 28 reports of anaphylaxis, according to the Brighton case definition, after vaccination with Gardasil.



*Weight of Mechanistic Evidence*

The publications described above presented clinical evidence sufficient for the committee to conclude the vaccine may be a contributing cause of anaphylaxis after administration of HPV vaccine. The clinical descriptions establish a strong temporal relationship between administration of the vaccine and the anaphylactic reaction.

*The committee assesses the mechanistic evidence regarding an association between HPV vaccine and anaphylaxis as intermediate based on 36 cases presenting temporality and clinical symptoms consistent with anaphylaxis.*

**Causality Conclusion**

**Conclusion 9.9:** The committee concludes that the evidence favors acceptance of a causal relationship between HPV vaccine and anaphylaxis.

**TRANSIENT ARTHRALGIA****Epidemiologic Evidence**

The committee reviewed one study to evaluate the risk of arthralgia after the administration of HPV vaccine. This one controlled study (Bhatla et al., 2010) contributed to the weight of epidemiologic evidence and is described below.

Bhatla et al. (2010) conducted a double-blind, randomized controlled trial in women (18 to 35 years of age) enrolled at four hospitals in India from July 2006 through March 2007. The patients were randomized in 1:1 ratio to receive HPV vaccine or placebo, and were given three doses at 0, 1, and 6 months. Diary cards were used to record any general symptoms that occurred during the 0–6 days following each dose. A total of 354 women were enrolled in the study and randomized to the vaccine group (176 women) or the placebo group (178 women). The safety analysis included patients who received at least one vaccine (167 women) or one placebo (170 women) during the study period. The diary cards were completed by 97.5 percent of the vaccine group and 98.1 percent of the placebo group. The incidence of arthralgia was similar among the two groups (approximately 10 percent of the women in both groups reported arthralgia); however, the study size and short-term follow-up make it difficult to draw conclusions.

*Weight of Epidemiologic Evidence*

*The committee has limited confidence in the epidemiologic evidence, based on one study that lacked validity and precision, to assess an association between HPV vaccine and transient arthralgia.*

**Mechanistic Evidence**

The committee identified two publications reporting arthralgia after administration of HPV vaccine. The publications did not provide evidence beyond temporality (Garcia-Sicilia et al., 2010; Rivera Medina et al., 2010). In addition, Garcia-Sicilia et al. (2010) also reported the concomitant administration of vaccines, making it difficult to determine which, if any, vaccine could have been the precipitating event. Neither publication reported the persistence of symptoms after vaccination. The publications did not contribute to the weight of mechanistic evidence.

*Weight of Mechanistic Evidence*

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of transient arthralgia. Auto-antibodies, T cells, complement activation, and immune complexes may contribute to the symptoms of transient arthralgia; however, the publications did not provide evidence linking these mechanisms to HPV vaccine.

*The committee assesses the mechanistic evidence regarding an association between HPV vaccine and transient arthralgia as lacking.*

**Causality Conclusion**

**Conclusion 9.10:** The evidence is inadequate to accept or reject a causal relationship between HPV vaccine and transient arthralgia.

**PANCREATITIS****Epidemiologic Evidence**

The committee reviewed one study to evaluate the risk of pancreatitis after the administration of HPV vaccine. This study (Slade et al., 2009) was not considered in the weight of epidemiologic evidence because it provided data from a passive surveillance system and lacked an unvaccinated comparison population.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between HPV vaccine and pancreatitis.*

**Mechanistic Evidence**

The committee identified two publications reporting pancreatitis after administration of HPV vaccine. Das et al. (2008) did not provide evidence beyond temporality. Slade et al. (2009) reported the development of pancreatitis in nine cases submitted to VAERS from June 2006 through December 2008. Two cases developed pancreatitis after the first dose and experienced a recurrence of symptoms after the second and third doses. However, the authors did not report the time frame between administration of the vaccine and development of pancreatitis; long latencies make it impossible to rule out other possible causes. In addition, all of the cases had preexisting risk factors for pancreatitis. The publications did not contribute to the weight of mechanistic evidence.

*Weight of Mechanistic Evidence*

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of pancreatitis, but the only evidence that could be attributable to the vaccine was recurrence of symptoms upon vaccine rechallenge; however, when reported without indicating the latency between vaccination and symptoms, these cases would not be considered cases of rechallenge. Antibodies and complement activation may contribute to the symptoms of pancreatitis; however, the publications did not provide evidence linking these mechanisms to HPV vaccine.

*The committee assesses the mechanistic evidence regarding an association between HPV vaccine and pancreatitis as lacking.*

**Causality Conclusion**

**Conclusion 9.11:** The evidence is inadequate to accept or reject a causal relationship between HPV vaccine and pancreatitis.

## THROMBOEMBOLIC EVENTS

### Epidemiologic Evidence

The committee reviewed two studies to evaluate the risk of thromboembolic events after the administration of HPV vaccine. These two studies (Borja-Hart et al., 2009; Slade et al., 2009) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between HPV vaccine and thromboembolic events.*

### Mechanistic Evidence

The committee identified two publications reporting thromboembolic events after administration of HPV vaccine. The publications did not provide evidence beyond temporality, some too short or too long based on the possible mechanisms involved (Borja-Hart et al., 2009; Slade et al., 2009). Long latencies between vaccine administration and development of symptoms make it impossible to rule out other possible causes. In addition, all of the cases reported in the publications had predisposing risk factors for thromboembolic events including, but not limited to, pregnancy, the use of oral contraceptives, inherited hypercoagulability syndromes, and an aneurysm. The publications did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of thromboembolic events. Alterations in the coagulation cascade may contribute to the symptoms of thromboembolic events; however, the publications did not provide evidence linking this mechanism to HPV vaccine.

*The committee assesses the mechanistic evidence regarding an association between HPV vaccine and thromboembolic events as lacking.*

### Causality Conclusion

**Conclusion 9.12:** The evidence is inadequate to accept or reject a causal relationship between HPV vaccine and thromboembolic events.

## HYPERCOAGULABLE STATES

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of hypercoagulable states after the administration of HPV vaccine.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between HPV vaccine and hypercoagulable states.*

### Mechanistic Evidence

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of hypercoagulable states after administration of HPV vaccine.

#### *Weight of Mechanistic Evidence*

Alterations in the coagulation cascade may contribute to the symptoms of hypercoagulable states; however, the committee did not identify literature reporting evidence of this mechanism after administration of HPV vaccine.

*The committee assesses the mechanistic evidence regarding an association between HPV vaccine and hypercoagulable states as lacking.*

### Causality Conclusion

**Conclusion 9.13:** The evidence is inadequate to accept or reject a causal relationship between HPV vaccine and hypercoagulable states.

## CONCLUDING SECTION

Table 9-1 provides a summary of the epidemiologic assessments, mechanistic assessments, and causality conclusions for HPV vaccine.

**TABLE 9-1** Summary of Epidemiologic Assessments, Mechanistic Assessments, and Causality Conclusions for HPV Vaccine

| Vaccine | Adverse Event                                    | Epidemiologic Assessment | Studies Contributing to the Epidemiologic Assessment | Mechanistic Assessment | Cases Contributing to the Mechanistic Assessment | Causality Conclusion |
|---------|--|--------------------------|--|------------------------|--|----------------------|
| HPV     | Acute Disseminated Encephalomyelitis             | Insufficient             | None   | Lacking                | None   | Inadequate           |
| HPV     | Transverse Myelitis                              | Insufficient             | None   | Lacking                | None   | Inadequate           |
| HPV     | Neuromyelitis Optica                             | Insufficient             | None   | Lacking                | None   | Inadequate           |
| HPV     | Multiple Sclerosis                               | Insufficient             | None   | Lacking                | None   | Inadequate           |
| HPV     | Guillain-Barré Syndrome                          | Insufficient             | None   | Lacking                | None   | Inadequate           |
| HPV     | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient             | None   | Lacking                | None   | Inadequate           |
| HPV     | Brachial Neuritis                                | Insufficient             | None   | Lacking                | None   | Inadequate           |
| HPV     | Amyotrophic Lateral Sclerosis                    | Insufficient             | None   | Lacking                | None   | Inadequate           |
| HPV     | Anaphylaxis                                      | Insufficient             | None   | Intermediate           | 36   | Favors Acceptance    |
| HPV     | Transient Arthralgia                             | Limited                  | 1  | Lacking                | None   | Inadequate           |
| HPV     | Pancreatitis                                     | Insufficient             | None   | Lacking                | None   | Inadequate           |
| HPV     | Thromboembolic Events                            | Insufficient             | None   | Lacking                | None   | Inadequate           |
| HPV     | Hypercoagulable States                           | Insufficient             | None   | Lacking                | None   | Inadequate           |

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## 10

# Diphtheria Toxoid–, Tetanus Toxoid–, and Acellular Pertussis– Containing Vaccines

## INTRODUCTION

### Diphtheria Toxoid

Diphtheria is an acute upper respiratory illness caused by *Corynebacterium diphtheriae*. *C. diphtheriae* is a minimally invasive gram-positive bacillus that is resistant to environmental change and whose virulence is mostly confined to the secretion of an exotoxin that inhibits protein synthesis in mammalian cells (MacGregor, 2010). *C. diphtheriae* is spread through direct contact with infected respiratory secretions and cutaneous lesions (MacGregor, 2010).

Following an incubation period of 1 to 5 days, diphtheria presents most commonly as local invasion of the respiratory tract including the back of the mouth and upper pharynx (Vitek and Wharton, 2008). Early symptoms may include low-grade fever (less than 101.3°F), malaise, and sore throat (Vitek and Wharton, 2008). Approximately 24 hours after disease onset, small patches of exudate are visible, and within 2 to 3 days a glossy, white membrane covers one or both tonsils and other oral structures including the tonsillar pillars, uvula, soft palate, oropharynx, and nasopharynx (Vitek and Wharton, 2008). The magnitude of the membrane is an indication of disease severity. Localized disease is often mild; however, the involvement of posterior structures like the soft palate and periglottal areas generally suggests the development of more substantial disease (Vitek and Wharton, 2008). In such cases, local lymph node enlargement also occurs due to

swelling and inflammation, and the individual may present with a “bulk neck” appearance (Vitek and Wharton, 2008).

While diphtheria in the respiratory tract is the most common manifestation, aural, conjunctival, cutaneous, and vaginal diphtheria can also occur and taken together account for approximately 2 percent of diphtheria cases (Vitek and Wharton, 2008).

The obvious consequences of diphtheria are manifested in the complications that arise from the presence and subsequent shedding of the membrane. In severe cases, the membrane may extend into the tracheo-bronchial tree causing pneumonia and expiratory respiratory obstruction and membrane aspiration (Vitek and Wharton, 2008). Other complications are caused by the effect of the absorbed diphtheria toxin on organs and organ systems proportional to the severity of the disease (Vitek and Wharton, 2008). Evidence of myocarditis has been found in up to 66 percent of patients with 10 to 25 percent developing clinically significant cardiac dysfunction (MacGregor, 2010). Neuropathy occurs rarely in mild disease but occurs in up to 75 percent of patients with severe diphtheria (MacGregor, 2010). Hypotension, pneumonia, and renal failure are also common in severe cases, while encephalitis and cerebral infarction has been described in rare cases (MacGregor, 2010). Death occurs most frequently within 3 to 4 days from disease onset and is most often caused by asphyxia or myocarditis (MacGregor, 2010).

Immunization with diphtheria toxoid has dramatically altered the epidemiology of diphtheria in the United States and data obtained from the 1988–1994 National Health and Nutrition Examination Survey (NHANES) III serosurvey indicated that 80 percent of persons age 12 to 19 years were immune to diphtheria (McQuillan et al., 2002).

The first vaccine against diphtheria was developed in the early 1800s and was widely used in the United States as early as 1914 (Vitek and Wharton, 2008). The vaccine consisted of a toxin-antitoxin formulation and was found to be 85 percent effective in preventing diphtheria (Vitek and Wharton, 2008). In the 1920s, Ramon found that by treating the toxin with formalin and creating the toxoid, the toxicity of the preparation could be reduced while maintaining the immunogenic properties (Vitek and Wharton, 2008). In 1926, Glenny and his associates discovered that alum-precipitated toxoid was even more effective, and by the mid-1940s diphtheria toxoid was being combined with tetanus toxoid and whole-cell pertussis vaccine to create the diphtheria-tetanus-pertussis (DTP) vaccine (Vitek and Wharton, 2008). Soon after, the DTP combination vaccine was adsorbed onto an aluminum salt and researchers noted the enhanced immunogenicity of the diphtheria and tetanus toxoid in the presence of pertussis vaccine and the aluminum salt (Vitek and Wharton, 2008).

### Tetanus Toxoid

Unique among the vaccine-preventable diseases, tetanus is not transmissible from person to person (Wassilak et al., 2008). The disease is caused by the gram-positive spore forming bacillus *Clostridium tetani*, which is widespread throughout the environment, particularly in the soil (Wassilak et al., 2008). *C. tetani* spores are introduced into the body through direct contact with compromised tissues, where they germinate and produce a plasmid-encoded exotoxin that binds to gangliosides at the myoneural junction of skeletal muscle and on neuronal membranes in the spinal cord, blocking inhibitory impulses to motor neurons (AAP, 2009; Wassilak et al., 2008). “The action of tetanus toxin on the brain and sympathetic nervous system is less well documented” (AAP, 2009).

The incubation period for tetanus can range from 1 day to several months but generally lasts 3 to 21 days (Weinstein, 1973). Shorter incubation periods are associated with more severe disease, while incubation periods of 10 or more days generally result in milder disease (Adams, 1968; Bruce, 1920; Garcia-Palmieri and Ramirez, 1957; LaForce et al., 1969).

There are three clinical descriptions of *C. tetani* infection: generalized, localized, and cephalic. Generalized tetanus occurs in more than 80 percent of all tetanus cases (Wassilak et al., 2008). Trismus (lockjaw) caused by spasm of the facial muscles is the most common manifestation of generalized tetanus (Newton-John, 1984; Pratt, 1945; Weinstein, 1973). Trismus may be followed by muscle spasms in other parts of the body including the neck, back, and abdomen (Wassilak et al., 2008). Tetanospasm, also known as generalized tonic tetanic seizure-like activity, is a sudden contraction of all the muscle groups and can occur in the presence of mild external stimuli such as sudden noise (Wassilak et al., 2008). In addition to these spasms, those with severe tetanus are at risk of developing severe autonomic nervous system abnormalities including diaphoresis, high or low blood pressure, flushing, and cardiac complications (Hollow and Clarke, 1975; Kanarek et al., 1973; Kerr et al., 1968). Tetanus neonatorum is the most common manifestation of generalized tetanus and occurs when the bacterium infects the umbilical stump (Wassilak et al., 2008). Typically manifesting 3 to 14 days after birth, tetanus neonatorum begins with excessive crying and decreased sucking capability, and is followed by trismus, difficulty swallowing, and tetanic spasm (Wassilak et al., 2008). Infants who survive this disease may experience neurologic damage and may also develop intellectual and behavioral abnormalities (Anlar et al., 1989; Barlow et al., 2001; Okan et al., 1997; Teknetzi et al., 1983). Localized tetanus is rare in humans and involves muscle spasms confined to areas. These spasms may last several months before subsiding or developing to generalized tetanus (Millard, 1954). Cephalic tetanus is associated with lesions on the head or

face in line with the facial nerve and orbits (Weinstein, 1973). Considered a form of localized tetanus, incubation is complete in 1 to 2 days after the initial insult, which is most often a head wound (Weinstein, 1973).

Following the widespread use of tetanus toxoid-containing vaccines, tetanus infections have become an uncommon occurrence in the United States. In 1947, the incidence of reported cases was 0.39 per 100,000 in the United States (Wassilak et al., 2008). This number dropped dramatically, and from 1998 to 2000, the average incidence was approximately 0.16 cases per 1,000,000 representing a 96 percent decrease in the incidence rate (CDC, 2003).

Tetanus infections peak in midsummer and are more common in warm, damp climates. This is likely due to soil conditions and increased exposure to spores as well as increased injuries that occur during the summer months (Axnick and Alexander, 1957; Bytchenko, 1966; Heath et al., 1964; LaForce et al., 1969).

Although described by the ancient Egyptians and Greeks, the origin of tetanus disease was not described until 1884 when Carle and Rattone showed that tetanus symptoms could be induced in rabbits when inoculated with pustular fluid from a fatal case of human tetanus (Wassilak et al., 2008). In the late 1800s, *C. tetani* spores were shown to survive heating and germinate in anaerobic environments, and the repeated inoculation with small quantities of toxin led to antibody production that was able to neutralize the effects of tetanus toxin (Wassilak et al., 2008). In 1924, the tetanus toxoid created by chemically inactivating the tetanus toxin was shown to induce active immunity to tetanus disease prior to exposure to the pathogen (Wassilak et al., 2008).

Currently, commercial tetanus toxoid is produced by culturing *C. tetani* in liquid medium and transforming the purified toxin with 40 percent formaldehyde at 37°C (Wassilak et al., 2008). In the United States, tetanus toxoid vaccines are available as a single tetanus toxoid vaccine (TT) (Sanofi Pasteur) and in combination with diphtheria toxoid as DT/Td, acellular pertussis as DTaP/Tdap, and as DTaP with other antigens such as *Haemophilus influenzae B* (HiB) conjugate (Wassilak et al., 2008).

### Pertussis Antigen

Pertussis (whooping cough) is an upper respiratory infection caused by *Bordetella pertussis*, a gram-negative, pleomorphic bacillus that attaches to cells lining the respiratory tract (Edwards and Decker, 2008). *B. pertussis* is not a particularly invasive bacterium and typically does not penetrate sub-mucosal cells or the bloodstream, although toxins secreted by the bacteria may produce systemic effects (Edwards and Decker, 2008).

The incubation period lasts 7 to 10 days, and pertussis disease is transmitted by large respiratory droplets (Waters and Halperin, 2010). *B. pertussis* infections range from asymptomatic to severe. Symptomatic disease is characterized by three phases: catarrhal, paroxysmal, and convalescent (Gordon and Hood, 1951). The catarrhal phase lasts 1–2 weeks; symptoms of this phase may include nasal discharge, eye redness, and frequent coughing and sneezing (Gordon and Hood, 1951; Waters and Halperin, 2010). The paroxysmal phase is characterized by periods of intense coughing (paroxysms) that may lead to choking, vomiting, and an inspiratory whoop (Gordon and Hood, 1951; Waters and Halperin, 2010). This phase may last 2–6 weeks, as does the convalescent phase during which the symptoms decline. Fever is rare in pertussis infection and usually results from a secondary infection or co-infection (Gordon and Hood, 1951; Waters and Halperin, 2010).

According to Cortese and her colleagues (2008), apnea and respiratory arrest was the most common complication of pertussis followed by pneumonia and gastroesophageal reflux. Pneumonia is the most common complication in hospitalized patients (Cortese et al., 2008). Encephalopathy is a rare complication and occurs most often in younger patients (Waters and Halperin, 2010). *B. pertussis* antibodies have been found in the cerebrospinal fluid (CSF) of patients with pertussis encephalopathy (Grant et al., 1998). Other complications include seizures, ataxia, aphasia, blindness, deafness, subconjunctival hemorrhages, syncope, and rib fractures (Waters and Halperin, 2010). Pertussis is most serious in infants less than 12 months of age, and the risk of death is highest among infants less than 6 months old (Cortese et al., 2008; Tanaka et al., 2003; Vincent et al., 1991; Vitek et al., 2003).

*B. pertussis* was first isolated and grown in culture by Jules Bordet and Octave Genou in 1906, and the first whole-cell pertussis vaccines were licensed in the United States in 1914 (Edwards and Decker, 2008). These vaccines were suspensions of killed bacteria and were improved upon by Kendrick and her colleagues before being combined with diphtheria and tetanus toxoids to produce DTP vaccine (Edwards and Decker, 2008). Owing to the reactogenicity of whole-cell vaccines, alternative vaccines were sought, and the first acellular vaccine was developed in Japan (Edwards and Decker, 2008). These vaccines were composed of purified filamentous hemagglutinin (FHA) and leukocytosis-promoting factor hemagglutinin (Sato et al., 1984) and were widely used in Japan starting in 1981. In 1996, acellular pertussis vaccines were licensed in the United States. Currently, the acellular pertussis vaccine is only available in combination with diphtheria and tetanus in the United States.

### Diphtheria Toxoid-, Tetanus Toxoid-, and Pertussis Antigen-Containing Vaccines

Vaccines to prevent diphtheria, tetanus, and pertussis are available in various formulations and are given in 0.5 mL doses (see Table 10-1). The four most common combination vaccines are DTaP, Tdap, DT, and Td. Of these vaccines, two (DTaP and DT) are given to children younger than 7 years of age, and two (Tdap and Td) are given to individuals 7 years or older.<sup>1</sup> The Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians recommend that children routinely receive a five-dose series of vaccine against diphtheria, tetanus, and pertussis before age 7 years. ACIP recommends that the first four doses be administered at ages 2, 4, 6, and 15–18 months and the fifth dose at age 4–6 years (CDC, 1997).

Because the immunity provided by childhood diphtheria, tetanus, and pertussis-containing vaccines is not lifelong, booster vaccinations are needed to maintain disease immunity. These booster vaccinations of either Td or Tdap, which in 2006 was recommended by the ACIP as a single-dose booster for those who previously had not been vaccinated with Tdap, are given every 10 years or after a tetanus exposure under certain circumstances (CDC, 2008).

According to the National Immunization Survey from 2005 through 2009 more than 95 percent of children age 19 to 35 months had received at least three doses of the DTP, DT, or DTaP vaccine and approximately 85 percent had received four doses (CDC, 2010b). In 2009, the National Immunization Survey estimated that 76.2 percent of adolescents between 13 and 17 years of age had received at least one dose of the Td or Tdap vaccines (CDC, 2010a).

One of the challenges the committee faced in assessing the safety of diphtheria toxoid-, tetanus toxoid-, and acellular pertussis-containing vaccines is that these particular antigens are often combined with other antigens in a number of different formulations (see Table 10-1). This variety at times made comparisons difficult. The committee was not charged with reviewing the evidence regarding whole cell pertussis vaccine. When the committee uses the phrase “diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine,” it is limiting the assessment to these antigens.

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<sup>1</sup>Upper-case letters denote full-strength doses of diphtheria (D) and tetanus (T) toxoids and pertussis (P) vaccines. Lower-case (d) and (p) denote reduced doses of diphtheria and pertussis used in the adolescent/adult formulations. The (a) in DTaP and Tdap stands for “acellular,” meaning that the pertussis component contains only a part of the pertussis organism (CDC, 1997).

**TABLE 10-1** Diphtheria Toxoid-, Tetanus Toxoid-, and Acellular Pertussis-Containing Vaccines Licensed and Available in the United States

| Vaccine | Trade Name    | Manufacturer                | Dose (Presentation)                     | Antigen Concentration  | Preservative                | Age Group       | Doses   | Route         |
|---------|---------------|-----------------------------|---|--|-----------------------------|-----------------|---------|---------------|
| DT      | No Trade Name | Sanofi Pasteur, Inc         | 0.5 mL (single-dose vials)              | 6.7 LF diphtheria toxoid;<br>5 LF tetanus toxoid   | ≤ 0.3 µg Hg/0.5 mL dose     | 6 weeks–6 years | 3 or 4* | Intramuscular |
| DT      | No Trade Name | Sanofi Pasteur, Inc         | 0.5 mL (single-dose vials)              | 25 LF diphtheria toxoid;<br>5 LF tetanus toxoid  | 0                           | 6 weeks–6 years | 5       | Intramuscular |
| DTaP    | Tripedia      | Sanofi Pasteur, Inc         | 0.5 mL (single-dose vials)              | 6.7 LF diphtheria toxoid;<br>5 LF tetanus toxoid;<br>23.4 µg PT;<br>23.4 µg FHA                                  | ≤ 0.3 µg Hg/<br>0.5 mL dose | 6 weeks–6 years | 5       | Intramuscular |
| DTaP    | Infanrix      | GlaxoSmithKline Biologicals | 0.5 mL (single-dose vials and syringes) | 25 LF diphtheria toxoid;<br>10 LF tetanus toxoid;<br>25 µg pertussis toxin;<br>25 µg FHA;<br>8.0 µg pertactin    | 0                           | 6 weeks–6 years | 5       | Intramuscular |
| DTaP    | DAPTACEL      | Sanofi Pasteur, Ltd         | 0.5 mL (single-dose vials)              | 15 LF diphtheria toxoid;<br>5 LF tetanus toxoid;<br>10 µg pertussis toxin;<br>5 µg FHA;<br>3 µg PRN;<br>5 µg FIM | 0                           | 6 weeks–6 years | 5       | Intramuscular |

*continued*



TABLE 10-1 Continued

| Vaccine        | Trade Name | Manufacturer                | Dose (Presentation)  | Antigen Concentration  | Preservative | Age Group           | Doses   | Route         |
|----------------|------------|-----------------------------|--|--|--------------|---------------------|---------|---------------|
| DTaP-IPV-Hep B | Pediarix   | GlaxoSmithKline Biologicals | 0.5 mL (single-dose vials and syringes)                                | 25 LF diphtheria toxoid;<br>10 LF tetanus toxoid;<br>25 µg pertussis toxin;<br>25 µg FHA;<br>8 µg pertactin;<br>10 µg HBsAg;<br>40 DU type 1 poliovirus;<br>8 DU type 2 poliovirus;<br>32 DU type 3 poliovirus                             | 0            | 6 weeks–<br>6 years | 3       | Intramuscular |
| DTaP-IPV       | KINRIX     | GlaxoSmithKline Biologicals | 0.5 mL (single-dose vials and syringes)                                | 25 LF diphtheria toxoid;<br>10 LF tetanus toxoid;<br>25 µg pertussis toxin;<br>25 µg FHA;<br>8 µg pertactin;<br>40 DU type 1 poliovirus;<br>8 DU type 2 poliovirus;<br>32 DU type 3 poliovirus   | 0            | 4–6 years           | Booster | Intramuscular |
| DTaP-IPV-Hib   | Pentacel   | Sanofi Pasteur Limited      | 0.5 mL (two vials; combination of DTaP-IPV vaccine and ActHIB vaccine) | 15 LF diphtheria toxoid;<br>5 LF tetanus toxoid;<br>20 µg PT;<br>20 µg FHA;<br>3 µg PRN;<br>5 µg FIM;<br>40 DU type 1 poliovirus;<br>8 DU type 2 poliovirus;<br>32 DU type 3 poliovirus;<br>10 mg PRP of Hib bound to 24 mg tetanus toxoid | 0            | 6 weeks–<br>4 years | 4       | Intramuscular |

|      |               |                             |   |   |                         |             |                  |                               |
|------|---------------|-----------------------------|---|---|-------------------------|-------------|------------------|-------------------------------|
| Td   | No Trade Name | MassBiologics               | 0.5 mL (single-dose vials)              | 2 LF tetanus toxoid;<br>2 LF diphtheria toxoid  | ≤ 0.3 µg Hg/0.5 mL dose | ≥ 7 years   | 3 and/or booster | Intramuscular                 |
| Td   | DECAVAC       | Sanofi Pasteur, Inc         | 0.5 mL (single-dose vials and syringes) | 5 LF tetanus toxoid;<br>2 LF diphtheria toxoid  | ≤ 0.3 µg Hg/0.5 mL dose | ≥ 7 years   | 3 and/or booster | Intramuscular                 |
| TT   | No Trade Name | Sanofi Pasteur, Inc         | 0.5 mL (7.5 mL 15 dose vials)           | 4 LF tetanus toxoid   | 2.5 µg Hg/0.5 mL dose   | ≥ 7 years   | Booster          | Intramuscular or Subcutaneous |
| Tdap | Adacel        | Sanofi Pasteur, Ltd         | 0.5 mL (single-dose syringes)           | 5 LF tetanus toxoid;<br>2 LF diphtheria toxoid;<br>2.5 µg PT;<br>5 µg FHA;<br>5 µg FIM;<br>3 µg PRN | 0                       | 11–64 years | Booster          | Intramuscular                 |
| Tdap | Boostrix      | GlaxoSmithKline Biologicals | 0.5 mL (single-dose vials and syringes) | 5 LF tetanus toxoid;<br>2.5 LF diphtheria toxoid;<br>8 µg PT;<br>8 µg FHA;<br>2.5 µg PRN            | 0                       | ≥ 10 years  | Booster          | Intramuscular                 |

\*This vaccine is given in a five-dose series to infants between the ages of 6 weeks and 12 months, and a three-dose series in children 1 to 6 years of age.

SOURCE: GlaxoSmithKline, 2010a,b,c, 2011; MassBiologics, 2009; Sanofi Pasteur, Inc., 2005a,b,c, 2008, 2009, 2010a,b, 2011.

## ENCEPHALITIS AND ENCEPHALOPATHY

### Epidemiologic Evidence

The committee reviewed nine studies to evaluate the risk of encephalitis or encephalopathy after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens alone or in combination. Seven studies (Geier and Geier, 2004; Gold et al., 1999; Isomura, 1991; Kuno-Sakai and Kimura, 2004; Rosenthal et al., 1996; Stetler et al., 1985; Zielinski and Rosinska, 2008) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

The two remaining controlled studies (Greco, 1985; Yih et al., 2009) contributed to the weight of epidemiologic evidence and are described below.

Greco (1985) conducted a case-control study in children (3 to 48 months of age) admitted to the Santobono Hospital in Campania, Italy, from January 1980 through February 1983. The cases were identified from the hospital intensive care unit register. Patients were included as an encephalopathy case if they were admitted to the intensive care unit for the following diagnoses, which were obtained from medical records: Reye's syndrome, coma due to unknown causes, convulsions due to unknown causes, death due to unknown causes, or stupor due to unknown causes. Two hospital controls were matched to each case on age (within 6 months), sex, and date of admission (within 30 days), and had confirmed diagnoses different from the cases. Two residence controls from the national birth register were matched to each case on age (within 1 month), sex, and place of residence (by zone or by town), and were alive during the time cases were hospitalized. A total of 45 cases, 90 matched hospital controls, and 90 matched residence controls were included in the analysis. Vaccination histories for the cases and controls were obtained from an extensive search of the national immunization register. During the 1 month preceding the hospital admission, 64 percent, 10 percent, and 13 percent of the cases, hospital controls, and residence controls received a diphtheria and tetanus toxoids vaccine, respectively. Oral polio vaccine was given at the same time as the diphtheria and tetanus toxoids vaccine in 51 percent of the cases and 28 percent of the controls; however, the authors did not explicitly state that other vaccinations were not also given. The odds ratio for encephalopathy within 1 month of the administration of diphtheria and tetanus toxoids vaccine compared to the hospital controls was 291.9 (95% CI, 53.3–1,596.9) and compared to the residence controls was 22.5 (95% CI, 8.2–62.1). The authors observed an increased risk but concluded that the study design

was insufficient to infer a causal relationship between the administration of diphtheria and tetanus toxoids vaccine and encephalopathy.

Yih et al. (2009) conducted a cohort study in patients (10 to 64 years of age) enrolled in seven managed care organizations (MCOs) participating in the Vaccine Safety Datalink (VSD) from August 2005 through May 2008. The study investigated the occurrence of adverse events (reported from outpatient, inpatient, and emergency department visits) following Tdap vaccination. The exposed group included approximately 660,000 patients that received a Tdap vaccination. Diagnoses of encephalopathy, encephalitis, and meningitis were obtained from the medical records and included in the analysis if they occurred within 42 days of vaccination. The disease incidence following Tdap vaccination was compared to the disease incidence 1 to 42 days after Td vaccination in a historical VSD comparison population; this could have introduced bias if coding practices or background disease incidences differed in the two cohorts. The comparison group included approximately 890,000 patients that received a Td vaccine from 2000 through 2004. The observed number of encephalopathy–encephalitis–meningitis events in the Tdap cohort (34 events) was less than the historical Td cohort (40.33 events), which resulted in a relative risk of 0.84 (confidence interval not provided). The authors concluded that the risk of encephalopathy–encephalitis–meningitis following Tdap vaccination is not significantly higher than the risk following Td vaccination, which only provides information on the safety of the acellular pertussis antigen component.

#### *Weight of Epidemiologic Evidence*

Greco et al. (1985) investigated the association of diphtheria and tetanus toxoids vaccine with encephalopathy; however, 50 percent of the cases considered had oral polio given with the diphtheria and tetanus toxoids vaccine, and it is not clear if any other vaccines were administered at the same time. Additionally, the case definition included a wide range of diagnoses. The paper by Yih et al. (2009) found no increased risk of encephalopathy–encephalitis–meningitis after Tdap vaccination compared to historical data on this adverse event after Td vaccination, which only provided information on the safety of the acellular pertussis antigen component.

*The committee has limited confidence in the epidemiologic evidence, based on two studies that lacked validity and precision, to assess an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and encephalitis or encephalopathy.*

### Mechanistic Evidence

The committee identified five publications reporting encephalitis or encephalopathy after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens alone or in combination. Four publications did not provide evidence beyond temporality (Casella et al., 2007; Ehrengut, 1986; Pollock and Morris, 1983; Sivertsen and Christensen, 1996). In addition, two of the publications also reported the administration of additional vaccines making it difficult to determine which, if any, vaccine could have been the precipitating event (Casella et al., 2007; Ehrengut, 1986). Furthermore, Ehrengut (1986) reported that one patient was sick 1 week prior to vaccination. These publications did not contribute to the weight of mechanistic evidence.

Described below is one publication reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Schwarz and colleagues (1988) described a 21-year-old man presenting with headache, clouding of consciousness, and tremors 7 days after administration of a tetanus toxoid vaccine and tetanus antitoxin while receiving treatment for contusions and lacerations of the elbow. Two days later the patient was unresponsive to pain and comatose. Physical examination revealed negative pupillary and corneal reflexes, divergent gaze, inadequate spontaneous respiration, spontaneous extensor posturing, and signs of meningismus. The patient recovered upon treatment with dexamethasone, amidopyrine, gentamycin, mezlocillin, and immunoglobulin. Two and one half years later the patient was administered a tetanus toxoid vaccine while receiving treatment for open injuries on the limbs. Eight days after vaccination the patient presented with signs of acute midbrain syndrome, similar to the first episode. The patient recovered upon similar treatment received during the first episode. Prior to the first episode the patient had received seven vaccinations against tetanus toxoid without incident.

#### *Weight of Mechanistic Evidence*

While rare, encephalitis and encephalopathy have been reported as complications of infection with *Corynebacterium diphtheriae* and *Bordetella pertussis*, respectively (MacGregor, 2010; Waters and Halperin, 2010). In addition, high antibody titers to pertussis toxin and filamentous hemagglutinin have been observed in the cerebrospinal fluid (CSF) of patients with pertussis encephalopathy indicating pertussis-specific antigens can cross the blood-brain barrier and directly affect the central nervous system (Waters and Halperin, 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

The publication, described above, did not present clinical evidence

sufficient for the committee to conclude tetanus toxoid vaccine may be a contributing cause of encephalitis or encephalopathy. The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of encephalitis or encephalopathy, but the only evidence that could be attributed to the vaccine was recurrence of symptoms upon vaccine rechallenge. T cells and complement activation may contribute to encephalitis and encephalopathy; however, the publications did not provide evidence linking these mechanisms to diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine.

*The committee assesses the mechanistic evidence regarding an association between tetanus toxoid vaccine and encephalitis or encephalopathy as weak based on one case.*

*The committee assesses the mechanistic evidence regarding an association between diphtheria toxoid or acellular pertussis vaccine and encephalitis or encephalopathy as weak based on knowledge about the natural infection.*

### Causality Conclusion

**Conclusion 10.1:** The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and encephalitis.

**Conclusion 10.2:** The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and encephalopathy.

## INFANTILE SPASMS

### Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of infantile spasms after the administration of vaccines containing diphtheria toxoid and tetanus toxoid antigens in combination. This one controlled study (Goodman et al., 1998) contributed to the weight of epidemiologic evidence and is described below.

Goodman et al. (1998) conducted a case-control study in children (2 to 35 months of age) enrolled in the National Childhood Encephalopathy Study (NCES) in England, Scotland, and Wales from 1976 through 1979. A monthly postal questionnaire was sent to participating pediatricians, neurosurgeons, and infectious disease physicians in order to identify pa-

tients hospitalized for acute neurological illnesses. A total of 262 children hospitalized and diagnosed with infantile spasms during the study period had sufficient clinical records for the analysis. Two controls were matched to each case on age, gender, and area of residence; however, the study did not specify further how the controls were selected. The notifying physician provided the patient's clinical history, and information on past immunizations was obtained from local sources (not defined). The analysis compared the frequency of DT immunizations 28 days prior to the date of seizure onset (case reference date) to the date for which the control was exactly the same age as the case at the date of first seizure (control reference date). The odds ratio for infantile spasms within 28 days of DT vaccination was 0.83 (95% CI, 0.45–1.49). The analysis suggested that DT vaccination was more likely to occur during the 0–6 days prior to seizure onset (OR, 1.43; 95% CI, 0.49–3.95) than any other period within the 28 days; however, the odds ratio was not statistically significant. The authors concluded that DT immunization is not associated with the onset of infantile spasms observed in the cases.

#### *Weight of Epidemiologic Evidence*

*The committee has limited confidence in the epidemiologic evidence, based on one study that lacked validity and precision, to assess an association between diphtheria toxoid or tetanus toxoid vaccine and infantile spasms.*

*The epidemiologic evidence is insufficient or absent to assess an association between acellular pertussis vaccine and infantile spasms.*

#### **Mechanistic Evidence**

The committee identified two publications reporting infantile spasms after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens alone or in combination. The publications did not provide evidence beyond temporality (Pollock and Morris, 1983; Schmitt et al., 1996). The publications did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

*The committee assesses the mechanistic evidence regarding an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and infantile spasms as lacking.*

### Causality Conclusion

**Conclusion 10.3:** The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and infantile spasms.

## SEIZURES

### Epidemiologic Evidence

The committee reviewed 14 studies to evaluate the risk of seizures after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens alone or in combination. Ten studies (DuVernoy and Braun, 2000; Geier and Geier, 2001, 2002, 2004; Gold et al., 1999; Kuno-Sakai and Kimura, 2004; Le Saux et al., 2003; Rosenthal et al., 1996; Stetler et al., 1985; Zielinski and Rosinska, 2008) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations. One controlled study (Crovari et al., 1984) had very serious methodological limitations that precluded its inclusion in this assessment. The case-control study from Crovari et al. (1984) provided inadequate information on how cases were ascertained and inappropriately combined coma and seizure symptoms.

The three remaining controlled studies (Andrews et al., 2007; Huang et al., 2010; Yih et al., 2009) contributed to the weight of epidemiologic evidence and are described below.

Andrews et al. (2007) conducted a self-controlled case-series study in children (28 days to 17 years of age) diagnosed with seizures from November 1999 through September 2003 in the United Kingdom. The cases were identified using diagnostic codes for seizures located in the hospital administrative data from the London and South East regions. The hospital data were linked to vaccination information in the child-health databases from the same regions. The study participants were divided into three age groups: 28–365 days (infants), 1 year of age (toddlers), and 2–17 years of age (children). Cases were excluded from the analysis if they received a vaccination outside the recommended age range; during this period, DT and Td vaccines were recommended for the children aged 2 to 17 years. Three risk periods were defined as 0–3 days, 4–7 days, and 8–14 days after vaccination, and were compared to the background risk of seizures among the study participants (excluding the 7-day period before vaccination). A total of 788 participants from the 2–17-year age group reported 862 seizures during the study period. The relative risk of seizures within 0–3 days of DT or Td vaccine administration was 2.87 (95% CI, 0.70–11.75), within



4–7 days was 1.13 (95% CI, 0.14–8.94), within 8–14 days was 0.60 (95% CI, 0.07–4.80), and within 0–14 days was 1.33 (95% CI, 0.44–4.00). The authors found no increased risk of seizures following DT or Td vaccination among the 2–17 year age group, but they noted the confidence intervals were wide.

The study by Yih et al. (2009) was described in detail in the section on encephalitis or encephalopathy. This cohort study compared the incidence of seizures after Tdap vaccine to a historical Td comparison population. The observed number of seizures in the Tdap cohort (34 events) was less than the historical Td cohort (40.35 events), which resulted in a relative risk of 0.84 (confidence interval not provided). The authors concluded that the risk of seizures following Tdap vaccination is not significantly higher than the risk following Td vaccination, which only provides information on the safety of the acellular pertussis antigen component.

Huang et al. (2010) conducted a retrospective cohort study in children (6 weeks to 23 months of age) enrolled in seven MCOs participating in the VSD from 1997 through 2006. Children with seizure diagnoses were identified using the *International Classification of Diseases, 9th revision (ICD-9)* codes for seizures, seizures in newborn, simple febrile seizures, complex febrile seizures, other seizures, epilepsy, and myoclonus. The events were limited to inpatient and emergency department visits, which could miss seizures that only required a physician visit. Vaccination information was obtained from the MCOs' automated immunization tracking systems. The participant follow-up began at 6 weeks of age and continued until 23 months of age, disenrollment from the MCO, death, or December 31, 2006, whichever occurred first. A total of 433,654 children were included in the analysis and received 1,343,067 doses of DTaP vaccine during the study period. The exposed person-time period was defined as 0 to 3 days after DTaP vaccination and the remaining observed person-time was classified as unexposed. The risk-interval cohort analysis compared all exposed person-time to unexposed person-time, adjusted for multiple factors (MCO, gender, calendar year, season, age, and receipt of MMR or MMRV within 8–14 days). The case-crossover analysis, which only included children with seizure diagnoses, matched each patient's exposed period with the unexposed period for the same patient and adjusted for multiple factors (calendar year, season, age, and receipt of MMR or MMRV within 8–14 days). The adjusted relative risk of seizures within 0–3 days of DTaP vaccination across all doses was 0.87 (95% CI, 0.72–1.05) for the risk-interval analysis and 0.91 (95% CI, 0.75–1.10) for the case-crossover analysis. The authors concluded that DTaP administration is not associated with a significantly increased risk of seizures within 0 to 3 days of vaccination. Stratifying by

dose and postvaccination risk interval did not change the association, which remained nonsignificant.

### *Weight of Epidemiologic Evidence*

Only one study (Huang et al., 2010) examined the association of DTaP vaccination and seizures; this study found no association. The study by Andrews et al. (2007) found no association of seizures with DT or Td vaccine in children  $\geq 2$  years of age, but since the confidence intervals were wide it was not able to rule out a clinically relevant association. The paper by Yih et al. (2009) found no increased risk of seizures after Tdap vaccination compared to historical data on this adverse event after Td vaccination, which only provided information on the safety of the acellular pertussis antigen component. Although the studies were consistent in failing to find an association between forms of DTaP vaccine and seizures, a true association may have been missed if only well children were selected for vaccination, thus at reduced risk of fever from background infections. See Table 10-2 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has limited confidence in the epidemiologic evidence, based on three studies that lacked validity and precision, to assess an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and seizures.*

### **Mechanistic Evidence**

The committee identified 20 publications reporting the development of seizures after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, or acellular pertussis antigens alone or in combination. Cizewska and colleagues (1981) reported electroencephalogram changes after administration of a diphtheria and tetanus toxoid vaccine but did not report any seizures. The remaining publications did not provide evidence beyond temporality (Berkovic et al., 2006; Decker and Edwards, 1996; Decker et al., 1995; Greco et al., 1996; Hamidon and Raymond, 2003; Herini et al., 2010; Knuf et al., 2006; McIntosh et al., 2010; Miyake et al., 2001; Netterlid et al., 2009; Pollock and Morris, 1983; Pollock et al., 1984; Preziosi et al., 1997; Ramsay et al., 1994; Satoh and Watanabe, 1997; Schmitt et al., 1996; Stehr et al., 1998; Uberall et al., 1997; Zimmerman and Pellitieri, 1994). In addition, two publications reported patients either ill at the time of vaccination or an infection diagnosed the day after vac-

**TABLE 10-2** Studies Included in the Weight of Epidemiologic Evidence for Diphtheria Toxoid-, Tetanus Toxoid-, and Acellular Pertussis-Containing Vaccines and Seizures

| Citation              | Operationally Defined Outcome  | Study Setting  | Defined Study Population   | Study Design   | Sample Size  | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)   | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|-----------------------|--|--|--|--|--|--|---|--|
| Andrews et al. (2007) | Seizure diagnoses reported in hospital administrative data   | Hospitals in the London and South East regions of the United Kingdom | Ages 28 days to 17 years<br>Analysis was restricted to ages 2–17 years | Self-controlled case series<br>Three risk periods: 0–3 days, 4–7 days, and 8–14 days after vaccination | 788 children from the 2–17 year age group reported<br>862 seizures during the study period                                   | RR of seizures within 0–3 days of DT or Td vaccination:<br><b>2.87 (95% CI, 0.70–11.75)</b><br>RR of seizures within 4–7 days of DT or Td vaccination:<br><b>1.13 (95% CI, 0.14–8.94)</b><br>RR of seizures within 8–14 days of DT or Td vaccination:<br><b>0.60 (95% CI, 0.07–4.80)</b> | None described                                      | Serious  |
| Yih et al. (2009)     | Diagnostic codes for seizures reported from outpatient, inpatient, and emergency department visits | Seven MCOs participating in the VSD from 8/2005 through 5/2008       | Ages 10–64 years   | Cohort with historical comparison group  | 660,000 patients received a Tdap vaccination from 8/2005–5/2008<br>890,000 patients received a Td vaccination from 2000–2004 | Relative risk of seizures in the Tdap cohort (34 events) compared to the Td cohort (40.35 events):<br><b>0.84</b>  | None described                                      | Serious  |

|                     |  |  |                        |   |   |  |                |         |
|---------------------|--|--|------------------------|---|---|--|----------------|---------|
| Huang et al. (2010) | Diagnostic codes for seizures, newborn, simple febrile seizures, complex febrile seizures, other seizures, epilepsy, and myoclonus reported from inpatient and emergency department visits | Seven MCOs participating in the VSD from 1997 through 2006 | Ages 6 weeks–23 months | Retrospective cohort<br>Risk period: 0–3 days after vaccination<br>Control period: Remaining observed person-time | 433,654 children received 1,343,067 doses of DTaP vaccine during the study period | Adjusted relative risk of seizures 0–3 days after DTaP vaccination for the risk-interval cohort analysis:<br><b>0.87 (95% CI, 0.72–1.05)</b><br><br>Adjusted relative risk of seizures 0–3 days after DTaP vaccination for the case-crossover analysis:<br><b>0.91 (95% CI, 0.75–1.10)</b> | None described | Serious |
|---------------------|--|--|------------------------|---|---|--|----------------|---------|

<sup>a</sup> The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup> The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup> Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.

ination (Knuf et al., 2006; Satoh and Watanabe, 1997). The publications did not contribute to the weight of mechanistic evidence.

### *Weight of Mechanistic Evidence*

Seizures are the most common complication of infection with *Bordetella pertussis* (Waters and Halperin, 2010). In addition, high antibody titers to pertussis components in the CSF indicate pertussis-specific antigens can cross the blood-brain barrier and directly affect the central nervous system (Waters and Halperin, 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of seizure. In some instances fever may contribute to the development of seizures; however, the publications did not provide evidence linking these mechanisms to diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine.

*The committee assesses the mechanistic evidence regarding an association between acellular pertussis vaccine and seizures as weak based on knowledge about the natural infection.*

*The committee assesses the mechanistic evidence regarding an association between diphtheria toxoid or tetanus toxoid vaccine and seizures as lacking.*

## Causality Conclusion

**Conclusion 10.4:** The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and seizures.

## ATAXIA

### Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of ataxia after the administration of DTaP vaccine. This one study (Geier and Geier, 2004) was not considered in the weight of epidemiologic evidence because it provided data from a passive surveillance system and lacked an unvaccinated comparison population.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and ataxia.*

**Mechanistic Evidence**

The committee identified one publication reporting the development of ataxia after the administration of DTaP vaccine. Kubota and Takahashi (2008) did not provide evidence of causality beyond a temporal relationship of 2 days between vaccine administration and development of cerebellar symptoms leading to a diagnosis of acute cerebellar ataxia. The publication did not contribute to the weight of mechanistic evidence.

*Weight of Mechanistic Evidence*

*The committee assesses the mechanistic evidence regarding an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and ataxia as lacking.*

**Causality Conclusion**

**Conclusion 10.5:** The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and ataxia.

**AUTISM****Epidemiologic Evidence**

The committee reviewed one study to evaluate the risk of autism after the administration of DTaP vaccine. This one study (Geier and Geier, 2004) was not considered in the weight of epidemiologic evidence because it provided data from a passive surveillance system and lacked an unvaccinated comparison population.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and autism.*

### Mechanistic Evidence

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of autism after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens alone or in combination.

#### *Weight of Mechanistic Evidence*

*The committee assesses the mechanistic evidence regarding an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and autism as lacking.*

### Causality Conclusion

**Conclusion 10.6:** The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and autism.

## ACUTE DISSEMINATED ENCEPHALOMYELITIS

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of acute disseminated encephalomyelitis (ADEM) after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, or acellular pertussis antigens alone or in combination.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccines and ADEM.*

### Mechanistic Evidence

The committee identified five publications of ADEM developing after the administration of vaccines containing diphtheria toxoid and tetanus toxoid antigens alone or in combination. Four publications did not provide evidence beyond temporality, one of which was deemed too short based on the possible mechanisms involved (Abdul-Ghaffar and Achar, 1994; Bolukbasi and Ozmenoglu, 1999; Hamidon and Raymond, 2003; Rogalewski et al., 2007). In addition, Rogalewski et al. (2007) reported the administration of vaccines against hepatitis B, hepatitis A, and poliovirus in

addition to diphtheria and tetanus toxoids, making it difficult to determine which vaccine, if any, could have been the precipitating event. These publications did not contribute to the weight of mechanistic evidence.

Described below is one publication reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Lopez-Pison and colleagues (2004) described a 14-year-old girl diagnosed with ADEM 7 to 20 days after receiving a tetanus toxoid vaccine. Eight years prior the patient developed neurological symptoms 15 days after receiving a diphtheria toxoid, tetanus toxoid, whole cell pertussis vaccine, and an oral polio vaccine.

#### *Weight of Mechanistic Evidence*

The publication described above did not present clinical evidence sufficient for the committee to conclude the tetanus toxoid vaccine may be a contributing cause of ADEM. The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of ADEM, but the only evidence that could be attributed to the vaccine was recurrence of symptoms upon vaccine rechallenge. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of ADEM; however, the publications did not provide evidence linking these mechanisms to diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine.

*The committee assesses the mechanistic evidence regarding an association between tetanus toxoid vaccine and ADEM as weak based on one case.*

*The committee assesses the mechanistic evidence regarding an association between diphtheria toxoid or acellular pertussis vaccine and ADEM as lacking.*

### Causality Conclusion

**Conclusion 10.7:** The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and ADEM.

## TRANSVERSE MYELITIS

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of transverse myelitis after the administration of vaccines con-



taining diphtheria toxoid, tetanus toxoid, or acellular pertussis antigens alone or in combination.

### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and transverse myelitis.*

### **Mechanistic Evidence**

The committee identified four publications reporting the development of transverse myelitis after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens alone or in combination. The publications did not provide evidence beyond temporality (Cizman et al., 2005; Riel-Romero, 2006; Whittle and Robertson, 1977; Zandoni et al., 2002). In addition, three publications reported the concomitant administration of vaccines, making it difficult to determine which, if any, vaccine could have been the precipitating event (Cizman et al., 2005; Whittle and Robertson, 1977; Zandoni et al., 2002). Furthermore, Cizman and colleagues (2005) reported that one patient had a concomitant infection with Epstein-Barr virus. The publications did not contribute to the weight of mechanistic evidence.

### *Weight of Mechanistic Evidence*

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of transverse myelitis. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of transverse myelitis; however, the publications did not provide evidence linking these mechanisms to diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine.

*The committee assesses the mechanistic evidence regarding an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and transverse myelitis as lacking.*

### **Causality Conclusion**

**Conclusion 10.8:** The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and transverse myelitis.

## OPTIC NEURITIS

### Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of optic neuritis after the administration of vaccines containing diphtheria toxoid and tetanus toxoid antigens alone or in combination. This one controlled study (DeStefano et al., 2003) was included in the weight of epidemiologic evidence and is described below.

DeStefano et al. (2003) conducted a case-control study to evaluate the association between tetanus toxoid vaccination and optic neuritis using data from three health maintenance organizations (HMOs) participating in the VSD. The optic neuritis analysis included 108 cases and 228 controls. The cases had a documented physician's diagnosis from 1995 through 1999, and were matched to controls from the HMO on date of birth (within 1 year) and sex. The authors evaluated the date of disease onset using data described in the medical record or reported in the telephone interview. The immunization status was obtained from vaccination records, medical records, and telephone interviews. The study had high rates of self-reported vaccinations from outside the HMO system (38 percent of cases and 30 percent of controls) that could not be verified, which may have biased the results. The odds ratio for ever vaccinated with tetanus toxoid or combined tetanus toxoid and diphtheria (Td) before optic neuritis diagnosis was 0.6 (95% CI, 0.4–1.1). The authors concluded that tetanus toxoid vaccination does not appear to be associated with an increased risk of optic neuritis in adults.

### *Weight of Epidemiologic Evidence*

*The committee has limited confidence in the epidemiologic evidence, based on one study that lacked validity and precision, to assess an association between diphtheria toxoid or tetanus toxoid vaccine and optic neuritis.*

*The epidemiologic evidence is insufficient or absent to assess an association between acellular pertussis vaccine and optic neuritis.*

### Mechanistic Evidence

The committee identified one publication reporting the development of optic neuritis after the administration of vaccines containing tetanus toxoid antigens. The publication did not provide evidence beyond temporality (Quast et al., 1979). The publication did not contribute to the weight of mechanistic evidence.

*Weight of Mechanistic Evidence*

The symptoms described in the publication referenced above are consistent with those leading to a diagnosis of optic neuritis. Autoantibodies, T cells, immune complexes, and molecular mimicry may contribute to the symptoms of optic neuritis; however, the publication did not provide evidence linking these mechanisms to diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine.

*The committee assesses the mechanistic evidence regarding an association between the diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and optic neuritis as lacking.*

**Causality Conclusion**

**Conclusion 10.9:** The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and optic neuritis.

**MULTIPLE SCLEROSIS ONSET IN ADULTS****Epidemiologic Evidence**

The committee reviewed five studies to evaluate the risk of onset (date of first symptom) of multiple sclerosis (MS) in adults after the administration of vaccines containing diphtheria toxoid and tetanus toxoid antigens alone or in combination. Three controlled studies (Kurtzke et al., 1997; Lauer and Firnhaber, 1990; Pekmezovic et al., 2004) had very serious methodological limitations that precluded their inclusion in this assessment. Kurtzke et al. (1997) enrolled controls (family members or neighbors of the cases) that could have introduced selection bias, and the vaccination information provided in the self-report questionnaire was not validated. The control group used in the study by Lauer et al. (1990) was flawed, and the authors may have selected a group at greater or lesser likelihood to receive the vaccine. The case-control study from Pekmezovic et al. (2004) used an inadequate control group that included patients diagnosed with other various neurological disorders.

The two remaining controlled studies (DeStefano et al., 2003; Hernan et al., 2004) were included in the weight of epidemiologic evidence and are described below.

The study by DeStefano et al. (2003) was described in detail in the section on optic neuritis. This case-control study evaluated the association between tetanus toxoid vaccination and MS or optic neuritis using data

from three HMOs participating in the VSD. The MS analysis included 332 cases and 722 controls. Although there is a large number of cases and controls, the study had high rates of self-reported vaccinations from outside the HMO system (38 percent of cases and 30 percent of controls) that could not be verified, which may have biased the results. The odds ratio for ever vaccinated with tetanus toxoid or Td before MS onset was 0.6 (95% CI, 0.4–0.8). The authors found tetanus toxoid vaccination to be associated with a significant decreased risk of MS onset in adults.

Hernan et al. (2004) used the General Practice Research Database (GPRD) to perform a nested case-control study. Cases with a confirmed MS diagnosis from 1993 through 2000, and a minimum of 3 years follow-up in the database, were selected and matched with controls on age (within 1 year), sex, general practice, and date of joining the practice (within 1 year). The study included 163 cases and 1,604 controls. The date of first symptom of MS and tetanus toxoid vaccination status were identified in the medical record. The rates of vaccination were very low among the cases and controls (11.7 percent and 17.4 percent, respectively), which raised the possibility that subjects selected for vaccination were importantly different. The odds ratio for MS onset within 3 years of immunization against tetanus toxoid was 0.6 (95% CI, 0.4–1.0). The authors concluded that tetanus toxoid vaccination does not appear to be associated with an increased risk of MS onset in adults.

### *Weight of Epidemiologic Evidence*

Neither of the two case-control studies considered in the assessment of the epidemiologic evidence found an association between tetanus toxoid vaccine and onset of MS in adults. However, there are some concerns about the study design and analyses. DeStefano et al. (2003) did not define a specific exposure time and had no short-term assessment in their primary analysis. The authors performed secondary analyses considering the timing of the tetanus toxoid vaccination (< 1 year, 1–5 years, and > 5 years) relative to the MS onset, which showed no significant association, but they did not state how they handled the timing of vaccination for those who had more than one tetanus toxoid vaccine before the onset of MS or when tetanus toxoid was given in combination with other vaccines. Hernan et al. (2004) considered a fixed exposure time of 3 years within the onset of MS but did not present results on any subanalysis considering the timing of the tetanus toxoid vaccination. In addition, the rates of vaccination were very low among the cases and controls. Given these study limitations and the small number of studies, the committee has limited confidence in the overall evidence. See Table 10-3 for a summary of the studies that contributed to the weight of epidemiologic evidence.

**TABLE 10-3** Studies Included in the Weight of Epidemiologic Evidence for Diphtheria Toxoid-, Tetanus Toxoid-, and Acellular Pertussis-Containing Vaccines and MS Onset in Adults

| Citation                      | Operational<br>Defined<br>Outcome   | Study<br>Setting                             | Defined Study Population   | Study<br>Design | Sample<br>Size                                  | Primary Effect Size<br>Estimate <sup>a</sup> (95% CI<br>or <i>p</i> value)                            | Heterogeneous<br>Subgroups at<br>Higher Risk <sup>b</sup> | Limitations<br>(Negligible<br>or Serious) <sup>c</sup> |
|-------------------------------|---|--|--|-----------------|---|---|---|--|
| DeStefano<br>et al.<br>(2003) | MS onset<br>reported<br>in medical<br>records or<br>telephone<br>interviews | Three<br>HMOs<br>participating<br>in the VSD | Ages < 18, 18–40, > 40 years<br>Cases had MS diagnosed<br>by a physician from 1995<br>through 1999     | Case<br>control | 332<br>patients<br>with MS<br>722<br>controls   | OR for MS onset<br>any time after<br>tetanus toxoid or<br>Td vaccination:<br>0.6 (95% CI,<br>0.4–0.8) | None<br>described   | Serious  |
| Hernan<br>et al.<br>(2004)    | MS onset<br>reported<br>in medical<br>records                               | GPRD   | Ages < 30, 30–49, > 50 years<br>Cases had MS diagnoses in<br>medical records from 1993<br>through 2000 | Case<br>control | 163<br>patients<br>with MS<br>1,604<br>controls | OR for MS onset<br>within 3 years of<br>tetanus toxoid<br>vaccination:<br>0.6 (95% CI,<br>0.4–1.0)    | None<br>described   | Serious  |

<sup>a</sup> The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup> The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup> Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.

*The committee has limited confidence in the epidemiologic evidence, based on two studies that lacked validity and precision, to assess an association between diphtheria toxoid or tetanus toxoid vaccine and onset of MS in adults.*

*The epidemiologic evidence is insufficient or absent to assess an association between acellular pertussis vaccine and onset of MS in adults.*

### Mechanistic Evidence

The committee identified one publication reporting the onset of MS in adults after the administration of vaccines containing diphtheria toxoid and tetanus toxoid antigens alone or in combination. The publication did not provide evidence beyond temporality (Rogalewski et al., 2007). In addition, the patient was vaccinated against hepatitis B, hepatitis A, and poliovirus concomitantly, making it difficult to determine which, if any, vaccine could have been the precipitating event. In addition, the committee identified two publications that studied whether the antibodies against tetanus toxoid and diphtheria toxoid are predictive of the development of MS (Massa et al., 2009; Salmi et al., 1981). The publications found no difference between the level of antibodies against tetanus toxoid and diphtheria toxoid between MS cases and matched controls. The publications did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

The symptoms described in the publication referenced above are consistent with those leading to a diagnosis of MS. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of MS; however, the publication did not provide evidence linking these mechanisms to diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine.

*The committee assesses the mechanistic evidence regarding an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and onset of MS in adults as lacking.*

### Causality Conclusion

**Conclusion 10.10:** The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and onset of MS in adults.

## MULTIPLE SCLEROSIS RELAPSE IN ADULTS

### Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of relapse of MS (date of third demyelinating episode) in adults after the administration of vaccines containing tetanus toxoid antigens. This one controlled study (Confavreux et al., 2001) contributed to the weight of epidemiologic evidence and is described below.

Confavreux et al. (2001) conducted a case-crossover study in adults attending neurology centers affiliated with the European Database for Multiple Sclerosis. The study included 643 adults with definite or probable MS diagnosis and at least one relapse of symptoms that occurred from 1993 through 1997. The relapse was confirmed during outpatient visits or during hospitalizations at the neurology centers. The immunization status was obtained from telephone questionnaires and confirmed with vaccination records or written confirmation from the physician. Vaccinations were confirmed for 260 participants, not confirmed for 57, and 326 reported receiving no vaccinations during the study period. Tetanus toxoid vaccinations were given alone or in combination with poliovirus or diphtheria or both. The risk period was defined as any time within 2 months before the relapse, and the four control periods were outlined as 2-month intervals prior to the risk period (2 to 10 months before the relapse). The relative risk of relapse of MS within 2 months of administration of tetanus toxoid vaccine was 0.75 (95% CI 0.23–2.46). The authors concluded that tetanus toxoid vaccination does not appear to increase the risk of MS relapse in adults.

### *Weight of Epidemiologic Evidence*

*The committee has limited confidence in the epidemiologic evidence, based on one study that lacked validity and precision, to assess an association between tetanus toxoid vaccine and relapse of MS in adults.*

*The epidemiologic evidence is insufficient or absent to assess an association between diphtheria toxoid or acellular pertussis vaccine and relapse of MS in adults.*

### Mechanistic Evidence

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of MS relapse in adults after the administration of

vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens alone or in combination.

### *Weight of Mechanistic Evidence*

Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of MS; however, the committee did not identify literature reporting evidence of these mechanisms after administration of vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens alone or in combination.

*The committee assesses the mechanistic evidence regarding an association between the diphtheria toxoid-, tetanus toxoid-, and acellular pertussis-containing vaccine and relapse of MS in adults as lacking.*

### Causality Conclusion

**Conclusion 10.11:** The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, and acellular pertussis-containing vaccine and relapse of MS in adults.

## MULTIPLE SCLEROSIS RELAPSE IN CHILDREN

### Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of relapse of MS (date of second episode) in children after the administration of vaccines containing diphtheria toxoid and tetanus toxoid antigens in combination. This one controlled study (Mikaeloff et al., 2007) contributed to the weight of epidemiologic evidence and is described below.

Mikaeloff et al. (2007) conducted a retrospective cohort study with children (younger than 16 years of age) enrolled in the French Kid Sclérose en Plaques (KIDSEP) neuropediatric dataset. The study included 356 children with a first episode of acute central nervous system (CNS) inflammatory demyelination that occurred from 1994 through 2003, of which 165 received tetanus toxoid vaccine and 191 were not vaccinated after the first episode. In all but one case, tetanus toxoid vaccination was combined with other vaccinations: tetanus toxoid, diphtheria, and polio (98 cases); tetanus toxoid, diphtheria, pertussis, and polio (45 cases); and tetanus toxoid, diphtheria, pertussis, polio, and *Haemophilus influenzae B* (22 cases). The outcome reported was a second episode of neurological symptoms. The



first episode was confirmed in the medical record, and the second episode was reported through routine clinical visits and telephone interviews until the end of 2005. The immunization status was obtained from vaccination certificates, and telephone interviews were used for six participants that did not provide certificates. The participants exposed to tetanus toxoid vaccine significantly differed from those without the vaccination. In particular, those who were vaccinated were more likely to have had infections during the month before a first episode, more frequently from low socioeconomic status families, younger at first episode, and less likely to have a first episode after 1997. The adjusted hazard ratio for relapse of MS within 3 years of tetanus toxoid vaccination was 0.99 (95% CI, 0.58–1.67). Adjusted hazard ratios were also reported for MS relapse within 3 months (HR, 0.79; 95% CI, 0.25–2.50), 6 months (HR, 1.22; 95% CI, 0.59–2.53), and 1 year (HR, 0.97; 95% CI, 0.51–1.84) of tetanus toxoid vaccination. The authors concluded that tetanus toxoid vaccination is not associated with a significant increased risk of a second episode of MS in children.

#### *Weight of Epidemiologic Evidence*

*The committee has limited confidence in the epidemiologic evidence, based on one study that lacked validity and precision, to assess an association between diphtheria toxoid or tetanus toxoid vaccine and relapse of MS in children.*

*The epidemiologic evidence is insufficient or absent to assess an association between acellular pertussis vaccine and relapse of MS in children.*

#### **Mechanistic Evidence**

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of relapse of MS in children after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens alone or in combination.

#### *Weight of Mechanistic Evidence*

Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of MS; however, the committee did not identify literature reporting evidence of these mechanisms after administration of vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens alone or in combination.

*The committee assesses the mechanistic evidence regarding an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and relapse of MS in children as lacking.*

### Causality Conclusion

**Conclusion 10.12:** The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and relapse of MS in children.

## GUILLAIN-BARRÉ SYNDROME

### Epidemiologic Evidence

The committee reviewed four studies to evaluate the risk of Guillain-Barré syndrome (GBS) after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens alone or in combination. Three studies (Kuno-Sakai and Kimura, 2004; Souayah et al., 2009; Tuttle et al., 1997) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations. The one remaining study (Yih et al., 2009) lacked an unvaccinated comparison population for the GBS analysis and thus did not contribute to the epidemiologic weight of evidence.

### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccines and GBS.*

### Mechanistic Evidence

The committee identified 10 publications reporting the development of GBS after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens alone or in combination. The publications did not provide evidence beyond temporality, some too long or too short based on the possible mechanisms involved (Bakshi and Graves, 1997; Holliday and Bauer, 1983; Hopf Ch, 1980; Newton and Janati, 1987; Pritchard et al., 2002; Quast et al., 1979; Schessl et al., 2006; Schlenska, 1977; Talbot et al., 2010; Zimmerman and Pellitieri, 1994). Long latencies

between vaccine administration and development of symptoms make it impossible to rule out other possible causes. One publication also reported the concomitant administration of vaccines, making it difficult to determine which, if any, vaccine could have been the precipitating event (Schessl et al., 2006). Furthermore, Schessl et al. (2006) reported that one patient had an upper respiratory infection in the 6 weeks preceding the diagnosis of GBS. The publications did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of GBS. Autoantibodies, complement activation, immune complexes, T cells, and molecular mimicry may contribute to the symptoms of GBS; however, the publications did not provide evidence linking these mechanisms to diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine.

*The committee assesses the mechanistic evidence regarding an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and GBS as lacking.*

#### **Causality Conclusion**

**Conclusion 10.13:** The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccines and GBS.

### **CHRONIC INFLAMMATORY DISSEMINATED POLYNEUROPATHY**

#### **Epidemiologic Evidence**

No studies were identified in the literature for the committee to evaluate the risk of chronic inflammatory disseminated polyneuropathy (CIDP) after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, or acellular pertussis antigens alone or in combination.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and CIDP.*

### Mechanistic Evidence

The committee identified five publications reporting CIDP after the administration of vaccines containing tetanus toxoid antigens. Two publications did not provide evidence beyond temporality (Pritchard et al., 2002; Quast et al., 1979). The publications did not contribute to the weight of mechanistic evidence. Described below are three publications that merit further discussion.

Pollard and Selby (1978) reported one case of a 42-year-old man who developed limb weakness, at times associated with numbness, after receiving tetanus toxoid vaccines administered after sustaining minor trauma or lacerations of the feet on three occasions. The first, second, and third episodes developed 3 weeks, 2 weeks, and 10 days, respectively, after vaccination. The first and second episodes were separated by 9 years while the second and third episodes were separated by 5 years. The patient was subsequently diagnosed with a spontaneously relapsing remitting neuropathy and experienced episodes in association with acute viral infections.<sup>2</sup> The authors did not rule out other possible causes (e.g., viral illnesses) and did not provide evidence beyond a temporal relationship between administration of the vaccine and development of symptoms after vaccination.

Reinstein et al. (1982) described a 33-year-old man presenting with occasional numbness of the feet 8 weeks after receiving a tetanus toxoid vaccine administered upon sustaining minor trauma. The patient received two additional tetanus toxoid vaccines, after sustaining minor trauma or lacerations, 4 and 5 months after the administration of the first vaccine. The patient noted increased numbness and weakness during the 6 weeks after administration of the third vaccine.

Hughes and colleagues (1996) described a 27-year-old man presenting with a peripheral neuropathy 8 weeks after administration of a tetanus toxoid vaccine. The patient experienced two relapses after administration of tetanus toxoid vaccines 21 and 25 years after the first episode. The latency between the relapses and vaccination were not reported.

#### *Weight of Mechanistic Evidence*

Pollard and Selby (1978) appear to present evidence of vaccine rechallenge leading to symptoms of peripheral neuropathy in a patient, subsequently diagnosed with a spontaneously relapsing remitting neuropathy, who developed symptoms in association with acute viral infections; however, the authors did not rule out other possible causes and did not provide

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<sup>2</sup>J. D. Pollard, Brain Mind Research Institute, personal communication, January 27, 1993.

evidence beyond a temporal relationship with vaccine administration. The spontaneous development of peripheral neuropathy makes it difficult to conclude that the tetanus toxoid vaccines were the causative agent. Reinstein et al. (1982) and Hughes and colleagues (1996) appear to present evidence of vaccine rechallenge leading to symptoms of CIDP; however, the committee determined the time frame of 8 weeks between administration of the first vaccine, in each case, and development of symptoms to be too long. In addition, the patient described by Reinstein et al. (1982) did not develop symptoms following administration of the second vaccine. Furthermore, Hughes and colleagues (1996) do not report the latency between administration of the additional tetanus toxoid vaccines and the development of peripheral neuropathy. Latencies considered to be long would reduce the association of the development of symptoms with the administration of the vaccine. Neither Reinstein et al. (1982) nor Hughes and colleagues (1996) ruled out other possible causes.

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of CIDP. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of CIDP; however, the publications did not provide evidence linking these mechanisms to diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine.

*The committee assesses the mechanistic evidence regarding an association between the diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and CIDP as lacking.*

### Causality Conclusion

**Conclusion 10.14:** The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and CIDP.

## OPSOCLONUS MYOCLONUS SYNDROME

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of opsoclonus myoclonus syndrome (OMS) after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, or acellular pertussis antigens alone or in combination.

### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and OMS.*

### Mechanistic Evidence

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of OMS after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens alone or in combination.

#### *Weight of Mechanistic Evidence*

Autoantibodies, T cells, complement activation, and molecular mimicry may contribute to the symptoms of OMS; however, the committee did not identify literature reporting evidence of these mechanisms after administration of vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens alone or in combination.

*The committee assesses the mechanistic evidence regarding an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and OMS as lacking.*

### Causality Conclusion

**Conclusion 10.15:** The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and OMS.

## BELL'S PALSY

### Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of Bell's palsy after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens alone or in combination. This one controlled study (Yih et al., 2009) contributed to the weight of epidemiologic evidence and is described below.

The study by Yih et al. (2009) was described in detail in the section on encephalitis or encephalopathy. This cohort study compared the incidence of cranial nerve disorders, including Bell's palsy, after Tdap vaccine to a historical Td comparison population. The observed number of cranial nerve disorders in the Tdap cohort (126 events) was greater than the historical Td cohort (100.8 events), which resulted in a relative risk of 1.25 (confidence interval not provided). The authors concluded that the risk of cranial nerve disorders following Tdap vaccination is not significantly higher than the risk following Td vaccination, which only provides information on the safety of the acellular pertussis antigen component.

### *Weight of Epidemiologic Evidence*

*The committee has limited confidence in the epidemiologic evidence, based on one study that lacked validity and precision, to assess an association between acellular pertussis vaccine and Bell's palsy.*

*The epidemiologic evidence is insufficient or absent to assess an association between diphtheria toxoid or tetanus toxoid vaccine and Bell's palsy.*

### **Mechanistic Evidence**

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of Bell's palsy after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens alone or in combination.

### *Weight of Mechanistic Evidence*

While rare, infection with *Clostridium tetani* or *Corynebacterium diphtheria* has been associated with facial nerve palsy (MacGregor, 2010; Reddy and Bleck, 2010). The committee considers the effects of natural infection one type of mechanistic evidence.

*The committee assesses the mechanistic evidence regarding an association between diphtheria toxoid or tetanus toxoid vaccine and Bell's palsy as weak based on knowledge about the natural infection.*

*The committee assesses the mechanistic evidence regarding an association between acellular pertussis vaccine and Bell's palsy as lacking.*

### **Causality Conclusion**

**Conclusion 10.16:** The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid–, tetanus toxoid–, or acellular pertussis–containing vaccine and Bell's palsy.

## ANAPHYLAXIS

### Epidemiologic Evidence

The committee reviewed eight studies to evaluate the risk of anaphylaxis after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, or acellular pertussis antigens alone or in combination. These eight studies (Bohlke et al., 2003; Gold et al., 1999; Jackson et al., 2009; Jacobs et al., 1982; Korger et al., 1986; Kuno-Sakai and Kimura, 2003; Nakayama et al., 1999; Thierry-Carstensen et al., 2004) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems or lacked unvaccinated comparison populations.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and anaphylaxis.*

### Mechanistic Evidence

The committee identified 11 publications describing clinical, diagnostic, or experimental evidence of anaphylaxis after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens alone or in combination. Two publications reported a temporal association between administration of a tetanus containing vaccine and development of symptoms, but the committee did not consider the symptoms to be definitive anaphylaxis (Bohlke et al., 2003; Chanukoglu et al., 1975). Four publications reported anaphylaxis after vaccination but did not report a time frame between vaccination and development of symptoms (Nakayama and Onoda, 2007; Peng and Jick, 2004; Pollock and Morris, 1983; Thierry-Carstensen et al., 2004). These publications did not contribute to the weight of mechanistic evidence.

Described below are five publications that contributed to the weight of mechanistic evidence.

Bhatia (1985) described a 12-year-old boy presenting with a deep wound on a lower limb. Due to a family history of allergy, a test dose of a 1:10 dilution of tetanus toxoid was administered intradermally. Within a few minutes the patient developed local pain and itching increasing to generalized urticaria, a rapid thready pulse, and severe bronchospasm.

Bilyk and Dubchik (1978) described the case of a 38-year-old patient



presenting with a laceration to the right hand. Two to three minutes after receiving purified and adsorbed tetanus toxoid the patient developed dizziness, tinnitus, nausea, vomiting, erythematous skin rash, tachycardia, and breathing difficulty.

Mandal and colleagues (1980) described the case of a 21-year-old woman (case 1) presenting with restlessness, itching over the tongue initially and then the whole body, a sensation of warmth, inspiratory difficulty with rhonchi, tightness in the throat with voice change, pain in the lower back and abdomen, erythema and swelling of the face and neck, and an urticarial rash on the limbs 2 to 3 minutes after receiving the second dose of a tetanus toxoid vaccine.

Mansfield and colleagues (1986) describe two cases of anaphylaxis after exposure to a tetanus toxoid vaccine. Case 1 describes a 33-year-old woman presenting with a severe anaphylactic reaction involving wheezing, facial edema, and peripheral urticaria 5 minutes after skin prick testing to full-strength tetanus toxoid. The patient was treated with epinephrine, corticosteroids, and antihistamines. Furthermore, at the age of 4 years the patient developed an urticarial rash and fever after receiving tetanus toxoid and tetanus antitoxin. Case 2 (case 3 in the publication) describes a 23-year-old highly atopic man who collapsed after experiencing wheezing and generalized itching after skin prick testing with full-strength tetanus toxoid.

Zaloga and Chernow (1982) reported the case of a 20-year-old man presenting with dyspnea, wheezing, lightheadedness, stridor, and the loss of consciousness within minutes of receiving purified fluid tetanus toxoid. The patient recovered after treatment with two doses of epinephrine and diphenhydramine hydrochloride.

### *Weight of Mechanistic Evidence*

The publications, described above, presented clinical evidence sufficient for the committee to conclude the vaccine was a contributing cause of anaphylaxis after administration of a tetanus toxoid vaccine. The clinical descriptions establish a strong temporal relationship between administration of a tetanus toxoid vaccine and anaphylaxis. In addition, two publications reported the development of symptoms after either skin prick or intradermal testing with either a full strength or dilution of a tetanus toxoid vaccine suggesting the presence of IgE to one or more components in the vaccine.

*The committee assesses the mechanistic evidence regarding an association between tetanus toxoid vaccine and anaphylaxis as strong based on six cases presenting temporality and clinical symptoms consistent with anaphylaxis.*

*The committee assesses the mechanistic evidence regarding an association between diphtheria toxoid or acellular pertussis vaccine and anaphylaxis as lacking.*

### Causality Conclusion

**Conclusion 10.17:** The evidence convincingly supports a causal relationship between tetanus toxoid vaccine and anaphylaxis.

**Conclusion 10.18:** The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid or acellular pertussis vaccine and anaphylaxis.

## CHRONIC URTICARIA

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of chronic urticaria after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, or acellular pertussis antigens alone or in combination.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and chronic urticaria.*

### Mechanistic Evidence

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of chronic urticaria after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens alone or in combination.

#### *Weight of Mechanistic Evidence*

Autoantibodies, complement activation, IgE hypersensitivity, and molecular mimicry may contribute to the development of chronic urticaria; however, the committee did not identify literature reporting evidence of these mechanisms after administration of vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens alone or in combination.

*The committee assesses the mechanistic evidence regarding an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and chronic urticaria as lacking.*

### Causality Conclusion

**Conclusion 10.19:** The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and chronic urticaria.

## SERUM SICKNESS

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of serum sickness after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, or acellular pertussis antigens alone or in combination.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and serum sickness.*

### Mechanistic Evidence

The committee identified one publication reporting clinical, diagnostic, or experimental evidence of serum sickness after the administration of vaccines containing diphtheria toxoid and tetanus toxoid antigens alone or in combination. Daschbach (1972) described a 7-year-old boy presenting with typical serum sickness 3 days after administration of a diphtheria and tetanus toxoid vaccine while being treated for a burn. The patient was treated with corticosteroids and antihistamines. Laboratory examination of the patient's serum revealed precipitins for tetanus but not diphtheria.

#### *Weight of Mechanistic Evidence*

The publication did not present clinical evidence sufficient for the committee to conclude the vaccine may be a contributing cause of serum sickness after administration of a diphtheria toxoid and tetanus toxoid vaccine. The presence of precipitins to tetanus could cause immune complexes in vivo, which are a known mechanism of serum sickness. In addition,

complement activation may contribute to the symptoms of serum sickness; however, the publication did not provide evidence linking these mechanisms to diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine.

*The committee assesses the mechanistic evidence regarding an association between diphtheria toxoid or tetanus toxoid vaccine and serum sickness as weak based on one case.*

*The committee assesses the mechanistic evidence regarding an association between acellular pertussis vaccine and serum sickness as lacking.*

### Causality Conclusion

**Conclusion 10.20:** The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and serum sickness.

## ARTHROPATHY

### Epidemiologic Evidence

The committee reviewed three studies to evaluate the risk of arthropathy after the administration of vaccines containing diphtheria toxoid and tetanus toxoid antigens alone or in combination. One study (Stetler et al., 1985) was not considered in the weight of epidemiologic evidence because it provided data from a passive surveillance system and lacked an unvaccinated comparison population.

Two controlled studies (Bengtsson et al., 2010; Pattison et al., 2008) were included in the weight of epidemiologic evidence and are described below.

Pattison et al. (2008) conducted a case-control study in 98 patients with psoriatic arthritis and 163 psoriasis controls in the United Kingdom. The cases were identified through a nationwide campaign and confirmed by local consultant rheumatologists, whereas controls were recruited from the Psoriasis Clinic at the Dermatology Centre, Hope Hospital, Salford. A self-report questionnaire was sent to the cases and controls to assess exposures in the 10 years before disease onset; 64.9 percent of the cases and 50.0 percent of the controls responded to the questionnaire. The authors reported an increased risk of psoriatic arthritis after tetanus toxoid vaccination (OR, 1.91; 95% CI, 1.0–3.7).

Bengtsson et al. (2010) conducted a case-control study in adults living

in parts of Sweden from May 1996 through June 2006. The cases were diagnosed with rheumatoid arthritis by a rheumatologist and were identified at rheumatology units in Sweden. Controls were selected from the national population register and matched to cases on age, sex, and residential area. A questionnaire was given to the cases and controls to report vaccination histories in the 5 years before disease onset. A total of 1,998 (95 percent) cases and 2,252 (81 percent) controls completed the questionnaire and were included in the analysis. The major weakness of the study was that it employed no independent verification of reported immunizations, and past studies have suggested that many people do not keep careful written records nor do they have accurate memories of past immunizations. The odds ratio for rheumatoid arthritis diagnosis within 5 years of administration of tetanus toxoid vaccine was 1.0 (95% CI, 0.8–1.2) and diphtheria vaccine was 1.0 (95% CI, 0.7–1.4). The authors concluded that tetanus toxoid or diphtheria vaccination does not increase the risk of rheumatoid arthritis. Apparently, combination vaccines with pertussis antigen were not studied.

#### *Weight of Epidemiologic Evidence*

The two studies described above had serious limitations and low precision. One study by Pattison et al. (2008) found an association with tetanus toxoid vaccine in a small subgroup—individuals with psoriasis; thus the results could not be generalized to all adults. The study by Bengtsson et al. (2010) found no association with tetanus toxoid or diphtheria vaccine, but it relied on subject self-report to determine immunization status. Also, there was no assessment of pertussis antigen exposure, which is a component of many vaccines for diphtheria and tetanus toxoid administered in the United States. The committee did not identify any controlled studies that investigated the risk of arthritis and DTaP vaccine, or the risk of arthralgia and tetanus toxoid-containing vaccines. Therefore, the weight of epidemiologic evidence has a narrow focus. See Table 10-4 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has limited confidence in the epidemiologic evidence, based on two studies that lacked validity and precision, to assess an association between diphtheria toxoid or tetanus toxoid vaccine and chronic arthritis.*

*The epidemiologic evidence is insufficient or absent to assess an association between acellular pertussis vaccine and arthropathy.*

**TABLE 10-4** Studies Included in the Weight of Epidemiologic Evidence for Diphtheria Toxoid-, Tetanus Toxoid-, and Acellular Pertussis-Containing Vaccines and Arthropathy

| Citation               | Operationally Defined Outcome   | Study Setting   | Defined Study Population  | Study Design | Sample Size   | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)                          | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|------------------------|---|---|---|--------------|---|---|---|--|
| Pattison et al. (2008) | Self-report tetanus toxoid vaccination within 10 years of disease onset | United Kingdom; cases identified through nationwide campaign and controls recruited from Psoriasis Clinic at the Dermatology Centre, Hope Hospital, Salford | Cases had psoriatic arthritis diagnosis confirmed by local consultant rheumatologists | Case control | 98 patients with psoriatic arthritis<br>163 control patients with psoriasis | OR for psoriatic arthritis diagnosis after tetanus toxoid vaccination: 1.91 (95% CI, 1.0–3.7) | None described                                      | Serious  |

*continued*

TABLE 10-4 Continued

| Citation                | Operationally Defined Outcome   | Study Setting   | Defined Study Population   | Study Design   | Sample Size  | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)                                      | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|-------------------------|---|---|--|--|--|---|---|--|
| Bengtsson et al. (2010) | Self-report tetanus toxoid or diphtheria toxoid vaccination within 5 years of disease onset | Sweden from 5/1996 through 6/2002<br>Cases were identified at rheumatology units in Sweden and controls were selected from the national population register | Cases were diagnosed with rheumatoid arthritis by a rheumatologist | Case control<br>Controls matched on age, sex, and residential area | 1,998 patients with rheumatoid arthritis<br>2,252 controls | OR for rheumatoid arthritis diagnosis within 5 years of tetanus toxoid vaccination: 1.0 (95% CI, 0.8–1.2) | None described                                      | Serious  |

<sup>a</sup> The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup> The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup> Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.

### Mechanistic Evidence

The committee identified 12 publications reporting arthropathy after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens alone or in combination. Sidebotham and Lenton (1996) did not provide clinical, diagnostic, or experimental evidence of causality, including the latency between administration of a diphtheria and tetanus toxoid vaccine and development of joint aches after vaccination. Eleven publications did not provide evidence beyond temporality (Aksu et al., 2006; Cassidy et al., 2005; David et al., 2006; Gasparini et al., 2010; Hong et al., 2000; Jawad and Scott, 1989; Kaul et al., 2002; Pichichero et al., 2005; Pou et al., 2008; Sahin et al., 2009; Zimmerman and Pellitieri, 1994). In addition, four publications reported the concomitant administration of vaccines, making it difficult to determine which, if any, vaccine could have been the precipitating event (Aksu et al., 2006; Cassidy et al., 2005; Gasparini et al., 2010; Pou et al., 2008). The publications did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

The symptoms described in the publications referenced above are consistent with those of arthropathy. Autoantibodies, T cells, complement activation, immune complexes, and infection may contribute to arthropathy; however, the publications did not provide evidence linking these mechanisms to diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine.

*The committee assesses the mechanistic evidence regarding an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and arthropathy as lacking.*

### Causality Conclusion

**Conclusion 10.21:** The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and arthropathy.

## TYPE 1 DIABETES

### Epidemiologic Evidence

The committee reviewed five studies to evaluate the risk of type 1 diabetes after the administration of vaccines containing diphtheria toxoid,



tetanus toxoid, and acellular pertussis antigens alone or in combination. These five controlled studies (Blom et al., 1991; DeStefano et al., 2001; Hviid et al., 2004; Klein et al., 2010; Patterson, 2000) contributed to the weight of epidemiologic evidence and are described below.

Blom et al. (1991) conducted a case-control study in diabetic children (0 to 14 years of age) enrolled in the Swedish Childhood Diabetes Register from September 1985 through August 1986. A total of 393 children with type 1 diabetes were matched to 786 controls (two controls for each case matched on age, sex, and county) from the official Swedish population register. The dates of vaccination were ascertained from questionnaires that were sent to the parents of cases and their matched controls within 4 weeks of disease diagnosis. Questionnaires were returned for 86 percent of the cases and 67 percent of the controls. There were no systematic differences in the age, sex, and county categories of those that returned the questionnaire compared to those that did not, but other factors that were not reported in the study could suggest selection bias. Self-report vaccination data were compared to vaccination records from the local child health care centers and school health units. The authors were able to validate the vaccination status of 88.5 percent and 82.1 percent of the cases and controls, respectively. Since the relative risk ratio of matched and unmatched data remained close to 1, the case and control matching was removed to avoid losing information during the analysis. The odds ratio for type 1 diabetes diagnosis any time after vaccination with combined diphtheria and tetanus toxoids vaccine is 0.96 (95% CI, 0.71–1.30), and for tetanus toxoid vaccine it is 0.96 (95% CI, 0.70–1.31). The authors concluded that combined diphtheria and tetanus toxoids vaccination, or tetanus toxoid vaccination, does not increase the risk of type 1 diabetes in children.

Patterson et al. (2000) conducted a case-control study in children (under 15 years of age) with type 1 diabetes enrolled at the seven centers participating in the European Diabetes: Aetiology of Childhood Diabetes on an Epidemiological Basis (EURODIAB ACE) Group from 1989 through 1995. Controls were selected at each center from population registers, general practitioners' lists, or school rolls, and matched to cases by age. Of the 1,028 cases and 3,044 controls invited to participate in the study, 900 (87.5 percent) and 2,302 (75.6) responded, respectively. The authors did not provide any information on the nonresponders. Vaccination data were obtained from parent interviews or questionnaires depending on the center, and were validated with official records or child health care booklets in 74 percent of the cases and 78 percent of the controls. A diagnosis date was assigned to each control based on the midpoint of the recruitment period for the corresponding diabetic child. The Mantel Haenszel approach was used to stratify the analysis by center; the odds ratio for type 1 diabetes diagnosis any time after tetanus toxoid vaccination was 1.20 (95% CI,

0.66–2.19), and any time after diphtheria toxoid vaccination it was 1.09 (95% CI, 0.62–1.93). A logistic regression analysis was used to adjust for confounding variables; the odds ratio for type 1 diabetes diagnosis any time after tetanus toxoid vaccination was 1.56 (95% CI, 0.73–3.33), and any time after diphtheria toxoid vaccination it was 1.27 (95% CI, 0.63–2.56). The authors concluded that administration of tetanus toxoid or diphtheria toxoid vaccine does not increase the risk of type 1 diabetes in children.

DeStefano et al. (2001) conducted a case-control study in children (10 months to 10 years of age) enrolled in four HMOs participating in the VSD. A total of 252 type 1 diabetes cases and 768 matched controls were included in the analysis. The study required participants to be born in 1988 through 1997, enrolled in the HMO since birth, and continuously enrolled for the first 6 months of life. Additionally, cases had to be enrolled at least 12 months before the diabetes diagnosis except when diagnosis occurred before 12 months of age. The case index date was defined as the first date of type 1 diabetes diagnosis in the medical record; controls were assigned the same index date as their matched case. At least three controls were matched to each case on sex, date of birth (within 7 days), HMO, and length of enrollment in the HMO (up to the index date). Trained chart abstractors obtained complete vaccination histories from the medical records of the cases and controls. Acellular pertussis vaccination was introduced in the later years of the study, and only 23 percent of the cases and controls received the vaccine. The results of two conditional logistic regression models were provided: model 1 stratified by the matching variables; model 2 stratified by the matching variables and race, ethnicity, and family history of type 1 diabetes (additional variables also obtained from medical records). The odds ratio for diabetes diagnosis any time after acellular pertussis vaccination using model 1 was 0.92 (95% CI, 0.53–1.57), and using model 2 it was 1.12 (95% CI, 0.63–1.99). The authors concluded that vaccination with acellular pertussis does not increase the risk of type 1 diabetes in children.

Hviid et al. (2004) conducted a retrospective cohort study in children born from January 1990 through December 2000 and who resided in Denmark through December 2001 (end of study period). The participants were identified in the Danish Civil Registration System, and linked to information on type 1 diabetes diagnoses in the Danish National Hospital Register and vaccination data from the National Board of Health. The children were followed from birth and removed from the study at the first occurrence of an outcome of interest. The study outcomes included diagnosis of type 1 diabetes, loss to follow-up or emigration, reaching 12 years of age, and death. Vaccination status was considered a time-varying variable and was classified according to the number of doses administered (zero, one, two, or three doses of each vaccine). A total of 739,694 children were included in the study, of whom 16,421 were prematurely removed from the analysis

because of loss to follow-up, emigration, or death. The rate ratio for type 1 diabetes diagnosis any time after at least one dose of combined DTaP-IPV vaccine (compared to the unvaccinated) was 0.96 (95% CI, 0.71–1.30). The study also evaluated the rate ratios of diabetes diagnosis 1, 2, 3, 4, and > 4 years after DTaP-IPV vaccination and found no significant differences. The authors concluded that DTaP-IPV vaccination does not increase the risk of type 1 diabetes in children.

Klein et al. (2010) conducted a cohort study in children (10 to 18 years of age) enrolled in the Northern California Kaiser Permanente (NCKP) Health Care Plan. Children who received a Tdap vaccination during September 2005 through December 2006 were included in the analysis and monitored for type 1 diabetes diagnoses for the 6 months following vaccination (ending in June 2007). To identify new cases of diabetes, no diagnoses could appear in the medical records during the year before vaccination. The study identified a historical NCKP comparison cohort who received a Td vaccination from June 2002 through September 2005, and was matched to the Tdap cohort on age, sex, geographic location, and season of vaccination. Each cohort included 12,509 children for a total of 25,018 study participants. The matched odds ratio for type 1 diabetes diagnosis within 6 months following Tdap vaccination (compared to type 1 diabetes within 6 months of Td vaccination) was 0.333 (95% CI, 0.006–4.151). However, only one event and three events of diabetes were observed in the Tdap and Td cohorts, respectively, which resulted in low statistical power to detect an association. The authors concluded that Tdap vaccination does not increase the risk of type 1 diabetes in children compared to Td vaccination, which only provides information on the safety of the acellular pertussis antigen component.

### *Weight of Epidemiologic Evidence*

The five observational studies consistently report no increased risk of type 1 diabetes following vaccination with diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens alone or in combination; two studies had negligible limitations (Patterson et al., 2000; Hviid et al., 2004). The five studies had relatively large sample sizes and were representative of European and U.S. populations of children across a broad range of ages and varying time periods at risk of type 1 diabetes following vaccination. See Table 10-5 for a summary of the studies that contributed to the weight of epidemiologic evidence.

*The committee has a high degree of confidence in the epidemiologic evidence based on five studies with validity and precision to assess an association between diphtheria toxoid-, tetanus toxoid-, or*

**TABLE 10-5** Studies Included in the Weight of Epidemiologic Evidence for Diphtheria Toxoid-, Tetanus Toxoid-, and Acellular Pertussis-Containing Vaccines and Type 1 Diabetes

| Citation           | Operationally Defined Outcome                                       | Study Setting | Defined Study Population   | Study Design | Sample Size   | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)   | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|--------------------|---|---------------|--|--------------|---|--|---|--|
| Blom et al. (1991) | Type 1 diabetes reported to the Swedish Childhood Diabetes Register | Sweden        | Children aged 0–14 years<br>Cases were enrolled in the Swedish Childhood Diabetes Register | Case-control | 393 children with type 1 diabetes<br>786 controls matched on age, sex, and county | OR for type 1 diabetes diagnosis any time after combined diphtheria and tetanus toxoid vaccination: <b>0.96 (95% CI, 0.71–1.30)</b><br>OR for type 1 diabetes diagnosis any time after tetanus toxoid vaccination: <b>0.96 (95% CI, 0.70–1.31)</b> | None described                                      | Serious  |

*continued*

TABLE 10-5 Continued

| Citation                | Operationally Defined Outcome                       | Study Setting  | Defined Study Population  | Study Design | Sample Size  | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)   | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|-------------------------|---|--|---|--------------|--|--|---|--|
| Patterson et al. (2000) | Type 1 diabetes diagnosed by the EURODIAB ACE Group | Europe (Austria, Latvia, Lithuania, Luxembourg, Romania, United Kingdom) | Children under 15 years of age enrolled at seven centers participating in the EURODIAB ACE Group from 1989 through 1995 | Case-control | 900 children with type 1 diabetes<br>2,302 controls matched on age | OR for type 1 diabetes diagnosis any time after tetanus toxoid vaccination using the Mantel Haenszel approach:<br><b>1.20 (95% CI, 0.66–2.19; <i>p</i> = .55)</b><br><br>OR for type 1 diabetes diagnosis any time after diphtheria toxoid vaccination using the Mantel Haenszel approach:<br><b>1.09 (95% CI, 0.62–1.93; <i>p</i> = .76)</b><br><br>OR for type 1 diabetes diagnosis any time after tetanus toxoid vaccination using a logistic regression analysis:<br><b>1.65 (95% CI, 0.73–3.33; <i>p</i> = .26)</b><br><br>OR for type 1 diabetes diagnosis any time after diphtheria toxoid vaccination using a logistic regression analysis:<br><b>1.27 (95% CI, 0.63–2.56; <i>p</i> = .51)</b> | None described                                      | Negligible                                       |

|                         |  |                                    |   |                      |   |  |                |            |
|-------------------------|--|------------------------------------|---|----------------------|---|--|----------------|------------|
| DeStéfano et al. (2001) | First date of type 1 diabetes diagnosis in the medical record      | Four HMOs participating in the VSD | Children born from 1988 through 1997, ages 10 months to 10 years                    | Case-control         | 252 children with type 1 diabetes<br>768 controls matched on sex, date of birth, HMO, and length of enrollment in the HMO | OR for type 1 diabetes diagnosis any time after acellular pertussis vaccination using Model 1: <b>0.92 (95% CI, 0.53–1.57)</b><br>OR for type 1 diabetes diagnosis any time after acellular pertussis vaccination using Model 2: <b>1.12 (95% CI, 0.63–1.99)</b> | None described | Serious    |
| Hviid et al. (2004)     | Type 1 diabetes diagnosis in the Danish National Hospital Register | Denmark                            | Children born from 1/1/1990 through 12/31/2000, residing in Denmark through 12/2001 | Retrospective cohort | 739,694 children  | Rate ratio for type 1 diabetes diagnosis any time after at least one dose of combined DTap-IPV vaccine compared to the unexposed: <b>0.96 (95% CI, 0.71–1.30)</b>  | None described | Negligible |

*continued*

TABLE 10-5 Continued

| Citation            | Operationally Defined Outcome                                   | Study Setting         | Defined Study Population     | Study Design   | Sample Size   | Primary Effect Size Estimate <sup>a</sup> (95% CI or <i>p</i> value)   | Heterogeneous Subgroups at Higher Risk <sup>b</sup> | Limitations (Negligible or Serious) <sup>c</sup> |
|---------------------|---|-----------------------|------------------------------|--|---|--|---|--|
| Klein et al. (2010) | Type 1 diabetes diagnosis within 6 months following vaccination | NCKP Health Care Plan | Children ages 10 to 18 years | Cohort<br>Children who received a Tdap vaccination from 9/2005 through 12/2006 were enrolled in Tdap cohort<br>Children who received a Td vaccination from 6/2002 through 9/2005 were enrolled in historical Td cohort | 12,509 children from Tdap cohort<br>12,509 children from Td cohort<br>matched on age, sex, geographic location, and season of vaccination | OR for type 1 diabetes diagnosis within 6 months following Tdap vaccination (compared to Td vaccination):<br>0.333 (95% CI, 0.006–4.151) | None described                                      | Serious  |

<sup>a</sup> The committee assumed statistical significance below the conventional 0.05 level unless otherwise stated by the authors.

<sup>b</sup> The risk/effect estimate for the subgroup/alternate definition of exposure or outcome differs significantly (e.g., is heterogeneous with nonoverlapping 95% confidence intervals) compared with the risk/effect estimate reported for the primary group/definition.

<sup>c</sup> Studies designated as serious had more methodological limitations than those designated as negligible. Studies assessed as having very serious limitations were not considered in the weight of epidemiologic evidence.

*acellular pertussis-containing vaccine and type 1 diabetes; these studies consistently report a null association.*

### Mechanistic Evidence

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of type 1 diabetes after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens alone or in combination.

#### *Weight of Mechanistic Evidence*

Autoantibodies, T cells, complement activation, and molecular mimicry may contribute to the symptoms of type 1 diabetes; however, the committee did not identify literature reporting evidence of these mechanisms after administration of vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens alone or in combination.

*The committee assesses the mechanistic evidence regarding an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and type 1 diabetes as lacking.*

### Causality Conclusion

**Conclusion 10.22:** The evidence favors rejection of a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and type 1 diabetes.

## MYOCARDITIS

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of myocarditis after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, or acellular pertussis antigens alone or in combination.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and myocarditis.*



### Mechanistic Evidence

The committee identified five publications reporting myocarditis developing after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens alone or in combination. The publications did not provide evidence beyond temporality (Amsel et al., 1986; Dilber et al., 2003; Korger et al., 1986; Langsjoen and Stinson, 1965; Thanjan et al., 2007). In addition, two publications also reported the administration of additional vaccines, making it difficult to determine which, if any, vaccine could have been the precipitating event (Amsel et al., 1986; Thanjan et al., 2007). The publications did not contribute to the weight of mechanistic evidence.

#### *Weight of Mechanistic Evidence*

As many as two-thirds of patients infected with *Corynebacterium diphtheriae* develop evidence of myocarditis with 10–25 percent developing cardiac dysfunction correlating directly with the severity of local disease (MacGregor, 2010). Myocarditis is a prominent effect of the exotoxin released by *Corynebacterium diphtheriae* (MacGregor, 2010); however, the toxoid in the vaccine does not cause cellular toxicity.

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of myocarditis. Autoantibodies, complement activation, molecular mimicry, and T cells may contribute to the symptoms of myocarditis; however, the publications did not provide evidence linking these mechanisms to diphtheria toxoid–, tetanus toxoid–, or acellular pertussis–containing vaccine.

*The committee assesses the mechanistic evidence regarding an association between diphtheria toxoid vaccine and myocarditis as weak based on knowledge about the natural infection.*

*The committee assesses the mechanistic evidence regarding an association between tetanus toxoid or acellular pertussis vaccine and myocarditis as lacking.*

### Causality Conclusion

**Conclusion 10.23:** The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid–, tetanus toxoid–, or acellular pertussis–containing vaccine and myocarditis.

## FIBROMYALGIA

### Epidemiologic Evidence

No studies were identified in the literature for the committee to evaluate the risk of fibromyalgia after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, or acellular pertussis antigens alone or in combination.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and fibromyalgia.*

### Mechanistic Evidence

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of fibromyalgia after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, or acellular pertussis antigens alone or in combination.

#### *Weight of Mechanistic Evidence*

*The committee assesses the mechanistic evidence regarding an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and fibromyalgia as lacking.*

### Causality Conclusion

**Conclusion 10.24:** The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and fibromyalgia.

## SUDDEN INFANT DEATH SYNDROME

### Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of sudden infant death syndrome (SIDS) after the administration of DTaP vaccine. This one study (Geier and Geier, 2004) was not considered in the weight of epidemiologic evidence because it provided data from a passive surveillance system and lacked an unvaccinated comparison population.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and SIDS.*

**Mechanistic Evidence**

The committee identified three publications reporting SIDS after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens alone or in combination. The publications did not provide evidence beyond temporality (Balci et al., 2007; Pollock et al., 1984; Schmitt et al., 1996). In addition, Balci and colleagues (2007) reported the administration of additional vaccines, making it difficult to determine which, if any, vaccine could have been the precipitating event. Also, Schmitt et al. (1996) reported that the incidence of SIDS after administration of Infanrix was not higher than expected based on the incidence of SIDS in the general population. The publications did not contribute to the weight of mechanistic evidence.

*Weight of Mechanistic Evidence*

*The committee assesses the mechanistic evidence regarding an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and SIDS as lacking.*

**Causality Conclusion**

**Conclusion 10.25:** The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and SIDS.

**IMMUNE THROMBOCYTOPENIC PURPURA****Epidemiologic Evidence**

No studies were identified in the literature for the committee to evaluate the risk of immune thrombocytopenic purpura (ITP) after the administration of vaccines containing diphtheria toxoid, tetanus toxoid, or acellular pertussis antigens alone or in combination.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and ITP.*

**Mechanistic Evidence**

The committee identified two publications reporting ITP developing after administration of DTaP vaccine. Demircioglu and colleagues (2009) did not provide evidence of causality beyond a temporal relationship of less than 1 month between administration of diphtheria, tetanus, pertussis and oral polio vaccines and development of ITP in two patients, younger than 2 years of age, diagnosed from 1995 through 2007. During the study period diphtheria, tetanus, whole cell pertussis, and DTaP vaccines were administered, and the authors did not indicate which vaccine was administered prior to the development of ITP. Furthermore, the concomitant administration of vaccines make it difficult to determine which, if any, vaccine could have been the precipitating event. Hsieh and Lin (2010) reported one case of thrombocytopenic purpura developing 88 days after administration of the second dose of a hepatitis B vaccine and the first dose of a DTaP vaccine in a 3-month-old patient. The long latency between vaccine administration and development of symptoms make it impossible to rule out other possible causes. The publications did not contribute to the mechanistic weight of evidence.

*Weight of Mechanistic Evidence*

The symptoms described in the publications referenced above are consistent with those leading to a diagnosis of ITP. Autoantibodies, complement activation, immune complexes, and T cells may contribute to the symptoms of ITP; however, the publications did not provide evidence linking these mechanisms to diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine.

*The committee assesses the mechanistic evidence regarding an association between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and ITP as lacking.*

### Causality Conclusion

**Conclusion 10.26:** The evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid–, tetanus toxoid–, or acellular pertussis–containing vaccine and ITP.

### CONCLUDING SECTION

Table 10-6 provides a summary of the epidemiologic assessments, mechanistic assessments, and causality conclusions for diphtheria toxoid–, tetanus toxoid–, and acellular-pertussis-containing vaccines.

**TABLE 10-6** Summary of Epidemiologic Assessments, Mechanistic Assessments, and Causality Conclusions for Diphtheria Toxoid (DT)–, Tetanus Toxoid (TT)–, and Acellular Pertussis (aP)–Containing Vaccines

| Vaccine                  | Adverse Event    | Epidemiologic Assessment                      | Studies Contributing to the Epidemiologic Assessment | Mechanistic Assessment                        | Cases Contributing to the Mechanistic Assessment | Causality Conclusion |
|--------------------------|------------------|---|--|---|--|----------------------|
| DT, TT, or aP containing | Encephalitis     | Limited                                       | 2  | Weak  | 1  | Inadequate           |
| DT, TT, or aP containing | Encephalopathy   | Limited                                       | 2  | Weak  | 1  | Inadequate           |
| DT, TT, or aP containing | Infantile Spasms | Limited (diphtheria toxoid or tetanus toxoid) | 1  | Lacking                                       | None   | Inadequate           |
|                          |                  | Insufficient (acellular pertussis)            | None   |   |  |                      |
| DT, TT, or aP containing | Seizures         | Limited                                       | 3  | Weak (acellular pertussis)                    | None   | Inadequate           |
|                          |                  |   |  | Lacking (diphtheria toxoid or tetanus toxoid) | None   |                      |
| DT, TT, or aP containing | Ataxia           | Insufficient                                  | None   | Lacking                                       | None   | Inadequate           |
| DT, TT, or aP containing | Autism           | Insufficient                                  | None   | Lacking                                       | None   | Inadequate           |

*continued*

TABLE 10-6 Continued

| Vaccine                  | Adverse Event                        | Epidemiologic Assessment                                | Studies Contributing to the Epidemiologic Assessment | Mechanistic Assessment                             | Cases Contributing to the Mechanistic Assessment | Causality Conclusion |
|--------------------------|--------------------------------------|---|--|--|--|----------------------|
| DT, TT, or aP containing | Acute Disseminated Encephalomyelitis | Insufficient  | None   | Weak (tetanus toxoid)                              | 1  | Inadequate           |
| DT, TT, or aP containing | Transverse Myelitis                  | Insufficient  | None   | Lacking (diphtheria toxoid or acellular pertussis) | None   | Inadequate           |
| DT, TT, or aP containing | Optic Neuritis*                      | Limited (diphtheria toxoid or tetanus toxoid)           | 1  | Lacking  | None   | Inadequate           |
| DT, TT, or aP containing | Multiple Sclerosis Onset in Adults   | Insufficient (acellular pertussis)                      | None   | Lacking  | None   | Inadequate           |
| DT, TT, or aP containing | Multiple Sclerosis Relapse in Adults | Limited (diphtheria toxoid or tetanus toxoid)           | 2  | Lacking  | None   | Inadequate           |
| DT, TT, or aP containing | Multiple Sclerosis Relapse in Adults | Insufficient (acellular pertussis)                      | None   | Lacking  | None   | Inadequate           |
| DT, TT, or aP containing | Multiple Sclerosis Relapse in Adults | Limited (tetanus toxoid)                                | 1  | Lacking  | None   | Inadequate           |
| DT, TT, or aP containing | Multiple Sclerosis Relapse in Adults | Insufficient (diphtheria toxoid or acellular pertussis) | None   | Lacking  | None   | Inadequate           |

|                          |  |  |           |   |           |                       |
|--------------------------|--|--|-----------|---|-----------|-----------------------|
| DT, TT, or aP containing | Multiple Sclerosis Relapse in Children           | Limited (DT or TT)<br>Insufficient (acellular pertussis) | 1<br>None | Lacking   | None      | Inadequate            |
| DT, TT, or aP containing | Guillain-Barré Syndrome                          | Insufficient   | None      | Lacking   | None      | Inadequate            |
| DT, TT, or aP containing | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient   | None      | Lacking   | None      | Inadequate            |
| DT, TT, or aP containing | Opsoclonus Myoclonus Syndrome                    | Insufficient   | None      | Lacking   | None      | Inadequate            |
| DT, TT, or aP containing | Bell's Palsy                                     | Limited (acellular pertussis)                            | 1         | Weak (diphtheria toxoid or tetanus toxoid)                                  | None      | Inadequate            |
|                          |  | Insufficient (diphtheria toxoid or tetanus toxoid)       | None      | Lacking (acellular pertussis)   | None      |                       |
| TT                       | Anaphylaxis                                      | Insufficient   | None      | Strong  | 6         | Convincingly Supports |
| DT or aP                 | Anaphylaxis                                      | Insufficient   | None      | Lacking   | None      | Inadequate            |
| DT, TT, or aP containing | Chronic Urticaria                                | Insufficient   | None      | Lacking   | None      | Inadequate            |
| DT, TT, or aP containing | Serum Sickness                                   | Insufficient   | None      | Weak (diphtheria toxoid or tetanus toxoid)<br>Lacking (acellular pertussis) | 1<br>None | Inadequate            |

*continued*



TABLE 10-6 Continued

| Vaccine                  | Adverse Event                   | Epidemiologic Assessment                      | Studies Contributing to the Epidemiologic Assessment | Mechanistic Assessment                          | Cases Contributing to the Mechanistic Assessment | Causality Conclusion |
|--------------------------|---------------------------------|---|--|---|--|----------------------|
| DT, TT, or aP containing | Arthropathy                     | Limited (diphtheria toxoid or tetanus toxoid) | 2  | Lacking   | None   | Inadequate           |
|                          |                                 | Insufficient (acellular pertussis)            | None   |   |  |                      |
| DT, TT, or aP containing | Type 1 Diabetes                 | High (null)                                   | 5  | Lacking   | None   | Favors Rejection     |
| DT, TT, or aP containing | Myocarditis                     | Insufficient                                  | None   | Weak (diphtheria toxoid)                        | None   | Inadequate           |
|                          |                                 |   |  | Lacking (tetanus toxoid or acellular pertussis) | None   |                      |
| DT, TT, or aP containing | Fibromyalgia                    | Insufficient                                  | None   | Lacking   | None   | Inadequate           |
| DT, TT, or aP containing | Sudden Infant Death Syndrome    | Insufficient                                  | None   | Lacking   | None   | Inadequate           |
| DT, TT, or aP containing | Immune Thrombocytopenic Purpura | Insufficient                                  | None   | Lacking   | None   | Inadequate           |

\*Although not originally charged to the committee by the sponsor, the committee considered this adverse event in its review of the literature.

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## 11

## Meningococcal Vaccine

## INTRODUCTION

Meningococcal disease describes the clinical manifestations of invasive infection with the gram-negative bacteria *Neisseria meningitides*. *N. meningitides* (meningococcus) colonizes the human nasopharynx and is transmitted through direct contact with respiratory secretions or aerosolized droplets of respiratory fluids (Granoff et al., 2008). Carried by approximately 10 percent of the population, meningococcus is generally a communal organism and invasive disease relies on a combination of host factors and strain qualities (Granoff et al., 2008). In the United States in 2004, 1,400–2,800 cases of invasive meningococcal disease were reported (CDC, 2005).

Common symptoms of meningococcal infection include meningitis, headache, fever, stiffness of the neck, nausea, vomiting, photophobia, and altered mental status (Granoff et al., 2008). Meningococemia (meningococcal sepsis) occurs in 10 to 20 percent of cases and is characterized by abrupt fever and a rash that may progress to purpura fulminans (Granoff et al., 2008). Meningococemia is associated with hypotension, acute adrenal hemorrhage (Waterhouse-Friderichsen syndrome), and multiorgan failure (Granoff et al., 2008). Pneumonia is also associated with meningococcal disease and occurs in 6 to 15 percent of patients (Racoosin et al., 1998; Rosenstein et al., 1999). Additionally, conjunctivitis, otitis media, epiglottitis, arthritis, urethritis, and pericarditis may occur because of invasive infection; however, these developments are rare (Apicella, 2010; Miller et al., 1979; Rosenstein et al., 1999; Schaad, 1980).

The risk of meningococcal disease is higher among asplenic individuals and those with deficiencies in the terminal common complement pathway of the immune system (CDC, 2005). Additionally, prior viral infection, crowding, active and passive smoking, attending bars or nightclubs, and imbibing in alcohol are all associated with higher risk of meningococcal disease (CDC, 2005).

Prior to the development of antibiotics, approximately 70 to 85 percent of cases of meningococcal disease were fatal (Granoff et al., 2008). With the introduction of antibiotics, the case-fatality rate has dropped to nearly 30 percent worldwide and 10–14 percent in the United States (CDC, 2005; Granoff et al., 2008). Ten to 20 percent of meningococcal disease survivors experience permanent sequelae such as limb loss, hearing loss, neurologic disability, and scarring (Granoff et al., 2008).

Meningococcus has been grouped into at least 13 different groups based on serological differences in the surface polysaccharides (Apicella, 2010). Of these, five serogroups—A, B, C, W-135, and Y—are responsible for almost all instances of meningococcal disease (Granoff et al., 2008). Group A meningococcus produces the majority of disease in the “meningitis belt” of sub-Saharan Africa but causes less than 0.3 percent of cases in the United States and Europe (Granoff et al., 2008). Serogroup W-135 was known to cause rare disease until demonstration of W-135 meningococcus in outbreaks in 2000 and 2001 during the Hajj in Mecca, Saudi Arabia (Granoff et al., 2008). In the United States, the majority of meningococcal disease is caused by serogroups B, C, and Y (Granoff et al., 2008). Serogroup B causes more than 50 percent of disease in infants less than 1 year old, and 75 percent of disease in individuals greater than 11 years is caused by serogroups C, Y, or W-135 (CDC, 2005).

Although various vaccines against meningococcal disease have been available for more than 30 years, currently there is no vaccine to protect against all five of the pathogenic serogroups. During the early 1900s, attempts were made to develop inactivated whole-cell vaccine, but this direction was abandoned due to ambiguous efficacy results and high rates of reactogenicity (Gates, 1918; Granoff et al., 2008; Sophian and Black, 1912; Underwood, 1940). The immunogenicity of exotoxin-containing culture filtrates was explored in the 1930s (Ferry and Steele, 1935; Kuhns et al., 1938). The development of antibiotics provided a more effective means to combat meningococcal infection. During the 1940s, it was demonstrated that inoculation with group-specific polysaccharides produced immunogenicity in mice (Scherp and Rake, 1945), but similar inoculation failed to produce the results in humans (Kabat et al., 1944; Watson and Scherp, 1958). It was later determined that the polysaccharide antigens capable of causing immunogenicity in humans were of a higher molecular weight than those used by Scherp and Rake (Gotschlich et al., 1972; Kabat and

Bezer, 1958). In the late 1960s, Gotschlich and his colleagues developed a purification process capable of isolating heavier antigens, and this became the basis of current polysaccharide vaccines (Gotschlich et al., 1969). These vaccines, including the Food and Drug Administration–licensed Menomune (Sanofi Pasteur, Inc.), produce a T cell–independent response and therefore are not very effective in young children and do not produce a booster effect at any age (Granoff et al., 2008). In the 1980s, researchers demonstrated that by conjugating polysaccharides to protein carriers, a T cell–dependent immune response could be induced (Anderson et al., 1985; Robbins et al., 1996). This was significant because polysaccharide vaccines do not induce T-dependent immunity (Kelly et al., 2005, 2006) and therefore do not confer lasting immunity or significant reduction of meningococcus carriage or transmission. In 2005, a tetravalent conjugate vaccine was licensed in the United States and approved for use in persons 11–55 years old (CDC, 2005).

Currently, there are two types of meningococcal vaccines available in the United States: polysaccharide and conjugate. Meningococcal polysaccharide vaccines (MPSVs) are available worldwide in bivalent (A and C) and tetravalent (A, C, W-135, and Y) formulations, but only the tetravalent MPSV4 Menomune-A/C/Y/W-135 (Sanofi Pasteur) is licensed in the United States. Menomune contains 50 µg each of lyophilized powder that is reconstituted prior to administration with sterile, pyrogen-free distilled water without preservative in the single-dose presentation and with sterile, pyrogen-free distilled water and thimerosal, a mercury derivative added as a preservative in the multidose presentation (Sanofi Pasteur, Inc., 2009). Two quadrivalent conjugate vaccines, Menectra (Sanofi Pasteur) and Menveo (Novartis Vaccines and Diagnostics) are licensed in the United States. Menectra, licensed in 2005, contains 4 µg each of the capsular polysaccharide for the four serogroups conjugated to 48 µg of diphtheria toxoid (Sanofi Pasteur, Inc., 2011). It is provided in a single-dose vial and contains no added preservative or adjuvant (Sanofi Pasteur, Inc., 2011). Menveo, licensed in 2011, is composed of 10 µg of A and 5 µg each of C, Y, and W-135 oligosaccharides covalently bonded to the CRM197 protein (Novartis Vaccines and Diagnostics, 2010). The vaccine is supplied in two single-dose vials (A and C-Y-W-135) and contains no preservative or adjuvant (Novartis Vaccines and Diagnostics, 2010).

The Advisory Committee on Immunization Practices currently recommends routine vaccination of persons 11 to 12 years of age and individuals at increased risk of meningococcal disease including college freshman living in dormitories, military recruits, and asplenic individuals (CDC, 2005). MCV4 is preferred for persons 11 to 55 years of age; however, MPSV4 is recommended for individuals between 2 and 10 years and those greater than 55 years old (CDC, 2005). In 2009, the National Immunization Survey

estimated that 53.6 percent of adolescents between 13 and 17 years of age had received at least one dose of the MCV4 vaccine (CDC, 2010).

## ENCEPHALITIS AND ENCEPHALOPATHY

### Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of encephalitis or encephalopathy after the administration of meningococcal vaccine. This one controlled study (Ward et al., 2007) contributed to the weight of epidemiologic evidence and is described below.

Ward et al. (2007) conducted a self-controlled case-series study in children (2 to 35 months of age) residing in the United Kingdom or Ireland between October 1998 and September 2001. The British Pediatric Surveillance Unit distributed monthly surveillance surveys to pediatricians in order to identify children with encephalitis, or suspected severe illness with fever and seizures. The questionnaires were reviewed by a physician to confirm patients met the case definition of severe neurologic disease (encephalitis or febrile seizures). Vaccination histories of confirmed cases were obtained from the child's general practitioner by the Immunization Department, Health Protection Agency, Centre for Infections, London. The risk periods considered were 0–3 and 0–7 days after meningococcal C conjugate vaccination; each child was categorized as having been vaccinated or unvaccinated, and with disease or without disease based on dates of vaccine administration and disease episodes. A total of 50 children (2 to 11 months of age) and 107 children (12 to 35 months of age) with confirmed severe neurologic disease were included in the analysis. The analysis was stratified by age group: 2–11 and 12–35 months. No cases were observed in the 0–3 day risk period for both age groups. For the 0–7 day risk period, no cases were observed for the 2- to 11-month age group but one case was observed for the 12- to 35-month age group.

The study did not find a significant association with any manifestation of encephalopathy. The relative risk of severe neurologic disease in the 0–7 day risk period after meningococcal C conjugate vaccination was estimated at 1.28 (95% CI, 0.17–9.75). As evidenced by the wide confidence interval, the sample size is not large enough to get a more precise estimate of the relative risk. The authors concluded that administration of meningococcal C conjugate vaccine is not associated with an increased risk of severe neurologic disease within 0 to 7 days of vaccination.

*Weight of Epidemiologic Evidence*

*The committee has limited confidence in the epidemiologic evidence, based on one study that lacked validity and precision, to assess an association between meningococcal vaccine and encephalitis or encephalopathy.*

**Mechanistic Evidence**

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of encephalitis or encephalopathy after administration of meningococcal vaccine.

*Weight of Mechanistic Evidence*

T cells and complement activation may contribute to the symptoms of encephalitis or encephalopathy; however, the committee did not identify literature reporting evidence of these mechanisms after administration of meningococcal vaccine.

*The committee assesses the mechanistic evidence regarding an association between meningococcal vaccine and encephalitis or encephalopathy as lacking.*

**Causality Conclusion**

**Conclusion 11.1:** The evidence is inadequate to accept or reject a causal relationship between meningococcal vaccine and encephalitis.

**Conclusion 11.2:** The evidence is inadequate to accept or reject a causal relationship between meningococcal vaccine and encephalopathy.

**ACUTE DISSEMINATED ENCEPHALOMYELITIS****Epidemiologic Evidence**

No studies were identified in the literature for the committee to evaluate the risk of acute disseminated encephalomyelitis (ADEM) after the administration of meningococcal vaccine.



*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between meningococcal vaccine and ADEM.*

**Mechanistic Evidence**

The committee identified one publication reporting ADEM after administration of a meningococcal vaccine. The publication did not present evidence beyond temporality (Py and Andre, 1997). The publication did not contribute to the weight of mechanistic evidence.

*Weight of Mechanistic Evidence*

The symptoms described in the publication referenced above are consistent with those leading to a diagnosis of ADEM. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of ADEM; however, the publication did not provide evidence linking these mechanisms to meningococcal vaccine.

*The committee assesses the mechanistic evidence regarding an association between meningococcal vaccine and ADEM as lacking.*

**Causality Conclusion**

**Conclusion 11.3:** The evidence is inadequate to accept or reject a causal relationship between meningococcal vaccine and ADEM.

**TRANSVERSE MYELITIS****Epidemiologic Evidence**

No studies were identified in the literature for the committee to evaluate the risk of transverse myelitis after the administration of meningococcal vaccine.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between meningococcal vaccine and transverse myelitis.*

### Mechanistic Evidence

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of transverse myelitis after administration of meningococcal vaccine.

#### *Weight of Mechanistic Evidence*

Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of transverse myelitis; however, the committee did not identify literature reporting evidence of these mechanisms after administration of meningococcal vaccine.

*The committee assesses the mechanistic evidence regarding an association between meningococcal vaccine and transverse myelitis as lacking.*

### Causality Conclusion

**Conclusion 11.4:** The evidence is inadequate to accept or reject a causal relationship between meningococcal vaccine and transverse myelitis.

## MULTIPLE SCLEROSIS

### Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of multiple sclerosis (MS) after the administration of meningococcal vaccine. This one study (Laribiere et al., 2005) was not considered in the weight of epidemiologic evidence because it provided data from a passive surveillance system and lacked an unvaccinated comparison population.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between meningococcal vaccine and MS.*

### Mechanistic Evidence

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of MS after administration of meningococcal vaccine.

*Weight of Mechanistic Evidence*

Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of MS; however the committee did not identify literature reporting evidence of these mechanisms after administration of meningococcal vaccine.

*The committee assesses the mechanistic evidence regarding an association between meningococcal vaccine and MS as lacking.*

**Causality Conclusion**

**Conclusion 11.5: The evidence is inadequate to accept or reject a causal relationship between meningococcal vaccine and MS.**

**GUILLAIN-BARRÉ SYNDROME****Epidemiologic Evidence**

The committee reviewed two studies to evaluate the risk of Guillain-Barré syndrome (GBS) after the administration of meningococcal vaccine. One study (Ball et al., 2001) was not considered in the weight of epidemiologic evidence because it provided data from a passive surveillance system and lacked an unvaccinated comparison population.

The one remaining controlled study (De Wals et al., 2008) contributed to the weight of epidemiologic evidence and is described below.

De Wals et al. (2008) conducted a retrospective cohort study on residents of Quebec, Canada, during the 2001 immunization campaign using meningococcal C vaccine. According to the Provincial Meningococcal Vaccine Registry, a total of 1,428,463 individuals (aged 2 months to 20 years) received at least one dose of vaccine from November 2000 through December 2002. The vaccination records were linked to hospital discharge records using information from the provincial database. Medical records were reviewed for patients who had diagnostic codes for GBS in the hospital discharge records; the authors classified cases as confirmed, possible, or probable. The risk period for observed GBS incidence was defined as 6 or 8 weeks following vaccination. The control period for expected GBS incidence included all other time observed during the study period. The analysis included 33 patients with GBS, of whom 19 received a meningococcal C vaccine. Only 2 cases had GBS onset within 8 weeks of vaccination, which was compared to 3.1 expected cases; the 6-week period included 1 observed case and 2.5 expected cases. The month- and age-adjusted incidence ratio of confirmed, probable, or possible cases of GBS within 8 weeks of menin-

gococcal C vaccination was 0.65 (95% CI, 0.01–2.41) and within 6 weeks of vaccination was 0.40 (95% CI, 0.02–2.21). The authors concluded that meningococcal C vaccination does not appear to be associated with an increased risk of GBS, but they noted the limited power of the study to detect a small increased risk.

#### *Weight of Epidemiologic Evidence*

*The committee has limited confidence in the epidemiologic evidence, based on one study that lacked validity and precision, to assess an association between meningococcal C vaccine and GBS.*

#### **Mechanistic Evidence**

The committee identified one publication reporting GBS after administration of meningococcal vaccine. The publication did not provide evidence beyond temporality and did not contribute to the weight of mechanistic evidence (Pritchard et al., 2002).

#### *Weight of Mechanistic Evidence*

The symptoms described in the publication referenced above are consistent with those leading to a diagnosis of GBS. Autoantibodies, complement activation, immune complexes, T cells, and molecular mimicry may contribute to the symptoms of GBS; however, the publication did not provide evidence linking these mechanisms to meningococcal vaccine.

*The committee assesses the mechanistic evidence regarding an association between meningococcal vaccine and GBS as lacking.*

#### **Causality Conclusion**

**Conclusion 11.6:** The evidence is inadequate to accept or reject a causal relationship between meningococcal vaccine and GBS.

## **CHRONIC INFLAMMATORY DISSEMINATED POLYNEUROPATHY**

#### **Epidemiologic Evidence**

No studies were identified in the literature for the committee to evaluate the risk of chronic inflammatory disseminated polyneuropathy (CIDP) after the administration of meningococcal vaccine.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between meningococcal vaccine and CIDP.*

**Mechanistic Evidence**

The committee identified one publication reporting CIDP after administration of meningococcal vaccine. The publication did not provide evidence beyond temporality, which was determined to be too long (Datie et al., 2003). Long latencies between vaccine administration and development of symptoms make it impossible to rule out other possible causes. The publication did not contribute to the weight of mechanistic evidence.

*Weight of Mechanistic Evidence*

The symptoms described in the publication referenced above are consistent with those leading to a diagnosis of CIDP. Autoantibodies, T cells, and molecular mimicry may contribute to the symptoms of CIDP; however, the publication did not provide evidence linking these mechanisms to meningococcal vaccine.

*The committee assesses the mechanistic evidence regarding an association between meningococcal vaccine and CIDP as lacking.*

**Causality Conclusion**

**Conclusion 11.7:** The evidence is inadequate to accept or reject a causal relationship between meningococcal vaccine and CIDP.

**ANAPHYLAXIS****Epidemiologic Evidence**

The committee reviewed three studies to evaluate the risk of anaphylaxis after the administration of meningococcal vaccine. These three studies (Ball et al., 2001; Bentsi-Enchill et al., 2007; Yergeau et al., 1996) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems and lacked unvaccinated comparison populations.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between meningococcal vaccine and anaphylaxis.*

**Mechanistic Evidence**

The committee identified four publications reporting anaphylaxis after administration of meningococcal vaccine. Two publications did not provide evidence including the time frame between vaccination and the development of symptoms (Makela et al., 1977; Peng and Jick, 2004). One publication reported the concomitant administration of vaccines making it difficult to determine which, if any, vaccine could have been the precipitating event (Ball et al., 2001). These publications did not contribute to the weight of mechanistic evidence.

Described below is one publication reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Yergeau et al. (1996) performed a retrospective descriptive study of adverse events reported to a central passive surveillance system after meningococcal vaccination in the province of Quebec, Canada, from December 1992 through March 1993. Meningococcal vaccines in use during the study period included groups A, C, Y, and W135 or only groups A and C. The authors reported one case of anaphylaxis developing 30 minutes postvaccination in a 12-year-old girl. The patient presented with decreased blood pressure, dyspnea, and bronchospasm despite two doses of adrenalin. The patient made a full recovery.

*Weight of Mechanistic Evidence*

The publication described above presented clinical evidence sufficient for the committee to conclude the vaccine was a contributing cause of anaphylaxis after administration of meningococcal vaccine. The clinical description established a strong temporal relationship between administration of the vaccine and the anaphylactic reaction.

*The committee assesses the mechanistic evidence regarding an association between meningococcal vaccine and anaphylaxis as strong based on one case presenting temporality and clinical symptoms consistent with anaphylaxis.*

### Causality Conclusion

**Conclusion 11.8:** The evidence convincingly supports a causal relationship between meningococcal vaccine and anaphylaxis.

## CHRONIC HEADACHE

### Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of chronic headache after the administration of meningococcal vaccine. This one study (Laribiere et al., 2005) was not considered in the weight of epidemiologic evidence because it provided data from a passive surveillance system and lacked an unvaccinated comparison population.

#### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between meningococcal vaccine and chronic headache.*

### Mechanistic Evidence

The committee did not identify literature reporting clinical, diagnostic, or experimental evidence of chronic headache after administration of meningococcal vaccine.

#### *Weight of Mechanistic Evidence*

*The committee assesses the mechanistic evidence regarding an association between meningococcal vaccine and chronic headaches as lacking.*

### Causality Conclusion

**Conclusion 11.9:** The evidence is inadequate to accept or reject a causal relationship between meningococcal vaccine and chronic headache.

## CONCLUDING SECTION

Table 11-1 provides a summary of the epidemiologic assessments, mechanistic assessments, and causality conclusions for meningococcal vaccine.

**TABLE 11-1** Summary of Epidemiologic Assessments, Mechanistic Assessments, and Causality Conclusions for Meningococcal Vaccine

| Vaccine       | Adverse Event                                    | Epidemiologic Assessment | Studies Contributing to the Epidemiologic Assessment | Mechanistic Assessment | Cases Contributing to the Mechanistic Assessment | Causality Conclusion  |
|---------------|--|--------------------------|--|------------------------|--|-----------------------|
| Meningococcal | Encephalitis                                     | Limited                  | 1  | Lacking                | None   | Inadequate            |
| Meningococcal | Encephalopathy                                   | Limited                  | 1  | Lacking                | None   | Inadequate            |
| Meningococcal | Acute Disseminated Encephalomyelitis             | Insufficient             | None   | Lacking                | None   | Inadequate            |
| Meningococcal | Transverse Myelitis                              | Insufficient             | None   | Lacking                | None   | Inadequate            |
| Meningococcal | Multiple Sclerosis                               | Insufficient             | None   | Lacking                | None   | Inadequate            |
| Meningococcal | Guillain-Barré Syndrome                          | Limited                  | 1  | Lacking                | None   | Inadequate            |
| Meningococcal | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient             | None   | Lacking                | None   | Inadequate            |
| Meningococcal | Anaphylaxis                                      | Insufficient             | None   | Strong                 | 1  | Convincingly Supports |
| Meningococcal | Chronic Headache                                 | Insufficient             | None   | Lacking                | None   | Inadequate            |



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## 12

## Injection-Related Adverse Events

The adverse events in this chapter were considered by the committee as potential consequences associated with direct trauma from the administration of various injected vaccines and not necessarily attributable to the contents of the vaccine.

**COMPLEX REGIONAL PAIN SYNDROME****Epidemiologic Evidence**

No studies were identified in the literature for the committee to evaluate the risk of complex regional pain syndrome (CRPS) after the injection of a vaccine.

*Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between the injection of a vaccine and CRPS.*

**Mechanistic Evidence**

The committee identified 10 publications reporting the development or exacerbation of CRPS after receiving an injection. Eight publications described cases that did not provide evidence beyond temporality (Bensasson et al., 1977; Genc et al., 2005; Jastaniah et al., 2003; Kachko et al., 2007; Palao Sanchez et al., 1997; Pirrung, 2010; Siegfried, 1997; Steinberg et al.,

1995). These cases did not contribute to the weight of mechanistic evidence. In addition, Kachko et al. (2007) attributed the development of CRPS to Crohn's disease. These publications did not contribute to the weight of mechanistic evidence.

Described below are publications reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Jastaniah et al. (2003) described four patients who developed complex regional pain syndrome after vaccination against hepatitis B. Case 2 described a 12-year-old girl presenting with swelling, decreased temperature, discoloration, and loss of function of the left arm lasting for 1 week. Symptom onset developed 30 minutes after receiving the first dose of a hepatitis B vaccine in the left deltoid muscle. The same symptoms developed within minutes and lasted for 1 week after administration of the second dose of a hepatitis B vaccine in the right arm. The patient was afflicted by two additional episodes developing spontaneously; one involved the development of an urticarial rash and pain in the left foot, the second involved swelling, pallor, coolness, and pain in the left arm and hand. Case 4 describes a 12-year-old girl presenting with discoloration, swelling, and the inability to clench the fingers of the right hand 15 minutes after receiving the first dose of a hepatitis B vaccine in the right deltoid muscle. Past history revealed an episode of leg swelling after injection of the first dose of a diphtheria-tetanus-pertussis vaccine in the thigh; no other physical exam findings were consistent with CRPS. Subsequent pertussis vaccines were withheld and the patient tolerated other vaccinations without incident.

Ali et al. (2000) conducted a study to determine if peripheral administration of physiologically relevant doses of an  $\alpha$ -adrenergic agonist resulted in pain in patients with sympathetically maintained pain. Twelve individuals with either type I or type II CRPS affecting either an upper or a lower extremity and normal individuals were recruited to take part in the study. The participants diagnosed with CRPS previously underwent local anesthetic blocks of the sympathetic ganglia. Each participant received saline, and three concentrations of norepinephrine were administered via intradermal injection twice each. One series of injections was administered on the unaffected extremity in the mirror image region to the area on the affected extremity. Pain to each of the injections was rated by the participant. Subsequently, the same series of injections were administered on the affected extremity, and the participants rated pain to each of the injections. None of the concentrations of norepinephrine elicited pain in the normal participants. Likewise, none of the concentrations of norepinephrine elicited significant pain in the participants diagnosed with CRPS when injected into the unaffected side. In contrast, the two highest concentrations of norepinephrine elicited significant pain in comparison to saline when injected in the affected extremity.

Mailis-Gagnon and Bennett (2004) conducted a study using normal

subjects, sympathetically independent pain (SIP) patients, and sympathetically maintained pain (SMP) patients to determine if intradermal injection of phenylephrine elicits a response similar to that elicited by norepinephrine. The SIP and SMP patients were diagnosed with either type I or type II CRPS. Intradermal injection of a placebo or 1 percent solution of phenylephrine were administered to the forearm, shin of the lower leg, or the suprapatellar area of the upper leg. Pain to each of the injections was rated by the participants. None of the participants reported unusual pain to the placebo. All participants reported stinging or burning pain lasting 15–90 seconds developing after intradermal injection of phenylephrine. Furthermore, all SMP patients reported burning pain developing after intradermal injection of phenylephrine in the symptomatic limb. In addition, three SMP patients reported the development of pain after intradermal injection of phenylephrine administered to the unaffected limb.

#### *Weight of Mechanistic Evidence*

The publications, described above, presented clinical evidence suggestive but not sufficient for the committee to conclude that the injection of a vaccine was a contributing cause of CRPS. The clinical description in one case provided by Jastaniah et al. (2003) included evidence of vaccine rechallenge and was consistent with CRPS. Furthermore, the latency between injection of a vaccine and the development of CRPS in the vaccine rechallenge case described above was 30 minutes or less, suggesting injury resulting from the injection of the vaccine. Approximately 50 percent of patients with CRPS have a history of antecedent trauma to the affected limb (Littlejohn, 2008). This is supported by controlled studies, not using vaccines, conducted by Ali and colleagues (2000) and Mailis-Ganon and Bennett (2004) in which pain was elicited after injection of norepinephrine and phenylephrine.

However, the three other cases described by Jastaniah et al. (2003) and cases described by other authors (Bensasson et al., 1977; Genc et al., 2005; Jastaniah et al., 2003; Palao Sanchez et al., 1997; Pirrung, 2010) did not include convincing evidence beyond a temporal relationship between injection of a vaccine and development of CRPS.

*The committee assesses the mechanistic evidence regarding an association between the injection of a vaccine and CRPS as low-intermediate based on experimental evidence and one case.*

#### **Causality Conclusion**

**Conclusion 12.1:** The evidence is inadequate to accept or reject a causal relationship between the injection of a vaccine and CRPS.

## DELTOID BURSTITIS

### Epidemiologic Evidence

The committee reviewed one study to evaluate the risk of deltoid bursitis after the injection of a vaccine. This one controlled study (Black et al., 2004) contributed to the weight of epidemiologic evidence and is described below.

Black et al. (2004) conducted a retrospective cohort study in patients (2 years of age or older) enrolled in the Northern California Kaiser Permanente Medical Care Program. The study investigated the occurrence of bursitis/synovitis/tenosynovitis (reported as outpatient clinic visits, emergency room visits, and hospitalizations) after receipt of hepatitis A vaccine from April 1997 through December 1998. A total of 49,932 doses of vaccine were administered to 14,898 children (2–17 years) and 35,034 adults ( $\geq 18$  years) during the study. The risk period for outpatient clinic visits and emergency room visits was defined as 30 days after vaccination, whereas the risk period for hospitalizations was defined as 60 days after vaccination. Two control periods were used to evaluate the risk prior to vaccine administration (31–60 or 31–90 days before vaccination) and following vaccine administration (91–120 or 91–150 days after vaccination). The two age groups (children and adults) and events following a first dose and second dose of hepatitis A vaccine were evaluated separately. The authors only reported statistically significant associations in the article, and only one analysis was listed. The relative risk of an emergency room visit for bursitis/synovitis/tenosynovitis within 30 days of administration of a second dose of hepatitis A vaccine among patients aged  $\geq 18$  years was 0.55 (95% CI, 0.32–0.92). The authors did not observe a consistent protective effect between the administration of hepatitis A vaccine (first or second dose) and bursitis/synovitis/tenosynovitis for either age group in the three defined settings.

### *Weight of Epidemiologic Evidence*

*The committee has limited confidence in the epidemiologic evidence, based on one study that lacked validity and precision, to assess an association between the injection of a vaccine and deltoid bursitis.*

### Mechanistic Evidence

The committee identified three publications and three Vaccine Adverse Event Reporting System (VAERS) reports describing the development of deltoid bursitis after administration of a vaccine by injection. Black and colleagues (2004) identified cases of bursitis/synovitis/tenosynovitis developing

after vaccination against hepatitis A using the vaccine VAQTA reported to the Kaiser Permanente Medical Care Program from April 1997 through December 1998. The location of the bursitis/synovitis/tenosynovitis was not indicated. Therefore, this publication did not contribute to the weight of mechanistic evidence.

Described below are two publications and three VAERS reports providing clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Atanasoff et al. (2010) identified 13 claims in the National Vaccine Injury Compensation Program (VICP) database in which injury to the shoulder was reported. All claimants were adult and 11 were women. Out of the women, eight received an influenza vaccine, two received a tetanus reduced diphtheria vaccine, and one received a human papillomavirus vaccine. The two men received tetanus, reduced diphtheria, and reduced pertussis vaccine. The onset of pain in the shoulder developed immediately or within 24 hours after vaccination in 54 percent and 93 percent of the cases respectively. Limited and painful range of motion was the most common finding, whereas weakness, tingling, and numbness were uncommon. Fluid collections in the deep deltoid, tendonitis, rotator cuff tears, subchondral changes in the humerus, bursitis, and increased fluid within the bursa were observed via MRI. In addition, 15 percent of the cases were found to have complete rotator cuff tears.

Three VAERS reports describing shoulder dysfunction after administration of influenza vaccines were identified by Vellozzi and colleagues (2009) and obtained via a Freedom of Information Act (FOIA) request (FDA, 2010). VAERS ID 28572 describes a 52-year-old woman presenting with muscle stiffness, swelling, and an arm hot to touch developing the same day after administration of an influenza vaccine. The patient reported similar symptoms accompanied by an inability to raise the arm laterally for more than 1 year after administration of an influenza vaccine 5 years earlier. VAERS ID 93764 describes a 63-year-old woman presenting with a reddened area tender to touch the size of a 25-cent piece and swelling of the arm and hand 10 minutes after administration of an influenza vaccine. The following day the patient had difficulty lifting the arm. The patient experienced similar symptoms with a previous influenza vaccine. VAERS ID 107626 describes a 55-year-old woman presenting with extreme pain and reduced range of motion 10 minutes after administration of an influenza vaccine. The patient reported similar symptoms after vaccination the previous year.

### *Weight of Mechanistic Evidence*

The publications, described above, presented clinical evidence sufficient for the committee to conclude that the injection of a vaccine was a contributing cause of deltoid bursitis. The clinical descriptions provided by



Atanasoff et al. (2010) were consistent with deltoid bursitis and established a strong temporal relationship between injection of a vaccine and development of deltoid bursitis. Furthermore, the observations made by MRI by Atanasoff et al. (2010) suggest that the injection, and not the contents of the vaccine, contributed to the development of deltoid bursitis.

*The committee assesses the mechanistic evidence regarding an association between the injection of a vaccine and deltoid bursitis as strong based on 16 cases presenting definitive clinical evidence.*

### Causality Conclusion

**Conclusion 12.2:** The evidence convincingly supports a causal relationship between the injection of a vaccine and deltoid bursitis.

## SYNCOPE

### Epidemiologic Evidence

The committee reviewed 21 studies to evaluate the risk of syncope after the injection of a vaccine. Eighteen studies (Bino et al., 2003; Braun et al., 1997; D’Heilly et al., 2006; Dobardzic et al., 2007; Dobson et al., 1995; D’Souza et al., 2000; DuVernoy and Braun, 2000; Ion-Nedelcu et al., 2001; Khetsuriani et al., 2010; Laribiere et al., 2005; Sejvar et al., 2005; Sever et al., 2004; Slade et al., 2009; Sri Ranganathan et al., 2003; Vahdani et al., 2005; Vika et al., 2006; Wise et al., 2004; Woo et al., 2006) were not considered in the weight of epidemiologic evidence because they provided data from passive surveillance systems or self-report surveys, and lacked unvaccinated comparison populations. Three controlled studies (Bernstein et al., 2005; Beytout et al., 2009; Block et al., 2010) had very serious methodological limitations that precluded their inclusion in this assessment. Bernstein et al. (2005), Beytout et al. (2009), and Block et al. (2010) conducted double-blind, randomized controlled trials, but too few events were reported to adequately assess the risk of syncope following the injection of various vaccines.

### *Weight of Epidemiologic Evidence*

*The epidemiologic evidence is insufficient or absent to assess an association between the injection of a vaccine and syncope.*

### Mechanistic Evidence

The committee identified 29 publications reporting syncope or syncopal seizure after receipt of an injection. Seventeen publications reported syn-

cope developing after vaccination but either did not provide a time frame between the two events or the time frame provided was nonspecific (Bino et al., 2003; D'Heilly et al., 2006; Dobardzic et al., 2007; Dobson et al., 1995; DuVerney and Braun, 2000; Ion-Nedelcu et al., 2001; Khetsuriani et al., 2010; Reisinger et al., 2010; Rivera Medina et al., 2010; Schnatz et al., 2010; Sejvar et al., 2005; Sever et al., 2004; Southern et al., 2006; Sri Ranganathan et al., 2003; Vahdani et al., 2005; Wise et al., 2004; Woo et al., 2006). These publications did not contribute to the weight of mechanistic evidence.

Described below are 12 publications reporting clinical, diagnostic, or experimental evidence that contributed to the weight of mechanistic evidence.

Buttery et al. (2008) identified adverse events following vaccination against human papillomavirus. The adverse events were reported to Surveillance of Adverse Events following Vaccination in the Community (SAFEVIC) in Australia in April 2007. The authors identified cases of syncope developing within 2 hours after vaccination. One case presented with a second episode of syncope 2 days later.

D'Souza et al. (2000) identified adverse events developing after administration of a measles, mumps, and rubella vaccine reported to the vaccine providers participating in the Measles Control Campaign (MCC), to the Serious Adverse Events Following Vaccination Surveillance Scheme (SAFEVSS), and to the Adverse Drug Reactions Advisory Committee (ADRAC) in Australia from August to November 1998. The authors identified 29 cases of syncope or syncopal seizure developing after vaccination. Twenty-one of the 29 cases developed within 1 hour after vaccination. Similarly, 21 of the 29 cases did not require medical attention.

Keyserling et al. (2005) conducted a randomized, double-blind trial at 11 clinical centers in the United States where meningococcal vaccines were administered to 881 individuals ranging from 11 to 18 years of age. Two participants experienced a vasovagal episode within 30 minutes after receiving a meningococcal vaccine. Medical intervention was not required.

Labribière et al. (2005) conducted a prospective study using surveys completed by physicians and families to study adverse events reported after administration of meningococcal vaccines in France. The authors identified 10 cases of seizures or tonic-clonic movements during syncope. In addition, the authors described one case of syncope in some detail. An 11-year-old boy presented with loss of consciousness, hypotension, bradypnea, and bradycardia 3 minutes after vaccination. The patient experienced two additional episodes within 1 hour.

Meyer et al. (2001) describe a 10-year-old boy presenting with loss of consciousness for 30 seconds after feeling dizzy and experiencing optic sensations a few minutes after receiving a vaccine against tick-borne encephalitis. The patient had a similar episode 4 months later after receiving a measles, mumps, and rubella vaccine. In addition, the patient had previ-

ously become pale, lost consciousness, and developed a seizure 2 minutes after venipuncture. Twenty seconds after venipuncture the patient's heart rate decreased from 110 to 50 beats per minute followed by 6 seconds of asystole. The patient recovered in less than 30 seconds.

Braun et al. (1997) analyzed reports to VAERS from its inception through October 1995. The authors identified 697 reports of syncope developing within 12 hours after vaccination. Of the 697 reports 323 occurred within 5 minutes, 454 occurred within 15 minutes, 500 occurred within 30 minutes, and 511 occurred within 1 hour after vaccination. Of the 697 reports, 67 required hospitalization. Six cases were described in detail. Case 1 describes a 17-year-old boy who developed syncope 10 minutes after receiving tetanus-diphtheria and measles, mumps, and rubella vaccines. The patient suffered a linear skull fracture and bilateral fronto-temporal contusions. Case 2 describes a 12-year-old boy who developed syncope 10 to 15 minutes after receiving a measles, mumps, and rubella vaccine. The patient suffered frontal cerebral contusions. Case 3 describes a 26-year-old man who developed syncope less than 3 minutes after receiving tetanus-diphtheria and measles, mumps, and rubella vaccines. The patient suffered a linear nondepressed skull fracture and contusions of the frontal and temporal regions. Depression and cognitive deficits continued through a follow-up 2 years after injury. Case 4 describes a 28-year-old man who developed syncope within 1 minute after receiving a measles vaccine. The patient suffered from a subdural and epidural hematoma compressing the right lateral ventricle. The patient experienced months of cognitive, behavioral, speech, and language problems after the injury. Case 5 describes a 15-year-old boy who developed syncope less than 10 minutes after receiving a tetanus-diphtheria vaccine. The patient suffered a massive cerebral hemorrhage from a lacerated middle meningeal artery. Two years after the injury the patient had a right hemiparesis. Case 6 describes an 18-year-old girl who developed syncope 5 minutes after receiving a tetanus-diphtheria vaccine. The patient suffered a skull fracture, cerebral contusions, and a right frontal hematoma.

Miller and Woo (2006) describe a teenage boy who experienced vasovagal syncope a few minutes after receiving the third dose of a hepatitis B vaccine. The patient fell striking his head. Upon regaining consciousness the patient developed seizures and cardiopulmonary arrest after complaining of pain in the chest and arms. Resuscitation attempts failed and the patient died. Frontal lobe contusions, edema, and cerebral hemorrhage were observed during autopsy. The fall and resulting head injuries were determined to be the cause of death. In addition, the authors identified 2,366 reports of syncope submitted to VAERS since 1990.

Slade et al. (2009) analyzed reports of adverse events developing after

vaccination with the quadrivalent human papillomavirus vaccine Gardasil received by VAERS from June 2006 through December 2008. The authors identified 1,896 cases reporting syncope. Syncope developed on the same day of vaccination in 90 percent of the cases reporting a time interval between the onset of symptoms and vaccination. Fifty percent of the cases occurring on the day of vaccination developed within 15 minutes after vaccination. Of the 1,896 reports of syncope, 293 resulted in a fall of which 200 resulted in a head injury.

One VAERS report describing syncope after administration of an influenza vaccine was identified by Vellozzi and colleagues (2009) and obtained via a FOIA request (FDA, 2010). VAERS ID 212825 describes a 49-year-old man presenting with brief syncope after vaccination. The patient's blood pressure was initially 80/60, and after 5 minutes it was reported to be 100/60. The patient experienced a similar episode after a previous influenza vaccination.

Konkel et al. (1993) and Wiersbitzky et al. (1993) describe a 6-year-old presenting with loss of consciousness, generalized tonic-clonic seizures, and enuresis 10 minutes after administration of a measles, mumps, and rubella vaccine.

Zimmerman et al. (2010) conducted a randomized trial of an alternate human papillomavirus vaccine administration schedule and received 114 and 95 reports of adverse events in the standard schedule group and the alternate schedule group, respectively. One case of syncope was reported and described in some detail. The patient developed syncope, which resolved without complications, immediately after receiving a dose of the quadrivalent human papillomavirus vaccine. The patient was on the examination table at the time.

### *Weight of Mechanistic Evidence*

The publications described above presented clinical evidence sufficient for the committee to conclude that the injection of a vaccine was a contributing cause of syncope. The clinical descriptions provided in many publications establish a strong temporal relationship between injection of a vaccine and development of syncope. Furthermore, the prodromal symptoms, including dizziness and pallor, described in some publications, are consistent with those developing before vasovagal syncope. Also, one patient experienced a decreased heart rate seconds after venipuncture and before fainting suggesting vasovagal syncope. This patient developed two additional episodes of syncope after injection of two different vaccines, suggesting that the injection, and not the contents of the vaccine, contributed to the development of syncope.

The latency, of 15 minutes or less, between injection of a vaccine and the development of syncope in many of the cases described above suggests vasovagal syncope as the mechanism.

*The committee assesses the mechanistic evidence regarding an association between the injection of a vaccine and syncope as strong based on 35 cases<sup>1</sup> presenting definitive clinical evidence.*

### Causality Conclusion

**Conclusion 12.3: The evidence convincingly supports a causal relationship between the injection of a vaccine and syncope.**

### CONCLUDING SECTION

Table 12-1 provides a summary of the epidemiologic assessments, mechanistic assessments, and causality conclusions for injection-related adverse events.

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<sup>1</sup>In addition, hundreds of cases have been reported to passive surveillance systems; however, it is not possible to know how many represent unique cases or were reported elsewhere.

**TABLE 12-1** Summary of Epidemiologic Assessments, Mechanistic Assessments, and Causality Conclusions for Injection-Related Adverse Events

| Vaccine                 | Adverse Event                  | Epidemiologic Assessment | Studies Contributing to the Epidemiologic Assessment | Mechanistic Assessment | Cases Contributing to the Mechanistic Assessment | Causality Conclusion  |
|-------------------------|--------------------------------|--------------------------|--|------------------------|--|-----------------------|
| Injection-Related Event | Complex Regional Pain Syndrome | Insufficient             | None   | Low-Intermediate       | 1  | Inadequate            |
| Injection-Related Event | Deltoid Bursitis               | Limited                  | 1  | Strong                 | 16   | Convincingly Supports |
| Injection-Related Event | Syncope                        | Insufficient             | None   | Strong                 | 35*  | Convincingly Supports |

\*In addition, hundreds of cases have been reported to passive surveillance systems; however, it is not possible to know how many represent unique cases or were reported elsewhere.

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## 13

## Concluding Comments

The committee acknowledges that some readers may have concerns about two aspects of the report. First, the committee does not make conclusions about how frequently vaccine adverse events occur. Secondly, the committee concluded, for most analyses, that the evidence is inadequate to accept or reject a causal relationship and some readers might interpret the committee's language in different and inaccurate ways. The committee offers concluding comments to address these two issues.

This report is not intended to answer the question "Are vaccines safe?". The committee was not charged with answering that question. Other bodies make that determination and contribute to ongoing safety monitoring, including governmental agencies, care providers, and industry, as they determine the benefits and risks of marketing a product. At all levels, policy determining vaccine use requires a balancing of risks and benefits. As described in Chapter 1 and the Preface, that is outside the bounds of this committee's assignment. It should also be noted that where the committee has found evidence of a causal relationship, it does not make conclusions about the rate or incidence of these adverse effects.

Determining the rate of specific adverse events following immunization, in the general population or a subset thereof, is challenging. It would be possible, for example, to estimate a rate of the occurrence of a specific adverse effect in a vaccinated population or susceptible subgroup of interest. This could be done using a summary relative risk or absolute risk difference (e.g., estimated from a set of consistent reports reviewed by the committee) if there were large population-based studies of the occurrence of the adverse event in unvaccinated individuals (e.g., in the general popu-

lation or susceptible subgroups of interest) who do not substantially differ from those vaccinated on any known, important confounders (e.g., age and exposure to other vaccinations or other agents or factors known to cause the adverse event). None of these preconditions is fully met for the adverse events reviewed in this report.

The committee also notes here that large epidemiologic studies that report no cases of the adverse event of interest in vaccinated study participants, if included in our analyses, raise particular concerns. If at least some cases of the adverse event occurred in a study's unvaccinated comparison population, an upper limit of the 95% confidence interval (CI) for the study's relative risk or absolute risk difference could be estimated, but one would be unable to rule out a possibly increased risk *unless* the vaccine was significantly protective against that particular adverse effect. Also, including such studies may have exacerbated problems with detection biases unless precautions were taken to ensure equal surveillance for the adverse event in the unvaccinated and vaccinated populations being compared.

Discussion of the adverse events where the committee concluded that there is evidence to support causation illustrates more fully the challenge of specifying rates, although for some estimates can be provided.

**MMR vaccine:** The committee concluded that the evidence favors acceptance of a causal relationship between measles, mumps, and rubella (MMR) vaccine and febrile seizures. Approximately 4 percent of children will experience a febrile seizure by 5 years of age (Marin et al., 2010). Fever may occur following MMR vaccination, and some children who have fever following MMR may have a febrile seizure. It is important to note that simple febrile seizures are benign and have no permanent sequelae. For example, children with simple febrile seizures have no greater chance of getting epilepsy or experiencing long-term brain damage than children who do not have febrile seizures.

Three of the studies the committee examined provided both a number of children vaccinated with MMR (the denominator) and the number of febrile seizures considered to be attributable to MMR (Farrington et al., 1995; Griffin et al., 1991; Vestergaard et al., 2004). Children who receive the MMR vaccine are at risk for febrile seizures 8–14 days after vaccination (Marin et al., 2010). About one additional febrile seizure occurs during the 30 days after vaccination among every 3,000–4,000 children who receive MMR vaccine, compared with children who are not vaccinated (Marin et al., 2010). Using the number of febrile seizures attributed to MMR vaccine, and dividing by the number of children in the cohort, each of the other studies provides a similar rate, between one in 1,000 and one in 4,000 doses.

**Varicella vaccine:** The varicella vaccine accounted for five of the affirmative causality conclusions. All were caused by infection of persons with

the varicella vaccine strain, usually in immunodeficient persons. Varicella vaccine is a live virus vaccine that is contraindicated in people with known, severe immunodeficiency, including severe combined immunodeficiency, other congenital immunodeficiencies, and immunodeficiency arising from long-term immunosuppressive therapy or from chemotherapy for hematologic or solid tumors. The evidence for the causal relationships for adverse events from infection by the vaccine virus came from case reports, so there was no cohort or background population to allow calculation of a rate, even among the population of people who have demonstrated immunodeficiencies.

Although the lifetime rate of shingles in the population has been estimated (9–10 percent for those under 45 years of age, 22–32 percent in older persons) (Chapman et al., 2003), the rate of shingles and other infection-related adverse events associated specifically with the varicella vaccine virus are not known for several reasons. First, while the rate of shingles can be estimated (see Chapman, above), in most cases the virus is not characterized, meaning no test is done to determine whether the virus is wild or vaccine type. Second, while the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) oversee a large database of reports, the Vaccine Adverse Event Reporting System (VAERS), those reports are often incomplete and do not always have the information that would document the vaccine strain or the presence or absence of immunodeficiency. However, it appears likely to the committee that the risk of vaccine-strain varicella infection and subsequent serious disease to persons demonstrated to be immunocompetent is exceedingly low, while the risk to those with severe immunodeficiency is real, which is what the CDC and FDA have concluded by deciding that varicella vaccination is contraindicated in such persons. And, of course, immunocompromised individuals benefit greatly from a high level of immunity to varicella within the community.

**Anaphylaxis:** Although it is also difficult to estimate rates for very rare conditions, the committee concluded that evidence supports the association of anaphylaxis with certain vaccines in certain circumstances, but the number of events related to each specific vaccine is not known. Rates can be estimated from surveillance studies, but often specific details are missing, and each case cannot be linked with certainty to vaccine. For example, Bohlke et al. (2003) (an uncontrolled study from the Vaccine Safety Datalink [VSD] network) reported three cases of anaphylaxis after administration of 848,945 doses of MMR vaccine. However, two of those children received vaccines in addition to MMR, and the confidence interval for the calculated rate per million doses was very wide (rate per million doses = 3.5, 95% CI, 0.7–10.3). Lastly, regarding this example of a rare condition, not only is the number of true anaphylactic reactions to vaccines not known, but also

the “denominator” of persons susceptible to anaphylaxis (rather than the general population of persons to be vaccinated) is unknown.

Anaphylactic reactions to several vaccines are likely caused by the presence of components introduced during manufacturing, such as egg protein, milk protein, or gelatin. When a specific inciting component of the vaccine has been identified and the manufacturers find ways to remove or drastically reduce the amount of the reactive antigen (e.g., egg protein in influenza vaccine), the number of reports of anaphylaxis in spontaneous reporting systems has decreased. It appears likely to the committee that the risk of anaphylaxis caused by vaccines is exceedingly low in the general population. The risk is obviously higher in people with known and demonstrably severe allergies to certain vaccine components, such as eggs or gelatin.

An affirmative finding for causality was determined for a very mild condition (oculorespiratory syndrome) subsequent to certain influenza vaccines used only in two seasons in Canada. The committee made no attempt to determine the rate of this condition.

Finally, the committee determined that evidence supported an association with what the committee considered to be injection-related events: deltoid bursitis and syncope. These injection-related events are known to be caused by many things other than vaccine administration and are likely often unreported. Estimates of the rates caused by vaccination are similarly not available, as population-based studies have not been conducted.

The seriousness of any particular adverse effect is a complex question, taking into account such factors as the degree and duration of disability and the type of health care needed as a result, recognizing that any individual who experiences an adverse effect may regard it as serious. All of these considerations have social and ethical components as well. Deeming this calculus to be too complex to define with particularity, the committee elected to defer to common understanding within the health care community for assessment of the seriousness of any particular adverse effect.

An issue that is likely to be of concern to some readers regards the very stringent approach our committee has taken. For the majority of adverse events the committee was asked to examine, the committee concludes that the evidence is inadequate to accept or reject a causal relationship. Some might interpret that to mean either of the following statements:

- Because the committee did not find convincing evidence that the vaccine *does* cause the adverse event, the vaccine is safe.
- Because the committee did not find convincing evidence that the vaccine does *not* cause the adverse event, the vaccine is unsafe.

*Neither of these interpretations is correct.* “Inadequate to accept or reject” means just that—inadequate. If there is evidence in either direction that is suggestive but not sufficiently strong about the causal relationship, it will be reflected in the weight-of-evidence assessments of the epidemiologic or the mechanistic data. However suggestive those assessments might be, in the end the committee concluded that the evidence was inadequate to accept or reject a causal association.

The committee does want to emphasize many of the adverse events examined are exceedingly rare in the population overall, and in most instances any particular adverse event, be it arthritis, meningitis, or any of the other vaccine–adverse events that the committee considered, are not preceded by immunization. The committee chose cautious and scientific language for our conclusions, because, especially with rare events, it is not possible to *prove* a negative (i.e., the vaccine did not and cannot cause the event). The committee cannot say that in a certain person at a certain time, some event cannot happen; there is much about biology that is not known.

The committee tried to apply consistent standards when reviewing individual articles and when assessing the bodies of evidence. Some of the conclusions were easy to reach; the evidence was clear and consistent or, in the other extreme, completely absent. Some conclusions required substantial discussion and debate. Inevitably, there are elements of expert clinical and scientific judgment involved.

The committee used the best evidence available at the time. The committee hopes that the report is sufficiently transparent such that when new information emerges from either the clinic or the laboratory, others will be able to assess the importance of that new information within the approach and set of conclusions set forth in this report.

The committee hopes this summary of the thinking of the committee is helpful to the reader.

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# Appendix A

## Glossary

**Acute disseminated encephalomyelitis (ADEM):** An acute demyelinating disorder of the central nervous system in which focal demyelination is present throughout the brain and spinal cord.<sup>1</sup>

**Afebrile convulsions:** A convulsion that occurs in the absence of fever.<sup>2</sup>

**Amyotrophic lateral sclerosis:** A fatal degenerative disease involving the corticobulbar, corticospinal, and spinal motor neurons, manifested by progressive weakness and wasting of muscles innervated by the affected neurons; fasciculations and cramps commonly occur.<sup>1</sup>

**Anaphylaxis/anaphylactic shock:** An immediate and severe allergic reaction to a substance.<sup>3</sup>

**Arthralgia:** Pain in a joint.<sup>1</sup>

**Arthritis:** Inflammation of one or more joints, which results in pain, swelling, stiffness, and limited movement.<sup>2</sup>

**Arthropathy:** Any disease affecting a joint.<sup>1</sup>

**Asthma:** An inflammatory disorder of the airways, which causes attacks of wheezing, shortness of breath, chest tightness, and coughing.<sup>2</sup>



**Ataxia:** An inability to coordinate muscle activity during voluntary movement; most often results from disorders of the cerebellum or the posterior columns of the spinal cord; may involve the limbs, head, or trunk.<sup>1</sup>

**Autism:** A developmental disorder that appears in the first 3 years of life, and affects the brain's normal development of social and communication skills.<sup>2</sup>

**Autoimmune hepatitis:** Chronic liver disease of unknown etiology characterized by histologic presence of periportal hepatitis with plasma cell infiltration, hypergammaglobulinemia, and presence of autoantibodies in the serum.<sup>1</sup>

**Bell's palsy:** Paresis or paralysis, usually unilateral, of the facial muscles, caused by dysfunction of the seventh cranial nerve; probably due to a viral infection; usually demyelinating in type.<sup>1</sup>

**Bias:** Systematic deviation of results or inferences from truth; processes leading to such deviation. An error in the conception and design of a study—or in the collection, analysis, interpretation, reporting, publication, or review of data—leading to results or conclusions that are systematically (as opposed to randomly) different from the truth.<sup>4</sup>

**Brachial neuritis:** Inflammation of nerves in the arm causing muscle weakness and pain.<sup>5</sup>

**Case-crossover study:** The method is akin to a matched case-control study, in which the controls are sampled from the person-time of the case prior to the event. Vaccinations are ascertained in a defined time period immediately prior to the event and in one or several earlier control periods of the same duration. This produces, for each case, a matched set of exposure variables corresponding to the event and control periods, which may be analyzed as in a case-control study.<sup>6</sup>

**Case-control study:** The observational epidemiologic study of persons with the disease (or another outcome variable) of interest and a suitable control group of persons without the disease (comparison group, reference group). The potential relationship of a suspected risk factor or an attribute to the disease is examined by comparing the diseased and nondiseased subjects with regard to how frequently the factor or attribute is present (or, if quantitative, the levels of the attribute) in each of the groups (diseased and nondiseased).<sup>4</sup>

**Case-only study:** A method that analyzes data from a case series. It may be seen as an epidemiologic equivalent of the “thought experiment” used by theoretical physicists. It is used in the case-crossover study, in case-specular designs, and in molecular and genetic epidemiology to assess relationships between environmental exposures and genotypes.<sup>4</sup>

**Case report:** Detailed description of a few patients or clinical cases (frequently, just one sick person) with an unusual disease or complication, uncommon combinations or diseases, or an unusual or misleading semiology, cause, or outcome.<sup>4</sup>

**Case series:** A collection of patients with common characteristics used to describe some clinical, pathophysiological, or operational aspect of a disease, treatment, or diagnostic procedure. Some are similar to the larger case reports and share the virtues of this design.<sup>4</sup>

**Cerebellar ataxia:** Loss of muscle coordination caused by disorders of the cerebellum.<sup>1</sup>

**Chronic fatigue syndrome:** Syndrome of persistent incapacitating weakness or fatigue, accompanied by nonspecific somatic symptoms, lasting at least 6 months, and not attributable to any known cause.<sup>1</sup>

**Chronic headache:** Pain in various parts of the head, not confined to the area of distribution of any nerve.<sup>1</sup>

**Chronic inflammatory disseminated polyneuropathy (CIDP):** An uncommon, acquired, demyelinating sensorimotor polyneuropathy, clinically characterized by insidious onset, slow evolution (either steady progression or stepwise), and chronic course; symmetric weakness is a predominant symptom, often involving proximal leg muscles, accompanied by paresthesias, but not pain; CSF examination shows elevated protein, whereas electrodiagnostic studies reveal evidence of a demyelinating process, primarily conduction slowing rather than block; sometimes responds to prednisone.<sup>1</sup>

**Chronic urticaria:** A form of urticaria in which the wheals recur frequently, or persist.<sup>1</sup>

**Cohort study:** The analytic epidemiologic study in which subsets of a defined population can be identified who are, have been, or in the future may be exposed or not exposed, or exposed in different degrees, to a factor or factors hypothesized to influence the occurrence of a given disease or other outcomes. The main feature of cohort study is observation of large numbers

over a long period (commonly years), with comparison of incidence rates in groups that differ in exposure levels. The alternative terms for a cohort study (i.e., follow-up, longitudinal, and prospective study) describe an essential feature of the method, which is observation of the population for a sufficient number of person-years to generate reliable incidence or mortality rates in the population subsets. This generally implies study of a large population, study for a longer period (years), or both. The denominators used for analysis may be persons or person-time.<sup>4</sup>

**Complex regional pain syndrome (CRPS):** A condition of chronic, severe, and often burning pain usually of part or all of one or more extremities that typically occurs following an injury, that is often accompanied by swelling, skin discoloration, allodynia, abnormal sweating, and impaired motor function in the affected area, and that is of unknown pathogenesis.<sup>3</sup>

**Confounding:** Loosely, the distortion of a measure of the effect of an exposure on an outcome caused by the association of the exposure with other factors that influence the occurrence of the outcome. Confounding occurs when all or part of the apparent association between the exposure and outcome is in fact accounted for by other variables that affect the outcome and are not themselves affected by exposure.<sup>4</sup>

**Convulsion:** See Seizure.

**Crossover experiment:** A method of comparing two (or more) treatments or interventions in which subjects, upon completion of one treatment, are switched to the other treatment or intervention. In the case of two treatments, A and B, half the patients are randomly allocated to receive these in the order “A first, then B” and half to receive them in the order “B first, then A.” The outcomes cannot be permanent changes (e.g., they can be symptoms, functional capacity).<sup>4</sup>

**Deltoid bursitis (frozen shoulder):** A condition in which joint motion becomes restricted because of inflammatory thickening of the capsule; a common cause of shoulder stiffness.<sup>1</sup>

**Demyelination:** Loss of myelin with preservation of the axons or fiber tracts.<sup>1</sup>

**Diphtheria:** A specific infectious disease due to the bacterium *Corynebacterium diphtheriae* and its highly potent toxin; marked by severe inflammation that can form a membranous coating, with formation of a thick fibrinous exudate, of the mucous membrane of the pharynx, the nose, and

sometimes the tracheobronchial tree; the toxin produces degeneration in peripheral nerves, heart muscle, and other tissues; diphtheria had a high fatality rate, especially in children, but is now rare because of an effective vaccine.<sup>1</sup>

**Disseminated varicella:** The spreading of the vesicular rash beyond the dermatome involved in the vaccination.<sup>5</sup>

**Embolism:** Obstruction or occlusion of a vessel by an embolus.<sup>1</sup>

**Encephalitis:** Irritation and swelling (inflammation) of the brain, most often due to infections.<sup>2</sup>

**Encephalopathy:** A general term describing brain dysfunction. Examples include encephalitis, meningitis, seizures, and head trauma.<sup>5</sup>

**Erythema nodosum:** A panniculitis marked by the sudden formation of painful nodes on the extensor surfaces of the lower extremities, with lesions that are self-limiting but tend to recur; associated with arthralgia and fever; may be the result of drug sensitivity or associated with sarcoidosis and various infections.<sup>1</sup>

**Febrile convulsions:** A brief seizure, lasting less than 15 minutes, seen in a neurologically normal infant or young child, associated with fever.<sup>1</sup>

**Fibromyalgia:** A chronic disorder characterized by widespread pain, tenderness, and stiffness of muscles and associated connective tissue structures that is typically accompanied by fatigue, headache, and sleep disturbances.<sup>3</sup>

**Guillain-Barré syndrome (GBS):** An acute, immune-mediated disorder of peripheral nerves, spinal roots, and cranial nerves, commonly presenting as a rapidly progressive, areflexive, relatively symmetric ascending weakness of the limb, truncal, respiratory, pharyngeal, and facial musculature, with variable sensory and autonomic dysfunction; typically reaches its nadir within 2–3 weeks, followed initially by a plateau period of similar duration, and then subsequently by gradual but complete recovery in most cases.<sup>1</sup>

**Hearing loss:** A reduction in the ability to perceive sound; may range from slight inability to complete deafness.<sup>1</sup>

**Hepatitis:** Inflammation of the liver, due usually to viral infection but sometimes to toxic agents.<sup>1</sup>

**Hepatitis A:** A viral disease with a short incubation period (usually 15–50 days), caused by hepatitis A virus, a member of the family Picornaviridae, often transmitted by fecal-oral route; may be inapparent, mild, severe, or occasionally fatal and occurs sporadically or in epidemics, commonly in school-age children and young adults; necrosis of periportal liver cells with lymphocytic and plasma cell infiltration is characteristic, and jaundice is a common symptom.<sup>1</sup>

**Hepatitis B:** A viral disease with a long incubation period (usually 50–160 days), caused by a hepatitis B virus, a DNA virus and member of the family Hepadnaviridae, usually transmitted by injection of infected blood or blood derivatives or by use of contaminated needles, lancets, or other instruments or by sexual transmission; clinically and pathologically similar to viral hepatitis type A, but there is no cross-protective immunity; HBsAg is found in the serum and the hepatitis delta virus occurs in some patients. May lead to acute or chronic liver disease.<sup>1</sup>

**Herpes zoster:** An infection caused by a herpesvirus (varicella zoster virus), characterized by an eruption of groups of vesicles on one side of the body following the course of a nerve due to inflammation of ganglia and dorsal nerve roots resulting from activation of the virus, which in many instances has remained latent for years following a primary chickenpox infection; the condition is self-limited but may be accompanied by or followed by severe postherpetic pain. Also known as the *shingles*.<sup>1</sup>

**Human papillomavirus (HPV):** An icosahedral DNA virus, 55 nm in diameter, of the genus *Papillomavirus*, family Papovaviridae; certain types cause cutaneous and genital warts; other types are associated with severe cervical intraepithelial neoplasia and anogenital and laryngeal carcinomas.<sup>1</sup>

**Hypercoagulable states:** Characterized by abnormally increased coagulation.<sup>1</sup>

**Immune thrombocytopenic purpura (ITP):** A systemic illness characterized by extensive ecchymoses and hemorrhages from mucous membranes and very low platelet counts; resulting from platelet destruction by macrophages due to an antiplatelet factor; childhood cases are usually brief and rarely present with intracranial hemorrhages, but adult cases are often recurrent and have a higher incidence of grave bleeding, especially intracranial. Also known as *idiopathic thrombocytopenic purpura*.<sup>1</sup>

**Infantile spasms:** An epileptic disorder characterized by flexion spasms of the neck, trunk, and limbs and psychomotor retardation.<sup>7</sup>

**Influenza:** An acute infectious respiratory disease, caused by Influenza viruses, which are in the family Orthomyxoviridae, in which the inhaled virus attacks the respiratory epithelial cells of those susceptible and produces a catarrhal inflammation; characterized by sudden onset, chills, fever of short duration (3–4 days), severe prostration, headache, muscle aches, and a cough that usually is dry and may be followed by secondary bacterial infections that can last up to 10 days.<sup>1</sup>

**Insulin-dependent diabetes mellitus:** Chronic (lifelong) disease that occurs when the pancreas does not produce enough insulin to properly control blood sugar levels, also known as *type 1 diabetes*.<sup>2</sup>

**Juvenile idiopathic arthritis:** Chronic arthritis beginning in childhood, most cases of which are pauciarticular, i.e., affecting few joints.<sup>1</sup>

**Measles:** An acute exanthematous disease, caused by measles virus (genus *Morbillivirus*), a member of the family Paramyxoviridae, and marked by fever and other constitutional disturbances, a catarrhal inflammation of the respiratory mucous membranes, and a generalized dusky red maculopapular eruption; the eruption occurs early on the buccal mucous membrane in the form of Koplik spots, a manifestation useful in early diagnosis; average incubation period is from 10–12 days.<sup>1</sup>

**Measles inclusion body encephalitis:** A rare chronic, progressive encephalitis that affects primarily children and young adults, caused by the measles virus. Death usually occurs within 3 years.<sup>1</sup>

**Meningitis:** Inflammation of the membranes of the brain or spinal cord.<sup>1</sup>

**Meningoencephalitis:** An inflammation of the brain and its membranes.<sup>1</sup>

**Multiple sclerosis (MS):** Common demyelinating disorder of the central nervous system, causing patches of sclerosis (plaques) in the brain and spinal cord; occurs primarily in young adults, and has protean clinical manifestations, depending on the location and size of the plaque; typical symptoms include visual loss, diplopia, nystagmus, dysarthria, weakness, paresthesias, bladder abnormalities, and mood alterations; characteristically, the plaques are “separated in time and space” and clinically the symptoms show exacerbations and remissions.<sup>1</sup>

**Mumps:** An acute infectious and contagious disease caused by a mumps virus of the genus *Rubulavirus* and characterized by fever, inflammation and

swelling of the parotid gland, and sometimes of other salivary glands, and occasionally by inflammation of the testis, ovary, pancreas, or meninges.<sup>1</sup>

**Myocardial infarction:** Infarction of a segment of heart muscle, usually due to occlusion of a coronary artery.<sup>1</sup>

**Myocarditis:** Inflammation of the muscular walls of the heart.<sup>1</sup>

**Myoclonic epilepsy:** Epilepsy marked by myoclonic seizures.<sup>3</sup>

***Neisseria meningitides:*** A bacterial species found in the nasopharynx of humans but not in other animals; the causative agent of meningococcal meningitis and meningococcemia; virulent organisms are strongly gram negative and occur singly or in pairs; in the latter case the cocci are elongated and are arranged with long axes parallel and facing sides kidney shaped; groups characterized by serologically specific capsular polysaccharides are designated by capital letters.<sup>1</sup>

**Nested case-control study:** An important type of case-control study in which cases and controls are drawn from the population in a fully enumerated cohort. Typically, some data on some variables are already available about both cases and controls; thus concerns about differential (biased) misclassification of these variables can be reduced (e.g., environmental or nutritional exposures may be analyzed in blood from cases and controls collected and stored years before disease onset). A set of controls is selected from subjects (i.e., noncases) at risk of developing the outcome of interest at the time of occurrence of each case that arises in the cohort.<sup>4</sup>

**Neuritis:** Inflammation of a nerve.<sup>1</sup>

**Neuromyelitis optica:** A demyelinating disorder consisting of a transverse myelopathy and optic neuritis.<sup>1</sup>

**Neuropathy:** A disease involving the cranial nerves or the peripheral or autonomic nervous system.<sup>1</sup>

**Oculorespiratory syndrome:** A usually transient syndrome of bilateral red eyes and upper respiratory symptoms, including cough, wheezing, chest discomfort, sore throat, and occasionally facial edema, following influenza vaccination.<sup>1</sup>

**Opsoclonus myoclonus syndrome:** A rare neurological disorder characterized by an unsteady, trembling gait, myoclonus (brief, shock-like muscle

spasms), and opsoclonus (irregular, rapid eye movements). Other symptoms may include difficulty speaking, poorly articulated speech, or an inability to speak. A decrease in muscle tone, lethargy, irritability, and malaise (a vague feeling of bodily discomfort) may also be present.<sup>8</sup>

**Optic neuritis:** Inflammation of the optic nerve.<sup>1</sup>

**Pancreatitis:** Inflammation of the pancreas.<sup>1</sup>

**Pertussis:** An acute infectious inflammation of the larynx, trachea, and bronchi caused by *Bordetella pertussis*; characterized by recurrent bouts of spasmodic coughing that continues until the breath is exhausted, then ending in a noisy inspiratory stridor (the “whoop”) caused by laryngeal spasm.<sup>1</sup>

**Pneumonia:** Inflammation of the lung parenchyma characterized by consolidation of the affected part, the alveolar air spaces being filled with exudate, inflammatory cells, and fibrin.<sup>1</sup>

**Polyarteritis nodosa:** Segmental inflammation, with infiltration by eosinophils, and necrosis of medium-sized or small arteries, more common in males, with varied symptoms related to involvement of arteries in the kidneys, muscles, gastrointestinal tract, and heart.<sup>1</sup>

**Psoriatic arthritis:** The concurrence of psoriasis and polyarthrits, resembling rheumatoid arthritis but thought to be a specific disease entity, seronegative for rheumatoid factor and often involving the digits.<sup>1</sup>

**Randomized controlled trial (RCT):** An epidemiologic experiment in which subjects in a population are randomly allocated into groups, usually called study and control groups, to receive or not receive an experimental preventive or therapeutic procedure, maneuver, or intervention. The results are assessed by rigorous comparison of rates of disease, death, recovery, or other appropriate outcome in the study and control groups. RCTs are generally regarded as the most scientifically rigorous method of hypothesis testing available in epidemiology and medicine. Nonetheless, they may suffer serious lack of generalizability, due, for example, to the nonrepresentativeness of patients who are ethically and practically eligible, chosen, or consent to participate.<sup>4</sup>

**Reactive arthritis:** Sterile, usually transient polyarthropathy following various infectious diseases.<sup>1</sup>



**Retrospective study:** A research design used to test etiologic hypotheses in which inferences about exposure to the putative causal factor(s) are derived from data relating to characteristics of the persons under study or to events or experiences in their past. The essential feature is that some of the persons under study have the disease or other outcome or condition of interest, and their characteristics and past experiences are compared with those of unaffected persons.<sup>4</sup>

**Rheumatoid arthritis:** A generalized disease, occurring more often in women, which primarily affects connective tissue; arthritis is the dominant clinical manifestation, involving many joints, especially those of the hands and feet, accompanied by thickening of articular soft tissue, with extension of synovial tissue over articular cartilages, which become eroded; the course is variable but often is chronic and progressive, leading to deformities and disability.<sup>1</sup>

**Rubella:** An acute but mild exanthematous disease caused by rubella virus (*Rubivirus* family *Togaviridae*), with enlargement of lymph nodes, but usually with little fever or constitutional reaction; a high incidence of birth defects in children results from maternal infection during the first trimester of fetal life (congenital rubella syndrome).<sup>1</sup>

**Seizure:** A violent spasm or series of jerkings of the face, trunk, or extremities. Also known as *convulsions*.<sup>1</sup>

**Self-controlled case-series study:** The method, like the case-crossover method, uses cases as their own controls. However, the similarity stops there, as the case-series method derives from cohort rather than case-control logic. In particular, ages at vaccination are regarded as fixed, and the random variable of interest is the age at adverse event, conditionally on its occurrence within a predetermined observation period.<sup>6</sup>

**Serum sickness:** An immune complex disease appearing some days (usually 1–2 weeks) after injection of a foreign serum or serum protein, with local and systemic reactions such as urticaria, fever, general lymphadenopathy, edema, arthritis, and occasionally albuminuria or severe nephritis; originally described in patients receiving serotherapy.<sup>1</sup>

**Shingles:** See Herpes zoster.

**Small fiber neuropathy:** Neuropathy of small unmyelinated axons.<sup>8</sup>

**Stroke:** Any acute clinical event, related to impairment of cerebral circulation, that lasts longer than 24 hours.<sup>1</sup>

**Sudden death:** Unexpected death that is instantaneous or occurs within minutes or hours from any cause other than violence.<sup>3</sup>

**Sudden infant death syndrome (SIDS):** The sudden death of an apparently healthy infant that remains unexplained after all known possible causes have been ruled out through autopsy, death scene investigation, and review of the medical history.<sup>1</sup>

**Surveillance:** Systematic and continuous collection, analysis, and interpretation of data, closely integrated with the timely and coherent dissemination of the results and assessment to those who have the right to know so action can be taken. It is an essential feature of epidemiologic and public health practice. The final phase in the surveillance chain is the application of information to health promotion and to disease prevention and control. A surveillance system includes functional capacity for data collection, analysis, and dissemination linked to public health programs.<sup>4</sup>

**Syncope:** Loss of consciousness and postural tone caused by diminished cerebral blood flow.<sup>1</sup>

**Systemic lupus erythematosus:** An inflammatory connective tissue disease with variable features, frequently including fever, weakness and fatigability, joint pains or arthritis resembling rheumatoid arthritis, diffuse erythematous skin lesions on the face, neck, or upper extremities, with liquefaction degeneration of the basal layer and epidermal atrophy, lymphadenopathy, pleurisy or pericarditis, glomerular lesions, anemia, hyperglobulinemia, and a positive LE cell test result, with serum antibodies to nuclear protein and sometimes to double-stranded DNA and other substances.<sup>1</sup>

**Tetanus:** A disease marked by painful tonic muscular contractions, caused by the neurotropic toxin (tetanospasmin) of *Clostridium tetani* acting on the central nervous system.<sup>1</sup>

**Thrombocytopenia:** A condition in which an abnormally small number of platelets is present in the circulating blood.<sup>1</sup>

**Thromboembolic events:** An occurrence that induces thromboembolism.<sup>2</sup>

**Thromboembolism:** Condition in which a blood clot forms in a vein that is deep inside the body; also known as *deep venous thrombosis*.<sup>2</sup>

**Transverse myelitis:** An abrupt onset inflammatory process involving almost the entire thickness of the spinal cord but of limited longitudinal extent, generally one or a few segments; of multiple etiologies, the most common being viral and postviral causes, and multiple sclerosis.<sup>1</sup>

**Urticaria:** An eruption of itching wheals, colloquially called hives, usually of systemic origin; it may be due to a state of hypersensitivity to foods or drugs, foci of infection, physical agents (heat, cold, light, friction), or psychic stimuli.<sup>1</sup>

**Vaccine Adverse Event Reporting System (VAERS):** A database managed by the Centers for Disease Control and Prevention and the Food and Drug Administration. VAERS provides a mechanism for the collection and analysis of adverse events associated with vaccines currently licensed in the United States. Reports to VAERS can be made by the vaccine manufacturer, recipient, their parent/guardian, or health care provider. For more information on VAERS call (800) 822-7967.<sup>5</sup>

**Vaccine Safety Datalink Project (VSD):** To increase knowledge about vaccine adverse events, the Centers for Disease Control and Prevention has formed partnerships with eight large health management organizations to continually evaluate vaccine safety. The project contains data on more than 6 million people. Medical records are monitored for potential adverse events following immunization. The VSD project allows for planned vaccine safety studies as well as timely investigations of hypothesis.<sup>5</sup>

**Varicella:** An acute contagious disease, usually occurring in children, caused by the varicella zoster virus genus, *Varicellovirus*, a member of the family Herpesviridae, and marked by a sparse eruption of papules, which become vesicles and then pustules, like that of smallpox although less severe and varying in stages, usually with mild constitutional symptoms; incubation period is about 14–17 days.<sup>1</sup>

**Vasculitis:** Inflammation of a blood vessel (arteritis, phlebitis) or lymphatic vessel (lymphangitis).<sup>1</sup>

## SOURCES

<sup>1</sup>This definition was obtained from *Stedman's Medical Dictionary*. The citation for the term is Stedman, Thomas Lathrop. 2006. *Stedman's medical dictionary*. Philadelphia: Lippincott Williams & Wilkins. © 2006.

<sup>2</sup>This definition was obtained by searching the term in the *A.D.A.M. Medical Encyclopedia*, a source used by the National Center for Biotechnology Information (NCBI), a division of the National Library of Medicine (NLM) at the National Institutes of Health (NIH). The citation

for the *A.D.A.M. Medical Encyclopedia* term is *A.D.A.M. Medical Encyclopedia* [Internet]. Atlanta (GA): A.D.A.M., Inc.; © 2010, and the specific term can be obtained on the following website: [http://www.ncbi.nlm.nih.gov/pubmedhealth/s/diseases\\_and\\_conditions](http://www.ncbi.nlm.nih.gov/pubmedhealth/s/diseases_and_conditions).

<sup>3</sup>This definition was obtained by searching the term in the *Merriam-Webster Medical Dictionary*, a source used by National Institutes of Health's Medline Plus website, which is produced by the National Library of Medicine. The citation for the *Merriam-Webster Medical Dictionary* term is *Merriam-Webster Medical Dictionary* [Internet]. [Springfield (MA)]: Merriam-Webster, Incorporated; © 2003, and the specific term can be obtained on the following website: <http://www.nlm.nih.gov/medlineplus/mplusdictionary.html>.

<sup>4</sup>This definition was obtained from *A Dictionary of Epidemiology*, fifth edition, a handbook sponsored by the International Epidemiology Association. The citation for the term is: Porta, M. 2008. *A Dictionary of Epidemiology*, 5th ed. New York, NY: Oxford University Press. © 2008.

<sup>5</sup>This definition was obtained from the Centers for Disease Control and Prevention as defined on the following webpage: [http://www.vaccines.gov/more\\_info/glossary/index.html](http://www.vaccines.gov/more_info/glossary/index.html).

<sup>6</sup>This definition was obtained from Farrington, C. P. 2004. Control without separate controls: Evaluation of vaccine safety using case-only methods. *Vaccine* 22(15-16):2064-2070. Elsevier Ltd. © 2004.

<sup>7</sup>This definition was obtained from Aminoff, M. J., and R. B. Daroff. 2003. *Encyclopedia of the neurological sciences*. 1st ed. 4 vols. Amsterdam: Boston. © 2003.

<sup>8</sup>This definition was obtained from the National Institute of Neurological Disorders and Stroke (NINDS) by searching the following webpage for the term: <http://www.ninds.nih.gov/>.



# Appendix B

## List of Adverse Events

TABLE B-1 Adverse Events Included in the Vaccine Chapters

| Adverse Event   | MMR Vaccine Chapter 4 | Varicella Vaccine Chapter 5 | Influenza Vaccine Chapter 6 | Hepatitis A Vaccine Chapter 7 | Hepatitis B Vaccine Chapter 8 | HPV Vaccine Chapter 9 | DT-, TT-, and aP-Containing Vaccines Chapter 10 | Meningococcal Vaccine Chapter 11 | Injected-Related Events Chapter 12 |
|---|-----------------------|-----------------------------|-----------------------------|-------------------------------|-------------------------------|-----------------------|---|----------------------------------|------------------------------------|
| Disseminated Oka VZV without Other Organ Involvement  |                       | ●                           |                             |                               |                               |                       |   |                                  |                                    |
| Disseminated Oka VZV with Subsequent Infection Resulting in Pneumonia, Meningitis, or Hepatitis     |                       | ●                           |                             |                               |                               |                       |   |                                  |                                    |
| Vaccine Strain Viral Reactivation without Other Organ Involvement                                   |                       | ●                           |                             |                               |                               |                       |   |                                  |                                    |
| Vaccine Strain Viral Reactivation with Subsequent Infection Resulting in Meningitis or Encephalitis |                       | ●                           |                             |                               |                               |                       |   |                                  |                                    |
| Measles Inclusion Body Encephalitis   | ●                     |                             |                             |                               |                               |                       |   |                                  |                                    |
| Encephalitis  | ●                     |                             | ●                           |                               | ●                             |                       | ●   | ●                                |                                    |
| Encephalopathy  | ●                     |                             | ●                           |                               | ●                             |                       | ●   | ●                                |                                    |
| Infantile Spasms  |                       |                             |                             |                               |                               |                       | ●   |                                  |                                    |
| Seizures  | ●                     |                             | ○                           |                               | ●                             |                       | ●   |                                  |                                    |





TABLE B-1 Continued

| Adverse Event                          | DT-, TT-, and aP-        |                                |                                |                                  |                                  |                          |                                   |                                     |   |   |   |   | Injected-Related Events<br>Chapter 12 |
|--|--------------------------|--------------------------------|--------------------------------|----------------------------------|----------------------------------|--------------------------|-----------------------------------|-------------------------------------|---|---|---|---|---------------------------------------|
|  | MMR Vaccine<br>Chapter 4 | Varicella Vaccine<br>Chapter 5 | Influenza Vaccine<br>Chapter 6 | Hepatitis A Vaccine<br>Chapter 7 | Hepatitis B Vaccine<br>Chapter 8 | HPV Vaccine<br>Chapter 9 | Containing Vaccines<br>Chapter 10 | Meningococcal Vaccine<br>Chapter 11 |   |   |   |   |                                       |
| Anaphylaxis                            | ●                        | ●                              | ●                              | ●                                | ●                                | ●                        | ●                                 | ●                                   | ● | ● | ● | ● |                                       |
| Chronic Urticaria                      |                          |                                |                                |                                  |                                  |                          |                                   |                                     |   |   |   |   | ●                                     |
| Serum Sickness                         |                          |                                |                                |                                  |                                  |                          |                                   |                                     |   |   |   | ● |                                       |
| Asthma                                 |                          | ●                              |                                |                                  |                                  |                          |                                   |                                     |   |   |   |   |                                       |
| Erythema Nodosum                       |                          |                                |                                |                                  | ○                                |                          |                                   |                                     |   |   |   |   |                                       |
| Systemic Lupus Erythematosus           |                          |                                | ●                              |                                  | ●                                |                          |                                   |                                     |   |   |   |   |                                       |
| Vasculitis                             |                          |                                | ●                              |                                  | ●                                |                          |                                   |                                     |   |   |   |   |                                       |
| Polyarteritis Nodosa                   |                          |                                | ●                              |                                  | ●                                |                          |                                   |                                     |   |   |   |   |                                       |
| Psoriatic Arthritis                    |                          |                                |                                |                                  | ●                                |                          |                                   |                                     |   |   |   |   |                                       |
| Reactive Arthritis                     |                          |                                |                                |                                  | ●                                |                          |                                   |                                     |   |   |   |   |                                       |
| Rheumatoid Arthritis                   |                          |                                |                                |                                  | ●                                |                          |                                   |                                     |   |   |   |   |                                       |
| Juvenile Idiopathic Arthritis          |                          |                                |                                |                                  | ●                                |                          |                                   |                                     |   |   |   |   |                                       |
| Arthropathy (Arthralgia and Arthritis) | ●                        | ●                              | ●                              |                                  |                                  | ●                        |                                   |                                     |   |   |   |   |                                       |
| Type 1 Diabetes                        | ●                        |                                |                                |                                  |                                  |                          |                                   |                                     |   |   |   |   | ●                                     |
| Hepatitis (Autoimmune)                 |                          |                                |                                | ●                                |                                  |                          |                                   |                                     |   |   |   |   |                                       |

|                                 |   |
|---------------------------------|---|
| Myocarditis                     | ● |
| Pancreatitis                    | ● |
| Hepatitis                       | ● |
| Thromboembolic Events           | ● |
| Stroke                          | ○ |
| Hypercoagulable States          | ● |
| Myocardial Infarction           | ● |
| Chronic Fatigue Syndrome        | ● |
| Chronic Headaches               | ● |
| Fibromyalgia                    | ● |
| Sudden Infant Death Syndrome    | ● |
| Hearing Loss                    | ● |
| All-Cause Mortality             | ○ |
| Oculorespiratory Syndrome       | ● |
| Thrombocytopenia                | ● |
| Immune Thrombocytopenic Purpura | ● |
| Complex Regional Pain Syndrome  | ● |
| Deltoid Bursitis                | ● |
| Syncope                         | ● |

NOTE: Adverse events indicated by “○” were added to the list by the committee.



## Appendix C

### Literature Search Strategy

This appendix contains a detailed explanation of how the literature searches were performed for each vaccine and adverse event reviewed by the committee. The searches were performed by William Mcleod, Senior Research Librarian at the National Academies.

#### DESCRIPTION OF THE DATABASES USED IN THE LITERATURE SEARCH

All searches were run against MEDLINE (1950–present), EMBASE (1980–present), BIOSIS (1969–2005), and Web of Science consisting of Science Citation Index (1900–present) and Social Science Citation Index (1956–present). There were no restrictions placed on year of publication, language, or publication type. All result sets were deduplicated to eliminate occurrence of the same reference two or more times among the databases employed, and all results were exported to an EndNote Library.

#### MEDLINE and EMBASE (in OVID SP)

OVID command-line syntax is provided below. Terms immediately followed by a forward slash (/) are Medical Subject Headings (MeSH headings from MEDLINE) or EMTREE terms (from the EMBASE controlled vocabulary). The asterisk after some terms (\*) is the OVID unlimited truncation symbol (for example, *rat\**, will retrieve *rat*, *rats*, *ratify*, *rational*, etc.). The postqualification *.ti,ab*. means that a term was searched only in the titles and abstracts. *Exp* means that a term was “exploded” in the MeSH

or EMTREE vocabulary to also capture all narrower terms associated with the broader concept.

### **BIOSIS (in OVID SP) and Web of Science (Science Citation Index and Social Science Citation Index)**

All BIOSIS search terms were submitted to the database using keyword or keyword-phrase searches and were not qualified or limited to a specific field. In OVID SP BIOSIS, when a search term is not qualified, it is automatically searched in the following fields: abstract; biosystematic code; book title; chemicals and biochemicals; concept codes; diseases; gene name; major concepts; miscellaneous descriptors; methods and equipment; organisms; parts, structure; sequence data; super taxa; titles; taxa notes; text words; heading words; subject headings; and meeting information.

All Web of Science searches were submitted to the databases as topic searches that automatically search titles, abstracts, and author-supplied keywords.

### **MEASLES, MUMPS, AND RUBELLA VACCINE**

#### **Measles, Mumps, and Rubella Vaccine Searches in MEDLINE and EMBASE (in OVID SP)**

Measles, mumps, and rubella vaccine searches in MEDLINE and EMBASE started with four “base sets” with which all specific adverse events identified for consideration were combined:

1. Measles mumps rubella vaccine/
2. (Measles vaccine/ or (vaccination/ and measles/))
3. (Mumps vaccine/ or (vaccination/ and mumps/))
4. (Rubella vaccine/ or (vaccination/ and rubella/))

Each set above was combined with each of the sets below. Each pair resulting from this combination was deduplicated, when the online database provided this utility, and then exported to an EndNote library:

- Anaphylaxis/ or anaphylactic shock/
- Exp arthralgia/ or exp arthritis/ or arthropathy, neurogenic/ or exp arthropathy/
- Autistic disorder/ or autism/ or infantile autism/
- (Asperger syndrome/ or Rett syndrome/ or schizophrenia, childhood/ or child development disorders, pervasive/ or childhood

disintegrative disorder/ or pervasive development disorder not otherwise specified/

- Exp ataxia/
- Brachial plexus neuritis/
- Chronic fatigue syndrome/ or fatigue syndrome, chronic/
- Chronic inflammatory demyelinating polyneuropathy/ or polyradiculoneuropathy, chronic inflammatory demyelinating/ or exp multiple sclerosis
- Exp complex regional pain syndromes/ or exp complex regional pain syndrome/
- Seizures/ or seizures, febrile/ or convulsion/ or exp epilepsies, myoclonic/ or spasms, infantile/ or myoclonus epilepsy/ or myoclonus seizure/ or myoclonus/ or convulsion?.ti,ab.
- Exp encephalitis/ or exp encephalitis, viral/
- Exp brain disease/ or encephal\*.ti,ab.
- Fibromyalgia/
- Frozen shoulder/ or exp bursitis/ or shoulder impingement syndrome/ or exp synovitis/
- Exp hearing loss/
- Hepatitis/
- Diabetes mellitus, type 1/ or insulin-dependent diabetes mellitus/
- Exp Guillain-Barré syndrome/ or myelitis, transverse/ or encephalomyelitis, acute disseminated/
- Opsoclonus-myoclonus syndrome/
- Exp syncope/

#### **Measles, Mumps, and Rubella Vaccine Searches in BIOSIS (in OVID SP) and Web of Science (Science Citation Index and Social Science Citation Index)**

Measles, mumps, and rubella vaccine searches in BIOSIS and Web of Science started with four “base sets” with which all specific adverse events identified for consideration were combined:

1. (((“Measles mumps rubella” or MMR) adj vaccin\*) or “Triviraten Berna” or Priorix or Trimovax or Virivac or Pluserix)
2. (Measles vaccin\* or ((vaccin\* or immuniz\*) and measles))
3. (Mumps vaccin\* or ((vaccin\* or immuniz\*) and mumps))
4. (Rubella vaccin\* or ((vaccin\* or immuniz\*) and rubella))

Each set above was combined with each of the sets below. Each pair was deduplicated, when the online database provided this utility, and then exported to an EndNote library:

- Anaphylaxis or anaphylactic shock or anaphylactic reaction
- Arthropath\* or arthrit\* or arthralgia
- (Autism or autistic or “Kanner? syndrome”)
- (“Autism spectrum” or “Rett? syndrome” or “Asperger? syndrome” or “child\* schizophrenia” or “pervasive child\* development\* disorder?” or “pervasive development disorder?” or “disintegrative disorder?”)
- (Ataxia? or “coordination impairment?” or dyssynergia or rubral tremor?)
- (“Brachial plexus neuritis” or “brachial neuritis” or “brachial neuralgia?” or “amyotroph\* neuralgi\*” or “cervicobrachial neuralgia?” or “cervico-brachial neuralgia?” or “Parsonage-Turner syndrome” or “Parsonage-Aldren-Turner syndrome” or “brachial neuritides” or “shoulder-girdle neuropath\*” or “brachial plexus neuritides”)
- (“Fatigue syndrome?” or “chronic fatigue” or “myalgic encephalomyelitis” or “fatigue disorder” or “royal free disease” or “postviral fatigue syndrome?”)
- (“Chronic remitting demyelinating disease?” or “disseminated neuropathy”)
- (Polyneuropath\* or polyradiculoneuropath\* or multiple sclerosis)
- (Complex regional pain or causalgia or reflex sympathetic dystrophy)
- (Epileps\* or myoclon\* or spasm\* or convulsion? or seizure?)
- (Encephalitis or brain inflammation or encephalomyelitis)
- Brain disease? or encephal\*
- (Fibromyalgia? or fibrositis or fibrositides or “myofascial pain syndrome”)
- (Frozen shoulder or bursitis or synovitis or synovitides or bursitides or adhesive capsulitis or adhesive capsulitides or peri-arthritis or peri-arthritis or shoulder impingement or subacromial impingement)
- (“Hearing loss” or deafness or hypoacusis or hypoacusis or “hearing impairment”)
- Hepatitis
- (“Insulin-dependent diabetes” or “type-1 diabetes” or “juvenile-onset diabetes” or “sudden-onset diabetes” or IDDM or “brittle diabetes” or “autoimmune diabetes” or “ketosis-prone diabetes”)
- (Meningitis or meningo\* or meningeal or arachnoiditis or meningitides or pachymeningitis or pachymeningitides)
- Demyelinating or encephalomyelitis or “Guillain Barre” or myelitis
- (“Opsoclonus myoclonus syndrome” or “dancing eyes dancing feet

syndrome” or “opsoclonus myoclonus ataxia” or “Kinsbourne syndrome”)

- (Syncope or syncopes or syncopal or fainting or (vasovagal adj (collapse or attack or shock or reaction)))

## VARICELLA VACCINE

### Varicella Vaccine Searches in MEDLINE and EMBASE (in OVID SP)

Varicella vaccine searches in MEDLINE and EMBASE started with one “base set” with which all specific adverse events identified for consideration were combined:

1. Exp chickenpox vaccine/ or ((vaccines/ or vaccination/) and chickenpox/)

The set above was combined with each of the sets below. Each pair resulting from this combination was deduplicated, when the online database provided this utility, and then exported to an EndNote library:

- Anaphylaxis/ or anaphylactic shock/
- Exp arthralgia/ or exp arthritis/ or arthropathy, neurogenic/ or exp arthropathy/
- Exp cerebellar ataxia/ or spinocerebellar ataxias/ or ataxia telangiectasia/ or Machado-Joseph disease/
- Exp myocardial infarction/ or exp stroke/ or exp death, sudden/
- Seizures/ or seizures, febrile/ or convulsion/ or exp epilepsies, myoclonic/ or spasms, infantile/ or myoclonus epilepsy/ or myoclonus seizure/ or myoclonus/ or convulsion?.ti,ab.
- “Oka VZV”.ti,ab,sh. or “Oka varicella”.ti,ab.
- (“Varicella zoster virus”.mp. or “herpesvirus 3, human”/) and (immunocompromis\* or immunosuppress\*)
- (Disseminat\* adj2 Oka)
- Exp brain disease/ or encephal\*.ti,ab.
- Exp encephalitis/ or exp encephalitis, viral/
- Frozen shoulder/ or exp bursitis/ or shoulder impingement syndrome/ or exp synovitis/
- (Hepatitis adj3 varicella).ti,ab. [Looks for hepatitis within 3 words, minus stop words (articles, prepositions) of varicella in any order.]
- Exp meningitis/
- Exp Guillain-Barré syndrome/ or myelitis, transverse/ or encephalomyelitis, acute disseminated/
- Exp pneumonia/



- Exp stroke/ or exp myocardial infarction/ or exp death, sudden/
- Exp syncope/
- Exp lupus erythematosus, systemic/
- Exp thrombocytopenia/ or hemolytic-uremic syndrome/ or Jacobson distal 11q deletion syndrome/ or purpura, thrombocytopenic/ or thrombocytopenia, neonatal alloimmune/

### **Varicella Vaccine Searches in BIOSIS (in OVID SP) and Web of Science (Science Citation Index and Social Science Citation Index)**

Varicella vaccine searches in BIOSIS and Web of Science started with one “base set” with which all specific adverse events identified for consideration were combined:

1. (Chickenpox vaccin\* or varicella vaccin\*) or ((vaccin\* or immuniz\*) and (chicken pox or varicella))

The set above was combined with each of the sets below. Each pair was deduplicated, when the online database provided this utility, and then exported to an EndNote library:

- Anaphylaxis or anaphylactic shock or anaphylactic reaction
- Arthropathy or arthritis or arthralgia
- Cerebellar ataxia? or cerebellar incoordination? or cerebellar dysmetria? or hypermetria? or adiadochokinesis or adiadochokineses or cerebellar hemiataxia? or spinocerebellar ataxia\* or spinocerebellar atrophy or ataxia telangiectasia or Machado-Joseph disease or Louis-Bar syndrome or Azorean disease
- (“Myocardial infarction?” or “heart attack” or stroke or “sudden death”)
- Convulsion? or spasm? or myoclon\* or seizure?
- Oka vzv or Oka varicella
- (Disseminat\* adj2 Oka)
- Brain disease? or encephal\* or brain disorder?
- (Frozen shoulder or bursitis or synovitis or synovitides or bursitides or adhesive capsulitis or adhesive capsulitides or peri-arthritis or peri-arthritis or shoulder impingement or subacromial impingement)
- Varicella adj3 hepatitis [varicella within 3 words, minus stop-words, of hepatitis]
- Meningitis or meningitides or pachymeningitis or pachymeningitides or meningoencephalitis or arachnoiditis
- Demyelinating or encephalomyelitis or “Guillain Barre” or myelitis

- (Varicella zoster virus or “herpesvirus 3” or “VZ virus\*” or “HHV-3” or “ocular herpes zoster virus” or “chickenpox virus\*” or “herpesvirus varicellae”) and (immunocompromis\* or immunosuppres\*)
- Pneumonia or “lung inflammation” or “pulmonary inflammation”
- (Stroke or “myocardial infarction?” or “heart attack” or “sudden death”)
- (Syncope or syncopes or syncopal or fainting or (vasovagal adj (collapse or attack or shock or reaction)))
- “Systemic lupus erythematosus” or “Libman-Sacks” or “systemic lupus”
- Thrombocytopenia? or thrombopenia? or hemolytic-uremic syndrome

## INFLUENZA VACCINE

### Influenza Vaccine Searches in MEDLINE and EMBASE (in OVID SP)

Influenza vaccine searches in MEDLINE and EMBASE started with one “base set” with which all specific adverse events identified for consideration were combined:

1. Influenza vaccines/ or (vaccination/ and influenza, human/)

The set above was combined with each of the sets below. Each pair resulting from this combination was deduplicated, when the online database provided this utility, and then exported to an EndNote library:

- Anaphylaxis/ or anaphylactic shock/
- Exp arthralgia/ or exp arthritis/ or arthropathy, neurogenic/ or exp arthropathy/
- Asthma/ or status asthmaticus/
- Bell palsy/
- Brachial plexus neuritis/
- Exp myocardial infarction/ or exp stroke/ or exp death, sudden/
- Chronic inflammatory demyelinating polyneuropathy/ or polyradiculoneuropathy, chronic inflammatory demyelinating/ or exp multiple sclerosis/ or neuromyelitis optica/
- Exp complex regional pain syndromes/ or exp complex regional pain syndrome/
- Seizures/ or seizures, febrile/ or convulsion/ or exp epilepsies, myoclonic/ or spasms, infantile/ or myoclonus epilepsy/ or myoclonus seizure/ or myoclonus/ or convulsion?.ti,ab.

- Exp encephalitis/ or exp encephalitis, viral/
- Exp brain disease/ or encephalopath\*.ti,ab.
- Fibromyalgia/
- Frozen shoulder/ or exp bursitis/ or shoulder impingement syndrome/ or exp synovitis/
- Exp Guillain-Barré syndrome/ or myelitis, transverse/ or encephalomyelitis, acute disseminated/
- “Oculorespiratory syndrome?”.ti,ab.
- Polyarteritis nodosa/
- “Small fiber neuropath\*”.ti,ab.
- Exp lupus erythematosus, systemic/
- Exp syncope/
- Exp Vasculitis/

#### **Influenza Vaccine Searches in BIOSIS (in OVID SP) and Web of Science (Science Citation Index and Social Science Citation Index)**

Influenza vaccine searches in BIOSIS and Web of Science started with one “base set” with which all specific adverse events identified for consideration were combined:

1. (Flu vaccine or influenza vaccine? or ((vaccin\* or immuniz\*) and (influenza or flu)))

The set above was combined with each of the sets below. Each pair was deduplicated, when the online database provided this utility, and then exported to an EndNote library:

- Anaphylaxis or anaphylactic shock or anaphylactic reaction
- Arthropath\* or arthrit\* or arthralgia
- Asthma\*
- (“Bell? palsy” or “facial paraly\*” or “facial neuropath\*”)
- (Brachial neuritis or brachial plexus neuritis or neuralgia or brachial plexus neuropath\*)
- (“Myocardial infarction?” or “heart attack” or stroke or “sudden death”)
- (“Chronic remitting demyelinating disease?” or “disseminated neuropathy” or “multiple sclerosis” or “neuromyelitis optica”)
- (Polyneuropath\* or polyradiculoneuropath\* or multiple sclerosis or neuromyelitis optica)
- (Complex regional pain or causalgia or reflex sympathetic dystrophy)
- (Epileps\* or myoclon\* or spasm\* or convulsion? or seizure?)

- (Encephalitis or brain inflammation or encephalomyelitis)
- Brain disease? or encephal\*"
- (Fibromyalgia? or fibrositis or fibrositides or "myofascial pain syndrome")
- (Frozen shoulder or bursitis or synovitis or synovitides or bursitides or adhesive capsulitis or adhesive capsulitides or peri-arthritis or peri-arthritis or shoulder impingement or subacromial impingement)
- Demyelinating or encephalomyelitis or "Guillain Barre" or myelitis
- "Oculorespiratory syndrome?"
- ("Polyarteritis nodosa" or "periarteritis nodosa" or "essential polyarteritis" or "necrotizing arteritis")
- "Small fiber neuropath\*"
- "Systemic lupus" or "Libman-Sacks"
- (Syncope or syncopes or syncopal or fainting or (vasovagal adj (collapse or attack or shock or reaction)))
- (Vasculitis or vasculitides or angiitis or angiitides or aortitis or arteritis or phlebitis or "Behcet syndrome" or "Wegener granulomatosis" or thrombophlebitis or papulosis)

## HEPATITIS A VACCINE

### Hepatitis A Vaccine Searches in MEDLINE and EMBASE (in OVID SP)

Hepatitis A vaccine searches in MEDLINE and EMBASE started with one "base set" with which all specific adverse events identified for consideration were combined:

1. (Hepatitis a vaccines/ or ((vaccination/ or vaccines/) and (hepatitis a/ or hepatitis a virus, human/)))

The set above was combined with each of the sets below. Each pair resulting from this combination was deduplicated, when the online database provided this utility, and then exported to an EndNote library:

- Anaphylaxis/ or anaphylactic shock/
- Bell palsy/
- Chronic inflammatory demyelinating polyneuropathy/ or polyradiculoneuropathy, chronic inflammatory demyelinating/ or exp multiple sclerosis
- Frozen shoulder/ or exp bursitis/ or shoulder impingement syndrome/ or exp synovitis/
- Hepatitis, autoimmune/ or autoimmune hepatitis/

- Exp Guillain-Barre syndrome/ or myelitis, transverse/ or encephalomyelitis, acute disseminated/
- Exp syncope/

### Hepatitis A Vaccine Searches in BIOSIS (in OVID SP) and Web of Science (Science Citation Index and Social Science Citation Index)

Hepatitis A vaccine searches in BIOSIS and Web of Science started with one “base set” with which all specific adverse events identified for consideration were combined:

1. (“Hepatitis a vaccin\*” or ((vaccin\* or immuniz\*) and hepatitis a))

The set above was combined with each of the sets below. Each pair was deduplicated, when the online database provided this utility, and then exported to an EndNote library:

- Anaphylaxis or anaphylactic shock or anaphylactic reaction
- (“Bell? palsy” or “facial paraly\*” or “facial neuropath\*”)
- (“Chronic remitting demyelinating disease?” or “disseminated neuropathy”)
- (Polyneuropath\* or polyradiculoneuropath\* or multiple sclerosis)
- (Frozen shoulder or bursitis or synovitis or synovitides or bursitides or adhesive capsulitis or adhesive capsulitides or peri-arthritis or peri-arthritis or shoulder impingement or subacromial impingement)
- Autoimmune hepatitis
- Demyelinating or encephalomyelitis or “Guillain Barre” or myelitis
- (Syncope or syncopes or syncopal or fainting or (vasovagal adj (collapse or attack or shock or reaction)))

## HEPATITIS B VACCINE

### Hepatitis B Vaccine Searches in MEDLINE and EMBASE (in OVID SP)

Hepatitis B vaccine searches in MEDLINE and EMBASE started with one “base set” with which all specific adverse events identified for consideration were combined:

1. Hepatitis b vaccines/ or (vaccination/ and (hepatitis b virus/ or hepatitis b/)) /)

The set above was combined with each of the sets below. Each pair result-

ing from this combination was deduplicated, when the online database provided this utility, and then exported to an EndNote library:

- Anaphylaxis/ or anaphylactic shock/
- Exp arthralgia/ or exp arthritis/ or arthropathy, neurogenic/ or exp arthropathy/
- Brachial plexus neuritis/
- Chronic inflammatory demyelinating polyneuropathy/ or polyradiculoneuropathy, chronic inflammatory demyelinating/ or exp multiple sclerosis/ or neuromyelitis optica/
- Exp complex regional pain syndrome/ or exp complex regional pain syndromes/
- Seizures/ or seizures, febrile/ or convulsion/ or exp epilepsies, myoclonic/ or spasms, infantile/ or myoclonus epilepsy/ or myoclonus seizure/ or myoclonus/ or convulsion?.ti,ab.
- Exp encephalitis/ or exp encephalitis, viral/
- Exp brain disease/ or encephalopath\*.ti,ab.
- Erythema nodosum/
- Fibromyalgia/
- Frozen shoulder/ or exp bursitis/ or shoulder impingement syndrome/ or exp synovitis/
- Exp Guillain-Barré syndrome/ or myelitis, transverse/ or encephalomyelitis, acute disseminated/
- Polyarteritis nodosa/
- Exp lupus erythematosus, systemic/
- Exp syncope/
- Exp vasculitis/

#### **Hepatitis B Vaccine Searches in BIOSIS (in OVID SP) and Web of Science (Science Citation Index and Social Science Citation Index)**

Hepatitis B vaccine searches in BIOSIS and Web of Science started with one “base set” with which all specific adverse events identified for consideration were combined:

1. (“Hepatitis b vaccin\*” or ((vaccin\* or immuniz\*) and hepatitis b))

The set above was combined with each of the sets below. Each pair was deduplicated, when the online database provided this utility, and then exported to an EndNote library:

- Anaphylaxis or anaphylactic shock
- (Arthrit\* or arthropath\* or arthralgia)

- (Brachial neuritis or brachial plexus neuritis or neuralgia or brachial plexus neuropath\*)
- (Polyneuropath\* or polyradiculoneuropath\* or multiple sclerosis or neuromyelitis optica)
- (Complex regional pain or causalgia or reflex sympathetic dystrophy)
- (Epileps\* or myoclon\* or spasm\* or convulsion? or seizure?)
- (Encephalitis or brain inflammation or encephalomyelitis)
- (Encephal\* or brain disease?)
- (Erythema nodosum or erythematous)
- (Fibromyalgia? or fibrositis or fibrositides or “myofascial pain syndrome”)
- (Frozen shoulder or bursitis or synovitis or synovitides or bursitides or adhesive capsulitis or adhesive capsulitides or peri-arthritis or periarthritides or shoulder impingement or subacromial impingement)
- (Guillain-Barré or myelitis or encephalomyelitis)
- (Polyarteritis or periarteritis or necrotizing arteritis)
- (Syncope or syncopes or syncopal or fainting or (vasovagal adj (collapse or attack or shock or reaction)))
- (Systemic lupus or Libman-Sacks disease)
- (Vasculitis or angiitis or angiitides or aortitis or arteritis or Behcet syndrome or phlebitis or thrombophlebitis or endarteritis)

## HUMAN PAPILLOMAVIRUS VACCINE

### Human Papillomavirus (HPV) Vaccine Searches in MEDLINE and EMBASE (in OVID SP)

HPV vaccine searches in MEDLINE and EMBASE started with one “base set” with which all specific adverse events identified for consideration were combined:

1. Papillomavirus vaccines/ or (vaccination/ and (papillomaviridae/ or papillomavirus infections/))

The set above was combined with each of the sets below. Each pair resulting from this combination was deduplicated, when the online database provided this utility, and then exported to an EndNote library:

- Amyotrophic lateral sclerosis/
- Anaphylactic shock/ or anaphylaxis/

- Exp arthralgia/ or exp arthritis/ or arthropathy, neurogenic/ or exp arthropathy/
- Brachial plexus neuritis/
- Chronic inflammatory demyelinating polyneuropathy/ or polyradiculoneuropathy, chronic inflammatory demyelinating/ or exp multiple sclerosis/ or neuromyelitis optica/
- Seizures/ or seizures, febrile/ or convulsion/ or exp epilepsies, myoclonic/ or spasms, infantile/ or myoclonus epilepsy/ or myoclonus seizure/ or myoclonus/ or convulsion?.ti,ab.
- Exp encephalitis/ or exp encephalitis, viral/
- Exp brain disease/ or encephal\*.ti,ab.
- Frozen shoulder/ or exp bursitis/ or shoulder impingement syndrome/ or exp synovitis/
- Hypercoagulab\*
- Exp Guillain-Barré syndrome/ or myelitis, transverse/ or encephalomyelitis, acute disseminated/
- Exp pancreatitis/
- Exp lupus erythematosus, systemic/
- Exp syncope/
- Thromboembolism/ or thromboembol\*

#### HPV Vaccine Searches in BIOSIS (in OVID SP) and Web of Science (Science Citation Index and Social Science Citation Index)

HPV vaccine searches in BIOSIS and Web of Science started with one “base set” with which all specific adverse events identified for consideration were combined:

1. (Papillomavirus vaccin\* or ((vaccin\* or immuniz\*) and (papillomaviridae or papillomavirus)))

The set above was combined with each of the sets below. Each pair was deduplicated, when the online database provided this utility, and then exported to an EndNote library:

- Amyotrophic lateral sclerosis
- Anaphylaxis or anaphylactic shock or anaphylactic reaction
- (Arthrit\* or arthropath\* or arthralgia)
- (Brachial neuritis or brachial plexus neuritis or neuralgia or brachial plexus neuropath\*)
- (Polyneuropath\* or polyradiculoneuropath\* or multiple sclerosis or neuromyelitis optica)
- (Epileps\* or myoclon\* or spasm\* or convulsion? or seizure?)



- (Encephalitis or brain inflammation or encephalomyelitis)
- (Encephal\* or brain disease?)
- (Frozen shoulder or bursitis or synovitis or synovitides or bursitides or adhesive capsulitis or adhesive capsulitides or peri-arthritis or peri-arthritis or shoulder impingement or subacromial impingement)
- Hypercoagulab\*
- (Guillain-Barré or encephalomyelitis or myelitis or demyelinating)
- Pancreatitis
- (Systemic lupus or Libman-Sacks disease)
- (Syncope or syncopes or syncopal or fainting or (vasovagal adj (collapse or attack or shock or reaction)))
- Thromboembol\*

### DIPHTHERIA TOXOID–, TETANUS TOXOID–, AND ACELLULAR PERTUSSIS–CONTAINING VACCINES

#### Diphtheria Toxoid (DT)–, Tetanus Toxoid (TT)–, and Acellular Pertussis (aP)–Containing Vaccine Searches in MEDLINE and EMBASE (in OVID SP)

DT–, TT–, and aP–containing vaccine searches in MEDLINE and EMBASE started with one “base set” with which all specific adverse events identified for consideration were combined:

1. (Diphtheria-tetanus-acellular pertussis vaccines/ or diphtheria pertussis tetanus vaccine/ or tetanus toxoid/ or “diphtheria-tetanus vaccine”/ or (“diphtheria tetanus” or “tetanus diphtheria” or “tetanus and diphtheria” or “diphtheria and tetanus”).ti,ab. or “tetanus toxoid”.mp. or DTaP.mp. or TDaP.mp. or (vaccin\* adj5 (DT or TD or TT)).mp. or “tetanus diphtheria acellular pertussis”.mp. or “tetanus diphtheria and acellular pertussis”.mp.)

The set above was combined with each of the sets below. Each pair resulting from this combination was deduplicated, when the online database provided this utility, and then exported to an EndNote library:

- Anaphylaxis/ or anaphylactic shock/
- Exp ataxia/
- Exp arthralgia/ or exp arthritis/ or arthropathy, neurogenic/ or exp arthropathy/
- Autistic disorder/ or autism/ or infantile autism/
- (Asperger syndrome/ or Rett syndrome/ or schizophrenia, childhood/ or child development disorders, pervasive/ or childhood disinte-

- grative disorder/ or pervasive development disorder not otherwise specified/
- Bell palsy/
  - Chronic inflammatory demyelinating polyneuropathy/ or polyradiculoneuropathy, chronic inflammatory demyelinating/ or exp multiple sclerosis
  - Exp urticaria/
  - Exp complex regional pain syndromes/ or exp complex regional pain syndrome/
  - Seizures/ or seizures, febrile/ or convulsion/ or exp epilepsies, myoclonic/ or spasms, infantile/ or myoclonus epilepsy/ or myoclonus seizure/ or myoclonus/ or convulsion?.ti,ab.
  - Exp encephalitis/ or exp encephalitis, viral/
  - Exp brain disease/ or encephal\*.ti,ab.
  - Fibromyalgia/
  - Frozen shoulder/ or exp bursitis/ or shoulder impingement syndrome/ or exp synovitis/
  - Exp purpura, thrombocytopenic, idiopathic/ or idiopathic thrombocytopenic purpura/
  - Diabetes mellitus, type 1/ or insulin-dependent diabetes mellitus/
  - Exp Guillain-Barré syndrome/ or myelitis, transverse/ or encephalomyelitis, acute disseminated/
  - Myocarditis/
  - Opsoclonus-myoclonus syndrome/
  - Exp optic neuritis/
  - Serum sickness/
  - Sudden infant death/
  - Exp syncope/

#### DT-, TT-, and aP-Containing Vaccine Searches in BIOSIS (in OVID SP) and Web of Science (Science Citation Index and Social Science Citation Index)

DT-, TT-, and aP-containing vaccine searches in BIOSIS and Web of Science started with one “base set” with which all specific adverse events identified for consideration were combined:

1. (((“Diphtheria tetanus acellular pertussis” or “tetanus diphtheria acellular pertussis” or “diphtheria tetanus” or “tetanus diphtheria” or “tetanus toxoid” or “tetanus and diphtheria” or “diphtheria and tetanus” or DTaP or TDAP or DT or TD or TT) adj5 (vaccin\* or immuniz\*)) or Tripedia or “Acel-Imune” or Acelimune or Infanrix)

The set above was combined with each of the sets below. Each pair was deduplicated, when the online database provided this utility, and then exported to an EndNote library:

- Anaphylaxis or anaphylactic shock or anaphylactic reaction
- Arthropath\* or arthrit\* or arthralgia
- (Autism or autistic or “Kanner? syndrome”)
- (“Autism spectrum” or “Rett? syndrome” or “Asperger? syndrome” or “child\* schizophrenia” or “pervasive child\* development\* disorder?” or “pervasive development disorder?” or “disintegrative disorder?”)
- (Ataxia? or “coordination impairment?” or dyssynergia or rubral tremor?)
- (“Bell? palsy” or “facial paraly\*” or “facial neuropath\*”)
- (“Chronic remitting demyelinating disease?” or “disseminated neuropathy”)
- (Polyneuropath\* or polyradiculoneuropath\* or multiple sclerosis)
- (Urticaria? or hives or angioedema)
- (Complex regional pain or causalgia or reflex sympathetic dystrophy)
- (Epileps\* or myoclon\* or spasm\* or convulsion? or seizure?)
- (Encephalitis or brain inflammation or encephalomyelitis)
- Brain disease? or encephal\*
- (Fibromyalgia? or fibrositis or fibrositides or “myofascial pain syndrome”)
- (Frozen shoulder or bursitis or synovitis or synovitides or bursitides or adhesive capsulitis or adhesive capsulitides or peri-arthritis or periarthritides or shoulder impingement or subacromial impingement)
- (“Idiopathic thrombocytopenic purpura?” or “Werlhof? disease” or “autoimmune thrombocytopenic purpura?” or “autoimmune thrombocytopenia?”)
- (“Insulin-dependent diabetes” or “type-1 diabetes” or “juvenile-onset diabetes” or “sudden-onset diabetes” or IDDM or “brittle diabetes” or “autoimmune diabetes” or “ketosis-prone diabetes”)
- Demyelinating or encephalomyelitis or “Guillain Barre” or myelitis
- (Myocarditis or carditis or myocarditides)
- (“Opsoclonus myoclonus syndrome” or “dancing eyes dancing feet syndrome” or “opsoclonus myoclonus ataxia” or “Kinsbourne syndrome”)
- (“Optic neuritis” or “optic neuritides” or neuropapillitis or neuro-papillitides or “retrobulbar neuritis”)
- (“Serum sickness?” or “serum disease” or “plasma sensitivity”)

- (“Sudden infant death” or SIDS or “cot death” or “unexpected infant death”)
- (Syncope or syncopes or syncopal or fainting or (vasovagal adj (collapse or attack or shock or reaction)))

## MENINGOCOCCAL VACCINE

### Meningococcal Vaccine Searches in MEDLINE and EMBASE (in OVID SP)

Meningococcal vaccine searches in MEDLINE and EMBASE started with one “base set” with which all specific adverse events identified for consideration were combined:

1. (Meningococcal vaccines/ or MPSV4.mp. or menomune.mp. or MCV4.mp. or menactra.mp. or ((vaccination/ or vaccines/) and exp meningitis/))

The set above was combined with each of the sets below. Each pair resulting from this combination was deduplicated, when the online database provided this utility, and then exported to an EndNote library:

- Anaphylaxis/ or anaphylactic shock/
- Exp headache disorders/ or (chronic adj2 headache?)
- Chronic inflammatory demyelinating polyneuropathy/ or polyradiculoneuropathy, chronic inflammatory demyelinating/ or exp multiple sclerosis
- Exp encephalitis/ or exp encephalitis, viral/
- Exp brain disease/ or encephal\*.ti,ab.
- Frozen shoulder/ or exp bursitis/ or shoulder impingement syndrome/ or exp synovitis/
- Exp Guillain-Barré syndrome/ or myelitis, transverse/ or encephalomyelitis, acute disseminated/
- Exp syncope/

### Meningococcal Vaccine Searches in BIOSIS (in OVID SP) and Web of Science (Science Citation Index and Social Science Citation Index)

Meningococcal vaccine searches in BIOSIS and Web of Science started with one “base set” with which all specific adverse events identified for consideration were combined:

1. (Mening\* vaccin\* or ((vaccin\* or immuniz\*) and meningitis))

The set above was combined with each of the sets below. Each pair was deduplicated, when the online database provided this utility, and then exported to an EndNote library:

- Anaphylaxis or anaphylactic shock or anaphylactic reaction
- ((Chronic adj2 headache?) or headache disorder? or headache syndrome? or cephalgia syndrome? or intractable headache?)
- (“Chronic remitting demyelinating disease?” or “disseminated neuropathy”)
- (Polyneuropath\* or polyradiculoneuropath\* or multiple sclerosis)
- (Encephalitis or brain inflammation or encephalomyelitis)
- Brain disease? or encephal\*
- (Frozen shoulder or bursitis or synovitis or synovitides or bursitides or adhesive capsulitis or adhesive capsulitides or peri-arthritis or periarthritides or shoulder impingement or subacromial impingement)
- Demyelinating or encephalomyelitis or “Guillain Barre” or myelitis
- (Syncope or syncopes or syncopal or fainting or (vasovagal adj (collapse or attack or shock or reaction)))

# Appendix D

## Causality Conclusion Tables

TABLE D-1 Causality Conclusions Organized by Chapter and Adverse Event

| Chapter | Vaccine | Adverse Event                        | Epidemiologic Assessment | Mechanistic Assessment  | Causality Conclusion   |
|---------|---------|--------------------------------------|--------------------------|---|--|
| 4       | MMR     | Measles Inclusion Body Encephalitis  | Insufficient             | Strong (measles; in individuals with demonstrated immunodeficiencies)<br>Lacking (mumps or rubella) | Convincingly Supports <sup>a</sup> (in individuals with demonstrated immunodeficiencies) |
| 4       | MMR     | Encephalitis                         | Limited                  | Weak  | Inadequate   |
| 4       | MMR     | Encephalopathy                       | Limited                  | Weak  | Inadequate   |
| 4       | MMR     | Febrile Seizures                     | High (increase)          | Intermediate  | Convincingly Supports  |
| 4       | MMR     | Afebrile Seizures                    | Limited                  | Lacking   | Inadequate   |
| 4       | MMR     | Meningitis <sup>b</sup>              | Moderate (null)          | Weak (mumps)<br>Lacking (measles or rubella)  | Inadequate   |
| 4       | MMR     | Ataxia                               | Insufficient             | Weak (measles or mumps)<br>Lacking (rubella)  | Inadequate   |
| 4       | MMR     | Autism                               | High (null)              | Lacking   | Favors Rejection   |
| 4       | MMR     | Acute Disseminated Encephalomyelitis | Insufficient             | Weak  | Inadequate   |
| 4       | MMR     | Transverse Myelitis                  | Insufficient             | Weak  | Inadequate   |

|   |     |  |                                 |  |                                |
|---|-----|--|---------------------------------|--|--------------------------------|
| 4 | MMR | Optic Neuritis <sup>b</sup>                      | Limited                         | Weak   | Inadequate                     |
| 4 | MMR | Neuromyelitis Optica <sup>b</sup>                | Insufficient                    | Weak (rubella)<br>Lacking (measles or mumps) | Inadequate                     |
| 4 | MMR | Multiple Sclerosis Onset in Adults               | Limited                         | Lacking                                      | Inadequate                     |
| 4 | MMR | Multiple Sclerosis Onset in Children             | Limited                         | Lacking                                      | Inadequate                     |
| 4 | MMR | Guillain-Barré syndrome                          | Insufficient                    | Weak   | Inadequate                     |
| 4 | MMR | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient                    | Lacking                                      | Inadequate                     |
| 4 | MMR | Opsoclonus Myoclonus Syndrome                    | Insufficient                    | Lacking                                      | Inadequate                     |
| 4 | MMR | Brachial Neuritis                                | Insufficient                    | Lacking                                      | Inadequate                     |
| 4 | MMR | Anaphylaxis                                      | Insufficient                    | Strong                                       | Convincingly Supports          |
| 4 | MMR | Transient Arthralgia in Women                    | Moderate (increase) (rubella)   | Intermediate (rubella)                       | Favors Acceptance <sup>c</sup> |
|   |     |  | Insufficient (measles or mumps) | Lacking (measles or mumps)                   |                                |
| 4 | MMR | Transient Arthralgia in Children                 | Moderate (increase)             | Weak (rubella)<br>Lacking (measles or mumps) | Favors Acceptance              |

*continued*



TABLE D-1 Continued

| Chapter | Vaccine | Adverse Event                   | Epidemiologic Assessment                             | Mechanistic Assessment                                   | Causality Conclusion |
|---------|---------|---------------------------------|--|--|----------------------|
| 4       | MMR     | Chronic Arthralgia in Women     | Limited (rubella)<br>Insufficient (measles or mumps) | Low-Intermediate (rubella)<br>Lacking (measles or mumps) | Inadequate           |
| 4       | MMR     | Chronic Arthritis in Women      | Limited (rubella)<br>Insufficient (measles or mumps) | Low-Intermediate (rubella)<br>Lacking (measles or mumps) | Inadequate           |
| 4       | MMR     | Chronic Arthropathy in Children | Insufficient   | Weak (rubella)<br>Lacking (measles or mumps)             | Inadequate           |
| 4       | MMR     | Arthropathy in Men              | Limited  | Weak (rubella)<br>Lacking (measles or mumps)             | Inadequate           |
| 4       | MMR     | Type 1 Diabetes                 | High (null)  | Lacking  | Favors Rejection     |
| 4       | MMR     | Hepatitis                       | Insufficient   | Weak   | Inadequate           |
| 4       | MMR     | Chronic Fatigue Syndrome        | Insufficient   | Lacking  | Inadequate           |
| 4       | MMR     | Fibromyalgia                    | Insufficient   | Lacking  | Inadequate           |

|   |           |   |   |  |   |
|---|-----------|---|---|--|---|
| 4 | MMR       | Hearing Loss  | Insufficient  | Low-Intermediate (measles or mumps)<br>Lacking (rubella)     | Inadequate  |
| 5 | Varicella | Disseminated Oka VZV without Other Organ Involvement  | Insufficient  | Strong   | Convincingly Supports   |
| 5 | Varicella | Disseminated Oka VZV with Subsequent Infection Resulting in Pneumonia, Meningitis, or Hepatitis     | Limited (subsequent infection resulting in pneumonia)<br>Insufficient (subsequent infection resulting in meningitis or hepatitis) | Strong (in individuals with demonstrated immunodeficiencies) | Convincingly Supports (in individuals with demonstrated immunodeficiencies) |
| 5 | Varicella | Vaccine Strain Viral Reactivation without Other Organ Involvement                                   | Insufficient  | Strong   | Convincingly Supports   |
| 5 | Varicella | Vaccine Strain Viral Reactivation with Subsequent Infection resulting in Meningitis or Encephalitis | Limited (subsequent infection resulting in encephalitis)<br>Insufficient (subsequent infection resulting in meningitis)           | Strong   | Convincingly Supports   |
| 5 | Varicella | Encephalopathy  | Insufficient  | Lacking  | Inadequate  |
| 5 | Varicella | Seizures  | Limited   | Weak   | Inadequate  |
| 5 | Varicella | Cerebellar Ataxia   | Insufficient  | Weak   | Inadequate  |
| 5 | Varicella | Acute Disseminated Encephalomyelitis  | Insufficient  | Weak   | Inadequate  |

*continued*

TABLE D-1 Continued

| Chapter | Vaccine   | Adverse Event                                    | Epidemiologic Assessment | Mechanistic Assessment | Causality Conclusion  |
|---------|-----------|--|--------------------------|------------------------|-----------------------|
| 5       | Varicella | Transverse Myelitis                              | Insufficient             | Weak                   | Inadequate            |
| 5       | Varicella | Guillain-Barré syndrome                          | Insufficient             | Weak                   | Inadequate            |
| 5       | Varicella | Small Fiber Neuropathy <sup>b</sup>              | Insufficient             | Lacking                | Inadequate            |
| 5       | Varicella | Anaphylaxis                                      | Limited                  | Strong                 | Convincingly Supports |
| 5       | Varicella | Onset or Exacerbation Arthropathy                | Insufficient             | Lacking                | Inadequate            |
| 5       | Varicella | Stroke <sup>b</sup>                              | Limited                  | Weak                   | Inadequate            |
| 5       | Varicella | Thrombocytopenia                                 | Insufficient             | Weak                   | Inadequate            |
| 6       | Influenza | Encephalitis                                     | Insufficient             | Weak                   | Inadequate            |
| 6       | Influenza | Encephalopathy                                   | Insufficient             | Weak                   | Inadequate            |
| 6       | Influenza | Seizures <sup>b</sup>                            | Moderate (null)          | Lacking                | Inadequate            |
| 6       | Influenza | Acute Disseminated Encephalomyelitis             | Insufficient             | Weak                   | Inadequate            |
| 6       | Influenza | Transverse Myelitis                              | Insufficient             | Weak                   | Inadequate            |
| 6       | Influenza | Optic Neuritis <sup>b</sup>                      | Limited                  | Weak                   | Inadequate            |
| 6       | Influenza | Neuromyelitis Optica                             | Insufficient             | Lacking                | Inadequate            |
| 6       | Influenza | Multiple Sclerosis Onset in Adults               | Limited                  | Lacking                | Inadequate            |
| 6       | Influenza | Multiple Sclerosis Relapse in Adults             | Limited                  | Lacking                | Inadequate            |
| 6       | Influenza | Guillain-Barré syndrome                          | Moderate (null)          | Weak                   | Inadequate            |
| 6       | Influenza | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient             | Weak                   | Inadequate            |

|   |           |  |  |  |                       |
|---|-----------|--|--|--|-----------------------|
| 6 | Influenza | Inactivated Influenza Vaccine and Bell's Palsy   | High (null)                                    | Lacking                                | Favors Rejection      |
| 6 | Influenza | Brachial Neuritis  | Insufficient                                   | Lacking                                | Inadequate            |
| 6 | Influenza | Small Fiber Neuropathy   | Insufficient                                   | Lacking                                | Inadequate            |
| 6 | Influenza | Anaphylaxis  | Limited  | Strong                                 | Convincingly Supports |
| 6 | Influenza | Inactivated Influenza Vaccine and Asthma Exacerbation or Reactive Airway Disease Episodes in Children and Adults                     | High (null)                                    | Weak                                   | Favors Rejection      |
| 6 | Influenza | Live Attenuated Influenza Vaccine or Asthma Exacerbation or Reactive Airway Disease Episodes in Children Younger Than 5 Years of Age | Moderate (null)                                | Weak                                   | Inadequate            |
| 6 | Influenza | Live Attenuated Influenza Vaccine or Asthma Exacerbation or Reactive Airway Disease Episodes in Persons 5 Years of Age or Older      | Moderate (null)                                | Weak                                   | Inadequate            |
| 6 | Influenza | Onset or Exacerbation of Systemic Lupus Erythematosus  | Limited (exacerbation)<br>Insufficient (onset) | Lacking                                | Inadequate            |
| 6 | Influenza | Onset or Exacerbation of Vasculitis  | Limited (exacerbation)<br>Insufficient (onset) | Weak (exacerbation)<br>Lacking (onset) | Inadequate            |

*continued*

TABLE D-1 Continued

| Chapter | Vaccine     | Adverse Event                        | Epidemiologic Assessment         | Mechanistic Assessment                   | Causality Conclusion           |
|---------|-------------|--------------------------------------|----------------------------------|--|--------------------------------|
| 6       | Influenza   | Polyarteritis Nodosa                 | Insufficient                     | Lacking                                  | Inadequate                     |
| 6       | Influenza   | Onset or Exacerbation of Arthropathy | Insufficient                     | Weak                                     | Inadequate                     |
| 6       | Influenza   | Stroke                               | Moderate (decrease)              | Lacking                                  | Inadequate                     |
| 6       | Influenza   | Myocardial Infarction                | Moderate (decrease)              | Weak (Live Attenuated Influenza Vaccine) | Inadequate                     |
|         |             |                                      |                                  | Lacking (Inactivated Influenza Vaccine)  |                                |
| 6       | Influenza   | Fibromyalgia                         | Insufficient                     | Lacking                                  | Inadequate                     |
| 6       | Influenza   | All-Cause Mortality <sup>b</sup>     | Moderate (decrease)              | Weak (Live Attenuated Influenza Vaccine) | Inadequate                     |
|         |             |                                      |                                  | Lacking (Inactivated Influenza Vaccine)  |                                |
| 6       | Influenza   | Oculorespiratory Syndrome            | Moderate (increase) <sup>d</sup> | Intermediate <sup>d</sup>                | Favors Acceptance <sup>d</sup> |
| 7       | Hepatitis A | Acute Disseminated Encephalomyelitis | Insufficient                     | Weak                                     | Inadequate                     |
| 7       | Hepatitis A | Transverse Myelitis                  | Insufficient                     | Weak                                     | Inadequate                     |
| 7       | Hepatitis A | Multiple Sclerosis                   | Insufficient                     | Lacking                                  | Inadequate                     |

|   |             |  |                 |                  |            |
|---|-------------|--|-----------------|------------------|------------|
| 7 | Hepatitis A | Guillain-Barré syndrome                          | Insufficient    | Weak             | Inadequate |
| 7 | Hepatitis A | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient    | Lacking          | Inadequate |
| 7 | Hepatitis A | Bell's Palsy                                     | Insufficient    | Lacking          | Inadequate |
| 7 | Hepatitis A | Anaphylaxis                                      | Insufficient    | Weak             | Inadequate |
| 7 | Hepatitis A | Autoimmune Hepatitis                             | Insufficient    | Weak             | Inadequate |
| 8 | Hepatitis B | Encephalitis                                     | Insufficient    | Lacking          | Inadequate |
| 8 | Hepatitis B | Encephalopathy                                   | Insufficient    | Lacking          | Inadequate |
| 8 | Hepatitis B | Seizures   | Limited         | Lacking          | Inadequate |
| 8 | Hepatitis B | Acute Disseminated Encephalomyelitis             | Insufficient    | Low-Intermediate | Inadequate |
| 8 | Hepatitis B | Transverse Myelitis                              | Insufficient    | Weak             | Inadequate |
| 8 | Hepatitis B | Optic Neuritis <sup>b</sup>                      | Limited         | Lacking          | Inadequate |
| 8 | Hepatitis B | Neuromyelitis Optica                             | Insufficient    | Lacking          | Inadequate |
| 8 | Hepatitis B | Multiple Sclerosis Onset in Adults               | Limited         | Lacking          | Inadequate |
| 8 | Hepatitis B | Multiple Sclerosis Onset in Children             | Limited         | Lacking          | Inadequate |
| 8 | Hepatitis B | Multiple Sclerosis Relapse in Adults             | Limited         | Lacking          | Inadequate |
| 8 | Hepatitis B | Multiple Sclerosis Relapse in Children           | Limited         | Lacking          | Inadequate |
| 8 | Hepatitis B | First Demyelinating Event in Adults              | Moderate (null) | Low-Intermediate | Inadequate |
| 8 | Hepatitis B | First Demyelinating Event in Children            | Limited         | Lacking          | Inadequate |
| 8 | Hepatitis B | Guillain-Barré syndrome                          | Insufficient    | Lacking          | Inadequate |

*continued*

TABLE D-1 Continued

| Chapter | Vaccine     | Adverse Event   | Epidemiologic Assessment                       | Mechanistic Assessment                  | Causality Conclusion                                   |
|---------|-------------|---|--|---|--|
| 8       | Hepatitis B | Chronic Inflammatory Polyneuropathy                   | Insufficient                                   | Lacking                                 | Inadequate   |
| 8       | Hepatitis B | Brachial Neuritis                                     | Insufficient                                   | Lacking                                 | Inadequate   |
| 8       | Hepatitis B | Anaphylaxis   | Insufficient                                   | Strong (in yeast-sensitive individuals) | Convincingly Supports (in yeast-sensitive individuals) |
| 8       | Hepatitis B | Erythema Nodosum <sup>b</sup>                         | Insufficient                                   | Weak                                    | Inadequate   |
| 8       | Hepatitis B | Onset or Exacerbation of Systemic Lupus Erythematosus | Limited (onset)                                | Weak                                    | Inadequate   |
| 8       | Hepatitis B | Onset or Exacerbation of Vasculitis                   | Insufficient                                   | Low-Intermediate                        | Inadequate   |
| 8       | Hepatitis B | Onset or Exacerbation of Polyarteritis Nodosa         | Insufficient                                   | Weak                                    | Inadequate   |
| 8       | Hepatitis B | Onset or Exacerbation of Psoriatic Arthritis          | Insufficient                                   | Lacking                                 | Inadequate   |
| 8       | Hepatitis B | Onset or Exacerbation of Reactive Arthritis           | Insufficient                                   | Weak                                    | Inadequate   |
| 8       | Hepatitis B | Onset and Exacerbation of Rheumatoid Arthritis        | Limited (exacerbation)<br>Insufficient (onset) | Weak                                    | Inadequate   |

|    |                          |  |                 |              |                   |
|----|--------------------------|--|-----------------|--------------|-------------------|
| 8  | Hepatitis B              | Onset or Exacerbation of Juvenile Idiopathic Arthritis | Insufficient    | Weak         | Inadequate        |
| 8  | Hepatitis B              | Type 1 Diabetes  | Moderate (null) | Lacking      | Inadequate        |
| 8  | Hepatitis B              | Fibromyalgia   | Insufficient    | Lacking      | Inadequate        |
| 9  | HPV                      | Acute Disseminated Encephalomyelitis                   | Insufficient    | Lacking      | Inadequate        |
| 9  | HPV                      | Transverse Myelitis                                    | Insufficient    | Lacking      | Inadequate        |
| 9  | HPV                      | Neuromyelitis Optica                                   | Insufficient    | Lacking      | Inadequate        |
| 9  | HPV                      | Multiple Sclerosis                                     | Insufficient    | Lacking      | Inadequate        |
| 9  | HPV                      | Guillain-Barré syndrome                                | Insufficient    | Lacking      | Inadequate        |
| 9  | HPV                      | Chronic Inflammatory Disseminated Polyneuropathy       | Insufficient    | Lacking      | Inadequate        |
| 9  | HPV                      | Brachial Neuritis                                      | Insufficient    | Lacking      | Inadequate        |
| 9  | HPV                      | Amyotrophic Lateral Sclerosis                          | Insufficient    | Lacking      | Inadequate        |
| 9  | HPV                      | Anaphylaxis  | Insufficient    | Intermediate | Favors Acceptance |
| 9  | HPV                      | Transient Arthralgia                                   | Limited         | Lacking      | Inadequate        |
| 9  | HPV                      | Pancreatitis   | Insufficient    | Lacking      | Inadequate        |
| 9  | HPV                      | Thromboembolic Events                                  | Insufficient    | Lacking      | Inadequate        |
| 9  | HPV                      | Hypercoagulable States                                 | Insufficient    | Lacking      | Inadequate        |
| 10 | DT, TT, or aP containing | Encephalitis   | Limited         | Weak         | Inadequate        |
| 10 | DT, TT, or aP containing | Encephalopathy   | Limited         | Weak         | Inadequate        |

*continued*



TABLE D-1 Continued

| Chapter | Vaccine                  | Adverse Event                        | Epidemiologic Assessment  | Mechanistic Assessment  | Causality Conclusion |
|---------|--------------------------|--------------------------------------|---|---|----------------------|
| 10      | DT, TT, or aP containing | Infantile Spasms                     | Limited (diphtheria toxoid or tetanus toxoid)<br>Insufficient (acellular pertussis) | Lacking   | Inadequate           |
| 10      | DT, TT, or aP containing | Seizures                             | Limited   | Weak (acellular pertussis)<br>Lacking (diphtheria toxoid or tetanus toxoid) | Inadequate           |
| 10      | DT, TT, or aP containing | Ataxia                               | Insufficient  | Lacking   | Inadequate           |
| 10      | DT, TT, or aP containing | Autism                               | Insufficient  | Lacking   | Inadequate           |
| 10      | DT, TT, or aP containing | Acute Disseminated Encephalomyelitis | Insufficient  | Weak (tetanus toxoid)<br>Lacking (diphtheria toxoid or acellular pertussis) | Inadequate           |
| 10      | DT, TT, or aP containing | Transverse Myelitis                  | Insufficient  | Lacking   | Inadequate           |

|    |                          |  |   |         |            |
|----|--------------------------|--|---|---------|------------|
| 10 | DT, TT, or aP containing | Optic Neuritis <sup>6</sup>                      | Limited (diphtheria toxoid or tetanus toxoid)<br>Insufficient (acellular pertussis) | Lacking | Inadequate |
| 10 | DT, TT, or aP containing | Multiple Sclerosis Onset in Adults               | Limited (diphtheria toxoid or tetanus toxoid)<br>Insufficient (acellular pertussis) | Lacking | Inadequate |
| 10 | DT, TT, or aP containing | Multiple Sclerosis Relapse in Adults             | Limited (tetanus toxoid)<br>Insufficient (diphtheria toxoid or acellular pertussis) | Lacking | Inadequate |
| 10 | DT, TT, or aP containing | Multiple Sclerosis Relapse in Children           | Limited (diphtheria toxoid or tetanus toxoid)<br>Insufficient (acellular pertussis) | Lacking | Inadequate |
| 10 | DT, TT, or aP containing | Guillain-Barré syndrome                          | Insufficient  | Lacking | Inadequate |
| 10 | DT, TT, or aP containing | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient  | Lacking | Inadequate |
| 10 | DT, TT, or aP containing | Opsoclonus Myoclonus Syndrome                    | Insufficient  | Lacking | Inadequate |

*continued*

TABLE D-1 Continued

| Chapter | Vaccine                  | Adverse Event     | Epidemiologic Assessment                           | Mechanistic Assessment                     | Causality Conclusion  |
|---------|--------------------------|-------------------|--|--|-----------------------|
| 10      | DT, TT, or aP containing | Bell's Palsy      | Limited (acellular pertussis)                      | Weak (diphtheria toxoid or tetanus toxoid) | Inadequate            |
|         |                          |                   | Insufficient (diphtheria toxoid or tetanus toxoid) | Lacking (acellular pertussis)              |                       |
| 10      | TT containing            | Anaphylaxis       | Insufficient                                       | Strong                                     | Convincingly Supports |
| 10      | DT and aP containing     | Anaphylaxis       | Insufficient                                       | Lacking                                    | Inadequate            |
| 10      | DT, TT, or aP containing | Chronic Urticaria | Insufficient                                       | Lacking                                    | Inadequate            |
| 10      | DT, TT, or aP containing | Serum Sickness    | Insufficient                                       | Weak (diphtheria toxoid or tetanus toxoid) | Inadequate            |
|         |                          |                   |  | Lacking (acellular pertussis)              |                       |
| 10      | DT, TT, or aP containing | Arthropathy       | Limited (diphtheria toxoid or tetanus toxoid)      | Lacking                                    | Inadequate            |
|         |                          |                   | Insufficient (acellular pertussis)                 |  |                       |
| 10      | DT, TT, or aP containing | Type 1 Diabetes   | High (null)  | Lacking                                    | Favors Rejection      |

|    |                          |  |              |   |                       |
|----|--------------------------|--|--------------|---|-----------------------|
| 10 | DT, TT, or aP containing | Myocarditis                                    | Insufficient | Weak (diphtheria toxoid)                        | Inadequate            |
|    |                          |  |              | Lacking (tetanus toxoid or acellular pertussis) |                       |
| 10 | DT, TT, or aP containing | Fibromyalgia                                   | Insufficient | Lacking   | Inadequate            |
| 10 | DT, TT, or aP containing | Sudden Infant Death Syndrome                   | Insufficient | Lacking   | Inadequate            |
| 10 | DT, TT, or aP containing | Immune Thrombocytopenic Purpura                | Insufficient | Lacking   | Inadequate            |
| 11 | Meningococcal            | Encephalitis                                   | Limited      | Lacking   | Inadequate            |
| 11 | Meningococcal            | Encephalopathy                                 | Limited      | Lacking   | Inadequate            |
| 11 | Meningococcal            | Acute Disseminated Encephalomyelitis           | Insufficient | Lacking   | Inadequate            |
| 11 | Meningococcal            | Transverse Myelitis                            | Insufficient | Lacking   | Inadequate            |
| 11 | Meningococcal            | Multiple Sclerosis                             | Insufficient | Lacking   | Inadequate            |
| 11 | Meningococcal            | Guillain-Barré syndrome                        | Limited      | Lacking   | Inadequate            |
| 11 | Meningococcal            | Chronic Inflammatory Dissecting Polyneuropathy | Insufficient | Lacking   | Inadequate            |
| 11 | Meningococcal            | Anaphylaxis                                    | Insufficient | Strong  | Convincingly Supports |
| 11 | Meningococcal            | Chronic Headache                               | Insufficient | Lacking   | Inadequate            |
| 12 | Injection-Related Event  | Complex Regional Pain Syndrome                 | Insufficient | Low-Intermediate                                | Inadequate            |

*continued*

TABLE D-1 Continued

| Chapter | Vaccine                 | Adverse Event    | Epidemiologic Assessment | Mechanistic Assessment | Causality Conclusion  |
|---------|-------------------------|------------------|--------------------------|------------------------|-----------------------|
| 12      | Injection-Related Event | Deltoid Bursitis | Limited                  | Strong                 | Convincingly Supports |
| 12      | Injection-Related Event | Syncope          | Insufficient             | Strong                 | Convincingly Supports |

NOTE: The measles-mumps-rubella; human papillomavirus; and diphtheria toxoid-, tetanus toxoid-, and acellular pertussis-containing vaccines have been abbreviated in the following ways: MMR; HPV; and DT, TT, and aP containing.

<sup>a</sup> The committee attributes causation to the measles component of the vaccine.

<sup>b</sup> Although not originally charged to the committee by the sponsor, the committee considered this adverse event in its review of the literature.

<sup>c</sup> The committee attributes causation to the rubella component of the vaccine.

<sup>d</sup> The committee attributes causation to two particular vaccines used in three particular years in Canada.

TABLE D-2 Causality Conclusions Organized by Adverse Event and Chapter

| Chapter | Vaccine   | Adverse Event   | Epidemiologic Assessment   | Mechanistic Assessment  | Causality Conclusion  |
|---------|-----------|---|--|---|---|
| 5       | Varicella | Disseminated Oka VZV without Other Organ Involvement  | Insufficient   | Strong  | Convincingly Supports   |
| 5       | Varicella | Disseminated Oka VZV with Subsequent Infection Resulting in Pneumonia, Meningitis, or Hepatitis     | Limited (subsequent infection resulting in pneumonia)                    | Strong (in individuals with demonstrated immunodeficiencies)          | Convincingly Supports (in individuals with demonstrated immunodeficiencies) |
| 5       | Varicella | Vaccine Strain Viral Reactivation without Other Organ Involvement                                   | Insufficient (subsequent infection resulting in meningitis or hepatitis) | Strong  | Convincingly Supports   |
| 5       | Varicella | Vaccine Strain Viral Reactivation with Subsequent Infection resulting in Meningitis or Encephalitis | Limited (subsequent infection resulting in encephalitis)                 | Strong  | Convincingly Supports   |
| 4       | MMR       | Measles Inclusion Body Encephalitis   | Insufficient (subsequent infection resulting in meningitis)              | Strong (measles; in individuals with demonstrated immunodeficiencies) | Convincingly Supports (in individuals with demonstrated immunodeficiencies) |
|         |           |   |  | Lacking (mumps or rubella)  |   |

*continued*

TABLE D-2 Continued

| Chapter | Vaccine                  | Adverse Event     | Epidemiologic Assessment                      | Mechanistic Assessment | Causality Conclusion  |
|---------|--------------------------|-------------------|---|------------------------|-----------------------|
| 4       | MMR                      | Encephalitis      | Limited                                       | Weak                   | Inadequate            |
| 6       | Influenza                | Encephalitis      | Insufficient                                  | Weak                   | Inadequate            |
| 8       | Hepatitis B              | Encephalitis      | Insufficient                                  | Lacking                | Inadequate            |
| 10      | DT, TT, or aP containing | Encephalitis      | Limited                                       | Weak                   | Inadequate            |
| 11      | Meningococcal            | Encephalitis      | Limited                                       | Lacking                | Inadequate            |
| 4       | MMR                      | Encephalopathy    | Limited                                       | Weak                   | Inadequate            |
| 5       | Varicella                | Encephalopathy    | Insufficient                                  | Lacking                | Inadequate            |
| 6       | Influenza                | Encephalopathy    | Insufficient                                  | Weak                   | Inadequate            |
| 8       | Hepatitis B              | Encephalopathy    | Insufficient                                  | Lacking                | Inadequate            |
| 10      | DT, TT, or aP containing | Encephalopathy    | Limited                                       | Weak                   | Inadequate            |
| 11      | Meningococcal            | Encephalopathy    | Limited                                       | Lacking                | Inadequate            |
| 10      | DT, TT, or aP containing | Infantile Spasms  | Limited (diphtheria toxoid or tetanus toxoid) | Lacking                | Inadequate            |
|         |                          |                   | Insufficient (acellular pertussis)            |                        |                       |
| 4       | MMR                      | Febrile Seizures  | High (increase)                               | Intermediate           | Convincingly Supports |
| 4       | MMR                      | Afebrile Seizures | Limited                                       | Lacking                | Inadequate            |
| 5       | Varicella                | Seizures          | Limited                                       | Weak                   | Inadequate            |

|    |                          |                                      |                 |   |                  |
|----|--------------------------|--------------------------------------|-----------------|---|------------------|
| 6  | Influenza                | Seizures <sup>b</sup>                | Moderate (null) | Lacking                                       | Inadequate       |
| 8  | Hepatitis B              | Seizures                             | Limited         | Lacking                                       | Inadequate       |
| 10 | DT, TT, or aP containing | Seizures                             | Limited         | Weak (acellular pertussis)                    | Inadequate       |
|    |                          |                                      |                 | Lacking (diphtheria toxoid or tetanus toxoid) |                  |
| 4  | MMR                      | Meningitis <sup>b</sup>              | Moderate (null) | Weak (mumps)                                  | Inadequate       |
| 5  | Varicella                | Cerebellar Ataxia                    | Insufficient    | Lacking (measles or rubella)                  | Inadequate       |
| 4  | MMR                      | Ataxia                               | Insufficient    | Weak (measles or mumps)                       | Inadequate       |
|    |                          |                                      |                 | Lacking (rubella)                             |                  |
| 10 | DT, TT, or aP containing | Ataxia                               | Insufficient    | Lacking                                       | Inadequate       |
| 4  | MMR                      | Autism                               | High (null)     | Lacking                                       | Favors Rejection |
| 10 | DT, TT, or aP containing | Autism                               | Insufficient    | Lacking                                       | Inadequate       |
| 4  | MMR                      | Acute Disseminated Encephalomyelitis | Insufficient    | Weak  | Inadequate       |
| 5  | Varicella                | Acute Disseminated Encephalomyelitis | Insufficient    | Weak  | Inadequate       |

*continued*



TABLE D-2 Continued

| Chapter | Vaccine                  | Adverse Event                        | Epidemiologic Assessment | Mechanistic Assessment  | Causality Conclusion |
|---------|--------------------------|--------------------------------------|--------------------------|---|----------------------|
| 6       | Influenza                | Acute Disseminated Encephalomyelitis | Insufficient             | Weak  | Inadequate           |
| 7       | Hepatitis A              | Acute Disseminated Encephalomyelitis | Insufficient             | Weak  | Inadequate           |
| 8       | Hepatitis B              | Acute Disseminated Encephalomyelitis | Insufficient             | Low-Intermediate  | Inadequate           |
| 9       | HPV                      | Acute Disseminated Encephalomyelitis | Insufficient             | Lacking   | Inadequate           |
| 10      | DT, TT, or aP containing | Acute Disseminated Encephalomyelitis | Insufficient             | Weak (tetanus toxoid)<br>Lacking (diphtheria toxoid or acellular pertussis) | Inadequate           |
| 11      | Meningococcal            | Acute Disseminated Encephalomyelitis | Insufficient             | Lacking   | Inadequate           |
| 4       | MMR                      | Transverse Myelitis                  | Insufficient             | Weak  | Inadequate           |
| 5       | Varicella                | Transverse Myelitis                  | Insufficient             | Weak  | Inadequate           |
| 6       | Influenza                | Transverse Myelitis                  | Insufficient             | Weak  | Inadequate           |
| 7       | Hepatitis A              | Transverse Myelitis                  | Insufficient             | Weak  | Inadequate           |
| 8       | Hepatitis B              | Transverse Myelitis                  | Insufficient             | Weak  | Inadequate           |
| 9       | HPV                      | Transverse Myelitis                  | Insufficient             | Lacking   | Inadequate           |

|    |                          |                                    |   |                            |            |
|----|--------------------------|------------------------------------|---|----------------------------|------------|
| 10 | DT, TT, or aP containing | Transverse Myelitis                | Insufficient                                  | Lacking                    | Inadequate |
| 11 | Meningococcal            | Transverse Myelitis                | Insufficient                                  | Lacking                    | Inadequate |
| 4  | MMR                      | Optic Neuritis <sup>b</sup>        | Limited                                       | Weak                       | Inadequate |
| 6  | Influenza                | Optic Neuritis <sup>b</sup>        | Limited                                       | Weak                       | Inadequate |
| 8  | Hepatitis B              | Optic Neuritis <sup>b</sup>        | Limited                                       | Lacking                    | Inadequate |
| 10 | DT, TT, or aP containing | Optic Neuritis <sup>b</sup>        | Limited (diphtheria toxoid or tetanus toxoid) | Lacking                    | Inadequate |
|    |                          |                                    | Insufficient (acellular pertussis)            |                            |            |
| 4  | MMR                      | Neuromyelitis Optica <sup>b</sup>  | Insufficient                                  | Weak (rubella)             | Inadequate |
|    |                          |                                    |   | Lacking (measles or mumps) |            |
| 6  | Influenza                | Neuromyelitis Optica               | Insufficient                                  | Lacking                    | Inadequate |
| 8  | Hepatitis B              | Neuromyelitis Optica               | Insufficient                                  | Lacking                    | Inadequate |
| 9  | HPV                      | Neuromyelitis Optica               | Insufficient                                  | Lacking                    | Inadequate |
| 4  | MMR                      | Multiple Sclerosis Onset in Adults | Limited                                       | Lacking                    | Inadequate |
| 6  | Influenza                | Multiple Sclerosis Onset in Adults | Limited                                       | Lacking                    | Inadequate |
| 8  | Hepatitis B              | Multiple Sclerosis Onset in Adults | Limited                                       | Lacking                    | Inadequate |

*continued*

TABLE D-2 Continued

| Chapter | Vaccine                  | Adverse Event                          | Epidemiologic Assessment                                | Mechanistic Assessment | Causality Conclusion |
|---------|--------------------------|--|---|------------------------|----------------------|
| 10      | DT, TT, or aP containing | Multiple Sclerosis Onset in Adults     | Limited (diphtheria toxoid or tetanus toxoid)           | Lacking                | Inadequate           |
| 4       | MMR                      | Multiple Sclerosis Onset in Children   | Limited   | Lacking                | Inadequate           |
| 8       | Hepatitis B              | Multiple Sclerosis Onset in Children   | Limited   | Lacking                | Inadequate           |
| 6       | Influenza                | Multiple Sclerosis Relapse in Adults   | Limited   | Lacking                | Inadequate           |
| 8       | Hepatitis B              | Multiple Sclerosis Relapse in Adults   | Limited   | Lacking                | Inadequate           |
| 10      | DT, TT, or aP containing | Multiple Sclerosis Relapse in Adults   | Limited (tetanus toxoid)                                | Lacking                | Inadequate           |
|         |                          |  | Insufficient (diphtheria toxoid or acellular pertussis) |                        |                      |
| 8       | Hepatitis B              | Multiple Sclerosis Relapse in Children | Limited   | Lacking                | Inadequate           |
| 10      | DT, TT, or aP containing | Multiple Sclerosis Relapse in Children | Limited (diphtheria toxoid or tetanus toxoid)           | Lacking                | Inadequate           |
|         |                          |  | Insufficient (acellular pertussis)                      |                        |                      |
| 7       | Hepatitis A              | Multiple Sclerosis                     | Insufficient  | Lacking                | Inadequate           |
| 9       | HPV                      | Multiple Sclerosis                     | Insufficient  | Lacking                | Inadequate           |

|    |                          |  |                 |                  |            |            |
|----|--------------------------|--|-----------------|------------------|------------|------------|
| 11 | Meningococcal            | Multiple Sclerosis                               |                 | Insufficient     | Lacking    | Inadequate |
| 8  | Hepatitis B              | First Demyelinating Event in Adults              | Moderate (null) | Low-Intermediate | Inadequate |            |
| 8  | Hepatitis B              | First Demyelinating Event in Children            | Limited         | Lacking          | Inadequate |            |
| 4  | MMR                      | Guillain-Barré syndrome                          | Insufficient    | Weak             | Inadequate |            |
| 5  | Varicella                | Guillain-Barré syndrome                          | Insufficient    | Weak             | Inadequate |            |
| 6  | Influenza                | Guillain-Barré syndrome                          | Moderate (null) | Weak             | Inadequate |            |
| 7  | Hepatitis A              | Guillain-Barré syndrome                          | Insufficient    | Weak             | Inadequate |            |
| 8  | Hepatitis B              | Guillain-Barré syndrome                          | Insufficient    | Lacking          | Inadequate |            |
| 9  | HPV                      | Guillain-Barré syndrome                          | Insufficient    | Lacking          | Inadequate |            |
| 10 | DT, TT, or aP containing | Guillain-Barré syndrome                          | Insufficient    | Lacking          | Inadequate |            |
| 11 | Meningococcal            | Guillain-Barré syndrome                          | Limited         | Lacking          | Inadequate |            |
| 4  | MMR                      | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient    | Lacking          | Inadequate |            |
| 6  | Influenza                | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient    | Weak             | Inadequate |            |
| 7  | Hepatitis A              | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient    | Lacking          | Inadequate |            |
| 8  | Hepatitis B              | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient    | Lacking          | Inadequate |            |
| 9  | HPV                      | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient    | Lacking          | Inadequate |            |

*continued*

TABLE D-2 Continued

| Chapter | Vaccine                  | Adverse Event                                  | Epidemiologic Assessment                           | Mechanistic Assessment                     | Causality Conclusion |
|---------|--------------------------|--|--|--|----------------------|
| 10      | DT, TT, or aP containing | Chronic Inflammatory Polyneuropathy            | Insufficient                                       | Lacking                                    | Inadequate           |
| 11      | Meningococcal            | Chronic Inflammatory Polyneuropathy            | Insufficient                                       | Lacking                                    | Inadequate           |
| 4       | MMR                      | Opsoclonus Myoclonus Syndrome                  | Insufficient                                       | Lacking                                    | Inadequate           |
| 10      | DT, TT, or aP containing | Opsoclonus Myoclonus Syndrome                  | Insufficient                                       | Lacking                                    | Inadequate           |
| 7       | Hepatitis A              | Bell's Palsy                                   | Insufficient                                       | Lacking                                    | Inadequate           |
| 10      | DT, TT, or aP containing | Bell's Palsy                                   | Limited (acellular pertussis)                      | Weak (diphtheria toxoid or tetanus toxoid) | Inadequate           |
|         |                          |  | Insufficient (diphtheria toxoid or tetanus toxoid) | Lacking                                    |                      |
| 6       | Influenza                | Inactivated Influenza Vaccine and Bell's Palsy | High (null)  | Lacking                                    | Favors Rejection     |
| 4       | MMR                      | Brachial Neuritis                              | Insufficient                                       | Lacking                                    | Inadequate           |
| 6       | Influenza                | Brachial Neuritis                              | Insufficient                                       | Lacking                                    | Inadequate           |
| 8       | Hepatitis B              | Brachial Neuritis                              | Insufficient                                       | Lacking                                    | Inadequate           |
| 9       | HPV                      | Brachial Neuritis                              | Insufficient                                       | Lacking                                    | Inadequate           |
| 9       | HPV                      | Amyotrophic Lateral Sclerosis                  | Insufficient                                       | Lacking                                    | Inadequate           |
| 5       | Varicella                | Small Fiber Neuropathy <sup>b</sup>            | Insufficient                                       | Lacking                                    | Inadequate           |

|    |                          |  |              |  |  |
|----|--------------------------|--|--------------|--|--|
| 6  | Influenza                | Small Fiber Neuropathy   | Insufficient | Lacking                                    | Inadequate   |
| 4  | MMR                      | Anaphylaxis  | Insufficient | Strong                                     | Convincingly Supports                                  |
| 5  | Varicella                | Anaphylaxis  | Limited      | Strong                                     | Convincingly Supports                                  |
| 6  | Influenza                | Anaphylaxis  | Limited      | Strong                                     | Convincingly Supports                                  |
| 7  | Hepatitis A              | Anaphylaxis  | Insufficient | Weak                                       | Inadequate   |
| 8  | Hepatitis B              | Anaphylaxis  | Insufficient | Strong (in yeast-sensitive individuals)    | Convincingly Supports (in yeast-sensitive individuals) |
| 9  | HPV                      | Anaphylaxis  | Insufficient | Intermediate                               | Favors Acceptance                                      |
| 10 | DT and aP containing     | Anaphylaxis  | Insufficient | Lacking                                    | Inadequate   |
| 10 | TT containing            | Anaphylaxis  | Insufficient | Strong                                     | Convincingly Supports                                  |
| 11 | Meningococcal            | Anaphylaxis  | Insufficient | Strong                                     | Convincingly Supports                                  |
| 10 | DT, TT, or aP containing | Chronic Urticaria  | Insufficient | Lacking                                    | Inadequate   |
| 10 | DT, TT, or aP containing | Serum Sickness   | Insufficient | Weak (diphtheria toxoid or tetanus toxoid) | Inadequate   |
|    |                          |  |              | Lacking (acellular pertussis)              |  |
| 6  | Influenza                | Inactivated Influenza Vaccine and Asthma Exacerbation or Reactive Airway Disease Episodes in Children and Adults | High (null)  | Weak                                       | Favors Rejection                                       |

*continued*

TABLE D-2 Continued

| Chapter | Vaccine     | Adverse Event  | Epidemiologic Assessment                       | Mechanistic Assessment                 | Causality Conclusion |
|---------|-------------|--|--|--|----------------------|
| 6       | Influenza   | Live Attenuated Influenza Vaccine or Asthma Exacerbation or Reactive Airway Disease Episodes in Children Younger Than 5 Years of Age | Moderate (null)                                | Weak                                   | Inadequate           |
| 6       | Influenza   | Live Attenuated Influenza Vaccine or Asthma Exacerbation or Reactive Airway Disease Episodes in Persons 5 Years of Age or Older      | Moderate (null)                                | Weak                                   | Inadequate           |
| 8       | Hepatitis B | Erythema Nodosum <sup>b</sup>  | Insufficient                                   | Weak                                   | Inadequate           |
| 6       | Influenza   | Onset or Exacerbation of Systemic Lupus Erythematosus  | Limited (exacerbation)<br>Insufficient (onset) | Lacking                                | Inadequate           |
| 8       | Hepatitis B | Onset or Exacerbation of Systemic Lupus Erythematosus  | Limited (onset)<br>Insufficient (exacerbation) | Weak                                   | Inadequate           |
| 6       | Influenza   | Onset or Exacerbation of Vasculitis  | Limited (exacerbation)<br>Insufficient (onset) | Weak (exacerbation)<br>Lacking (onset) | Inadequate           |
| 8       | Hepatitis B | Onset or Exacerbation of Vasculitis  | Insufficient                                   | Low-Intermediate                       | Inadequate           |
| 6       | Influenza   | Polyarteritis Nodosa   | Insufficient                                   | Lacking                                | Inadequate           |

|   |             |  |  |  |                                |
|---|-------------|--|--|--|--------------------------------|
| 8 | Hepatitis B | Onset or Exacerbation of Polyarteritis Nodosa          | Insufficient   | Weak   | Inadequate                     |
| 8 | Hepatitis B | Onset or Exacerbation of Psoriatic Arthritis           | Insufficient   | Lacking  | Inadequate                     |
| 8 | Hepatitis B | Onset or Exacerbation of Reactive Arthritis            | Insufficient   | Weak   | Inadequate                     |
| 8 | Hepatitis B | Onset and Exacerbation of Rheumatoid Arthritis         | Limited (exacerbation)<br>Insufficient (onset)         | Weak   | Inadequate                     |
| 8 | Hepatitis B | Onset or Exacerbation of Juvenile Idiopathic Arthritis | Insufficient   | Weak   | Inadequate                     |
| 4 | MMR         | Transient Arthralgia in Women                          | Moderate (increase) (rubella)                          | Intermediate (rubella)                                   | Favors Acceptance <sup>c</sup> |
| 4 | MMR         | Transient Arthralgia in Children                       | Insufficient (measles or mumps)<br>Moderate (increase) | Lacking (measles or mumps)<br>Weak (rubella)             | Favors Acceptance              |
| 9 | HPV         | Transient Arthralgia                                   | Limited  | Lacking (measles or mumps)                               | Inadequate                     |
| 4 | MMR         | Chronic Arthralgia in Women                            | Limited (rubella)<br>Insufficient (measles or mumps)   | Low-Intermediate (rubella)<br>Lacking (measles or mumps) | Inadequate                     |

*continued*



TABLE D-2 Continued

| Chapter | Vaccine                  | Adverse Event                        | Epidemiologic Assessment  | Mechanistic Assessment                                   | Causality Conclusion |
|---------|--------------------------|--------------------------------------|---|--|----------------------|
| 4       | MMR                      | Chronic Arthritis in Women           | Limited (rubella)<br>Insufficient (measles or mumps)                                | Low-Intermediate (rubella)<br>Lacking (measles or mumps) | Inadequate           |
| 4       | MMR                      | Chronic Arthropathy in Children      | Insufficient  | Weak (rubella)<br>Lacking (measles or mumps)             | Inadequate           |
| 4       | MMR                      | Arthropathy in Men                   | Limited   | Weak (rubella)<br>Lacking (measles or mumps)             | Inadequate           |
| 5       | Varicella                | Onset or Exacerbation Arthropathy    | Insufficient  | Lacking  | Inadequate           |
| 6       | Influenza                | Onset or Exacerbation of Arthropathy | Insufficient  | Weak   | Inadequate           |
| 10      | DT, TT, or aP containing | Arthropathy                          | Limited (diphtheria toxoid or tetanus toxoid)<br>Insufficient (acellular pertussis) | Lacking  | Inadequate           |
| 4       | MMR                      | Type 1 Diabetes                      | High (null)   | Lacking  | Favors Rejection     |
| 8       | Hepatitis B              | Type 1 Diabetes                      | Moderate (null)   | Lacking  | Inadequate           |

|    |                          |                          |                     |   |                  |
|----|--------------------------|--------------------------|---------------------|---|------------------|
| 10 | DT, TT, or aP containing | Type 1 Diabetes          | High (null)         | Lacking   | Favors Rejection |
| 7  | Hepatitis A              | Autoimmune Hepatitis     | Insufficient        | Weak  | Inadequate       |
| 10 | DT, TT, or aP containing | Myocarditis              | Insufficient        | Weak (diphtheria toxoid)<br>Lacking (tetanus toxoid or acellular pertussis)         | Inadequate       |
| 9  | HPV                      | Pancreatitis             | Insufficient        | Lacking   | Inadequate       |
| 4  | MMR                      | Hepatitis                | Insufficient        | Weak  | Inadequate       |
| 9  | HPV                      | Thromboembolic Events    | Insufficient        | Lacking   | Inadequate       |
| 5  | Varicella                | Stroke <sup>b</sup>      | Limited             | Weak  | Inadequate       |
| 6  | Influenza                | Stroke                   | Moderate (decrease) | Lacking   | Inadequate       |
| 9  | HPV                      | Hypercoagulable States   | Insufficient        | Lacking   | Inadequate       |
| 6  | Influenza                | Myocardial Infarction    | Moderate (decrease) | Weak (Live Attenuated Influenza Vaccine)<br>Lacking (Inactivated Influenza Vaccine) | Inadequate       |
| 4  | MMR                      | Chronic Fatigue Syndrome | Insufficient        | Lacking   | Inadequate       |
| 11 | Meningococcal            | Chronic Headache         | Insufficient        | Lacking   | Inadequate       |
| 4  | MMR                      | Fibromyalgia             | Insufficient        | Lacking   | Inadequate       |

*continued*

TABLE D-2 Continued

| Chapter | Vaccine                  | Adverse Event                    | Epidemiologic Assessment         | Mechanistic Assessment  | Causality Conclusion           |
|---------|--------------------------|----------------------------------|----------------------------------|---|--------------------------------|
| 6       | Influenza                | Fibromyalgia                     | Insufficient                     | Lacking   | Inadequate                     |
| 8       | Hepatitis B              | Fibromyalgia                     | Insufficient                     | Lacking   | Inadequate                     |
| 10      | DT, TT, or aP containing | Fibromyalgia                     | Insufficient                     | Lacking   | Inadequate                     |
| 10      | DT, TT, or aP containing | Sudden Infant Death Syndrome     | Insufficient                     | Lacking   | Inadequate                     |
| 4       | MMR                      | Hearing Loss                     | Insufficient                     | Low-Intermediate (measles or mumps)<br>Lacking (rubella)                            | Inadequate                     |
| 6       | Influenza                | All-Cause Mortality <sup>b</sup> | Moderate (decrease)              | Weak (Live Attenuated Influenza Vaccine)<br>Lacking (Inactivated Influenza Vaccine) | Inadequate                     |
| 6       | Influenza                | Oculorespiratory Syndrome        | Moderate (increase) <sup>d</sup> | Intermediate <sup>d</sup>   | Favors Acceptance <sup>d</sup> |
| 5       | Varicella                | Thrombocytopenia                 | Insufficient                     | Weak  | Inadequate                     |
| 10      | DT, TT, or aP containing | Immune Thrombocytopenic Purpura  | Insufficient                     | Lacking   | Inadequate                     |
| 12      | Injection-Related Event  | Complex Regional Pain Syndrome   | Insufficient                     | Low-Intermediate  | Inadequate                     |

|    |                         |                  |              |        |                       |
|----|-------------------------|------------------|--------------|--------|-----------------------|
| 12 | Injection-Related Event | Deltoid Bursitis | Limited      | Strong | Convincingly Supports |
| 12 | Injection-Related Event | Syncope          | Insufficient | Strong | Convincingly Supports |

NOTE: The measles-mumps-rubella; human papillomavirus; and diphtheria toxoid-, tetanus toxoid-, and acellular pertussis-containing vaccines have been abbreviated in the following ways: MMR; HPV; and DT, TT, and aP containing.

<sup>a</sup> The committee attributes causation to the measles component of the vaccine.

<sup>b</sup> Although not originally charged to the committee by the sponsor, the committee considered this adverse event in its review of the literature.

<sup>c</sup> The committee attributes causation to the rubella component of the vaccine.

<sup>d</sup> The committee attributes causation to two particular vaccines used in three particular years in Canada.

TABLE D-3 Causality Conclusions Organized by Causality Conclusion, Adverse Event, and Chapter

| Chapter | Vaccine   | Adverse Event   | Epidemiologic Assessment   | Mechanistic Assessment  | Causality Conclusion  |
|---------|-----------|---|--|---|---|
| 5       | Varicella | Disseminated Oka VZV without Other Organ Involvement  | Insufficient   | Strong  | Convincingly Supports   |
| 5       | Varicella | Disseminated Oka VZV with Subsequent Infection Resulting in Pneumonia, Meningitis, or Hepatitis     | Limited (subsequent infection resulting in pneumonia)                    | Strong (in individuals with demonstrated immunodeficiencies)          | Convincingly Supports (in individuals with demonstrated immunodeficiencies) |
| 5       | Varicella | Vaccine Strain Viral Reactivation without Other Organ Involvement                                   | Insufficient (subsequent infection resulting in meningitis or hepatitis) | Strong  | Convincingly Supports   |
| 5       | Varicella | Vaccine Strain Viral Reactivation with Subsequent Infection resulting in Meningitis or Encephalitis | Limited (subsequent infection resulting in encephalitis)                 | Strong  | Convincingly Supports   |
| 4       | MMR       | Measles Inclusion Body Encephalitis   | Insufficient (subsequent infection resulting in meningitis)              | Strong (measles; in individuals with demonstrated immunodeficiencies) | Convincingly Supports (in individuals with demonstrated immunodeficiencies) |
| 4       | MMR       | Febrile Seizures  | High (increase)  | Intermediate (mumps or rubella)                                       | Convincingly Supports   |

|    |                         |                                  |                                  |   |  |
|----|-------------------------|----------------------------------|----------------------------------|---|--|
| 4  | MMR                     | Anaphylaxis                      | Insufficient                     | Strong                                  | Convincingly Supports                                  |
| 5  | Varicella               | Anaphylaxis                      | Limited                          | Strong                                  | Convincingly Supports                                  |
| 6  | Influenza               | Anaphylaxis                      | Limited                          | Strong                                  | Convincingly Supports                                  |
| 8  | Hepatitis B             | Anaphylaxis                      | Insufficient                     | Strong (in yeast-sensitive individuals) | Convincingly Supports (in yeast-sensitive individuals) |
| 10 | TT containing           | Anaphylaxis                      | Insufficient                     | Strong                                  | Convincingly Supports                                  |
| 11 | Meningococcal           | Anaphylaxis                      | Insufficient                     | Strong                                  | Convincingly Supports                                  |
| 12 | Injection-Related Event | Deltoid Bursitis                 | Limited                          | Strong                                  | Convincingly Supports                                  |
| 12 | Injection-Related Event | Syncope                          | Insufficient                     | Strong                                  | Convincingly Supports                                  |
| 9  | HPV                     | Anaphylaxis                      | Insufficient                     | Intermediate                            | Favors Acceptance                                      |
| 4  | MMR                     | Transient Arthralgia in Women    | Moderate (increase) (rubella)    | Intermediate (rubella)                  | Favors Acceptance <sup>b</sup>                         |
|    |                         |                                  | Insufficient (measles or mumps)  | Lacking (measles or mumps)              |  |
| 4  | MMR                     | Transient Arthralgia in Children | Moderate (increase)              | Weak (rubella)                          | Favors Acceptance                                      |
|    |                         |                                  |                                  | Lacking (measles or mumps)              |  |
| 6  | Influenza               | Oculorespiratory Syndrome        | Moderate (increase) <sup>c</sup> | Intermediate <sup>c</sup>               | Favors Acceptance <sup>c</sup>                         |
| 4  | MMR                     | Autism                           | High (null)                      | Lacking                                 | Favors Rejection                                       |

*continued*

TABLE D-3 Continued

| Chapter | Vaccine                  | Adverse Event  | Epidemiologic Assessment | Mechanistic Assessment | Causality Conclusion |
|---------|--------------------------|--|--------------------------|------------------------|----------------------|
| 6       | Influenza                | Inactivated Influenza Vaccine and Bell's Palsy   | High (null)              | Lacking                | Favors Rejection     |
| 6       | Influenza                | Inactivated Influenza Vaccine and Asthma Exacerbation or Reactive Airway Disease Episodes in Children and Adults | High (null)              | Weak                   | Favors Rejection     |
| 4       | MMR                      | Type 1 Diabetes  | High (null)              | Lacking                | Favors Rejection     |
| 10      | DT, TT, or aP containing | Type 1 Diabetes  | High (null)              | Lacking                | Favors Rejection     |
| 4       | MMR                      | Encephalitis   | Limited                  | Weak                   | Inadequate           |
| 6       | Influenza                | Encephalitis   | Insufficient             | Weak                   | Inadequate           |
| 8       | Hepatitis B              | Encephalitis   | Insufficient             | Lacking                | Inadequate           |
| 10      | DT, TT, or aP containing | Encephalitis   | Limited                  | Weak                   | Inadequate           |
| 11      | Meningococcal            | Encephalitis   | Limited                  | Lacking                | Inadequate           |
| 4       | MMR                      | Encephalopathy   | Limited                  | Weak                   | Inadequate           |
| 5       | Varicella                | Encephalopathy   | Insufficient             | Lacking                | Inadequate           |
| 6       | Influenza                | Encephalopathy   | Insufficient             | Weak                   | Inadequate           |
| 8       | Hepatitis B              | Encephalopathy   | Insufficient             | Lacking                | Inadequate           |
| 10      | DT, TT, or aP containing | Encephalopathy   | Limited                  | Weak                   | Inadequate           |

|    |                          |                         |   |   |            |
|----|--------------------------|-------------------------|---|---|------------|
| 11 | Meningococcal            | Encephalopathy          | Limited                                       | Lacking                                       | Inadequate |
| 10 | DT, TT, or aP containing | Infantile Spasms        | Limited (diphtheria toxoid or tetanus toxoid) | Lacking                                       | Inadequate |
|    |                          |                         | Insufficient (acellular pertussis)            |   |            |
| 4  | MMR                      | Afebrile Seizures       | Limited                                       | Lacking                                       | Inadequate |
| 5  | Varicella                | Seizures                | Limited                                       | Weak  | Inadequate |
| 6  | Influenza                | Seizures <sup>d</sup>   | Moderate (null)                               | Lacking                                       | Inadequate |
| 8  | Hepatitis B              | Seizures                | Limited                                       | Lacking                                       | Inadequate |
| 10 | DT, TT, or aP containing | Seizures                | Limited                                       | Weak (acellular pertussis)                    | Inadequate |
|    |                          |                         |   | Lacking (diphtheria toxoid or tetanus toxoid) |            |
| 4  | MMR                      | Meningitis <sup>d</sup> | Moderate (null)                               | Weak (mumps)                                  | Inadequate |
|    |                          |                         |   | Lacking (measles or rubella)                  |            |
| 5  | Varicella                | Cerebellar Ataxia       | Insufficient                                  | Weak  | Inadequate |
| 4  | MMR                      | Ataxia                  | Insufficient                                  | Weak (measles or mumps)                       | Inadequate |
|    |                          |                         |   | Lacking (rubella)                             |            |

*continued*



TABLE D-3 Continued

| Chapter | Vaccine                  | Adverse Event                        | Epidemiologic Assessment | Mechanistic Assessment  | Causality Conclusion |
|---------|--------------------------|--------------------------------------|--------------------------|---|----------------------|
| 10      | DT, TT, or aP containing | Ataxia                               | Insufficient             | Lacking   | Inadequate           |
| 10      | DT, TT, or aP containing | Autism                               | Insufficient             | Lacking   | Inadequate           |
| 4       | MMR                      | Acute Disseminated Encephalomyelitis | Insufficient             | Weak  | Inadequate           |
| 5       | Varicella                | Acute Disseminated Encephalomyelitis | Insufficient             | Weak  | Inadequate           |
| 6       | Influenza                | Acute Disseminated Encephalomyelitis | Insufficient             | Weak  | Inadequate           |
| 7       | Hepatitis A              | Acute Disseminated Encephalomyelitis | Insufficient             | Weak  | Inadequate           |
| 8       | Hepatitis B              | Acute Disseminated Encephalomyelitis | Insufficient             | Low-Intermediate  | Inadequate           |
| 9       | HPV                      | Acute Disseminated Encephalomyelitis | Insufficient             | Lacking   | Inadequate           |
| 10      | DT, TT, or aP containing | Acute Disseminated Encephalomyelitis | Insufficient             | Weak (tetanus toxoid)<br>Lacking (diphtheria toxoid or acellular pertussis) | Inadequate           |
| 11      | Meningococcal            | Acute Disseminated Encephalomyelitis | Insufficient             | Lacking   | Inadequate           |

|    |                          |                                   |   |                            |            |
|----|--------------------------|-----------------------------------|---|----------------------------|------------|
| 4  | MMR                      | Transverse Myelitis               | Insufficient                                  | Weak                       | Inadequate |
| 5  | Varicella                | Transverse Myelitis               | Insufficient                                  | Weak                       | Inadequate |
| 6  | Influenza                | Transverse Myelitis               | Insufficient                                  | Weak                       | Inadequate |
| 7  | Hepatitis A              | Transverse Myelitis               | Insufficient                                  | Weak                       | Inadequate |
| 8  | Hepatitis B              | Transverse Myelitis               | Insufficient                                  | Weak                       | Inadequate |
| 9  | HPV                      | Transverse Myelitis               | Insufficient                                  | Lacking                    | Inadequate |
| 10 | DT, TT, or aP containing | Transverse Myelitis               | Insufficient                                  | Lacking                    | Inadequate |
| 11 | Meningococcal            | Transverse Myelitis               | Insufficient                                  | Lacking                    | Inadequate |
| 4  | MMR                      | Optic Neuritis <sup>d</sup>       | Limited                                       | Weak                       | Inadequate |
| 6  | Influenza                | Optic Neuritis <sup>d</sup>       | Limited                                       | Weak                       | Inadequate |
| 8  | Hepatitis B              | Optic Neuritis <sup>d</sup>       | Limited                                       | Lacking                    | Inadequate |
| 10 | DT, TT, or aP containing | Optic Neuritis <sup>d</sup>       | Limited (diphtheria toxoid or tetanus toxoid) | Lacking                    | Inadequate |
|    |                          |                                   | Insufficient (acellular pertussis)            |                            |            |
| 4  | MMR                      | Neuromyelitis Optica <sup>d</sup> | Insufficient                                  | Weak (rubella)             | Inadequate |
|    |                          |                                   |   | Lacking (measles or mumps) |            |
| 6  | Influenza                | Neuromyelitis Optica              | Insufficient                                  | Lacking                    | Inadequate |
| 8  | Hepatitis B              | Neuromyelitis Optica              | Insufficient                                  | Lacking                    | Inadequate |

*continued*

TABLE D-3 Continued

| Chapter | Vaccine                  | Adverse Event                          | Epidemiologic Assessment                                | Mechanistic Assessment | Causality Conclusion |
|---------|--------------------------|--|---|------------------------|----------------------|
| 9       | HPV                      | Neuromyelitis Optica                   | Insufficient  | Lacking                | Inadequate           |
| 4       | MMR                      | Multiple Sclerosis Onset in Adults     | Limited   | Lacking                | Inadequate           |
| 6       | Influenza                | Multiple Sclerosis Onset in Adults     | Limited   | Lacking                | Inadequate           |
| 8       | Hepatitis B              | Multiple Sclerosis Onset in Adults     | Limited   | Lacking                | Inadequate           |
| 10      | DT, TT, or aP containing | Multiple Sclerosis Onset in Adults     | Limited (diphtheria toxoid or tetanus toxoid)           | Lacking                | Inadequate           |
|         |                          |  | Insufficient (acellular pertussis)                      |                        |                      |
| 4       | MMR                      | Multiple Sclerosis Onset in Children   | Limited   | Lacking                | Inadequate           |
| 8       | Hepatitis B              | Multiple Sclerosis Onset in Children   | Limited   | Lacking                | Inadequate           |
| 6       | Influenza                | Multiple Sclerosis Relapse in Adults   | Limited   | Lacking                | Inadequate           |
| 8       | Hepatitis B              | Multiple Sclerosis Relapse in Adults   | Limited   | Lacking                | Inadequate           |
| 10      | DT, TT, or aP containing | Multiple Sclerosis Relapse in Adults   | Limited (tetanus toxoid)                                | Lacking                | Inadequate           |
|         |                          |  | Insufficient (diphtheria toxoid or acellular pertussis) |                        |                      |
| 8       | Hepatitis B              | Multiple Sclerosis Relapse in Children | Limited   | Lacking                | Inadequate           |

|    |                          |  |   |                  |            |
|----|--------------------------|--|---|------------------|------------|
| 10 | DT, TT, or aP containing | Multiple Sclerosis Relapse in Children           | Limited (diphtheria toxoid or tetanus toxoid)<br>Insufficient (acellular pertussis) | Lacking          | Inadequate |
| 7  | Hepatitis A              | Multiple Sclerosis                               | Insufficient  | Lacking          | Inadequate |
| 9  | HPV                      | Multiple Sclerosis                               | Insufficient  | Lacking          | Inadequate |
| 11 | Meningococcal            | Multiple Sclerosis                               | Insufficient  | Lacking          | Inadequate |
| 8  | Hepatitis B              | First Demyelinating Event in Adults              | Moderate (null)   | Low-Intermediate | Inadequate |
| 8  | Hepatitis B              | First Demyelinating Event in Children            | Limited   | Lacking          | Inadequate |
| 4  | MMR                      | Guillain-Barré syndrome                          | Insufficient  | Weak             | Inadequate |
| 5  | Varicella                | Guillain-Barré syndrome                          | Insufficient  | Weak             | Inadequate |
| 6  | Influenza                | Guillain-Barré syndrome                          | Moderate (null)   | Weak             | Inadequate |
| 7  | Hepatitis A              | Guillain-Barré syndrome                          | Insufficient  | Weak             | Inadequate |
| 8  | Hepatitis B              | Guillain-Barré syndrome                          | Insufficient  | Lacking          | Inadequate |
| 9  | HPV                      | Guillain-Barré syndrome                          | Insufficient  | Lacking          | Inadequate |
| 10 | DT, TT, or aP containing | Guillain-Barré syndrome                          | Insufficient  | Lacking          | Inadequate |
| 11 | Meningococcal            | Guillain-Barré syndrome                          | Limited   | Lacking          | Inadequate |
| 4  | MMR                      | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient  | Lacking          | Inadequate |
| 6  | Influenza                | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient  | Weak             | Inadequate |

*continued*

TABLE D-3 Continued

| Chapter | Vaccine                  | Adverse Event                       | Epidemiologic Assessment                           | Mechanistic Assessment                     | Causality Conclusion |
|---------|--------------------------|-------------------------------------|--|--|----------------------|
| 7       | Hepatitis A              | Chronic Inflammatory Polyneuropathy | Insufficient                                       | Lacking                                    | Inadequate           |
| 8       | Hepatitis B              | Chronic Inflammatory Polyneuropathy | Insufficient                                       | Lacking                                    | Inadequate           |
| 9       | HPV                      | Chronic Inflammatory Polyneuropathy | Insufficient                                       | Lacking                                    | Inadequate           |
| 10      | DT, TT, or aP containing | Chronic Inflammatory Polyneuropathy | Insufficient                                       | Lacking                                    | Inadequate           |
| 11      | Meningococcal            | Chronic Inflammatory Polyneuropathy | Insufficient                                       | Lacking                                    | Inadequate           |
| 4       | MMR                      | Opsoclonus Myoclonus Syndrome       | Insufficient                                       | Lacking                                    | Inadequate           |
| 10      | DT, TT, or aP containing | Opsoclonus Myoclonus Syndrome       | Insufficient                                       | Lacking                                    | Inadequate           |
| 7       | Hepatitis A              | Bell's Palsy                        | Insufficient                                       | Lacking                                    | Inadequate           |
| 10      | DT, TT, or aP containing | Bell's Palsy                        | Limited (acellular pertussis)                      | Weak (diphtheria toxoid or tetanus toxoid) | Inadequate           |
|         |                          |                                     | Insufficient (diphtheria toxoid or tetanus toxoid) | Lacking (acellular pertussis)              |                      |
| 4       | MMR                      | Brachial Neuritis                   | Insufficient                                       | Lacking                                    | Inadequate           |
| 6       | Influenza                | Brachial Neuritis                   | Insufficient                                       | Lacking                                    | Inadequate           |
| 8       | Hepatitis B              | Brachial Neuritis                   | Insufficient                                       | Lacking                                    | Inadequate           |

|    |                          |  |                 |   |            |
|----|--------------------------|--|-----------------|---|------------|
| 9  | HPV                      | Brachial Neuritis  | Insufficient    | Lacking   | Inadequate |
| 9  | HPV                      | Amyotrophic Lateral Sclerosis  | Insufficient    | Lacking   | Inadequate |
| 5  | Varicella                | Small Fiber Neuropathy <sup>d</sup>  | Insufficient    | Lacking   | Inadequate |
| 6  | Influenza                | Small Fiber Neuropathy   | Insufficient    | Lacking   | Inadequate |
| 7  | Hepatitis A              | Anaphylaxis  | Insufficient    | Weak  | Inadequate |
| 10 | DT and aP containing     | Anaphylaxis  | Insufficient    | Lacking   | Inadequate |
| 10 | DT, TT, or aP containing | Chronic Urticaria  | Insufficient    | Lacking   | Inadequate |
| 10 | DT, TT, or aP containing | Serum Sickness   | Insufficient    | Weak (diphtheria toxoid or tetanus toxoid)<br>Lacking (acellular pertussis) | Inadequate |
| 6  | Influenza                | Live Attenuated Influenza Vaccine or Asthma Exacerbation or Reactive Airway Disease Episodes in Children Younger Than 5 Years of Age | Moderate (null) | Weak  | Inadequate |
| 6  | Influenza                | Live Attenuated Influenza Vaccine or Asthma Exacerbation or Reactive Airway Disease Episodes in Persons 5 Years of Age or Older      | Moderate (null) | Weak  | Inadequate |
| 8  | Hepatitis B              | Erythema Nodosum <sup>d</sup>  | Insufficient    | Weak  | Inadequate |

*continued*

TABLE D-3 Continued

| Chapter | Vaccine     | Adverse Event   | Epidemiologic Assessment                       | Mechanistic Assessment                 | Causality Conclusion |
|---------|-------------|---|--|--|----------------------|
| 6       | Influenza   | Onset or Exacerbation of Systemic Lupus Erythematosus | Limited (exacerbation)<br>Insufficient (onset) | Lacking                                | Inadequate           |
| 8       | Hepatitis B | Onset or Exacerbation of Systemic Lupus Erythematosus | Limited (onset)<br>Insufficient (exacerbation) | Weak                                   | Inadequate           |
| 6       | Influenza   | Onset or Exacerbation of Vasculitis                   | Limited (exacerbation)<br>Insufficient (onset) | Weak (exacerbation)<br>Lacking (onset) | Inadequate           |
| 8       | Hepatitis B | Onset or Exacerbation of Vasculitis                   | Insufficient                                   | Low-Intermediate                       | Inadequate           |
| 6       | Influenza   | Polyarteritis Nodosa                                  | Insufficient                                   | Lacking                                | Inadequate           |
| 8       | Hepatitis B | Onset or Exacerbation of Polyarteritis Nodosa         | Insufficient                                   | Weak                                   | Inadequate           |
| 8       | Hepatitis B | Onset or Exacerbation of Psoriatic Arthritis          | Insufficient                                   | Lacking                                | Inadequate           |
| 8       | Hepatitis B | Onset or Exacerbation of Reactive Arthritis           | Insufficient                                   | Weak                                   | Inadequate           |
| 8       | Hepatitis B | Onset and Exacerbation of Rheumatoid Arthritis        | Limited (exacerbation)<br>Insufficient (onset) | Weak                                   | Inadequate           |

|   |             |  |                                 |                            |            |
|---|-------------|--|---------------------------------|----------------------------|------------|
| 8 | Hepatitis B | Onset or Exacerbation of Juvenile Idiopathic Arthritis | Insufficient                    | Weak                       | Inadequate |
| 9 | HPV         | Transient Arthralgia                                   | Limited                         | Lacking                    | Inadequate |
| 4 | MMR         | Chronic Arthralgia in Women                            | Limited (rubella)               | Low-Intermediate (rubella) | Inadequate |
|   |             |  | Insufficient (measles or mumps) | Lacking (measles or mumps) |            |
| 4 | MMR         | Chronic Arthritis in Women                             | Limited (rubella)               | Low-Intermediate (rubella) | Inadequate |
|   |             |  | Insufficient (measles or mumps) | Lacking (measles or mumps) |            |
| 4 | MMR         | Chronic Arthropathy in Children                        | Insufficient                    | Weak (rubella)             | Inadequate |
|   |             |  |                                 | Lacking (measles or mumps) |            |
| 4 | MMR         | Arthropathy in Men                                     | Limited                         | Weak (rubella)             | Inadequate |
|   |             |  |                                 | Lacking (measles or mumps) |            |
| 5 | Varicella   | Onset or Exacerbation Arthropathy                      | Insufficient                    | Lacking                    | Inadequate |
| 6 | Influenza   | Onset or Exacerbation of Arthropathy                   | Insufficient                    | Weak                       | Inadequate |

*continued*



TABLE D-3 Continued

| Chapter | Vaccine                  | Adverse Event          | Epidemiologic Assessment  | Mechanistic Assessment  | Causality Conclusion |
|---------|--------------------------|------------------------|---|---|----------------------|
| 10      | DT, TT, or aP containing | Arthropathy            | Limited (diphtheria toxoid or tetanus toxoid)<br>Insufficient (acellular pertussis) | Lacking   | Inadequate           |
| 8       | Hepatitis B              | Type 1 Diabetes        | Moderate (null)   | Lacking   | Inadequate           |
| 7       | Hepatitis A              | Autoimmune Hepatitis   | Insufficient  | Weak  | Inadequate           |
| 10      | DT, TT, or aP containing | Myocarditis            | Insufficient  | Weak (diphtheria toxoid)<br>Lacking (tetanus toxoid or acellular pertussis) | Inadequate           |
| 9       | HPV                      | Pancreatitis           | Insufficient  | Lacking   | Inadequate           |
| 4       | MMR                      | Hepatitis              | Insufficient  | Weak  | Inadequate           |
| 9       | HPV                      | Thromboembolic Events  | Insufficient  | Lacking   | Inadequate           |
| 5       | Varicella                | Stroke <sup>d</sup>    | Limited   | Weak  | Inadequate           |
| 6       | Influenza                | Stroke                 | Moderate (decrease)   | Lacking   | Inadequate           |
| 9       | HPV                      | Hypercoagulable States | Insufficient  | Lacking   | Inadequate           |

|    | Influenza                | Myocardial Infarction            | Moderate (decrease) | Weak (Live Attenuated Influenza Vaccine)<br>Lacking (Inactivated Influenza Vaccine) | Inadequate |
|----|--------------------------|----------------------------------|---------------------|---|------------|
| 6  | MMR                      | Chronic Fatigue Syndrome         | Insufficient        | Lacking   | Inadequate |
| 11 | Meningococcal            | Chronic Headache                 | Insufficient        | Lacking   | Inadequate |
| 4  | MMR                      | Fibromyalgia                     | Insufficient        | Lacking   | Inadequate |
| 6  | Influenza                | Fibromyalgia                     | Insufficient        | Lacking   | Inadequate |
| 8  | Hepatitis B              | Fibromyalgia                     | Insufficient        | Lacking   | Inadequate |
| 10 | DT, TT, or aP containing | Fibromyalgia                     | Insufficient        | Lacking   | Inadequate |
| 10 | DT, TT, or aP containing | Sudden Infant Death Syndrome     | Insufficient        | Lacking   | Inadequate |
| 4  | MMR                      | Hearing Loss                     | Insufficient        | Low-Intermediate (measles or mumps)<br>Lacking (rubella)                            | Inadequate |
| 6  | Influenza                | All-Cause Mortality <sup>d</sup> | Moderate (decrease) | Weak (Live Attenuated Influenza Vaccine)<br>Lacking (Inactivated Influenza Vaccine) | Inadequate |

*continued*

TABLE D-3 Continued

| Chapter | Vaccine                  | Adverse Event                   | Epidemiologic Assessment | Mechanistic Assessment | Causality Conclusion |
|---------|--------------------------|---------------------------------|--------------------------|------------------------|----------------------|
| 5       | Varicella                | Thrombocytopenia                | Insufficient             | Weak                   | Inadequate           |
| 10      | DT, TT, or aP containing | Immune Thrombocytopenic Purpura | Insufficient             | Lacking                | Inadequate           |
| 12      | Injection-Related Event  | Complex Regional Pain Syndrome  | Insufficient             | Low-Intermediate       | Inadequate           |

NOTE: The measles-mumps-rubella; human papillomavirus; and diphtheria toxoid-, tetanus toxoid-, and acellular pertussis-containing vaccines have been abbreviated in the following ways: MMR; HPV; and DT, TT, and aP containing.

<sup>a</sup> The committee attributes causation to the measles component of the vaccine.

<sup>b</sup> The committee attributes causation to the rubella component of the vaccine.

<sup>c</sup> The committee attributes causation to two particular vaccines used in three particular years in Canada.

<sup>d</sup> Although not originally charged to the committee by the sponsor, the committee considered this adverse event in its review of the literature.

TABLE D-4 Causality Conclusions Organized by Epidemiologic Assessment, Adverse Event, and Chapter

| Chapter | Vaccine                  | Adverse Event  | Epidemiologic Assessment         | Mechanistic Assessment     | Causality Conclusion           |
|---------|--------------------------|--|----------------------------------|----------------------------|--------------------------------|
| 4       | MMR                      | Febrile Seizures   | High (increase)                  | Intermediate               | Convincingly Supports          |
| 4       | MMR                      | Autism   | High (null)                      | Lacking                    | Favors Rejection               |
| 6       | Influenza                | Inactivated Influenza Vaccine and Bell's Palsy   | High (null)                      | Lacking                    | Favors Rejection               |
| 6       | Influenza                | Inactivated Influenza Vaccine and Asthma Exacerbation or Reactive Airway Disease Episodes in Children and Adults | High (null)                      | Weak                       | Favors Rejection               |
| 4       | MMR                      | Type 1 Diabetes  | High (null)                      | Lacking                    | Favors Rejection               |
| 10      | DT, TT, or aP containing | Type 1 Diabetes  | High (null)                      | Lacking                    | Favors Rejection               |
| 4       | MMR                      | Transient Arthralgia in Women  | Moderate (increase) (rubella)    | Intermediate (rubella)     | Favors Acceptance <sup>a</sup> |
|         |                          |  | Insufficient (measles or mumps)  | Lacking (measles or mumps) |                                |
| 4       | MMR                      | Transient Arthralgia in Children   | Moderate (increase)              | Weak (rubella)             | Favors Acceptance              |
|         |                          |  |                                  | Lacking (measles or mumps) |                                |
| 6       | Influenza                | Oculorespiratory Syndrome  | Moderate (increase) <sup>b</sup> | Intermediate <sup>b</sup>  | Favors Acceptance <sup>b</sup> |
| 6       | Influenza                | Seizures <sup>c</sup>  | Moderate (null)                  | Lacking                    | Inadequate                     |

*continued*

TABLE D-4 Continued

| Chapter | Vaccine     | Adverse Event  | Epidemiologic Assessment | Mechanistic Assessment  | Causality Conclusion |
|---------|-------------|--|--------------------------|---|----------------------|
| 4       | MMR         | Meningitis <sup>c</sup>  | Moderate (null)          | Weak (mumps)<br>Lacking (measles or rubella)  | Inadequate           |
| 8       | Hepatitis B | First Demyelinating Event in Adults  | Moderate (null)          | Low-Intermediate  | Inadequate           |
| 6       | Influenza   | Guillain-Barré syndrome  | Moderate (null)          | Weak  | Inadequate           |
| 6       | Influenza   | Live Attenuated Influenza Vaccine or Asthma Exacerbation or Reactive Airway Disease Episodes in Children Younger Than 5 Years of Age | Moderate (null)          | Weak  | Inadequate           |
| 6       | Influenza   | Live Attenuated Influenza Vaccine or Asthma Exacerbation or Reactive Airway Disease Episodes in Persons 5 Years of Age or Older      | Moderate (null)          | Weak  | Inadequate           |
| 8       | Hepatitis B | Type 1 Diabetes  | Moderate (null)          | Lacking   | Inadequate           |
| 6       | Influenza   | Stroke   | Moderate (decrease)      | Lacking   | Inadequate           |
| 6       | Influenza   | Myocardial Infarction  | Moderate (decrease)      | Weak (Live Attenuated Influenza Vaccine)<br>Lacking (Inactivated Influenza Vaccine) | Inadequate           |

|    | All-Cause Mortality <sup>c</sup> | Moderate (decrease)   | Weak (Live Attenuated Influenza Vaccine)<br>Lacking (Inactivated Influenza Vaccine)   | Inadequate  |
|----|----------------------------------|---|---|---|
| 6  | Influenza                        |   |   |   |
| 5  | Varicella                        | Disseminated Oka VZV with Subsequent Infection Resulting in Pneumonia, Meningitis, or Hepatitis     | Limited (subsequent infection resulting in pneumonia)<br>Insufficient (subsequent infection resulting in meningitis or hepatitis) | Strong (in individuals with demonstrated immunodeficiencies)<br>Convincingly Supports (in individuals with demonstrated immunodeficiencies) |
| 5  | Varicella                        | Vaccine Strain Viral Reactivation with Subsequent Infection Resulting in Meningitis or Encephalitis | Limited (subsequent infection resulting in encephalitis)<br>Insufficient (subsequent infection resulting in meningitis)           | Strong<br>Convincingly Supports   |
| 4  | MMR                              | Encephalitis  | Limited   | Weak<br>Inadequate  |
| 10 | DT, TT, or aP containing         | Encephalitis  | Limited   | Weak<br>Inadequate  |
| 11 | Meningococcal                    | Encephalitis  | Limited   | Lacking<br>Inadequate   |
| 4  | MMR                              | Encephalopathy  | Limited   | Weak<br>Inadequate  |
| 10 | DT, TT, or aP containing         | Encephalopathy  | Limited   | Weak<br>Inadequate  |

*continued*

TABLE D-4 Continued

| Chapter | Vaccine                  | Adverse Event               | Epidemiologic Assessment                      | Mechanistic Assessment                        | Causality Conclusion |
|---------|--------------------------|-----------------------------|---|---|----------------------|
| 11      | Meningococcal            | Encephalopathy              | Limited                                       | Lacking                                       | Inadequate           |
| 10      | DT, TT, or aP containing | Infantile Spasms            | Limited (diphtheria toxoid or tetanus toxoid) | Lacking                                       | Inadequate           |
|         |                          |                             | Insufficient (acellular pertussis)            |   |                      |
| 4       | MMR                      | Afebrile Seizures           | Limited                                       | Lacking                                       | Inadequate           |
| 5       | Varicella                | Seizures                    | Limited                                       | Weak  | Inadequate           |
| 8       | Hepatitis B              | Seizures                    | Limited                                       | Lacking                                       | Inadequate           |
| 10      | DT, TT, or aP containing | Seizures                    | Limited                                       | Weak (acellular pertussis)                    | Inadequate           |
|         |                          |                             |   | Lacking (diphtheria toxoid or tetanus toxoid) |                      |
| 4       | MMR                      | Optic Neuritis <sup>c</sup> | Limited                                       | Weak  | Inadequate           |
| 6       | Influenza                | Optic Neuritis <sup>c</sup> | Limited                                       | Weak  | Inadequate           |
| 8       | Hepatitis B              | Optic Neuritis <sup>c</sup> | Limited                                       | Lacking                                       | Inadequate           |
| 10      | DT, TT, or aP containing | Optic Neuritis <sup>c</sup> | Limited (diphtheria toxoid or tetanus toxoid) | Lacking                                       | Inadequate           |
|         |                          |                             | Insufficient (acellular pertussis)            |   |                      |

|    |                          |  |   |         |            |
|----|--------------------------|--|---|---------|------------|
| 4  | MMR                      | Multiple Sclerosis Onset in Adults     | Limited   | Lacking | Inadequate |
| 6  | Influenza                | Multiple Sclerosis Onset in Adults     | Limited   | Lacking | Inadequate |
| 8  | Hepatitis B              | Multiple Sclerosis Onset in Adults     | Limited   | Lacking | Inadequate |
| 10 | DT, TT, or aP containing | Multiple Sclerosis Onset in Adults     | Limited (diphtheria toxoid or tetanus toxoid)           | Lacking | Inadequate |
|    |                          |  | Insufficient (acellular pertussis)                      |         |            |
| 4  | MMR                      | Multiple Sclerosis Onset in Children   | Limited   | Lacking | Inadequate |
| 8  | Hepatitis B              | Multiple Sclerosis Onset in Children   | Limited   | Lacking | Inadequate |
| 6  | Influenza                | Multiple Sclerosis Relapse in Adults   | Limited   | Lacking | Inadequate |
| 8  | Hepatitis B              | Multiple Sclerosis Relapse in Adults   | Limited   | Lacking | Inadequate |
| 10 | DT, TT, or aP containing | Multiple Sclerosis Relapse in Adults   | Limited (tetanus toxoid)                                | Lacking | Inadequate |
|    |                          |  | Insufficient (diphtheria toxoid or acellular pertussis) |         |            |
| 8  | Hepatitis B              | Multiple Sclerosis Relapse in Children | Limited   | Lacking | Inadequate |
| 10 | DT, TT, or aP containing | Multiple Sclerosis Relapse in Children | Limited (diphtheria toxoid or tetanus toxoid)           | Lacking | Inadequate |
|    |                          |  | Insufficient (acellular pertussis)                      |         |            |
| 8  | Hepatitis B              | First Demyelinating Event in Children  | Limited   | Lacking | Inadequate |

*continued*



TABLE D-4 Continued

| Chapter | Vaccine                  | Adverse Event   | Epidemiologic Assessment                           | Mechanistic Assessment                     | Causality Conclusion  |
|---------|--------------------------|---|--|--|-----------------------|
| 11      | Meningococcal            | Guillain-Barré syndrome                               | Limited  | Lacking                                    | Inadequate            |
| 10      | DT, TT, or aP containing | Bell's Palsy  | Limited (acellular pertussis)                      | Weak (diphtheria toxoid or tetanus toxoid) | Inadequate            |
|         |                          |   | Insufficient (diphtheria toxoid or tetanus toxoid) | Lacking (acellular pertussis)              |                       |
| 5       | Varicella                | Anaphylaxis   | Limited  | Strong                                     | Convincingly Supports |
| 6       | Influenza                | Anaphylaxis   | Limited  | Strong                                     | Convincingly Supports |
| 6       | Influenza                | Onset or Exacerbation of Systemic Lupus Erythematosus | Limited (exacerbation)                             | Lacking                                    | Inadequate            |
|         |                          |   | Insufficient (onset)                               |  |                       |
| 8       | Hepatitis B              | Onset or Exacerbation of Systemic Lupus Erythematosus | Limited (onset)                                    | Weak                                       | Inadequate            |
|         |                          |   | Insufficient (exacerbation)                        |  |                       |
| 6       | Influenza                | Onset or Exacerbation of Vasculitis                   | Limited (exacerbation)                             | Weak (exacerbation)                        | Inadequate            |
|         |                          |   | Insufficient (onset)                               | Lacking (onset)                            |                       |

|    |                          |  |   |  |                       |
|----|--------------------------|--|---|--|-----------------------|
| 8  | Hepatitis B              | Onset and Exacerbation of Rheumatoid Arthritis | Limited (exacerbation)<br>Insufficient (onset)                                      | Weak   | Inadequate            |
| 9  | HPV                      | Transient Arthralgia                           | Limited   | Lacking  | Inadequate            |
| 4  | MMR                      | Chronic Arthralgia in Women                    | Limited (rubella)<br>Insufficient (measles or mumps)                                | Low-Intermediate (rubella)<br>Lacking (measles or mumps) | Inadequate            |
| 4  | MMR                      | Chronic Arthritis in Women                     | Limited (rubella)<br>Insufficient (measles or mumps)                                | Low-Intermediate (rubella)<br>Lacking (measles or mumps) | Inadequate            |
| 4  | MMR                      | Arthropathy in Men                             | Limited   | Weak (rubella)<br>Lacking (measles or mumps)             | Inadequate            |
| 10 | DT, TT, or aP containing | Arthropathy                                    | Limited (diphtheria toxoid or tetanus toxoid)<br>Insufficient (acellular pertussis) | Lacking  | Inadequate            |
| 5  | Varicella                | Stroke <sup>e</sup>                            | Limited   | Weak   | Inadequate            |
| 12 | Injection-Related Event  | Deltoid Bursitis                               | Limited   | Strong   | Convincingly Supports |

*continued*

TABLE D-4 Continued

| Chapter | Vaccine                  | Adverse Event   | Epidemiologic Assessment | Mechanistic Assessment  | Causality Conclusion  |
|---------|--------------------------|---|--------------------------|---|---|
| 5       | Varicella                | Disseminated Oka VZV without Other Organ Involvement              | Insufficient             | Strong  | Convincingly Supports   |
| 5       | Varicella                | Vaccine Strain Viral Reactivation without Other Organ Involvement | Insufficient             | Strong  | Convincingly Supports   |
| 4       | MMR                      | Measles Inclusion Body Encephalitis                               | Insufficient             | Strong (measles; in individuals with demonstrated immunodeficiencies)<br>Lacking (mumps or rubella) | Convincingly Supports <sup>d</sup><br>(in individuals with demonstrated immunodeficiencies) |
| 6       | Influenza                | Encephalitis  | Insufficient             | Weak  | Inadequate  |
| 8       | Hepatitis B              | Encephalitis  | Insufficient             | Lacking   | Inadequate  |
| 5       | Varicella                | Encephalopathy  | Insufficient             | Lacking   | Inadequate  |
| 6       | Influenza                | Encephalopathy  | Insufficient             | Weak  | Inadequate  |
| 8       | Hepatitis B              | Encephalopathy  | Insufficient             | Lacking   | Inadequate  |
| 5       | Varicella                | Cerebellar Ataxia   | Insufficient             | Weak  | Inadequate  |
| 4       | MMR                      | Ataxia  | Insufficient             | Weak (measles or mumps)<br>Lacking (rubella)  | Inadequate  |
| 10      | DT, TT, or aP containing | Ataxia  | Insufficient             | Lacking   | Inadequate  |

|    |                          |                                      |              |   |            |
|----|--------------------------|--------------------------------------|--------------|---|------------|
| 10 | DT, TT, or aP containing | Autism                               | Insufficient | Lacking   | Inadequate |
| 4  | MMR                      | Acute Disseminated Encephalomyelitis | Insufficient | Weak  | Inadequate |
| 5  | Varicella                | Acute Disseminated Encephalomyelitis | Insufficient | Weak  | Inadequate |
| 6  | Influenza                | Acute Disseminated Encephalomyelitis | Insufficient | Weak  | Inadequate |
| 7  | Hepatitis A              | Acute Disseminated Encephalomyelitis | Insufficient | Weak  | Inadequate |
| 8  | Hepatitis B              | Acute Disseminated Encephalomyelitis | Insufficient | Low-Intermediate  | Inadequate |
| 9  | HPV                      | Acute Disseminated Encephalomyelitis | Insufficient | Lacking   | Inadequate |
| 10 | DT, TT, or aP containing | Acute Disseminated Encephalomyelitis | Insufficient | Weak (tetanus toxoid)<br>Lacking (diphtheria toxoid or acellular pertussis) | Inadequate |
| 11 | Meningococcal            | Acute Disseminated Encephalomyelitis | Insufficient | Lacking   | Inadequate |
| 4  | MMR                      | Transverse Myelitis                  | Insufficient | Weak  | Inadequate |
| 5  | Varicella                | Transverse Myelitis                  | Insufficient | Weak  | Inadequate |
| 6  | Influenza                | Transverse Myelitis                  | Insufficient | Weak  | Inadequate |

*continued*

TABLE D-4 Continued

| Chapter | Vaccine                  | Adverse Event                     | Epidemiologic Assessment | Mechanistic Assessment                       | Causality Conclusion |
|---------|--------------------------|-----------------------------------|--------------------------|--|----------------------|
| 7       | Hepatitis A              | Transverse Myelitis               | Insufficient             | Weak   | Inadequate           |
| 8       | Hepatitis B              | Transverse Myelitis               | Insufficient             | Weak   | Inadequate           |
| 9       | HPV                      | Transverse Myelitis               | Insufficient             | Lacking                                      | Inadequate           |
| 10      | DT, TT, or aP containing | Transverse Myelitis               | Insufficient             | Lacking                                      | Inadequate           |
| 11      | Meningococcal            | Transverse Myelitis               | Insufficient             | Lacking                                      | Inadequate           |
| 4       | MMR                      | Neuromyelitis Optica <sup>c</sup> | Insufficient             | Weak (rubella)<br>Lacking (measles or mumps) | Inadequate           |
| 6       | Influenza                | Neuromyelitis Optica              | Insufficient             | Lacking                                      | Inadequate           |
| 8       | Hepatitis B              | Neuromyelitis Optica              | Insufficient             | Lacking                                      | Inadequate           |
| 9       | HPV                      | Neuromyelitis Optica              | Insufficient             | Lacking                                      | Inadequate           |
| 7       | Hepatitis A              | Multiple Sclerosis                | Insufficient             | Lacking                                      | Inadequate           |
| 9       | HPV                      | Multiple Sclerosis                | Insufficient             | Lacking                                      | Inadequate           |
| 11      | Meningococcal            | Multiple Sclerosis                | Insufficient             | Lacking                                      | Inadequate           |
| 4       | MMR                      | Guillain-Barré syndrome           | Insufficient             | Weak   | Inadequate           |
| 5       | Varicella                | Guillain-Barré syndrome           | Insufficient             | Weak   | Inadequate           |
| 7       | Hepatitis A              | Guillain-Barré syndrome           | Insufficient             | Weak   | Inadequate           |
| 8       | Hepatitis B              | Guillain-Barré syndrome           | Insufficient             | Lacking                                      | Inadequate           |

|    |                          |  |              |         |            |
|----|--------------------------|--|--------------|---------|------------|
| 9  | HPV                      | Guillain-Barré syndrome                          | Insufficient | Lacking | Inadequate |
| 10 | DT, TT, or aP containing | Guillain-Barré syndrome                          | Insufficient | Lacking | Inadequate |
| 4  | MMR                      | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient | Lacking | Inadequate |
| 6  | Influenza                | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient | Weak    | Inadequate |
| 7  | Hepatitis A              | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient | Lacking | Inadequate |
| 8  | Hepatitis B              | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient | Lacking | Inadequate |
| 9  | HPV                      | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient | Lacking | Inadequate |
| 10 | DT, TT, or aP containing | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient | Lacking | Inadequate |
| 11 | Meningococcal            | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient | Lacking | Inadequate |
| 4  | MMR                      | Opsoclonus Myoclonus Syndrome                    | Insufficient | Lacking | Inadequate |
| 10 | DT, TT, or aP containing | Opsoclonus Myoclonus Syndrome                    | Insufficient | Lacking | Inadequate |
| 7  | Hepatitis A              | Bell's Palsy                                     | Insufficient | Lacking | Inadequate |
| 4  | MMR                      | Brachial Neuritis                                | Insufficient | Lacking | Inadequate |
| 6  | Influenza                | Brachial Neuritis                                | Insufficient | Lacking | Inadequate |
| 8  | Hepatitis B              | Brachial Neuritis                                | Insufficient | Lacking | Inadequate |

*continued*

TABLE D-4 Continued

| Chapter | Vaccine                  | Adverse Event                       | Epidemiologic Assessment | Mechanistic Assessment  | Causality Conclusion                                   |
|---------|--------------------------|-------------------------------------|--------------------------|---|--|
| 9       | HPV                      | Brachial Neuritis                   | Insufficient             | Lacking   | Inadequate   |
| 9       | HPV                      | Amyotrophic Lateral Sclerosis       | Insufficient             | Lacking   | Inadequate   |
| 5       | Varicella                | Small Fiber Neuropathy <sup>c</sup> | Insufficient             | Lacking   | Inadequate   |
| 6       | Influenza                | Small Fiber Neuropathy              | Insufficient             | Lacking   | Inadequate   |
| 4       | MMR                      | Anaphylaxis                         | Insufficient             | Strong  | Convincingly Supports                                  |
| 7       | Hepatitis A              | Anaphylaxis                         | Insufficient             | Weak  | Inadequate   |
| 8       | Hepatitis B              | Anaphylaxis                         | Insufficient             | Strong (in yeast-sensitive individuals)                                     | Convincingly Supports (in yeast-sensitive individuals) |
| 9       | HPV                      | Anaphylaxis                         | Insufficient             | Intermediate  | Favors Acceptance                                      |
| 10      | TT containing            | Anaphylaxis                         | Insufficient             | Strong  | Convincingly Supports                                  |
| 10      | DT and aP containing     | Anaphylaxis                         | Insufficient             | Lacking   | Inadequate   |
| 11      | Meningococcal            | Anaphylaxis                         | Insufficient             | Strong  | Convincingly Supports                                  |
| 10      | DT, TT, or aP containing | Chronic Urticaria                   | Insufficient             | Lacking   | Inadequate   |
| 10      | DT, TT, or aP containing | Serum Sickness                      | Insufficient             | Weak (diphtheria toxoid or tetanus toxoid)<br>Lacking (acellular pertussis) | Inadequate   |

|    |                          |  |              |   |            |
|----|--------------------------|--|--------------|---|------------|
| 8  | Hepatitis B              | Erythema Nodosum <sup>c</sup>                          | Insufficient | Weak  | Inadequate |
| 8  | Hepatitis B              | Onset or Exacerbation of Vasculitis                    | Insufficient | Low-Intermediate  | Inadequate |
| 6  | Influenza                | Polyarteritis Nodosa                                   | Insufficient | Lacking   | Inadequate |
| 8  | Hepatitis B              | Onset or Exacerbation of Polyarteritis Nodosa          | Insufficient | Weak  | Inadequate |
| 8  | Hepatitis B              | Onset or Exacerbation of Psoriatic Arthritis           | Insufficient | Lacking   | Inadequate |
| 8  | Hepatitis B              | Onset or Exacerbation of Reactive Arthritis            | Insufficient | Weak  | Inadequate |
| 8  | Hepatitis B              | Onset or Exacerbation of Juvenile Idiopathic Arthritis | Insufficient | Weak  | Inadequate |
| 4  | MMR                      | Chronic Arthropathy in Children                        | Insufficient | Weak (rubella)<br>Lacking (measles or mumps)                                | Inadequate |
| 5  | Varicella                | Onset or Exacerbation Arthropathy                      | Insufficient | Lacking   | Inadequate |
| 6  | Influenza                | Onset or Exacerbation of Arthropathy                   | Insufficient | Weak  | Inadequate |
| 7  | Hepatitis A              | Autoimmune Hepatitis                                   | Insufficient | Weak  | Inadequate |
| 10 | DT, TT, or aP containing | Myocarditis  | Insufficient | Weak (diphtheria toxoid)<br>Lacking (tetanus toxoid or acellular pertussis) | Inadequate |

*continued*



TABLE D-4 Continued

| Chapter | Vaccine                  | Adverse Event                   | Epidemiologic Assessment | Mechanistic Assessment              | Causality Conclusion |
|---------|--------------------------|---------------------------------|--------------------------|-------------------------------------|----------------------|
| 9       | HPV                      | Pancreatitis                    | Insufficient             | Lacking                             | Inadequate           |
| 4       | MMR                      | Hepatitis                       | Insufficient             | Weak                                | Inadequate           |
| 9       | HPV                      | Thromboembolic Events           | Insufficient             | Lacking                             | Inadequate           |
| 9       | HPV                      | Hypercoagulable States          | Insufficient             | Lacking                             | Inadequate           |
| 4       | MMR                      | Chronic Fatigue Syndrome        | Insufficient             | Lacking                             | Inadequate           |
| 11      | Meningococcal            | Chronic Headache                | Insufficient             | Lacking                             | Inadequate           |
| 4       | MMR                      | Fibromyalgia                    | Insufficient             | Lacking                             | Inadequate           |
| 6       | Influenza                | Fibromyalgia                    | Insufficient             | Lacking                             | Inadequate           |
| 8       | Hepatitis B              | Fibromyalgia                    | Insufficient             | Lacking                             | Inadequate           |
| 10      | DT, TT, or aP containing | Fibromyalgia                    | Insufficient             | Lacking                             | Inadequate           |
| 10      | DT, TT, or aP containing | Sudden Infant Death Syndrome    | Insufficient             | Lacking                             | Inadequate           |
| 4       | MMR                      | Hearing Loss                    | Insufficient             | Low-Intermediate (measles or mumps) | Inadequate           |
|         |                          |                                 |                          | Lacking (rubella)                   |                      |
| 5       | Varicella                | Thrombocytopenia                | Insufficient             | Weak                                | Inadequate           |
| 10      | DT, TT, or aP containing | Immune Thrombocytopenic Purpura | Insufficient             | Lacking                             | Inadequate           |

|    |                         |                                |              |                  |                       |
|----|-------------------------|--------------------------------|--------------|------------------|-----------------------|
| 12 | Injection-Related Event | Complex Regional Pain Syndrome | Insufficient | Low-Intermediate | Inadequate            |
| 12 | Injection-Related Event | Syncope                        | Insufficient | Strong           | Convincingly Supports |

NOTE: The measles-mumps-rubella; human papillomavirus; and diphtheria toxoid-, tetanus toxoid-, and acellular pertussis-containing vaccines have been abbreviated in the following ways: MMR; HPV; and DT, TT, and aP containing.

<sup>a</sup> The committee attributes causation to the rubella component of the vaccine.

<sup>b</sup> The committee attributes causation to two particular vaccines used in three particular years in Canada.

<sup>c</sup> Although not originally charged to the committee by the sponsor, the committee considered this adverse event in its review of the literature.

<sup>d</sup> The committee attributes causation to the measles component of the vaccine.

TABLE D-5 Causality Conclusions Organized by Mechanistic Assessment, Adverse Event, and Chapter

| Chapter | Vaccine   | Adverse Event   | Epidemiologic Assessment   | Mechanistic Assessment  | Causality Conclusion  |
|---------|-----------|---|--|---|---|
| 5       | Varicella | Disseminated Oka VZV without Other Organ Involvement  | Insufficient   | Strong  | Convincingly Supports   |
| 5       | Varicella | Disseminated Oka VZV with Subsequent Infection Resulting in Pneumonia, Meningitis, or Hepatitis     | Limited (subsequent infection resulting in pneumonia)                    | Strong (in individuals with demonstrated immunodeficiencies)          | Convincingly Supports (in individuals with demonstrated immunodeficiencies) |
|         |           |   | Insufficient (subsequent infection resulting in meningitis or hepatitis) |   |   |
| 5       | Varicella | Vaccine Strain Viral Reactivation without Other Organ Involvement                                   | Insufficient   | Strong  | Convincingly Supports   |
| 5       | Varicella | Vaccine Strain Viral Reactivation with Subsequent Infection resulting in Meningitis or Encephalitis | Limited (subsequent infection resulting in encephalitis)                 | Strong  | Convincingly Supports   |
|         |           |   | Insufficient (subsequent infection resulting in meningitis)              |   |   |
| 4       | MMR       | Measles Inclusion Body Encephalitis   | Insufficient   | Strong (measles; in individuals with demonstrated immunodeficiencies) | Convincingly Supports (in individuals with demonstrated immunodeficiencies) |
|         |           |   |  | Lacking (mumps or rubella)  |   |
| 4       | MMR       | Anaphylaxis   | Insufficient   | Strong  | Convincingly Supports   |

|    |                         |                                      |                                  |   |  |
|----|-------------------------|--------------------------------------|----------------------------------|---|--|
| 5  | Varicella               | Anaphylaxis                          | Limited                          | Strong                                  | Convincingly Supports                                  |
| 6  | Influenza               | Anaphylaxis                          | Limited                          | Strong                                  | Convincingly Supports                                  |
| 8  | Hepatitis B             | Anaphylaxis                          | Insufficient                     | Strong (in yeast-sensitive individuals) | Convincingly Supports (in yeast-sensitive individuals) |
| 10 | TT containing           | Anaphylaxis                          | Insufficient                     | Strong                                  | Convincingly Supports                                  |
| 11 | Meningococcal           | Anaphylaxis                          | Insufficient                     | Strong                                  | Convincingly Supports                                  |
| 12 | Injection-Related Event | Deltoid Bursitis                     | Limited                          | Strong                                  | Convincingly Supports                                  |
| 12 | Injection-Related Event | Syncope                              | Insufficient                     | Strong                                  | Convincingly Supports                                  |
| 4  | MMR                     | Febrile Seizures                     | High (increase)                  | Intermediate                            | Convincingly Supports                                  |
| 9  | HPV                     | Anaphylaxis                          | Insufficient                     | Intermediate                            | Favors Acceptance                                      |
| 4  | MMR                     | Transient Arthralgia in Women        | Moderate (increase) (rubella)    | Intermediate (rubella)                  | Favors Acceptance <sup>b</sup>                         |
|    |                         |                                      | Insufficient (measles or mumps)  | Lacking (measles or mumps)              |  |
| 6  | Influenza               | Oculorespiratory Syndrome            | Moderate (increase) <sup>c</sup> | Intermediate <sup>c</sup>               | Favors Acceptance <sup>c</sup>                         |
| 8  | Hepatitis B             | Acute Disseminated Encephalomyelitis | Insufficient                     | Low-Intermediate                        | Inadequate   |
| 8  | Hepatitis B             | First Demyelinating Event in Adults  | Moderate (null)                  | Low-Intermediate                        | Inadequate   |
| 8  | Hepatitis B             | Onset or Exacerbation of Vasculitis  | Insufficient                     | Low-Intermediate                        | Inadequate   |

*continued*

TABLE D-5 Continued

| Chapter | Vaccine                  | Adverse Event                  | Epidemiologic Assessment                             | Mechanistic Assessment                                   | Causality Conclusion |
|---------|--------------------------|--------------------------------|--|--|----------------------|
| 4       | MMR                      | Chronic Arthralgia in Women    | Limited (rubella)<br>Insufficient (measles or mumps) | Low-Intermediate (rubella)<br>Lacking (measles or mumps) | Inadequate           |
| 4       | MMR                      | Chronic Arthritis in Women     | Limited (rubella)<br>Insufficient (measles or mumps) | Low-Intermediate (rubella)<br>Lacking (measles or mumps) | Inadequate           |
| 4       | MMR                      | Hearing Loss                   | Insufficient   | Low-Intermediate (measles or mumps)<br>Lacking (rubella) | Inadequate           |
| 12      | Injection-Related Event  | Complex Regional Pain Syndrome | Insufficient   | Low-Intermediate   | Inadequate           |
| 4       | MMR                      | Encephalitis                   | Limited  | Weak   | Inadequate           |
| 6       | Influenza                | Encephalitis                   | Insufficient   | Weak   | Inadequate           |
| 10      | DT, TT, or aP containing | Encephalitis                   | Limited  | Weak   | Inadequate           |
| 4       | MMR                      | Encephalopathy                 | Limited  | Weak   | Inadequate           |
| 6       | Influenza                | Encephalopathy                 | Insufficient   | Weak   | Inadequate           |
| 10      | DT, TT, or aP containing | Encephalopathy                 | Limited  | Weak   | Inadequate           |

|    |                          |                                      |                 |   |            |
|----|--------------------------|--------------------------------------|-----------------|---|------------|
| 5  | Varicella                | Seizures                             | Limited         | Weak  | Inadequate |
| 10 | DT, TT, or aP containing | Seizures                             | Limited         | Weak (acellular pertussis)<br>Lacking (diphtheria toxoid or tetanus toxoid) | Inadequate |
| 4  | MMR                      | Meningitis <sup>d</sup>              | Moderate (null) | Weak (mumps)<br>Lacking (measles or rubella)                                | Inadequate |
| 5  | Varicella                | Cerebellar Ataxia                    | Insufficient    | Weak  | Inadequate |
| 4  | MMR                      | Ataxia                               | Insufficient    | Weak (measles or mumps)<br>Lacking (rubella)                                | Inadequate |
| 4  | MMR                      | Acute Disseminated Encephalomyelitis | Insufficient    | Weak  | Inadequate |
| 5  | Varicella                | Acute Disseminated Encephalomyelitis | Insufficient    | Weak  | Inadequate |
| 6  | Influenza                | Acute Disseminated Encephalomyelitis | Insufficient    | Weak  | Inadequate |
| 7  | Hepatitis A              | Acute Disseminated Encephalomyelitis | Insufficient    | Weak  | Inadequate |
| 10 | DT, TT, or aP containing | Acute Disseminated Encephalomyelitis | Insufficient    | Weak (tetanus toxoid)<br>Lacking (diphtheria toxoid or acellular pertussis) | Inadequate |

*continued*

TABLE D-5 Continued

| Chapter | Vaccine     | Adverse Event                                    | Epidemiologic Assessment | Mechanistic Assessment     | Causality Conclusion |
|---------|-------------|--|--------------------------|----------------------------|----------------------|
| 4       | MMR         | Transverse Myelitis                              | Insufficient             | Weak                       | Inadequate           |
| 5       | Varicella   | Transverse Myelitis                              | Insufficient             | Weak                       | Inadequate           |
| 6       | Influenza   | Transverse Myelitis                              | Insufficient             | Weak                       | Inadequate           |
| 7       | Hepatitis A | Transverse Myelitis                              | Insufficient             | Weak                       | Inadequate           |
| 8       | Hepatitis B | Transverse Myelitis                              | Insufficient             | Weak                       | Inadequate           |
| 4       | MMR         | Optic Neuritis <sup>d</sup>                      | Limited                  | Weak                       | Inadequate           |
| 6       | Influenza   | Optic Neuritis <sup>d</sup>                      | Limited                  | Weak                       | Inadequate           |
| 4       | MMR         | Neuromyelitis Optica <sup>d</sup>                | Insufficient             | Weak (rubella)             | Inadequate           |
|         |             |  |                          | Lacking (measles or mumps) |                      |
| 4       | MMR         | Guillain-Barré syndrome                          | Insufficient             | Weak                       | Inadequate           |
| 5       | Varicella   | Guillain-Barré syndrome                          | Insufficient             | Weak                       | Inadequate           |
| 6       | Influenza   | Guillain-Barré syndrome                          | Moderate (null)          | Weak                       | Inadequate           |
| 7       | Hepatitis A | Guillain-Barré syndrome                          | Insufficient             | Weak                       | Inadequate           |
| 6       | Influenza   | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient             | Weak                       | Inadequate           |

|    |                          |  |  |  |                  |
|----|--------------------------|--|--|--|------------------|
| 10 | DT, TT, or aP containing | Bell's Palsy   | Limited (acellular pertussis)                      | Weak (diphtheria toxoid or tetanus toxoid) | Inadequate       |
| 7  | Hepatitis A              | Anaphylaxis  | Insufficient (diphtheria toxoid or tetanus toxoid) | Lacking (acellular pertussis)              | Inadequate       |
| 10 | DT, TT, or aP containing | Serum Sickness   | Insufficient                                       | Weak (diphtheria toxoid or tetanus toxoid) | Inadequate       |
| 6  | Influenza                | Inactivated Influenza Vaccine and Asthma Exacerbation or Reactive Airway Disease Episodes in Children and Adults                     | High (null)  | Lacking (acellular pertussis)              | Favors Rejection |
| 6  | Influenza                | Live Attenuated Influenza Vaccine or Asthma Exacerbation or Reactive Airway Disease Episodes in Children Younger Than 5 Years of Age | Moderate (null)                                    | Weak                                       | Inadequate       |
| 6  | Influenza                | Live Attenuated Influenza Vaccine or Asthma Exacerbation or Reactive Airway Disease Episodes in Persons 5 Years of Age or Older      | Moderate (null)                                    | Weak                                       | Inadequate       |
| 8  | Hepatitis B              | Erythema Nodosum <sup>d</sup>  | Insufficient                                       | Weak                                       | Inadequate       |

*continued*



TABLE D-5 Continued

| Chapter | Vaccine     | Adverse Event  | Epidemiologic Assessment                       | Mechanistic Assessment                       | Causality Conclusion |
|---------|-------------|--|--|--|----------------------|
| 8       | Hepatitis B | Onset or Exacerbation of Systemic Lupus Erythematosus  | Limited (onset)<br>Insufficient (exacerbation) | Weak   | Inadequate           |
| 6       | Influenza   | Onset or Exacerbation of Vasculitis                    | Limited (exacerbation)<br>Insufficient (onset) | Weak (exacerbation)<br>Lacking (onset)       | Inadequate           |
| 8       | Hepatitis B | Onset or Exacerbation of Polyarteritis Nodosa          | Insufficient                                   | Weak   | Inadequate           |
| 8       | Hepatitis B | Onset or Exacerbation of Reactive Arthritis            | Insufficient                                   | Weak   | Inadequate           |
| 8       | Hepatitis B | Onset and Exacerbation of Rheumatoid Arthritis         | Limited (exacerbation)<br>Insufficient (onset) | Weak   | Inadequate           |
| 8       | Hepatitis B | Onset or Exacerbation of Juvenile Idiopathic Arthritis | Insufficient                                   | Weak   | Inadequate           |
| 4       | MMR         | Transient Arthralgia in Children                       | Moderate (increase)                            | Weak (rubella)<br>Lacking (measles or mumps) | Favors Acceptance    |

|    |                          |                                      |                     |   |            |
|----|--------------------------|--------------------------------------|---------------------|---|------------|
| 4  | MMR                      | Chronic Arthropathy in Children      | Insufficient        | Weak (rubella)<br>Lacking (measles or mumps)  | Inadequate |
| 4  | MMR                      | Arthropathy in Men                   | Limited             | Weak (rubella)<br>Lacking (measles or mumps)  | Inadequate |
| 6  | Influenza                | Onset or Exacerbation of Arthropathy | Insufficient        | Weak  | Inadequate |
| 7  | Hepatitis A              | Autoimmune Hepatitis                 | Insufficient        | Weak  | Inadequate |
| 10 | DT, TT, or aP containing | Myocarditis                          | Insufficient        | Weak (diphtheria toxoid)<br>Lacking (tetanus toxoid or acellular pertussis)         | Inadequate |
| 4  | MMR                      | Hepatitis                            | Insufficient        | Weak  | Inadequate |
| 5  | Varicella                | Stroke <sup>d</sup>                  | Limited             | Weak  | Inadequate |
| 6  | Influenza                | Myocardial Infarction                | Moderate (decrease) | Weak (Live Attenuated Influenza Vaccine)<br>Lacking (Inactivated Influenza Vaccine) | Inadequate |

*continued*

TABLE D-5 Continued

| Chapter | Vaccine                  | Adverse Event                    | Epidemiologic Assessment                      | Mechanistic Assessment  | Causality Conclusion |
|---------|--------------------------|----------------------------------|---|---|----------------------|
| 6       | Influenza                | All-Cause Mortality <sup>d</sup> | Moderate (decrease)                           | Weak (Live Attenuated Influenza Vaccine)<br>Lacking (Inactivated Influenza Vaccine) | Inadequate           |
| 5       | Varicella                | Thrombocytopenia                 | Insufficient                                  | Weak  | Inadequate           |
| 8       | Hepatitis B              | Encephalitis                     | Insufficient                                  | Lacking   | Inadequate           |
| 11      | Meningococcal            | Encephalitis                     | Limited                                       | Lacking   | Inadequate           |
| 5       | Varicella                | Encephalopathy                   | Insufficient                                  | Lacking   | Inadequate           |
| 8       | Hepatitis B              | Encephalopathy                   | Insufficient                                  | Lacking   | Inadequate           |
| 11      | Meningococcal            | Encephalopathy                   | Limited                                       | Lacking   | Inadequate           |
| 10      | DT, TT, or aP containing | Infantile Spasms                 | Limited (diphtheria toxoid or tetanus toxoid) | Lacking   | Inadequate           |
|         |                          |                                  | Insufficient (acellular pertussis)            |   |                      |
| 4       | MMR                      | Afebrile Seizures                | Limited                                       | Lacking   | Inadequate           |
| 6       | Influenza                | Seizures <sup>d</sup>            | Moderate (null)                               | Lacking   | Inadequate           |
| 8       | Hepatitis B              | Seizures                         | Limited                                       | Lacking   | Inadequate           |
| 10      | DT, TT, or aP containing | Ataxia                           | Insufficient                                  | Lacking   | Inadequate           |

|    |                          |                                      |   |         |                  |
|----|--------------------------|--------------------------------------|---|---------|------------------|
| 4  | MMR                      | Autism                               | High (null)                                   | Lacking | Favors Rejection |
| 10 | DT, TT, or aP containing | Autism                               | Insufficient                                  | Lacking | Inadequate       |
| 9  | HPV                      | Acute Disseminated Encephalomyelitis | Insufficient                                  | Lacking | Inadequate       |
| 11 | Meningococcal            | Acute Disseminated Encephalomyelitis | Insufficient                                  | Lacking | Inadequate       |
| 9  | HPV                      | Transverse Myelitis                  | Insufficient                                  | Lacking | Inadequate       |
| 10 | DT, TT, or aP containing | Transverse Myelitis                  | Insufficient                                  | Lacking | Inadequate       |
| 11 | Meningococcal            | Transverse Myelitis                  | Insufficient                                  | Lacking | Inadequate       |
| 8  | Hepatitis B              | Optic Neuritis <sup>d</sup>          | Limited                                       | Lacking | Inadequate       |
| 10 | DT, TT, or aP containing | Optic Neuritis <sup>d</sup>          | Limited (diphtheria toxoid or tetanus toxoid) | Lacking | Inadequate       |
|    |                          |                                      | Insufficient (acellular pertussis)            |         |                  |
| 6  | Influenza                | Neuromyelitis Optica                 | Insufficient                                  | Lacking | Inadequate       |
| 8  | Hepatitis B              | Neuromyelitis Optica                 | Insufficient                                  | Lacking | Inadequate       |
| 9  | HPV                      | Neuromyelitis Optica                 | Insufficient                                  | Lacking | Inadequate       |
| 4  | MMR                      | Multiple Sclerosis Onset in Adults   | Limited                                       | Lacking | Inadequate       |
| 6  | Influenza                | Multiple Sclerosis Onset in Adults   | Limited                                       | Lacking | Inadequate       |
| 8  | Hepatitis B              | Multiple Sclerosis Onset in Adults   | Limited                                       | Lacking | Inadequate       |

*continued*

TABLE D-5 Continued

| Chapter | Vaccine                  | Adverse Event                          | Epidemiologic Assessment                                | Mechanistic Assessment | Causality Conclusion |
|---------|--------------------------|--|---|------------------------|----------------------|
| 10      | DT, TT, or aP containing | Multiple Sclerosis Onset in Adults     | Limited (diphtheria toxoid or tetanus toxoid)           | Lacking                | Inadequate           |
| 4       | MMR                      | Multiple Sclerosis Onset in Children   | Limited   | Lacking                | Inadequate           |
| 8       | Hepatitis B              | Multiple Sclerosis Onset in Children   | Limited   | Lacking                | Inadequate           |
| 6       | Influenza                | Multiple Sclerosis Relapse in Adults   | Limited   | Lacking                | Inadequate           |
| 8       | Hepatitis B              | Multiple Sclerosis Relapse in Adults   | Limited   | Lacking                | Inadequate           |
| 10      | DT, TT, or aP containing | Multiple Sclerosis Relapse in Adults   | Limited (tetanus toxoid)                                | Lacking                | Inadequate           |
|         |                          |  | Insufficient (diphtheria toxoid or acellular pertussis) |                        |                      |
| 8       | Hepatitis B              | Multiple Sclerosis Relapse in Children | Limited   | Lacking                | Inadequate           |
| 10      | DT, TT, or aP containing | Multiple Sclerosis Relapse in Children | Limited (diphtheria toxoid or tetanus toxoid)           | Lacking                | Inadequate           |
|         |                          |  | Insufficient (acellular pertussis)                      |                        |                      |
| 7       | Hepatitis A              | Multiple Sclerosis                     | Insufficient  | Lacking                | Inadequate           |
| 9       | HPV                      | Multiple Sclerosis                     | Insufficient  | Lacking                | Inadequate           |

|    |                          |  |              |         |                  |
|----|--------------------------|--|--------------|---------|------------------|
| 11 | Meningococcal            | Multiple Sclerosis                               | Insufficient | Lacking | Inadequate       |
| 8  | Hepatitis B              | First Demyelinating Event in Children            | Limited      | Lacking | Inadequate       |
| 8  | Hepatitis B              | Guillain-Barré syndrome                          | Insufficient | Lacking | Inadequate       |
| 9  | HPV                      | Guillain-Barré syndrome                          | Insufficient | Lacking | Inadequate       |
| 10 | DT, TT, or aP containing | Guillain-Barré syndrome                          | Insufficient | Lacking | Inadequate       |
| 11 | Meningococcal            | Guillain-Barré syndrome                          | Limited      | Lacking | Inadequate       |
| 4  | MMR                      | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient | Lacking | Inadequate       |
| 7  | Hepatitis A              | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient | Lacking | Inadequate       |
| 8  | Hepatitis B              | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient | Lacking | Inadequate       |
| 9  | HPV                      | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient | Lacking | Inadequate       |
| 10 | DT, TT, or aP containing | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient | Lacking | Inadequate       |
| 11 | Meningococcal            | Chronic Inflammatory Disseminated Polyneuropathy | Insufficient | Lacking | Inadequate       |
| 4  | MMR                      | Opsoclonus Myoclonus Syndrome                    | Insufficient | Lacking | Inadequate       |
| 10 | DT, TT, or aP containing | Opsoclonus Myoclonus Syndrome                    | Insufficient | Lacking | Inadequate       |
| 6  | Influenza                | Inactivated Influenza Vaccine and Bell's Palsy   | High (null)  | Lacking | Favors Rejection |

*continued*

TABLE D-5 Continued

| Chapter | Vaccine                  | Adverse Event   | Epidemiologic Assessment | Mechanistic Assessment | Causality Conclusion |
|---------|--------------------------|---|--------------------------|------------------------|----------------------|
| 7       | Hepatitis A              | Bell's Palsy  | Insufficient             | Lacking                | Inadequate           |
| 4       | MMR                      | Brachial Neuritis                                     | Insufficient             | Lacking                | Inadequate           |
| 6       | Influenza                | Brachial Neuritis                                     | Insufficient             | Lacking                | Inadequate           |
| 8       | Hepatitis B              | Brachial Neuritis                                     | Insufficient             | Lacking                | Inadequate           |
| 9       | HPV                      | Brachial Neuritis                                     | Insufficient             | Lacking                | Inadequate           |
| 9       | HPV                      | Amyotrophic Lateral Sclerosis                         | Insufficient             | Lacking                | Inadequate           |
| 5       | Varicella                | Small Fiber Neuropathy <sup>d</sup>                   | Insufficient             | Lacking                | Inadequate           |
| 6       | Influenza                | Small Fiber Neuropathy                                | Insufficient             | Lacking                | Inadequate           |
| 10      | DT and aP containing     | Anaphylaxis   | Insufficient             | Lacking                | Inadequate           |
| 10      | DT, TT, or aP containing | Chronic Urticaria                                     | Insufficient             | Lacking                | Inadequate           |
| 6       | Influenza                | Onset or Exacerbation of Systemic Lupus Erythematosus | Limited (exacerbation)   | Lacking                | Inadequate           |
| 6       | Influenza                | Polyarteritis Nodosa                                  | Insufficient (onset)     | Lacking                | Inadequate           |
| 8       | Hepatitis B              | Onset or Exacerbation of Psoriatic Arthritis          | Insufficient             | Lacking                | Inadequate           |
| 9       | HPV                      | Transient Arthralgia                                  | Limited                  | Lacking                | Inadequate           |
| 5       | Varicella                | Onset or Exacerbation Arthropathy                     | Insufficient             | Lacking                | Inadequate           |

|    |                          |                              |   |         |                  |
|----|--------------------------|------------------------------|---|---------|------------------|
| 10 | DT, TT, or aP containing | Arthropathy                  | Limited (diphtheria toxoid or tetanus toxoid) | Lacking | Inadequate       |
| 4  | MMR                      | Type 1 Diabetes              | High (null)                                   | Lacking | Favors Rejection |
| 8  | Hepatitis B              | Type 1 Diabetes              | Moderate (null)                               | Lacking | Inadequate       |
| 10 | DT, TT, or aP containing | Type 1 Diabetes              | High (null)                                   | Lacking | Favors Rejection |
| 9  | HPV                      | Pancreatitis                 | Insufficient                                  | Lacking | Inadequate       |
| 9  | HPV                      | Thromboembolic Events        | Insufficient                                  | Lacking | Inadequate       |
| 6  | Influenza                | Stroke                       | Moderate (decrease)                           | Lacking | Inadequate       |
| 9  | HPV                      | Hypercoagulable States       | Insufficient                                  | Lacking | Inadequate       |
| 4  | MMR                      | Chronic Fatigue Syndrome     | Insufficient                                  | Lacking | Inadequate       |
| 11 | Meningococcal            | Chronic Headache             | Insufficient                                  | Lacking | Inadequate       |
| 4  | MMR                      | Fibromyalgia                 | Insufficient                                  | Lacking | Inadequate       |
| 6  | Influenza                | Fibromyalgia                 | Insufficient                                  | Lacking | Inadequate       |
| 8  | Hepatitis B              | Fibromyalgia                 | Insufficient                                  | Lacking | Inadequate       |
| 10 | DT, TT, or aP containing | Fibromyalgia                 | Insufficient                                  | Lacking | Inadequate       |
| 10 | DT, TT, or aP containing | Sudden Infant Death Syndrome | Insufficient                                  | Lacking | Inadequate       |

*continued*



TABLE D-5 Continued

| Chapter | Vaccine                  | Adverse Event                   | Epidemiologic Assessment | Mechanistic Assessment | Causality Conclusion |
|---------|--------------------------|---------------------------------|--------------------------|------------------------|----------------------|
| 10      | DT, TT, or aP containing | Immune Thrombocytopenic Purpura | Insufficient             | Lacking                | Inadequate           |

NOTE: The measles-mumps-rubella; human papillomavirus; and diphtheria toxoid-, tetanus toxoid-, and acellular pertussis-containing vaccines have been abbreviated in the following ways: MMR; HPV; and DT, TT, and aP containing.

<sup>a</sup>The committee attributes causation to the measles component of the vaccine.

<sup>b</sup>The committee attributes causation to the rubella component of the vaccine.

<sup>c</sup>The committee attributes causation to two particular vaccines used in three particular years in Canada.

<sup>d</sup>Although not originally charged to the committee by the sponsor, the committee considered this adverse event in its review of the literature.

# Appendix E

## References

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## Appendix F

### Committee Biosketches

**Ellen Wright Clayton, J.D., M.D.** (*Chair*), is Craig-Weaver Chair in Pediatrics as well as Professor of Law and the Director of the Center for Biomedical Ethics and Society at Vanderbilt University. Her research and teaching interests include pediatrics, medical and research ethics, legal and ethical issues in children's and women's health, and genetics and health policy. She has served as a member on numerous committees for the National Institutes of Health as well as the Ethical, Legal, and Social Issues Working Group of the Newborn Screening Taskforce, Maternal and Child Health Bureau, Health Resources Services Administration. Dr. Clayton has served as a consultant to the Food and Drug Administration on the topic of clinical pharmacology during pregnancy. She is a member of the Institute of Medicine (IOM) and has served on several National Academies committees as well as the IOM's Health Sciences Policy Board and is currently a member of its National Advisory Council. She has numerous publications in books, medical journals, interdisciplinary journals, and law journals on the intersection of law, medicine, and public health. Dr. Clayton received her M.D. from Harvard University in 1985 and her J.D. from Yale University in 1979.

**Inmaculada B. Aban, Ph.D., M.S.**, is currently an Associate Professor in the Research Methods and Clinical Trials Section in the Department of Biostatistics at University of Alabama at Birmingham. She has considerable experience in clinical studies and statistical methodology research. She was Director of the Biostatistics Core of the National Institutes of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI)-sponsored SCCOR Program on Heart Failure that ended in 2010. She is currently the Deputy



Director of an international multicenter Data Coordinating Center funded by the National Institute of Neurological Disorders and Stroke (NINDS) on myasthenia gravis, a rare disease. She serves as the primary Biostatistician for Collaborative Antiviral Study Group pediatric trials on rare diseases. She also provides statistical support regarding study design, protocol development, study monitoring, quality assurance, report generation, and statistical analyses. She has years of experience in writing and presenting Data and Safety Monitoring Board (DSMB) reports. She served as a DSMB member in an NIH/NINDS study and had served as a temporary member of NHLBI study sections. Her current research interests are statistical methods in clinical trials, survival and reliability analysis, analysis of pool screening and count data, goodness-of-fit and model diagnostics, inference for heavy tail distribution, and propensity scores applied to epidemiologic data.

**Douglas J. Barrett, M.D.**, is a Professor in the Department of Pediatrics, the Department of Molecular Genetics & Microbiology, and the Department of Pathology, Immunology, & Laboratory Medicine at the University of Florida College of Medicine. Dr. Barrett is a practicing pediatrician, a researcher, and the author or coauthor of three books, several book chapters, and more than 110 journal articles. Dr. Barrett's clinical and research expertise is in childhood immune responses, immunodeficiency diseases, and transplantation. His research has been supported by grants from the National Institutes of Health, the American Heart Association, and the American Cancer Society. Dr. Barrett is active in the American Academy of Pediatrics, American Board of Pediatrics, Association for Academic Health Centers, and the Society for Pediatric Research. He serves on the editorial board for *Contemporary Pediatrics* and is a reviewer for multiple journals. Dr. Barrett received his M.D. in 1974 as a charter class member of the University of South Florida College of Medicine. He completed his pediatric internship training at Tampa General Hospital and All Children's Hospital. After completing a pediatric residency at SUNY/Upstate Medical Center in New York, he pursued fellowship training in pediatric immunology in the Department of Pediatrics at the University of California, San Francisco. Dr. Barrett joined the University of Florida in 1980. He served as the Chief of the Division of Pediatric Immunology from 1986 to 1990, as the Chairman of the Department of Pediatrics from 1990 to 2001, and as Senior Vice President for Health Affairs at the University of Florida from 2001 to 2009. In the latter position he was responsible for maximizing the performance of the educational, research, and clinical programs in the six colleges of the University of Florida's Health Sciences Center.

**Martina Bebin, M.D., M.P.A.**, is associate professor of neurology and pediatrics at the University of Alabama at Birmingham. She is a practicing

child neurologist, and her research interests include pediatric clinical drug development for epilepsy and outcomes research of epilepsy patients, with a focus on treatment of epilepsy in children. She has clinical responsibility for the care of children enrolled in a clinical trial supported by Novartis for treatment of tuberous sclerosis patients with subependymal giant cell tumors of the brain. She is currently working on the Tuberous Sclerosis Alliance Natural History Database Project, funded by the Tuberous Sclerosis Alliance and the Centers for Disease Control and Prevention. She is a former Robert Wood Johnson Foundation Health Policy fellow. Dr. Bebin received her M.D. from the University of Mississippi School of Medicine in 1986. She completed her pediatric and neurology training at the Mayo Clinic in Rochester, Minnesota, and a fellowship in epilepsy at the University of Virginia. In 2005 she earned her M.P.A. from Harvard University-Kennedy School of Government.

**Kirsten Bibbins-Domingo, Ph.D., M.D., M.A.S.**, is associate professor of medicine and epidemiology and biostatistics at the University of California, San Francisco, and an attending physician at San Francisco General Hospital. Dr. Bibbins-Domingo is an active researcher in preventive cardiology, the epidemiology of cardiovascular disease in young adults, and race and gender health and health care disparities. Her research has examined the development of cardiovascular risk factors in young adults, the effectiveness of screening and diagnostic tests for cardiovascular disease, and computer-simulated projections of future cardiovascular disease trends and the impact of public health and clinical interventions on cardiovascular disease prevention. Dr. Bibbins-Domingo served on the IOM Committee on Evaluation of the Presumptive Disability Decision-Making Process for Veterans from 2006 to 2007. She received her undergraduate degree in molecular biology and public policy from Princeton University and her medical degree, Ph.D. in biochemistry, and Masters of Clinical Research from the University of California, San Francisco.

**Martha Constantine-Paton, Ph.D.**, is investigator at the McGovern Institute for Brain Research and Professor in the departments of Brain and Cognitive Sciences and Biology at the Massachusetts Institute of Technology (MIT). Previously, she was professor of biology at Yale University from 1985 until 1999, and a faculty member at Princeton University from 1976 through 1984, before joining MIT in 1999. Dr. Constantine-Paton studies activity-dependent brain development, glutamate receptor regulation, and physiology of the developing visual system in animal models. She is interested in the biochemical, structural, or genetic programs that cause the developing brain to lose its plasticity or to compensate for genetic mutations or trauma as the brain matures, possibly leading to loss of learning and memory or to

neurological or neuropsychiatric disease. Dr. Constantine-Paton earned her Ph.D. in 1976 from Cornell University. She has received a number of honors and awards, among them the Young Investigator Award from the Society of Neuroscience and a Merit Award from the National Eye Institute. She has served on numerous committees and councils. She has previously worked for the Institute of Medicine on panels that suggested new nutritional guidelines and explored the ethics and value of fetal tissue use. She has been a member of several grant review panels at the National Institutes of Health, including the National Advisory Eye Council and the Child Council Workgroup for the National Institute of Mental Health.

**Deborah J. del Junco, Ph.D.**, is the director of outcomes research at the Center for Translational Injury Research and senior epidemiologist at the Center for Clinical and Translational Sciences at the University of Texas Health Science Center-Houston (UTHealth-H). She is associate professor in the Departments of Surgery and Pediatrics (UTHealth-H School of Medicine) and the Division of Epidemiology, Human Genetics and Environmental Sciences (UTHealth-H School of Public Health). Her research and teaching have focused on epidemiology methods, gene-environment, and other complex interactions among etiologic factors in chronic disease, records linkage, meta-analysis, reproductive health, autoimmune disease, and Rett syndrome. She is a Fellow of the American College of Epidemiology and has served as an executive editor of *Epidemiologic Perspectives and Innovations*. She has many publications in peer-reviewed journals and has served on a large number of review panels and advisory committees for the National Institutes of Health, Centers for Disease Control and Prevention, and Department of Defense. Dr. del Junco completed a fellowship in the Department of Epidemiology and Biostatistics at the Mayo Clinic in Rochester, Minnesota, in 1984 and received her Ph.D. in epidemiology from the University of Texas Houston Health Science Center in 1988.

**Betty A. Diamond, M.D.**, is head of the Center for Autoimmune and Musculoskeletal Disease at the Feinstein Institute for Medical Research. Her research has focused on the immune system and autoimmune diseases, with an interest in systemic lupus erythematosus. Dr. Diamond is a practicing rheumatologist and has received many honors, including the Outstanding Investigator Award from the American College of Rheumatology, the Lee Howley Award from the Arthritis Foundation, the Recognition Award from the National Association of M.D.-Ph.D. Programs, and election to the Institute of Medicine. She has served on the Scientific Council of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the Board of Directors of the American College of Rheumatology, and is a past-president of the American Association of Immunologists. She has a

grant from Autism Speaks to study the effects of maternal autoantibodies on fetal development. Dr. Diamond earned her medical degree from Harvard Medical School in 1973, and then completed a residency in internal medicine at Columbia Presbyterian Medical Center and a postdoctoral fellowship in immunology at the Albert Einstein College of Medicine.

**S. Claiborne Johnston, M.D., Ph.D.**, is Associate Vice Chancellor of Research, Director of the Clinical and Translational Science Institute, Professor of Neurology and Epidemiology, and Director of the Stroke Service at the University of California, San Francisco. He is a practicing neurologist, and his research has focused on stroke treatment and prevention. In the past, he has had funding from both Sanofi and Novartis to study drugs used in the treatment of stroke. His current funding from NINDS oversees the POINT multicenter randomized trial of Clopidogrel versus placebo in patients taking aspirin after TIA or minor ischemic stroke. He is also PI of a large trial of platinum versus coated coils in treating intracranial aneurysms sponsored by Stryker. Dr. Johnston has authored over 250 publications in scientific journals and has won several national awards for his research and teaching. He was a member of the California Health Disease and Stroke Prevention Advisory Council, which advises the Department of Health Services, and was co-director of Prevention Education Programs for the National Stroke Association. Dr. Johnston received his M.D. from Harvard Medical School and Ph.D. in epidemiology from the University of California, Berkeley School of Public Health.

**Anthony L. Komaroff, M.D.**, is the Steven P. Simcox, Patrick A. Clifford, and James H. Higby Professor of Medicine at Harvard Medical School, senior physician at Brigham and Women's Hospital, and editor-in-chief of *Harvard Health Publications*. He was director of the Division of General Medicine and Primary Care at Brigham and Women's Hospital for 15 years and is the founding editor of *Journal Watch*, a summary medical information newsletter for physicians published by the Massachusetts Medical Society. Dr. Komaroff practices internal medicine (primary care and consultative medicine). For 25 years, he has conducted research on chronic fatigue syndrome, including studies of the prevalence of the illness, symptom presentation, and functional capacity, as well as virologic, immunologic, and neurologic studies. He is the author of over 200 journal articles, several book chapters, and one book, and is a fellow of the American College of Physicians and of the American Association for the Advancement of Science. Dr. Komaroff received his M.D. from the University of Washington.

**B. Paige Lawrence, Ph.D.**, is associate professor of environmental medicine and microbiology and immunology at the University of Rochester School

of Medicine and Dentistry. Dr. Lawrence's research is focused on defining the cellular and molecular mechanisms by which environmental factors adversely affect the development and function of the immune system. This work includes the impact of acute exposure to environmental contaminants and pharmacological agents, as well as the consequences of prenatal (maternal) exposures on immune function in the next generation. Her work has shown that an environment-sensing transcription factor may have a complex mediating effect in the body, and results have demonstrated impacts on immune system function, including inflammatory responses and fighting viral infections. Dr. Lawrence has numerous peer-reviewed publications and professional awards, and serves on the editorial board for several toxicology journals. She has also served as a member of a science advisory panel for the U.S. Environmental Protection Agency and provides service to various review committees for the National Institutes of Health. She received her Ph.D. in cell biology from Cornell University in 1993, and postdoctoral training in immunology and toxicology at Oregon State University.

**M. Louise Markert, M.D., Ph.D.**, is associate professor of pediatrics and immunology in the Division of Pediatric Allergy and Immunology at Duke University School of Medicine. Dr. Markert has pioneered the development of thymus transplantation for T cell reconstitution in infants born with complete DiGeorge anomaly. DiGeorge anomaly is a congenital disorder characterized by defects of the heart, parathyroid, and thymus. Complete DiGeorge anomaly is fatal because of the absence of functional thymus leading to profound primary immunodeficiency. In research protocols to date, 61 infants with complete DiGeorge anomaly have been transplanted with postnatal cultured human thymic epithelial tissue. Over 70 percent of these infants survive and have developed functional T cells. Dr. Markert graduated from Smith College with a B.A. in biochemistry and then completed the M.D./Ph.D. program at Duke University. She received her Ph.D. in immunology, completed a 2-year pediatric residency at Duke, and then a 3-year fellowship in pediatric allergy and immunology. Dr. Markert joined the Duke faculty in 1987. She was program director of the Duke NIH-funded General Clinical Research Center from 1993 to 2004. From 1996 to 2004, she served on the American Board of Allergy and Immunology and was chair of the Board in 2002. Dr. Markert has published over 40 research articles plus invited chapters and reviews.

**Marc C. Patterson, M.D.**, is chair of the Division of Child and Adolescent Neurology and professor of neurology, pediatrics, and medical genetics at Mayo Clinic. Dr. Patterson is a child neurologist with special expertise in neurometabolic and neurogenetic disorders. His research has focused on neurometabolic disorders, with a particular focus on Niemann-Pick disease,

Type C, Gaucher disease, and congenital disorders of glycosylation. Dr. Patterson was born and educated in Australia, where he graduated from the University of Queensland, before training in medicine, pediatrics, and neurology at the Royal Brisbane, Royal Children's, and Royal Women's Hospitals in Brisbane. He completed further training in pediatrics and child neurology at Mayo Graduate School of Medicine, and a fellowship in neurometabolic diseases with Roscoe Brady at the National Institutes of Health. On completion of training, Dr. Patterson joined the staff of Mayo Clinic and faculty of Mayo Medical School, where he was associate professor in the Departments of Neurology, Pediatric and Adolescent Medicine, and Medical Genetics. In 2001, he moved to New York and was professor of clinical neurology and pediatrics at Columbia University and director of pediatric neurology at the Neurologic Institute of New York and Children's Hospital of New York–Presbyterian. In 2007, he returned to the Mayo Clinic.

**Hugh A. Sampson, M.D.**, is professor of pediatrics and immunology at the Mount Sinai School of Medicine. He is also director of the Jaffe Food Allergy Institute, dean for Translational Biomedical Sciences at the Mount Sinai Medical Center, and a practicing pediatric allergist. Dr. Sampson's research has focused on food allergic disorders, including work on the immuno-pathogenic role of food hypersensitivity in atopic dermatitis, the pathogenesis of food-induced anaphylaxis, characterization of food-induced gastrointestinal hypersensitivities, and immunotherapeutic strategies for treating food allergies. He holds a patent for a potential treatment vaccine for peanut allergy. Dr. Sampson is the past president of the American Academy of Allergy, Asthma, and Immunology and a member of the Institute of Medicine. He is a co-editor of *Pediatric Allergy and Immunology* and has served on the editorial board of the *Journal of Allergy and Clinical Immunology*, and *Clinical and Experimental Allergy*. Dr. Sampson received his medical degree from the State University of New York, then finished a residency in pediatrics at the Children's Memorial Hospital, and completed a fellowship in allergy and immunology at Duke University.

**Pauline A. Thomas, M.D.**, is associate professor in the Department of Preventive Medicine and Community Health in the New Jersey Medical School, and associate professor in the School of Public Health at the University of Medicine and Dentistry of New Jersey. She is Co-Director of the NJMS Preventive Medicine Residency, and is also a practicing pediatrician. Her research interests include pediatric HIV, public health practice and surveillance methodology, and health care delivery. She served as assistant commissioner for surveillance in the Division of Epidemiology at the New York City Department of Health and Mental Hygiene and director of the

Health Department's Office of AIDS Surveillance. Dr. Thomas received her medical degree from Yale University School of Medicine in 1977 and completed her residency in pediatrics at Strong Memorial Hospital of the University of Rochester, New York. Following residency she worked 2 years with the Centers for Disease Control and Prevention as an epidemic intelligence service officer.

**Leslie P. Weiner, M.D.**, is professor of neurology and molecular microbiology and immunology and holds the Richard Angus Grant, Sr., Chair in Neurology at the Keck School of Medicine of the University of Southern California (USC). Dr. Weiner earned his medical degree from the University of Cincinnati and completed his neurology residency at the Johns Hopkins Hospital. At Johns Hopkins, he also pursued a fellowship in neurology and epidemiology, focusing on viruses of the nervous system. He then completed a fellowship at the National Institutes of Health Laboratory of Slow Virus Infections. Dr. Weiner served as chair of the USC Department of Neurology for 25 years and he remains a practicing neurologist. Dr. Weiner's research interests include a human T cell vaccine for the treatment of secondary progressive multiple sclerosis (MS), gene therapy for MS, molecular mimicry, and, more recently, neural stem cells. He has written more than 200 papers and has received numerous honors. He served as an expert witness for a federal judge in cases regarding adverse effects of the swine flu vaccine in the 1970s.

# Appendix G

## Meeting Agendas

Monday, April 20, 2009

Keck Center of the National Academies  
500 Fifth Street, NW  
Washington, DC 20001

- 1:00–1:10 pm Committee Introductions and Chair’s Opening Statement  
*Ellen Wright Clayton*  
*Committee Chair*
- 1:10–1:30 pm Charge to the Committee  
*Joyce G. Somsak, M.A.*  
*Associate Administrator*  
*Healthcare Systems Bureau*  
*Health Resources and Services Administration (HRSA)*  
*U.S. Department of Health and Human Services*
- Rosemary Johann-Liang, M.D.*  
*Chief Medical Officer*  
*National Vaccine Injury Compensation Program*  
*Health Resources and Services Administration (HRSA)*  
*U.S. Department of Health and Human Services*
- 1:30–2:00 pm Discussion about the Charge  
*Committee and HRSA Representatives*



836

ADVERSE EFFECTS OF VACCINES: EVIDENCE AND CAUSALITY

2:00–3:00 pm Public comment (in person, e-mail, and via teleconference)

3:00 pm **Adjourn**

**Wednesday, June 24, 2009**

**Keck Center of the National Academies**

**500 Fifth Street, NW**

**Washington, DC 20001**

- 9:00–9:45 am Causal Inference  
*Steven Goodman, M.D., M.H.S., Ph.D.*  
*Professor of Oncology*  
*Division of Biostatistics, Johns Hopkins Kimmel Cancer Center*  
*Departments of Pediatrics, Biostatistics, and Epidemiology*  
*Johns Hopkins Schools of Medicine and Public Health*
- 9:45–10:30 am Biologic Mechanisms: Weighing the Evidence  
*Douglas L. Weed, M.D., M.P.H., Ph.D.*  
*Founder and Managing Member*  
*DLW Consulting Services, LLC*
- 10:30–10:45 am **Break**
- 10:45–11:30 am Multiple Sclerosis  
*Stephen L. Hauser, M.D.*  
*Professor and Chair, Department of Neurology*  
*University of California, San Francisco*
- 11:30 am–12:30 pm **Lunch**
- 12:30–1:15 pm Molecular Mimicry  
*Robert Fujinami, Ph.D.*  
*Professor of Neurology and Pathology*  
*University of Utah*
- 1:15–2:00 pm Molecular Mimicry  
*Madeleine W. Cunningham, Ph.D.*  
*George Lynn Cross Research Professor*

*Microbiology and Immunology*  
*University of Oklahoma College of Medicine*

2:00–2:45 pm Genetic Susceptibility in Vaccine Adverse Effects  
*Jason H. Moore, Ph.D.*  
*Frank Lane Research Scholar in Computational Genetics*  
*Professor of Genetics*  
*Professor of Community and Family Medicine*  
*Dartmouth Medical School*

2:45 pm **Adjourn**

**Wednesday, August 26, 2009**

**Keck Center of the National Academies**  
**500 Fifth Street, NW**  
**Washington, DC 20001**

9:45–10:00 am Welcome and Introduction of the Committee  
*Ellen Wright Clayton, M.D.*  
*Committee Chair*

10:00–10:45 am The Immune Response to Vaccines and Natural Infection  
*Neal Halsey, M.D.*  
*Professor*  
*Departments of International Health, Disease Prevention & Control, and Pediatrics*  
*Johns Hopkins Bloomberg School of Public Health*

10:45–11:00 am Discussion

11:00–11:45 am Antibodies, Vaccines, Neuroinflammation, and the Blood-Brain Barrier  
*William Banks, M.D.*  
*Professor*  
*Departments of Internal Medicine, Geriatric Division, and Pharmacological and Physiological Science*  
*Saint Louis University School of Medicine*

11:45 am–12:00 pm Discussion

12:00–12:45 pm Metabolic and Other Genetic Syndromes  
*Bruce Cohen, M.D.*  
*Chief, Section of Pediatric Neurology*  
*Departments of Neurosurgery and Pediatrics*  
*Taussig Cancer Center*  
*Cleveland Clinic*

12:45–1:00 pm Discussion

1:00 pm **Adjourn**

# Index

[Page numbers followed by italic letter *n* or *t* refer to footnotes or tables.]

## A

- Acellular pertussis vaccine
  - development, 529
  - formulations, 530
  - summary of evidence and causality
    - conclusions, 585–588*t*
- Acute disseminated encephalomyelitis
  - definition, 635
  - DTaP vaccine and, 546–547, 586*t*
  - hepatitis A vaccine and, 423–424, 431*t*
  - hepatitis B vaccine and, 440–442, 491*t*
  - human papillomavirus vaccine and, 507–508, 521*t*
  - influenza vaccine and, 308–309, 402*t*
  - mechanism(s) that may contribute to symptoms of, 154, 271, 308, 423–424, 441, 507, 547, 604
  - meningococcal vaccine and, 603–604, 611*t*
  - MMR vaccine and, 153–154, 219*t*
  - varicella zoster vaccine and, 271, 284*t*
- Acute motor axonal neuropathy (AMAN), 71–72
- Adjuvants, 59
  - mechanism of action, 59
  - See also* Alum; ASO4
- Adverse events, generally
  - animal models, 89–91
  - brain development alterations, 85–89
  - definition, 1*n*, 30*n*
  - frequency and rate determinations, 629–632
  - injection-related, 78–81, 615–624, 625*t*
  - limitations of data sources and findings, 629–633
  - mechanisms of, 57, 65, 67–68, 72–73, 74, 76
  - methodology for evaluation of evidence, 10–14, 40–48
  - prior reviews, 1–2, 29–30, 39
  - recognized risk, 28
  - reporting requirements, 29
  - scope of review, 2–10, 30–36
  - seriousness of, 632
  - susceptibility, 24, 54, 82–84
  - See also* Causality
- Advisory Committee on Immunization Practices
  - DTaP vaccination recommendations, 530
  - hepatitis B vaccination recommendations, 437

- human papillomavirus vaccination
  - recommendations, 506–507
- influenza vaccination recommendations, 295–296
- meningococcal vaccination
  - recommendations, 601
- MMR vaccination recommendations, 108, 242
- varicella vaccination recommendations, 242
- Age
  - as adverse event risk factor, 24, 84
  - human papillomavirus infection risk, 505–506
- Alterations in brain development. *See*
  - Biological mechanisms, pathophysiologies, and susceptibilities with the potential to contribute to adverse events
- Alum, 59
- American Academy of Family Physicians, 437, 530
- American Academy of Pediatrics, 437, 530
- Amyotrophic lateral sclerosis
  - definition, 635
  - human papillomavirus vaccine and, 513–515
  - mechanism(s) that may contribute to symptoms of, 514
- Anaphylaxis
  - causes, 65, 66, 632
  - complement-mediated, 65–66
  - definition, 635
  - DTaP vaccine and, 563–565, 587*t*
  - hepatitis A vaccine and, 428–429, 431*t*
  - hepatitis B vaccine and, 18, 20*t*, 468–469, 492*t*
  - human papillomavirus vaccine and, 21*t*, 515–516, 521*t*
  - immunoglobulin E-mediated hypersensitivity in, 64–65
  - influenza vaccine and, 18, 20*t*, 341–345, 403*t*
  - limitations of data sources, 631–632
  - mechanism(s) that may contribute to symptoms of, 64–66
  - meningococcal vaccine and, 18, 20*t*, 608–610, 611*t*
  - MMR vaccine and, 18, 20*t*, 169–174, 219*t*, 631–632
  - recognized risks, 28
  - susceptibility to, 83–84
  - tetanus toxoid vaccine and, 18, 20*t*, 565, 587*t*
  - varicella zoster vaccine and, 18, 20*t*, 275–278, 284*t*
- Animal models
  - application of evidence from, 89–91
  - contribution to the weight of mechanistic evidence, 14, 45, 47
  - disease processes affecting the brain, 86
  - influenza vaccine and Guillain-Barré syndrome, 333–334
  - MMR vaccine and hearing loss, 153
- Antibodies and autoantibodies. *See*
  - Biological mechanisms, pathophysiologies, and susceptibilities with the potential to contribute to adverse events
- Antigen persistence. *See* Biological mechanisms, pathophysiologies, and susceptibilities with the potential to contribute to adverse events
- Antigen-presenting cells, 58, 59
- Antigenic drift, 293
- Antigenic shift, 293
- Arthralgia
  - chronic, in women, MMR vaccine and, 190–195, 220*t*
  - definition, 635
  - mechanism(s) that may contribute to symptoms of, 181, 185, 194, 517
  - transient, human papillomavirus vaccine and, 516–517, 521*t*
  - transient, in children, MMR vaccine and, 18, 21*t*, 182–190, 220*t*
  - transient, in women, MMR vaccine and, 18, 21*t*, 174–181, 219*t*
- Arthritis, chronic
  - definition, 635
  - mechanism(s) that may contribute to symptoms of, 198
  - in women, MMR vaccine and, 195–199, 220*t*
- Arthritis, juvenile idiopathic
  - definition, 641
  - hepatitis B vaccine and, 485–488, 493*t*
  - mechanism(s) that may contribute to symptoms of, 488
  - MMR vaccine and, transient arthralgia in children, 184

- Arthritis, psoriatic  
 definition, 643  
 hepatitis B vaccine, onset or exacerbation of, 479–480, 492*t*
- Arthritis, reactive  
 definition, 643  
 hepatitis B vaccine and, 480–482, 493*t*  
 mechanism(s) that may contribute to symptoms of, 481–482
- Arthritis, rheumatoid  
 definition, 644  
 hepatitis B vaccine, onset or exacerbation of, 482–485, 493*t*  
 immune complexes and, 67  
 mechanism(s) that may contribute to symptoms of, 485
- Arthropathy  
 chronic, in children, MMR vaccine and, 199–200, 220*t*  
 definition, 635  
 DTaP vaccine and, 567–571, 588*t*  
 influenza vaccine, onset or exacerbation of, 384–385, 403*t*  
 mechanism(s) that may contribute to symptoms of, 200, 202, 279, 385, 571  
 in men, MMR vaccine and, 201–204, 220*t*  
 varicella vaccine, onset or exacerbation of, 278–279, 284*t*
- ASO4, 59
- Assessment of causality  
 DTaP vaccine  
 acute disseminated encephalomyelitis, 546–547  
 anaphylaxis, 563–565  
 arthropathy, 567–571  
 ataxia, 544–545  
 autism, 545–546  
 Bell's Palsy, 561–562  
 chronic inflammatory disseminated polyneuropathy, 558–560  
 chronic urticaria, 565–566  
 encephalitis and encephalopathy, 534–537  
 fibromyalgia, 581  
 Guillain-Barré syndrome, 557–558  
 immune thrombocytopenic purpura, 582–584  
 infantile spasms, 537–539  
 multiple sclerosis onset in adults, 550–553  
 multiple sclerosis relapse in adults, 554–555  
 multiple sclerosis relapse in children, 555–557  
 myocarditis, 579–580  
 opsoclonus myoclonus syndrome, 560–561  
 optic neuritis, 549–550  
 seizures, 539–544  
 serum sickness, 566–567  
 sudden infant death syndrome, 581–582  
 summary of evidence and causality conclusions, 22*t*, 585–588*t*, 683–687*t*  
 transverse myelitis, 547–548  
 type 1 diabetes, 22*t*, 571–579
- hepatitis A vaccine  
 acute disseminated encephalomyelitis, 423–424  
 anaphylaxis, 428–429  
 autoimmune hepatitis, 429–430  
 Bell's palsy, 427–428  
 chronic inflammatory disseminated polyneuropathy, 427  
 Guillain-Barré syndrome, 426  
 multiple sclerosis, 425  
 summary of evidence and causality conclusions, 431*t*, 680–681*t*  
 transverse myelitis, 424–425
- hepatitis B vaccine  
 acute disseminated encephalomyelitis, 440–442  
 anaphylaxis, 468–469  
 brachial neuritis, 467–468  
 chronic inflammatory disseminated polyneuropathy, 466–467  
 encephalitis and encephalopathy, 437–438  
 erythema nodosum, 469–471  
 fibromyalgia, 490  
 first demyelinating event in adults, 458–464  
 first demyelinating event in children, 464–465  
 Guillain-Barré syndrome, 465–466  
 juvenile idiopathic arthritis, onset or exacerbation, 485–488

- multiple sclerosis onset in adults, 447–450, 451–453*t*
- multiple sclerosis onset in children, 454–455
- multiple sclerosis relapse in adults, 455–456
- multiple sclerosis relapse in children, 457–458
- neuromyelitis optica, 446–447
- optic neuritis, 443–446
- polyarteritis nodosa, onset or exacerbation, 477–479
- psoriatic arthritis, onset or exacerbation, 479–480
- reactive arthritis, onset or exacerbation, 480–482
- rheumatoid arthritis, onset or exacerbation, 482–485
- seizures, 438–440
- summary of evidence and causality
  - conclusions, 20*t*, 491–493*t*, 681–683*t*
- systemic lupus erythematosus, onset or exacerbation, 471–473
- transverse myelitis, 442–443
- type 1 diabetes, 488–490
- vasculitis, onset or exacerbation, 473–477
- human papillomavirus vaccine
  - acute disseminated encephalomyelitis, 507–508
  - amyotrophic lateral sclerosis, 513–515
  - anaphylaxis, 515–516
  - brachial neuritis, 512–513
  - chronic inflammatory disseminated polyneuropathy, 512
  - Guillain-Barré syndrome, 511–512
  - hypercoagulable states, 520
  - multiple sclerosis, 510
  - neuromyelitis optica, 509
  - pancreatitis, 517–518
  - summary of evidence and causality
    - conclusions, 21*t*, 521*t*, 683*t*
  - thromboembolic events, 519–520
  - transient arthralgia, 516–517
  - transverse myelitis, 508
- influenza vaccine
  - acute disseminated encephalomyelitis, 308–309
  - all-cause mortality, 390–391
  - anaphylaxis, 341–345
  - arthropathy, onset or exacerbation, 384–385
  - asthma exacerbation or reactive airway disease episodes in children and adults, inactivated influenza vaccine, 345–356
  - asthma exacerbation or reactive airway disease episodes in children younger than 5 years of age, live attenuated influenza vaccine, 356–366
  - asthma exacerbation or reactive airway disease episodes in persons 5 years of age or older, live attenuated influenza vaccine, 366–373
  - Bell’s palsy, 335–337, 338–339*t*
  - brachial neuritis, 340
  - chronic inflammatory disseminated polyneuropathy, 334–335
  - encephalitis and encephalopathy, 296, 299–301
  - fibromyalgia, 389
  - Guillain-Barré syndrome, 321–334
  - multiple sclerosis onset in adults, 314–318
  - multiple sclerosis relapse in adults, 318–321
  - myocardial infarction, 387–389
  - neuromyelitis optica, 314
  - oculorespiratory syndrome, 391–401
  - optic neuritis, 310–313
  - polyarteritis nodosa, 383–384
  - seizures, 301–304, 305–307*t*
  - small fiber neuropathy, 340–341
  - stroke, 386–387
  - summary of evidence and causality
    - conclusions, 20–22*t*, 402–404*t*, 678–680*t*
  - systemic lupus erythematosus, onset or exacerbation, 373–379
  - transverse myelitis, 309–310
  - vasculitis, onset or exacerbation, 379–383
- injection-related adverse events
  - complex regional pain syndrome, 615–617
  - deltoid bursitis, 618–620
  - summary of evidence and causality
    - conclusions, 21*t*, 625*t*, 687–688*t*
  - syncope, 620–624

- meningococcal vaccine  
 acute disseminated encephalomyelitis, 603–604  
 anaphylaxis, 608–610  
 chronic headache, 610  
 chronic inflammatory disseminated polyneuropathy, 607–608  
 encephalitis and encephalopathy, 602–603  
 Guillain-Barré syndrome, 606–607  
 multiple sclerosis, 605–606  
 summary of evidence and causality conclusions, 20*t*, 611*t*, 687*t*  
 transverse myelitis, 604–605
- MMR vaccine  
 acute disseminated encephalomyelitis, 153–154  
 afebrile seizures, 133–137  
 anaphylaxis, 169–174  
 arthropathy in men, 201–204  
 ataxia, 143–144  
 autism, 145–153  
 brachial neuritis, 168–169  
 chronic arthralgia in women, 190–195  
 chronic arthritis in women, 195–199  
 chronic arthropathy in children, 199–200  
 chronic fatigue syndrome, 212–213  
 chronic inflammatory disseminated polyneuropathy, 166–167  
 encephalitis and encephalopathy, 111–119  
 febrile seizures, 119–132  
 fibromyalgia, 213–214  
 Guillain-Barré syndrome, 165–166  
 hearing loss, 214–217  
 hepatitis, 211–212  
 measles inclusion body encephalitis, 108–110  
 meningitis, 137–143  
 multiple sclerosis onset in adults, 159–164  
 multiple sclerosis onset in children, 164–165  
 neuromyelitis optica, 158–159  
 opsoclonus myoclonus syndrome, 167–168  
 optic neuritis, 156–158  
 summary of evidence and causality conclusions, 20–22*t*, 218–221*t*, 674–677*t*  
 transient arthralgia in children, 182–190  
 transient arthralgia in women, 174–181  
 transverse myelitis, 154–156  
 type 1 diabetes, 204–211  
 prior reviews, 1–2, 29–30, 39  
 process  
 categorization of findings, 14–18, 23–24, 48–53  
 contradictory evidence, 23  
 framework for, 10–18, 23–24, 42–53  
 weight-of-evidence evaluations, 10–14, 42–48
- varicella zoster vaccine  
 acute disseminated encephalomyelitis, 271  
 anaphylaxis, 275–278  
 arthropathy, onset or exacerbation, 278–279  
 cerebellar ataxia, 269–270  
 disseminated Oka VZV with subsequent infection resulting in pneumonia, meningitis, or hepatitis, 249–256  
 disseminated Oka VZV without other organ involvement, 242–249  
 encephalopathy, 267–268  
 Guillain-Barré syndrome, 273–274  
 seizures, 268–269  
 small fiber neuropathy, 274–275  
 stroke, 279–280  
 summary of evidence and causality conclusions, 19–20*t*, 283–284*t*, 677–678*t*  
 thrombocytopenia, 281–282  
 transverse myelitis, 272–273  
 vaccine strain viral reactivation with subsequent infection resulting in meningitis or encephalitis, 261–267  
 vaccine strain viral reactivation without other organ involvement, 256–261
- See also* Causality
- Asthma and reactive airway disease episodes  
 definition, 635  
 inactivated influenza vaccine and, 22*t*, 23, 345–356, 403*t*  
 live attenuated influenza vaccine and, 356–373, 403*t*



- mechanism(s) that may contribute to symptoms of, 356, 366, 369, 373
  - Ataxia
    - definition, 636
    - DTaP vaccine and, 544–545, 585*t*
    - mechanism(s) that may contribute to symptoms of, 144
    - MMR vaccine and, 143–144, 218*t*
  - Attribution elements, 13, 46
  - Autism
    - definition, 636
    - diagnosis and biological mechanism, 57, 85–89
    - DTaP vaccine and, 545–546, 585*t*
    - MMR vaccine and, 21*t*, 23, 145–153, 218*t*
    - See also* Biological mechanisms, pathophysiologies, and susceptibilities with the potential to contribute to adverse events
  - Autoimmune hepatitis
    - definition, 636
    - hepatitis A vaccine and, 429–430, 431*t*
    - mechanism(s) that may contribute to symptoms of, 430
  - Autoreactivity. *See* Biological mechanisms, pathophysiologies, and susceptibilities with the potential to contribute to adverse events
- B**
- B cell response to antigen exposure, 57–58, 60, 63
  - Bell’s palsy
    - definition, 636
    - DTaP vaccine and, 561–562, 587*t*
    - hepatitis A vaccine and, 427–428, 431*t*
    - influenza vaccine and, 21*t*, 23, 335–337, 338–339*t*, 402*t*
  - Benefits of vaccination, 27
  - Biological mechanisms, pathophysiologies, and susceptibilities with the potential to contribute to adverse events
    - alterations in brain development, 85–86
    - autism, 86–89
    - coagulation and hypercoagulable states, 81–82
    - immune mediated mechanisms, 59–76
    - antigen persistence, 73–74
    - autoreactivity, 75
    - bystander activation, 75
    - complement activation, 62–64
    - effector functions of antibodies and autoantibodies, 60–62
    - effector functions of T cells, 59–60
    - epitope spreading, 74–75
    - hyperresponsiveness, 75
    - hypersensitivity reactions, 64–66
      - complement mediated hypersensitivity, 65–66
      - immunoglobulin E hypersensitivity, 64–65
    - immune complexes, 66–68
    - increased cytokines, 75–76
    - molecular mimicry, 70–73
    - superantigens, 76
    - tissue responses (fever and seizure), 68–70
  - increased susceptibility, 82–84
  - injection-related adverse events
    - complex regional pain syndrome, 78–80
    - deltoid bursitis, 80
    - syncope, 80–81
  - latency between antigen exposure and peak adaptive immune response, 57–59
  - viral activity, 76–78
    - direct or primary infection, 76–77
    - persistent infection, 77
    - viral reactivation, 77–78
- Bordetella pertussis*
- bacteria description, 528
  - clinical description, 529, 643
  - complications, 529
  - encephalitis and encephalopathy and, 529, 536
  - seizures and, 529, 544
  - transmission, 529
  - vaccine development and recommendations, 529, 530
  - See also* Diphtheria toxoid, tetanus toxoid, and acellular pertussis antigen-containing (DTaP) vaccines
- Brachial neuritis
- definition, 636
  - hepatitis B vaccine and, 467–468, 492*t*

- human papillomavirus vaccine and, 512–513, 521*t*
  - influenza vaccine and, 340, 402*t*
  - mechanism(s) that may contribute to symptoms of, 168, 340, 468, 513
  - MMR vaccine and, 168–169, 219*t*
  - Brain development, alterations, 85–86
  - Bystander activation. *See* Biological mechanisms, pathophysiology, and susceptibilities with the potential to contribute to adverse events
- C**
- Campylobacter jejuni*, 72, 333, 423, 426
  - Canada, 18, 392–401
  - Cardiopulmonary disease, complications of influenza infection, 294–295
  - Case-control study
    - definition, 636
    - studies contributing to the weight of epidemiologic evidence, 111–112, 114–115*t*, 137–138, 140*t*, 147–148, 151–152*t*, 156, 160, 162–163*t*, 164, 201, 203*t*, 204–206, 208–210*t*, 310–311, 312*t*, 315, 317*t*, 443–444, 445*t*, 448, 452*t*, 454, 458–459, 461*t*, 464, 471, 488–489, 534–535, 537, 549, 550–551, 552*t*, 567–568, 569–570*t*, 572–573, 575–577*t*
  - Case-crossover study
    - definition, 636
    - studies contributing to the weight of epidemiologic evidence, 120–121, 125*t*, 138–139, 141*t*, 301–302, 305–306*t*, 318–319, 320*t*, 348–349, 354–355*t*, 393–394, 398*t*, 455–456, 554
  - Case-only study, definition, 637
  - Case reports, 12–13, 46–47, 52, 53
    - definition, 637
  - Case series, definition, 637
  - Causality
    - adverse effects versus adverse events, 1*n*
    - categories and explanations of, 14–24, 48–53
    - evidence convincingly supports, 15, 17–18, 49, 50–52
    - evidence favoring acceptance of, 15, 18–23, 49, 52–53
    - evidence favoring rejection of, 15, 23, 49, 53, 389*n*
    - evidence inadequate to accept or reject, 15, 23–24, 49, 53
  - DTaP vaccine
    - acute disseminated encephalomyelitis, 547
    - anaphylaxis, 565
    - arthropathy, 571
    - ataxia, 545
    - autism, 546
    - Bell’s Palsy, 562
    - chronic inflammatory disseminated polyneuropathy, 560
    - chronic urticaria, 566
    - encephalitis and encephalopathy, 537
    - fibromyalgia, 581
    - Guillain-Barré syndrome, 558
    - immune thrombocytopenic purpura, 584
    - infantile spasms, 539
    - multiple sclerosis onset in adults, 553
    - multiple sclerosis relapse in adults, 555
    - multiple sclerosis relapse in children, 557
    - myocarditis, 580
    - opsoclonus myoclonus syndrome, 561
    - optic neuritis, 550
    - seizures, 544
    - serum sickness, 567
    - sudden infant death syndrome, 582
    - summary of evidence and causality
      - conclusions, 22*t*, 585–588*t*, 683–687*t*
    - transverse myelitis, 548
    - type 1 diabetes, 579
  - finding of no causal relationship, 15, 49
  - hepatitis A vaccine
    - acute disseminated encephalomyelitis, 424
    - anaphylaxis, 429
    - autoimmune hepatitis, 430
    - Bell’s palsy, 428
    - chronic inflammatory disseminated polyneuropathy, 427
    - Guillain-Barré syndrome, 426
    - multiple sclerosis, 425
    - summary of evidence and causality
      - conclusions, 431*t*, 680–681*t*
    - transverse myelitis, 425

- hepatitis B vaccine
  - acute disseminated encephalomyelitis, 442
  - anaphylaxis, 469
  - brachial neuritis, 468
  - chronic inflammatory disseminated polyneuropathy, 467
  - encephalitis and encephalopathy, 438
  - erythema nodosum, 471
  - fibromyalgia, 490
  - first demyelinating event in adults, 463
  - first demyelinating event in children, 465
  - Guillain-Barré syndrome, 466
  - juvenile idiopathic arthritis, onset or exacerbation, 488
  - multiple sclerosis onset in adults, 450
  - multiple sclerosis onset in children, 455
  - multiple sclerosis relapse in adults, 456
  - multiple sclerosis relapse in children, 458
  - neuromyelitis optica, 447
  - optic neuritis, 446
  - polyarteritis nodosa, onset or exacerbation, 479
  - psoriatic arthritis, onset or exacerbation, 480
  - reactive arthritis, onset or exacerbation, 482
  - rheumatoid arthritis, onset or exacerbation, 485
  - seizures, 440
  - summary of evidence and causality
    - conclusions, 20*t*, 491–493*t*, 681–683*t*
  - systemic lupus erythematosus, onset or exacerbation, 473
  - transverse myelitis, 443
  - type 1 diabetes, 490
  - vasculitis, onset or exacerbation, 477
- human papillomavirus vaccine
  - acute disseminated encephalomyelitis, 508
  - amyotrophic lateral sclerosis, 515
  - anaphylaxis, 516
  - brachial neuritis, 513
  - chronic inflammatory disseminated polyneuropathy, 512
  - Guillain-Barré syndrome, 512
  - hypercoagulable states, 520
  - multiple sclerosis, 510
  - neuromyelitis optica, 509
  - pancreatitis, 518
  - summary of evidence and causality
    - conclusions, 21*t*, 521*t*, 683*t*
  - thromboembolic events, 520
  - transient arthralgia, 517
  - transverse myelitis, 508
- influenza vaccine
  - acute disseminated encephalomyelitis, 309
  - all-cause mortality, 391
  - anaphylaxis, 345
  - arthropathy, onset or exacerbation, 385
  - asthma exacerbation or reactive airway disease episodes in children and adults, inactivated influenza vaccine, 356
  - asthma exacerbation or reactive airway disease episodes in children younger than 5 years of age, live attenuated influenza vaccine, 366
  - asthma exacerbation or reactive airway disease episodes in persons 5 years of age or older, live attenuated influenza vaccine, 373
  - Bell's palsy, 337
  - brachial neuritis, 340
  - chronic inflammatory disseminated polyneuropathy, 335
  - encephalitis, 299
  - encephalopathy, 301
  - fibromyalgia, 389
  - Guillain-Barré syndrome, 334
  - multiple sclerosis onset in adults, 318
  - multiple sclerosis relapse in adults, 321
  - myocardial infarction, 389
  - neuromyelitis optica, 314
  - oculorespiratory syndrome, 401
  - optic neuritis, 313
  - polyarteritis nodosa, 384
  - seizures, 304
  - small fiber neuropathy, 341
  - stroke, 386
  - summary of evidence and causality
    - conclusions, 20–22*t*, 402–404*t*, 678–680*t*
  - systemic lupus erythematosus, onset or exacerbation, 379
  - transverse myelitis, 310
  - vasculitis, onset or exacerbation, 383

- injection-related adverse events
    - complex regional pain syndrome, 617
    - deltoid bursitis, 620
    - summary of evidence and causality
      - conclusions, 21*t*, 625*t*, 678–680*t*
    - syncope, 624
  - limitations of data sources and findings, 629–633
  - meningococcal vaccine
    - acute disseminated encephalomyelitis, 604
    - anaphylaxis, 610
    - chronic headache, 610
    - chronic inflammatory disseminated polyneuropathy, 608
    - encephalitis and encephalopathy, 603
    - Guillain-Barré syndrome, 607
    - multiple sclerosis, 606
    - summary of evidence and causality
      - conclusions, 20*t*, 611*t*, 687*t*
    - transverse myelitis, 605
  - MMR vaccine
    - acute disseminated encephalomyelitis, 154
    - afebrile seizures, 137
    - anaphylaxis, 174
    - arthropathy in men, 204
    - ataxia, 144
    - autism, 153
    - brachial neuritis, 169
    - chronic arthralgia in women, 195
    - chronic arthritis in women, 199
    - chronic arthropathy in children, 200
    - chronic fatigue syndrome, 213
    - chronic inflammatory disseminated polyneuropathy, 167
    - encephalitis, 118
    - encephalopathy, 119
    - febrile seizures, 132
    - fibromyalgia, 214
    - Guillain-Barré syndrome, 166
    - hearing loss, 217
    - hepatitis, 212
    - measles inclusion body encephalitis, 110
    - meningitis, 143
    - multiple sclerosis onset in adults, 164
    - multiple sclerosis onset in children, 165
    - neuromyelitis optica, 159
    - opsoclonus myoclonus syndrome, 168
    - optic neuritis, 158
    - summary of evidence and causality
      - conclusions, 20–22*t*, 218–221*t*, 674–677*t*
    - transient arthralgia in children, 190
    - transient arthralgia in women, 181
    - transverse myelitis, 156
    - type 1 diabetes, 211
    - summary of evidence and causality
      - conclusions, 19–22*t*, 674–748*t*
      - DTaP vaccine and, 585–588*t*
      - hepatitis A vaccine and, 431*t*
      - hepatitis B vaccine and, 491–493*t*
      - human papillomavirus vaccine and, 521*t*
      - influenza vaccine and, 402–404*t*
      - injection related adverse events and, 625*t*
      - meningococcal vaccine and, 611*t*
      - MMR vaccine and, 218–221*t*
      - varicella vaccine and, 283–284*t*
    - varicella zoster vaccine
      - acute disseminated encephalomyelitis, 271
      - anaphylaxis, 278
      - arthropathy, onset or exacerbation, 279
      - cerebellar ataxia, 270
      - disseminated Oka VZV with
        - subsequent infection resulting in pneumonia, meningitis, or hepatitis, 256
      - disseminated Oka VZV without other organ involvement, 249
      - encephalopathy, 268
      - Guillain-Barré syndrome, 274
      - seizures, 269
      - small fiber neuropathy, 275
      - stroke, 280
      - summary of evidence and causality
        - conclusions, 19–20*t*, 283–284*t*, 677–678*t*
      - thrombocytopenia, 282
      - transverse myelitis, 273
      - vaccine strain viral reactivation with
        - subsequent infection resulting in meningitis or encephalitis, 267
      - vaccine strain viral reactivation without other organ involvement, 261
- See also* Assessment of causality

- Centers for Disease Control and Prevention, 2, 29, 30
- Cephalic tetanus, 527–528
- Cerebellar ataxia  
 definition, 637  
 mechanism(s) that may contribute to symptoms of, 270  
 varicella zoster vaccine and, 269–270, 284*t*
- Chemotherapy, 73, 82, 241, 246–248, 253, 254–255, 260, 264, 265
- Chronic fatigue syndrome  
 definition, 637  
 MMR vaccine and, 212–213, 221*t*
- Chronic inflammatory disseminated polyneuropathy  
 definition, 637  
 DTaP vaccine and, 558–560, 587*t*  
 hepatitis A vaccine and, 427, 431*t*  
 hepatitis B vaccine and, 466–467, 492*t*  
 human papillomavirus vaccine and, 512, 521*t*  
 influenza vaccine and, 334–335, 402*t*  
 mechanism(s) that may contribute to symptoms of, 167, 335, 427, 467, 512, 560, 608  
 meningococcal vaccine and, 607–608, 611*t*  
 MMR vaccine and, 166–167, 219*t*
- Chronic urticaria  
 definition, 637  
 DTaP vaccine and, 565–566, 587*t*  
 mechanism(s) that may contribute to symptoms of, 565
- Clostridium tetani*  
 bacteria description, 527  
 Bell's palsy and, 562  
 clinical description, 527, 645  
 complications, 527–528  
 incidence, 528  
 transmission, 527  
 vaccine development and recommendations, 528, 530  
*See also* Diphtheria toxoid, tetanus toxoid, and acellular pertussis antigen-containing (DTaP) vaccines
- Coagulation and hypercoagulable states.  
*See* Biological mechanisms, pathophysiologies, and susceptibilities with the potential to contribute to adverse events
- Cohort studies  
 contributing to the weight of epidemiologic evidence, 322–323, 328*t*, 374, 375, 376*t*, 377*t*, 438–439, 535, 540, 542*t*, 561, 574, 578*t*  
 definition, 637–638  
 prospective cohort studies contributing to the weight of epidemiologic evidence, 374, 376–377*t*, 482–483  
 retrospective cohort studies contributing to the weight of epidemiologic evidence, 111, 114*t*, 120, 121–122, 125–127*t*, 133–134, 135–136*t*, 138, 140–141*t*, 146, 151*t*, 174–175, 177–178*t*, 183, 184, 187*t*, 189*t*, 190, 192*t*, 195, 197*t*, 201, 203*t*, 206, 210*t*, 250–251, 262, 268, 275, 279, 303, 307*t*, 323, 325–326, 329*t*, 331–332*t*, 336–337, 339*t*, 341, 358–359, 363–364*t*, 367, 371–372*t*, 379, 381*t*, 390, 457, 540–541, 543*t*, 555–556, 573–574, 577*t*, 606–607, 618
- Compensation for adverse events for effects of vaccines not on Vaccine Injury Table, 29, 30  
 legislation in support of, 1, 28, 29
- Complement activation. *See* Biological mechanisms, pathophysiologies, and susceptibilities with the potential to contribute to adverse events
- Complement-mediated hypersensitivity.  
*See* Biological mechanisms, pathophysiologies, and susceptibilities with the potential to contribute to adverse events
- Complex regional pain syndrome  
 definition, 638  
 injection-related, 78–80, 615–617, 625*t*  
*See also* Biological mechanisms, pathophysiologies, and susceptibilities with the potential to contribute to adverse events
- Confounding variables, definition, 638
- Consumer education, legislation in support of, 1, 28–29
- Contradictory evidence, 23, 53

## INDEX

Convulsion. *See* Febrile seizures; Seizures  
*Corynebacterium diphtheriae*  
 bacteria description, 525  
 Bell's palsy and, 562  
 clinical description, 525–526, 638–639  
 complications, 526  
 encephalitis and encephalopathy and,  
 526, 536  
 myocarditis and, 526, 580  
 transmission, 525  
 vaccine development and  
 recommendations, 526, 530  
*See also* Diphtheria toxoid, tetanus  
 toxoid, and acellular pertussis  
 antigen-containing (DTaP)  
 vaccines  
 Countermeasures Injury Compensation  
 Program, 2*n*  
 Critical periods, 84  
 Crossover experiment, definition, 638  
 Cytokine storm, 75–76

## D

Defense Medical Surveillance System,  
 310–311, 312*t*, 444, 445*t*, 461*t*  
 Deltoid bursitis  
 definition, 80, 638  
 injection of vaccine and, 18, 21*t*,  
 618–620, 625*t*  
*See also* Biological mechanisms,  
 pathophysiologies, and  
 susceptibilities with the potential  
 to contribute to adverse events  
 Demyelination, definition, 638  
 Department of Health and Human Services  
 National Vaccine Program Office, 29  
 prior reviews of adverse events, 1–2,  
 29–30  
 Developmental problems, brain  
 development, 85–89  
 Diabetes, type 1  
 definition, 641  
 DTaP vaccine and, 22*t*, 571–579, 588*t*  
 evidence favoring rejection of vaccine  
 causality, 23  
 hepatitis B vaccine and, 488–490, 493*t*  
 mechanism(s) that may contribute to  
 symptoms of, 211, 489, 571  
 MMR vaccine and, 22*t*, 204–211, 220*t*  
 molecular mimicry, 71  
 mumps and, 105, 211  
 Diabetes mellitus, insulin-dependent. *See*  
 Diabetes, type 1  
 Diphtheria toxoid, tetanus toxoid, and  
 acellular pertussis antigen-  
 containing (DTaP) vaccines  
 acute disseminated encephalomyelitis,  
 546–547  
 anaphylaxis, 563–565  
 arthropathy, 567–571  
 ataxia, 544–545  
 autism, 545–546  
 Bell's Palsy, 561–562  
 booster vaccinations, 530  
 as cause of adverse events. *See* Causality,  
 DTaP vaccine  
 chronic inflammatory disseminated  
 polyneuropathy, 558–560  
 chronic urticaria, 565–566  
 development of, 526  
 effectiveness, 526, 528  
 encephalitis and encephalopathy,  
 534–537  
 fibromyalgia, 581  
 formulations and dosages, 530, 531–533*t*  
 Guillain-Barré syndrome, 557–558  
 immune thrombocytopenic purpura,  
 582–584  
 infantile spasms, 537–539  
 multiple sclerosis onset in adults,  
 550–553  
 multiple sclerosis relapse in adults,  
 554–555  
 multiple sclerosis relapse in children,  
 555–557  
 myocarditis, 579–580  
 opsoclonus myoclonus syndrome,  
 560–561  
 optic neuritis, 10, 36, 549–550  
 prior reviews into adverse events, 1–2,  
 30  
 seizures, 539–544  
 serum sickness, 566–567  
 sudden infant death syndrome, 581–582  
 transverse myelitis, 547–548  
 type 1 diabetes, 23, 571–579  
 summary of evidence and causality  
 conclusions, 20*t*, 22*t*, 585–588*t*,  
 683–687*t*  
 vaccination rates, 530

- with whole cell pertussis component, 2, 30, 84, 529, 530
  - See also* Acellular pertussis vaccine; Pertussis vaccine, whole cell; Tetanus toxoid-containing vaccines
  - Double blind controlled crossover study studies contributing to the weight of epidemiologic evidence, 182–183, 186*t*
  - Double blind randomized controlled crossover trial studies contributing to the weight of epidemiologic evidence, 345–346, 347, 351–352*t*, 353*t*
  - DTaP. *See* Diphtheria toxoid, tetanus-toxoid, and acellular pertussis antigen-containing vaccines
- E**
- Egg sensitivity, 83, 170–172, 277, 342–343, 344, 632
  - Embolism, definition, 639
  - Encephalitis and encephalopathy
    - autism and, 85, 88–89
    - as *Bordetella pertussis* infection complication, 529, 536
    - as *Corynebacterium diphtheriae* infection complication, 526, 536
    - definition, 639
    - DTaP vaccine and, 534–537, 585*t*
    - genetic risk, 84, 85, 88–89
    - hepatitis B vaccine and, 437–438, 491*t*
    - as influenza infection complication, 299
    - influenza vaccine and, 296, 299–301, 402*t*
    - as measles infection complication, 77, 103, 117, 118
    - mechanism(s) that may contribute to symptoms of, 117, 119, 266, 267, 299, 300, 537, 603
    - meningococcal vaccine and, 602–603, 611*t*
    - MMR vaccine and, 111–119, 218*t*
    - as mumps infection complication, 105, 117, 118
    - as rubella infection complication, 77, 106–107, 117
    - varicella vaccine and, 262–263, 265–266, 267–268, 283*t*
    - as varicella zoster virus complication, 266
  - See also* Measles inclusion body encephalitis
  - Encephalomyelitis, acute disseminated. *See* Acute disseminated encephalomyelitis
  - Epidemiologic evidence
    - categorization of causality based on, 10, 12, 14–18, 23–24, 42–45, 48–53
  - DTaP vaccine
    - acute disseminated encephalomyelitis, 546
    - anaphylaxis, 563
    - arthropathy, 567–578, 569–570*t*
    - ataxia, 544–545
    - autism, 545
    - Bell’s Palsy, 561–562
    - chronic inflammatory disseminated polyneuropathy, 558
    - chronic urticaria, 565
    - encephalitis and encephalopathy, 534–535
    - fibromyalgia, 581
    - Guillain-Barré syndrome, 557
    - immune thrombocytopenic purpura, 582–583
    - infantile spasms, 537–538
    - multiple sclerosis onset in adults, 550–553
    - multiple sclerosis relapse in adults, 554
    - multiple sclerosis relapse in children, 555–556
    - myocarditis, 579
    - opsoclonus myoclonus syndrome, 560
    - optic neuritis, 549
    - seizures, 539–541, 542–543*t*
    - serum sickness, 566
    - sudden infant death syndrome, 581–582
    - summary of evidence and causality conclusions, 22*t*, 585–588*t*, 683–687*t*
    - transverse myelitis, 547–548
    - type 1 diabetes, 571–579
  - for evaluation of causality, 39–40
  - hepatitis A vaccine
    - acute disseminated encephalomyelitis, 423
    - anaphylaxis, 428
    - autoimmune hepatitis, 429
    - Bell’s palsy, 427

- chronic inflammatory disseminated polyneuropathy, 427
- Guillain-Barré syndrome, 426
- multiple sclerosis, 425
- summary of evidence and causality conclusions, 431*t*, 680–681*t*
- transverse myelitis, 424
- hepatitis B vaccine
  - acute disseminated encephalomyelitis, 440
  - anaphylaxis, 468
  - brachial neuritis, 467
  - chronic inflammatory disseminated polyneuropathy, 466–467
  - encephalitis and encephalopathy, 437
  - erythema nodosum, 469
  - fibromyalgia, 490
  - first demyelinating event in adults, 458–460, 461–462*t*
  - first demyelinating event in children, 464–465
  - Guillain-Barré syndrome, 465–466
  - juvenile idiopathic arthritis, onset or exacerbation, 485–486
  - multiple sclerosis, onset in adults, 447–450, 451–453*t*
  - multiple sclerosis, onset in children, 454
  - multiple sclerosis, relapse in adults, 455–456
  - multiple sclerosis, relapse in children, 457
  - neuromyelitis optica, 446
  - optic neuritis, 443–444, 445*t*
  - polyarteritis nodosa, onset or exacerbation, 477
  - psoriatic arthritis, onset or exacerbation, 479–480
  - reactive arthritis, onset or exacerbation, 480
  - rheumatoid arthritis, onset or exacerbation, 482–483
  - seizures, 438–439
  - summary of evidence and causality conclusions, 20*t*, 491–493*t*, 681–683*t*
  - systemic lupus erythematosus onset or exacerbation, 471–472
  - transverse myelitis, 442
  - type 1 diabetes, 488–489
  - vasculitis, onset or exacerbation, 473
- human papillomavirus vaccine
  - acute disseminated encephalomyelitis, 507
  - amyotrophic lateral sclerosis, 513
  - anaphylaxis, 515
  - brachial neuritis, 512–513
  - chronic inflammatory disseminated polyneuropathy, 512
  - Guillain-Barré syndrome, 511
  - hypercoagulable states, 520
  - multiple sclerosis, 510
  - neuromyelitis optica, 509
  - pancreatitis, 517–518
  - summary of evidence and causality conclusions, 21*t*, 521*t*, 683*t*
  - thromboembolic events, 519
  - transient arthralgia, 516–517
  - transverse myelitis, 508
- influenza vaccine
  - acute disseminated encephalomyelitis, 308
  - all-cause mortality, 390
  - anaphylaxis, 341–342
  - arthropathy, onset or exacerbation, 384
  - asthma exacerbation or reactive airway disease episodes in children and adults, inactivated influenza vaccine, 345–350, 351–355*t*
  - asthma exacerbation or reactive airway disease episodes in children younger than 5 years of age, live attenuated influenza vaccine, 356–361, 362–365*t*
  - asthma exacerbation or reactive airway disease episodes in persons 5 years of age or older, live attenuated influenza vaccine, 366–369, 370–372*t*
  - Bell's palsy, 335–337, 338–339*t*
  - brachial neuritis, 340
  - chronic inflammatory disseminated polyneuropathy, 334
  - encephalitis and encephalopathy, 296
  - fibromyalgia, 389
  - Guillain-Barré syndrome, 321–327, 328–332*t*
  - multiple sclerosis, onset in adults, 314–316, 317*t*
  - multiple sclerosis, relapse in adults, 318–319, 320*t*



- myocardial infarction, 387–388
- neuromyelitis optica, 314
- oculorespiratory syndrome, 391–398
- optic neuritis, 310–311, 312*t*
- polyarteritis nodosa, 383
- seizures, 301–304, 305–307*t*
- small fiber neuropathy, 340–341
- stroke, 386
- summary of evidence and causality
  - conclusions, 20–22*t*, 402–404*t*, 678–680*t*
- systemic lupus erythematosus, onset or exacerbation, 373–375, 376–377*t*
- transverse myelitis, 309
- vasculitis, onset or exacerbation, 379–380, 381*t*
- injection-related outcomes
  - complex regional pain syndrome, 615
  - deltoid bursitis, 618
  - summary of evidence and causality
    - conclusions, 21*t*, 625*t*, 687–688*t*
  - syncope, 620
- limitations of current data, 630
- meningococcal vaccine
  - acute disseminated encephalomyelitis, 603–604
  - anaphylaxis, 608–609
  - chronic headache, 610
  - chronic inflammatory disseminated polyneuropathy, 607–608
  - encephalitis and encephalopathy, 602–603
  - Guillain-Barré syndrome, 606–607
  - multiple sclerosis, 605
  - summary of evidence and causality
    - conclusions, 20*t*, 611*t*, 687*t*
  - transverse myelitis, 604
- MMR vaccine
  - acute disseminated encephalomyelitis, 153
  - afebrile seizures, 133–134, 135–136*t*
  - anaphylaxis, 169
  - arthropathy in men, 201–202, 203*t*
  - ataxia, 143
  - autism, 145–148, 149–152*t*
  - brachial neuritis, 168
  - chronic arthralgia in women, 190–191, 192*t*
  - chronic arthritis in women, 195–196, 197*t*
  - chronic arthropathy in children, 199
  - chronic fatigue syndrome, 212–213
  - chronic inflammatory disseminated polyneuropathy, 166–167
  - encephalitis and encephalopathy, 111–113, 114–115*t*
  - febrile seizures, 119–124, 125–130*t*
  - fibromyalgia, 213
  - Guillain-Barré syndrome, 165
  - hearing loss, 214
  - hepatitis, 211
  - measles inclusion body encephalitis, 108
  - meningitis, 137–139, 140–141*t*
  - multiple sclerosis, onset in adults, 159–161, 162–163*t*
  - multiple sclerosis, onset in children, 164
  - neuromyelitis optica, 158
  - opsoclonus myoclonus syndrome, 167
  - optic neuritis, 156
  - summary of evidence and causality
    - conclusions, 20–22*t*, 218–221*t*, 674–677*t*
  - transient arthralgia in children, 182–185, 186–189*t*
  - transient arthralgia in women, 174–176, 177–179*t*
  - transverse myelitis, 154
  - type 1 diabetes, 204–207, 208–210*t*
- varicella zoster vaccine
  - acute disseminated encephalomyelitis, 271
  - anaphylaxis, 275
  - arthropathy, onset or exacerbation, 278
  - cerebellar ataxia, 269–270
  - disseminated Oka VZV with subsequent infection resulting in pneumonia, meningitis, or hepatitis, 250–251
  - disseminated Oka VZV without other organ involvement, 243
  - encephalopathy, 267
  - Guillain-Barré syndrome, 273
  - seizures, 268
  - small fiber neuropathy, 274
  - stroke, 279–280
  - summary of evidence and causality
    - conclusions, 19*t*, 20*t*, 283–284*t*, 677–678*t*
  - thrombocytopenia, 281

- transverse myelitis, 272
  - vaccine strain viral reactivation with subsequent infection resulting in meningitis or encephalitis, 262–263
  - vaccine strain viral reactivation without other organ involvement, 256–257
  - weight-of-evidence evaluations, 10, 12, 42–45
  - Epilepsy, myoclonic, definition, 642
  - Epitope spreading. *See* Biological mechanisms, pathophysiologies, and susceptibilities with the potential to contribute to adverse events
  - Erythema nodosum
    - definition, 639
    - hepatitis B vaccine and, 10, 36, 469–471, 492*t*
    - mechanism(s) that may contribute to symptoms of, 470
- F**
- Febrile seizures
    - clinical significance, 630
    - definition, 639
    - influenza infection, 294
    - mechanism(s) that may contribute to symptoms of, 132
    - MMR vaccine and, 18, 20*t*, 119–132, 218*t*, 630
    - tissue responses, 68–70
  - Fibromyalgia
    - DTaP vaccine and, 581, 588*t*
    - hepatitis B vaccine and, 490, 493*t*
    - influenza vaccine and, 389, 404*t*
    - MMR vaccine and, 213–214, 221*t*
  - First demyelinating event
    - hepatitis B vaccine and, in adults, 458–460, 461–462*t*, 491*t*
    - hepatitis B vaccine and, in children, 464–465, 492*t*
    - mechanism(s) that may contribute to symptoms of, 463, 465
  - Food and Drug Administration, 29
  - Food hypersensitivity reactions, 65, 171–173
  - See also* Egg sensitivity; Gelatin
- G**
- Gelatin, 83, 171–173, 276–277, 342–344, 632
  - Gender differences
    - as susceptibility factor, 84
  - General Practice Research Database, 147, 151*t*, 315, 317*t*, 323–325, 329–330*t*, 336, 338*t*, 344, 346, 352*t*, 386, 387–388, 448–449, 452*t*, 551, 552*t*
  - Genetic risk factors
    - autism, 87–88
    - febrile seizures, 69–70
    - neuronal development, 85, 86
    - susceptibility to adverse events, 24, 83–84
  - German measles. *See* Rubivirus (rubella infection)
  - Guillain-Barré syndrome
    - acute motor axonal neuropathy in, 71–72
    - definition, 639
    - DTaP vaccine and, 557–558, 587*t*
    - evaluation of adverse event data, 47
    - hepatitis A vaccine and, 426, 431*t*
    - hepatitis B vaccine and, 465–466, 492*t*
    - human papillomavirus vaccine and, 511–512, 521*t*
    - influenza vaccine and, 321–334, 402*t*
    - mechanism(s) that may contribute to symptoms of, 166, 274, 334, 426, 466, 511, 558, 607
    - meningococcal vaccine and, 606–607, 611*t*
    - MMR vaccine and, 165–166, 219*t*
    - swine influenza vaccine and, 321*n*
    - varicella zoster vaccine and, 273–274, 284*t*
- H**
- H1N1 vaccine, 2*n*, 30
  - H5N1 vaccine, 294
  - Haemophilus influenzae* type B vaccine, 2, 30
  - Health Resources and Services
    - Administration, 2, 29, 30, 36
  - Hearing loss
    - definition, 639
    - mechanism(s) that may contribute to symptoms of, 217
    - MMR vaccine and, 214–217, 221*t*

- Hemagglutinin surface proteins, 294
- Hepatitis, as an adverse event of vaccination  
 definition, 639  
 mechanism(s) that may contribute to  
 symptoms of, 212, 256  
 MMR vaccine and, 211–212, 221*t*  
 varicella vaccine and, 251, 254–256, 283*t*
- Hepatitis A infection  
 acute disseminated encephalomyelitis  
 and, 423  
 autoimmune hepatitis and, 421–422, 430  
 clinical description, 421–422, 640  
 complications, 421–422  
 Guillain-Barré syndrome and, 426  
 transmission, 422  
 transverse myelitis and, 424  
 vaccine development, 422  
 virus description, 421
- Hepatitis A vaccine  
 acute disseminated encephalomyelitis,  
 423–424  
 anaphylaxis, 428–429  
 autoimmune hepatitis, 429–430  
 Bell's palsy, 427–428  
 as cause of adverse events. *See* Causality,  
 hepatitis A vaccine  
 chronic inflammatory disseminated  
 polyneuropathy, 427  
 development, 422  
 formulations, 422–423  
 Guillain-Barré syndrome, 426  
 multiple sclerosis, 425  
 summary of evidence and causality  
 conclusions, 431*t*, 680–681*t*  
 transverse myelitis, 424–425
- Hepatitis B infection  
 clinical description, 435–436, 640  
 complications, 435–436  
 onset or exacerbation of juvenile  
 idiopathic arthritis and, 435, 487  
 onset or exacerbation of polyarteritis  
 nodosa and, 435, 478–479  
 onset or exacerbation of rheumatoid  
 arthritis and, 435, 484  
 onset or exacerbation of vasculitis and,  
 435, 476  
 transmission, 435  
 vaccine development and  
 recommendations, 436–437  
 virus description, 435
- Hepatitis B vaccine  
 acute disseminated encephalomyelitis,  
 440–442  
 anaphylactic reactions, 18  
 anaphylaxis, 468–469  
 brachial neuritis, 467–468  
 as cause of adverse events. *See* Causality,  
 hepatitis B vaccine  
 chronic inflammatory disseminated  
 polyneuropathy, 466–467  
 cytokine imbalance and, 76  
 development, 436  
 encephalitis and encephalopathy,  
 437–438  
 erythema nodosum, 10, 36, 469–471  
 fibromyalgia, 490  
 first demyelinating event in adults,  
 458–464  
 first demyelinating event in children,  
 464–465  
 formulations, 436–437  
 Guillain-Barré syndrome, 465–466  
 immune complex-mediated effects, 68  
 injection-related adverse events, 616  
 juvenile idiopathic arthritis, onset or  
 exacerbation, 485–488  
 multiple sclerosis onset in adults,  
 447–450, 451–453*t*  
 multiple sclerosis onset in children,  
 454–455  
 multiple sclerosis relapse in adults,  
 455–456  
 multiple sclerosis relapse in children,  
 457–458  
 neuromyelitis optica, 446–447  
 optic neuritis, 10, 36, 443–446  
 polyarteritis nodosa, onset or  
 exacerbation, 477–479  
 prior reviews into adverse events, 2, 30  
 psoriatic arthritis, onset or exacerbation,  
 479–480  
 reactive arthritis, onset or exacerbation,  
 480–482  
 rheumatoid arthritis, onset or  
 exacerbation, 482–485  
 seizures, 438–440  
 summary of causality studies and  
 conclusions, 20*t*, 491–493*t*,  
 681–683*t*  
 systemic lupus erythematosus onset or  
 exacerbation, 471–473

- transverse myelitis, 442–443
  - type 1 diabetes, 488–490
  - vasculitis, onset or exacerbation, 473–477
  - Herd immunity, 28
  - Herpes zoster
    - cause, 240
    - definition, 640
    - mechanism(s) that may contribute to symptoms of, 261
    - rate, 631
    - varicella vaccine and, 256–267, 283*t*
  - Human papillomavirus infection
    - clinical description, 506, 640
    - complications, 506
    - nomenclature, 505
    - transmission, 505
    - vaccine development and recommendations, 506–507
    - virus description, 505, 640
  - Human papillomavirus vaccine
    - acute disseminated encephalomyelitis, 507–508
    - amyotrophic lateral sclerosis, 513–515
    - anaphylaxis, 18, 515–516
    - brachial neuritis, 512–513
    - as cause of adverse events. *See* Causality, human papillomavirus vaccine
    - chronic inflammatory disseminated polyneuropathy, 512
    - current formulations, 506
    - cytokine imbalance and, 76
    - development, 506
    - Guillain-Barré syndrome, 511–512
    - hypercoagulable states, 520
    - multiple sclerosis, 510
    - neuromyelitis optica, 509
    - pancreatitis, 517–518
    - prevalence of use, 507
    - recommendations for, 506–507
    - summary of evidence and causality conclusions, 21*t*, 521*t*, 683*t*
    - thromboembolic events, 519–520
    - transient arthralgia, 516–517
    - transverse myelitis, 508
  - Hypercoagulable states
    - definition, 640
    - human papillomavirus vaccine and, 520, 521*t*
    - mechanism(s) that may contribute to symptoms of, 520
  - Hyperresponsiveness. *See* Biological mechanisms, pathophysiologies, and susceptibilities with the potential to contribute to adverse events
  - Hypersensitivity reactions. *See* Biological mechanisms, pathophysiologies, and susceptibilities with the potential to contribute to adverse events
- I**
- Immune complexes. *See* Biological mechanisms, pathophysiologies, and susceptibilities with the potential to contribute to adverse events
  - Immune thrombocytopenic purpura
    - definition, 640
    - DTaP vaccine and, 582–584, 588*t*
    - mechanism(s) that may contribute to symptoms of, 583
  - Immunocompromised individuals
    - complications of varicella zoster infection, 240
    - influenza vaccine recommendations in, 296
    - measles inclusion body encephalitis and MMR vaccine, 109–110
    - meningococcal disease, 600
    - treatment of varicella zoster infection in, 241
    - varicella vaccine and, 241–242, 244–249, 252–256, 258–262, 264–265, 630–631
  - Immunoglobulin E hypersensitivity. *See* Biological mechanisms, pathophysiologies, and susceptibilities with the potential to contribute to adverse events
  - Increased cytokines. *See* Biological mechanisms, pathophysiologies, and susceptibilities with the potential to contribute to adverse events
  - Increased susceptibility. *See* Biological mechanisms, pathophysiologies, and susceptibilities with the potential to contribute to adverse events

- Infant mortality, historical evolution, 27
- Infantile spasms  
 definition, 640  
 DTaP vaccine and, 537–539, 585*t*
- Influenza infection  
 acute disseminated encephalomyelitis, 308  
 all-cause mortality, 391  
 asthma exacerbation and, 295, 356, 366, 369  
 clinical description, 294–295, 641  
 complications, 294–295  
 encephalitis and, 299  
 Guillain-Barré syndrome, 333  
 mutagenesis, 293  
 myocardial infarction, 388  
 nomenclature, 293–294  
 onset or exacerbation of arthropathy and, 385  
 transmission, 294  
 transverse myelitis and, 309  
 vaccine development and  
   recommendations, 295–296  
 virus description, 293–294
- Influenza vaccine  
 acute disseminated encephalomyelitis, 308–309  
 all-cause mortality, 390–391  
 anaphylaxis, 18, 341–345  
 arthropathy, onset or exacerbation, 384–385  
 asthma exacerbation or reactive airway disease episodes in children and adults, inactivated influenza vaccine, 23, 345–356  
 asthma exacerbation or reactive airway disease episodes in children younger than 5 years of age, live attenuated influenza vaccine, 356–366  
 asthma exacerbation or reactive airway disease episodes in persons 5 years of age or older, live attenuated influenza vaccine, 366–373  
 Bell's palsy, 23, 335–337, 338–339*t*  
 brachial neuritis, 340  
*Campylobacter jejuni* contamination, 333  
 as cause of adverse events. *See* Causality, influenza vaccine  
 chronic inflammatory disseminated polyneuropathy, 334–335  
 development of, 295  
 encephalitis and encephalopathy, 296, 299–301  
 fibromyalgia, 389  
 formulations, 295  
 Guillain-Barré syndrome, 321–334  
 H1N1, 2*n*  
 multiple sclerosis onset in adults, 314–318  
 multiple sclerosis relapse in adults, 318–321  
 myocardial infarction, 387–389  
 neuromyelitis optica, 314  
 oculorespiratory syndrome, 18, 391–401, 632  
 optic neuritis, 18, 36, 310–313  
 polyarteritis nodosa, 383–384  
 recommendations for administration, 295–296  
 seizures, 2, 36, 301–304, 305–307*t*  
 small fiber neuropathy, 340–341  
 stroke, 386–387  
 summary of evidence and causality  
   conclusions, 20–22*t*, 402–404*t*, 678–680*t*  
 systemic lupus erythematosus onset or exacerbation, 373–379  
 transverse myelitis, 309–310  
 trivalent, definition, 295–296  
 vaccination rates, 296  
 vasculitis, onset or exacerbation, 379–383
- Injection of vaccine,  
 as cause of adverse event, evidence convincingly supporting, 18  
 as cause of adverse events. *See* Causality, injection-related adverse events  
 complex regional pain syndrome, 78–80, 615–617  
 deltoid bursitis, 80, 618–620, 632  
 summary of evidence and causality  
   conclusions, 21*t*, 625*t*, 687–688*t*  
 syncope, 80–81, 620–624, 632  
 Institute of Medicine, 1–2, 29–30, 39

## L

- Latency between antigen exposure and peak adaptive immune response.  
*See* Biological mechanisms, pathophysiologies, and susceptibilities with the potential to contribute to adverse events
- Lockjaw, 527

## M

- Manufacturers of vaccine, legislative relief from tort liability, 1, 28
- Measles, mumps, and rubella (MMR) vaccine
- acute disseminated encephalomyelitis, 153–154
  - afebrile seizures, 133–137
  - anaphylaxis, 18, 169–174, 631–632
  - arthropathy in men, 201–204
  - ataxia, 143–144
  - autism, 23, 88, 145–153
  - brachial neuritis, 168–169
  - causality conclusions. *See* Causality, MMR vaccine
  - chronic arthralgia in women, 190–195
  - chronic arthritis in women, 195–199
  - chronic arthropathy in children, 199–200
  - chronic fatigue syndrome, 212–213
  - chronic inflammatory disseminated polyneuropathy, 166–167
  - cytokine imbalance and, 76
  - encephalitis and encephalopathy, 111–119
  - febrile seizures, 18, 119–132, 630
  - fibromyalgia, 213–214
  - formulation, 107–108
  - Guillain-Barré syndrome, 165–166
  - hearing loss, 214–217
  - hepatitis, 211–212
  - measles inclusion body encephalitis, 18, 108–110
  - measles virus strain, 104
  - meningitis, 10, 36, 137–143
  - multiple sclerosis onset in adults, 159–164
  - multiple sclerosis onset in children, 164–165
  - mumps virus strain, 106
  - neuromyelitis optica, 10, 36, 158–159

- opsoclonus myoclonus syndrome, 167–168
  - optic neuritis, 2–10, 36, 156–158
  - prior reviews into adverse events, 1–2, 30
  - rubella virus strain, 107
  - summary of evidence and causality
    - conclusions, 20–22*t*, 218–221*t*, 674–677*t*
  - transient arthralgia in children, 18, 182–190
  - transient arthralgia in women, 174–181
  - transverse myelitis, 154–156
  - type 1 diabetes, 23, 204–211
- Measles, mumps, rubella, and varicella vaccine, 108, 242
- Measles inclusion body encephalitis
- definition, 641
  - mechanism(s) that may contribute to symptoms of, 110
  - MMR vaccine and, 18, 20*t*, 108–110, 218*t*
- Measles infection
- acute disseminated encephalomyelitis, 154
  - ataxia and, 144
  - clinical description, 103, 641
  - complications, 103
  - encephalitis and, 103, 117
  - encephalopathy and, 118
  - febrile seizures and, 132
  - Guillain-Barré syndrome and, 166
  - hearing loss and, 216
  - hepatitis and, 104, 212
  - measles inclusion body encephalitis and, 110
  - optic neuritis and, 157
  - transmission, 103
  - transverse myelitis and, 155
  - vaccine development and
    - recommendations, 104, 108
  - virus description, 103
  - See also* Measles, mumps, and rubella (MMR) vaccine
- Mechanistic evidence
- categorization of causality based on, 12–14, 45–48
- DTaP vaccine
- acute disseminated encephalomyelitis, 546–547
  - anaphylaxis, 563–565
  - arthropathy, 571
  - ataxia, 545

- autism, 546
- Bell's Palsy, 562
- chronic inflammatory disseminated polyneuropathy, 559–560
- chronic urticaria, 565–566
- encephalitis and encephalopathy, 536–537
- fibromyalgia, 581
- Guillain-Barré syndrome, 557–558
- immune thrombocytopenic purpura, 583
- infantile spasms, 538
- multiple sclerosis onset in adults, 553
- multiple sclerosis relapse in adults, 554–555
- multiple sclerosis relapse in children, 556–557
- myocarditis, 580
- opsoclonus myoclonus syndrome, 561
- optic neuritis, 549–550
- seizures, 541, 544
- serum sickness, 566–567
- sudden infant death syndrome, 582
- summary of evidence and causality
  - conclusions, 22*t*, 585–588*t*, 683–687*t*
- transverse myelitis, 548
- type 1 diabetes, 579
- hepatitis A vaccine
  - acute disseminated encephalomyelitis, 423–424
  - anaphylaxis, 428–429
  - autoimmune hepatitis, 429–430
  - Bell's palsy, 428
  - chronic inflammatory disseminated polyneuropathy, 427
  - Guillain-Barré syndrome, 426
  - multiple sclerosis, 425
  - summary of evidence and causality
    - conclusions, 431*t*, 680–681*t*
  - transverse myelitis, 424
- hepatitis B vaccine
  - acute disseminated encephalomyelitis, 440–441
  - anaphylaxis, 468–469
  - brachial neuritis, 467–468
  - chronic inflammatory disseminated polyneuropathy, 467
  - encephalitis and encephalopathy, 438
  - erythema nodosum, 470
  - fibromyalgia, 490
  - first demyelinating event in adults, 460, 463
  - first demyelinating event in children, 465
  - Guillain-Barré syndrome, 466
  - juvenile idiopathic arthritis, onset or exacerbation, 486–488
  - multiple sclerosis onset in adults, 450
  - multiple sclerosis onset in children, 455
  - multiple sclerosis relapse in adults, 456
  - multiple sclerosis relapse in children, 457–458
  - neuromyelitis optica, 446–447
  - optic neuritis, 444, 446
  - polyarteritis nodosa, onset or exacerbation, 477–479
  - psoriatic arthritis, onset or exacerbation, 480
  - reactive arthritis, onset or exacerbation, 480–482
  - rheumatoid arthritis, onset or exacerbation, 483–485
  - seizures, 439
  - summary of evidence and causality
    - conclusions, 20*t*, 491–493*t*, 681–683*t*
  - systemic lupus erythematosus, 472–473
  - transverse myelitis, 442–443
  - type 1 diabetes, 489
  - vasculitis, onset or exacerbation, 473–476
- human papillomavirus vaccine
  - acute disseminated encephalomyelitis, 507
  - amyotrophic lateral sclerosis, 514
  - anaphylaxis, 515–516
  - brachial neuritis, 513
  - chronic inflammatory disseminated polyneuropathy, 512
  - Guillain-Barré syndrome, 511
  - hypercoagulable states, 520
  - multiple sclerosis, 510
  - neuromyelitis optica, 509
  - pancreatitis, 518
  - summary of evidence and causality
    - conclusions, 21*t*, 521*t*, 683*t*
  - thromboembolic events, 519
  - transient arthralgia, 517
  - transverse myelitis, 508

- influenza vaccine
  - acute disseminated encephalomyelitis, 308
  - all-cause mortality, 390–391
  - anaphylaxis, 342–344
  - arthropathy, onset or exacerbation, 384–385
  - asthma exacerbation or reactive airway disease episodes in children and adults, inactivated influenza vaccine, 350, 356
  - asthma exacerbation or reactive airway disease episodes in children younger than 5 years of age, live attenuated influenza vaccine, 361, 366
  - asthma exacerbation or reactive airway disease episodes in persons 5 years of age or older, live attenuated influenza vaccine, 369, 373
  - Bell’s palsy, 337
  - brachial neuritis, 340
  - chronic inflammatory disseminated polyneuropathy, 334–335
  - encephalitis and encephalopathy, 299–300
  - fibromyalgia, 389
  - Guillain-Barré syndrome, 327, 333–334
  - multiple sclerosis onset in adults, 316
  - multiple sclerosis relapse in adults, 319, 321
  - myocardial infarction, 388
  - neuromyelitis optica, 314
  - oculorespiratory syndrome, 399–401
  - optic neuritis, 311, 313
  - polyarteritis nodosa, 383–384
  - seizures, 304
  - small fiber neuropathy, 341
  - stroke, 386–387
  - summary of evidence and causality conclusions, 20–22*t*, 401–404*t*, 678–680*t*
  - systemic lupus erythematosus, onset or exacerbation, 375, 378–379
  - transverse myelitis, 309
  - vasculitis, onset or exacerbation, 380, 382–383
- injection-related outcomes
  - complex regional pain syndrome, 615–617
  - deltoid bursitis, 618–620
  - summary of evidence and causality conclusions, 21*t*, 625*t*, 687–688*t*
  - syncope, 620–624
- meningococcal vaccine
  - acute disseminated encephalomyelitis, 604
  - anaphylaxis, 609
  - chronic headache, 610
  - chronic inflammatory disseminated polyneuropathy, 608
  - encephalitis and encephalopathy, 603
  - Guillain-Barré syndrome, 607
  - multiple sclerosis, 605–606
  - summary of evidence and causality conclusions, 20*t*, 611*t*, 687*t*
  - transverse myelitis, 605
- MMR vaccine
  - acute disseminated encephalomyelitis, 153–154
  - afebrile seizures, 134, 137
  - anaphylaxis, 169–174
  - arthropathy in men, 202
  - ataxia, 143–144
  - autism, 148, 153
  - brachial neuritis, 168–169
  - chronic arthralgia in women, 191, 193–194
  - chronic arthritis in women, 196, 198
  - chronic arthropathy in children, 199–200
  - chronic fatigue syndrome, 213
  - chronic inflammatory disseminated polyneuropathy, 167
  - encephalitis and encephalopathy, 116–119
  - febrile seizures, 124, 131–132
  - fibromyalgia, 213
  - Guillain-Barré syndrome, 165–166
  - hearing loss, 214–217
  - hepatitis, 212
  - measles inclusion body encephalitis, 109–110
  - meningitis, 139, 142–143
  - multiple sclerosis onset in adults, 161
  - multiple sclerosis onset in children, 165
  - neuromyelitis optica, 158–159



- opsochonus myoclonus syndrome, 167–168
- optic neuritis, 156–157
- summary of evidence and causality
  - conclusions, 20–22*t*, 218–221*t*, 674–677*t*
- transient arthralgia in children, 185, 190
- transient arthralgia in women, 176, 180–181
- transverse myelitis, 154–156
- type 1 diabetes, 207, 211
- varicella zoster vaccine
  - acute disseminated encephalomyelitis, 271
  - anaphylaxis, 276–278
  - arthropathy, onset or exacerbation, 278–279
  - cerebellar ataxia, 270
  - disseminated Oka VZV with
    - subsequent infection resulting in pneumonia, meningitis, or hepatitis, 251–256
  - disseminated Oka VZV without other organ involvement, 243–249
  - encephalopathy, 267
  - Guillain-Barré syndrome, 273–274
  - seizures, 269
  - small fiber neuropathy, 274–275
  - stroke, 280
  - summary of evidence and causality
    - conclusions, 19–20*t*, 283–284*t*, 677–678*t*
  - thrombocytopenia, 281–282
  - transverse myelitis, 272–273
  - vaccine strain viral reactivation with
    - subsequent infection resulting in meningitis or encephalitis, 263–266
  - vaccine strain viral reactivation without other organ involvement, 257–261
- weight-of-evidence evaluations, 12–14, 45–48
- Meningitis
  - definition, 641
  - mechanism(s) that may contribute to symptoms of, 143, 256, 266
  - MMR vaccine and, 10, 36, 137–143, 218*t*
  - varicella vaccine and, 19*t*, 251, 253, 255–256, 262, 263–267, 283*t*
- Meningococcal disease, 599–600
  - as cause of adverse events. *See* Causality, meningococcal vaccine
  - See* *Neisseria meningitidis*
- Meningococcal vaccine
  - acute disseminated encephalomyelitis, 603–604
  - anaphylactic reactions, 18
  - anaphylaxis, 608–610
  - chronic headache, 610
  - chronic inflammatory disseminated polyneuropathy, 607–608
  - development, 600–601
  - encephalitis and encephalopathy, 602–603
  - formulations, 601
  - Guillain-Barré syndrome, 606–607
  - multiple sclerosis, 605–606
  - summary of evidence and causality
    - conclusions, 20*t*, 611*t*, 687*t*
  - transverse myelitis, 604–605
  - vaccination rate, 601–602
- Meningococemia, 599
- Meningoencephalitis
  - definition, 641
  - influenza vaccine and, 299
- MMR. *See* Measles, mumps, and rubella vaccine
- Molecular mimicry. *See* Biological mechanisms, pathophysiologies, and susceptibilities with the potential to contribute to adverse events
- Mortality
  - infant, 27
  - influenza vaccine and all-cause mortality, 390–391
- Multiple sclerosis
  - definition, 641
  - DTaP vaccine and, 550–557, 586–587*t*
  - hepatitis A vaccine and, 425, 431*t*
  - hepatitis B vaccine and, 447–458, 491*t*
  - human papillomavirus vaccine and, 510, 521*t*
  - influenza vaccine and, 314–321, 402*t*
  - mechanism(s) that may contribute to symptoms of, 161, 165, 316, 321, 425, 450, 455, 456, 458, 510, 553, 555, 556, 606
  - meningococcal vaccine and, 605–606, 611*t*

- MMR vaccine and, 159–165, 219*t*  
 molecular mimicry, 71  
 onset in adults  
   DTaP vaccine, 550–553, 586*t*  
   hepatitis B vaccine and, 447–450, 451–453*t*, 491*t*  
   influenza vaccine and, 314–318, 402*t*  
   MMR vaccine and, 159–164, 219*t*  
 onset in children  
   hepatitis B vaccine and, 454–455, 491*t*  
   MMR vaccine and, 164–165, 219*t*  
 relapse in adults  
   DTaP vaccine, 554–555, 586*t*  
   hepatitis B vaccine and, 455–456, 491*t*  
   influenza vaccine and, 318–321, 402*t*  
 relapse in children  
   DTaP vaccine, 555–557, 587*t*  
   hepatitis B vaccine and, 457–458, 491*t*
- Mumps infection  
 acute disseminated encephalomyelitis, 154  
 ataxia and, 144  
 clinical description, 105, 641–642  
 complications, 105  
 encephalitis and, 105, 117  
 encephalopathy and, 118  
 febrile seizures and, 132  
 Guillain-Barré syndrome and, 166  
 meningitis and, 105, 142  
 hearing loss and, 105, 216  
 hepatitis and, 212  
 optic neuritis and, 157  
 transmission, 104–105  
 transverse myelitis and, 105, 155  
 type 1 diabetes and, 105, 211  
 vaccine development and  
   recommendations, 105–106, 108  
 virus description, 104  
*See also* Measles, mumps, and rubella (MMR) vaccine
- Myocardial infarction  
 definition, 642  
 influenza vaccine and, 387–389, 404*t*  
 mechanism(s) that may contribute to symptoms of, 388
- Myocarditis  
 definition, 642  
 DTaP vaccine and, 579–580, 588*t*  
 mechanism(s) that may contribute to symptoms of, 580
- Myoclonic epilepsy, 84, 642
- N**
- National Childhood Vaccine Injury Act, 1, 28–29
- National Vaccine Injury Compensation Program  
 purpose, 29  
 scientific basis for adjudication under, 30  
 scope of coverage, 1–2, 2*n*, 30*n*  
 structure, 29
- National Vaccine Program Office, 29
- Neisseria meningitidis*  
 bacteria description, 599  
 clinical description, 599  
 complications, 599, 600  
 nomenclature, 600  
 transmission, 599  
 vaccine development and  
   recommendations, 600–602
- Nested case-control studies  
 definition, 642  
 studies contributing to the weight of epidemiologic evidence, 302–303, 306*t*, 315, 317*t*, 324–325, 330*t*, 447–449, 451*t*, 452*t*, 551, 552*t*
- Neuraminidase surface proteins, 294
- Neuritis, definition of, 642
- Neuromyelitis optica  
 definition, 642  
 hepatitis B vaccine and, 446–447, 491*t*  
 human papillomavirus vaccine and, 509, 521*t*  
 influenza vaccine and, 314, 402*t*  
 mechanism(s) that may contribute to symptoms of, 158–159, 314, 447, 509  
 MMR vaccine and, 10, 36, 158–159, 219*t*
- Neuropathy, definition of, 642
- Northern California Kaiser Permanente Patients, 133–134, 135*t*, 175, 178*t*, 192*t*, 197*t*, 250, 268, 275, 438–439, 574, 578*t*, 618
- Nurses' Health Study, 447–448, 451*t*
- O**
- Oculorespiratory syndrome  
 definition, 642  
 influenza vaccine and, 18, 21*t*, 391–401, 404*t*, 632

- mechanism(s) that may contribute to symptoms of, 400
  - Opsoclonus myoclonus syndrome
    - definition, 642–643
    - DTaP vaccine and, 560–561, 587*t*
    - mechanism(s) that may contribute to symptoms of, 168, 561
    - MMR vaccine and, 167–168, 219*t*
  - Optic neuritis
    - definition, 643
    - DTaP vaccine and, 549–550, 586*t*
    - hepatitis B vaccine and, 443–446, 491*t*
    - influenza vaccine and, 310–313, 402*t*
    - mechanism(s) that may contribute to symptoms of, 157, 313, 446, 550
    - MMR vaccine and, 156–158, 219*t*
    - scope of review into vaccine events, 2, 10, 36
  - Orthomyxoviridae, 293
- P**
- Pancreatitis
    - definition, 643
    - human papillomavirus vaccine and, 517–518, 521*t*
    - mechanism(s) that may contribute to symptoms of, 518
  - Pertussis vaccine, acellular. *See* Acellular pertussis vaccine
  - Pertussis vaccine, whole cell
    - adverse event review, 1–2, 30, 530
    - development, 529
    - susceptibility to adverse events, 84
    - See also* Diphtheria toxoid, tetanus-toxoid, and acellular pertussis antigen-containing (DTaP) vaccines
  - Pneumonia
    - definition, 643
    - influenza infection and, 294–295
    - meningococcal infection and, 599
    - varicella vaccine and, 250–253, 255–256, 283*t*
    - varicella vaccine and mechanism(s) contributing to symptoms of, 256
  - Polio vaccine, 2, 28, 30
  - Polyarteritis nodosa
    - definition, 643
    - hepatitis B infection and, 67
    - hepatitis B vaccine and onset or exacerbation of, 477–479, 492*t*
    - influenza vaccine and, 383–384, 403*t*
    - mechanism(s) that may contribute to symptoms of, 67, 383–384, 479
  - Pregnancy, rubella infection in, 106–107
  - Preventive interventions
    - accomplishments, 27
    - evolution of vaccination programs, 27
  - ProQuad, 107–108, 242
  - Psychogenic factors in complex regional pain syndrome, 79
  - Purpura. *See* Immune thrombocytopenic purpura
- R**
- Randomized clinical trials, 43–44
  - Randomized controlled crossover trials, studies contributing to the weight of epidemiologic evidence, 392–393, 395–397*t*
  - Randomized controlled trials
    - contributing to the weight of epidemiologic evidence, 359–360, 365*t*, 367–368, 372*t*, 379–380, 381*t*
    - definition, 643
    - double blind randomized controlled trials
      - contributing to the weight of epidemiologic evidence, 175–176, 178–179*t*, 183–184, 188*t*, 190, 192*t*, 195, 197*t*, 318, 320*t*, 345, 347–348, 351*t*, 353*t*, 354*t*, 357–358, 362*t*, 367, 370–371*t*, 373–374, 376*t*, 516–517
  - Rechallenge reports
    - as an attribution element, 13, 46–47, 84
  - Research and development, vaccine, 28
  - Retrospective studies, 644
  - Rubivirus* (rubella infection)
    - acute disseminated encephalomyelitis, 154
    - arthropathy in men and, 106, 202
    - chronic arthralgia in women and, 106, 194
    - chronic arthritis in women and, 106, 198
    - chronic arthropathy in children and, 106, 200
    - clinical description, 106–107, 644
    - encephalitis, 106, 117
    - Guillain-Barré syndrome and, 106, 166

- hepatitis and, 212
  - optic neuritis and, 157
  - neuromyelitis optica, 158
  - transient arthralgia in children and, 106, 185
  - transient arthralgia in women and, 106, 181
  - transmission, 106
  - transverse myelitis and, 155
  - vaccine development and
    - recommendations, 107, 108
  - virus description, 106
  - See also* Measles, mumps, and rubella (MMR) vaccine
- S**
- Seizures
    - afebrile, definition, 635
    - definition, 644
    - DTaP vaccine and, 537–544, 585*t*
    - hepatitis B vaccine and, 438–440, 491*t*
    - influenza infection and, 294
    - influenza vaccine and, 2, 36, 301–304, 305–307*t*, 402*t*
    - mechanism(s) that may contribute to symptoms of, 68–70, 132, 269, 304, 439, 544
    - MMR vaccine and, 18, 20*t*, 119–137, 218*t*
    - varicella vaccine and, 268–269, 283*t*
    - See also* Febrile seizures; Infantile spasms
  - Self-controlled case-series study
    - definition, 644
    - studies contributing to the weight of epidemiologic evidence, 112, 115*t*, 121, 122–124, 128–130*t*, 145–146, 149–150*t*, 184, 188*t*, 323–324, 325, 329–330*t*, 336, 338*t*, 346, 352*t*, 386, 387–388, 449, 453*t*, 459, 462*t*, 539–540, 542*t*, 602
  - Sequential vaccination, 36
  - Serum sickness
    - definition, 644
    - DTaP vaccine and, 566–567, 587*t*
    - mechanism(s) that may contribute to symptoms of, 566–567
  - Shingles. *See* Herpes zoster
  - Shoulder pain and stiffness, 80
    - See also* Deltoid bursitis
  - Small fiber neuropathy
    - definition, 644
    - influenza vaccine and, 340–341, 402*t*
    - mechanism(s) that may contribute to symptoms of, 274–275, 341
    - varicella vaccine and, 10, 36, 274–275, 284*t*
  - Smallpox, 27
  - Special Masters, 2, 29, 30
  - Streptococcal infection
    - immune complexes, 67
    - molecular mimicry, 71
    - superantigens, 76
  - Streptococcus pneumoniae*, 61
  - Stroke
    - definition, 645
    - influenza vaccine and, 386–387, 403*t*
    - mechanism(s) that may contribute to symptoms of, 280, 386–387
    - varicella vaccine and, 10, 36, 279–280, 284*t*
  - Subunit vaccines, 59
  - Sudden infant death syndrome
    - definition, 645
    - DTaP vaccine and, 581–582, 588*t*
  - Superantigens. *See* Biological mechanisms, pathophysiologies, and susceptibilities with the potential to contribute to adverse events
  - Surveillance system for adverse events
    - definition and features, 645
    - legislation in support of, 1, 28–29
    - See also* Vaccine Adverse Event Reporting System (VAERS)
  - Susceptible individuals and populations
    - application to adverse event review, 24, 54
    - hypersensitivity mechanisms, 64–66
    - predispositions in, 82–84
    - See also* Genetic risk factors
  - Swine influenza vaccine, 321*n*
  - Syncope
    - clinical features, 80–81
    - definition, 645
    - injection-related adverse events, 620–624, 625*t*
    - mechanism(s) that may contribute to symptoms of, 623–624
    - as result of vaccine injection, 18

- See also* Biological mechanisms, pathophysiologies, and susceptibilities with the potential to contribute to adverse events
- Systemic lupus erythematosus  
 definition, 645  
 hepatitis B vaccine and, 471–473, 492*t*  
 immune complexes in, 67  
 influenza vaccine and, 373–379, 403*t*  
 mechanism(s) that may contribute to symptoms of, 67, 378, 473
- T**
- T cells. *See* Biological mechanisms, pathophysiologies, and susceptibilities with the potential to contribute to adverse events
- Tetanospasm, 527
- Tetanus infection, 527–528, 562, 645
- Tetanus toxoid-containing vaccines  
 anaphylactic reactions, 18  
 development, 528  
 effectiveness, 528  
 non-whole cell pertussis, 1*n*, 2  
 summary of evidence and causality conclusions, 20*t*, 22*t*, 585–588*t*, 683–687*t*
- See also* Diphtheria toxoid, tetanus-toxoid, and acellular pertussis antigen-containing (DTaP) vaccines
- Thrombocytopenia  
 definition, 645  
 mechanism(s) that may contribute to symptoms of, 282  
 varicella zoster vaccine and, 281–282, 284*t*
- Thromboembolic events  
 definition, 645  
 human papillomavirus vaccine and, 519–520, 521*t*  
 mechanism(s) that may contribute to symptoms of, 519
- Thromboembolism, definition of, 645
- Time interval between vaccine administration and adverse event case report evaluations, 13
- Vaccine Injury Table reporting requirements, 29
- Tissue responses. *See* Biological mechanisms, pathophysiologies, and susceptibilities with the potential to contribute to adverse events
- Transverse myelitis  
 definition, 646  
 DTaP vaccine and, 547–548, 586*t*  
 hepatitis A vaccine and, 424–425, 431*t*  
 hepatitis B vaccine and, 442–443, 491*t*  
 human papillomavirus vaccine and, 508, 521*t*  
 influenza vaccine and, 309–310, 402*t*  
 mechanism(s) that may contribute to symptoms of, 155, 273, 309, 424, 443, 508, 548, 605  
 meningococcal vaccine and, 604–605, 611*t*  
 MMR vaccine and, 154–156, 219*t*  
 varicella zoster vaccine and, 272–273, 284*t*
- Trismus, 527
- Type 1 autoimmune chronic hepatitis, 421–422
- U**
- Urticaria  
 definition, 646  
*See also* Chronic urticaria
- V**
- Vaccine Adverse Event Reporting System (VAERS), 29, 171–172, 215, 244–245, 257–258, 263, 276, 277, 281, 313, 335, 343–344, 382, 469, 474, 477, 515, 618–619, 622, 623, 631, 646
- Vaccine information statement (VIS), 29
- Vaccine Injury Table  
 purpose, 29
- Vaccine Safety Datalink (VSD), 111–112, 121, 156, 160, 170, 205–206, 262, 279, 301, 302, 303, 310, 315, 326, 336, 342, 348–349, 428, 443, 448, 458–459, 488, 535, 540, 551, 573, 646
- Vaccines, general  
 historical evolution, 27

- mechanism of action, 28, 57–59
- public health benefits, 28
- recognized risks, 28
- See also* Adverse events, generally;  
*specific vaccines*
- Varicella Vaccine Collaborative Study,  
241–242
- Varicella zoster vaccine
  - acute disseminated encephalomyelitis,  
271
  - anaphylaxis, 18, 20*t*, 275–278
  - arthropathy, onset or exacerbation,  
278–279
  - causality conclusions. *See* Causality,  
varicella zoster vaccine
  - as cause of adverse events. *See* Causality,  
varicella zoster vaccine
  - cerebellar ataxia, 269–270
  - development of, 241–242
  - disseminated Oka VZV with subsequent  
infection resulting in pneumonia,  
meningitis, or hepatitis, 249–256
  - disseminated Oka VZV without other  
organ involvement, 242–249
  - dosage, 242
  - encephalopathy, 267–268
  - Guillain-Barré syndrome, 273–274
  - in immunodeficient individuals, 241–242,  
245–248, 255, 630–631
  - limitations of data sources, 631
  - seizures, 268–269
  - small fiber neuropathy, 10, 36, 274–275
  - stroke, 10, 36, 279–280
  - summary of evidence and causality  
conclusions, 19–20*t*, 283–284*t*,  
677–678*t*
  - thrombocytopenia, 281–282
  - transverse myelitis, 272–273
  - vaccine strain viral reactivation with  
subsequent infection resulting in  
meningitis or encephalitis, 78,  
261–267
  - vaccine strain viral reactivation without  
other organ involvement, 18, 78,  
256–261
- Varicella zoster virus infection
  - acute disseminated encephalomyelitis  
and, 271
  - cerebellar ataxia and, 240, 270
  - clinical description, 239–240, 646
  - complications, 239–241
  - disseminated Oka VZV without other  
organ involvement and, 239, 248
  - disseminated Oka VZV with subsequent  
infection resulting in pneumonia,  
meningitis, or hepatitis and,  
239–240, 255
  - Guillain-Barré syndrome and, 240, 274
  - incidence, 240–241
  - stroke and, 280
  - thrombocytopenia, 239, 282
  - transmission, 239
  - transverse myelitis and, 240, 272
  - vaccine development and  
recommendations, 241–242
  - vaccine-strain viral reactivation with  
subsequent infection resulting in  
meningitis or encephalitis and,  
240, 266
  - vaccine-strain viral reactivation without  
other organ involvement and,  
240, 260
  - virus description, 239
- Vasculitis
  - definition, 646
  - hepatitis B vaccine and onset or  
exacerbation of, 473–477, 492*t*
  - influenza vaccine and onset or  
exacerbation of, 379–383, 403*t*
  - mechanism(s) that may contribute to  
symptoms of, 383, 476
- Viral activity. *See* Biological mechanisms,  
pathophysiologies, and  
susceptibilities with the potential  
to contribute to adverse events

## W

- Weight-of-evidence evaluations, 10–14,  
42–48
- Worldwide Adverse Event System, 244–245,  
257, 258, 263, 277

