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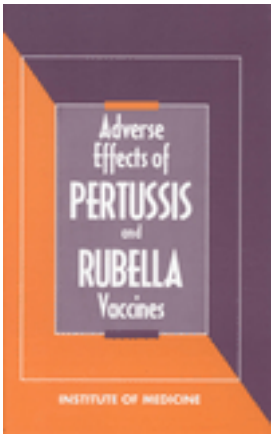

Adverse Effects of Pertussis and Rubella Vaccines

Christopher P. Howson, Cynthia J. Howe, and Harvey V. Fineberg, Editors;Committee to Review the Adverse Consequences of Pertussis and RubellaVaccines, Institute of Medicine

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A Report of the Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines

Christopher P. Howson, Cynthia J. Howe, and Harvey V. Fineberg, Editors

Division of Health Promotion and Disease Prevention
INSTITUTE OF MEDICINE

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This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The image adopted as a logotype by the Institute of Medicine is based on a relief carving from ancient Greece, now held by the Staatlichemusseen in Berlin.

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Preface

Although vaccines have markedly reduced the toll of many childhood illnesses, the practice of vaccination is not always without risk. Minor side effects are common, and serious side effects, although less numerous, have been observed on rare occasions with certain vaccines. Whether there are increased risks of serious adverse events following whole-cell pertussis and rubella vaccines, however, is controversial. The fact that pertussis and rubella vaccination is mandatory in many states has heightened public awareness of controversy and concern about the safety of the two vaccines.

In response to concerns about possible adverse consequences of legally mandated vaccines, the U.S. Congress in 1986 passed the National Childhood Vaccine Injury Act (Public Law 99-660), followed by the Vaccine Compensation Amendments of 1987 (Public Law 100-203). The core of the legislation was the establishment of a federal compensation scheme for persons potentially injured by vaccines, to be funded by excise taxes imposed on manufacturers of vaccines. In addition, Section 312 of Public Law 99-660 also called for a review of scientific and other information on possible adverse consequences of the pertussis and rubella vaccines. The Institute of Medicine (IOM) was specifically asked to conduct this review, and funds coordinated by the National Institute of Allergy and Infectious Diseases were made available for this purpose in September 1989.

In November 1989, IOM established the Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines. The specific charge

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to the committee, as outlined in Section 312 of the National Childhood Vaccine Injury Act, was to:

- identify and review all available medical and scientific literature on the nature, circumstance, and extent of the relationship, if any, between vaccines containing pertussis (including whole cells, extracts, and specific antigens) and the following illnesses and conditions: hemolytic anemia, hypsarrhythmia, infantile spasms, Reye syndrome, peripheral mononeuropathy, deaths classified as sudden infant death syndrome (SIDS), aseptic meningitis, juvenile diabetes, autism, learning disabilities, hyperactivity, and other such illnesses as recommended by the committee or the Advisory Commission on Childhood Vaccines, and inquire into the possible association between pertussis vaccines and permanent neurologic damage;
- conduct a similar review of the potential relationship between rubella vaccines (including the measles-mumps-rubella combination vaccine) and radiculoneuritis;
- sponsor a workshop on pertussis and rubella vaccines that shall include invited researchers and experts on vaccine-related illness and conditions;
- conduct a public meeting covering both pertussis and rubella vaccines to obtain information from a variety of interested parties; and
- prepare a report that presents the committee's assessment of evidence and conclusions about the possible association between pertussis and rubella vaccines and these specific adverse events.

At its first meeting in January 1990, the committee voted to add chronic arthritis to the list of adverse events to be examined with respect to rubella vaccines. In May 1990, at the request of the Advisory Commission on Childhood Vaccines, the committee agreed to consider seven additional adverse events: anaphylaxis; erythema multiforme or other rashes; GuillainBarrè syndrome (polyneuropathy); protracted inconsolable crying or screaming; thrombocytopenia; and shock and "unusual shock-like state" with hypotonicity, hyporesponsiveness, and short-lived convulsions (usually febrile), with respect to pertussis vaccines; and thrombocytopenic purpura, with respect to rubella vaccines.

The 11-member interdisciplinary committee appointed to conduct the study included individuals with expertise in infectious diseases, pediatrics, internal medicine, neurology, epidemiology, biostatistics, decision analysis, biologic mechanisms of vaccines, immunology, and public health. During the course of the 20-month study, the committee examined a wide range of information sources, including case series and individual case reports published in peer-reviewed journals and reported by vaccine manufacturers; unpublished case reports from physicians, parents, and other concerned persons; epidemiologic studies; studies in animals; and other laboratory studies. Whenever possible, the committee examined primary sources of data.

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Other works, for example, the *Report of the Task Force on Pertussis and Pertussis Immunization—1988* published in 1988 by the American Academy of Pediatrics, *DPT: A Shot in the Dark* published in 1985 by Coulter and Fisher, and the 1985 Institute of Medicine report *Vaccine Supply and Innovation* provided secondary sources of information. The committee also considered a variety of other data sources, including conference and symposium proceedings, legal judgments, and academic dissertations. By drawing on a variety of information sources, the committee has attempted to ensure a comprehensive and critical review.

The committee held five meetings during which it evaluated the literature and prepared its general review and summary. A public meeting convened at the outset of the study served as a forum for open discussion and presentation of views and information by individual scientists and by representatives of medical specialty organizations, parent groups, vaccine manufacturers, and the legal community.

The committee also conducted one workshop during which it interacted with and shared the expertise and research findings of a larger community of scientists representing a range of views on topics pertinent to the committee's charge. The workshop provided an opportunity for the committee members to consider new or controversial data and various points of view and to identify gaps in knowledge. The subjects considered in the workshop included the time course of events following pertussis or rubella vaccination, variations in pertussis and rubella vaccine compositions and their implications for evaluating possible adverse events following vaccination, evidence concerning the possible relationship of pertussis vaccines to irreversible encephalopathy and sudden infant death syndrome, and evidence concerning any relationship of rubella vaccines to radiculoneuritis, peripheral neuropathy, and chronic arthritis.

The committee's report is presented in seven chapters and six appendixes. The report also includes a glossary of terms and a bibliography of information sources. Chapter 1 provides an executive summary of the report. Chapter 2 offers a brief history of the development of pertussis and rubella vaccines and of the controversy concerning their possible associations with severe adverse events. Chapter 3 details the methodologic considerations of the committee in its evaluation of the evidentiary base. Chapters 4 through 6 present the evidence pertaining to pertussis vaccines and specific adverse events, and Chapter 7 presents evidence pertaining to rubella vaccine and specific adverse events. An afterword on research needs follows Chapter 7. Appendix A describes the strategies the committee used to gather its information. Appendix B provides a brief chronology of pertussis and rubella vaccines. Appendix C discusses animal models used in studying pertussis and in the testing of vaccines. Appendix D describes the technical details of the committee's power calculations and meta-analyses.

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Appendix E discusses the possible involvement of aluminum salts in adverse events following pertussis immunization. Appendix F provides brief biographies of committee members. In preparing its report, the committee recognized that its charge was to focus on questions of causation and not broader, although important, topics, such as cost-benefit or risk-benefit analyses of vaccination.

We hope that this report will provide a foundation of evidence and methods that may also be useful to others concerned with assessing the safety of vaccines.

Harvey V. Fineberg, *Chairman*

Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines

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tious Diseases; Daniel Lahn, National Vaccine Program; Leonard P. Kurland, Mayo Clinic; John R. LaMontagne, National Institute of Allergy and Infectious Diseases; Stephan Lawton, Reed, Smith, Shaw & McClay; Charles R. Manclark, Food and Drug Administration; Cynthia McCormick, Vaccine Injury Compensation Program; David L. Miller, St. Mary's Hospital Medical School, London; John Mullen, Centers for Disease Control; J. Anthony Morris, The Bell of Atri, Inc.; Edward A. Mortimer, Jr., Case Western Reserve University School of Medicine; Yuth Nimit, National Vaccine Program; Walter A. Orenstein, Centers for Disease Control; Georges Peter, Rhode Island Hospital; Stanley A. Plotkin, Pasteur Mèrieux Connaught Company; Keith Redhead, National Institute for Biological Standards and Control; Joseph Reini, Embassy of Finland; Noel R. Rose, The Johns Hopkins School of Hygiene and Public Health; Jeffrey Schwartz, Jellinek, Schwartz, Connolly & Freshman, Inc.; John Sladky, Children's Hospital of Philadelphia; Martin Smith, pediatrician; Mark E. Thoman, Iowa Poison Control Center; Dirk Teuwen, SmithKline Biologicals; Puru Thapa, University of Washington; Aubrey Tingle, British Columbia Children's Hospital; Alexander Walker, Harvard School of Public Health; Steven G. Wassilak, Centers for Disease Control; Jeanette Wilkins, University of Southern California School of Medicine; and Arthur C. Zahalsky, Southern Illinois University.

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1

Executive Summary

Next to clean water, no single intervention has had so profound an effect on reducing mortality from childhood diseases as has the widespread introduction of vaccines. Immunization, the process in which the body's own protective mechanisms are primed to thwart the invasion or multiplication of pathogens, is effective and relatively inexpensive, simple, and easy to deliver.

The use of vaccines is not entirely without risk, however. Vaccines, including the whole-cell pertussis (whooping cough) vaccine and the rubella (German measles) vaccine, the subjects of this report, typically contain small quantities of material derived from disease-causing organisms. The pertussis vaccine contains dead bacteria and is termed a *killed* or *inactivated vaccine;* the rubella vaccine contains laboratory-weakened live viruses and is termed a *live, attenuated vaccine.*

This study responds to a request to the Institute of Medicine (IOM) to conduct a thorough review of the evidence pertaining to a set of serious adverse events and immunization with pertussis or rubella vaccine. The request to IOM originated in the 1986 National Childhood Vaccine Injury Act (Public Law 99-660), whose primary purpose was to establish a federal compensation scheme for persons potentially injured by a vaccine. Section 312 of Public Law 99-660 called for IOM review of scientific and other information on specific adverse consequences of pertussis and rubella vaccines. The 11-member interdisciplinary committee, constituted

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by IOM to conduct this study, recognized that its charge was to focus on questions of causation and not broader topics, such as cost-benefit or risk-benefit analyses of vaccination. These topics are therefore not addressed in the report.

After formation of the committee, additional adverse events were added both by the committee and at the request of the Advisory Commission on Childhood Vaccines. During the 20 months of the study, the committee reviewed altogether *17 adverse events for pertussis vaccine—infantile* spasms; hypsarrhythmia; aseptic meningitis; encephalopathy (including acute encephalopathy and chronic neurologic damage); deaths classified as sudden infant death syndrome (SIDS); anaphylaxis; autism; erythema multiforme or other rashes; Guillain-Barrè syndrome (polyneuropathy); peripheral mononeuropathy; hemolytic anemia; juvenile diabetes; learning disabilities and hyperactivity; protracted inconsolable crying or screaming; Reye syndrome; shock and "unusual shock-like state" with hypotonicity, hyporesponsiveness, and short-lived convulsions (usually febrile); and thrombocytopenia—and *3 adverse events for rubella vaccine—arthritis* (acute and chronic); radiculoneuritis and other neuropathies; and thrombocytopenic purpura. Although the committee was not asked expressly to examine febrile seizures, afebrile seizures, or epilepsy in relation to diphtheria-pertussis-tetanus (DPT) vaccine, it did so because these conditions may also be serious and are considered by some to be components of encephalopathy. Conclusions regarding these conditions are given in Chapter 4. The committee's conclusions on acute encephalopathy, also presented in Chapter 4, refer only to conditions diagnosed as encephalopathy, encephalitis, or encephalomyelitis. (For additional information on the committee's charge and the events leading to the enactment of Public Law 99-660, see the Preface and Appendix B, Pertussis and Rubella Vaccines: A Brief Chronology.)

The following three sections of this summary briefly review the methods used by the committee to evaluate the evidence relating the 20 adverse events to pertussis or rubella vaccine, the evidence considered and the conclusions reached for each adverse event, and the research directions recommended by the committee.

METHODOLOGIC CONSIDERATIONS IN EVALUATING THE EVIDENCE

The committee undertook the task of judging whether each of a set of adverse events can occur as a result of exposure to pertussis or rubella vaccine. These judgments have both quantitative and qualitative aspects; they reflect the nature of the exposures, events, and populations at issue; the specific questions to be considered; the characteristics of the evidence examined; and the approach taken to evaluate that evidence. To facilitate the

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independent assessment of the committee's conclusions, the committee wishes to make the process of its evaluation as explicit as possible.

The adverse events under consideration by the committee are, in most instances, rare in the exposed population. They also are known to occur in the absence of vaccination, are clinically ill-defined, and are generally of unknown causation in the general population. The exposures—pertussis and rubella vaccinations—are very widespread in the population, so that the absence of exposure may itself require an explanation in the interpretation of comparative studies. These and other features raise a number of difficulties both in the investigation and in the evaluation of the resulting evidence.

The committee considered causal questions of three kinds in connection with adverse events that have been reported to occur after administration of pertussis or rubella vaccine. The first of these questions about exposure to pertussis or rubella vaccine is, in general, *can it cause* the specified adverse condition? For example, can rubella vaccine cause chronic arthritis? If the conclusion is affirmative, a second question becomes pertinent: *How frequently does it cause* that condition? Or, how frequently is arthritis a result of rubella vaccination? The third question, which applies to a particular instance or case of an adverse event, is *did it cause* that specific event? Or, did rubella vaccine cause this particular individual to develop arthritis? The committee has undertaken its evaluation from a neutral posture, presuming neither the existence nor the absence of association between these vaccines and the events under consideration.

The identification and acquisition of the relevant evidence were major tasks of the committee throughout the course of its work. The preponderance of this material comprised either reports of controlled, observational epidemiologic studies (case-comparison or cohort studies) or uncontrolled case reports or case series. There was no experimental evidence, whether in humans or animals, that clearly proved or disproved a causal relation. Each study or report reviewed by the committee was first assessed individually and then, as appropriate, incorporated into the collective results that underlie the committee's conclusions.

Both quantitative and qualitative approaches to integration of the evidence were utilized. Formal meta-analysis was applied when it was feasible and appropriate. All of the studies were assessed insofar as possible with respect to the roles of error, bias, confounding, and chance in producing the observed results. Several considerations bearing on the inference that an association may reflect a true causal relation were also included in the committee's evaluation of the overall body of evidence pertaining to each type of adverse event under review. These included the strength of association, temporal relation between exposure and event, consistency of results between studies, specificity of the relation between exposure and event, and biologic plausibility of such a relation.

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SUMMARY AND CONCLUSIONS

Table 1-1 summarizes the categories of evidence reviewed for each adverse event and the respective contribution of each to the committee's judgments about causation. The evidence is organized under five headings: (1) human experiments; (2) animal experiments; (3) case-comparison, cohort, and other controlled studies, (4) case reports and case series; and (5) biologic plausibility. Methods for interpreting evidence in the first four categories are discussed in Chapter 3. The fifth category, biologic plausibility, includes background knowledge concerning the pathophysiology of an adverse event, attributes of a particular vaccine, or other biologic information derived from research in such areas as immunology and physiology. The evidence in these five categories, elaborated in the body of the report, forms the basis of the committee's conclusions.

Where evidence was available in a particular category, the committee judged whether that evidence was generally supportive or not supportive of causation or whether it was insufficient for a determination. For example, where there were relevant controlled studies which, overall, found relative risks greater than 1, the evidence was classified as "supportive of causation." Blanks for any given category of evidence indicate that evidence of that type was lacking. It is important to note that any one category of evidence generally was not sufficient in itself to support a conclusion of causality, since other aspects of the evidence, including the details of the results and the number and quality of contributing studies, as well as the assessment of the other categories of evidence, were also considered in the evaluation.

Table 1-2 summarizes the committee's conclusions about the 20 adverse events evaluated in this report. As shown in the table, the committee found it convenient to organize its conclusions about the adverse events into five categories. These categories reflect the strength and direction of the conclusions about the causal relations between DPT or rubella vaccine and the 20 adverse events evaluated in the report. The bases of these conclusions are discussed in Chapters 4 through 7 of the report. Conclusions on rubella vaccine apply to the RA 27/3 rubella strain currently in use. Evidence does not differentiate between DPT vaccine and the pertussis component of DPT vaccine, except in the case of protracted crying (see below). As shown in Table 1-2, the committee found:

- no evidence bearing on a causal relation between DPT vaccine and autism;
- insufficient evidence to indicate a causal relation between DPT vaccine and aseptic meningitis, chronic neurologic damage, erythema multiforme or other rash, Guillain-Barrè syndrome, hemolytic anemia, juvenile diabetes, learning disabilities and attention deficit disorder, peripheral mononeurop

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TABLE 1-1 Categories of Evidence Reviewed for Each Adverse Event: Is the Evidence Supportive of Causation?[a]

Vaccine and Adverse Event (Chapter of Report)	Human Experiments			Animal Experiments			Case-Comparison, Cohort, and Other Controlled Studies			Case Reports and Case Series			Biologic Plausibility		
	Yes[b]	?[c]	No[d]	Yes	?	No	Yes	?	No	Yes	?	No	Yes	?	No
DPT															
Infantile spasms (4)									X		X				
Hypsarrhythmia (4)			X								X				
Aseptic meningitis (4)								X			X				
Acute encephalopathy[e] (4)					X		X			X				X	
Chronic neurologic damage (4)					X			X			X			X	
Sudden infant death syndrome (5)									X		X				
Anaphylaxis (6)					X			X		X			X		
Autism (6)															
Erythema multiforme or other rash (6)											X		X		
Guillain-Barré syndrome (polyneuropathy) (6)											X				
Peripheral mononeuropathy (6)											X				
Hemolytic anemia (6)											X		X		
Juvenile diabetes (6)					X			X			X				
Learning disabilities and hyperactivity (6)									X		X				
Protracted inconsolable crying and screaming (6)							X			X			X		
Reye syndrome (6)								X				X			

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Vaccine and Adverse Event	Human Experiments			Animal Experiments			Case-Comparison Cohort, and Other Controlled Studies			Case Reports and Case Series			Biologic Plausibility		
(Chapter of Report)	Yes[b]	?[c]	No[d]	Yes	?	No	Yes	?	No	Yes	?	No	Yes	?	No
Shock and "unusual shock-like state" (6)								X		X				X	
Thrombocytopenia (6)											X				
RA 27/3 Rubella Arthritis (7)															
Acute	X									X			X		
Chronic		X					X			X			X		
Radiculoneuritis and other neuropathies (7)											X		X		
Thrombocytopenic purpura (7)											X		X		

[a] Blanks for any given category of evidence indicate that evidence of this kind is lacking.

[b] Yes, Evidence of this kind is supportive of causation.

[c] ?, Evidence of this kind cannot be classified either as supportive or as not supportive of causation.

[d] No, Evidence of this kind is not supportive of causation.

[e] Defined in controlled studies reviewed as encephalopathy, encephalitis, or encephalomyelitis.

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TABLE 1-2 Summary of Conclusions by Adverse Event for DPT[a] and RA 27/3 MMR[b] Vaccines

Conclusion	Adverse Events Reviewed	
	DPT Vaccine	RA 27/3 Rubella Vaccine
1. No evidence bearing on a causal relation[c]	Autism	
2. Evidence insufficient to indicate a causal relation[d]	Aseptic meningitis Chronic neurologic damage Erythema multiforme or other rash Guillain-Barré syndrome Hemolytic anemia Juvenile diabetes Learning disabilities and attention-deficit disorder Peripheral mononeuropathy Thrombocytopenia	Radiculoneuritis and other neuropathies Thrombocytopenic purpura
3. Evidence does not indicate a causal relation[e]	Infantile spasms Hypsarrythmia Reye syndrome Sudden infant death syndrome	
4. Evidence is consistent with a causal relation[f]	Acute encephalopathy[g] Shock and "unusual shock-like state"	Chronic arthritis
5. Evidence indicates a causal relation[h]	Anaphylaxis Protracted, inconsolable crying	Acute arthritis

[a]Evidence does not differentiate between DPT vaccine and the pertussis component of DPT vaccine except in the case of protracted, inconsolable crying where the evidence implicates the pertussis component specifically.

[b]RA 27/3 MMR, Trivalent measles-mumps-rubella vaccine containing the RA 27/3 rubella strain.

[c]No category of evidence was found bearing on a judgment about causation (all categories of evidence left blank in Table 1-1).

[d]Relevant evidence in one or more categories was identified but was judged to be insufficient to indicate whether or not a causal relation exists (no category of evidence checked as supporting causation in Table 1-1; exceptions are this designation under biologic plausibility for erythema multiforme and hemolytic anemia).

[e]The available evidence, on balance, does not indicate a causal relation (one or more categories of evidence checked as not supporting causation in Table 1-1, with evidence supporting causation being either absent or outweighed by the other evidence).

[f]The available evidence, on balance, tends to support a causal relation (one or more categories of evidence checked as supporting causation in Table 1-1, with evidence checked as insufficient or not supporting causation being absent or outweighed by the other evidence).

[g]Defined in controlled studies reviewed as encephalopathy, encephalitis, or encephalomyelitis.

[h]The available evidence, on balance, supports a causal relation, and the evidence is more persuasive than that for conclusion 4 above (the categories of evidence are coded similarly to those in conclusion 4, with evidence checked as insufficient or not supporting causation in Table 1-1 being absent or less than for 4).

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- athy, or thrombocytopenia, and between the currently used rubella vaccine (RA 27/3) and radiculoneuritis and other neuropathies or thrombocytopenic purpura;
- that the evidence does not indicate a causal relation between DPT vaccine and infantile spasms, hypsarrythmia, Reye syndrome, or SIDS;
- that the evidence is consistent with a causal relation between DPT vaccine and acute encephalopathy and shock and "unusual shock-like state," and between RA 27/3 rubella vaccine and chronic arthritis; and
- that the evidence indicates a causal relation between DPT vaccine and anaphylaxis, between the pertussis component of DPT vaccine and protracted, inconsolable crying, and between RA 27/3 rubella vaccine and acute arthritis.[1]

RESEARCH NEEDS

In the course of its review, the committee encountered many gaps and limitations in knowledge bearing directly and indirectly on the safety of vaccines. These include inadequate understanding of the biologic mechanisms underlying adverse events following natural infection or immunization, insufficient or inconsistent information from case reports and case series, inadequate size or length of follow-up of many population-based epidemiologic studies, and limited capacity of existing surveillance systems of vaccine injury to provide persuasive evidence of causation. The committee found few experimental studies published in relation to the number of epidemiologic studies published. Clearly, if research capacity and accomplishment in these areas are not improved, future reviews of vaccine safety will be similarly handicapped.

With respect to pertussis and rubella vaccines, careful review is needed to identify what sorts of questions might be best answered by further investigations and which kinds of studies could be carried out economically. The availability and introduction of new forms of pertussis vaccine, for example, could offer valuable opportunities for comparison of vaccine safety as well as efficacy. The committee's experience points to fresh possibilities and to the need for such a review.

[1] The available evidence is consistent with a causal relation, but, on balance, is more persuasive than that in the previous bullet.

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2

Histories of Pertussis and Rubella Vaccines

PERTUSSIS VACCINES

Epidemiology of Whooping Cough

Clinical Description

Pertussis, or whooping cough,[1] is a serious epidemic respiratory infection caused by *Bordetella pertussis,* a gram-negative bacillus. Pertussis is characterized by a paroxysmal, spasmodic cough that usually ends in a prolonged, high-pitched crowing inspiration or whoop (American Academy of Pediatrics, 1986; Berkow, 1987; Cherry et al., 1988; Mortimer, 1988). Children are most commonly affected, although there are current indications that the disease, in a milder form, may be more prevalent in adults than was previously believed (Aoyama et al., 1990; Farizo et al., 1990). In fact, evidence suggests that immunized[2] adults in developed nations are the most common source of pertussis infections in neonates and children (Nelson, 1978).

The first recorded description of a pertussis epidemic was made by a Parisian, Guillaume de Baillou, in 1578 (Holmes, 1940). His characterization of the disease is graphic.

[1] The terms *pertussis* and *whooping cough* are used interchangeably throughout this report.

[2] The terms *immunization* and *vaccination* are used interchangeably throughout this report.

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> The lung is so irritated by every attempt to expel that which is causing the trouble it neither admits the air nor again easily expels it. The patient is seen to swell up and as if strangled holds his breath tightly in the middle of his throat . . . For they are without the troublesome coughing for the space of four or five hours at a time, then this paroxysm of coughing returns, now so severe that blood is expelled with force through the nose and through the mouth. Most frequently an upset stomach follows. . . . For we have seen so many coughing in such a manner, in whom after a vain attempt semiputrid matter in an incredible quantity was ejected.

Opinions differ as to why a clinically characteristic disease like pertussis was not described prior to de Baillou's description. Kloos and colleagues (1981) suggest that the absence of a clinical description of pertussis prior to the sixteenth century may reflect adaptation of a close genetic variant of *B. pertussis* to humans as recently as five centuries ago. Holmes (1940), in contrast, as noted by Mortimer (1988), attributed the lack of a prior description to an earlier preoccupation of physicians with other serious infections such as plague, smallpox, and typhus and to the possibility that they may have relegated the care of pertussis patients to "old women."

The incubation period of unmodified pertussis averages 7 to 14 days, with a maximum of 21 days (Berkow, 1987). Clinically, pertussis can be divided into three sequential stages: the catarrhal, paroxysmal, and convalescent stages (Cherry et al., 1988; Mortimer, 1988). The onset of illness in the early catarrhal stage is subtle and is generally indistinguishable from that of a minor upper-respiratory infection. Early symptoms include rhinorrhea, mild conjunctival injection, sneezing, anorexia, listlessness, and a hacking nocturnal cough that gradually becomes diurnal as well. Fever is usually absent. During this time, coughing continues to increase in frequency and intensity and, by 7 to 10 days after the onset of illness, becomes explosive and episodic, heralding the onset of the paroxysmal stage. The disease is most infectious during the catarrhal stage, after which infectivity gradually declines.

The paroxysmal stage, which lasts 1 to 4 weeks, is dominated by severe episodes of coughing, which can occur 10 times or more in a 24-hour period. Each paroxysm is characterized by five or more rapid short coughs followed by a deep hurried inspiration. It is this hurried inspiration through a narrowed airway that produces the characteristic whoop.

Paroxysms are thought to be caused by efforts to expel the thick mucus that characteristically accumulates in the tracheobronchial tree. During such episodes, copious amounts of this mucus are expelled, often causing vomiting and, in infants, choking spells and cyanosis. The child is often exhausted following a paroxysm, although he or she can appear happy and relatively normal between episodes. Multiple paroxysms tend to occur within

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a short period of time. A variety of stimuli, including feeding, sucking, or crying, can trigger an attack. Very young infants tend to have apneic spells rather than paroxysms of cough.

The convalescent stage, which usually begins 4 to 6 weeks after the onset of disease, is characterized by a gradually diminishing frequency and severity of paroxysms. The whoop soon disappears, although a nonparoxysmal cough may persist for several months.

Diagnosis

B. pertussis can be cultured by inoculation of nasopharyngeal mucus, obtained by swab, on special agar such as Bordet-Gengou with added methicillin or Regan-Lowe with added cephalexin. A positive culture is diagnostic. False-negative cultures are common, particularly in persons receiving antibiotics (Berkow, 1987). *B. pertussis* can also be detected by direct immunofluorescence, although the test has been hampered by relatively frequent false-positive and false-negative results (Wirsing von König et al., 1990). Serologic tests, including enzyme-linked immunosorbent assays, to detect antibody to filamentous hemagglutinin (FHA) and other *B. pertussis* components are being developed for diagnostic purposes (Berkow, 1987; Storsaeter et al., 1990; Wirsing von König et al., 1990). Probing for *Bordetella* DNA, either directly or after preliminary amplification by the polymerase chain reaction or culture, may provide another useful means of detection (Wirsing von König et al., 1990).

Complications

Minor complications of pertussis include subconjunctival hemorrhages and epistaxis secondary to the paroxysmal coughing. Suppurative otitis media is a frequent complication, especially in infants (Mortimer, 1988).

Major complications of pertussis can be fatal. They are divided into three general categories: respiratory, central nervous system (CNS), and nutritional. The most common are respiratory, including asphyxia in infants. Other severe respiratory complications include bronchopneumonia, a frequent complication in elderly people, atelectasis, bronchiectasis, interstitial and subcutaneous emphysema, and pneumothorax.

CNS complications following pertussis include acute encephalitis that can progress to convulsions, stupor, and coma. Pathologic findings reveal cerebral hemorrhage and edema (Dolgopol, 1941). Long-term sequelae include spastic paralysis, mental retardation, or other permanent neurologic disorders. Rates of CNS complications differ widely among studies. For example, 1.7 to 7 percent or more of pertussis cases in large series of hospitalized children developed CNS complications (Zellweger, 1959), whereas

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the incidence rates of encephalopathy[3] ranged from an estimated 0.08 per 1,000 cases in a case series collected from 1932 to 1946 in Brooklyn, New York (Litvak et al., 1948; Mortimer, 1988), to 0.8 per 1,000 cases in the National Childhood Encephalopathy Study (Alderslade, 1981). Current data from the Supplementary Pertussis Surveillance System (SPSS) of the U.S. Centers for Disease Control (CDC) indicate that of the 8,682 total cases reported to the CDC from 1986 to 1988, 0.7 percent were diagnosed with encephalopathy and 1.8 percent were diagnosed with seizures (Centers for Disease Control, 1990). The accuracy of these figures, however, is uncertain because the CDC estimates that only 5 to 10 percent of pertussis cases in the United States during this time period were captured by SPSS (Centers for Disease Control, 1990).

Nutritional deficiencies seen with pertussis result directly from the inability of patients to retain feedings. Feeding precipitates paroxysms of coughing which in turn produces repeated vomiting (Mortimer, 1988). The combination of the disease and malnutrition can lead to death.

Descriptive Epidemiology

Ecology of B. pertussis *B. pertussis* is transmitted by direct respiratory contact with infected persons in the catarrhal or early paroxysmal stage of disease (Berkow, 1987). Humans are the sole host. Indirect transmission by contact with the organism on fomites or on dust is rare (Mortimer, 1988). Pertussis is highly infectious; attack rates in nonimmunized populations have been reported to range from 25 to 50 percent in schools and from 70 to 100 percent in susceptible household contacts (Centers for Disease Control, 1985; Gordon and Hood, 1951; Kendrick, 1940; Linnemann, 1979). Epidemiologic and laboratory studies suggest that natural pertussis infection confers vigorous, long-lasting immunity (Gordon and Hood, 1951; Huang et al., 1962; Stallybrass, 1931). The chronic carrier state appears to be extremely rare and is not a factor in disease transmission (Cherry et al., 1988; Lambert, 1986; Linnemann et al., 1968). Pertussis is an epidemic disease, occurring every 2 to 5 years in endemic areas, with an average interval of 3.3 years (Cherry, 1984). No consistent seasonal pattern has

[3] Encephalopathy as defined by Zellweger (1959) follows two clinical forms. "The first form begins suddenly with convulsions, followed by a state of unconsciousness or coma with varying neurological symptoms. In the second form, the onset is more insidious; the temperature rises within a few days to a high fever, even to hyperpyrexia, the patients become progressively somnolent, comatose and even unconscious. In this form convulsions, as well as other neurological symptoms, as paresis, hemiplegia, paraplegia, motor aphasia, and decerebrate rigidity may appear. Exceptionally pertussis encephalopathy imitates an acrodynia-like picture of a confused state" (Zellweger and Steinegger, 1950, pp. 381-382).

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been identified (Friedlander, 1925; Kanai, 1980; Luttinger, 1916; Mortimer, 1988; Nelson, 1978).

Distribution by Person Pertussis can occur at any age. Prior to mass immunization, an estimated 95 percent of people contracted pertussis during their lifetimes (Gordon and Hood, 1951), with 20 percent of cases seen in children under age 1 year and 60 percent occurring in children from ages 1 to 4 years (Luttinger, 1916). After the introduction of widespread immunization, age-specific attack rates shifted upward. The CDC's SPSS indicates that for the years 1986 to 1988, 46 percent of cases in the United States were reported in children less than age 1 year, with approximately 35 percent occurring in children less than age 6 months. Twenty-one percent of total cases were seen in children ages 1 to 4 years. Of the remaining cases, 16, 5, and 11 percent occurred in people ages 5 to 9, 10 to 14, and 15 years or older, respectively (Centers for Disease Control, 1990). It should be reiterated in reviewing these figures that the SPSS captures only an estimated 5 to 10 percent of pertussis cases in the United States (Centers for Disease Control, 1990). In light of the vagaries of pertussis detection and diagnosis, pertussis mortality and incidence rates worldwide substantially underestimate the true magnitude of the disease.

Incidence rates of pertussis are consistently higher in females than they are in males across all geographic areas and ages, with the exception of children less that age 1 year. The excess of cases in females, which has been evident in both the pre- and postvaccination eras, differs from other communicable diseases of childhood, which tend to occur more frequently in males (Cherry, 1984; Gordon and Hood, 1951). With respect to race, incidence rates are similar in whites and nonwhites in the United States (Cherry et al., 1988).

Mortality rates, like incidence rates, are highest in the first 6 months of life. The case fatality rate for infants less than age 6 months has been reported to be 0.5 percent (Centers for Disease Control, 1990). Case fatality rates, like attack rates, are reported to be higher in females than in males. The reasons for this are not clear (Cherry et al., 1988).

Distribution by Place Pertussis continues to be a major cause of infant and child mortality in the developing world. World Health Organization (WHO) data collected in 1983 indicate that 600,000 of the 100 million children born annually in less developed countries die of pertussis or its complications (Grant, 1986). The following annual crude incidence rates were reported for 1982: 2 to 2,000 per 100,000 population in the WHO Africa region, <1 to 590 per 100,000 population in the Western Pacific region, and 0.25 to 85 per 100,000 population in the European region (Muller et al., 1986). The wide ranges in these statistics most likely reflect differ

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ences in reporting rates as well as in disease incidence. The crude incidence rate of pertussis in the United States in 1988 was estimated to be 1.4 per 100,000 population (Centers for Disease Control, 1990).

Time Trends Mortality rates from pertussis in the industrialized world have declined significantly in the twentieth century. In Great Britain, at the turn of the century, approximately 1 in 1,000 children under age 15 years died of pertussis, with mortality rates being significantly higher among infants less than age 1 year. Rates then began to decline in the first few decades of the century and, by World War II, were approximately one-tenth of what they had been 40 years earlier (Department of Health and Social Security, 1976). Mortality rates declined even more rapidly in the postwar period, although epidemics of pertussis continued to occur (Department of Health and Social Security, 1981; Miller et al., 1982).

Mortality from pertussis in the United States has also declined in the twentieth century. Mortality rates in the United States, like those in Great Britain, began to decline in the early decades of the century, declining more rapidly after World War II (Mortimer, 1980; Mortimer and Jones, 1979). Incidence rates also declined, leveling out in the early 1970s. Since then, age-adjusted incidence rates have fluctuated between 0.5 and 1.5 per 100,000 population (Centers for Disease Control, 1987).

Nature of the Causative Organism, B. pertussis

B. pertussis is a gram-negative pleomorphic bacillus. The genus *Bordetella* contains four species: *B. pertussis,* which is the agent responsible for human pertussis; *B. parapertussis,* which causes a mild pertussis-like syndrome in humans; *B. bronchiseptica,* which produces a respiratory illness in animals but can also infect humans; and *B. avium,* which causes a respiratory illness in birds (Kersters et al., 1984; Manclark and Cowell, 1984). Kloos and colleagues (1981) reported that the four species are genetically similar and may be more appropriately considered as biotypes of the same species. They further hypothesized that the lack of clinical description of pertussis prior to the sixteenth century may represent an adaptation of an earlier variant of *B. pertussis* from an animal to the human host (Kloos et al., 1981).

B. pertussis contains many biologically active and antigenic factors (see Table 2-1). Although the effects of these various factors following natural infection or injection with killed *B. pertussis* bacilli have been examined in a number of studies in animals, understanding of the organism's biology and pathogenesis remains incomplete.

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TABLE 2-1 Biologically Active and Antigenic Components of *B. pertussis*[a]

Factor	Location and Structure	Biologic Functions
Agglutinogens	Protein surface antigens; multiple serotypes, some located in fimbriae (pili)	Provide serologic markers for study of epidemiologic characteristics of pertussis; may play a role in the attachment of bacteria to ciliated cells; antibody to agglutinogens may contribute to protection against infection
Filamentous hemagglutinin (FHA)	A cell surface protein that is a hemagglutinin; it is liberated into fluid of statically grown broth cultures	Important mediator of attachment of bacteria to ciliated epithelial cells; antibody to FHA may protect against infection of ciliated cells
Pertussis toxin (PT), also called lymphocytosis-promoting factor, leukocytosis-promoting factor, histamine-sensitizing factor, islet-activating protein, and pertussigen	An envelope protein that is a hemagglutinin; it is liberated into the fluid of static or submerged cultures; five-subunit structure	A toxin with many biologic functions in animal models, e.g., histamine sensitization, lymphocytosis promotion, enhancement of insulin secretion, and adjuvant activity; antibody to PT is protective in intracerebral mouse protection test; it is probably a major virulence factor
Adenylate cyclase	Enzyme that is liberated into culture supernatants	Has potential to interfere with phagocyte function
Heat-labile toxin, also called dermonecrotic toxin, lethal toxin, or lienotoxin	Heat-labile protein toxin found in the cytoplasmic fraction of cell lysates	Causes skin necrosis in mice, rabbits, and guinea pigs and is lethal in mice after intravenous administration
Endotoxin, also called lipopolysaccharide	Envelope toxin	Activities similar to those of endotoxins of other gram-negative bacteria
Tracheal cytotoxin	Small glycopeptide found in culture supernatants	Causes ciliostasis and cytopathology of hamster tracheal epithelial cells in organ culture
Hemolysin	Unknown	Hemolysin-deficient mutant was shown to have reduced virulence in mice
Outer membrane protein	Outer membrane of organism	Antibodies to this protein protect mice against respiratory infection

[a]Modified from Cherry et al. (1988) and Mortimer (1988). Reproduced by permission of *Pediatrics*.

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B. pertussis Virulence Factors and Pathogenesis of Whooping Cough

When *B. pertussis* invades susceptible humans, the organism adheres to ciliated epithelial cells of the respiratory tract and multiples there without invading the tissues (Lapin, 1943; Pittman, 1970). Yet, this colonization leads to profound changes in tissues that persist long after the responsible bacteria have been cleared. Such observations suggest that a toxin or toxins from the bacteria play an important part in the pathogenesis of the syndrome.

Among the putative pertussis toxins, the secreted pertussis toxin (PT) is currently considered the best candidate as a major virulence factor (Cherry et al., 1988; Mortimer, 1988; Pittman, 1979, 1984; Weiss and Hewlett, 1986). PT is now believed to be responsible for many of the characteristic activities attributed in the past to "toxins" in culture filtrates or cell lysates of *B. pertussis.* These include lymphocytosis, which is often seen in patients with whooping cough, increased sensitivity to shock on injection of histamine into mice (histamine-sensitizing factor), and hyperinsulinemia and hypoglycemia (islet-activating protein) (Pittman, 1984).

PT is a protein composed of five linked subunits (S1, S2, S3, S4, and S5). The subunits S2 to S5 form a nontoxic unit that binds to the cell membrane; toxicity is mediated by the subunit S1, which acts as an enzyme (Pizza et al., 1989). The activity of subunit S1 inhibits a subclass of proteins (G proteins) that are essential for transmission of biochemical messages from receptors on the cell surface to the intracellular machinery that permits the cell to function. Genetic engineering has been used to replace one or two key amino acids within the enzymatically active S1 subunit, resulting in a stable nontoxic form of PT. Such an agent has the potential to be used as a safe immunogen (Pizza et al., 1989).

Other toxins have been proposed, but there is less experimental evidence to support the participation of these other toxins in the pathogenesis of pertussis. Two forms of the enzyme adenylate cyclase, one of which is released into culture fluids and the other of which is intracellular, are associated with *B. pertussis* (Confer and Eaton, 1982; Hewlett and Wolff, 1976; Hewlett et al., 1976; Weiss et al., 1984). The latter can be internalized by phagocytic cells and inhibit their function through elevation of intracellular cyclic adenosine monophosphate (Confer and Eaton, 1982). There is a lipopolysaccharide that possesses all of the usual properties of enterobacterial endotoxins, except that it is less pyrogenic on a weight basis (Chaby et al., 1979). It is present in whole-cell vaccines (Cameron, 1988; Pittman, 1984). A dermonecrotic toxin (Livey and Wardlaw, 1984; Nakase and Endoh, 1986) and a tracheal cytotoxin (Goldman et al., 1982) have been purified and studied in tissue culture or animals. Adherence of *B. pertussis* to respiratory epithelium is required for the pathogenesis of whooping cough (Pittman, 1970). Adherence appears to involve a bacterial outer membrane

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protein with a molecular mass of 69 kilodaltons, termed the 69-kD outer membrane protein (Charles et al., 1989; Shahin et al., 1990). Injection of this protein into mice elicits a protective antibody response in a respiratory model (Charles et al., 1989).

Two other bacterial surface structures have been proposed to play a role in the pathogenesis of whooping cough through the promotion of adherence to respiratory cilia. These are FHA (Sato et al., 1983) and serotype-specific agglutinogens (Preston et al., 1982). Immunization with cellular vaccines raises antibody to both of these (Pittman, 1984).

Major Milestones in the Development of Pertussis Vaccines

Whole-Cell Vaccines

When the description of the Bordet-Gengou technique for isolating the pertussis bacterium was published (Bordet and Gengou, 1906), numerous researchers began to experiment with vaccines from killed whole-cell *B. pertussis.* Such vaccines were developed, and used in children, by Bordet and Gengou in 1912, Nicolle of the Pasteur Institute in Tunis in 1913, and Madsen of the Danish State Serum Institute in 1914, among others (Chase, 1982). By 1914, pertussis vaccine was listed in *New and Nonofficial Remedies,* a publication of the American Medical Association (Council on Pharmacy and Chemistry, 1914, 1931).

Kendrick, of the State of Michigan Health Department, further refined and used whole-cell pertussis vaccines in children (Kendrick, 1942, 1943; Kendrick and Eldering, 1936, 1939). In 1942, Kendrick and colleagues combined her improved killed vaccine with diphtheria and tetanus toxoids to produce the diphtheria-pertussis-tetanus (DPT)[4] combination vaccine. In 1944, the Committee on Infectious Diseases of the American Academy of Pediatrics suggested routine use of pertussis vaccine and, in 1947, recommended its use in the form of the DPT combination (American Academy of Pediatrics, 1944; Cherry, 1984). During the 1940s and 1950s, vaccination of U.S. children against pertussis became a routine procedure. By the mid-1960s, many states had passed laws requiring that all children be vaccinated with the DPT vaccine prior to entry into school (Coulter and Fisher, 1985).

For additional information on the development of pertussis whole-cell vaccines, see Appendix B, Pertussis and Rubella Vaccines: A Brief Chronology.

Acellular Vaccines

Acellular pertussis vaccines were developed in Japan, prompted by ad

[4] Throughout this report, the acronym DPT has been adopted for the triple vaccine because of its historic usage. It is synonymous with DTP.

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verse experiences with the whole-cell vaccine. Japan made pertussis vaccination mandatory in 1948, but it was not until 1950 that nationwide immunization was undertaken, using whole-cell vaccine (Kanai, 1980). By the early 1970s, the incidence of pertussis in Japan had fallen so precipitously that some questioned the need for continued routine immunization against the disease, especially given the occasional reports of adverse events following immunization (Kanai, 1980; Public Health Service, 1986). Several jurisdictions, in fact, abandoned pertussis immunization at about that time (Public Health Service, 1986). A vaccine injury compensation system was established in 1970.

Within a 2-month period in 1974-1975, two Japanese infants died less than 24 hours after receiving the DPT vaccine (Hinman and Onorato, 1987; Public Health Service, 1986; Sato et al., 1984). Although investigators concluded that the whole-cell pertussis component of DPT had not caused the deaths, vaccination policy was affected by the occurrences. Use of the pertussis vaccine was suspended temporarily during the investigation, and when its use was resumed, recommendations were made to raise the age of first administration from 3 months to 2 years. In addition, the Japanese Ministry of Health and Welfare established a Pertussis Vaccine Study Group to facilitate research on an improved vaccine. Clinical trials of acellular vaccines began in 1979; routine use of the new vaccines was initiated in 1981 (Public Health Service, 1986).

Two types of acellular pertussis vaccines, the B type and the T type, are currently manufactured and distributed in Japan. The B type is made up of lymphocytosis-promoting factor (LPF) and FHA in approximately equal amounts; the T type (which is used more frequently) consists of significantly more FHA than LPF and includes agglutinogens (Hinman and Onorato, 1987). The vaccination series is begun at age 2 years and consists of three consecutive doses given at 1-month intervals and a fourth dose given 1 year later. The T-type vaccine has been evaluated in several preliminary studies of immunogenicity and toxicity in the United States (Anderson et al., 1985; Edwards et al., 1986; Lewis et al., 1986; Pichichero et al., 1987; Rodgers and Badgett, 1985). Trials of the Japanese vaccines have also been carried out in Sweden (Blackwelder et al., 1988; Hallander and Mollby, 1988; National Institutes of Health, 1988). Clinical trials of acellular pertussis vaccines are in progress in the United States.

Brief History of the Controversy Pertaining to Adverse Events Following Pertussis Vaccination

Madsen, of the State Serum Institute in Copenhagen, Denmark, was the first to describe the use of whole-cell pertussis vaccine on a large scale (Madsen, 1925, 1933). His vaccine successfully controlled two outbreaks in the Faroe Islands. His 1933 account reported two deaths within 48 hours

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of immunization, the first published report of serious adverse effects after pertussis vaccination. In the same year, Sauer of Northwestern University Medical School in Chicago described minor reactions to a whole-cell pertussis vaccine being used in the United States (Sauer, 1933a,b).

In the late 1940s, the first published reports of irreversible or chronic neurologic damage following vaccination against pertussis appeared (Brody and Sorley, 1947; Byers and Moll, 1948). Brody and Sorley reported only one case, but their report led to the first warnings that pertussis vaccine should not be administered to those with a known neurologic disorder.

In Britain in 1974, questions about the safety of pertussis vaccines were widely publicized in the popular press after newspaper accounts of a study suggesting adverse reactions (Kulenkampff et al., 1974), and an Association of Parents of Vaccine Damaged Children was formed (Alderslade et al., 1981). Between 1974 and 1978, the proportion of British children vaccinated against pertussis fell from 80 to 30 percent, on average, dropping as low as 9 percent in some areas (British Medical Journal, 1981). An epidemic of pertussis subsequently occurred; between 1977 and 1979, more than 100,000 cases and 36 deaths were reported (Koplan and Hinman, 1987).

The controversy over the safety of pertussis vaccines reached the U.S. public in 1982, when the television program, "DPT: Vaccine Roulette," was first broadcast by NBC affiliate WRC-TV in Washington, D.C. The program depicted children with severe injury allegedly caused by pertussis vaccines (Griffith, 1989; Koplan and Hinman, 1987). Following broadcast of that program, an advocacy group, Dissatisfied Parents Together, was formed in the United States. Its members called for research toward a safer pertussis vaccine and mandatory reporting of adverse reactions. Some members of the group called for a cessation of the use of whole-cell vaccines (Coulter and Fisher, 1985; Koplan and Hinman, 1987).

For additional information on the controversy surrounding pertussis whole cell vaccines, see Appendix B, Pertussis and Rubella Vaccines: A Brief Chronology.

RUBELLA VACCINES

Epidemiology of the Disease Rubella

Clinical Description

Rubella is commonly a mild disease; it afflicts children and young adults. It is characterized by an erythematous, maculopapular, discrete rash; postauricular and suboccipital lymphadenopathy; and minimal fever (American Academy of Pediatrics, 1986). The disease is caused by an RNA virus belonging to the togavirus family. It can be transmitted transplacentally to the fetus, sometimes with devastating results (Berkow, 1987).

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Rubella was first clinically differentiated from other exanthematous illnesses by German physicians in the late eighteenth century, hence its popular name, German measles. The Latin term *rubella,* or "little red," was coined by a British physician who reported on an epidemic of the disease among schoolboys in India in 1841 (Veale, 1866). Rubella subsequently evoked little interest in the medical community until 1941, when a report appeared associating congenital cataracts with maternal exposure to the disease during pregnancy (Gregg, 1941). A flurry of subsequent reports confirmed this association and further noted increased risks of congenital heart disease and deafness following maternal exposure to the disease, thus establishing the classical congenital rubella triad (Greenberg et al., 1957; Lundstrom, 1962; Manson et al., 1960; Pitt and Keir, 1965). Intrauterine rubella exposure is now known to be associated with a wide variety of abnormalities, including, for example, encephalitis, mental retardation, glaucoma, thrombocytopenic purpura, hypoplastic right heart, and diabetes (Alford and Griffiths, 1983; Cooper et al., 1969; Plotkin et al., 1965b).

The incubation period of rubella is 14 to 21 days, with the characteristic rash appearing within 14 to 17 days after exposure. The patient is usually asymptomatic in the first week after exposure. By early in the second week, lymphadenopathy becomes apparent and rubella virus can usually be cultured from nasopharyngeal secretions. By the end of the second week, virus is detectable in the blood. After the 14to 21-day incubation period, a 1- to 5-day prodromal illness consisting of malaise, low-grade fever, mild conjunctivitis, and, occasionally, arthralgia can occur, but it may be minimal or absent. The rash, in most cases, appears at this time, beginning on the face and neck and spreading quickly to the trunk and extremities. It usually lasts for about 5 days (Cherry et al., 1988; Plotkin, 1988).

Diagnosis

Diagnosis of rubella can be made in several ways. Virus can be most consistently isolated by inoculation of appropriate tissue culture media with nasal secretions. Virus can also be isolated from the throat, blood, urine, and cerebrospinal fluid, particularly in congenitally infected infants. Serologic testing of acute- and convalescent-phase serum is also useful in diagnosis, with seroconversion indicating infection. Diagnosis based on history of German measles or on clinical findings is unreliable without laboratory confirmation, because other viral exanthems mimic rubella.

Complications

Although a number of acute, transient sequelae of postnatal rubella, including polyarthralgia, polyarthritis, and testicular pain, have been noted

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(Berkow, 1987; Schlossberg and Topolsky, 1977), serious complications are few and rare. Encephalitis, occasionally resulting in death, and thrombocytopenia have been reported (Morse et al., 1966; Sherman et al., 1965), as have chronic arthralgia, arthritis, and polyneuritis (Ogra and Herd, 1971; Ogra et al., 1975; Schaffner et al., 1974). The latter vary in frequency with age and sex, being greatest in adult females and least in prepubertal children. Complications of congenital rubella are numerous and profound (see the section Clinical Description). A rare late syndrome of congenital rubella is rubella panencephalitis (Townsend et al., 1975; Weil et al., 1975).

Descriptive Epidemiology

Ecology of the Rubella Virus Rubella virus is spread by airborne droplet nuclei or by close contact. Rubella does not appear to be as contagious as certain other common viral childhood diseases are, as indicated by seroepidemiologic studies showing that even after explosive outbreaks, 10 to 20 percent of young adults may remain susceptible (Plotkin, 1988). However, under crowded conditions where the proportion of susceptible individuals is high, rubella can be highly infective (Brody, 1966; Grayston et al., 1972; Halstead et al., 1969). Exposure to rubella disease is believed to confer life-long immunity (Berkow, 1987).

Humans are the sole host of the rubella virus, and subclinical cases are common. Virus has been shown to be present in nasopharyngeal secretions from 7 days before to 14 days after onset of the rash in postnatal cases. Infants with congenital rubella can shed the virus in nasopharyngeal secretions and urine for a year or more after birth (Cooper et al., 1965; Scheie et al., 1967).

Distribution by Person Age at the time of infection varies geographically for postnatal rubella. In areas where living conditions are crowded, rubella tends to occur at an early age; in areas that are less crowded or that are isolated, such as island nations, rubella tends to occur at a later age, with a significant number of people remaining seronegative into young adulthood (Ingalls, 1967). Congenital rubella affects more infants of younger mothers than infants of older mothers, perhaps because the former are more likely to be seronegative (Plotkin, 1988).

Distribution by Place Rubella occurs worldwide (Assaad and LjungarsEsteves, 1985; Cockburn, 1969). The disease is probably more common in areas where living conditions are crowded, although accurate incidence rates are difficult to obtain in the absence of seroepidemiologic confirmation, because many childhood cases are asymptomatic and therefore go undetected (Plotkin, 1988).

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Little is known about the geographic distribution of congenital rubella in much of the developing world (Mingle, 1985; Seth et al., 1985), although incidence rates tend to vary at a given time according to the number of susceptible (seronegative) adult women and the presence of the virus (Plotkin, 1988). In the United States, prior to widespread vaccination, incidence rates of congenital rubella syndrome in nonepidemic years averaged 4 to 8 per 10,000 pregnancies (Williams and Preblud, 1984). A similar rate of 4.6 per 10,000 births was observed in the United Kingdom (Peckham, 1985).

Time Trends Prior to mass immunization, rubella was both an endemic and an epidemic disease in the United States. The disease occurred year-round, but tended to peak in the spring. Epidemics occurred at 7-year intervals (Witte et al., 1969). With the advent of mass immunization, rubella incidence rates declined by more than 95 percent compared with those in the prevaccination era, although isolated epidemics in susceptible groups have continued to occur (Cherry et al., 1988).

Nature of the Rubella Virus

The initial realization of the teratogenic potential of maternal rubella in the early 1940s spurred attempts to isolate and characterize the responsible agent. It was not until 1962, however, that Weller and Neva (1962) and Parkman and colleagues (1962) independently isolated the rubella virus; the latter group used the technique of interference with the growth of enteroviruses in African green monkey kidney tissue culture that was to become a standard method for virus isolation (Plotkin, 1988).

The rubella virus was subsequently found to be a cubical, medium-sized, lipid-enveloped virus, ultimately classified in the togavirus family. The virus, in addition to its lipid envelope, is composed of three proteins, two in the envelope and one in the core (Pettersson et al., 1985). Upon infection, it replicates in the nasopharynx, from which it spreads to the local lymph nodes. During viremia, the placenta can be infected, leading to introduction of the virus into the fetal bloodstream and to the subsequent disruption of organogenesis (Alford et al., 1964; Naeye and Blanc, 1965; Plotkin et al., 1965a; Tondury and Smith, 1965). The exact pathologic mechanisms underlying the disruption of organogenesis are unclear (Plotkin, 1988), but they may, in part, involve inhibition of fetal cell mitosis by a soluble protein inhibitor (Naeye and Blanc, 1965; Plotkin and Vaheri, 1967; Plotkin et al., 1965a).

Major Milestones in the Development of Rubella Vaccines

In 1938, Hiro and Tasaka succeeded in transmitting rubella by inoculating healthy nonimmune children with filtrates taken from children with

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active cases of rubella. The causative agent remained unidentified (Chase, 1982). By 1948, Burnet and colleagues were using gamma globulin from patients with rubella to confer short-term passive immunity on pregnant women recently exposed to rubella (Chase, 1982). The practice became common in a number of industrialized countries.

In the early 1960s, the rubella virus was isolated by Weller and colleagues at the Harvard School of Public Health (Weller and Neva, 1962) and by Parkman and colleagues at the Walter Reed Army Institute of Research (Parkman et al., 1962). The rubella epidemic in Europe and the United States between 1962 and 1965 led to thousands of cases of congenital rubella syndrome and lent impetus to the search for a vaccine (Chase, 1982; Plotkin, 1988). Between 1965 and 1967, several vaccines made from attenuated rubella strains were developed and tested in clinical trials (Plotkin, 1988).

Three rubella vaccines were licensed in the United States in 1969-1970 and became widely used: HPV-77 (high passage virus) grown in dog kidney, HPV-77 grown in duck embryo, and Cendehill grown in rabbit kidney (Plotkin, 1988). A human diploid fibroblast vaccine, RA 27/3, also developed in the United States in the 1960s, was first licensed in Europe and came to be used extensively in the United Kingdom, France, Switzerland, and Italy. It was not licensed in the United States until 1979. By that time, the manufacturers of the dog kidney and Cendehill strains had left the U.S. market. In 1979, Merck Sharp & Dohme, the only remaining manufacturer of the duck embryo vaccine in the United States, began making and selling RA 27/3 instead. It has been the only rubella vaccine manufactured or distributed in the United States since that time.

Although the rates of rubella and congenital rubella syndrome dropped dramatically after the introduction of rubella vaccines, medical policymakers in the United States became convinced by the late 1970s that to eradicate rubella and congenital rubella syndrome entirely, it would be advisable to vaccinate women of childbearing years as well as young children (Preblud, 1985; Tingle, 1990). Recommendations were made that women be vaccinated for rubella postpartum, and that female medical and health-care workers be vaccinated. Some institutions began to require such immunization for female health-care professionals; some universities also started to require immunization for female students.

For additional information on the development of rubella vaccines, see Appendix B, Pertussis and Rubella Vaccines: A Brief Chronology.

Brief History of the Controversy Pertaining to Adverse Events Following Rubella Vaccination

Two types of adverse events after rubella immunization have primarily been reported. Postvaccination neuropathies were observed in children early in the experience with the vaccine. Between 1970 and 1974, a number of

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reports described two temporary conditions that came to be known as the "arm syndrome" and the "leg syndrome" (or the "catcher's crouch syndrome") (Gilmartin et al., 1972; Kilroy et al., 1970; Schaffner et al., 1974). Evidence indicated that these events were especially likely to occur with the dog kidney vaccine (e.g., Grand et al., 1972; Kilroy et al., 1970). Such reports contributed to the decision to license RA 27/3 in the United States and to the withdrawal of the other vaccine strains from distribution in the United States and a number of other countries (Plotkin, 1988).

Acute arthralgia and arthritis following vaccination were also reported in the earliest studies of rubella vaccines (American Journal of Diseases of Children, 1969; Barnes et al., 1972; Horstmann et al., 1970; Lerman et al., 1971; Spruance and Smith, 1971). All rubella vaccine strains have been associated, to some extent, with reactions in the joints. Again, the HPV-77 dog kidney vaccine appeared to be most often associated with such events (Barnes et al., 1972; Spruance and Smith, 1971), but other strains, including RA 27/3, have been implicated as well (Fox et al., 1976; Freestone et al., 1971; Horstmann et al., 1970; Lerman et al., 1971; Rowlands and Freestone, 1971; Swartz et al., 1971; Tingle et al., 1979, 1985, 1986; Weibel et al., 1972). It has been reported that arthritis, arthralgia, and other joint disorders are observed with greater frequency after natural rubella infection than after administration of rubella vaccine (Tingle, 1990).

The incidence of arthritis and arthralgia following rubella vaccination, as is the case with natural rubella infection, is low in infants and young children, but is higher and more severe in adults (Best et al., 1974; Dudgeon et al., 1969; Polk et al., 1982). There are reports of chronic, severe arthritis and related conditions in postadolescent women who have received the vaccine (Tingle et al., 1979, 1985, 1986). Some have charged that results of prelicensure clinical trials carried out primarily in children were improperly generalized to adults, leading to the assumption that the vaccine is safe for adults as well (Hatem, 1990; Tingle, 1990). A randomized, double-blind, placebo-controlled trial of rubella vaccine and chronic arthritis is currently in progress in Vancouver, British Columbia, Canada (A. Tingle, British Columbia Children's Hospital, personal communication, 1991). In addition, as of April 1991, the CDC is considering issuing a request for proposals for a study of chronic arthritis following rubella vaccination that would include detailed laboratory studies of participants.

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3

Methodologic Considerations in Evaluating the Evidence

THE NATURE OF THE EVIDENCE

The committee has undertaken the task of judging whether each of a set of adverse events may occur as a result of exposure to pertussis or rubella vaccines. These judgments have both quantitative and qualitative aspects, and they reflect the evidence examined and the approach taken to evaluate it. In this chapter, the committee describes more fully how it has approached its task, in the hope that readers may then be in a better position to assess and interpret the committee's findings. By offering this information, the committee wishes to make the report useful to those who may seek to update its conclusions as new information is obtained. This chapter outlines the specific questions the committee posed, the types of evidence it identified, its approaches to evaluating reports both singly and collectively, and the nature of the conclusions it felt that logic and evidence permitted. Against this background, details of the analysis and specific conclusions concerning each type of adverse event appear in subsequent chapters.

Attributes both of the adverse events being considered and of the population exposed to vaccine influenced the committee's analysis. The events can be characterized, for example, by their frequency, discreteness, and specificity and by prior knowledge of their etiology and pathogenesis. Events that occur only rarely in exposed persons are more difficult to study than those that occur more frequently. Conditions that are ill-defined, that are

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known to occur in the absence of vaccine exposure, or that generally have unknown causes or mechanisms of development are also inherently difficult to investigate. Under these circumstances, epidemiologic studies offer important advantages over clinical experience and intuition, although these limiting characteristics affect epidemiologic studies also.

When the great majority of the population is exposed, as is generally true for pertussis and rubella vaccines, comparisons between exposed and nonexposed persons become clouded. This is due to the potential for selective factors against vaccination to confound the relation between immunization status and the occurrence of adverse events. For example, a decreased relative risk of SIDS has been observed in several studies in the time period immediately following DPT immunization. Although a protective effect of vaccine cannot be ruled out, it is more plausible that children who are *not* immunized by the recommended age are at *increased* risk for SIDS because of other factors, such as socioeconomic status, that are associated with both delaying immunization and SIDS (see Chapter 5). Other aspects of vaccine exposure, such as changes in vaccine formulation, single versus multiple occasions of administration, and the age pattern of administration also bear on interpretation of the evidence.

QUESTIONS TO BE ADDRESSED

What would it mean to say that a vaccine causes one or another type of adverse event? It would not mean that exposure invariably produces the adverse event, nor that all cases of the event were due to the vaccine. Such complete correspondence between exposures and events is by far the exception in public health and does not occur in the present context, or the present review would not be required.

In general matters of health and disease, different causal explanations may apply even to a single disease. For example, the question of what causes typical cases of a particular disease is quite distinct from the question of what causes epidemic outbreaks of that disease. The answers are also distinct, in that the first might be a specific microorganism and exposure conditions of the individual case, whereas the second could entail complex ecologic and social factors suddenly favoring the widespread transmission of the microorganism. Clearly, different senses of "cause" are implied in these two questions. Although each of these questions concerns the causation of disease, the answers require different types of evidence. This example suggests the importance of stating clearly the questions about causation to be answered.

In the present review, the committee has been concerned with causal questions of three kinds. The first of these questions about exposure to pertussis or rubella vaccine is, in general, *can it cause* the specified adverse

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condition? For example, can rubella vaccine cause chronic arthritis? If the conclusion is affirmative, a second question becomes pertinent: *How frequently does it cause* that condition? Or, how frequently is arthritis a result of rubella vaccination? The third question, which applies to a particular instance or case of an adverse event, is *did it cause* that specific event? Or, did rubella vaccine cause this particular individual to develop arthritis? Discussion of each of these three types of questions will help to indicate the committee's view of its task.

(1) Can vaccine cause the adverse event?

While the nature of causation has a deep philosophical underpinning, the work of the committee necessarily focused on a pragmatic question: What is the nature of the evidence relevant to drawing its conclusion about causation? In pursuing this question, the committee recognized that an absolute conclusion about the absence of causation may never be attained. As in science generally, studies of adverse events following vaccination are not capable of demonstrating a zero effect, that is, that the purported effect is impossible or could not ever occur. Any instrument of observation has a limit to its resolving power, and this is true as well of randomized clinical trials and epidemiologic studies. Hence, the committee could not prove the absence of any possibility of an adverse event caused by vaccine. Rather, in the absence of evidence suggesting an effect, and especially in the presence of evidence not consistent with causation, the committee could only conclude that the evidence fails to demonstrate an effect.

The evidentiary base that the committee found to be most helpful derived from epidemiologic studies of populations. Here, the primary question is whether an association exists between the exposure (immunization) and the event. To determine whether an association exists, epidemiologists estimate the magnitude of an appropriate quantitative measure (such as the relative risk or the odds ratio[1]) that describes the joint occurrence of exposures and events in defined populations or groups. Values of relative risk greater than 1 may indicate a positive, or direct (harmful), association and are emphasized in this discussion; values between 1 and 0 may indicate a negative, or inverse (protective), association. The observed relative risk in the study population must be sufficiently distant from unity to meet a stated criterion of significance before an association is said to be apparent.

[1] Usage of "relative risk," "odds ratio," or "estimate of relative risk" is not consistent in the literature reviewed and cited in this report. In its own usage, the committee intends that "relative risk" be used to refer to the results of cohort studies and "estimates of relative risk" or "odds ratio" be used to refer to the results of case-comparison studies (see Glossary of Terms for definitions).

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Formally, in planning an investigation, an epidemiologist poses a hypothesis to the effect that the exposures and events under study are independent, or not associated. Under this hypothesis, the value of the measure of association used is theoretically expected to be approximately 1. This is termed the *null hypothesis* or the hypothesis of no association. The measure of association derived from the investigation is then tested statistically. To "reject the null hypothesis," or to conclude that exposures and events are not independent, is to conclude that there is evidence of an association.

When more than one epidemiologic study has been conducted, it may be instructive to combine their results so as to reach a stronger conclusion than a single study can provide. This process is described more fully later in this chapter.

Determining whether an observed association is causal requires additional scrutiny. This is because there may be alternative explanations for an observed association. These include errors in the design, conduct, or analysis of the investigation; bias, or a systematic tendency to distort the measure of association from representing the true relation between exposures and events; confounding, or distortion of the measure of association because another factor, related to both exposures and events, has not been recognized or taken into account in the analysis; and chance, the effect of random variation in producing observations that can, in reality, only be approximations to the truth and can, with some probability, sometimes depart widely from the truth.

In deciding whether vaccine can cause any particular type of event, then, it has been the committee's task to judge in each instance whether there is evidence of association from the available studies, and if so, whether it is direct or inverse, and whether it is due to error, bias, confounding, or chance or, instead, due to a causal relation between vaccine and event.

(2) How frequently does vaccine cause the event?

The second type of causal question, which becomes pertinent only if the answer to the first question is affirmative, concerns the proportion of individuals in a specified population who experience the adverse event because of the exposure. The most desirable evidence as a basis for answering this type of question involves knowledge of the rate of occurrence of the event in those who are exposed, the rate in those who are not exposed (the "background" rate of the event in the population), and the degree to which any other differences between exposed and unexposed persons influence the difference in rates. The term *attributable risk* is generally used to denote the difference in rates between exposed and unexposed groups. This is a simple measure of the frequency with which the occurrence of the event in exposed persons may be due to the vaccine exposure and not to the other

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causes that account for the event in the absence of vaccine exposure (see Glossary of Terms). By also taking into account the frequency of exposure in the population, a further measure can be calculated which indicates the number of cases in a total population that may be due to the exposure.

When information was available, in the presence of an association judged by the committee to be causal, the committee has attempted to indicate how much of the occurrence of the event in question might be caused by vaccine exposure.

(3) Did vaccination cause a particular case of the adverse event?

A third type of causal question is whether, in a specific instance of exposure and an adverse event, it can be concluded that the event was caused by the vaccine exposure. This question is especially pertinent to those types of adverse events for which case reports constitute a substantial part of the evidence available for review. Three different sets of circumstances bear on the nature of this question. First, it may have been judged in general that the exposure can cause this type of event. In this instance the question concerning any particular case needs to consider the similarity between the circumstances of that case and the circumstances in which the general conclusion was reached that such causation can occur. If other causes of the same type of event are known, their possible role in this individual case must be considered also.

Second, most evidence for a general proposition of causation may be negative, yet circumstances surrounding a single case may raise the question of whether causation may be attributed to the exposure of this individual. To judge that a particular case was caused by the exposure under these circumstances would entail the reversal of the more general conclusion on the basis of a single case. It seems extremely unlikely that such a reversal could be justified on the basis of the evidence concerning an individual case.

Third, there may be no evidence of the sort required to judge the presence or absence of association. Here the judgment in a specific case would depend on the circumstances concerning that case alone, in isolation from any conclusion about a causal relation in general. On consideration of several aspects of the evaluation of case reports, discussed in the section below, even the strongest affirmative answer based on the individual case would be inherently weaker, or less securely supported, than it would be if a general conclusion supporting vaccination as a cause of the event had been reached. This is not to say that any such conclusion reached on the basis of the case report alone is necessarily incorrect. However, it would be highly subject to error in light of the properties of most of the events considered here and the nature of the evidence available about them in the case report.

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THE BURDEN OF PROOF

In approaching its task, the committee considered the concept of "burden of proof' and its place in such an evaluation. This concept implies that one position or another concerning causation is presumed to be true unless it is offset by evidence to the contrary. The prior position might be either affirmative or negative. That is, it may be assumed that an exposure is harmful unless sufficient evidence of safety is present; alternatively, it may be assumed that an exposure is safe unless convincing evidence of harmful effects is present. In either case, it is sometimes argued that a burden of proof must be fulfilled before the presumed position is rejected.

In general, it is desirable to avoid making an error in either direction, concluding either that there is or that there is not a causal relation when the opposite is true. Reducing the chance of such mistaken conclusions depends on careful assessment of the evidence, including consideration of possible errors, bias, and confounding.

The role of chance in leading to erroneous conclusions as a result of random variation in sampling or in other respects is customarily handled through formal statistical analyses, which are based on assumptions from probability theory. Statistical measures can suggest the likelihood that conclusions of the presence or absence of association will each be in error. In general, a result is said to have greater statistical significance as the probability of error in accepting an association becomes smaller.[2] The likelihood that a true association will be correctly detected in an investigation is a statistical property of the investigation, termed its *power.* Both statistical significance and power reflect the role of chance in scientific observations and the concomitant uncertainty in all scientific conclusions. One obvious implication of this understanding is that the concept of "proof" in its common-sense meaning is not strictly applicable to scientific observations. Even when scientists conclude that an experiment demonstrates ("proves") causation, they know there is a small, statistically definable probability that the conclusion is incorrect.

The committee began its evaluation presuming neither the existence nor the absence of association. It has sought to characterize and weigh the strengths and limitations of the available evidence. Subsequent chapters of the report summarize the evidence concerning each vaccine-event relation under review and present the committee's conclusions. If the first question (can the vaccine cause the adverse event?) was answered affirmatively, and

[2] More technically, the level of statistical significance is the probability of observing by chance at least as great a difference as that observed between an "experimental" (exposed) and a "control" (unexposed) group, if the risk of the adverse event were, in truth, identical in the two groups.

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if available information permitted, the second question (how frequently does the vaccine cause the adverse event?) was answered. In a few cases, conclusions based on the answer to the third question (did the vaccine cause the adverse event in this individual case?) are proposed (see, for example, the section on hemolytic anemia in Chapter 6). Of necessity, such a conclusion is especially tentative if the more general question of whether the vaccine can cause the adverse event remains unanswered. Furthermore, the committee's task was not to judge individual cases, except when this was the only way to shed light on the general question of causality.

It should be noted that the committee's charge was to focus on questions of causation and not broader topics, such as cost-benefit or risk-benefit analyses of vaccination, which are not considered in this report. With this orientation to the committee's task and approach in mind, the following sections discuss the characteristics of the types of evidence that bear on the causal questions at hand.

CATEGORIES OF EVIDENCE

Experiments in Humans

Randomized Controlled Trials

Theoretically, the ideal method for assessment of causal relations between treatments and adverse events is the randomized controlled trial because, when appropriate and feasible, it is the most scientifically rigorous method for testing such hypotheses. Randomized controlled trials are experiments in which subjects are randomly allocated, often in a masked fashion, into "treatment" and "control" groups, to receive or not to receive an intervention such as, in the present context, a monovalent vaccine; the control group receives an injection of an inert substance (placebo) or an established alternative vaccine; and both groups are followed up in a strictly comparable manner to determine the relative frequencies of outcomes and events of interest.

Although they are theoretically ideal, such trials have ethical and practical limitations for investigating the causal connections of concern here. Widespread acceptance of routine immunization against pertussis and rubella creates ethical barriers to withholding vaccination from some participants to permit a placebo-controlled trial (Cherry et al., 1988). In addition, because these adverse events are generally rare, the sample sizes required to detect them reliably would be much larger than those required to evaluate vaccine efficacy. In fact, since the first reports of serious adverse events following administration of pertussis and rubella vaccines (Madsen, 1933; Modlin et al., 1975), virtually no placebo-controlled or other experimental

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studies in humans of the adverse events covered in this report have been published (Cherry et al., 1988; Plotkin, 1988; Preblud, 1985).

A number of early studies of pertussis vaccine in the United States and the United Kingdom did include unexposed controls, but these studies were primarily concerned with efficacy and not with adverse events (e.g., Kendrick and Eldering, 1939; Lapin, 1943; Medical Research Council, 1951, 1956, 1959). More recently, a small number of studies have compared adverse reaction rates in children following DPT versus DT vaccine administration (Cody et al., 1981; Pollock et al., 1984) or in adults following rubella vaccine versus natural rubella infection (Tingle et al., 1986). Predominantly, however, pertinent randomized trials have focused on comparisons of pertussis vaccine reaction rates between different injection sites, vaccines of different manufacturers, prior reaction histories, or different immunization schedules (Baraff et al., 1984, 1985; Barkin and Pichichero, 1979). Other studies have compared reaction rates by vaccine type, for example, whole-cell versus acellular pertussis vaccines (e.g., Edwards et al., 1986; Lewis et al., 1986; Pichichero et al., 1987) or between rubella vaccine strains (e.g., Barnes et al., 1972; Isacson et al., 1971; Polk et al., 1982). In general, these studies have been primarily concerned with evaluation of transient reactions, whether local or systemic, and not chronic adverse events of the types included in this review. One exception is a randomized, double-masked, placebo-controlled trial of rubella vaccine and chronic arthritis that is currently in progress in Vancouver, British Columbia, Canada. Results are expected in 1992 (A. Tingle, British Columbia Children's Hospital, personal communication, 1991).

Other Experimental Studies

Thus, few randomized controlled trials contribute to the assessment of the causal questions considered in this report. And although it should be noted for completeness that other experimental approaches, such as formal community wide comparisons of the impact of vaccination programs, including both beneficial outcomes and adverse events, are applicable in principle, evidence of this type is also generally unavailable.

Experiments in Animals: Animal Models

In principle, experimental studies in animals allow for both rigid control over vaccine exposure and intensive observation for any adverse events that may follow. If an animal model is to be considered valid for the study of a human disease, however, the manifestations of the disease should be similar in the two species. The starting point is generally what is currently known about the human disease.

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With respect to evaluation of pertussis vaccine, the committee found that the information gained from animal models of whooping cough is difficult to apply to humans for two critical reasons: Knowledge of virulence factors for the organism and of the pathogenesis of whooping cough is incomplete and largely superficial, and *Bordetella pertussis* is not a natural pathogen for animals. Nonetheless, several studies have been conducted and are reviewed below. With respect to rubella, the committee could find no studies of animal models of either the disease or rubella vaccine-related illness that were specific to the adverse events under consideration. The discussion below therefore refers specifically to pertussis.

Several additional factors make it difficult to apply findings in animal models of infection to their human counterparts, and these difficulties hold for the study of pertussis. These factors are either specific characteristics of infection and response in a particular species or more general considerations in judging the relevance to humans of studies in animals.

First, the capacity of any particular organism to infect (i.e., to colonize and replicate in) a host varies a great deal across host species. This variability depends in turn on several factors, including how closely the organism's surface antigens resemble those of the host. If the microbe's prominent antigens are like those of the host, rapid replication might occur before the host would recognize the invader as foreign. Some organisms initiate their relationship with the host by binding to specific host receptors or antigens; these binding sites vary among species. An animal's immunologic repertoire, consisting of antibodies and programmed lymphocytes, is generated by natural exposure to antigens. Across species this experience with antigens varies with diet and habitat, particularly proximity to humans or other animals.

Second, disease is the product of a stimulus (such as a bacterium and its toxins) and the host response. The inflammatory response is similar but far from identical across mammalian species, and the disease can be expressed differently in different species. For example, different animals vary in their capacity to inactivate bacterial endotoxin and in their susceptibility to allergic anaphylaxis.

Third, results in animal models of infectious diseases can vary greatly with the conditions of the initial exposure of the host to the organism. If animal models of infection involve the same point of entry, the same vehicle (e.g., dust or aerosolized droplets), and similar numbers of organisms in order to produce natural infection, they are more likely than less analogous models to predict the results that will be obtained in humans.

Fourth, the material used for studies in animals (in this case, the organism and its products) should, ideally, be the same as that to which the human is exposed. Attention must be paid to the bacterial strain and to possible differences in metabolism and virulence within the strain.

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Fifth, host defense mechanisms mature at markedly different rates in different species. The stage of immunologic development in the test animal needs to be understood in relation to development of the immune system in the human.

Results with animal models can only suggest possible relations or outcomes in humans. Observations made in animal models represent only an initial step in the process of applying animal experience to human disease and its prevention. Findings from the animal model must be confirmed by the study of humans, and that principle is clearly relevant to the study of either whooping cough or the adverse events that follow pertussis vaccination. With respect to the study of adverse events following exposure to rubella or rubella vaccine, such questions of relevance are moot, since it has not been possible to develop an animal model for rubella infection.

These general requirements for the applicability of data from animal models to human conditions limit the usefulness of the information currently available regarding pertussis vaccine. No pertinent information is available from animal models regarding rubella vaccine. Observational studies in humans have been a more useful basis for making judgments about the possibility of causation of adverse events by pertussis and rubella vaccines. (See Appendix C for further discussion of the animal models used to study pertussis and pertussis vaccine.)

Controlled Epidemiologic Studies (Observational)

In contrast to randomized controlled trials and other experimental studies in humans, many epidemiologic investigations are observational. This means simply that the occurrences of exposures or events of concern, such as pertussis vaccination or a particular adverse event, are studied as they arise in the usual course of life and not under the conditions of a planned experiment.

Observational studies in populations are often controlled, however, through various strategies of formal comparative investigation. For example, the experience of adverse events in a group after receiving pertussis vaccine can be compared with that in an unvaccinated group (unexposed control group). Alternatively, the prior vaccination history of a group that has developed irreversible encephalopathy can be compared with that of a group free of this condition (unaffected control group). In these two strategies, the experience of the control or comparison group provides an estimate of the frequency either of events in the absence of exposure or of exposure in the absence of the event, as experienced in the general population. Thus, the contribution of the control group in such studies is analogous to that of the placebo group in a controlled trial.

The most relevant types of such controlled, observational studies for the

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present review and their main characteristics are described in this section. Examples of studies related to pertussis or rubella vaccine and adverse events serve for illustration.

Cohort Studies

Cohort studies track groups that are defined by common characteristics, including their exposure status, for example, vaccinated and unvaccinated, at the starting point of observation. The rates of occurrence of adverse events are compared between these groups over time. All study participants are known or presumed to be free of the disease or events under investigation at the start of the study. In the well-designed cohort study, reliable estimates of event rates in each group can be obtained. Especially for uncommon events, large populations, prolonged periods of observation, or both are required (Last, 1988).

Such studies can provide evidence that bears on both the first and second types of causal questions discussed earlier in this chapter. By direct comparison of rates in exposed versus nonexposed groups, a measure of association, termed the *relative risk,* is derived. From the same results, the attributable risk can be determined, and with knowledge of the frequency of exposure in the general population, the population attributable risk can also be calculated. Thus, the questions of whether exposure is associated with the event and, if so, to what degree can both be answered with the results of the cohort study.

The starting point of the investigation can be either contemporaneous or in the past. In the first case, termed *concurrent cohort studies,* all observations, including both exposures and events, may be subject to direct observation by the investigator. In the second case, which typically depends on the availability of records of past exposures and events, the entire study may relate to experience prior to the start of the investigation. Such studies are termed *historical cohort studies.* Some features are common to both types of cohort studies, and others are distinct in accordance with their different temporal strategies.

For example, in a historical cohort study, Griffin and colleagues (1990) evaluated the risks of seizures and encephalopathy in a cohort of 38,171 children in Tennessee on Medicaid who had collectively received a standard schedule of 107,154 DPT immunizations in the first 3 years of life (see Chapter 4 for details). The use of historical records permitted a more rapid and less expensive investigation than would have been afforded by a concurrent cohort design.

One potential weakness of the historical cohort study design, the dependence on possibly incomplete and unreliable historical records for information, was reduced in the study of Griffin and colleagues because of the

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availability of multiple sources of high-quality information. Still, dependence in that study on hospital-based medical encounters to identify cases of seizures may have meant that the rates in both groups were underestimated if, in some cases, no medical encounter or only an outpatient contact occurred. The effect of missed cases would be to reduce the sensitivity (power) of the study (see more detailed discussion below). If, in addition, the likelihood of missed events had, for any reason, been disproportionate between the vaccinated and unvaccinated groups, there would be a corresponding bias in the comparison of rates between groups. A further concern in such studies of pertussis or rubella vaccination is the very high proportion of the population that is exposed. This circumstance requires consideration of factors that might affect selection for nonvaccination status and their possible role as confounders between vaccination status and the occurrence of health outcomes, including the adverse events under study.

The attempt to investigate encephalopathy, as well as seizures, in the study of Griffin and colleagues illustrates another feature of cohort studies generally: the fact that especially rare conditions may not be detectable within the limits of sample size and duration which characterize many such studies. No cases of encephalopathy were identified within 2 weeks of immunization, the period judged to be relevant to the question of a causal association. Because the outcomes in question are generally rare, the case-comparison design has more often been used in the investigation of the rare adverse events considered in this report.

Case-Comparison Studies

Controlled epidemiologic studies in which the subjects are selected in accordance with their disease status, for example, with or without encephalopathy, and investigated to determine their prior histories of exposure, for example, whether or not they had received pertussis vaccine, are termed *case-comparison* or *case-control studies.* Unlike cohort studies, case-comparison studies do not provide direct estimates of adverse event rates in the study groups. This is because the groups are defined by the presence or absence of events, and the cases are not ordinarily drawn from a defined population in a way that permits the calculation of event rates.

Instead, the result of the case-comparison study is expressed as the ratio of the odds of having been exposed as a member of the case group versus the odds of having been exposed as a member of the comparison group. As such, the *odds ratio* is a measure of association that can contribute to answering the first type of causal question, whether exposure can cause the adverse event under consideration. If there is no association between exposure status and the adverse event, the expected odds ratio is 1. If, on the other hand, the risk of the adverse event is higher in the exposed group,

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even though the risk cannot be directly observed, the expected odds ratio is greater than 1. Because this strategy of investigation begins with the identification of cases, such as those identified from existing hospital or other medical records, it is not dependent, as is the cohort study, on the gradual accumulation of sufficient numbers of events for analysis. Therefore, results can often be obtained in much less time and at a lower cost than they can with the cohort approach.

The National Childhood Encephalopathy Study (NCES) of Great Britain is an example of the case-comparison design applied to the study of rare neurologic events following pertussis vaccination (see Chapter 4 for further details). In that investigation, physicians were asked to notify study personnel of all cases of serious neurologic illnesses in infants and children ages 2 to 36 months. Over a 3-year period, 1,182 cases were identified. Two control children were selected for each case from immunization or birth registers and were matched to the case by sex, age (within 1 month), and residential area. Information on immunization history for both cases and controls was obtained from the children's medical records, which were kept by the local health authority or family doctor.

Immunization histories of cases and controls were then compared at a series of intervals prior to various defined reference dates. For cases, two reference dates were used: the date of hospital admission and the date of onset of the relevant neurologic illness. The reference date for controls was the date on which the control child was exactly the same age as the corresponding index child on either the day of admission or the estimated day of disease onset.

A key concern in interpreting the results of case-comparison studies such as the NCES is the potential for bias in the selection of cases and controls. Evaluation of an association depends on having valid estimates of the exposure frequencies in both the case and the comparison groups. An atypical case or comparison group may seriously bias the odds ratio. In the NCES, for example, investigators debated whether to choose controls from patients admitted to the same hospital as the cases (hospital controls) or from registers of children in the same neighborhood as the cases (neighborhood controls). The likelihood of being admitted to a hospital when ill can vary not only with the nature and severity of the illness but also with many social and cultural factors. With respect to the NCES, it was thought that control children admitted to hospitals in the study area would be more likely both to come from homes of lower socioeconomic status and to have had a recent illness than would controls chosen as a random sample of the population. Since both of these factors would tend to reduce the likelihood of recent immunization, selection of hospital controls would tend to lead to an artificially low frequency of exposure in the controls and a correspondingly high odds ratio. The NCES investigators decided on neighborhood controls in

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stead, recognizing that such controls, chosen as they were from birth registers or health visitors' lists, would favor the inclusion of less mobile families, which might carry an opposite bias (Alderslade et al., 1981). Some case-comparison studies include both neighborhood and hospital controls to permit estimation of such potential selection biases, but this was not done in the case of NCES for reasons of cost. Such choices and their possible effects make it difficult to ensure the comparability of cases and controls; the desired comparability is that which is achieved in principle by randomization at the outset of a randomized controlled trial. Merely increasing the size of a study will not avoid the bias which is implied by insufficient comparability between groups.

Another potential source of bias in many case-comparison studies relates to the information about exposure collected from cases and controls. Under the circumstances of many case-comparison studies, there is some prior knowledge about the problem under study on the part of study subjects as well as data collectors, such as interviewers or record abstractors. There may also be suspicion on the part of respondents about factors thought to explain the occurrence of the event. These circumstances lead to potential for bias, especially if information about exposure is not pursued in comparable ways between the case and comparison groups. Thus, "information bias" is a concern in case-comparison studies that does not arise in the same way in cohort studies, in which exposure is documented in advance of the adverse event.

A number of other sources of bias potentially enter into case-comparison studies, cohort studies, or both. Some apply to experimental studies also. Variously defined and described in standard texts (e.g., Kleinbaum et al., 1982; Mausner and Kramer, 1985; Rothman, 1986), they all require consideration before the results of any study are accepted as providing valid evidence. Similarly, potential confounding is considered in the process of evaluating each study.

Other Controlled Studies

The design of both cohort and case-comparison studies can vary in many respects, and still other types of controlled or comparative studies may be carried out, such as comparative cross-sectional surveys or studies of long-term trends in the frequencies of adverse events of interest, perhaps linked with trends in the frequency of vaccination. In some instances, groups of cases are compared in a manner distinct from the case-comparison approach described above. For example, Melchior (1977) compared the distributions of ages of onset of infantile spasms for two calendar periods during which different immunization schedules were used (see Chapter 4 for additional details). In that study, both the pertussis component of the vaccine and its

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adjuvant varied between the two time periods examined. Thus, in such further variations of controlled observational approaches, there are also issues of interpretation to be addressed, here concerning the comparability of the exposures and methods of case ascertainment among persons immunized in the two time periods being studied. In addition, methods of case identification were noted to have varied. The potential effects of these changes therefore had to be considered. Another example is the use of data concerning time intervals between pertussis immunization and the occurrence of sudden infant death syndrome (SIDS) (see Chapter 5 and Appendix D). The analysis included estimation of the expected frequencies of SIDS in specific intervals determined from background rates in the general population.

Case Reports and Case Series

Observations of single or multiple human cases of a disease, without formal comparison with a reference group, are termed *case reports* and *case series.* Such reports appear in several types of sources, including peer-reviewed literature; passive surveillance reports of organizations such as the Food and Drug Administration, the CDC, or vaccine manufacturers; and informal reports from physicians, parents, or others. In the present context, such reports generally describe clinical situations in which a child has received a vaccine and subsequently manifested one or more clinical events.

Case reports and case series constitute a substantial proportion of the total number of reports on possible adverse consequences of pertussis immunization. Following Madsen's first report of serious adverse events following immunization (Madsen, 1933), numerous cases have been reported in the peer-reviewed literature (e.g., Berg, 1958; Byers and Moll, 1948; Corsellis et al., 1983; Martin and Weintraub, 1973; Tingle et al., 1979, 1985) and elsewhere (e.g., Centers for Disease Control, 1984, 1986, 1989; Coulter and Fisher, 1985; M. Grant, Determined Parents to Stop Hurting Our Tots, case reports, personal communication to the committee, 1989). To date, such noncontrolled clinical studies provide the only source of information for 7 of the 20 adverse events under review by the committee: in relation to pertussis vaccine, erythema multiforme and other rash, GuillainBarrè syndrome, peripheral mononeuropathy, hemolytic anemia, and thrombocytopenia; and in relation to rubella vaccines, radiculoneuritis and other neuropathies, and thrombocytopenic purpura.

Searching for Patterns

One application of the case reports and case series available concerning a particular adverse event is to seek clinical or epidemiologic patterns within the

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set of collected cases. Such an analysis would proceed by coding case information from each of these reports and searching systematically for distinct clusters that might turn out to be causally related. The committee attempted to carry out such a strategy but was unsuccessful for several reasons.

First, cases reported in the medical literature and to surveillance systems are not a random sample of all adverse events that are potentially vaccine-related. In particular, cases that match prevailing clinical and popular conceptions about what causes the adverse event and the pattern of associated signs and symptoms are more likely to be reported than others. As a result, the data available for analysis will be dominated by a pattern that matches the prevailing conceptions, and any statistical search for patterns will tend to detect this same pattern.

Second, for most of the adverse events under consideration, the cases potentially caused by a vaccine constitute a small proportion of all cases of the adverse event. Thus, even if there is a distinct cluster of vaccine-caused cases, they will represent a small part of the statistical sample available for analysis. This makes their detection difficult.

More immediate limitations lie in the nature of the information often available concerning the reported cases. Most cases presented in the literature are severely under documented. The less the information reported about each case, the less the chance of finding constellations of features with possible causal significance. Many reports in the literature provide only the barest summary information about each case, with little indication of how the data were obtained that would permit an independent judgment of their reliability. In addition, frequently the data reported are simply not comparable from one report to another. Diagnostic criteria or ascertainment techniques for such data as time of vaccination and onset of the adverse event can differ so much that no meaningful comparison can be made between reports.

In view of such difficulties, the committee used information abstracted from case reports for the limited purpose of testing propositions found in the literature that particular constellations of features exist for events that are caused by vaccine. The information obtained is shown in the Case Report Review Form (Appendix A). Data included the source of the report, characteristics of the exposure and the subject, clinical features of the subject, clinical characteristics of the adverse event, and permanent sequelae of the event, if any. Despite the more than 100 cases abstracted, the committee was not able to identify a specific and consistent syndrome of vaccine-induced encephalopathy, the condition for which this question was considered most worth investigating in this manner.

In special circumstances, for example, in the absence of a controlled study or other epidemiologic data and in the presence of supportive clinical evidence, the committee considered that specific reports of an adverse event following vaccination might suggest a biologically plausible relation. This

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was true, as noted above, for the adverse events anaphylaxis and erythema multiforme or other rash. In the case of hemolytic anemia, a single striking case report was sufficient to suggest biologic relevance (see Chapter 6).

Historical Comparisons

Another aspect of case reports and case series that bears on the use of such evidence is their lack of external comparative observations. Accordingly, the measures of association described earlier in this chapter that provide evidence on the question of causation in general and, if affirmative, the extent of such causation are not attainable from these reports. In unusual circumstances, a case series may reflect the ascertainment of all cases from a defined population over a given period of time. It may therefore be possible to estimate rates of events for that population, and if such information is available for two distinct periods or over a very extended interval, historical comparisons or trends might be constructed. Such opportunities were not found, however, in the material available concerning pertussis or rubella vaccine and adverse events. Were it available, evidence of this kind would be applicable to the question of how much vaccine exposure might contribute to the occurrence of the event in the population.

Causation of the Individual Case

Case reports and case series data also bear on the question of causation of an individual case, for example, whether a given adverse event is an allergic response to pertussis vaccine. Individual cases of the adverse event could be examined to determine whether the event occurred in a clear sequence following each pertussis immunization in the series. An increasing severity of the event with increasing dose number would tend to support a causal interpretation. If the event tended to diminish in severity or was absent for later doses in the series, this evidence would tend to detract from a causal interpretation.

Although the temporal relation between the exposure and the event can at times seem to provide compelling evidence toward a causal interpretation, the possibility of simple coincidence, in light of the known background occurrence of most of the events under consideration, adds to the importance of careful evaluation of alternative explanations. Rarely, on the basis of case information alone, can alternative explanations be excluded.

Monitoring System for Adverse Events Following Immunization

Because of its prominence among sources of case reports, special note should be made of the CDC's Monitoring System for Adverse Events Fol

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lowing Immunization (MSAEFI). In this system (now replaced by the Vaccine Adverse Event Reporting System or VAERS; see below), data were collected on illnesses temporally associated with the administration of publicly purchased vaccines. Unlike "active" disease surveillance systems that use aggressive methods to identify all new or existing cases of disease (e.g., local cancer registries that actively review, on an ongoing basis, all discharge summaries at all hospitals within their catchment areas), MSAEFI calculated its incidence rates of adverse events following vaccination on the basis of voluntary reports from physicians, allied health professionals, and others. Being dependent on voluntary reports, MSAEFI is a "passive" surveillance system. Cases reported to MSAEFI between 1978 and 1990 were enumerated for each of the adverse events considered in this report (J. Mullen, Centers for Disease Control, personal communication, 1991).

The inherent limitations of MSAEFI must be kept in mind when interpreting these data. First, despite efforts to encourage physicians and allied health professionals to submit reports, MSAEFI is likely to have represented only partial ascertainment of reportable cases. This is because reporting depended on retention and reading of reporting guidelines, the presence of a suspicion of a possible connection between an event and immunization, and a decision by the parents or guardians to make a report. It is reasonable to expect that reporting of a given adverse event was therefore influenced by a number of factors, including the certainty of its clinical presentation or its proximity in time to vaccination. Second, clinical information was often obtained from family members and collected by nonmedical personnel. The information was sometimes clinically nonspecific, and although the MSAEFI reporting form was standardized, it may have been completed incorrectly. Third, all reports submitted to the CDC for illnesses with onset within 28 days of receipt of a vaccine and requiring a visit to a medical care provider were included in the MSAEFI data base, regardless of whether these were confirmed or whether alternative explanations of the illness were known. Neither of these factors was routinely recorded.

Changes effected in January 1985 alleviated some of these limitations, although MSAEFI was still not able to provide information about all illnesses following immunization. The system did generate useful data on secular trends of selected illnesses and indices of rates of illnesses and assisted in identifying risk factors that may predispose an individual to adverse events following immunization (Centers for Disease Control, 1984, 1986, 1989).

In November 1990, a new federal system replacing MSAEFI, VAERS, went into effect for the monitoring of adverse events after vaccination (Centers for Disease Control, 1990). Reports of adverse events from a variety of sources (e.g., health care providers, parents, and manufacturers) are now received by a single office. VAERS is operated by a private contractor with

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the support of the Public Health Service. VAERS data relevant to the committee's task were not available by the time of completion of this report.

ASSESSMENT OF THE EVIDENCE

Evaluation of Single Studies

The foregoing discussion of categories of evidence has indicated many features of experiments in humans and animals, controlled and uncontrolled observational studies, and comparative case series which are considered in the evaluation of single reports of such studies. It is important to emphasize the evaluation of the single study, because synthesis of an identified body of evidence begins with this step.

A systematic evaluation of a single study will take account of the hypothesis, the design, the methods of conduct and analysis,[3] and both the author's and the reviewer's conclusions and interpretations. This information was part of that abstracted from single studies as the first step in the committee's evaluation. (For details concerning the process of abstraction, the information obtained, and the Controlled Study Review Form, see Appendix A.)

In its review of single studies, the committee recognized that the completeness and reliability of the data, the appropriateness of analysis, and the exclusion of alternative interpretations or explanations of the results all require evaluation. The potential roles of bias and confounding need to be taken into account in studies in which measures of association are produced. Assessing the role of chance requires detailed information about the design and conduct of the study, but this can sometimes be accomplished even if the necessary calculations were not presented in the original report. (It is beyond the scope of this assessment to discuss the details of these aspects of assessment; standard textbooks of epidemiology [e.g., Kleinbaum et al., 1982; Mausner and Kramer, 1985; Rothman, 1986] may be consulted for further information.)

The validity of a study, which is the focus of this initial assessment, is rarely an absolute judgment but differs by degree for different aspects of the study. Strengths and limitations of individual studies, in various re

[3] A special note concerning the reporting of incidence rates of adverse events following pertussis immunization is merited. Incidence rates are usually cited either as rates per individual dose or rates per child (generally three doses). When available in a given study, the committee reported both rates, although the latter was thought to be preferable, since the committee was concerned with risk to the individual and since risk often varies across doses (see the example of shock and "unusual shock-like state" in Chapter 6).

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spects, are to be anticipated. Weighing of these in a quantitative sense is, to varying degrees, possible, especially in the context of certain (but not all) methods of meta-analysis (see section on meta-analysis below). Usually, a subjective sense of the merit of the results of a given study carries over from the initial evaluation to the stage of integrating results from the whole body of available evidence.

Integration of the Collective Results

Inferences concerning causality are commonly made on the basis of epidemiologic and related biomedical evidence. Many policy decisions and practical actions are based on such inferences made by persons with widely varied backgrounds—professional and nonprofessional, technical and nontechnical. The process of reaching such conclusions is ordinarily personal and often is private. By contrast, when this process is conducted formally in the manner of the present review, it is collective and interactive. As indicated earlier in this chapter, it is also desirable that reasoning be made explicit, in order that others may be enabled to evaluate the committee's conclusions independently.

Two aspects of the integration of evidence used by the committee are explained here. First is the quantitative approach of meta-analysis whose principles and methods are discussed briefly below. In the four instances in which it was deemed appropriate, this approach was applied and the results are presented in the corresponding section below. For the remainder of the types of adverse events for which meta-analyses were not undertaken, the committee's rationale for not doing so is provided.

The second aspect is the partially quantitative, but largely qualitative, process sometimes termed *causal inference,* for which a general approach has long been recognized in the epidemiologic literature. This will also be discussed below, to indicate the committee's view of that approach and its application to the present evaluation.

Meta-Analysis

A review of the major studies on which this report is based suggests that the sample sizes of many studies are insufficient to detect clinically important excess risks. As will be seen in Chapter 5, for instance, a number of the studies on the timing of SIDS deaths relative to DPT immunization (studies that offer the least biased information on the potential impact of the vaccine on SIDS) describe so few cases that large relative risks cannot be ruled out.

When a number of sufficiently similar studies of the same adverse event are available, it is sometimes possible to pool statistical information from

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the studies to develop an estimate of the relative risk, or the odds ratio, of the event in question that is more precise than the estimates from the individual studies. After considering whether meta-analysis could be used to estimate the risk of a number of adverse events following pertussis or rubella vaccination, the committee decided that data adequate to justify a meta-analysis were available for four adverse events following pertussis immunization: febrile seizures, afebrile seizures, SIDS, and hypotonic, hyporesponsive episodes. For instance, seven studies with information on the timing of SIDS had sufficiently large sample sizes to be included in the calculation. Four of these studies had more satisfactory study designs because they included control groups. Because it was not clear that the studies were sufficiently homogeneous to be compared, the committee analyzed all seven studies together and then studied separately the four studies with better control groups. The details of these analyses are given in Chapters 4 and 5 and in Appendix D.

The committee was not able to use meta-analysis data for other adverse events, primarily because a sufficient number of comparable studies were not available. For most of the adverse events under consideration in this report, there exists, at most, one controlled epidemiologic study. There were four controlled epidemiologic studies of encephalopathy reviewed (see Chapter 4, Table 4-4), but these are dominated in size by a single study, the NCES. As described in Chapter 4, the NCES includes 389 children with encephalopathy, whereas the other available studies include a total of 29 cases of encephalopathy. Any pooled estimate based on these studies would clearly be dominated by the NCES results, so the committee judged that meta-analysis would not yield useful information.

Considerations in Inferring Causality

For each adverse event for which the evidence indicated the presence of an association with vaccine exposure, the committee assessed the applicability of each of six general considerations, patterned after those attributed to Hill (1971). Reflecting thought about the problem of causal inferences in chronic disease epidemiology that had evolved over several years, Hill proposed the following guidelines for judgment: strength of association, dose-response relations, temporally correct association, consistency of association, specificity of association, and biologic plausibility. It should be noted that Hill's formulation has often been applied to the question of what considerations are supportive of a causal interpretation of an association. The committee was charged with judging whether a causal interpretation concerning a particular adverse event was either supported or not supported by the evidence. Accordingly, these considerations were applied, where possible, to aid interpretation in both directions.

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Three of these considerations (strength of association, dose-response relation, and temporally correct association) can be applied to the findings of single studies and can therefore be regarded, in part, as measures of internal validity. Any of these considerations can be satisfied in some, but not necessarily in all, studies testing a particular causal hypothesis. The other three considerations (consistency of association, specificity of association, and biologic plausibility) are not necessarily study specific and depend to varying degrees on prior knowledge.

Strength of Association Strength of association is usually expressed in epidemiologic studies as the magnitude of the measure of effect, for example, relative risk or odds ratio. Generally, the larger the relative risk, the greater the likelihood that the vaccine-event association is causal or, in other words, the less likely it is due to undetected error, bias, or confounding. Measures of statistical significance such as p values are not indicators of the strength of association.

Dose-Response Relation The existence of a dose-response relation—that is, an increased strength of association with increased exposures or other appropriate relation—strengthens an inference that an association is causal.

Temporally Correct Association If an observed association is causal, exposure must precede the event by at least the duration of disease induction. The committee, in addition, considered whether the adverse event occurred within a time interval following vaccination that was consistent with current understanding of its natural history. The committee interpreted the lack of an appropriate time sequence as strong evidence against causation, but recognized that insufficient knowledge about the natural history and pathogenesis of many of the adverse events under review limited the utility of this consideration.

Consistency of Association Consistency of association requires that an association be found regularly in a variety of studies, for example, in more than one study population and with different study methods. The committee considered findings consistent across different categories of studies as being supportive of a causal interpretation of the evidence.

Specificity of Association Specificity of association is the degree to which a given exposure predicts the frequency or magnitude of a particular outcome; if the association of the exposure and the event is unique to both, a causal interpretation seems more strongly justified than when the association is nonspecific to both the exposure and the event. The committee

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recognized, however, that perfect specificity could not be expected given the multifactorial etiology of many of the adverse events under examination.

Biologic Plausibility Biologic plausibility is based on whether a possible causal association fits existing biologic or medical knowledge. The existence of a possible mechanism, such as an established association of the adverse event with natural disease (e.g., thrombocytopenic purpura following natural rubella infection), was thought to increase the likelihood that the vaccine-event association could be causal.

Other Considerations As noted above, it is important also to consider whether alternative explanations—error, bias, confounding, or chance—might account for the finding of an association. If an association could be sufficiently explained by one or more of these considerations, there would be no need to invoke the several considerations listed above. From this viewpoint, an inference of causation could be based solely on the exclusion of these alternatives. Because these alternative explanations can rarely be excluded sufficiently, however, assessment of the applicable considerations listed above almost invariably remains. The final judgment is then a balance between the strength of support for the causal interpretation and the degree of exclusion of alternatives.

Other considerations were also entertained in the evaluation of the evidence of association. One special consideration in evaluating summary evidence on the relation of adverse events to pertussis or rubella immunization was that of the variation in vaccine composition observed across manufacturers.

With respect to the whole-cell pertussis vaccine, for example, the committee recognized that methods of production, seed bacteria, preservatives, and adjuvants used in manufacturing the vaccine have varied substantially over the years (Cox et al., 1987; Ross, 1988) and vary even now by manufacturer and country. In some countries, such as the United States, adsorbed vaccines are used exclusively. In others, both plain (fluid) and adsorbed vaccines are available, and in some, only plain vaccines are available. In most countries, pertussis immunization is given in conjunction with diphtheria and tetanus toxoids in a combined DPT product. In countries where inactivated polio vaccine is used, a quadruple antigen (diphtheria, tetanus, pertussis, and polio) vaccine is used. In yet other countries, pertussis vaccine is given primarily as a monovalent vaccine.

The committee also recognized that pertussis immunization schedules have varied markedly by country and time period. In the United States, for example, DPT vaccine is currently administered in five doses at ages 2, 4, 6, and 18 months and 4 to 6 years (American Academy of Pediatrics, 1988).

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In The Netherlands, DPT-polio vaccine is given in four doses at ages 3, 4, 5, and 11 to 14 months (Health Council of The Netherlands, 1987). Rubella-containing vaccines, like pertussis vaccine, have also varied considerably across place and time. For example, three vaccine strains were used initially in the United States following licensure in 1969-1970: HPV-77 (duck embryo), HPV-77 (dog kidney), and Cendehill (rabbit kidney) (Hilleman et al., 1969; Meyer et al., 1969; Prinzie et al., 1969). Soon after, the RA 27/3 human diploid fibroblast vaccine was licensed in Europe (Plotkin et al., 1969), and both the HPV-77 (dog kidney) and the Cendehill vaccines were subsequently withdrawn from U.S. licensure. In 1979, RA 27/3 was licensed in the United States, and the HPV-77 (duck embryo) vaccine was withdrawn, leaving RA 27/3 as the only U.S.-licensed rubella vaccine (Perkins, 1985).

In addition to strain variations, rubella-containing vaccines also vary in composition. In the United States, and increasingly elsewhere, rubella vaccines are combined in a triple vaccine also containing measles and mumps vaccine viruses (MMR). However, bivalent vaccines containing rubella and measles or rubella and mumps vaccines are also used.

What, then, are the implications of these variations in vaccine composition and schedules for the evaluation of vaccine-adverse event associations? With respect to rubella vaccines, rates of arthritis and arthralgia following immunization were found to differ by strain (see Chapter 7). Integration of evidence across studies was therefore problematic. This issue was considered moot with respect to radiculoneuritis and other neuropathies and thrombocytopenic purpura, since the evidence for these adverse events was limited to isolated case reports.

Unlike rubella vaccines, however, the committee considered the potential problem of variability in whole-cell pertussis vaccine composition to be much greater. For example, in the last 10 years of testing of pertussis vaccines at the National Institute for Biological Standards and Control (NIBSC) in the United Kingdom, whole-cell vaccines have shown wide variation in biologic activity from batch to batch, although with no significant time-related trends (K. Redhead, National Institute for Biological Standards and Control, personal communication, 1990). Testing did reveal that plain pertussis vaccines are usually more active than adsorbed vaccines, a finding consistent with studies cited in the report (e.g., Pollock et al., 1984) which indicate that the frequency of moderate systemic reactions following primary immunization with adsorbed DPT vaccine is similar to that with adsorbed DT vaccine, but considerably less than that with plain DPT vaccine.

In summary, the general approach to evaluation outlined in this chapter was applied to each type of adverse event as dictated by the nature of the available evidence.

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THE NATURE OF THE CONCLUSIONS

This chapter has demonstrated that judgments about the possible causation of adverse events by pertussis or rubella vaccine and similar causal questions reflect both quantitative and qualitative reasoning. Some final observations will help to clarify the nature of the committee's conclusions.

Quantitation

Resolution

Resolution refers to the fineness or sharpness of detail that can be discriminated by a particular mode of observation. In light microscopy, for example, observations are described by reference to the optical properties of the lens, such as 10x, 100x, or higher magnification. Electron microscopy, with very much higher resolution, distinguishes structural features not detectable with light microscopy.

Resolution in epidemiologic studies concerns the capacity of a study to discriminate between the frequencies of events or of exposures between groups in order to determine the presence or absence of associations. By analogy, resolution in epidemiology also depends in a sense on magnification, that is, on the order of magnitude of the numbers of participants—for example, from tens to hundreds of cases and controls in case-comparison studies and from hundreds to thousands of exposed and unexposed subjects in cohort studies. With equally valid observations, results based on the experience of increasing numbers of persons, from single individuals to tens, hundreds, or thousands of individuals, provide successively greater resolution.

The resolution or discriminating capacity of epidemiologic studies could theoretically be increased indefinitely through ever larger study populations. However, there are many constraints on the feasibility of large studies. Rarity of exposures or events or other circumstances may limit the resolution even of large studies. Meta-analysis can, under the appropriate circumstances discussed above, be used to offset the limited size of individual studies, but the collective magnitude of the contributing studies may still be less than desired. It should be emphasized that in all such studies the potential for bias is a key problem and that enlarging the study only reduces random error, not systematic error. Therefore, if bias is present, a firmer but still erroneous conclusion will result from a larger study than from a smaller one.

Power calculations indicate the probability of achieving discrimination of a predetermined degree under the design of a given study. Power is thus a quantitative measure of the capacity of a study to achieve a given degree

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of resolution. In particular, it provides guidance against overconfidence in the absence of an association when a study with relatively low power has failed to demonstrate one. As such, it is an aid in appreciating the nature of the evidence that underlies conclusions about causation and is described further here to indicate its role in the present review.

As discussed earlier in this chapter, two types of error must be taken into account in designing and interpreting statistical tests. Epidemiologic studies are often designed to provide statistical tests that minimize *type I error,* the probability that the null hypothesis is falsely rejected. Commonly, such tests are designed so that there is less than a 5 percent chance that the test will incorrectly indicate an association between a vaccine and an adverse event if no association truly exists. For any given test and sample size, on the other hand, there is some chance that the test will err in failing to find an association when one truly exists. This is called a *type II error.* The chance of making such an error increases when both the true excess risk and the sample size are small. From another perspective, given a particular sample size and a specified probability of a type I error, one can calculate the power of a test to detect an assumed association of a given magnitude. Because the power of a test is the opposite (technically, the complement) of the probability of making a type II error, the power of a test increases when both the true excess risk and the sample size are large.

For example, Shields and colleagues (Melchior, 1977; Shields et al., 1988) compared the ages of onset of various disorders under different vaccination schedules in two time periods in Denmark and found no statistically significant differences between the two periods in the onset of infantile spasms. However, there were only 80 cases of infantile spasms in the two study periods combined, and the lack of a significant statistical association may therefore reflect the small sample size rather than a true absence of association. In other words, if this investigation were replicated in a country with more cases of infantile spasms than occurred in Denmark, a statistically significant difference might be detected, if the relation was, in truth, causal.

Furthermore, according to the power calculations described in Appendix D, if 50 percent of cases of infantile spasms were caused by pertussis vaccine, there would be nearly a 90 percent chance that a sample of the size used by Shields and colleagues would detect this relationship. If, on the other hand, only 25 percent of the cases of infantile spasms were caused by pertussis vaccine, Shields and colleagues' test has about a 45 percent chance of detecting the relationship.

Power calculations are also valuable in interpreting apparently conflicting results of multiple studies of the same vaccine-adverse event combination. If findings of no association were concentrated in the low-power studies, for instance, the suggestion that no association exists would be weakened.

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Because power calculations help to illuminate an important aspect of the uncertainty in the evidence it evaluated, the committee decided to calculate, whenever possible, the power of the statistical tests on which its conclusions were based. These calculations are described in Appendix D.

Uncertainty and Confidence

All science, including the spectrum from particle physics to astrophysics, is characterized by uncertainty. Scientific conclusions concerning the result of a particular analysis or set of analyses can range from highly uncertain to highly confident. As discussed earlier in this chapter, the theoretical concept of proof does not apply in evaluating actual observations. In its review, the committee attempted to assess the degree of uncertainty associated with the results on which it had to base its conclusions.

For individual studies, confidence intervals around estimated results such as relative risks represent a quantitative measure of uncertainty. Confidence intervals present a range of results that, with a predetermined level of probability, include the true relative risk being estimated. When it is possible to use meta-analysis to combine the results of different studies, a combined estimate of the relative risk and confidence interval may be obtained. Appendix D describes the methods used for meta-analysis in the report.

For an overall judgment about causation based on a whole body of evidence, beyond the results of single studies or of meta-analyses, no quantitative method exists for characterizing the uncertainty of the conclusions. Thus, to assess the appropriate level of confidence to be placed on the ultimate causal conclusions, it may be useful to consider qualitative as well as quantitative aspects.

Quality

Comprehensiveness

An important aspect of the quality of a review such as the present one is comprehensiveness. This is to ensure against the possibility of any serious omission or inappropriate exclusion of evidence from consideration. If any such omission should be identified, a determination would be needed of whether its inclusion would likely affect the overall results and, if so, in what way.

In this report the committee has documented in detail its approach to seeking and identifying the evidence to be reviewed (see Appendix A, Strategies for Gathering Information). Numerous parties were invited to supplement the materials already under review and to notify the committee of any recognized omissions of importance.

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Neutrality

Neutrality is another important consideration in the quality of such conclusions as those presented by the committee. This is to ensure a fair weighing of all of the evidence. In this connection, the committee avoided the posture of the burden of proof approach, as discussed earlier in this chapter. The essential evidence, its main strengths and limitations, and the conclusions that follow are stated for each adverse event considered.

Judgment

The evaluation of evidence to reach conclusions about causation goes beyond quantitative procedures, at several stages: assessing the relevance and validity of individual reports; deciding on the possible influence of error, bias, or confounding on the reported results; integrating the overall evidence, within and across diverse areas of research; and formulating the conclusions themselves. These aspects of the review required thoughtful consideration of alternative approaches at several points. They could not be accomplished by adherence to a prescribed formula.

Rather, the approach described here evolved throughout the process of the review and was determined in important respects by the nature of the evidence, exposures, and events at issue. Both the quantitative and the qualitative aspects of the process that could be made explicit were important to the overall review. Ultimately, the conclusions expressed in this report about causation are based on the committee's collective judgment. The committee endeavored to express its judgments as clearly and precisely as the available data allowed.

SUMMARY OF THE EVIDENCE

Table 3-1 summarizes the types of evidence reviewed for each adverse event and the respective contribution of each to the committee's judgments about causation. The evidence is organized under five headings: (1) human experiments; (2) animal experiments; (3) case-comparison, cohort, and other controlled studies, (4) case reports and case series; and (5) biologic plausibility. The first four categories were discussed earlier in this chapter. The fifth category, biologic plausibility, includes background knowledge concerning the pathophysiology of an adverse event, attributes of a particular vaccine, or other biologic information derived from research in such areas as immunology and physiology.

Where evidence was available in a particular category, the committee judged whether that evidence was generally supportive or not supportive of causation or whether it was insufficient for a determination. For example,

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TABLE 3-1 Categories of Evidence Reviewed for Each Adverse Event: Is the Evidence Supportive of Causation?[a]

Vaccine and Adverse Event (Chapter of Report)	Human Experiments			Animal Experiments			Case-Comparison, Cohort, and Other Controlled Studies			Case Reports and Case Series			Biologic Plausibility		
	Yes[b]	?[c]	No[d]	Yes	?	No	Yes	?	No	Yes	?	No	Yes	?	No
DPT															
Infantile spasms (4)									X		X				
Hypsarrhythmia (4)			X								X				
Aseptic meningitis (4)								X			X				
Acute encephalopathy[e] (4)					X		X			X				X	
Chronic neurologic damage (4)					X			X			X			X	
Sudden infant death syndrome (5)									X		X				
Anaphylaxis (6)					X			X		X			X		
Autism (6)															
Erythema multiforme or other rash (6)											X		X		
Guillain-Barré syndrome (polyneuropathy) (6)											X				
Peripheral mononeuropathy (6)											X				
Hemolytic anemia (6)											X		X		

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Juvenile diabetes (6)					X			X			X				
Learning disabilities and hyperactivity (6)									X		X				
Protracted inconsolable crying and screaming (6)							X			X				X	
Reye syndrome (6)								X				X			
Shock and "unusual shock-like state" (6)								X		X					X
Thrombocytopenia (6)											X				
RA 27/3 Rubella															
Arthritis (7)															
Acute	X						X			X				X	
Chronic		X								X				X	
Radiculoneuritis and other neuropathies (7)											X			X	
Thrombocytopenic purpura (7)											X			X	

[a]Blanks for any given category of evidence indicate that evidence of this kind is lacking.
[b]Yes, Evidence of this kind is supportive of causation.
[c]?, Evidence of this kind cannot be classified either as supportive or as not supportive of causation.
[d]No, Evidence of this kind is not supportive of causation.
[e]Defined in controlled studies reviewed as encephalopathy, encephalitis, or encephalomyelitis.

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where there were relevant controlled studies which, overall, had relative risks of greater than 1, the evidence was classified as "supportive of causation." Blanks for any given category of evidence indicate that evidence of that type was lacking. It is important to note that any one category of evidence generally was not sufficient in itself to support a conclusion of causality, since other aspects of the evidence, including the number and quality of contributing studies, the details of results obtained, and other considerations outlined earlier in this chapter all weighed into the committee's evaluation.

The committee found it convenient to classify its conclusions about each adverse event under one of five categories, reflecting the strength and direction of its conclusions. These categories are:

1. **No evidence bearing** on a causal relation
2. Evidence **insufficient to indicate** a causal relation
3. Evidence **does not indicate** a causal relation
4. Evidence **is consistent with** a causal relation
5. Evidence **indicates** a causal relation.

The remaining chapters elaborate on the evidence assembled as the basis of the committee's findings and conclusions.

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4

Evidence Concerning Pertussis Vaccines and Central Nervous System Disorders, Including Infantile Spasms, Hypsarrhythmia, Aseptic Meningitis, and Encephalopathy

INFANTILE SPASMS

Clinical Description

Infantile spasms are a type of epileptic disorder in young children characterized by flexor (34 percent), extensor (22 percent), and mixed flexor-extensor (42 percent) seizures that tend to occur in clusters or flurries (Kellaway et al., 1979). The earliest manifestations of infantile spasms can be subtle and are easily missed, making it difficult to identify the precise age at onset.

Infantile spasms, in combination with an electroencephalogram (EEG) pattern of hypsarrhythmia and psychomotor retardation or regression, is referred to as West syndrome. Approximately 80 percent of infants with infantile spasms have, at some time, a characteristic EEG pattern of hypsarrhythmia, whereas this pattern is seen in only ~4 percent of cases with other types of epilepsy (Jeavons and Bower, 1964). The hypsarrhythmic EEG pattern usually disappears with maturation, and ~50 percent of cases may have normal EEGs by age 8 years, although ~65 percent of children with infantile spasms will go on to have other types of seizures (Glaze and Zion, 1985).

Descriptive Epidemiology

Age-specific incidence rates are not available, although the vast majority of studies report a peak onset between ages 4 and 6 months (Cowan and

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Hudson, in press). For 85 to 90 percent of cases, onset of spasms is within the first year of life. Incidence rates of infantile spasms range from 0.25 per 1,000 live births in Denmark and the United States to 0.4 per 1,000 live births in Finland (Leviton and Cowan, 1981).

Most investigators divide infantile spasms cases into two categories which are defined on the basis of the presence or absence of a presumed cause and the child's developmental status prior to the onset of spasms. What are commonly referred to as "symptomatic cases" are those in whom a presumed cause can be identified. Idiopathic cases are defined as infants with no identifiable causes for their spasms. This group is further subdivided by some into cryptogenic (those for whom there is no known cause of infantile spasms and whose development was essentially normal prior to the onset of spasms; ~10 percent of all cases) and doubtful (those for whom there is no known cause of infantile spasms but whose development prior to the onset of spasms may have been delayed).

Those cases considered to be idiopathic range between 30 and 50 percent (Cowan and Hudson, in press), although this proportion may be declining because of more sensitive diagnostic methods, such as neuroimaging techniques and positron tomography (Chugani et al., 1990). However, although approximately 70 to 90 percent of infantile spasms cases are reported to have abnormal computed tomography (CT) scans (Glaze and Zion, 1985; Pinsard and Saint-Jean, 1985), the significance of some CT diagnoses, for example, cortical atrophy, has been questioned (Ludwig, 1987). Thus, it is unclear that the proportion of infantile spasms cases considered to be idiopathic is really decreasing because of improved diagnosis of cerebral anomalies.

Among symptomatic cases, presumed causes are frequently grouped according to the timing of the suspected insult as occurring pre-, peri-, or postnatally. Prenatal factors are thought to account for 20 to 30 percent of cases. This category includes cerebral anomalies, chromosomal disorders, neurocutaneous syndromes such as tuberous sclerosis, inherited metabolic disorders, intrauterine infections, family history of seizures, and microcephaly (Bobele and Bodensteiner, 1990; Kurokawa et al., 1980; Ohtahara, 1984; Riikonen and Donner, 1979). Perinatal factors are thought to account for from 25 to 50 percent of infantile spasms cases. This category includes perinatal hypoxia, birth trauma, and metabolic disorders (Kurokawa et al., 1980; Pollack et al., 1979). Approximately 8 to 14 percent of infantile spasms are attributed to postnatal factors, including central nervous system (CNS) infections, trauma, immunizations, and intracranial hemorrhage (Bobele and Bodensteiner, 1990; Gibbs et al., 1954; Kurokawa et al., 1980; Lombroso, 1983a). Few of these factors have been subjected to systematic investigation, however, and the etiology of infantile spasms remains unknown for 30 to 50 percent of cases (Cowan and Hudson, in press).

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History of Suspected Association with Pertussis Vaccines

Among the earliest case reports suggesting a possible link between infantile spasms and pertussis immunization are those of Baird and Borofsky (1957). They described 24 children who had hypsarrhythmia and infantile myoclonic seizures and whose development prior to the onset of spasms was apparently normal. Nine cases of infantile spasms were reported to have occurred between 1 and 5 days after DPT vaccination. Three of these nine children also had a history of perinatal complications that the authors thought might have been related to a risk of infantile spasms. The authors also stated, on the basis of a review of published EEG tracings, that hypsarrhythmia was present in two of the affected children described by Byers and Moll (1948). Since these early case reports, additional cases of infantile spasms in association with pertussis immunization have been described in the literature (Fukuyama et al., 1977; Millichap, 1987; Portoian-Shuhaiber and Al Rashied, 1986). The time intervals reported between vaccination and the onset of infantile spasms have been from minutes to weeks (Melchior, 1971).

Evidence from Studies in Humans

Case Reports and Case Series

One of the largest case series of infantile spasms following pertussis immunization was published by Millichap (1987). Six children ranging in age from 2 to 9 months were included. The time interval from immunization to the onset of spasms was from 6.5 hours to 5 days, and first seizures were reported to have occurred in conjunction with the first, second, or third doses of pertussis vaccine. Except for one case who had experienced myoclonic seizures since birth, no mention was made of the children having seizures prior to immunization. In reviewing the etiology and treatment of infantile spasms, Millichap (1987) listed the postulated mechanisms for pertussis-related seizures as (1) a direct neurotoxic effect, (2) an immediate immune reaction, (3) delayed cellular hypersensitivity reaction, and (4) vaccine-induced activation of a latent neurotropic virus infection.

In addition to the variability in age at the time of onset of spasms, associated vaccine dose, and time from immunization to the onset of spasms, there was no consistent pattern in the types of neurologic abnormalities reported in conjunction with infantile spasms. These included spastic diplegia, psychomotor retardation, hypotonic diplegia, and progressive neurologic deterioration. Not all children with infantile spasms have other neurologic or developmental problems, and when they do, diversity of expression of these associated neurologic conditions is typically reported (Lacy and Penry, 1976). This case series

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provides some of the better clinical descriptions available in the published literature of seizures occurring after immunization with DPT. Although typical of many cases of infantile spasms, information from this series also suggests that there is no consistent syndrome of neurologic manifestations among children whose spasms follow DPT immunization.

Fukuyama and colleagues (1977) studied 185 cases of infantile spasms seen in the Department of Pediatrics of the Tokyo Women's Medical College from 1968 to 1972. Table 2 of their paper lists "DPT or DT" as one of the types of vaccines to which cases were exposed, whereas the text and all other tables and figures refer to "DPT or DP." Thus, although there is some uncertainty about the precise vaccines to which these children were exposed, the committee considered DP to be the exposure the authors intended to describe. Complete information on immunization histories and health status prior to vaccination was available for 110 of the 185 infantile spasms cases. Of these 110 children, 22 (20 percent) had been immunized within 1 month of the onset of spasms, 10 with DPT or DP vaccine alone, 5 with DPT vaccine in combination with one or more other vaccines, 4 with smallpox vaccine alone, 2 with Japanese encephalitis vaccine alone, and 1 with polio vaccine alone. Of the 15 cases of infantile spasms with onset after immunization with either DPT or DP vaccine alone or DPT vaccine in combination with another vaccine, onset occurred after the first immunization in 3 cases, after the second in 10 cases, and after the third in 2 cases. The interval from immunization to the reported onset of spasms ranged from less than 48 hours to more than 7 days. The remaining cases had been vaccinated either more than 1 month before or more than 1 month after the onset of spasms (n = 44, 40 percent) or had never been immunized (n = 44, 40 percent). The authors gave no indication that any of the cases had had whooping cough, either before or after the onset of infantile spasms.

The authors considered vaccination as the etiology of infantile spasms if cases met the following three criteria: (1) no other identifiable cause, (2) normal development prior to the onset of spasms, and (3) the interval from immunization to the onset of spasms was within 48 hours for pertussis-containing vaccines and within 18 days for smallpox, polio, and Japanese encephalitis vaccines. Given these criteria, 5 of the 110 cases were considered by the authors to have infantile spasms caused by vaccination. It was not possible to determine from the data given in the paper how many of these five cases followed administration of DPT vaccine, since detailed information was given only for three of the five cases. At least one of the five cases occurred following smallpox vaccination alone, and at least two occurred following administration of DP vaccine.

It could not be determined from the information provided whether cases were representative of all those with infantile spasms from a defined geographic area or whether they were a selected group who were referred to

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these experts in pediatric neurology. The investigators acknowledged that because there is no biologic marker for vaccine-associated infantile spasms, the assignment of cause was made "solely from the clinical standpoint." They stated that because of the diversity of the etiology of infantile spasms, "there is still free space for any agent to be suspected as an injurious factor causative of infantile spasms" (Fukuyama et al., 1977, p. 229).

Jeavons and colleagues (1970) reported on a follow-up of 98 cases of infantile spasms, 13 of which were attributed to immunization (type not specified). The follow-up ranged from 4 to 12 years. Outcomes were similar in the cryptogenic and immunization groups, among whom the survivorship, percent without neurologic abnormality at follow-up, and percent in regular school were higher than for those cases of infantile spasms attributed to perinatal or other causes (e.g., tuberous sclerosis).

Factors that should be considered in evaluating the study findings are that the patient groups were highly selected, the different lengths of follow-up were not considered in comparing outcomes among the groups, criteria for defining mental outcome were not given, and developmental status at follow-up was not ascertained uniformly for all cases. The first weakness affects the generality of the findings, and the last three problems given above make it difficult to compare outcomes between the groups studied.

Fifty-eight cases of infantile spasms (International Classification of Disease [ICD] 9 code 345.6 includes hypsarrhythmia and drop seizures) occurring within 28 days of DPT immunization were reported through the Centers for Disease Control's (CDC's) Monitoring System for Adverse Events Following Immunization (MSAEFI) system from 1978 to 1990, a period in which approximately 80.1 million doses of DPT vaccine were administered through public mechanisms in the United States (J. Mullen, Centers for Disease Control, personal communication, 1990). Of these 58 cases, 41 (71 percent) also received at least one other vaccine at the time of DPT immunization. No follow-up of the cases was made, and a physicians's diagnosis was not required.

Controlled Epidemiologic Studies

If pertussis immunization were an important cause of infantile spasms, then one could expect a change in the ages at which immunizations were given to be followed by a change in the ages at the time of onset of infantile spasms. This issue was specifically addressed in a study by Melchior (1977) that examined changes in the distributions of ages of onset of infantile spasms and changes in the ages of immunization in Denmark. Prior to April 1, 1970, DPT vaccine was given to Danish children at ages 5, 6, 7, and 15 months. After that date, monovalent pertussis vaccine was given at ages 5 and 9 weeks and 10 months.

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Melchior (1977) compared the distributions of ages at the time of onset of infantile spasms for two time periods, 1957 to 1967 and 1970 to 1975, which encompassed the different immunization schedules. Although there was some increase from the first to the second time period in the percentage of cases with onset under age 3 months (12 versus 23 percent), there was no significant difference in the overall distributions of age at onset for the two time periods. In both time intervals, the peak ages at onset for infantile spasms were in the 4- to 6-month range.

In addition to the comparison of the age distributions, medical records of the 113 cases of infantile spasms from 1970 to 1975 were examined to determine possible etiologies. Sixty cases were considered by the authors to be symptomatic, 40 were considered to be cryptogenic, and 13 were due to immunization. Of the 13 cases attributed to vaccination, 6 occurred after receipt of the monovalent pertussis vaccine and 7 occurred after receipt of diphtheria-tetanus-polio triple vaccine. Thus, infantile spasms occurring after immunization were reported in approximately equal numbers following administration of pertussis-and non-pertussis-containing vaccines.

After mid-1970, the "potency of the pertussis vaccine was reduced by 20 percent and the aluminum adjuvant was removed" (Shields et al., 1988, p. 802). Thus, immunization schedule was not the only factor that was different in the two time periods. In addition, the total number of immunizations given in the population for pertussis and for diphtheria-tetanus-polio was not reported, and therefore, the rate of infantile spasms associated with each type of immunization cannot be determined and, therefore, it is not possible to determine whether the risks are equivalent.

Another potential limitation of Melchior's (1977) study is that cases identified for the first time interval (i.e., 1957 to 1967) were taken from a previous study and did not represent a nationwide survey or a national sample of all cases. Thus, it is possible that they had an unusual distribution of onset ages and were not appropriate for comparison with the 1970 to 1975 cases, which included all children with infantile spasms in Denmark. However, the range of peak age at the time of onset for the cases from the earlier interval corresponds to that usually reported, and thus, they are probably not a biased group with respect to age.

A similar analysis, also based on data from Denmark, was done by Shields and colleagues (1988). The study considered the frequencies of epilepsy, febrile seizures, infantile spasms (as a subgroup of all cases of epilepsy), and CNS infections (bacterial meningitis and aseptic meningitis) in children aged 1 month to 2 years identified from hospital or outpatient clinic records from 12 of 22 pediatric departments in Denmark. Two time periods, 1967 to 1968 and 1972 to 1973, were selected for comparison to reflect changes in the immunization schedule and in vaccine composition.

The exact dates of pertussis immunization were known for 372 children

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in the first time period and for 432 children in the second time period. Comparison of the distributions of the ages at the time of immunization for the two time intervals showed a marked difference in the frequency of immunization at different ages, corresponding with the ages at which immunizations were recommended. That is, in the 1967 to 1968 interval the peak ages at immunization were 5, 6, 7, and 15 months, while for the 1972 to 1973 interval immunizations peaked at ages 5 and 9 weeks and 10 months. Despite this difference, however, there was no significant difference in the age distributions of incident cases of infantile spasms in the two time periods. The results of this study are thus not consistent with the hypothesis that pertussis immunization is associated with the risk of infantile spasms, since there was no change in the distribution of ages at the time of onset when the ages at immunization were changed. However, only 80 cases were included in the study, and given this relatively small sample size, the study had a low statistical power to detect a difference in the distributions unless the association of infantile spasms and pertussis immunization was relatively large (see Appendix D). For instance, even if 29 percent of all cases of infantile spasms were caused by DPT immunization, the data of Shields and colleagues would have only about a 50 percent chance of finding a significant difference. To have an 80 percent power, about 40 percent of all infantile spasms cases would have to be caused by DPT. The data abstracters were not masked to the hypothesis of the study, but all events in a defined population were included, and no attempt was made during data collection to relate the events to the time of immunization.

The North West Thames Study (Pollock and Morris, 1983) describes voluntary reports of suspected vaccine reactions from 1975 through 1981 and a separate review of hospitalized cases of neurologic disorders in children for 1979. During the 7 years of the study, approximately equal numbers of children in the population completed courses of DPT and DT immunizations (134,700 and 133,500, respectively). Most of these children were also given oral polio vaccine. During this 7-year interval, 1,172 reports of "vaccine-associated" events were received. Of these, 926 (79 percent) were considered to be "simple" reactions. Of the remaining 246 reports, 114 (10 percent) children experienced anaphylaxis or collapse, convulsions, neurologic disorders, or death. Forty-five (39 percent) of these more serious events were observed following receipt of DPT or monovalent pertussis vaccines, 20 (18 percent) occurred following DT immunization, 37 (32 percent) followed administration of the measles vaccine, and the remaining 12 (11 percent) followed immunization for rubella or other infectious diseases.

Five of the 114 children with more serious vaccine-associated reactions identified through the voluntary reporting system were diagnosed with infantile spasms. Among these five children, four had received DPT vaccine from 8 days to 6 weeks prior to the onset of spasms, and 1 had received the

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DT vaccine. The onset of infantile spasms reportedly occurred 1 month prior to immunization in the latter case. On the basis of these data, the relative risk (RR) is 4.0, but the 95 percent confidence interval (CI) is wide: 0.6 to 25.2. Despite the large denominators for these rates, the power of this test is low: 50 percent for an RR of 6.3 and 80 percent for an RR of 14.0.

In the review of discharge diagnoses for 1979, there were 682 children less than age 2 years who had relevant neurologic illnesses, and hospital records were obtained for 642 of them (94 percent). Five hundred twenty six (82 percent) of these children had febrile convulsions, but only three children with infantile spasms in association with immunization were reported from the review of discharge diagnoses. One child with infantile spasms attributed to *Haemophilus influenzae* meningitis had received DPT vaccine 19 days prior to the onset of spasms. A second child developed infantile spasms 6 weeks after DPT immunization, and the third child had onset of infantile spasms 12 weeks after immunization with the DT vaccine. Neither the expected number of cases of infantile spasms in a population of the size studied nor the number of cases identified in children who had not been immunized was reported. Thus, it is not possible to determine whether the observed cases were in excess of the expected number.

Results based on data from voluntary reporting of events thought to be associated with immunization and those based on data from review of discharge diagnoses are somewhat different. Although the number of cases of infantile spasms is small in both instances, voluntary reporting might suggest that infantile spasms occurred more often after DPT than after DT immunization, whereas review of discharge diagnoses found one case occurring after DPT immunization and one after DT immunization. The opportunity for bias is greater in the voluntary reporting data, since if a particular exposure is under suspicion as a cause of infantile spasms (in this case, the exposure being DPT), it is more likely that events occurring in temporal association with that exposure will be reported.

Walker and colleagues (1988) identified from medical and pharmacy records all cases of neurologic illnesses without an apparent predisposing cause in approximately 26,600 children born in Group Health Cooperative hospitals from 1972 to 1983. Medical records for cases and a control group born at the same hospitals during the same calendar period were reviewed for information on immunization status. Fifty-five cases of first afebrile seizures were identified; two of these children had infantile spasms, but the onset of spasms did not occur within 30 days of DPT immunization in either of them. The authors pointed out that since adrenocorticotropic hormone and steroids were not among the drugs for which pharmacy records were screened, some cases of infantile spasms may have been missed. However, only if these children had also not been hospitalized would they have been

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completely excluded from the study. In addition, children recently immunized with DPT vaccine would have to be more likely to be missed than children immunized more than 30 days prior to the onset of spasms.

The largest controlled study of the association between immunization and risk of infantile spasms was done among cases identified as part of the British National Childhood Encephalopathy Study (NCES) (Bellman et al., 1983a). This study is described in more detail later in this chapter. Briefly, the study included 269 children aged 2 to 35 months admitted to hospitals in England, Scotland, and Wales with a diagnosis of infantile spasms. Of these cases, 64 percent had EEGs with typical or atypical hypsarrhythmia, 30 percent had other EEG abnormalities, and 6 percent were reported to have normal EEGs (Bellman, 1983). Two controls were chosen for each case and were matched for age, sex, and area of residence. Immunization histories of cases and controls were obtained from the records of the children's general practitioners. Risk of infantile spasms associated with immunization was assessed within four time intervals, defined by the following days postimmunization: 0 to 6 days, 7 to 13 days, 14 to 20 days, and 21 to 28 days. For the first period, the RR was 1.2 with a 95 percent CI of 0.5 to 3.0 (Miller et al., 1988). With a sample of the size used, there was 50 percent power to detect an RR of 2.5 and 80 percent power to detect an RR of 3.7.

Among the cases, 9 percent had been immunized with DPT vaccine within the preceding 28 days and 8 percent had been immunized with DT vaccine during the same time interval. Comparable percentages for the matched controls were 13 percent for DPT vaccine and 9 percent for DT vaccine. Immunization with neither DPT nor DT vaccine was statistically significantly associated with an increased risk of infantile spasms in any 7-day interval examined. However, risks of infantile spasms were higher within the first 7 days following administration of both DPT and DT vaccines than they were for the other three time periods, when there appeared to be a deficit of infantile spasms cases (RRs for the four time periods 0 to 6, 7 to 13, 14 to 20, and 21 to 28 days were 1.2, 0.6, 0.4, and 0.6, respectively, following DPT immunization and 1.3, 0.7, 0.8, and 0.5, respectively, following DT immunization). These differences in risk across time periods, however, were not statistically significant. Similar results were observed when analyses were confined to the 152 cases who were apparently neurologically normal prior to the onset of infantile spasms (RRs for the four time periods 0 to 6, 7 to 13, 14 to 20, and 21 to 28 days were 2.5, 0.3, 0.5, and 1.5, respectively, following DPT immunization and 2.0, 0.4, 1.0, and 0.3, respectively, following DT immunization). Whether the apparent clustering of cases that was observed within the first 6 days after immunization for both DPT and DT represents a triggering phenomenon, bias in assigning the date of onset of spasms, or simply a chance observation cannot be determined from these data. Looking at cases immunized within 28 days of

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diagnosis (a period similar to that used in the other controlled studies on infantile spasms), the RR was 0.6 (95 percent CI, 0.4 to 1.0) for all children in the NCES study and 0.7 (95 percent CI, 0.5 to 1.6) for previously normal children (Bellman et al., 1983a). The power of a test based on these data is somewhat higher than one based on data from the early period only (i.e., 0 to 6 days). For all children in the study, there was 50 percent power to detect an RR of 1.6 and 80 percent power to detect an RR of 2.0. For the previously normal children, the respective RRs were 1.9 and 2.4.

The NCES is the largest population-based, controlled study of the association of immunization and risk of infantile spasms. A limitation of the NCES data with respect to infantile spasms was the lack of a uniform case definition, in that children were considered infantile spasms cases if they were so designated by the admitting physician (Bellman et al., 1983b). Those conducting the NCES were notified of cases by physicians from all of England, Scotland, and Wales, and no set of standardized clinical criteria were used. In addition, 41 percent (48 of 116) of previously normal infantile spasms cases were in the "normal-normal" group (Alderslade et al., 1981). That is, they were considered to be neurologically normal both before their initial admission for infantile spasms and at 15 days postadmission or discharge. Although the prognosis for children with infantile spasms without a known cause and who are developmentally normal prior to the onset of spasms is reported to be better than that for symptomatic cases (Lacy and Penry, 1976), 41 percent is a rather high proportion of cases to "recover" from infantile spasms within 2 weeks. This raises the question as to whether these children really had infantile spasms, because the diagnosis was not confirmed and no uniform rules for diagnosis were applied to the group of potential cases. What effect the inclusion of children without infantile spasms would have had on the analysis depends on the true nature of the associations of their conditions with pertussis vaccination.

Comparisons of the estimates of risk of infantile spasms done separately for DPT and DT vaccinees can be used to examine the influence of the pertussis component of the vaccine. The fact that nearly identical results were observed for children who received the DPT and DT vaccines suggests that exposure to the pertussis component of the DPT vaccine does not increase the risk of infantile spasms.

The Study of Neurological Illness in Children (SONIC) was a large case-control investigation of the association between the risk of serious acute neurologic illness and DPT immunization in young children. A detailed description of SONIC is given later in this chapter. Briefly, the study was conducted in the states of Washington and Oregon from August 1, 1987, through July 31, 1988, and included children aged 1 to 24 months. Cases were identified primarily through systematic review of emergency room, outpatient clinic, and inpatient discharge listings. A panel of international

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experts on neurologic illnesses in children confirmed diagnoses by review of medical records and the use of uniform, prespecified criteria. The panel was unaware of the immunization history of cases. Two controls per case were selected from birth certificate registries of the states of Washington and Oregon. Controls were matched to cases by age (within 5 days), sex, and county of birth. Immunization histories for both cases and controls were obtained from interviews with parents, and attempts were made to validate these data by using medical records.

Preliminary findings from SONIC have been reported recently (Gale et al., 1990). In the population studied, 10 incident cases of infantile spasms were identified. Of these, three had onset of spasms within 28 days following immunization with DPT. A six fold increased risk of infantile spasms among children exposed to DPT within 28 days was observed. These results suggest the possibility that recent exposure to DPT is related to an increased risk of infantile spasms. However, the number of cases on which this estimate is based is small, and thus, the confidence interval is wide (95 percent CI = 0.6-57.7), indicating that the estimate of risk of infantile spasms observed in SONIC was very imprecise. The power of the statistical test was correspondingly low: 50 percent for an RR of 9.6 and 80 percent for an RR of 25.4. Because of the small number of cases of infantile spasms, estimates could not be calculated for exposure intervals shorter than 28 days.

Hunt (1983) reported on the association between the time of vaccination and the onset of seizures among individuals with tuberous sclerosis who responded to a survey questionnaire. Of 150 families contacted through the Tuberous Sclerosis Association of Great Britain, 97 (65 percent) responded. Of the responders, 82 (84 percent) had had seizures, 66 (80 percent) of whom had infantile spasms. The age range of cases in the survey was less than 1 to 51 years. Outcome was compared among subgroups of responders, defined on the basis of their immunization status at the time of their first seizure. Of the 82 people with tuberous sclerosis who had seizures, 20 had never been immunized, 27 had been immunized after their first seizure, 17 had been immunized within 1 month prior to their first seizure, and 18 had been immunized more than 1 month prior to their first seizure. Profoundly handicapped children, defined as those older than age 5 who could neither walk nor talk, were more often observed among the tuberous sclerosis cases with seizures who were immunized after their first seizure (8 of 27). Of those immunized after their first seizure and for whom the type of immunization was known, the frequency of profound handicap was 6 of 13 who received DT vaccine and 2 of 14 who received DPT vaccine. All of the profoundly handicapped children had their first seizure before the age of 7 months.

Although this study suggests that DPT vaccine does not add to the sei

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zure burden among children with tuberous sclerosis or increase the risk of neurologic handicap, the study design has weaknesses that reduce the utility of its results in addressing the question of an association between pertussis and the risk of infantile spasms. For example, the sampling frame from which subjects were chosen is not representative of all people with tuberous sclerosis, and the response rate was low. The age range of cases was also very wide, with some individuals being as old as 51 years, thus introducing the possibility of recall bias regarding immunization histories.

Summary

Case reports of children who develop infantile spasms after receipt of pertussis vaccine prompt concern regarding a possible relation between immunization and seizures. However, the reported time intervals between immunization and onset vary widely, from hours to months, and no consistent pattern of timing or associated neurologic disorders is reported. Given the insidious onset of infantile spasms, the temporal relation of immunization and onset is difficult to establish with certainty.

The body of evidence concerning the possible relation between vaccination with DPT or its pertussis component and infantile spasms includes a number of case reports, case series, and four controlled observational epidemiologic studies, which are summarized in Table 4-1. Risk estimates were not consistent and varied widely across studies, ranging from 0.3 to 6.0, depending on the time interval examined. None of the risk estimates was statistically significant, and the NCES had sufficient statistical power (80 percent) to detect an RR of 2.0 to 2.4, depending on which data are used to make the comparison. Direct comparisons between studies is hampered by differences in the definitions of infantile spasms cases and the time intervals used. Although the results tended to be inconsistent, most controlled studies did not observe an increased risk. Only two studies reported risks greater than 2.5: the analysis of voluntary reporting data from the North West Thames study and SONIC. The risk estimate from SONIC is highly uncertain because of the small number of cases on which it is based.

The strongest evidence bearing on the question of a relation between DPT immunization and the risk of infantile spasms comes from the controlled studies from Denmark that compared the distributions of ages at the time of onset of infantile spasms under two different immunization schedules and the large case-control study of infantile spasms from the NCES. Comparison of the ages at onset of cases of infantile spasms for two different time periods in Denmark showed nearly identical distributions (Shields et al., 1988). Odds ratios for infantile spasms calculated separately for DPT

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or DT vaccines in the NCES (Bellman et al., 1983a) were essentially the same for each time interval investigated. These results argue against an excess risk of infantile spasms attributable to the pertussis component of the vaccine. Given the insidious onset of infantile spasms, it is difficult to establish a temporal sequence with certainty, and there are no other aspects of the clinical presentation that suggest a relation to DPT immunization. Considerations of the specificity of the association are not relevant since a causal relation is not suggested by the evidence. There are no data bearing on mechanisms or biologic plausibility.

Conclusion

The evidence does not indicate a causal relation between DPT vaccine or the pertussis component of DPT and infantile spasms.

HYPSARRHYTHMIA

Clinical Description

Hypsarrhythmia (mountainous arrhythmia), a term originally proposed in 1952 by Gibbs and Gibbs, refers to an EEG pattern that is frequently associated with infantile spasms. The EEG is characterized by high-voltage, arrhythmic, slow interictal patterns. Spikes and sharp waves with multifocal origins occur nearly continuously, and there is poor synchrony between hemispheres (Lombroso, 1983b). Although not pathognomonic for infantile spasms, this EEG pattern is seen at some time during the course of illness in 70 to 80 percent of cases of infantile spasms, whereas it is uncommon (<5 percent) in children with other types of seizure disorders (Jeavons and Bower, 1964).

Descriptive Epidemiology

There is no descriptive epidemiology available specifically for hypsarrhythmia. Information on infantile spasms may provide a reasonable estimate.

History of Suspected Association with Pertussis Vaccines

The suspected association between pertussis immunization and hypsarrhythmia probably derives from the case reports of vaccination and infantile spasms. Low (1955) investigated the EEGs of children before and after receipt of pertussis-containing vaccines, but did not observe hypsarrhythmia. Strom (1967) specifically used the term *hypsarrhythmia* in his report of neurologic conditions following vaccination in Sweden.

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TABLE 4-1 Summary of Controlled Studies on DPT Immunization and Infantile Spasms (IS)

Reference	Design[a]	Years	Description
Pollock and Morris, 1983	Cohort (voluntary reporting)	1975-1981	134,700 children completed a course of DPT; 133,500 children completed a course of DT
	Cohort (hospital based)	1979	17,000 children completed a primary course of DPT; 18,000 completed a primary course of DT
Bellman et al., 1983a; Miller et al., 1988	Matched case-control (NCES)	1976-1979	Ages 2-35 months; resident of England, Scotland, or Wales
Walker et al., 1988	Matched case-cohort	1972-1983	26,600 members of Group Health Cooperative, Puget Sound
Gale et al., 1990	Matched case-control (SONIC)	1987-1988	~109,000 children aged 1-24 months; resident of Washington or Oregon

[a]NCES, National Childhood Encephalopathy Study; SONIC, Study of Neurologic Illness in Children.

[b]RR (95% CI), Relative risk (95 percent confidence interval). RRs and CIs for Pollock and Morris (1983), Bellman et al. (1983a), and Miller et al. (1988) were calculated by the committee using data from these reports (see Appendix D).

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Sample Size	Time Interval	No. of Cases in Interval	RR (95% CI)[b]	Power[c] 50%	Power[c] 80%
5 IS cases	<6 weeks	4	4.0 (0.6, 25.2)	6.4	14.0
2 IS cases	≤12 weeks	1	1.1 (0.1, 10.2)	9.6	25.4
262 IS cases/ 524 controls	DPT				
	0-6 days	9	1.2 (0.5, 2.6)	2.3	3.2
	0-28 days	24	0.7 (0.4, 1.1)	1.6	2.0
	DT				
	0-6 days	8	1.4 (0.6, 3.5)	2.5	3.6
	0-28 days	19	0.8 (0.5, 1.4)	1.7	2.2
152 previously normal cases/ 304 controls	DPT				
	0-6 days	7	2.3 (0.8, 6.7)	2.9	4.6
	0-28 days	15	0.9 (0.5, 1.7)	1.9	2.5
	DT				
	0-6 days	4	2.0 (0.5, 7.4)	3.8	6.6
	0-28 days	8	0.8 (0.3, 1.8)	2.3	3.2
2 IS cases/ 262 controls	<30 days	0	0	NC[d]	NC[d]
10 IS cases/ 20 controls	<28 days	3	6.0 (0.6, 57.7)	9.6	25.4

[c]"Power" denotes the probability that a statistical test based on a sample of the same size as the one in the study cited would find a statistically significant increased risk (with alpha = 0.05), given that the true RR in the population being studied is the number stated in the table. The numbers tabulated are the RRs such that the powers are 50 and 80 percent, respectively.

[d]NC, Not calculated, given that no infantile spasms cases were identified within the time interval.

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Evidence from Studies in Humans

Case Reports and Case Series

Neurologic reactions reported to have occurred in conjunction with DPT immunization were identified from all vaccination clinics in Sweden for the years 1959 to 1965 (Strom, 1967). Among 516,276 children vaccinated during the 7 years of the study, 167 neurologic reactions were reported, 4 of which were cases of hypsarrhythmia. Two of the four cases were reported 2 to 3 days after DPT immunization and the two others were reported after 1 week. The clinical manifestations leading to identification of these children were not described.

The incidence of hypsarrhythmia is unknown, and thus, it is not possible to determine precisely whether the observed number of cases reported by Strom (1967) is in excess of the number expected. However, if the incidence of hypsarrhythmia is similar to that for infantile spasms, then the number of cases reported in that study is far smaller than the number that would be expected in a population of this size over the time interval studied (expected, ~18 to 30 cases; Leviton and Cowan, 1981).

Controlled Epidemiologic Studies

EEGs obtained before and after immunization with pertussis-containing vaccines were compared in 83 infants who had not previously had any type of immunization (Low, 1955). Each child served as his or her own control, and all second EEGs were done within 16.5 to 48 hours postimmunization. Of the 83 infants, 40 were given alum-precipitated DPT vaccine and 43 received pertussis vaccine alone. Eighty infants had normal EEGs, both before and after pertussis immunization. Of the remaining three, one child had the same abnormality on EEG both before and after immunization. Thus, two infants with previously normal EEGs showed some abnormality on the postimmunization EEG. Both cases were febrile and showed nonspecific EEG abnormalities on the initial postimmunization EEG (one described as "marked diffuse slowing" and the other as "less marked slowing") which disappeared within 1 week. Apart from these nonspecific, short-term EEG changes, neither child demonstrated any clinical abnormality.

This study has several strengths, including the facts that infants had not previously been exposed to any type of vaccine and that each child served as his or her own control. A major limitation of the study is that the EEGs were not read in a masked fashion. It is not possible to determine what effect, if any, this may have had on the results. It would also be helpful in interpreting the results to have compared EEG patterns before and during febrile illness in unimmunized children. This study demonstrated no asso

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ciation between exposure to pertussis vaccine and increased frequency of hypsarrhythmia or any other type of significant EEG abnormality. However, the number of children included was relatively small, and therefore, a small difference in pre- and postimmunization EEGs might have been missed.

Hughes and Tomasi (1985) reported a dramatic decline in the frequency of hypsarrhythmic EEGs over a 40-year interval. Data were obtained by counting the first EEG record with hypsarrhythmia for patients seen from 1943 to 1983 at the University of Illinois Medical Center. All EEG referrals for children less than age 1 year were also counted. A similar analysis was done of records from Children's Memorial Hospital, Chicago, Illinois, for the time period 1973 to 1984. The number of EEGs with hypsarrhythmia peaked in 1952, 1958, and 1963, at about 50 to 75 patients per year. After 1963, 10 or fewer cases of hypsarrhythmia were seen in each successive year. From 1974 to 1984, the percentage of referrals with hypsarrhythmia declined from 1.3 to 0.1 percent, although the total number of referrals remained relatively constant. A similar decline was noted over the same time period in records from Children's Memorial Hospital (1.6 to 0.4 percent).

Peaks in the frequency of EEGs with hypsarrhythmia appeared to correspond to measles outbreaks, with a 1-year lag, although no formal tests of the fit of the curves were done. The authors suggested that the frequency of hypsarrhythmia had decreased dramatically and that the decline could be linked to the institution of immunization programs for a number of viral diseases, especially measles, mumps, rubella, and polio.

A major deficiency of this study is that the data represent the number of EEG records with hypsarrhythmia, not rates of hypsarrhythmia referable to a defined population base. The authors considered the possibility that the incidence of hypsarrhythmia had not declined, but that referral patterns in the study area had changed, such that cases were being seen elsewhere. They argued against this, however, stating that the patient base had remained relatively stable over time. In addition, similar observations of a decline in the frequency of hypsarrhythmia were observed at both hospitals studied, and at least at the University of Illinois Medical Center, the number of referrals for EEGs in children less than age 1 year was relatively constant over the 1974 to 1984 interval.

A study in Finland by Riikonen and Donner (1979) found essentially no change in the incidence rates of infantile spasms between 1960 and 1976 in the county of Uusimaa (average annual rates per 1,000 live births were as follows: 1960 to 1966, 0.42; 1967 to 1971, 0.38; 1972 to 1976, 0.42). All cases had hypsarrhythmia. In the population and time interval studied, there appeared to be no temporal trend in the incidence of infantile spasms.

Among the 113 cases of infantile spasms admitted to pediatric departments in Denmark (Melchior, 1977), 72 percent had typical or atypical hypsarrhythmia on their EEGs, 21 percent had severely abnormal EEGs of

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other types, and 6 percent had normal EEGs. Analysis of the age distributions of cases over the two time periods when different schedules of pertussis immunization were used was not done separately by EEG pattern.

Summary

Hypsarrhythmia refers to a particular EEG pattern that is almost always associated with infantile spasms, and its occurrence should be interpreted in conjunction with data on infantile spasms.

The body of evidence concerning the possible relation between vaccination with DPT or its pertussis component and hypsarrhythmia is limited to one case series and one nonmasked experimental study with a limited number of cases. The latter study was the only one that directly observed EEG patterns pre- and postimmunization. No EEGs with hypsarrhythmia were observed.

Conclusion

Evidence does not indicate a causal relation between DPT vaccine or the pertussis component of DPT and hypsarrhythmia.

ASEPTIC MENINGITIS

Clinical Description

Aseptic meningitis is defined as inflammation of the meninges characterized by abnormal numbers of leukocytes in the cerebral spinal fluid (CSF) with a predominance of mononuclear cells, normal glucose, and an absence of bacteria on examination and culture (Berkow, 1987). Others consider the diagnosis of aseptic meningitis to apply only to meningitis of known or suspected viral etiology (Beghi et al., 1984). The course of the disease is relatively benign, with most patients (~95 percent) recovering completely and few (5 percent) experiencing mild residua (Beghi et al., 1984). In contrast to what is observed for other CNS infections such as viral encephalitis or bacterial meningitis, the risk of subsequent, unprovoked seizures after aseptic meningitis is not increased over the incidence in the general population (Annegers et al., 1988).

A variety of factors have been identified as causes of aseptic meningitis, including viruses, such as entero-, mumps, herpes simplex, Eastern and Western equine encephalitis, and infectious hepatitis viruses; bacteria (tuberculosis and syphilis); other agents (cat-scratch disease, toxoplasma); and parainfectious processes (varicella, measles, and rubella). Noninfectious causes include parameningeal disease (tumor, stroke, otitis media), reaction

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to intrathecal injections, and lead poisoning. In addition, vaccine reactions, have been implicated (Berkow, 1987).

In their review of the 283 cases of aseptic meningitis occurring in Rochester, Minnesota, over a 30-year period, Beghi and colleagues (1984) reported the most common antecedent events (within 4 weeks prior to onset) were respiratory infections, including influenza (19 percent) and mumps (11 percent). Enteroviruses (15 of 33 isolates) and mumps virus (7 of 33 isolates) were the most frequently identified viruses. One of 283 cases had been immunized with DPT vaccine within 3 weeks of the onset of aseptic meningitis.

Descriptive Epidemiology

Aseptic meningitis is relatively rare, occurring in about 1 per 10,000 people each year. The population-based estimate of the average annual age-and sex-adjusted incidence rate from Rochester, Minnesota, was 10.9 per 100,000 for the time period 1950 to 1981 (Beghi et al., 1984). Rates were significantly higher in males than in females, and incidence rates varied considerably by age. The highest rate (82.4 per 100,000) was in those less than age 1 year, and in this age group, the incidence of aseptic meningitis was four to eight times higher than that in those of other ages.

For the most recent period covered in the Rochester study (i.e., 1976 to 1981), the incidence rate of aseptic meningitis in children less than age 1 year was 338 per 100,000 (Beghi et al., 1984), which represents a 26-fold increase in incidence in this age group compared with that of the earliest period studied (1950 to 1959). Increases of this magnitude were not observed in other age groups. A seasonal pattern was also observed, with the highest percentage of cases occurring in July to September.

History of Suspected Association with Pertussis Vaccines

The basis for suspecting an association between pertussis vaccination and aseptic meningitis is unclear, but it may have developed, in part, because of the difficulty inherent in identifying a causal agent in cases of viral meningitis. Data from Rochester, Minnesota, for the time period 1950 to 1981 indicate that in the absence of intensive laboratory investigation, evidence of a virus was obtained for only 12 percent of cases of aseptic meningitis (Beghi et al., 1984). Thus, many of these cases would have been considered to be of unknown etiology, and a recent immunization could have been suspected. Cavanagh and colleagues (1981) have postulated, on the basis of results from animal studies, that pertussis immunization may affect susceptibility to other infections, and thereby increase the risk of aseptic meningitis.

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Evidence from Studies in Humans

Case Reports and Case Series

The diagnosis of aseptic meningitis is difficult, since appropriate and timely cultures may not be obtained and it is frequently not possible to culture a virus from CSF. Thus, many cases reported as "meningitis" may, in fact, be cases of aseptic meningitis. Case reports of meningitis in association with pertussis immunization have been reported (Coulter and Fisher, 1985).

Forty cases of aseptic meningitis (ICD 9 code 047.9) occurring within 28 days of DPT immunization were reported through the CDC's MSAEFI system from 1978 to 1990, a period in which approximately 80.1 million doses of DPT vaccine were administered through public mechanisms in the United States (J. Mullen, Centers for Disease Control, personal communication, 1990). Of these 40 cases, 32 (80 percent) also received at least one other vaccine at the time of DPT immunization. No follow-up of the cases was made, and a physician's diagnosis was not required.

Controlled Epidemiologic Studies

Beghi and colleagues (1984) commented specifically on the possible link between pertussis immunization and CNS infection. Among 56 cases of encephalitis and aseptic meningitis combined in children less than age 1 year, 3 (5 percent) had been immunized with DPT and polio vaccines within 1 week prior to the onset of symptoms. Given the recommended immunization schedule in this age group, the expected frequency is 6 percent. Based on these data, the RR is 0.9 with a wide 95 percent CI: (0.2 to 4.1). The power is correspondingly low: 50 percent for an RR of 4.6 and 80 percent for an RR of 8.9.

The only other piece of information specifically related to the possible association of pertussis immunization and aseptic meningitis comes from the study of Shields and coworkers (1988). The ages at the time of diagnosis of children with aseptic meningitis in Denmark were compared for two calendar periods in which the immunization schedules for DPT differed. Although the recommended time for immunizations changed from ages 5, 6, 7, and 15 months prior to April 1970 to ages 5 and 9 weeks and 10 months after that date, there was no appreciable change in the distribution of ages at the time of onset of cases of aseptic meningitis. The power of this test was also low. As many as 21 percent of all cases of aseptic meningitis would have to be due to DPT to achieve 50 percent power, and 29 percent would be needed for 80 percent power.

The estimated rate of CNS infections in children less than age 2 years,

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approximately one-third of which were aseptic meningitis, was significantly higher in the 1972 to 1973 interval (29 per 10,000) than in the 1967 to 1968 interval (16 per 10,000) (Shields et al., 1988). The authors concluded that the increase in frequency of CNS infections was due to a change in the referral patterns for cases over the time intervals studied, such that cases were more likely to enter the study hospitals during the second time interval than they were during the first. Thus, they did not consider the change in immunization schedule to have accounted for the increased rate of CNS infections.

Summary

With the exception of a single case occurring within 4 weeks of DPT vaccination reported during a 30-year interval from Rochester, Minnesota (Beghi et al., 1984), the committee found no evidence in the case report literature for a causal relation between DPT immunization and aseptic meningitis.

It has been postulated that pertussis immunization influences susceptibility to other infections (Cavanagh et al., 1981), and thus could increase the risk of aseptic meningitis. Data from Denmark (Shields et al., 1988) are not consistent with this hypothesis, since there was no change in the age distribution of cases of aseptic meningitis when the ages at the time of immunization were changed. Large increases over time in the incidence of aseptic meningitis observed in Rochester, Minnesota (Beghi et al., 1984), are also not consistent with a causal relation between DPT immunization and aseptic meningitis, since there were no known temporal changes in immunization practices or vaccines that could explain this large increase. The July—September clustering of cases of aseptic meningitis in children less than age 1 year (Beghi et al., 1984) is also not consistent with a causal relation to DPT immunization, since there was no indication that immunizations also clustered during these months. In addition, data from Rochester, Minnesota, suggest that the risk of aseptic meningitis within 1 week of immunization with pertussis vaccine was not increased over the expected frequency (Beghi et al., 1984).

The body of evidence concerning the possible relation between vaccination with DPT or its pertussis component and aseptic meningitis consists of isolated case reports and two population-based comparative studies. Data from Rochester, Minnesota, indicated that 5 percent of cases followed DPT immunization, when 6 percent would have been expected. Comparisons of the age distributions of cases from Denmark under two different immunization schedules showed no significant differences in ages at the time of diagnosis for cases of aseptic meningitis. It has been proposed that immunization might activate a latent CNS infection, resulting in meningitis.

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However, the committee found no data to evaluate the biologic plausibility of this hypothesis.

Conclusion

There is insufficient evidence to indicate a causal relation between DPT vaccine and aseptic meningitis.

ENCEPHALOPATHY

Clinical Description

Before discussing the evidence for an association between pertussis immunization and encephalopathy, it is reasonable to consider what is meant by the term *encephalopathy.* Encephalopathy has been used in the literature to characterize a constellation of symptoms and signs reflecting a generalized disturbance in brain function. Encephalopathy is used in a very general way to indicate a "disease of the brain" (Gove, 1981, p. 746). Others have defined encephalopathy as "a diffuse interference with brain function resulting from a generalized or multifocal insult that causes a widespread disorder in the function of neurons" (Dodson, 1978). In NCES, the terms *acute* or *subacute encephalitis, encephalomyelitis,* and *encephalopathy* were used to denote a spectrum of clinical characteristics, including "altered levels of consciousness, confusion, irritability, changes in behavior, screaming attacks, neck stiffness, convulsions, visual, auditory and speech disturbances, motor and sensory deficit" (Alderslade et al., 1981, p. 157). The term *encephalopathy* was used "when the cause of the cerebral disorder is not immediately obvious" (Alderslade et al., 1981, p. 157). Stephenson (1987) recognized that encephalopathy represents a vague term, difficult to define, "used to denote any neurological abnormality of the brain" (p. 2). He would apply the term *acute encephalopathy* to a clinical picture characterized by the sudden onset of convulsions, impaired consciousness, motor or sensory deficits, "or other evidence of acute illness involving the brain" (p. 2). Fenichel (1982) noted that the terms *encephalopathy* and *encephalitis* are used interchangeably to refer to a constellation of symptoms and signs, including alterations in behavior or level of consciousness, convulsions, headache, and focal neurologic deficits. In general, when fever or CSF pleocytosis is present as well, the term *encephalitis* is usually used, implying an inflammatory response within the brain. On the other hand, the term *encephalopathy* is used when an illness clinically appears like an encephalitis but no inflammatory response is evident (Cherry et al., 1988). In the remainder of this chapter, *encephalopathy* will be defined as it is in the controlled studies reviewed as *encephalopathy, encephalitis,* or *encephalomyelitis.*

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If a child fails to recover from the acute event, the terms *chronic encephalopathy* and *irreversible encephalopathy* are often used.

The occurrence of an encephalopathy in a child does not imply a particular severity or duration of illness, nor does the diagnosis of encephalopathy necessarily indicate that the child will exhibit symptoms and signs of irreversible brain injury. Similarly, the terms *serious neurologic disease, serious neurologic injury, acute neurologic disorder,* and *acute neurologic reaction* are sometimes confused with the terms *permanent brain damage* or *brain damage.* However, because many children with serious neurologic illness do, indeed, recover, it is important to recognize that a serious neurologic illness may or may not result in permanent brain damage.

Reports indicate a considerable variation in the clinical presentation of what various clinicians have termed *pertussis vaccine-induced encephalopathy.* Some reports have suggested a prototypic description of pertussis vaccine-induced encephalopathy. One presentation referred to as the "more classic" (Cherry et al., 1988, p. 961) is that of a generalized tonic-clonic (grand mal) seizure frequently associated with fever within 48 hours of receiving the first, second, or third pertussis immunization. According to this description, in most cases the initial seizure is brief and the child appears to recover. In days or weeks the seizures begin to increase in frequency and motor and mental retardation becomes evident. Stewart (1977, p. 236) described what he referred to as "a pertussis reaction syndrome" characterized by some or all of the following features: (1) persistent crying or screaming 4 to 48 hours after a pertussis immunization; (2) pallor and shock within 48 hours, usually 6 to 12 hours after immunization; (3) irritability and interrupted sleep; (4) refusal or vomiting feedings; (5) altered response to parents; (6) weakness or paralysis; (7) one or more convulsions, with or without fever. Stewart (1977) noted that in the majority of cases the symptoms resolved in days or weeks, but some children went on to develop recurrent seizures, paralysis, and progressive mental deterioration. This specific clinical picture has not been confirmed by other investigators. Symptoms such as irritability, fretfulness, or drowsiness, so commonly observed in the usual childhood febrile illnesses, do not in themselves represent encephalopathy, and reports dealing with these symptoms are not considered here. High-pitched crying is considered in Chapter 6.

Seizures in themselves are not sufficient to constitute a diagnosis of encephalopathy and, in fact, most seizures occur without encephalopathy. Seizures may occur with or without the loss of consciousness and can include a variety of sensory experiences (e.g., auditory seizures) and/or motor manifestations (e.g., focal motor or tonic-clonic seizures). The terms *fits* and *convulsions* are frequently used as synonyms for motor seizures. In addition to the various ways in which seizures may present clinically, they can occur with or without fever. *Febrile seizures* are well-defined, rela

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tively common events. In the National Collaborative Perinatal Project (NCPP), approximately 82 percent of all seizures in children under age 7 years were febrile seizures (Nelson and Ellenberg, 1976, 1986). These seizures are generally benign and of brief duration. If more than one of these seizures occurs within 24 hours or if they last longer than usual or are accompanied by transient focal neurologic features, they are termed *complex febrile seizures. Acute symptomatic seizures* are those that occur in association with an acute process that affects the brain, such as head trauma or a bacterial infection. *Afebrile seizures* are those that occur in the absence of fever or other acute provocation. Recurrent afebrile seizures are referred to as *epilepsy.*

Encephalopathies are frequently accompanied by seizures (both those occurring with fever and those occurring in the absence of fever). Most of the studies of neurologic events following pertussis immunization have included both encephalopathy and seizure as outcomes of interest. Given that seizures are much more common in children than is encephalopathy (Beghi et al., 1984; Hauser and Kurland, 1975), the great preponderance of cases in these studies are likely to be children with febrile or acute symptomatic seizures. In this report, encephalopathy and seizures are discussed separately, when the data permit. It is important to note, however, that there may not always be a clear distinction between the two, and that there may not be uniformity of clinical opinion on whether a particular illness in a child represents, for example, a complex febrile seizure or an encephalopathy.

Encephalopathy Following Whooping Cough

The clinical presentation, natural course, and pathology of encephalopathy following the natural occurrence of pertussis are relevant to the discussion of encephalopathy following pertussis immunization. Because the occurrence of pertussis in most developed countries is relatively rare (see Chapter 2), reports of the neurologic complications of pertussis are also quite rare. In the most comprehensive review in the English-language literature, Zellweger (1959) reviewed 148 cases of whooping cough encephalopathy. He noted two clinical presentations: (1) the sudden onset of convulsions followed by coma and (2) a more insidious onset with somnolence progressing to coma over a period of days. Cases of both types were more common in children under age 10 years and were more common in females. Onset was usually during the second to fourth weeks of illness. Laboratory findings indicated elevations of blood lymphocytes and normal CSF. The duration of the encephalopathy varied from several days to several weeks. One-third of the children died, one-third recovered completely, and one-third were left with varying degrees of neurologic disability, including mental retardation of varying severity, paralyses and palsies, focal or generalized

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convulsions, ataxias, amauroses, and changes of personality or behavior (Zellweger, 1959).

Pathology

No signs of CNS inflammation have been noted in the majority of cases of whooping cough encephalopathy. Findings are generally nonspecific and include brain edema, eosinophilic degeneration, multiple petechiae, lymphocytic plugs in veins and capillaries, and small subarachnoid hemorrhages (Dolgopol, 1941). Zellweger (1959) notes that "[t]oxic effects and anoxemia due to circulatory stasis can account for most of the anatomical findings" (p. 383) noted above.

It is difficult to understand what Zellweger, writing over three decades ago, meant by the term *toxic effects.* There is no evidence that any of the toxins associated with pertussis vaccine have produced specific pathologic effects in either animals or children (see below). Certainly, the effects of anoxemia (used synonymously with asphyxia or hypoxia or hypoxic-ischemic encephalopathy) have been well described in both preclinical and human investigations (Volpe, 1987).

In theory, pathologic studies of children who have died after an encephalopathy temporally related to the administration of pertussis vaccine could help to clarify the vague clinical picture of encephalopathy in general and encephalopathy associated with pertussis immunization in particular. However, to date, only one systematic review of the neuropathologic features of children who have died following pertussis vaccination has been conducted. In that study, Corsellis and colleagues (1983) examined data on childhood deaths which, on circumstantial grounds, were considered to have been related to vaccines against pertussis. The authors conducted two reviews, one based on 12 previously published case reports or series of pertussis vaccine-associated deaths and the other based on their own retrospective review of infant or child deaths that occurred in England and Wales between 1960 and 1980 and that were reported as being associated with pertussis vaccines. In their review of the published case data, the authors identified 33 deaths; necropsy data were available for 27 of the deaths. The postmortem findings of these 27 cases were considered "difficult to interpret" because of the often imprecise terminology used to describe the cases and the frequently incomplete description of neuropathologic findings. Review of the data that were available, however, indicated no features of the cases that were consistently observed following administration of pertussis vaccine.

In their population-based review, Corsellis and colleagues (1983) identified 40 deaths and obtained information that included details of a general postmortem examination for 29 of these deaths. The 29 cases were categorized into one of two groups: an "acute group" of infants dying within 3

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weeks of immunization (n = 18) and a "chronic group" of children dying 6 months to 12 years after vaccination (n = 11). Clinical documentation on most of the acute cases was incomplete; that on the chronic cases generally was complete. Review of both the acute and chronic groups again indicated no specific findings that were consistently observed following administration of pertussis vaccine. The authors concluded that "neither [the cerebral changes] in the present study nor those abstracted from the previous literature have provided evidence of a pattern of damage in the brain identifiable as a specific reaction to immunization against whooping cough" (p. 267). The authors acknowledged deficiencies in the neuropathologic data examined, for example, sparse documentation of immunization and confounding with associated neurologic problems. They recommended more careful and complete collection of such data in the future.

Descriptive Epidemiology

There are few studies from which to obtain information on the frequency and distribution of encephalopathy. The problems and variations in defining encephalopathy, which were described above, also make it difficult to compare rates among studies. Average annual incidence rates from Rochester, Minnesota, for the years 1950 to 1981 were 22.5 per 100,000 for children less than age 1 year and 15.2 per 100,000 for those aged 1 to 4 years (Beghi et al., 1984). Cases were defined as individuals with diagnoses of encephalitis or encephalopathy. Peak incidence rates were observed in 5- to 9-year-olds and in the months of July through September. On the basis of data provided in several other studies (Gale et al., 1990; Pollock and Morris, 1983; Walker et al., 1988), most estimated rates of encephalopathy for children less than age 2 years were somewhat lower than those reported from Rochester, Minnesota, and ranged from 5 per 100,000 (Walker et al., 1988) to 10 per 100,000 (Gale et al., 1990).

Considering seizure disorders separately, annual incidence rates in children range from 0.53 per 1,000 in Carlisle, England (Brewis et al., 1966), to 1.52 per 1,000 in England and Wales (Crombie et al., 1960), depending on whether or not febrile seizures are included in the rate calculation. The cumulative incidence rate of one or more seizures by age 12 months is 3.3 per 1,000 children (Van den Berg and Yerushalmy, 1969). The cumulative incidence of febrile seizures through age 5 years ranges between 2.3 and 4.6 per 100 children (Harker, 1977; Hauser and Kurland, 1975; Nelson and Ellenberg, 1976; Van den Berg and Yerushalmy, 1969). Reported prevalence rates of epilepsy, that is, recurrent afebrile seizures, in children tend to range between 4 and 5 per 1,000 (Leviton and Cowan, 1982).

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History of Suspected Association with Pertussis Vaccines

The possibility that pertussis immunization might cause adverse neurologic events resulting in permanent brain injury was first raised following a report of two cases by Madsen (1933) and case reports published in the 1940s (e.g., Byers and Moll, 1948; Globus and Kohn, 1949; Toomey, 1949). Subsequent descriptions of encephalopathies of various types occurring at differing time periods after pertussis immunization followed (e.g., Berg, 1958; Cockburn, 1958; Globus and Kohn, 1949; Malmgren et al., 1960; Sutherland, 1953). On the basis of these reports, Strom (1960) questioned whether the risk of adverse neurologic effects following immunization might be more of a concern than the risk of pertussis itself, a view reiterated in reports by Aicardi and Chevrie (1975), Cavanagh et al. (1981), Ehrengut (1980), Kulenkampff et al. (1974), and Stewart (1977, 1979). (See Appendix B for further historical details.)

Evidence from Studies in Humans

Case Reports and Case Series

The earliest report of an adverse event following administration of pertussis vaccine came from an era when pertussis vaccine was prepared by emulsifying a culture of *Bordetella pertussis* with saline solution and 1 percent formaldehyde. Madsen (1933) reported two cases of sudden death in infants administered the preparation. The first death occurred after the second immunization and was characterized by contractions of the arms and legs, cyanosis, hiccups, convulsions, and death within 30 minutes. The age and weight of the infant were not recorded.

Generalized hypotonia and weakness with increased deep tendon reflexes in the lower extremities were reported by Brody and Sorley (1947) in a 10-month-old, 3 days following his third pertussis immunization. Similar episodes occurred 2 weeks after his first immunization and 1 week after his second immunization. A fourth episode occurred spontaneously at age 25 months. Neurologic disability persisted, with spasticity in the left arm and both legs. At age 43 months, the child received a fourth pertussis immunization and within 25 minutes became somnolent. Severe flaccid paralysis developed within 12 hours, and he died of bronchopneumonia 7 weeks later. No autopsy was performed.

Despite these early reports, it was the report by Byers and Moll (1948) of encephalopathy following pertussis immunization in 15 children that spurred interest in the possibility of adverse consequences of pertussis immunization. That report contains the largest group of reasonably full clinical de

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scriptions of what they termed "pertussis-induced encephalopathy." These 15 cases occurred between 1939 and 1947 in children ages 5 to 18 months and were identified from a review of the records of the Children's Hospital in Boston. The presentations were explosive, consisting of fever, irritability, convulsions, and coma occurring within 12 hours of a pertussis immunization. At follow-up, only one child was normal, two had died of pneumonia, six had cerebral palsy with or without seizures, and the others had seizures and mental retardation. Two additional case reports with clinical pictures similar to those described by Byers and Moll (1948) were reported the following year by Globus and Kohn (1949).

Berg (1958) reviewed 107 cases of neurologic illness following pertussis vaccination that had been previously reported by Köng (1953) and an additional case whom he had treated at Fountain Hospital, London. The neurologic illnesses observed in these 108 cases followed any one of the four immunizations in the pertussis series, and most occurred within 48 hours of the immunization.

A number of similar cases have been reported (Aicardi and Chevrie, 1975; Baird and Borofsky, 1957; Bower and Jeavons, 1960; Cockburn, 1959; Dick, 1972, 1974; Dudgeon et al., 1981; Forrester, 1965; Halpern and Halpern, 1955; Meade et al., 1981; Stewart, 1977; Strom, 1960, 1967; Tonz and Bajc, 1980). Ehrengut (1974) reported on 59 cases of encephalopathy from Hamburg, Germany, that had occurred since 1950. All but 10 were cases of seizures associated with fever. Thirty-nine cases occurred within the first 48 hours after immunization, and 11 of the cases had pathologic EEG findings. Most cases recovered completely. In the same year, Kulenkampff and colleagues (1974) reported on 36 cases of encephalopathy referred to the Hospital for Sick Children at Great Ormond Street, London, between 1961 and 1972. The adverse events occurred usually within 24 hours after pertussis immunization, with the majority (32 of 36) of events being convulsions. Two of the children died within 6 months of symptom onset, and only four recovered completely. Of the remaining 30 cases, 4 were moderately or severely retarded, 3 had epilepsy, and 22 had both epilepsy and mental retardation. One child with persistent hemiparesis developed normally otherwise.

Stewart (1977) collected a case series of adverse events following administration of pertussis vaccine and following whooping cough from retrospective data obtained from parent organizations, hospital records, physician reports, and parent reports. From the 160 reported cases of adverse effects of pertussis vaccine, Stewart postulated the pertussis reaction syndrome described earlier in this section.

Hennessen and Quast (1979) reported on 149 infants who experienced adverse events following pertussis vaccination. All cases were reported to vaccine manufacturers in Switzerland and/or Germany (location not speci

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fied). Thirteen (9 percent) of the reports concerned infants who died following vaccination. Fifty-nine (40 percent) of the cases were characterized as severe adverse events; these included fever, convulsion, shock, persistent screaming, and "various involvement of the CNS" (p. 96). The remaining 77 (51 percent) reports concerned infants who had local reactions only. Severe reactions were more frequently reported after the first dose of vaccine. Fatalities and local reactions were more common after the second dose. The former observation may reflect a decreased rate of subsequent vaccination in infants exhibiting severe reactions after the first dose.

Murphy and colleagues (1984) investigated 22 children with recurrent seizures following DPT vaccination. To identify potential study subjects, the authors sent questionnaires to 80 families who had responded to one of the authors following the 1982 television program "DPT: Vaccine Roulette," first broadcast by NBC affiliate WRC-TV in Washington, D.C., or whose names had been submitted by Dissatisfied Parents Together. Questionnaires were returned by 43 (54 percent) of the 80 families, and 22 (28 percent) children met the criteria for study inclusion: a history of recurrent seizures, with the occurrence of the first seizure within 24 hours of a DPT immunization. The authors concluded that "patients with recurrent seizures starting immediately after a DTP immunization have a poor prognosis for normal development" (p. 910). The authors cautioned, however, that their findings were probably biased because of weaknesses in case ascertainment (e.g., the mailing of questionnaires to parents who already suspected that their child had had an adverse reaction to the vaccine) and the low response rate.

Siddiqui and colleagues (1989), using data from the MSAEFI system, identified 10 cases of seizures occurring within 28 days of DPT vaccination in the state of Maryland in 1987. Seven cases had elevated temperatures and none had a prior history of seizures or neurologic illness. The onset of seizures occurred within 24 hours of immunization in 8 of 10 cases, with the other two cases having onset several days after immunization. Three of the cases received measles-mumps-rubella vaccine (MMR) and one case received oral polio vaccine (OPV) at the time of DPT immunization. No information on long-term outcome was provided.

Menkes (1990) followed 46 children who reportedly experienced the first onset of neurologic symptoms within the 72 hours following DPT immunization. No other cause of symptoms was found. The reported events (74 percent of which occurred between 4 and 24 hours postimmunization) were acute encephalopathy (2 cases); SIDS (2 cases); hypotonic, hyporesponsive state (1 case); possible hypoglycemia (1 case); and seizures (40 cases). The seizures ranged in duration from 1 to 210 minutes, and temperature at the time of seizure was less than 101.5°F in 77 percent of the children whose temperatures were recorded. Of the surviving children, 58 percent were moderately or severely retarded and 72 percent had uncontrolled seizures,

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some of which fit the criteria for severe infantile myoclonic epilepsy described by Lombroso (1990).

Blumberg and colleagues (in press) examined physician and nurse reports from the Los Angeles area to identify severe adverse events following DPT vaccination. Cases were considered eligible for study if the onset of the adverse event was within 48 hours of immunization and if the study staff was able to evaluate the child within 24 hours of symptom onset. Fifty-six cases of severe adverse events meeting the above study criteria were identified. Thirty-seven cases were seizures, with 33 of these having a documented temperature greater than or equal to 38°C. Laboratory tests offered no evidence that altered insulin/glucose metabolism or biologically active lymphocytosis-promoting factor (also known as pertussis toxin) were related to the onset.

Baraff and colleagues (1989) prospectively studied 9,920 infants and children immunized with DPT vaccine from 25 different vaccine lots. Local reactions (redness, swelling, pain), fever, drowsiness, fretfulness, and anorexia were common (from 10 to 69 percent of subjects across lots), with vomiting and screaming being less frequent (0 to 11 percent across lots). Convulsions were rare. Differences between the rates of reactions by lot were significant for all examined events except convulsions, of which there were insufficient cases (number not given) for analyses. There was a significant positive association between endotoxin unit content and the percentage of vaccine recipients who developed fever. There were also significant positive associations between all local reactions and both pertussis vaccine potency and percent mouse weight gain, a test of pertussis vaccine toxicity (see Appendix C for description). For the majority of reactions, however, the differences, although statistically significant, were small and of questionable clinical relevance.

A total of 708 cases of encephalopathy/encephalitis (ICD 9 code 348.3) occurring within 28 days of DPT immunization were reported through the MSAEFI system from 1978 to 1990, a period in which approximately 80.1 million does of DPT vaccine were administered through public mechanisms in the United States (J. Mullen, Centers for Disease Control, personal communication, 1990). Of these 708 cases, 545 (77 percent) also received at least one other vaccine at the time of DPT immunization.

A total of 2,531 cases of febrile seizures (combined ICD 9 codes 780.3 [idiopathic convulsions] plus 780.5 [fever]) and 344 cases of afebrile seizures/idiopathic convulsions (ICD 9 code 780.3) occurring within 28 days of DPT immunization were also reported through the MSAEFI system from 1978 to 1990. A total of 1,284 (75 percent) of the 2,531 cases of febrile seizures and 258 (75 percent) of the 344 cases of afebrile seizures/convulsions also received at least one other vaccine at the time of DPT immunization. No follow-up of the cases was made, and a physician's diagnosis was

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not required. No cases of epilepsy (ICD 9 code 345.9) were reported within this 13-year period.

Studies in Defined Populations

There are three studies (Cody et al., 1981; Pollock and Morris, 1983; Pollock et al., 1984) in which rates of selected events in children who were immunized with DPT vaccine were compared with those immunized with DT vaccine (Table 4-2). In most reports the number of encephalopathies and seizures that occurred within 48 hours of immunization can be ascertained. In these three studies (excluding the data from Pollock and Morris voluntary reports), children were evaluated following a total of 51,794 DPT immunizations and 35,385 DT immunizations. Pooling these data, there were 17 (3.3 per 10,000 doses) and 6 (1.7 per 10,000 doses) seizures reported in the 48 hours following DPT and DT immunizations, respectively. If the data from Pollock and Morris voluntary reports are included, the incidence rates of seizure are 7.2 per 10,000 DPT doses and 2.0 per 10,000 DT doses. At least 81 percent of all seizures reported in Table 4-2 were febrile (Cody et al., 1981; Pollock and Morris, 1983; Pollock et al., 1984). Thus, the results of pooling these data should be interpreted cautiously since age at the time of immunization should affect the incidence of febrile seizures and these data could not be age adjusted. Five additional studies (Feery et al., 1985; Harker, 1977; Hirtz et al., 1983; Long et al., 1990; Strom, 1967) tried to ascertain the rates of selected events in defined populations of children immunized with DPT (Table 4-2). Thus, five of the eight studies listed in Table 4-2 attempted to identify cases of encephalopathy. There were two cases of encephalopathy reported among 555,570 children within 48 hours of receipt of DPT vaccine if one excludes the data from Pollock and Morris based on voluntary reports, and six cases of encephalopathy among 690,270 children if one includes those data. All eight of these studies are discussed in more detail below.

Cody and colleagues (1981) compared the reactions that occurred in the first 48 hours after vaccination in 15,752 children receiving DPT vaccine and in 784 children receiving DT vaccine. The children were ages 0 to 6 years. Nine seizures were reported following receipt of DPT vaccine, while none were reported following receipt of DT vaccine. No cases of diagnosed encephalopathy, permanent neurologic damage, or death were observed in the first 48 hours following immunization. The cases of seizures occurred following any one of the three primary series or the first booster DPT immunization. All cases experienced the onset of symptoms within 24 hours of immunization, with a median time of 14 hours. All but two of the seizure cases had elevated temperatures following immunization, and two of these had a history of previous febrile convulsions. None of the other

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TABLE 4-2 Studies of Acute Neurologic Events Occurring Within 48 Hours of DPT Immunization in Defined Populations

Reference	Years	Age	Vaccine	Children (No.)	Immunizations (No.)	Encephalopathy (No.)	Seizures (No.)
			Including DPT and DT[a]				
Cody et al., 1981	1978-1979	0-6 years	DPT	15,752	15,752	0	9
			DT	784	784	0	0
Pollock and Morris, 1983[b]	1979	<2 years	DPT	134,700	404,100	4	16
			DT	135,500	406,500	1	3
			DPT	~17,000	~21,000	1?	6[c]
			DT	~18,000	~24,000	0	5[c]
Pollock et al., 1984	1978-1980	3 months-1 year	DPT	6,004	15,042	0	2
			DT	4,024	10,601	0	1
			Including DPT only				
Strom, 1967	1959-1965	NR[d]		516,276	NA[e]	1	59
Harker, 1977	1972-1975	0-5 years		~11,028	~32,000	NA[e]	0
Hirtz et al., 1983	1959-1966	0-7 years		~54,000	NA[e]	NA[e]	8
Feery et al., 1985	1983	<1 year		1,075	2,041	NA[e]	2
Long et al., 1990	1984-1985	2-20 months		538	1,771	0	0

[a]Relative risks (RRs) and 95 percent confidence intervals (95% CIs) for these studies were calculated by the committee using data from the reports (see Appendix D) and are presented in the text.
[b]First study based on voluntary reporting; second study based on systematic hospital activity analysis.
[c]Events within 1 week.
[d]NR, Not reported.
[e]NA, Not available.

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children had a past history of seizure activity or neurologic illness. In most cases, seizures were of brief duration, lasting from 10 seconds to 5 minutes. EEGs were performed in four cases, and eight cases were later examined neurologically; findings were reported to be normal in all cases. A followup examination of the nine seizure cases was attempted 7 years later (Baraff et al., 1988). Eight of the nine children were contacted by study personnel, and seven of the eight were given a complete neurologic and psychometric evaluation, the latter consisting of the Wechsler Intelligence Scale for Children—Revised. Verbal IQ scores were less than 80 in two of the seven cases tested, and complete IQ was less than 80 in one of these. The authors attributed the lower mean verbal IQ scores in the overall sample (91.8 ¬ 18.4) to the proportion whose primary language was not English.

Pollock and Morris (1983) analyzed data from the North West Thames region of England, where an intensified effort over the previous 7 years had been undertaken to identify all severe adverse events following immunization. The authors studied events identified in two different ways: one from physicians' voluntary reports from 1975 through 1981 and the other from systematic review of hospital discharge diagnoses for 1979 only.

In the study which relied on physicians' voluntary reports, approximately 134,700 and 135,500 children completed courses of three doses of DPT and DT vaccines, respectively. Sixteen children with seizures (without associated encephalopathies) within 48 hours of DPT vaccination were identified. About half had subsequent seizures, but all were noted to be developmentally normal on follow-up. There were three reports of seizures within 48 hours of DT immunization: one associated with primary DT vaccination and two with a boosting dose of DT vaccine. Temporary or permanent neurologic impairment with or without associated seizure (encephalopathy) was reported in an additional four children in the 48 hours following DPT and in one child following DT immunizations, respectively. Two of the children with an event following DPT immunization were impaired on follow-up. Of note is that six and two similar events were reported more than a week following DPT and DT immunizations, respectively. Comparing children vaccinated with DPT to those receiving DT, the RR of seizures within 48 hours was 5.3, with a 95 percent CI of 1.7 to 16.8. Although the voluntary reports of neurologic events in the 48 hours postimmunization were more frequent with DPT immunization than with DT immunization, these reports also reveal differences in the rates of events for several weeks following immunization, and no such differences in events were found when hospital discharges were routinely screened. This suggests that events following DPT immunization were preferentially reported and that the results of the study which relied on voluntary reports are unreliable.

The systematic review of hospital discharge diagnoses included surveillance of approximately 17,000 children who had received approximately

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21,000 DPT immunizations and 18,000 children who had received 24,000 DT immunizations. Review of hospital discharge diagnoses for 1979 identified six children who had been hospitalized with febrile seizures within 1 week of DPT vaccination and five children who had been hospitalized with febrile seizures within 1 week of DT vaccination (the review was unable to determine the number hospitalized with febrile seizures within 48 hours). There was one child with a transient hemiparesis 36 hours following DPT immunization (possible encephalopathy) and no encephalopathies within 48 hours of DT immunization. Comparing DPT to DP immunized cases, the RR of febrile seizures within 1 week of vaccination was 1.3, with a 95 percent CI of 0.4 to 4.0. The power of this study was relatively weak: 50 percent for an RR of 3.1 and 80 percent for an RR of 5.7.

Pollock and colleagues (1984) compared rates of adverse events in 10,028 infants, of whom 6,004 started primary immunization with DPT vaccine and 4,024 with DT vaccine. The DPT group was further divided into those receiving plain versus those receiving adsorbed vaccine. The first vaccine dose for each child was scheduled at age 3 months, the second dose 6 to 8 weeks later, and the third, final dose 4 to 6 months following the second dose. A total of 25,643 doses of vaccine were given: 1,125 of plain DPT, 13,917 of adsorbed DPT, and 10,601 of adsorbed DT. Children were followed throughout the immunization series, and their parents were contacted both within 48 hours and 6 to 8 weeks following each vaccination. Rates of twitching or jerking were similar in the adsorbed DPT and DT groups (2.3 and 2.2 per 1,000 doses, respectively). Convulsions were reported within 48 hours of immunization in one child given DPT vaccine and in one child given DT vaccine. Another child had a brief episode of staring eyes and stiffened limbs 3 hours after receiving the adsorbed DPT vaccine. None of these children had sequelae. At the 6- to 8-week follow-up, one additional child in the DPT group was reported to have developed epilepsy about 1 month after the first dose. Epilepsy was diagnosed in two additional children in the DT group during the same interval.

In 1967, Strom (1967) examined adverse neurologic events in 516,276 Swedish children vaccinated for DPT between 1959 and 1965. Case notification was obtained through voluntary reports from vaccination clinics, through annual reports of treated cases of postvaccinal complications from children's hospitals, and for the years 1962 to 1964, from special reports from welfare clinics where vaccination had been carried out. Adverse events included 3 children with cerebral injury, 80 with convulsions, 4 with hypsarrhythmia, 54 with shock, 2 with abnormal spinal fluid, and 24 with abnormal screaming. Three cases of "cerebral injury" were reported, only one of which could be classified as a possible encephalopathy within 48 hours of immunization. The second child had an adverse event onset 9 days following DPT vaccination, and the third child, who had a febrile seizure with focal

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features shortly after DPT, developed recurrent seizures and developmental regression weeks later (this was included in Strom's analysis as a seizure). Of the 80 reported convulsions, 58 were known to have occurred within 48 hours, and 2 were known to have occurred more than 48 hours later, but for 20 the time of onset was unknown.

Harker (1977) attempted to identify all febrile seizures occurring in children from Oxford, England, up to age 5 years during a 3-year period (19721975). One hundred seventeen children with febrile seizures were identified through notifications from general practitioners and health visitors. Additional information was obtained by hospital and physician record reviews. No seizures were reported within 48 hours of DPT immunization, and only one was reported within 28 days.

Hirtz and colleagues (1983) reported on children who exhibited seizures within 2 weeks of immunization. The children were identified from data collected in the NCPP (Niswander and Gordon, 1972). Of approximately 54,000 children registered in the NCPP, 2,766 experienced one or more seizures during the first 7 years of life. Eight of these children had their seizures within 48 hours and one at an unknown time following DPT vaccination. On follow-up at age 7, one child who had multiple right focal seizures for 6 hours following her third DPT dose had an expressive speech disorder, with a normal performance IQ but a verbal IQ of 69. None of the other children had mental retardation or an underlying neurologic disease on follow-up that was unrecognized at the time of the seizure.

Feery and colleagues (1985) compared the incidence and types of adverse events following administration of plain or adsorbed DPT vaccines in a masked prospective study of 2,041 vaccinations in 1,075 infants receiving routine childhood immunization. One recipient of each type of vaccine suffered a single convulsion within 48 hours; there were no sequelae.

Long and colleagues (1990) assessed the rates of adverse events following pertussis vaccination in 538 children who were recruited into the study at age 2 months and who were observed longitudinally to age 20 months. Subjects were randomized either to the standard four-dose immunization schedule or to a three-dose schedule with a saline injection substituted for DPT vaccine at age 6 months. In all, 1,553 doses of DPT vaccines were given. No cases of seizures, encephalopathy, or temperature greater than 40.5°C (104.9°F) were observed in either group.

The National Childhood Encephalopathy Study

The NCES was a large, case-control study initiated in 1976 in response to concerns about declining levels of DPT immunization among children in Great Britain (Alderslade et al., 1981). Because this study is much larger in number of cases than any of the other studies that have addressed the rela

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tion between DPT immunization and acute neurologic events in children, it has received intense scrutiny and merits special attention here as well. The stated goals of the NCES were "to assess the risks of certain serious neurological disorders associated with immunization in early childhood and to identify factors that might cause or predispose to such disorders" (Alderslade et al., 1981, p. 80). The study included 1,182 cases of serious acute neurologic illnesses in infants and children ages 2 to 35 months in England, Scotland, and Wales between July 1976 and June 1979. Physicians were asked to notify the NCES of all children who were admitted to a hospital with confirmed or possible diagnoses of:

1. acute or subacute encephalitis, encephalopathy, or encephalomyelitis (including postinfectious encephalitis but not pyogenic infections);
2. unexplained loss of consciousness with or without abnormalities in CSF or EEG;
3. convulsions complicated by one or more of the following: seizures lasting 30 minutes or more, coma lasting 2 hours or more, paralysis, or other neurologic signs not previously present lasting 24 hours or more;
4. infantile spasms; or
5. Reye syndrome.

Cases were subsequently divided into two groups on the basis of their neurologic status prior to the onset of the acute illness: previously normal and previously abnormal. In addition, neurologic status of cases at 15 days postadmission or at the time of discharge was categorized as normal or abnormal. Immunization data were available for 1,167 (99 percent) of the 1,182 cases.

Two control children were selected for each case from immunization or birth registers and were matched to the case by sex, age (within I month), and residential area. Information on immunization histories for both cases and controls was obtained from the child's medical record, which was kept by the local health authority or family doctor. A total of 2,307 controls with recorded immunization histories were included in the study.

In order to address the long-term sequelae of acute neurologic events, two follow-up contacts were made, the first within 12 to 18 months of the initial hospitalization and the second approximately a decade later, when the children were ages 10 to 12 years. For the first follow-up contact, only those cases who were classified as abnormal 15 days after admission were examined at home. Otherwise, information on the developmental and functional status of the case was obtained by mail. Thus, information on the condition of cases approximately 1 year after their acute illness was not obtained in the same manner for all children, and no follow-up data were available for controls. For the second, later follow-up contact, attempts were made to trace all cases and controls who participated in the initial

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study, and information on their neurologic, developmental, and behavioral status was obtained by questionnaires submitted to parents, teachers, and physicians.

This study addressed two major questions about DPT immunization. First, does DPT immunization cause an increase in serious acute neurologic events in children; and second, does DPT immunization cause permanent brain damage? The former is considered first.

Of the 1,167 cases of acute neurologic disease, 263 were infantile spasms, which were discussed above. Of the remaining 904 cases, the onsets for 30 (3.3 percent) were within 7 days of DPT immunization compared with 23 (1.3 percent) controls, whose index date was within 7 days of DPT immunization, yielding an estimated RR of 3.3 (95 percent CI = 1.7-6.5) for acute neurologic illness within 7 days of DPT immunization (Miller et al., 1988) (Table 4-3). Of the 515 cases of seizures and 389 cases of encephalopathy, onsets were within 7 days of DPT vaccination for 18 (3.5 percent) and 12 (3.1 percent), respectively; the RRs associated with DPT immunization within 7 days were 3.3 (95 percent CI = 1.4-8.2) for convulsions and 3.1 (95 percent CI = 1.010.5) for encephalopathy (Miller et al., 1988). Of the 904 cases, 770 were in children with no previously identified neurologic abnormality. Twenty-six (3.4 percent) of these children had the onset of their acute neurologic event within 7 days of DPT immunization, yielding an RR of 3.0 (95 percent CI = 1.5-6.2). Corresponding to these significant results, the power of the statistical tests on which the results were based was high. As Table 4-3 shows, the tests had 50 percent power for RRs of as low as 2.0.

These results suggest that DPT immunization is associated with an increased risk, within 7 days, of seizures and encephalopathy. The potential for error and bias in this study has been extensively discussed by others (Griffith, 1989; MacRae, 1988; Marcuse and Wentz, 1990; Miller et al., 1989; Stuart-Smith, 1988; Wentz and Marcuse, 1991). Major criticisms have involved potential bias and error in (1) case ascertainment, (2) determination of onset of illness, and (3) lack of control for potential confounding factors. Each of these is discussed briefly below.

(1) Case Ascertainment Incomplete case ascertainment, if it was nondifferential with respect to immunization status, would reduce the ability of the study to demonstrate an effect if one existed and, if differential, could result in either over- or underestimation of the true relative risk. The NCES would have missed those cases that did not result in a hospital admission; however, it is likely that most cases meeting the NCES case definition would have been hospitalized. In the Olmsted County, Minnesota, study of encephalitis that included a review of all inpatient and outpatient records, about 90 percent of all cases of encephalitis in young children resulted in hospital admission (Beghi et al., 1984).

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TABLE 4-3 National Childhood Encephalopathy Study Estimated Relative Risks of Specific Acute Neurologic Conditions Following DPT Immunization Within the Previous 7 Days

	Total Cases	DPT Within 7 Days (No.)			Power[b]	
Category	(No.)	Cases	Control	RR *(95% CI)*[a]	50%	80%
All cases	1,167	39	38	2.3 (1.4-3.9)	1.7	2.1
All except infantile spasms	904	30	23	3.3 (1.7-6.5)	2.0	2.6
Seizures	515	18	12	3.3 (1.4-8.2)	2.5	3.7
Encephalopathy	389	12	11	3.1 (1.0-10.5)	3.4	5.7
All except infantile spasms and viral	773	28	23	3.0 (1.5-6.0)	2.0	2.7
Seizure and encephalopathy in previously normal children	770	26	?	3.0 (1.5-6.2)	2.1	2.8
Previously normal; died or neurologically impaired at age 12 months	241	7	3[c]	4.7 (1.1-28.0)	6.0	12.8

[a] RR (95% CI), Estimated relative risk (95 percent confidence interval).
[b] "Power" denotes the probability that a statistical test based on a sample of the same size as the one in the study cited would find a statistically significant increased risk (with alpha = 0.05), given that the true RR in the population being studied is the number stated in the table. The numbers tabulated are the RRs such that the powers are 50 and 80 percent, respectively.
[c] From Madge et al. (1990).
SOURCE: Miller et al. (1988).

Because of concern about the side effects of DPT vaccine at the time of the study, it is possible that children with an acute neurologic illness that occurred in close proximity to immunization would be more likely to be hospitalized or reported to the study investigators and/or included in the final case group than would children with events that did not occur in close proximity to immunization. Miller and colleagues (1988) demonstrated that it would require on the order of 30 percent underreporting of non-vaccine associated cases (about 400 cases) to obtain a result that showed no significant association of serious acute neurologic events with DPT immunization. It is unlikely that underreporting of this magnitude occurred, since participating physicians were sent cards each month to remind them to report cases, selective review of hospital discharge records as part of the study did not reveal substantial underreporting, the overall incidence rate of encephalopathy (7 per 100,000 children) was similar to that reported by others, and the rates of all serious neurologic disease did not vary markedly within the 16

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study regions: 11 to 24 events per 100,000 for all regions and between 14 and 18 events per 100,000 for 11 of the 16 regions (Alderslade et al., 1981).

The selective inclusion of less serious events that occurred in close proximity to immunization would overestimate the true relative risk. However, there is evidence that this did not occur, since the ratio of less serious events (seizures) to the more serious encephalopathies was 1.2 in both vaccine-associated and non-vaccine-associated cases (Miller et al., 1988). The decision to include cases of viral encephalitis and Reye syndrome has been faulted on the grounds that they are unlikely to be caused by immunization. The risk of acute neurologic illness remains essentially unchanged when viral cases are excluded (Miller et al., 1988) (Table 4-3). In a separate analysis of the 37 cases of Reye syndrome, investigators reported that only one of these cases occurred within 7 days of DPT immunization (Bellman, 1983). Therefore, the effect of including these cases would be negligible.

(2) Determination of Onset of Illness Because the onset of some of the neurologic events studied may occur over several days or weeks, an exact date of onset may be difficult to determine. Two study investigators together decided on the date of onset on the basis of all available evidence accumulated on each case without reference to previous immunizations (Alderslade et al., 1981). However, investigators may have been aware of the dates of immunizations, and parents' or physicians' recall of the onset of illness may have been influenced by a recent immunization. The effect of such "recall bias" would be to elevate the risk estimates in the early postimmunization period. There are several lines of evidence that suggest that this type of bias was not a major problem. By using an alternate date unlikely to be influenced by recall bias—the date of hospital admission—similar results were obtained. For infantile spasms, which had the greatest disparity between onset and admission dates, there was only a modest increased relative risk in the early postimmunization period, which was followed by a compensatory decline, so that there was no cumulative increase in cases over the 28 days following immunization. In contrast, for other serious neurologic events there was no compensatory decline in cases, so there was a cumulative increase in cases over the 28 days following immunization (Miller et al., 1988). Finally, an increase in serious neurologic events was found in the 7 to 14 days following measles immunization, the period of time that corresponds to the time of peak fever incidence following administration of this vaccine (Alderslade et al., 1981). Thus, recall bias probably did not influence determination of the onset date for cases occurring in close proximity to measles immunization.

(3) Confounding Factors Relative risks could be over- or underestimated if factors (confounding factors) associated with the development of

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acute neurologic events were also associated with different likelihoods of receipt of DPT vaccine. Children with a history of prior seizures may be more likely both to avoid DPT vaccine and to develop an acute serious neurologic illness. Children with no prior history of seizures were examined separately, and none of the risk estimates changed significantly, except for the RR in the 72-hour to 7-day interval, which increased from 2.1 to 3.2. Socioeconomic status may influence both receipt of vaccine and incidence of neurologic events. An analysis with a broad stratification by socioeconomic status found similar relative risks in both strata.

Since the authors of the NCES were able to estimate the total number of DPT immunizations given to children in the NCES study population, they were able to calculate an attributable risk, that is, the number of excess cases seen in the population receiving DPT vaccine. The calculated attributable risk for acute neurologic illness in the week following DPT immunization in previously normal children was 6.8 per million immunizations.[1] Because of the relatively small number of case-control sets on which the RR estimate of 3.3 was based, the 95 percent CI around the attributable risk estimate was wide: 2.1 per million to 15.9 per million vaccinations. The attributable risk for encephalopathy alone in previously normal children would be on the order of 2.7 per million immunizations, with a 95 percent CI of 0 to 10.5 per million vaccinations.

The second question the NCES tried to address was whether DPT immunization was associated with permanent neurologic damage in children. Neurologic and developmental status at 12 to 18 months after discharge was assessed directly for those cases considered to be abnormal at the time of discharge and by postal inquiry for all other cases. Neurologic impairment at the time of follow-up was defined on the basis of the results of neurologic examination or developmental assessment. Cases not directly examined were assumed to be normal (Madge et al., 1990; Miller et al., 1988). The analysis of risk was confined to those 241 cases who were apparently neurologically normal prior to the onset of their acute illness and who had died or had a developmental deficit (developmental quotient, <70 in one or more fields) at ages 12 to 18 months and their controls. Of these 241 cases, 7 (2.9 percent) were immunized with DPT vaccine within 7 days compared with 3 of 478 controls (0.6 percent), yielding an RR of 4.7 (95 percent CI = 1.1-28.0) (Madge et al., 1990). Attempts were made to trace all cases and one control per case 10 to 12 years after initial recruitment in the NCES (Madge et al., 1990). The com

[1] This and the other attributable risk figures in this paragraph were calculated using the methods of Alderslade et al. (1981, pp. 162-189) applied to the updated relative risk estimates reported in Miller (1988).

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mittee had available to it a brief report of preliminary results and a general description of the follow-up methods. The report was based on a poster presentation at the Sixth International Symposium on Pertussis in September 1990. Follow-up contact was achieved for 81 percent of cases and 83 percent of controls, and information on neurologic, educational, behavioral, and other functions was obtained from questionnaires submitted to parents, teachers, and physicians. Analyses were confined to children designated as neurologically normal prior to their acute illness, and *late dysfunction* was defined as death or any degree of reported dysfunction in any developmental or functional area (e.g., neurologic, behavioral, or educational). Results were based on 515 case children, of whom 15 received DPT vaccine within 1 week of their acute illness. The percentage with any dysfunction or death was similar in "vaccine-associated" (~58 percent) and "non-vaccine-associated" cases (~63 percent) (Madge et al., 1990). Among control children, this value was ~20 percent, suggesting that in comparison with controls, children with a history of acute neurologic illness are at greater risk of long-term neurologic problems, regardless of vaccination status. Information was not available to the committee on the criteria used to define each type of dysfunction, the exact methods for evaluating functional and developmental status of cases and controls after 10 to 12 years of follow-up, or whether the assessments were conducted in a masked fashion. Thus, it is unclear what conditions or problems have been included as late outcomes. Given the limited information available, especially regarding the methods used to assess and define *late dysfunction,* the committee was unable to apply the follow-up data of Madge and colleagues to its assessment of the relation of pertussis vaccine to permanent neurologic damage.

The analyses relating to permanent neurologic damage have also received intense scrutiny (Griffith, 1989; MacRae, 1988; Marcuse and Wentz, 1990; Miller et al., 1989; Stuart-Smith, 1988; Wentz and Marcuse, 1991). The two major problems are (1) the number and composition of cases on which the estimates were based and (2) the nature of the relationship between an episode of acute neurologic illness and subsequent demonstration of neurologic or developmental abnormalities.

Cases Since the RR estimate of 4.7 for permanent neurologic damage is based on a very small number, that is, seven cases, it is particularly vulnerable to the effects of chance, error, or bias (Miller et al., 1988). Of the seven cases, there were two deaths, one associated with Reye syndrome and one with an overwhelming viral infection. Of the remaining five cases, the acute event was a seizure in two cases (one with a major and one with a minor delay in development) and encephalopathy in three cases (one a case of viral encephalitis associated with major impairments and the two others associated with a major and a minor developmental delay, respectively)

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(Alderslade et al., 1981). It has been suggested that if cases with other etiologies for their illness were eliminated from the analysis, the results would no longer be statistically significant. However, it is not sound practice epidemiologically to eliminate any of these cases and recalculate relative risks without similarly evaluating the non-vaccine-associated cases; this has not been done. It is clear, however, that the risk estimates are very fragile and could be very sensitive to the reclassification of two or three cases. In addition, if results for seizures and encephalopathies were calculated separately, it is likely that neither result would be statistically significant.

Relationship Between Acute Event and Follow-up Results It is important to consider whether acute neurologic events are a necessary cause of later observed neurologic impairment or whether, at least at times, these events are markers of children who have an underlying neurologic abnormality. It is well recognized that seizures with fever are more likely to occur in children with underlying neurologic abnormalities than in neurologically normal children. In a group of 96 children followed for febrile seizures or epilepsy by Livingston (1972), about 10 percent of those with a history of febrile seizures were noted to have a recurrent febrile seizure within 24 hours of initial pertussis immunization (none of whom subsequently developed epilepsy), and of 284 patients with epilepsy and frequent seizures, a few had a temporary increase in severity or frequency of seizures following pertussis immunization, but no apparent permanent effects were noted (Livingston, 1972). Other data also indicate that children with a personal or family history of convulsions are more likely to experience a febrile seizure following DPT immunization (Livengood et al., 1989; Stetler et al., 1985a,b).

The NCPP (Niswander and Gordon, 1972), a large longitudinal study, attempted to follow closely approximately 54,000 children from birth to age 7 years. In this population, 1,706 children developed febrile convulsions, 518 developed afebrile seizures, and 233 developed epilepsy by age 7 years. Two studies in which children's intellectual performance both before and after the onset of their seizure disorders and at age 7 years was compared with that of a sibling with no seizures demonstrated that neither febrile (Ellenberg and Nelson, 1978) nor afebrile (Ellenberg et al., 1986) seizures cause intellectual deterioration in children. For febrile seizures, developmental regression was associated only with neurologic and developmental status prior to the onset of seizures and not the number of seizures, presence of focal features, or the duration of the seizure (14 children had seizures of longer than 1 hour). About 22 percent of children with febrile seizures were neurologically abnormal or were suspected to be neurologically abnormal prior to the first febrile seizure (Nelson and Ellenberg, 1976). Most of

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these children did not have obvious malformations, but they were judged to be suspect because of lags in development. The prevalence of epilepsy at age 7 years was 5 per 1,000 in children with no febrile seizures, 11 per 1,000 in those previously normal with simple febrile seizures, 17 per 1,000 in those previously normal with complex febrile seizures (lasting longer than 15 minutes, focal features, or more than 1 in 24 hours), and 28 and 92 per 1,000 in those previously abnormal or suspect with simple and complex febrile seizures, respectively. Thus, children who were judged to be previously abnormal or suspect were more likely to have febrile seizures and to develop epilepsy following either simple or complex febrile seizures.

Of those children in the NCES study with an acute serious neurologic event (encephalopathy or seizure) within 7 days of DPT immunization who were judged to be neurologically normal prior to immunization, seven were neurologically impaired or had died at the 12-month follow-up evaluation. Estimates of permanent neurologic damage following DPT immunization have been based on data for these seven children, five of whose acute event was classified as encephalopathy and two of whose event was classified as seizure. Although these children were presumed to be normal at the time of immunization, no prevaccine neurologic testing was performed. Available evidence, such as that from the NCPP (Ellenberg and Nelson, 1978; Ellenberg et al., 1986; Nelson and Ellenberg, 1976) and from the studies of Livengood et al. (1989), Livingston (1972), and Stetler et al. (1985a,b) reviewed above, suggests that seizures do not produce neurologic impairment but, rather, may be markers of those children with underlying neurologic disease. For the two children with seizures, it is therefore possible that DPT immunization caused the seizure but unlikely that it caused the subsequently diagnosed neurologic impairment. Of the remaining five children with encephalopathy, three had evidence of other conditions (one of Reye syndrome, two of viral encephalitis) known to produce neurologic damage or death.

Other Controlled Studies in Humans

The onset of neurologic disorders in children was examined in Denmark in two different eras, corresponding to changes in the schedule and type of vaccination (Jacobsen et al., 1988; Shields et al., 1988). Before 1970, DPT vaccine was administered at ages 5, 6, 7, and 15 months. Since 1970, monovalent pertussis vaccine is given at ages 5 and 9 weeks and 10 months. All records of children age 7 years or less hospitalized in seven counties in Denmark (serving about 50 percent of the population) with a diagnosis of convulsive disorder, CNS infection, or encephalopathy were reviewed for two time periods: 1967 to 1968 and 1972 to 1973. The age-specific distribution of the time of onset of the first febrile seizure was similar in the two time periods until age 10 months, when there was a significant increase in

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the second time period, which corresponded to the recommended age of the third pertussis immunization. Following this, the age-specific distributions were again similar until 16 months, when there was an increase in the first time period corresponding to the third DPT immunization. The two distributions were found to be significantly different with $p = 0.004$.

On the basis of these data, the authors calculated that approximately 5.4 percent of first febrile seizures occurred in association with pertussis immunization. It is noteworthy that a shift in the distribution of febrile seizures was not observed for those less than age 10 months, suggesting that febrile seizures following administration of DPT vaccine occur during the ages when children are most likely to experience these seizures related to other febrile events (American Academy of Pediatrics, 1980; Hirtz and Nelson, 1983; Nelson and Ellenberg, 1978).

No similar correlations were observed in the distributions of the times of onset of epilepsy. The power of the test to detect such an effect was reasonably high. For instance, if 10 percent of all cases of epilepsy first occurring in the age range under study were due to DPT immunizations, the test would have 50 percent power to detect an increased relative risk. If 15 percent of cases were caused by the vaccine, the power would be 80 percent.

Walker and colleagues (1988) conducted a case-cohort study in a population of 26,600 children born in Group Health Cooperative hospitals from 1972 through 1983 with normal birth weights and no congenital disorders or perinatal events that might predispose them to seizure disorders. New neurologic disorders without an obvious predisposing cause (e.g., trauma) occurring from ages 30 days to 6 years were identified through inpatient hospital records and pharmacy records. There were 5 cases identified with encephalopathy (clinical diagnosis) and 231 cases with one or more seizures. Fifty-five of these cases had at least one afebrile seizure, and the remaining 176 cases had only febrile seizures. The timing of DPT immunization for case children and a random sample of 262 control children matched to cases was obtained through a review of outpatient records. It was estimated that the study population received a total of 106,000 doses of DPT vaccine.

None of the five cases of encephalopathies (Table 4-4) occurred in the first 30 days following DPT immunization. Using the period 30 or more days following DPT immunization as the reference period, the authors identified one, one, and four afebrile seizures in the 0 to 3, 4 to 7, and 8 to 29 days after DPT vaccination, respectively, compared with 1.1, 0.9, and 3.1 expected cases, respectively (Table 4-5). The RRs for these periods were 1.0, 1.2, and 1.5, respectively, but none were significantly elevated. The powers of these tests were low, however. For the first two periods, RRs of over 9.2 would have been needed to achieve 50 percent power. The age-

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TABLE 4-4 Summary of Controlled Studies on DPT Immunization and Encephalopathy

Reference	Design	Years	Age	No. Child-Years (No. Children)	No. DPT	All Encephalopathy		Encephalopathy Within 7 Days of DPT			
						No.	Incidence/ 100,000	No.	Odds Ratio (95% CI)[a]	Power[b] 50%	80%
Alderslade et al., 1981; Miller et al., 1988	Matched case-control	July 1976-June 1979	2-35 months	~5.4 million	~2.2 million	389	7	12	3.1 (1.0-10.5)	3.4	5.7
Walker et al., 1988	Matched case-cohort	1972-1983	30 days-6 years	~100,000 (26,000)	~106,000	5	5	0	—		
Griffin et al., 1990	Cohort	1974-1984	29 days-3 years	~60,562 (38,171)	107,000	2	3	0	—		
Gale et al., 1990	Matched case-control	1987-1988	1-24 months	218,000 (equivalent to a cohort of 109,000)	~368,878	22	10	2	4.0 (0.4-44.1)	11.0	30.8

[a] 95% CI, 95 percent confidence interval.

[b] "Power" denotes the probability that a statistical test based on a sample of the same size as the one in the study cited would find a statistically significant increased risk (with alpha = 0.05), given that the true RR in the population being studied is the number stated in the table. The numbers tabulated are the RRs such that the powers are 50 and 80 percent, respectively.

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adjusted incidence of identified febrile seizures in the immediate postimmunization period was 3.7 times (95 percent CI = 1.4-10.0) that in the period 30 or more days after immunization (Table 4-6). In concert with this result, the power of this test was higher than that for afebrile seizures. An RR of 2.7 for febrile seizures had 50 percent power and an RR of 4.1 had 80 percent power.

TABLE 4-5 Summary of Controlled Studies on DPT Immunization and Afebrile Seizures

Reference	Design	No. of Cases in Interval	Time Interval (days)	RR (95% CI)[a]	Power[b] 50%	Power[b] 80%
Walker et al., 1988	Matched case-cohort	1	0-3	1.0 (0.1-9.7)	9.7	25.7
		1	4-7	1.3 (0.1-12.0)	9.2	23.9
		4	8-29	1.5 (0.4-5.5)	3.7	6.4
Griffin et al., 1990	Cohort	1	0-3	1.3 (0.2-9.7)	7.5	17.7
		2	4-7	2.2 (0.5-9.9)	4.5	8.6
		1	8-14	0.6 (0.1-4.9)	8.2	20.1
		3	15-29	0.9 (0.3-3.1)	3.4	5.9
Gale et al., 1990	Matched case-control (SONIC)[c]	?	<7	0.5 (0.2-1.5)	3.0	4.8
		14	<14	0.8 (0.4-1.5)	1.9	2.5
		25	<28	0.6 (0.3-1.1)	1.8	2.4

[a]RR (95% CI), Estimated relative risk (95 percent confidence interval).
[b]"Power" denotes the probability that a statistical test based on a sample of the same size as the one in the study cited would find a statistically significant increased risk (with alpha = 0.05), given that the true RR in the population being studied is the number stated in the table. The numbers tabulated are the RRs such that the powers are 50 and 80 percent, respectively.
[c]SONIC, Study of Neurologic Illness in Children.

This study thus demonstrated no increase in afebrile seizures or encephalopathies in the early postimmunization period. However, the study examined only seizures serious enough to warrant either admission to a hospital or the use of anticonvulsant medications, and it had limited power to study encephalopathies or permanent neurologic damage. Febrile seizures were reported to be 3.7 times greater in the early postimmunization period, but no other details about this estimate were presented.

Griffin and colleagues (1990) linked computerized immunization files available for four Tennessee counties from 1974 through 1984 to Tennessee birth certificates and to Tennessee Medicaid files, which contain information on Medicaid enrollment, diagnoses associated with all medical encounters, and records of all filled prescriptions. They studied a cohort of children born in Tennessee who were enrolled in the Medicaid program and

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who received at least one DPT immunization through the county clinic system. The first neurologic event after initiation of DPT immunization was ascertained by obtaining medical records of children with diagnoses or prescriptions indicating a possible seizure or new neurologic event. Medical records for review were available for emergency room and hospital admissions and for hospital-based clinics. Other outpatient records were not reviewed, so events that resulted in no medical encounter or those that initiated only an outpatient visit are likely to have been missed.

TABLE 4-6 Summary of Controlled Studies on DPT Immunization and Febrile Seizures[a]

Reference	Design	No. of Cases in Interval	Time Interval (days)	RR (95% CI)[b]	Power[c] 50%	Power[c] 80%
Walker et al., 1988	Matched case-cohort	?	0-3	3.7 (1.4-10.0)	2.7	4.1
Griffin et al., 1990	Cohort	6	0-3	1.5 (0.6-3.3)	2.2	3.1
		4	4-7	0.9 (0.3-2.3)	2.6	3.8
		6	8-14	0.7 (0.3-1.7)	2.4	3.6
		19	15-29	1.1 (0.7-1.8)	1.6	2.0
Gale et al., 1990	Matched case-control (SONIC)[d]	6	<7	1.9 (0.6-5.9)	3.1	5.1
		11	<14	1.8 (0.8-4.4)	2.4	3.6
		13	<28	1.1 (0.5-2.3)	2.1	2.9

[a]For NCES data, see Table 4-3.
[b]RR (95% CI), Estimated relative risk (95 percent confidence interval).
[c]"Power" denotes the probability that a statistical test based on a sample of the same size as the one in the study cited would find a statistically significant increased risk (with alpha = 0.05), given that the true RR in the population being studied is the number stated in the table. The numbers tabulated are the RRs such that the powers are 50 and 80 percent, respectively.
[d]SONIC, Study of Neurologic Illness in Children.

By using a cohort analysis, the risks of seizures and encephalopathy (NCES definition used) were evaluated following DPT immunization in 38,171 children on Medicaid in Tennessee who received 107,154 DPT immunizations in their first 3 years of life. Only two children with encephalopathy were identified (Table 4-4); the onset of symptoms did not occur within 2 weeks of immunization in either child. There were one, two, one, and three children with afebrile seizures in the intervals 0 to 3, 4 to 7, 8 to 14, and 15 to 29 days, respectively, following DPT immunization compared with 35 in the interval 30 or more days post-DPT vaccination, yielding RR estimates (95 percent CIs given in parentheses) of 1.3 (0.2-9.7), 2.2 (0.59.9), 0.6 (0.1-4.9), and 0.9 (0.3-3.1), respectively (Table 4-5). The power

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of these tests was relatively low. For the early interval, for instance, the RR would have to be 7.5 to achieve 50 percent power and 17.7 to achieve 80 percent power.

This study demonstrated no significant increase in febrile seizures in the 0 to 3 days following DPT immunization (RR, 1.5); however, the upper bound of the 95 percent CI was 3.3. For febrile seizures, the power was greater than those for afebrile seizures and encephalopathy: 50 percent for an RR of 2.2 and 80 percent for an RR of 3.1.

SONIC was a large case-control investigation of the association between the risk of serious acute neurologic illness and DPT immunization in young children. The study was conducted in the states of Washington and Oregon from August 1, 1987, through July 31, 1988, and included children aged 1 to 24 months. The primary purpose of SONIC was to evaluate the feasibility of conducting in the United States a study similar to the British NCES but that avoided the methodologic problems for which the NCES had been criticized.

Attempts were made to identify, through active surveillance of hospital and physician records, all eligible cases in the two states. Cases were primarily identified through systematic review of emergency room, outpatient clinic, and inpatient discharge listings for 98 percent of the acute-care hospitals with pediatric beds in the two-state area. The conditions included in SONIC (see below) were similar to those in the NCES. Case definitions were determined by a panel of international experts on neurologic illness in childhood. Excluded were acute neurologic illnesses caused by trauma, poisoning, or bacterial infections of the CNS identified by culture or equivalent measures. Cases included children with the following diagnoses: acute encephalitis or encephalopathy; Reye syndrome; loss of consciousness of unknown etiology; acute paralytic syndromes; infantile spasms; and seizures without fever, all seizures in children ages I to 3 months, afebrile seizure or series of febrile seizures with a duration of approximately 15 minutes or longer, and febrile seizures accompanied by focal neurologic signs. A panel of experts confirmed the diagnoses by review of medical records without knowledge of immunization history.

Two controls per case were selected from the birth certificate registries of the states of Washington and Oregon. Controls were matched to cases by age (within 5 days), sex, and county of birth. Parents of both cases and controls were interviewed by telephone to obtain information on potential risk factors, including immunization histories. Attempts were made to validate immunization information for all cases and controls by using medical record data.

The major differences in the research designs and procedures for data collection between SONIC and the NCES were that (1) the NCES included only hospitalized cases, whereas SONIC included both hospitalized and outpatient cases; (2) case ascertainment in the NCES relied primarily on

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reporting from the hospitals, whereas SONIC used an active surveillance system; (3) in the NCES, the reporting physician's diagnosis was assumed to be correct, whereas in SONIC, diagnoses were confirmed by a masked expert panel using uniform, prespecified criteria; and (4) in the NCES, both immunization histories and children's previous levels of function were obtained solely from a questionnaire submitted to the local physician, whereas in SONIC, the former were independently verified by study staff and the latter were determined from medical records.

Preliminary findings from SONIC have been reported recently (Gale et al., 1990) and are shown in Table 4-7. In the population studied, 358 eligible children with incident neurologic illnesses and verified immunizations were identified. Of these, the onset of illness was within 28 days of a previous DPT vaccination for 48 children and within 7 days of a previous DPT vaccination for 14 children. The odds ratio for the occurrence of any of the neurologic illnesses included in SONIC within 7 days of DPT immunization was 1.2 (95 percent CI = 0.6-2.3). Regardless of the definition of the case group (i.e., whether total or only new-onset or NCES-compatible cases were included), whether statistical adjustment was done for potential confounders, or whether the exposure-to-onset interval was <7, <14, or <28 days, no statistically significant increases in risk were observed, although all odds ratios for exposure intervals of <7 days were greater than 1.0. The power of the SONIC study was reasonably high. For the comparison cited above, for instance, the test had 50 percent power for an RR of 1.9 and 80 percent power for an RR of 2.5.

Considering separately the results of analyses of the relationship of DPT immunization within the previous 7 days and the risk of specific types of illnesses, the odds ratio was 4.0 (95 percent CI = 0.4-44.1) for encephalopathy, 0.5 (95 percent CI = 0.2-1.5) for afebrile seizures, and 1.9 (95 percent CI = 0.6-5.9) for complex febrile seizures. Thus, no statistically significant increases or decreases in risk were observed for specific types of neurologic illnesses. However, the study had limited statistical power to detect changes in risk associated with DPT exposure within strata defined by specific types of acute neurologic illnesses. The RRs at which 50 percent power would be achieved for these three outcomes were, respectively, 11.3, 3.0, and 3.1. SONIC was not designed to assess the association of DPT and the risk of long-term neurologic problems and thus did not provide any information on this question.

In all of the preceding studies where encephalopathies were ascertained, it is possible to count the number of DPT-vaccinated children whose experiences subsequent to vaccination were monitored and recorded in the relevant papers. The studies cited in Tables 4-2 and 4-4 (Cody et al., 1981; Gale et al., 1990; Griffin et al., 1990; Long et al., 1990; Pollock and Morris, 1983; Pollock et al., 1984; Strom, 1967; Walker et al., 1988) include a total

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of 864,000 children. Six encephalopathies were recorded within 2 days, and two (in the SONIC study) were recorded as occurring within "1 week" of vaccination. Using a "background" rate of encephalopathy of 78 per 100,000 children per year,[2] it is possible to estimate the attributable risk for encephalopathies following vaccination. If data from all cited studies are included, the attributable risk estimate is 7.2 per million children. In these

TABLE 4-7 Study of Neurologic Diseases in Children (SONIC) Estimated Relative Risks for Pertussis Vaccine Exposure by Case Class and Exposure Interval, With and Without Adjustment for Potential Confounders

Analysis Group[a]	Matched Sets[b] (No.)	Time Interval (days)	RR (95% CI)[c]	Power[d] 50%	80%
All cases	424	<7	1.1 (0.6-2.0)	1.82	2.35
		<14	1.2 (0.8-2.0)	1.67	2.07
		<28	0.9 (0.6-1.3)	1.44	1.69
Incident cases	358	<7	1.2 (0.6-2.3)	1.92	2.53
		<14	1.2 (0.8-2.0)	1.67	2.07
		<28	1.9 (0.6-1.3)	1.44	1.69
Incident cases, adjusted[e]	358	<7	1.1 (0.5-2.3)	2.09	2.87
		<14	1.2 (0.7-2.1)	1.75	2.22
		<28	0.9 (0.6-1.5)	1.67	2.07
NCES eligible cases[f]	100	<7	2.5 (0.7-9.3)	3.72	6.53
		<14	1.8 (0.8-4.4)	2.44	3.59
		<28	1.1 (0.5-2.3)	2.09	2.87
NCES eligible cases, adjusted[e,f]	100	<7	3.6 (0.8-15.2)	4.22	7.83
		<14	2.1 (0.8-5.8)	2.76	4.27
		<28	1.2 (0.5-2.9)	2.42	3.53

[a] NCES, National Childhood Encephalopathy Study.
[b] Matched case-comparison study design.
[c] RR (95% CI), Estimated relative risk (95 percent confidence interval).
[d] "Power" denotes the probability that a statistical test based on a sample of the same size as the one in the study cited would find a statistically significant increased risk (with alpha = 0.05), given that the true RR in the population being studied is the number stated in the table. The numbers tabulated are the RRs such that the powers are 50 and 80 percent, respectively.
[e] Incident cases adjusted for prior seizure, prior major DPT reaction, family history of seizures, and illness within 30 days.
[f] NCES eligible cases, see Chapter 4.

[2] This rate was calculated from data in the NCES (Alderslade et al., 1981; Miller et al., 1981), Walker et al. (1988), Griffin et al. (1990), and SONIC (Gale et al., 1990) studies, with an age adjustment derived from Beghi et al. (1984). For details, see Appendix D.

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studies, children received on average three DPT immunizations; therefore, the estimated attributable risk of encephalopathy is 2.4 per million immunizations. If the studies of Pollock and Morris (1983) and Strom (1967), which relied on spontaneous reports for ascertainment, are excluded, the attributable risk estimate is 2.3 per million immunizations. Relying only on the data in controlled studies of well-defined populations (Gale et al., 1990; Griffin et al., 1990; Walker et al., 1988), the estimate of the attributable risk is 3.3 per million immunizations.

In the case of febrile and afebrile seizures, the committee was able to carry out a meta-analysis of the other studies in defined populations (Gale et al., 1990; Griffin et al., 1990; Walker et al., 1988). Three of these studies provide information specifically on afebrile seizures (Gale et al., 1990; Griffin et al., 1990; Walker et al., 1988). Using the methods described in Appendix D, the pooled RR estimate from these studies is 0.6 (95 percent CI = 0.4-1.1), assuming a fixed-effects model, and 0.7 (95 percent CI = 0.3-1.5), under a random-effects model. Thus, even pooling of the available data provides no evidence of a statistically significant increase in the risk of afebrile seizures following DPT vaccination.

Combining data from the same three studies on febrile seizures yields a pooled RR of 1.8 (95 percent CI = 1.2-2.7), assuming a fixed-effects model, and 1.9 (95 percent CI = 1.0-3.3), under a random-effects model. Thus, regardless of the kind of statistical model assumed, the pooled data from these three studies indicate an increased relative risk for febrile seizures following DPT immunization.

Evidence from Studies in Animals

The same limitations that apply to the use of animal models to gain understanding of pathogenesis and immunity in human whooping cough (see Chapter 3) pertain to their use for the study of pertussis vaccine-induced encephalopathy. Superficial understanding of the effects on the human brain of various putative virulence factors and of pertussis vaccine makes it impossible to interpret previous results in animals with any certainty. Unless the basic nature of the postulated vaccine-induced encephalopathy in humans is understood, preferably at the molecular and cellular levels, it is not possible to determine whatever abnormalities produced in an animal represent a valid "model."

Retrospective analysis of work that has been done to date yields little useful information. Mice die from an apparent toxemia after intraperitoneal inoculation of large numbers of viable *B. pertussis* organisms (Pittman, 1970; Proom, 1947). The reasons for death are not understood, as is the case for most infectious diseases. Intracerebral inoculation of viable *B. pertussis* organisms in mice induces an encephalopathy (Cameron, 1988), which is not

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surprising. Any relationship of this encephalopathy to the cerebral effects of injecting a vaccine at an extracerebral site is speculative. Amiel (1976) and Bergman and colleagues (1978) found changes in the permeability of the cerebral vasculature of rodents given pertussis vaccine, but it has not been clear how this might relate to encephalopathy in rodents or humans.

Steinman and colleagues (1982) have proposed a mouse model for pertussis vaccine-induced encephalopathy that is linked to the genetic locus H-2. In this model, animals with a certain H-2 type that had been given a large number of heat-killed *B. pertussis* organisms 2 days earlier died within 30 minutes to 2 hours after injection of bovine serum albumin. Postmortem examination of the brain revealed diffuse vascular congestion and parenchymal hemorrhage, which the authors believed resembles the findings in human cases in whom death occurred quickly after immunization. The model raises interesting questions regarding possible genetic control and a role for immediate hypersensitivity in postulated vaccine-induced encephalopathy, but the relationship of these variables to the proposed response in humans is speculative. Moreover, it is not clear whether these pathologic changes represent a primary encephalopathy or the agonal effects of shock, hypovolemia, and the like.

Presumably, the vaccine lots that have been suspected of causing irreversible encephalopathy in children have passed the intracerebral mouse protection test or the intranasal mouse protection test for vaccine potency and the mouse weight gain test for toxicity. Therefore, the capacity to cause serious encephalopathy in mice, if present, has been missed. The endpoint of the intracerebral mouse protection test is death from active infection within 14 days. The interval between injection of vaccine and intracerebral injection of viable organisms, a matter of a few weeks, might not be sufficient for detection of late neurologic effects. More importantly, neurologic sequelae that might relate to changes in memory, learning ability, emotional control, and the like might not be obvious in mice. Similar considerations apply to the mouse weight gain test, which is carried out for up to 7 days and which focuses on weight gain as an endpoint. In summary, it is not evident that the studies in animals completed to date provide information useful to understanding the possible relation of encephalopathy to pertussis immunization in children.

Aluminum Salts

The possibility has been raised that the aluminum salts regularly present in DPT vaccines might play a role in the occurrence of encephalopathy following DPT immunization (see Appendix E for discussion). There are no data bearing on this possible mechanism.

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Summary

Case reports and case series offer no consistent evidence for a clinically distinctive pertussis vaccine-induced encephalopathy. The limited understanding of the underlying disease process and an inability to diagnose encephalopathy accurately or uniformly, particularly in infants, also hinder the design, conduct, and interpretation of human studies. Comparisons of results among different studies are difficult, since different types of events are included under the term *encephalopathy* in different studies.

The animal models of pertussis vaccine-induced encephalopathy (e.g., Cameron, 1988; Steinman et al., 1982) do not appear to be pertinent to human disease (e.g., they require intracerebral inoculation). In addition, the superficial understanding of the pathophysiology of encephalopathy, the difficulties of accurately diagnosing even severe cases, the lack of understanding of pertussis virulence factors, and the variability in pertussis vaccine composition across manufacturers and time make it almost impossible to extrapolate animal findings to humans with any certainty. There are no data to indicate a mechanism of cerebral injury.

In light of the considerations listed above and given the limitations of case reports and animal studies (see Chapter 3), the studies that could best address the question of the possible relation between pertussis vaccination and encephalopathy have been controlled epidemiologic studies. To date, four such studies have been reported (Alderslade et al., 1981; Gale et al., 1990; Griffin et al., 1990; Walker et al., 1988). The NCES reported a statistically significant RR of encephalopathy of 3.1 (associated with an attributable risk of 2.7 per million immunizations) in the early postimmunization period. None of the other studies demonstrated a statistically significant risk. However, the total number of cases reported in the other three studies was consistent with the attributable risks found in the NCES.

Data bearing on the question of a possible relation between pertussis vaccination and chronic neurologic damage are limited to one controlled study (Alderslade et al., 1981; Miller et al., 1988), in which the neurologic status of children prior to their acute illness was not directly measured and the definition and measurement of late outcomes were not uniformly applied to all participants. In addition, the total number of children with chronic conditions on which risk estimates were based was very small, and estimates of chronic neurologic damage following specific types of acute illnesses, especially encephalopathy, could not be calculated.

The results of studies comparing rates of febrile seizures following DPT versus DT vaccine (Cody et al., 1981; Pollock and Morris, 1983; Pollock et al., 1984), the ecologic study of Shields and colleagues (1988) showing a shift in occurrence of febrile seizures following change in time of DPT immuniza

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tion, the NCES results on seizures (80 percent of which were febrile) (Alderslade et al., 1981), and the findings of three additional controlled studies on febrile seizures (Gale et al., 1990; Griffin et al., 1990; Walker et al., 1988) suggest that DPT vaccine may cause a doubling or tripling of the febrile seizure rate in the first few days following immunization.

The three controlled studies that directly addressed afebrile seizures (Gale et al., 1990; Griffin et al., 1990; Walker et al., 1988) were consistent in showing no relation to DPT vaccination, although each had limited statistical power to detect risks unless they were on the order of 2.4 or larger. Only the study of Shields and colleagues (1988) addressed epilepsy specifically, and it found no relation between the onset of epilepsy and the timing of DPT immunization. However, the power of this study was limited.

No animal models for seizures and DPT vaccine have been developed.

Conclusion

The evidence is consistent with a causal relation between DPT vaccine and acute encephalopathy,[3] defined in the controlled studies reviewed as encephalopathy, encephalitis, or encephalomyelitis. On the basis of a review of the evidence bearing on this relation, the committee concludes that the range of excess risk of acute encephalopathy following DPT immunization is consistent with that estimated for the NCES: 0.0 to 10.5 per million immunizations.

There is insufficient evidence to indicate a causal relation between DPT vaccine and permanent neurologic damage.

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[3] Although the committee was not asked expressly to examine febrile seizures, afebrile seizures, or epilepsy in relation to DPT vaccine, it did so because these conditions are considered by some to be components of encephalopathy. The committee's conclusions on the relation of these adverse events to DPT immunization are as follows—febrile seizures: the evidence indicates a causal relation between DPT vaccine and febrile seizures; afebrile seizures: the evidence does not indicate a causal relation between DPT vaccine and afebrile seizures; epilepsy: there is insufficient evidence to indicate a causal relation between DPT vaccine and epilepsy.

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5

Evidence Concerning Pertussis Vaccines and Deaths Classified as Sudden Infant Death Syndrome

CLINICAL DESCRIPTION, DIAGNOSIS, AND PATHOLOGY

Prior to the 1960s, little was known about the epidemiology of the sudden infant death syndrome (SIDS). Deaths that occurred suddenly and unexpectedly were generally certified as being due to another cause of death such as pneumonitis rather than an unknown cause (Peterson, 1980). In an international conference in 1969, SIDS became defined as "the sudden death of any infant or young child, which is unexpected by history, and in which a thorough postmortem examination fails to demonstrate an adequate cause of death" (Bergman et al., 1970, p. 18). The postmortem examination to be performed was specified to include gross examination of the thorax, abdomen, brain, and larynx; histologic examination of the brain, heart, lungs, liver, kidney, and any other organs suspected to be involved by either history or macroscopic findings; and any additional studies (e.g., cultures and toxicology) indicated by any of those findings. In many children who die from SIDS, petechiae are found on the surfaces of the lung, pericardium, and thymus and have been ascribed to nonspecific agonal anoxia. However, there are no pathognomonic findings; the diagnosis therefore is one of exclusion, a process that depends on the training, experience, and judgment of the examiner (Peterson, 1980).

It was not until 1975 that the coding of such deaths was modified, so that these deaths could be classified specifically as SIDS. The use of a standard

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definition and the specific classification of SIDS as a distinct syndrome has facilitated identification of such cases, permitting the emergence of the descriptive epidemiology of SIDS in the 1970s and 1980s.

DESCRIPTIVE EPIDEMIOLOGY

SIDS occurs almost exclusively in infants between the ages of 2 weeks and 1 year. In industrialized countries, it is the most common diagnosis in infants who die between the ages of 1 month and 1 year (Thach, 1986). The age distribution of cases peaks at age 2 to 3 months and then gradually subsides, with only a small percentage of cases occurring after age 6 months. In the words of Peterson (1980, p. 100), "This [age} pattern has been documented time after time and constitutes the single most consistent, provocative and unique characteristic of SIDS yet identified."

Crude mortality as a result of SIDS reported from throughout the world has ranged from 0.3 to 5.2 per 1,000 live births (Golding et al., 1985). Although these differences in reported rates may be explained partly by differences in classification of deaths caused by SIDS, most of the variation in rates is probably due to real differences in the occurrence of SIDS in diverse populations. The great majority of SIDS deaths occur at home or en route to a hospital (Golding et al., 1985). A number of investigators have reported seasonal variations in SIDS mortality rates, with a relative increase in frequency in winter months (Golding et al., 1985).

Predictors of SIDS include individual characteristics (male sex, low birth weight, multiple births, and black race), maternal characteristics (young age, low education, and cigarette smoking), and low family income (Haglund and Cnattingius, 1990; Hoffman et al., 1987; Kraus et al., 1989). Rates in blacks have consistently been reported to be higher than those in whites; however, in one analysis (Kraus et al., 1989), this difference disappeared after controlling for maternal education and family income.

It has been postulated that apnea during sleep is a mechanism of SIDS, and evidence concerning this hypothesis has recently been reviewed (Sullivan, 1988). Ventilatory patterns during sleep have been studied (Keens et al., 1985), and home apnea monitors have been used for infants thought to be at risk for SIDS (Bryan, 1988). However, it remains uncertain whether there is a relationship between abnormal ventilatory patterns or recurrent apnea episodes and SIDS. In the National Institute of Child Health and Human Development (NICHD) SIDS Cooperative Epidemiologic Study (reviewed below), only 6 of the first 400 SIDS cases (1.5 percent) studied and 1 (0.3 percent) of the matched controls had medically documented apnea (Damus et al., 1988).

Although deaths from SIDS are, by definition, unexpected, children who

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die of SIDS tend to be in poorer health than their peers in the week or two prior to death. Stanton and colleagues (1978) found that parents reported symptoms considered severe enough to warrant medical attention or close supervision in the 48 hours before death or interview for 69 of 145 (48 percent) children who died of SIDS and only 19 of 154 (12 percent) control children. Gilbert and colleagues (1990), in a similar study found that parents reported major or minor signs of illness in the previous week in 66 of 95 (69 percent) SIDS victims and only 71 of 190 (41 percent) control children matched with cases for age, area of residence, and time of year. In addition, Gilbert and colleagues (1990) found that 17 (18 percent) SIDS victims had been seen by their general practitioner during the week preceding death, whereas 11 (6 percent) control children had been seen by their general practitioner in the corresponding period. Less pronounced differences in the relative frequencies of reported symptoms before death or interview were found in the NICHD SIDS Cooperative Epidemiologic Study (Hoffman et al., 1988). Although parents of children who died from SIDS may be more likely to recall and thus report more symptoms in their children, reporting of doctor's visits over a short time period is likely to be complete for both cases and controls.

It is noteworthy that some of the factors associated with SIDS, such as low birth weight, young maternal age, and black race, are also associated with delaying early childhood immunization past the recommended age (Hoffman et al., 1987; Walker et al., 1987). The influence of such delays on the time of occurrence of SIDS in relation to the time of DPT immunization would depend on the specific ages over which such delays occurred. The effect could be to cause children to be immunized at ages associated with either higher or lower than expected rates of SIDS, and thus produce spurious direct or inverse associations, respectively, between SIDS and DPT immunization. Clearly, all factors associated with delaying immunization should be measured and controlled for as far as possible in studies of SIDS in relation to DPT vaccine administration. The ages of study subjects should be considered as precisely as possible as well. Although the Immunization Practices Advisory Committee advises the deferral of routine DPT immunization only for those with a febrile illness (Centers for Disease Control, 1985), in practice, some clinicians may postpone immunizations because of other minor illnesses (American Academy of Pediatrics, 1986). Since minor illnesses often precede SIDS, the effect of delaying immunization during such illnesses would be to produce a spuriously low rate of SIDS in the immediate postimmunization period. Thus, in addition to age and possible delaying factors, the potential role of minor illnesses in the timing of immunization is important to address in evaluating the studies of SIDS and DPT vaccine administration.

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HISTORY OF SUSPECTED ASSOCIATION WITH PERTUSSIS VACCINES

In 1933, Madsen reported on two infants who received immunizations against pertussis shortly after birth and died within 2 hours of their second shot at ages 4 and 11 days, respectively. Although there were other isolated case reports of death following DPT immunization, current concern about pertussis and SIDS dates from March 1979, when the Tennessee Department of Health (Hutcheson, 1979a,b) reported that four sudden and unexplained deaths had occurred since November 1978; these infants had all died within 24 hours following their first DPT immunization. All four children had received vaccine from the same lot (lot A), which was the predominant lot in use in Tennessee at that time. A subsequent investigation confirmed a greater than expected temporal relation between lot A DPT vaccine and SIDS. However, the overall incidence of SIDS in Tennessee did not increase during the time period when lot A was in use, samples of lot A were found acceptable with regard to potency and freedom from toxicity when tested, and no other clusters of cases of SIDS associated with lot A (361,000 doses distributed) were reported (Bernier et al., 1982). Therefore, no other evidence was found to support a causal relationship. However, that report as well as other case reports prompted further investigation of the possibility of a relationship between DPT immunization and SIDS.

EVIDENCE FROM STUDIES IN HUMANS

Case Reports and Case Series

In addition to those just cited, case reports of SIDS include the deaths of 5- and 10-month-old twins within 3 and 24 hours, respectively, of DPT immunization (Roberts, 1987; Werne and Garrow, 1946). Episodes of death following administration of DPT vaccine were reported for six additional children, five of whom died within 48 hours of immunization (Coulter and Fisher, 1985). Torch (1986) summarized case reports of more than 150 deaths, post-DPT immunization, which had been reported by 37 authors in 12 countries; approximately 50 percent of these deaths occurred within 24 hours, 75 percent within 72 hours, and 90 percent within 1 week following DPT administration. For most of these events, no specific cause of death could be found, and many of these cases were designated as SIDS. (This summary of case reports was published in abstract form only.)

Since SIDS occurs primarily in the first year of life, and since in the United States most children receive three DPT immunizations during this first year, some cases of SIDS are to be expected in the early postimmunization period. Accordingly, in the United States, approximately 55 cases of SIDS

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per year would be expected to occur within 24 hours of receipt of DPT vaccine (Stetler et al., 1985). If one member of a twin pair dies of SIDS, the other twin, who is also at higher risk of dying of SIDS, could, by coincidence, die on the same day (Roberts, 1987). Thus, the deaths in twins cited above could be coincidental.

Torch (1982) reported, though only in abstract form, preliminary data on 70 of 200 (35 percent) "randomly reported" cases of SIDS. He reported clustering of cases within the first 2 to 3 weeks following DPT immunization. Autopsy findings in children who died in this early postimmunization interval were no different from those in other children who died from SIDS. Baraff and colleagues (1983) were able to interview parents of 145 of 382 (38 percent) identified cases of SIDS that occurred in Los Angeles County during a 20-month period. Fifty-three cases had received DPT vaccine prior to death, 11 percent within 1 day of death, 32 percent within 1 week of death, and 51 percent within 4 weeks of death. The authors assumed that cases should have occurred with uniform frequency throughout the 28 days following immunization, but noted instead a significant increase in the frequencies of reported cases in both the first day and the first week following DPT vaccination. These investigators also noted a similar clustering of cases of SIDS following physician visits that did not include DPT immunization, a finding that suggests that the prior assumption of uniform frequency was incorrect.

As pointed out by Mortimer and colleagues (1983), such analyses are flawed because they do not take into account the age distribution of cases of SIDS as noted above. Approximately 14 percent of cases of SIDS are age 2 months, 7 percent are age 3 months, and 3 percent are age 6 months at the time of death (Hoffman et al., 1987). After about age 10 weeks, a day-by-day decrease in the risk of SIDS has been observed in diverse populations (Solberg, 1985). If DPT immunization is initiated at about this age, more SIDS cases would be expected to occur in the early postimmunization period than later, contrary to the assumption made by Torch (1982) and Baraff and colleagues (1983). In addition, both of these case series (Baraff et al., 1983; Torch, 1982) were limited by their failure to include all eligible cases; only 35 and 38 percent of SIDS cases, respectively, were included in these analyses, raising the question of whether those cases who had been recently immunized were selectively included in these studies.

Three hundred fifty cases of SIDS (ICD 9 code 798.0) occurring within 28 days of DPT immunization were reported through the Centers for Disease Control's Monitoring System for Adverse Events Following Immunization system for 1978 to 1990, a period in which approximately 80.1 million doses of DPT vaccine were administered through public mechanisms in the United States (J. Mullen, Centers for Disease Control, personal communication, 1990). Of these 350 cases, 332 (94.9 percent) occurred in infants

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who had received at least one other vaccine at the time when DPT was administered. No follow-ups of the cases were conducted, and a physician's diagnosis was not required.

For the reasons discussed above, reports of single or multiple cases of death within hours, days, or weeks of DPT administration offer limited insight into the possibility of a causal connection between this immunization and the occurrence of SIDS. Therefore, it is important to consider the reports of controlled studies of SIDS, in which the questions of an increased risk in the early postimmunization period can be addressed more adequately.

Controlled Epidemiologic Studies

Seven studies of DPT immunization and SIDS that include age-matched controls have been published (Bouvier-Colle et al., 1989; Griffin et al., 1988; Hoffman et al., 1987; Pollock et al., 1984; Solberg, 1985; Taylor and Emery, 1982; Walker et al., 1987). In general, these studies take one or both of the following two approaches. Some investigators look for an association between DPT immunization status and SIDS in children. This can be done either through cohort studies of children vaccinated and not vaccinated or through case-control studies comparing children who died of SIDS with other children to see whether the SIDS cases were more likely to have received DPT in an interval before the death. These studies are summarized in Table 5-1. The second approach involves comparison of the timing of SIDS deaths relative to DPT vaccination, to see whether SIDS deaths are clustered in the few days following vaccination. Because this approach is limited to exposed cases only, that is, those children who receive DPT vaccination and die of SIDS, the power to detect an elevated risk is lower than in the first approach. On the other hand, potential biases arising from inclusion of unvaccinated children are avoided. The studies of the timing of SIDS cases relative to DPT administration are summarized in Table 5-2.

In a study reported as a letter to the editor (Taylor and Emery, 1982), 26 children who died from SIDS were identified over a 3-year period in Sheffield, England, and 2 age-matched controls were selected for each child who died from SIDS. Five of 26 (19 percent) cases and 19 of 52 (37 percent) controls had had a previous DPT immunization. No significant association of SIDS with DPT immunization was demonstrated, but the study had a small sample. The committee's power calculations suggest, for example, that with a study of this size, a fivefold increase in the risk of SIDS would have less than an 80 percent chance of being detected, and a tripling of the risk would have only slightly more than an even chance of being detected.

Pollock and colleagues (1984) studied a cohort of children attending regional immunization clinics in Hertfordshire, England, of whom 6,004

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were immunized with DPT vaccine and 4,024 were immunized with DT vaccine. All children were scheduled to receive the primary series of three immunizations starting at age 3 months. Follow-up was conducted by a study nurse within 2 days following each immunization and again 6 to 8 weeks afterward. Combining all doses, 13,917 DPT and 10,601 DT immunizations were administered. Although the ages at the time of immunization were reportedly similar among those receiving DPT and DT vaccines, age was not formally controlled for in the analysis. In addition, other factors that, if distributed differently between the two groups of children, could have influenced the relative risk of SIDS were not addressed in that report.

There were seven cases of SIDS within 6 weeks of immunization, three (2.2 per 10,000 doses) in the DPT group, at 4, 20, and 37 days, and four (3.8 per 10,000 doses) in the DT group, at 2, 5, 37, and 40 days. Treating the children who received DT as a control group, the relative risk of SIDS is 0.6, with a 95 percent confidence interval of 0.1 to 2.3.[1] Although this finding indicates an inverse association between DPT vaccine and SIDS, the relative risk is not significantly below 1.0. Because the sample size was very small, however, the study had low power to detect direct (or inverse) associations. For example, the relative risk would have had to be 4.0 to achieve 50 percent power and 7.4 to achieve 80 percent power.

In an investigation of 24 postneonatal deaths in Oslo, Norway, occurring from 1979 through 1982, it was noted that among 12 children who died within 4 weeks of DPT immunization, there was an apparent excess of deaths in the first week. Therefore, a larger study was conducted of 222 deaths from SIDS in five parishes in Norway (including Oslo and the original 12 cases) from 1975 through 1982 (Solberg, 1985). Within 4 weeks of DPT administration, 53 deaths from SIDS occurred. They were distributed as expected on the basis of the age distribution of the occurrence of SIDS in three U.S. populations. Fifteen cases occurred in the first 7 days following DPT vaccination, and 15.2 cases were expected. Thus, no relation was found between DPT vaccine and SIDS. The power of this study was relatively high. A relative risk of 2.0 had an 80 percent chance of being detected, and the study had 50 percent power against a relative risk of 1.6. When the original cluster of cases was examined by this same methodology, an increased rate of SIDS in the first week post-DPT immunization relative to that observed in the later period was evident, a result that tends to validate the author's methods of investigation. Solberg also noted that other areas of Norway in which the same lot of vaccine was used as was used in

[1] The relative risk and confidence interval were calculated by the committee from data provided by Pollock et al. (1984).

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TABLE 5-1 Summary of Controlled Studies Evaluating Estimated Relative Risk (RR) of SIDS Associated with DPT Immunization

Reference	Design	Years	Population, No. Births	Description
Taylor and Emery, 1982	Matched case-control	1979-1982	~30,000	Sheffield, England
Pollock et al., 1984	Cohort	1978-1980	10,028	6,004 and 4,024 children who received 13,917 DPT and 10,601 DT immunizations, respectively, in Hertfordshire, England
Hoffman et al., 1987	Matched case-control	1978-1979	347,800	Six sites that included ~10% of U.S. births
Walker et al., 1987	Matched case-cohort	1972-1983	26,500	Members of Group Health Cooperative, Puget Sound
Bouvier-Colle et al., 1989	Matched case-control	1986	Unknown	322 of 522 (62%) registered deaths in France over 3 months in children ages 85 to 365 days in which physician responded to a questionnaire

[a]RR (95% CI), Estimated relative risk (95 percent confidence interval). RRs and CIs for Pollock et al. (1984), Walker et al. (1987), and Bouvier-Colle et al. (1989) were calculated by the committee using data from these reports (see Appendix D).

[b]"Power" denotes the probability that a statistical test based on a sample of the same size as

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No. SIDS	No. Controls	Percent Immunized with DPT		RR (95% CI)[a]	Power[b]	
		SIDS	Controls		50%	80%
26	52 age-matched	19	37	0.4 (0.1-1.3)	3.2	5.4
7 within 6 weeks of DPT or DT immunization	Compare number of SIDS per number of DPT (3) versus DT (4) immunizations			0.6 (0.1-2.3)	4.0	7.4
1. 716 autopsy-confirmed	1. 757 age-matched	40	55	0.5 (0.4-0.7)	1.4	1.6
2. Same	2. 757 age-, race-, low-birth-weight matched	40	53	0.6 (0.5-0.7)	1.2	1.2
29 healthy at birth with birth weight ≥2,500 g	262 healthy at birth with birth weight of ≥2,500 g, random sample age- and period-matched (to generate expected number of cases)	79	95	0.2 (0.05-0.4)	2.9	4.7
1. 152 of 230 (66%) registered SIDS cases	1. 173 of 292 (59%) registered other deaths	40	29	1.6 (1.0-2.5)	1.6	1.9
2. 135 of 152 item 1 above	2. 401 living age- and sex-matched	40	47	0.7 (0.5-1.1)	1.6	1.9

the one in the study cited would find a statistically significant increased risk (with alpha = 0.05), given that the true RR in the population being studied is the number stated in the table. The numbers tabulated are the RRs such that the powers are 50 and 80 percent, respectively.

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TABLE 5-2 Summary of Controlled Studies Among Immunized Children Only, Evaluating Estimated Relative Risk (RR) of SIDS in the Time Interval Immediately Following DPT Immunization

Reference	Design	Years	Population, No. Births	Description	No. SIDS
Solberg, 1985	Ecologic	1975-1982	161,379	Five parishes that included ~40% of Norway's births	53 within 28 days of immunization
Hoffman et al., 1987	Matched case-control	1978-1979	347,800	Six sites that included ~10% of U.S. births	1. 285 autopsy-confirmed 2. Same
Walker et al., 1987	Matched case-cohort	1972-1983	26,500	Members of Group Health Cooperative, Puget Sound	23 healthy at birth with birth weight ≥2,500 g
Griffin et al., 1988	Cohort	1974-1984	129,834	Children born in Tennessee and immunized at four county public health clinics	109

[a]RR (95% CI), Estimated relative risk (95 percent confidence interval).

[b]"Power" denotes the probability that a statistical test based on a sample of the same size as the one in the study cited would find a statistically significant increased risk (with alpha =

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No. Controls	Interval	No. Immunized in Interval		RR (95% CI)[a]	Power[b]	
		Observed	Expected		50%	80%
Age distribution of observed SIDS cases compared with expected distribution based on three U.S. populations	≤7 days	15	15.2	1.0 (0.6-1.6)	1.6	2.0
1. 416 age-matched	<24 hours	5	13.2	0.3 (0.1-0.9)	3.0	4.8
2. 403 age-, race-, low-birth-weight matched		5	8.0	0.8 (0.3-2.4)	3.0	4.8
262 healthy at birth with birth weight of ≥2,500 g, random sample age- and period-matched (to generate expected number of cases)	≤3 days	4	1.4	7.3 (1.7-31.0)	4.2	7.9
Rates of SIDS 0-3 days compared with those ≥31 days post-DPT, controlling for age	≤3 days	2	7	0.2 (0.04-0.8)	4.4	8.4

0.05), given that the true RR in the population being studied is the number stated in the table. The numbers tabulated are the RRs such that the powers are 50 and 80 percent, respectively.

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Oslo did not have such a clustering of cases of SIDS following vaccination. He concluded that the original cluster was a chance occurrence unrelated to the lot of vaccine used.

The largest study to date is the NICHD SIDS Cooperative Epidemiologic Study (Hoffman et al., 1987). All cases of SIDS were identified in six geographically distinct areas of the United States in which there were altogether nearly 350,000 live births during a 15-month period in 1978 and 1979. Using strict pathologic criteria and including as cases only singleton births with known immunization status, the investigators identified 716 cases of SIDS, of whom 40 percent had received at least one DPT immunization. In two sets of control children, the first set matched only for age and the second for age, race, and birth weight, 55 percent (416 of 757) and 53 percent (403 of 757), respectively, had been immunized. The odds ratio for the risk of SIDS is 0.5 with a 95 percent confidence interval from 0.4 to 0.7 with the first control group and 0.6 with a confidence interval from 0.5 to 0.7 with the second control group. This study also has high power; an increased odds ratio of only 1.6 with the first control group and 1.25 with the second control group would have an 80 percent chance of being detected with a sample of this size; the comparable figures for 50 percent power are 1.4 and 1.2.[2] After adjustment for 11 other potential risk factors for SIDS, including maternal age, education, cigarette smoking, and infant low birth weight, the odds ratios were 0.7 for vaccinees versus each of the control groups. This slight decrease in magnitude of the inverse association indicates that some of these factors are also associated with a failure to have children immunized at an appropriate age.

A further analysis of the timing of SIDS relative to DPT vaccination in the Hoffman data was confined to children who had received at least one DPT immunization and their matched controls: 5 of 277 (1.8 percent) cases of SIDS had been immunized within 24 hours of death compared with 21 of 416 (5 percent) age-matched controls (odds ratio, 0.3) and 9 of 403 (2.2 percent) controls matched for age, race, and birth weight (odds ratio, 0.8). Therefore, there was no evidence for an increased risk of SIDS in the early postimmunization period. The power of this analysis, however, is considerably weaker than the one described above because fewer cases are involved. With either control group, the analysis had only 50 percent power against an odds ratio of 3.0 and 80 percent power against an odds ratio of 4.8.

A group of 43 infants identified as possible cases of SIDS but excluded

[2] The stated confidence intervals were calculated by the committee, ignoring the matching between cases and controls, because the requisite data were not available to make the proper matched calculation. Assuming a positive correlation between cases and controls, these intervals thus overstate the degree of uncertainty in the estimates by an unknown degree and understate the power to detect an elevated odds ratio.

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from the previous analyses because they did not meet the strict case definition had a history of immunization indistinguishable from that of the definite cases (37 versus 40 percent, respectively). Thus, no SIDS-like group of deaths was found to be associated with DPT immunization.

Walker and colleagues (1987) linked vital records and the membership files of the Group Health Cooperative of Puget Sound from 1972 to 1983 to identify all deaths at ages from 30 to 365 days among children who had been born at Group Health Cooperative hospitals. Twenty-nine deaths from SIDS occurred among approximately 26,500 children with normal birth weights and no serious medical conditions at birth. Immunization records of cases were compared with those of a sample of 262 other children in the total birth cohort. Cases of SIDS were less likely to have been immunized with DPT (the estimated relative risk in the matched analysis was 0.2 with a 95 percent confidence interval of 0.05 to 0.4) than were controls. Despite this finding of a statistically significant inverse association, the study had relatively low power to detect direct (or inverse) associations. A study of this size has 50 percent power against a relative risk of 2.9 and 80 percent power against a relative risk of 4.7.

Among those who received at least one immunization in this study, the rate of SIDS in the 0 to 3 days following immunization was 7.3 times higher than that in the period beginning 30 days after immunization. Although this ratio is based on only four cases of SIDS in the 0 to 3 days following immunization, the relative risk is significantly increased (the 95 percent confidence interval runs from 1.7 to 31.0). No non-SIDS death occurred in close temporal proximity to an immunization (Walker, 1990).

Griffin and colleagues (1988) linked computerized immunization files from four Tennessee counties with vital records and identified a cohort of 129,834 children born from 1974 through 1984 who received at least one DPT immunization in their first year of life. In this cohort, 204 deaths were identified between the first DPT immunization and 365 days of life; 109 of these were classified as SIDS. The analysis was based on comparing the incidence of SIDS per person-year of exposure by time postimmunization, and the calculations were carried out within six age groups within which the risk of SIDS was relatively homogeneous. Controlling for age, the rates of SIDS in the 0- to 3- and 4- to 7-day intervals postimmunization were about 80 percent lower than those in the reference period more than 30 days postimmunization (odds ratio, 0.2). Similar results were found after controlling for sex, race, year, birth weight, and enrollment in Medicaid (as an indicator of socioeconomic status). Since vital records were used to identify all deaths in the study cohort, it is unlikely that deaths that occurred in the early postimmunization period were missed selectively. The observed decreased risk is unexplained, although the authors speculated that children may be immunized selectively at times when they appear healthier, and may

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therefore be at decreased risk for SIDS. The authors also examined the 95 deaths from causes other than SIDS. No increase in these deaths in the early postimmunization period was observed.

A study of all deaths from SIDS in France from January through March 1986 (Bouvier-Colle et al., 1989) followed the report of five deaths from SIDS within 1 week of DPT immunization over a 2-week period in March 1986. The investigators compared immunization histories in 152 of 230 (66 percent) children who died of SIDS both to 173 of 292 (59 percent) children who died of other causes and to 3 age-and sex-matched living controls per case. The estimated relative risks (and 95 percent confidence intervals) for these comparisons were 1.6 (1.0 to 2.5) for decedent controls and 0.7 (0.5 to 1.1) for living controls. As reported, these studies had reasonable power for detecting positive (or inverse) associations (approximately 80 percent for an estimated relative risk of 1.9 and 50 percent for an estimated relative risk of 1.6 for the decedent control group and 1.8 and 1.5, respectively, for the living controls), so the absence of a statistically significant increased risk is important. These results are of limited value, however, in view of the loss of large proportions of two study groups because of missing information and the consequent potential for bias in comparing the remaining subjects.

Because of the relatively small size of the samples used in the studies of the timing of SIDS relative to DPT immunization, the committee carried out a meta-analysis of these data, using the methods described in Chapter 3 and Appendix D. Data on the association between SIDS and vaccination status were not combined because of the bias in these studies owing to confounding between vaccination and SIDS because of the socioeconomic and medical factors discussed by Fine and Chen (1991).

Data from three case series studies (Baraff et al., 1983; Bernier et al., 1982; Torch, 1982) were also included in this analysis, once a correction was made for the age pattern of SIDS (see Appendix D). Estimates of the odds ratio of SIDS cases in approximately the first 3 days postvaccination relative to approximately days 8 to 30 postvaccination were estimated from all studies and combined in a meta-analysis by using the model developed by DerSimonian and Laird (1986).

The results depend on a number of statistical assumptions, but the qualitative results are similar regardless of which assumptions are made. The results of this analysis, shown in Figure 5-1, reflect whether (1) data from all seven eligible studies with information on the timing of SIDS relative to DPT vaccination or only data from the four studies with appropriate controls are used; (2) the studies were considered a random sample from all possible studies of the same risk (in statistical terms, a random-effects model) or a closed set of homogeneous estimates of the same relative risk (a fixed-effects model); or (3) two, one, or neither of the results for the two control groups from the study of Hoffman et al. (1987) are included in the meta-

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analysis. Alternative assumptions were also made about including cases occurring more than 30 days postvaccination and to test the sensitivity of the results to the adjustment for the age pattern of SIDS, but these had negligible effects on the results.

As Figure 5-1 shows, the pooled relative risk estimate is higher if the poorly controlled studies are included and varies somewhat with the treatment of the two control groups from the study of Hoffman et al. (1987). As expected, the confidence intervals are wider under the random-effects model, which seems more reasonable on statistical grounds. None of the calculations, however, leads to a significantly increased risk of SIDS in the early postimmunization period. Indeed, if only the well-controlled studies are

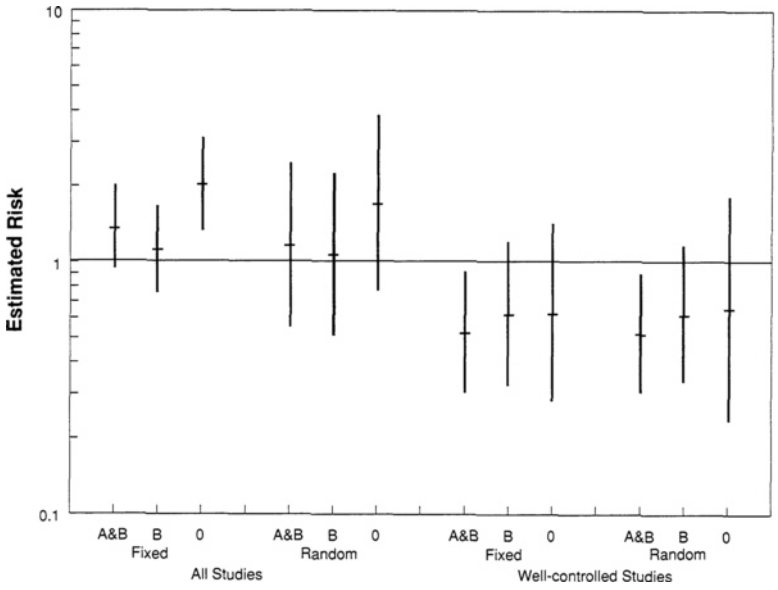

FIGURE 5-1 Meta-analysis results comparing the estimated risk of SIDS in the early period postvaccination with that in the late part of the first month, under various assumptions: (1) whether all studies or only well-controlled studies are included in the meta-analysis, (2) whether a fixed- or a random-effects model is assumed, and (3) whether the meta-analysis includes results from the study of Hoffman et al. (1987) based on age-matched controls (A) and age-, race-, and birth-weight-matched controls (B), on B alone, or on neither (0). For each set of assumptions, the mean and 95 percent confidence interval from the meta-analysis are shown on a logarithmic scale.

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included, the protective effect seen in some of the individual studies begins to emerge as significant. Because of questions surrounding the use of meta-analysis in epidemiologic research (Fleiss and Gross, 1991; Spitzer, 1991), these results cannot be viewed as definitive. They do indicate, however, that combining the information from the existing studies of the timing of SIDS and DPT vaccination is not likely to lead to a statistically significant finding of an increased risk.

The meta-analysis results give a rough sense of the power of the pooled data to detect elevated relative risk estimates. The ratio of the upper confidence interval to the average estimated relative risk in the meta-analysis results (Figure 5-1) is about 2. This suggests that a doubling of the risk of SIDS in the period immediately following DPT vaccination would have only about a 50 percent chance of being detected, even with the pooled data. On the basis of the studies at hand, about 10 percent of SIDS deaths that occur within 1 month after DPT vaccination occur within 3 days of vaccination. If half of these, 5 percent, were caused by DPT, there would be only an even chance of detecting it in the pooled analysis. In his paper prepared for the committee, Walker (1990) estimated that about 20 percent of the 5,000 annual U.S. SIDS deaths occur within 2 weeks of immunization, so perhaps 40 percent, or 2,000, occur within 1 month. A 5 percent increase in this number, 100 cases per year, could go undetected in the data available.

SUMMARY

All controlled studies that have compared immunized versus nonimmunized children (Table 5-1) have found either no association (Bouvier-Colle et al., 1989; Pollock et al., 1984; Taylor and Emery, 1982) or a decreased risk (Hoffman et al., 1987; Walker et al., 1987) of SIDS among immunized children. As a group, these studies have good power, most having more than an 80 percent chance of being able to detect a doubling of the risk. Although a protective effect of vaccine cannot be ruled out, it is more plausible that children who are not immunized by the recommended age are at an increased risk for SIDS because of other factors, such as socioeconomic status, that are associated both with delaying immunization and with SIDS (Fine and Chen, 1991). One small controlled study of infants with unexplained apnea, who may be at increased risk for SIDS, demonstrated improvement in ventilatory patterns following DPT immunization (Keens et al., 1985). There are no data that bear on a possible biologic basis for a relation between DPT immunization and SIDS, but neither is there biologic evidence to support a protective effect.

A number of studies offer some information on the timing of SIDS relative to immunization. The controlled studies shown in Table 5-2 (Griffin et

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al., 1988; Hoffman et al., 1987; Solberg, 1985; Walker et al., 1987) differ substantially in their estimates of the increased risk in the early postimmunization period. These differences may arise because children who are at risk for SIDS because of factors not included in the analyses are immunized on a different schedule than their peers, thus, depending on the comparison population, placing them either farther or closer to an immunization at the time of death. However, the results of three of these four studies indicate either an inverse association or no association between SIDS and DPT immunization. The exception is the study of Walker and colleagues (1987), which showed a significantly elevated risk of SIDS in the 0 to 3 days following immunization. It is possible that adverse events following administration of DPT vaccine are lot-specific. However, the two studies that examined vaccine lot as an etiologic factor in deaths from SIDS (Bernier et al., 1982; Solberg, 1985) found no relation between vaccine lot and deaths from SIDS.

Also worth considering is whether some deaths following immunization are not classified as SIDS and therefore would be missed in studies examining only deaths from SIDS. In three of the studies, deaths from causes other than SIDS were examined (Griffin et al., 1988; Hoffman et al., 1987; Walker, 1990). None of these showed an increased rate of deaths from other causes in the early post-DPT immunization time period.

A meta-analysis of the data on timing of SIDS deaths relative to DPT immunization shows that, although the specific numerical estimates of the relative risk of SIDS depend to some extent on the analytic assumptions that were made (see preceding section and Appendix D), there is no indication of a statistically significant increased risk of SIDS in the early postimmunization period. Even with the pooled data, however, a doubling of the risk of SIDS in the period immediately following vaccination would have only about a 50 percent chance of being found to be statistically significant.

CONCLUSION

The evidence does not indicate a causal relation between DPT vaccine and SIDS. Studies showing a temporal relation between these events are consistent with the expected occurrence of SIDS over the age range in which DPT immunization typically occurs.

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6

Evidence Concerning Pertussis Vaccines and Other Illnesses and Conditions

ANAPHYLAXIS

Clinical Description and Pathologic Aspects

The term *anaphylaxis* generally refers to a sudden, potentially life-threatening, systemic condition mediated by highly reactive molecules released from mast cells and basophils. Mediators include histamine, platelet-activating factor, and products of arachidonic acid metabolism (Fisher, 1987). Release of mediators depends typically upon the interaction of antigen with specific antibodies of the immunoglobulin E (IgE) class that are bound to the mast cells and basophils. Antibodies of other immunoglobulin classes are thought to mediate anaphylaxis on occasion. By definition, the antibodies are formed by prior exposure to the same or a closely related antigen. Anaphylaxis results from widespread release of mediators that enter the circulation, and thus, anaphylaxis is an expression of allergy that is systemic. At a cellular level, the reaction begins within seconds of exposure to the inciting antigen. However, depending upon the degree of sensitization (IgE antibody formation), and presumably upon the rate with which the antigen enters the circulation, localized or systemic symptoms may not be expressed for minutes or a few hours (Dolovich et al., 1973; Pearlman and Bierman, 1989). Symptoms are due to leaking of fluid from blood vessels, constriction of smooth muscle in certain viscera, and relaxation of vascular

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smooth muscle. Classic symptoms include pallor and then diffuse erythema, urticaria and itching, subcutaneous edema, edema and spasm of the larynx, wheezing, tachycardia, hypotension, and hypovolemic shock (Kniker, 1988; Pearlman and Bierman, 1989). If death occurs, it is most commonly from airway obstruction caused by laryngeal edema or bronchospasm, or cardiovascular collapse from transudation of fluids from the intravascular space (Pearlman and Bierman, 1989). The tissues at autopsy show primarily widespread edema.

The clinical presentation of anaphylaxis can be produced by intravascular antigen-antibody reactions that activate the complement system. In this case, the antibodies may be of the IgG or IgM class. Peptides that are split from activated complement components act on mast cells and basophils to induce the release of the same mediators (Kniker, 1988). This reaction is recognized most clearly after intravenous administration of antigen; it has been hypothesized to occur rarely after intramuscular or subcutaneous injection through rapid entry (within 1 to 5 minutes) of large amounts of the antigen into the venous circulation. This reaction in an infant presumably could be mediated by IgG antibody received transplacentally from the mother; such antibody would be expected to persist for the first 6 months of life and possibly longer (Benacerraf and Kabat, 1950; Cohen and Scadron, 1946). Anaphylaxis also can occur without an obvious cause (Wiggins et al., 1989).

Shock caused by bacteremia with circulating bacterial endotoxin also appears to involve activation of the complement system (Fearon et al., 1975; Lachmann and Peters, 1982). Endotoxin shock has a clinical presentation different from that of anaphylaxis, however; it develops more slowly and is almost always associated with disseminated intravascular coagulation, with consumption of clotting factors and hemorrhage (Colman, 1989; Suffredini et al., 1989a,b). Endotoxin elicits the release of mediators of inflammation in addition to those from mast cells and basophils, including interleukin-1 and tumor necrosis factor (Michie et al., 1988; Morrison and Ryan, 1987). The Jarisch-Herxheimer reaction, described classically in patients with spirochetal disease within hours after beginning drug therapy, may be a form of endotoxemia or, at least, complement activation caused by circulating bacterial products (Bryceson, 1976).

The Arthus reaction is another immunologic response that can be associated with tissue damage. This reaction is mediated differently from anaphylaxis. The formation of antigen-antibody complexes with deposition in the walls of blood vessels is basic to this reaction. This is not an acute, immediately overwhelming condition. It generally develops over 12 to 24 hours if antibody levels are already high, or it can develop over several days (e.g., in serum sickness) as antibody levels increase and antigen persists. In this reaction, immune complexes in the walls of blood vessels

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initiate an inflammatory reaction involving complement and white blood cells, particularly neutrophils. Tissue sections show acute inflammation, and profound tissue destruction can occur. The most common target organs in an Arthus-type reaction include kidney, skin, joints, lung, and brain (Henson, 1982).

History of Suspected Association with Pertussis Vaccines

Identical twins died 16 and 20 hours after their second DPT shot given at age 10 months (Werne and Garrow, 1946). Autopsy showed evidence of the vascular smooth muscle contraction and increased capillary permeability expected with anaphylaxis. Adverse reactions were not reported in other infants who received the same batch of vaccine. The injected material was sterile. The delayed response was noted to be atypical of the anaphylactic reactions reported to that time. The authors found no cases of anaphylactic reactions to DPT reported in the world's literature.

Evidence from Studies in Humans

Case Reports and Controlled Epidemiologic Studies

Anaphylaxis with shock is uncommon in infancy, but the exact frequency is unknown. Since the original reports in 1946, "anaphylaxis" (sometimes used less strictly to apply to any type I or immediate hypersensitivity reaction) has been reported in additional infants after routine immunization with DPT. Osvath and colleagues (1979) reported 31 total complications that developed within 36 hours of injection of DPT vaccine into an estimated 300,000 children in Hungary. Five of the 31 reactions were urticaria, which is typically an IgE-mediated response; 7 other infants had severe shock with loss of consciousness (not necessarily allergic in origin) or laryngeal edema, a rate of 2.3 such reactions per 100,000 injections. Eight of these 12 reactions occurred after the first injection, when specific IgE antibodies would not be expected to be present. (These are not passed from mother to infant across the placenta.) IgG antibodies to antigens in DPT might be present, however. Serum total IgE levels were considered "moderately elevated" in 29 of the total 31 infants; the 2 babies with normal IgE levels were among those with allergic symptoms. Thus, serum IgE levels were not helpful in considering the possibility of allergy in these patients, and anaphylaxis was not proven.

Pollock and Morris (1983) analyzed data from the North West Thames region of England, where an intensified effort over the previous 7 years had

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been undertaken to identify all severe adverse events following immunization. The authors identified events in two different ways: one derived from physicians' voluntary reports and the other from systematic review of hospital discharge diagnoses. Approximately 134,700 children completed courses of three doses of DPT vaccine (404,000 doses), and 135,500 children completed courses of DT vaccines. Eight children exhibited symptoms of anaphylaxis or collapse within 24 hours of receipt of DPT vaccine (some within minutes), for a rate of 6 cases per 100,000 children vaccinated (2 cases per 100,000 injections); an additional eight children exhibited similar symptoms after receiving primary or booster DT vaccine for an identical rate. The timing suggests that at least some of these cases may have been anaphylaxis. All children recovered without sequelae.

One hundred eighty-seven cases of anaphylaxis (ICD 9 code 995.0/999.4) occurring within 28 days of DPT immunization were reported through the CDC's MSAEFI system from 1978 to 1990, a period in which approximately 80.1 million doses of DPT vaccine were administered through public mechanisms in the United States (J. Mullen, Centers for Disease Control, personal communication, 1990). Of these 187 cases, 130 (70 percent) also received at least one other vaccine at the time of DPT immunization. No follow-up of the cases was made, and a physician's diagnosis was not required.

Two recent case reports (one an adult) describe a close temporal relationship between injection of DPT vaccine and an anaphylactic reaction (Leung, 1985; Ovens, 1986). Both patients survived without apparent long-term adverse effects.

Occurrence of a hypotonic, hyporesponsive state, or actual "collapse," has been reported after DPT administration (Cody et al., 1981; Galazka and Andrzejczak-Kardymowicz, 1972; Health Council of The Netherlands, 1987, 1988; Hopper, 1961). Its onset between 1 and 12 hours after immunization is compatible with an anaphylactic reaction, but other explanations are possible. Data regarding pathophysiology have not been given. (See the description of hypotonic, hyporesponsive episodes later in this chapter.)

Three of 13 children given three injections of DPT produced IgE antibody (in low levels) to the one pertussis antigen tested, pertussis toxin (PT) (Hedenskog et al., 1989), demonstrating that at least a weak IgE antibody response can occur after immunization.

Bordetella pertussis vaccine has been shown to increase the sensitivity of rodents to the effects of injected histamine (Arora et al., 1970; Munoz, 1985; Munoz and Bergman, 1968). Conceivably related is the finding that intradermal injection of histamine produced significantly larger wheals in infants after (compared to before) immunization with DPT vaccine (Sen et al., 1974). Results were maximal after 24 hours and increased markedly for 5 to 7 days. Reactions were equivalent after the first, second, or third

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DPT shots. Injection of DT into children aged 2 to 5 years (a control group) did not increase the dermal response to histamine, but this population was not age-matched to that given DPT. It is not clear that these findings have any relationship to the occurrence of anaphylaxis after injection of DPT.

A 45-year-old male volunteer who was hyperimmunized with pertussis vaccine (eight shots of 2.4 NIH [National Institutes of Health] protective units each) to produce anti-pertussis immune globulin died of progressive renal failure secondary to a chronic diffuse vasculitis (Bishop et al., 1966). No etiology was proven for the vasculitis, but the case raises the possibility that an Arthus-type reaction was initiated by an antigen in the vaccine. The extraordinary hyperimmunization makes it impossible to extrapolate to possible responses to standard immunization practices.

Evidence from Studies in Animals

Pertussis vaccine is said to act as an adjuvant in the formation of skinsensitizing, IgE-like antibody in mice and rats (Clausen et al., 1970; Munoz and Bergman, 1977). At least two substances in the DPT vaccine, PT protein and endotoxin, are believed to have the potential for such an adjuvant effect (Munoz and Bergman, 1977; Tada et al., 1972).

Injection of *B. pertussis* vaccine has been shown to facilitate the induction of anaphylactic shock in the rat and mouse but not in the hamster, guinea pig, rabbit, or dog (Arora et al., 1970; Chang and Gottshall, 1974; Csaba and Muszbek, 1972; Munoz et al., 1987).

Injection of pertussis vaccine (0.1 ml/mouse, roughly 200 times the human dose) increased the susceptibility of mice to the lethal effects of various bacterial endotoxins injected subsequently (Kind, 1958). The increased endotoxin sensitivity was not present 1 or 3 days after administration of pertussis vaccine but was pronounced after 5 to 20 days.

Steinman and colleagues (1982) have developed a mouse model in which they can regularly induce a lethal shock-like syndrome by injection of 3×10^{10} heat-killed *B. pertussis* into mice sensitized by repeated injections of 1 mg of bovine serum albumin. Only mouse strains with certain histocompatibility (H-2) genotypes are susceptible, which is compatible with an immunologic basis for the reaction. PT is required for induction of this toxicity (Steinman et al., 1985), and immunization with PT antigens protects the mice against the reaction (Oksenberg et al., 1989). Pretreatment of the mice with histamine H1 receptor antagonists also protected the mice; this result is compatible with an allergic-immunologic basis for the reaction, but it does not prove such, since other actions of the antagonists are possible (Peroutka et al., 1987). Relatively large doses of pertussis vaccine and sensitizing antigen are used in this model compared with injections given to

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humans; a particular immunizing schedule and certain mouse strains are required. Thus, the relevance of this reaction to that in infants is speculative. Munoz and colleagues (1987) and Wiedmeier and colleagues (1987) have described data suggesting that this reaction represents anaphylaxis and not encephalopathy, as some had hypothesized. The development of the reaction was unrelated to the capacity of PT to act as a toxin through its characteristic activity of ribosylation of key cellular proteins (Wiedmeier et al., 1987).

Endotoxin

Commercial DPT vaccines across the world have been reported to contain bacterial endotoxin, usually in concentrations of about 1 to 10 μg/ml (Geier et al., 1978; Ibsen et al., 1988). There was a direct correlation between endotoxin content and the percentage of DPT vaccine recipients who developed fever (Baraff et al., 1989), and it has been questioned whether the endotoxin in DPT vaccine might be responsible, at least in part, for immunologic reactions or encephalopathy. Animal studies have been cited in support of this hypothesis, for example, those showing that endotoxin or DPT vaccine can induce an increase in the permeability of cerebral blood vessels, which might predispose an individual to brain damage (Amiel, 1976; Bergman et al., 1978; Eckman et al., 1958). However, the use of animals to explore this hypothesis is complicated by the fact that different species respond differently to different endotoxins. Moreover, endotoxins from different bacteria cannot be compared on the basis of weight since weight does not accurately reflect biologic activity (Chaby et al., 1979). In short, data do not exist at present to indicate that the endotoxin present in DPT vaccines plays a role in the anaphylaxis associated with injection of DPT. Nor do data exist to support a role for endotoxin in the other immunologic reactions or in the encephalopathies that have been suspected sequelae of DPT immunization.

Summary

The body of evidence concerning the possible relation between vaccination with DPT or its pertussis component and anaphylaxis includes a number of case reports, case series, studies in animals, and one controlled epidemiologic study. Anaphylaxis is rare in infants in the absence of an obvious exciting cause. Rates of anaphylaxis estimated from two reports (Osvath et al., 1979; Pollock and Morris, 1983) have been approximately 2 per 100,000 injections. The clinical presentation of cases with rapid onset after injection of vaccine and (in two cases) autopsy findings suggest that anaphylaxis can be caused by DPT injection. Laboratory studies to link an

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immunologic reaction with the clinical event in such cases have not been reported, however. Specifically, no exciting antigen has been demonstrated, and whether or not specific antibody of the IgE (or another) class is required for such events to occur after DPT injection has not been shown. It has been postulated that endotoxin in the DPT vaccine might be involved in tissue damage distant from the site of injection or that an Arthus- or Jarisch-Herxheimer-type reaction might be initiated by constituents in the DPT vaccine; however, the clinical presentations and the pathologic findings, when available, of the adverse events discussed in this report do not clearly support these hypotheses. Furthermore, the animal models described to date employ antigen loads, dosage schedules, pathologic endpoints, add-on antigens, or other experimental conditions that deviate from the human situation that is the subject of concern. Consequently, although the data from animal experiments may be useful in formulating or modifying hypotheses, they do not implicate an immunologic or endotoxin-initiated basis for possible adverse events following DPT immunization.

The possibility of a causal relation with anaphylaxis is supported by biologic plausibility and clinical observation. Biologic plausibility derives largely from the knowledge that injection of foreign proteins into humans (and there are many foreign proteins in DPT vaccine) can be expected to elicit in some percentage of recipients IgE-mediated responses that present as anaphylaxis. The biochemical, immunologic, or immunohistologic techniques that could provide relevant evidence have not been applied. Nevertheless, the classic presentation and timing strongly suggest that DPT injection can cause anaphylaxis.

Reports of hives or angioneurotic edema following DPT administration have been obtained only through the CDC's MSAEFI system and are not well substantiated. Furthermore, in contrast to anaphylaxis, the occurrence of hives or angioneurotic edema in infancy without a known cause is not rare, so that the concurrence of DPT immunization and these conditions is, therefore, more likely to be observed coincidentally than anaphylaxis is. No biologically meaningful connection can be said, at present, to exist between DPT injection and hives, angioneurotic edema, an Arthus or Jarisch-Herxheimer reaction, or endotoxin-mediated tissue damage.

Conclusion

The evidence indicates a causal relation between DPT vaccine and anaphylaxis, although there is no reason to implicate the pertussis component more than the diphtheria or tetanus components of DPT vaccine. In the absence of formal studies of incidence, rates of anaphylaxis are estimated to be approximately 2 cases per 100,000 injections of DPT (6 per 100,000 children given three doses of DPT).

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AUTISM

Clinical Description

Infantile autism represents one of the group of disorders now referred to as pervasive developmental disorders (Rutter, 1985; Volkmar and Cohen, 1986). The disorder, termed *autism* by Kanner in 1943, is characterized as having its onset before age 30 months, with disturbances in social relationships and language and stereotyped behaviors. Autistic children exhibit a failure to develop specific attachment relationships. For example, they do not follow their parents around the house or go to them to seek comfort, and they frequently fail to use eye contact as a social signal. Their language acquisition is not only markedly delayed but they fail to use social imitation. Most importantly, they fail to use speech for social communication. Little is known of the etiology or pathogenesis of autism. Two-thirds of autistic children remain severely disabled as adults, but a small percentage are able to work and interact with other individuals.

Descriptive Epidemiology

Prevalence rates of autism are estimated to be between 4 and 5 per 100,000 children under age 15 years (Wing et al., 1976). Rates are lower when administrative records, rather than interviews or case reviews, are used and when more restricted definitions of the syndrome are employed (DeMyer et al., 1981). Prevalence rates of autism must be viewed with caution given the heterogeneity of case definitions of pervasive developmental disorders and potential for biased case detection (Volkmar and Cohen, 1986). All studies report a higher incidence in males, with a male:female sex ratio on the order of 3:1 to 4:1 (Wing, 1981); however, girls as a group may be more severely affected (Volkmar and Cohen, 1986). An increased incidence of prenatal and perinatal complications has been noted in cases of pervasive developmental disorders (DeMyer et al., 1981). However, factors such as maternal age at birth, birth order, ordinal position, and season of birth have not been related to incidence rates (Volkmar and Cohen, 1986).

Evidence from Studies in Humans

The committee identified no case reports or other studies of autism following pertussis immunization. The sources examined include the CDC's MSAEFI system, which received no reports of autism (ICD 9 code 299.0) occurring within 28 days of DPT immunization from 1978 to 1990, a period in which approximately 80.1 million doses of DPT vaccine were administered through public mechanisms in the United States (J. Mullen, Centers

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for Disease Control, personal communication, 1990). The lack of reports of cases within 28 days of DPT immunization is not surprising, however, given that a diagnosis of autism is difficult, if not impossible, before age 3 years.

Summary

No data were identified that address the question of a relation between vaccination with DPT or its pertussis component and autism. There are no experimental data bearing on a possible biologic mechanism.

Conclusion

There is no evidence to indicate a causal relation between DPT vaccine or the pertussis component of DPT vaccine and autism.

ERYTHEMA MULTIFORME OR OTHER RASH

Clinical Description

Erythema multiforme is an acute, self-limited eruption characterized by symmetric erythematous, edematous, or bullous lesions of the skin or mucous membranes (or both) that pass through multiple morphologic stages (Hebra, 1866). A hypersensitivity reaction to a number of substances, including infectious agents, is a proposed mechanism, but the pathophysiology has not been defined.

Descriptive Epidemiology

Erythema multiforme, although rare, can occur in infancy and childhood. No population-based incidence rates were identified for the pediatric population.

Evidence from Studies in Humans

Case Reports

Erythema multiforme has been reported in association with several vaccines, including DPT (Leung, 1984; Leung and Szabo, 1987). These reports describe three cases, ranging in age from 2 months to 19 months, in which a maculopapular rash consisting of symmetrical lesions with central clearing ("iris" lesions) developed following DPT vaccination. A fourth case in a 5-year-old consisted of blisters on an erythematous base. The eruptions occurred from 2 hours to 3 days after receiving DPT vaccine and, at least in

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two cases, cleared spontaneously within several days. The outcome in the other two cases was not reported.

Ten cases of erythema multiforme (ICD 9 code 695.1) occurring within 28 days of DPT immunization were reported through the CDC's MSAEFI system from 1978 to 1990, a period in which approximately 80.1 million doses of DPT vaccine were administered through public mechanisms in the United States (J. Mullen, Centers for Disease Control, personal communication, 1990). Of these 10 cases, 5 received oral poliovirus vaccine (OPV) at the time of DPT immunization, 1 case received OPV plus *Haemophilus influenzae* type b vaccine with DPT, and 3 cases received OPV plus measles-mumps-rubella vaccine (MMR) with DPT. No follow-up of the cases was made, and a physician's diagnosis was not required. If all 10 cases represent a reaction to DPT, which is unlikely in view of the long time frame and the administration of other vaccines, the frequency of erythema multiforme after DPT immunization would be approximately 1 per 8 million doses of DPT.

Rash as an adverse reaction to DPT vaccine appears to be rare; several reports of large series do not mention rashes (Cody et al., 1981). Isolated case reports describe a variety of self-limited rashes following DPT immunization, ranging from eczematous reactions (Hopper, 1961; Illingworth, 1987) and macular rashes involving the head and trunk (Hopper, 1961; Denning et al., 1987) to localized lesions at the injection site (Laude, 1981; Orlans and Verbov, 1982). None of these reports presents evidence specifically implicating the pertussis component of the vaccine.

Pertussis vaccine has been associated with increased skin reactions to injected histamine in mice (e.g., Parfentjev and Goodline, 1948). Various heat-killed gram-negative bacteria as well as their common endotoxin, lipopolysaccharide W, injected intradermally into a patient with erythema multiforme have reproduced its classic iris lesions (Shelley, 1980). Denning and colleagues (1987) raised the possibility that vaccine-associated rash may be due to the preservative thiomersal.

Aluminum Salts

The possibility has been raised that the aluminum salts regularly present in DPT vaccines might cause vaccination-associated rashes (see Appendix E for discussion). There are no data to indicate that aluminum salts play a role in DPT-associated rashes.

Summary

The body of evidence concerning the possible relation between vaccination with DPT or its pertussis component and erythema multiforme or other rash is limited to 4 cases reported in the literature and 10 unconfirmed cases

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reported through the CDC's MSAEFI system. The unambiguous clinical presentation of erythema multiforme suggests that the vaccine exposure truly preceded the event. The relation is biologically plausible, since erythema multiforme is thought to be a dermal hypersensitivity reaction to a drug or other foreign antigen and pertussis vaccine could provide such a sensitizing antigen.

The temporal relation between DPT injection and the onset of rash suggests a possible causal relation. However, only four cases of such a relation have been documented, and none specifically implicates the pertussis component of the vaccine.

Conclusion

There is insufficient evidence to indicate a causal relation between DPT vaccine or the pertussis component of DPT vaccine and erythema multiforme or other rash.

GUILLAIN-BARRÉ SYNDROME (POLYNEUROPATHY)

Clinical Description

The condition referred to as the Guillain-Barrè syndrome (GBS) was described by Chomel (1828), Graves (1843), Landry (1859), and Guillain, Barrè, and Strohl (1916) and is variously known as acute idiopathic, acute inflammatory, and postinfectious polyradiculopathy or polyneuropathy. The term *Guillain-Barrè syndrome* avoids the historical confusion and etiologic uncertainty of this disorder (Lancet, 1988). The severity and duration of the illness depends upon the degree to which spinal roots and peripheral nerves are affected by focal inflammation.

Infectious agents and other trigger factors have been thought to precipitate the illness. An epidemic of acute polyneuritis formed the basis for Chomel's original description. A more recent example is the association seen between influenza vaccination and GBS in 1976. Human immunodeficiency virus infection and Lyme disease are being increasingly identified as causes of acute painful polyradiculitis. Other infectious agents have been associated with the onset of GBS, including cytomegalovirus, Epstein-Barr virus, mycoplasma, and *Campylobacter jejuni.* Tetanus vaccine has also been related to GBS (e.g., Newton and Janati, 1987; Pollard and Selby, 1978).

Diagnosis of GBS is sometimes difficult. The classic features of GBS are progression over days to a few weeks, relative symmetry, mild sensory signs or symptoms, cranial nerve involvement, onset of recovery 2 to 4 weeks after the halt of progression of symptoms, autonomic dysfunction,

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initial absence of fever, elevated CSF protein after 1 week of symptoms, and abnormal results of electrodiagnostic studies with slowed conduction of F waves. The presence of ridiculer deficits, sensory disturbance, and areflexia and the absence of fever are all helpful in the diagnosis. Poliomyelitis, diphtheria, botulism, hysterical or tick paralysis, and acute toxic neuropathy (especially from organophosphorus compounds or hexacarbon abuse, as in glue sniffing) must be considered in the differential diagnosis.

Between 80 and 90 percent of patients with GBS have distinctive features on electrophysiologic studies that are characteristic of an acquired demyelinating neuropathy seen only with GBS, diphtheria, or exposure to organophosphorus compounds (McLeod, 1981; Miller, 1985).

Descriptive Epidemiology

GBS occurs at a rate of 1.7 per 100,000 persons in the United States. It is the most common cause of acute weakness in patients under age 40 years and is one of the most common neurologic causes of admission to intensive care units (Miller, 1985). The disorder is rare in children under age 2 years, although cases in infants and one case of neonatal GBS have been reported (Al-Qudah et al., 1988; Carroll et al., 1977; Eden, 1961; Evans, 1986; Gilmartin and Chien, 1977). No population-based incidence or prevalence rates of mono- or polyneuropathy were identified for the pediatric population.

Evidence from Studies in Humans

Case Reports

Eleven cases of GBS (ICD 9 code 357.0) and no cases of polyneuropathy (ICD 9 code 356.9) occurring within 28 days of DPT immunization were reported through the CDC's MSAEFI system from 1978 to 1990, a period in which approximately 80.1 million doses of DPT vaccine were administered through public mechanisms in the United States (J. Mullen, Centers for Disease Control, personal communication, 1990). All 11 cases received at least one other vaccine at the time of DPT immunization: 6 cases received OPV, 1 case received OPV plus mumps monovalent vaccine, 1 case received OPV plus hepatitis B conjugate vaccine, and 3 cases received OPV plus MMR. No follow-up of the cases was made, and a physician's diagnosis was not required.

Summary

Information concerning the possible relation between vaccination with DPT or its pertussis component and GBS is limited to 11 unconfirmed cases

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reported through the CDC's MSAEFI system. GBS is a profound disorder whose diagnosis is reasonably reliable; thus, the vaccine exposure probably truly preceded the event in these cases. The specificity of an association, if present, would not be established, since all cases at the time of pertussis immunization also received tetanus antigen, which has been related to GBS. The fact that GBS is believed to be caused by or, at least, precipitated by a number of infectious agents also limits the specificity of association. There are no experimental data bearing on a possible biologic mechanism.

Conclusion

There is insufficient evidence to indicate a causal relation between DPT vaccine or the pertussis component of DPT vaccine and GBS.

PERIPHERAL MONONEUROPATHY

Clinical Description

Peripheral mononeuropathy is a syndrome of sensory, motor, reflex, and vasomotor symptoms, singly or in any combination, produced by disease of a single peripheral nerve. Trauma is the most common cause of a localized injury to a single nerve. Mononeuropathy has also been observed following administration of monovalent tetanus vaccine (e.g., Blumstein and Kreithen, 1966; Quast et al., 1979; Reinstein et al., 1982; Tsairis et al., 1972).

Descriptive Epidemiology

Peripheral mononeuropathy is rare in infants and children. No population-based incidence or prevalence rates were identified for the pediatric population.

Evidence from Studies in Humans

Case Reports

Martin and Weintraub (1973) reported one case of brachial neuritis in a 5-month-old boy 2 days after receipt of a first dose of DPT in the left thigh. The neuritis was followed days later by an isolated seventh-nerve palsy. The brachial neuritis cleared within 48 hours, and the facial palsy resolved 2 weeks after onset. No antibodies against peripheral and central myelin were detected in the CSF.

Ehrengut (1977) reported a case of paresis of the sixth cranial nerve in a

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child of unknown age 6 days after receiving a third dose of quadrivalent vaccine. The paresis was observed only "briefly." No further information was given.

No cases of peripheral mononeuropathy (ICD 9 code 355.9) occurring within 28 days of DPT immunization were reported through the CDC's MSAEFI system from 1978 to 1990, a period in which approximately 80.1 million doses of DPT vaccines were administered through public mechanisms in the United States (J. Mullen, Centers for Disease Control, personal communication, 1990).

Summary

The body of evidence concerning the possible relation between vaccination with DPT or its pertussis component and peripheral mononeuropathy is limited to two case reports, one of brachial neuritis and one of paresis of the sixth cranial nerve. The unambiguous clinical presentation of both cases occurred 2 to 6 days after the administration of DPT vaccine. Tetanus antigen, administered in conjunction with pertussis vaccine in DPT, has been related to peripheral mononeuropathy. There are no data bearing on a possible biologic mechanism.

Conclusion

There is insufficient evidence to indicate a causal relation between DPT vaccine or the pertussis component of DPT vaccine and peripheral mononeuropathy.

HEMOLYTIC ANEMIA

Clinical Description

Hemolytic anemia results from the lysis of red blood cells, which leads to shortened in vivo survival of red blood cells and an inability of the bone marrow to compensate for their decreased life span. The hemolysis may be acute, chronic, or episodic in nature.

Infections and the use of biologic agents have both been associated with the development of hemolytic anemia (Zuelzer et al., 1970). Immune mechanisms could play an etiologic role in such associations. For example, antibodies to components of the vaccine could cross-react with red blood cell antigens, or vaccine antigens could bind to the red blood cell surface and react there with antibodies. Antibodies on the cell surface could fix complement and lyse the cell or expedite splenic clearance of the cells (Facktor et al., 1973).

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Descriptive Epidemiology

Acute hemolytic anemia is not common at any age, but it can occur in early infancy. No population-based incidence rates were identified for the pediatric population.

Evidence from Studies in Humans

Case Reports

Evidence for a relation between hemolytic anemia and DPT vaccines is limited to rare case reports (Coulter and Fisher, 1985; Haneberg et al., 1978). Haneberg and colleagues (1978) described three cases of hemolytic anemia in infants following repeat doses of DPT vaccine. Case 1 was a 4-month-old boy hospitalized with a diagnosis of hemolytic anemia 4 days after receiving his second dose of DPT vaccine. Case 2 was a 6-month-old girl hospitalized with anemia 3 weeks after receiving a second dose of DPT vaccine and a concomitant first dose of trivalent OPV. Her parents reported evidence of jaundice and reddish discoloration of the urine 2 weeks after receipt of the vaccines. Case 3 was a boy who was hospitalized at age 10 months and who had received his third dose of DPT vaccine at age 5.5 months and his first trivalent OPV at age 9 months. The date of symptom onset was not noted, although the authors reported that the infant was very pale "for weeks" prior to admission. Antibodies to diphtheria and tetanus and a trace of antibody to pertussis were eluted from the red blood cells of case 3, but not from the red blood cells of controls. Red blood cells from the other two patients had antibodies of undetermined specificity on their surfaces. These findings suggest an immunologic basis for the hemolysis.

Zupanska and colleagues (1976) reviewed a case series of 44 children, ages 3 months to 14 years, with autoimmune hemolytic anemia. The authors identified one case of acute disease following DPT immunization. The child recovered; no other details specific to the case were provided.

Coulter and Fisher (1985) reported on one case of hemolytic anemia in a 2.5-year-old boy, which first occurred following a fourth dose of DPT vaccine. Six days after vaccination, the boy became irritable and anorectic. Fever, vomiting, and apparent jaundice and anemia developed over the next 7 days, at which point the boy was hospitalized with a diagnosis of hemolytic anemia. The boy returned to a state of health until 6 days after his fifth DPT vaccination (age not specified), when he developed the same constellation of symptoms, plus loss of consciousness. The boy was rehospitalized with a diagnosis of hemolytic anemia. No laboratory tests were reported and, again, the boy recovered.

No cases of hemolytic anemia (ICD 9 code 282.9) occurring within 28 days

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of DPT immunization were reported through the CDC's MSAEFI system from 1978 to 1990, a period in which approximately 80.1 million doses of DPT vaccine were administered through public mechanisms in the United States (J. Mullen, Centers for Disease Control, personal communication, 1990).

Summary

Although the body of evidence concerning the possible relation between vaccination with DPT or its pertussis component and hemolytic anemia is limited to rare case reports, the case described by Coulter and Fisher (1985) is suggestive of a causal relation because hemolytic anemia was detected 6 days after a DPT immunization on two separate occasions. Case 1 of Haneberg and colleagues (1978) had hemolysis within 4 days after DPT immunization. This could have been due to a chance concurrence, although antibodies to antigens found in each of the components of DPT vaccine were detected on the red blood cells of case 3 of Haneberg and colleagues, an observation that is compatible with a causal relation through the mechanism of an immunologic reaction. However, controls were not well described, and the antibodies detected were not shown to be specific to DPT vaccine. Evidence of a shared antigen in the DPT vaccine and on the human red blood cell would strongly increase the plausibility of a causal relation with the vaccine, but no such evidence has been reported. Pertussis antigens are not implicated any more strongly than the other constituents of the DPT vaccine are.

Conclusion

There is insufficient evidence to indicate a causal relation between DPT vaccine or the pertussis component of DPT vaccine and hemolytic anemia.

JUVENILE DIABETES

Clinical Description

Juvenile diabetes, or, as it has been more recently classified, insulin-dependent diabetes mellitus (IDDM; also called type 1 diabetes), results from damage to pancreatic beta cells caused by an autoimmune reaction. Viral infection has been proposed as a trigger of the autoimmunity).

Descriptive Epidemiology

The annual incidence of IDDM in the United States is about 12 to 14 new cases per 100,000 children ages 0 to 16 years. By age 20, approximately 0.3 percent of persons will have developed the disease. Incidence

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rates of IDDM are similar in males and females, but they are 1.5 times higher in whites than in blacks. The risk for siblings of IDDM cases is 7 to 18 times higher than the risk in the general population, suggesting that a genetic factor may be involved (LaPorte and Cruickshanks, 1985).

Evidence from Studies in Humans

Controlled Epidemiologic Study

Blumberg and colleagues (1988), in a surveillance study conducted in Los Angeles County in 1986, identified five children with hypotonic, hyporesponsive episodes (HHE) and six children who cried persistently for more than 3 hours following DPT immunization. A physical examination and medical history were conducted on and blood samples were collected from each child. Results were compared with those for 16 control children, ages 4 to 6 years, who had no reactions following DPT immunization. No abnormalities were noted in plasma insulin or serum glucose.

Case Report

A 16-month-old girl was reported to have developed IDDM about 3 weeks after injection of DPT (Champsaur et al., 1982). The authors proposed that the IDDM was caused by a coxsackievirus infection that began after the DPT shot. The child was genetically predisposed to IDDM in that she had the lymphocyte surface markers and the biochemical types of the complement proteins factor B and C4 that have been seen with increased frequency in individuals with IDDM. The possibility of whether DPT might have had an immunoboosting (adjuvant) effect was raised.

No cases of IDDM (ICD 9 code 250.1) occurring within 28 days of DPT immunization were reported through the CDC's MSAEFI system from 1978 to 1990, a period in which approximately 80.1 million doses of DPT vaccine were administered through public mechanisms in the United States (J. Mullen, Centers for Disease Control, personal communication, 1990).

Evidence from Studies in Animals

In animal studies, vaccines containing killed *B. pertussis* have been reported to induce hyperinsulinemia with variable hypoglycemia (reviewed in Furman et al., 1981). Islet-activating protein (pertussis toxin), which stimulates insulin release in animals, produced long-lasting amelioration of diabetes in spontaneously diabetic strains of rodents (Wardlaw and Parton, 1983). At a theoretical level, pertussis vaccines have been shown in animals and humans to have an adjuvant effect (Munoz and Bergman, 1977),

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which might have the potential to enhance an autoimmune reaction. However, data are not available that support the possibility that injection of DPT might cause or facilitate the development of IDDM.

Summary

Information concerning the possible relation between vaccination with DPT or its pertussis component and IDDM consists of one controlled study of plasma insulin and serum glucose levels in 11 children with HHE or persistent crying following DPT immunization, one case report in which the authors suggested that a concomitant viral infection rather than the immunization was the causative factor, and animal studies of the effects of whole-cell pertussis vaccines or pertussis toxin on insulin and glucose metabolism. No biologic mechanism supporting a causal association has been proposed.

Conclusion

There is insufficient evidence to indicate a causal relation between DPT vaccine or the pertussis component of DPT vaccine and IDDM.

LEARNING DISABILITIES AND HYPERACTIVITY

Clinical Description

The terms *learning disability* and *hyperactivity* (or, more currently, attention deficit disorder [ADD]) are frequently used in a general way to describe a heterogeneous group of problems. Recent studies, however, have focused on developing rigorous, operational definitions for both learning disability and ADD.

Learning Disability, Reading Disability, and Dyslexia

Learning disability is most commonly defined as "a severe discrepancy between achievement and intellectual ability" (Cone and Wilson, 1981; Reynolds, 1984; Rutter and Yule, 1975; Thorndike, 1963; United States Office of Education, 1977). The diagnosis of learning disability is established on the basis of performance on tests of ability (e.g., the Wechsler Intelligence Scales for Children) and achievement (e.g., the Woodcock-Johnson Psychoeducational Scales).

Most cases of learning disability represent difficulties in reading, and the terms *learning disability* and *reading disability* are frequently used interchangeably. To add further to this semantic confusion, *reading disability is* used interchangeably with the term *dyslexia.* The work of Liberman and

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Vellutino and their colleagues (Liberman and Shankweiler, 1985; Mann et al., 1989; Vellutino, 1978, 1979; Vellutino and Scanlon, 1987) and others supports the belief that reading disability is the result of difficulties with language and words—their use, significance, meaning, pronunciation, and spelling.

Hyperactivity, Hyperkinesis, and Attention Deficit Disorder

ADD has, in the past, been referred to as *brain damage, brain dysfunction, minimal brain dysfunction, hyperactivity,* and *hyperkinesis.* These terms reflect earlier concepts of the pathogenesis of what Still (1902) described as "morbid defects in moral control." In the first half of the twentieth century, behavioral disorders, including hyperactivity, were attributed to brain damage from trauma or infection, whether or not such an insult had been recognized (Bender 1942; Goldstein, 1936; Hohman, 1922; Meyer, 1904; Strauss and Lehtinen, 1947; Werner and Strauss, 1941).

By the 1950s, the concept of brain "dysfunction" rather than brain "damage" began to emerge in relation to hyperactivity. "Minimal brain dysfunction" was inferred from the presence of a cluster of symptoms, including specific learning deficits, hyperactivity, impulsivity, short attention span with or without mild neurologic signs, and changes in the EEG (Clements and Peters, 1962). Two subsequent decades of research have led to the recognition that minimal brain dysfunction is a meaningless concept. At present, the *Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association (1987) uses the term ADD, a term developed because most investigators believed that an attentional rather than an activity problem was the cardinal symptom of the disorder (Cantwell, 1983).

Descriptive Epidemiology

Given the definition of learning disability, prevalence rates are especially sensitive to the cutoff score used to define the difference between ability and achievement. These cutoff scores are generally represented as standard deviations from the mean. For example, if the difference between the ability and achievement score is set at 1.5 standard deviations (approximately a 20-point difference between IQ and achievement), this will dictate a prevalence rate of 9 percent, assuming a normal distribution, and if a cutoff of 1.0 standard deviations is employed, the corresponding rate will be 16 percent.

Definitional issues certainly affect prevalence rates for ADD, and these issues have been discussed in detail previously (Shaywitz and Shaywitz, 1988). Not surprisingly, prevalence rates vary considerably, from less than

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1 percent to above 20 percent (reviewed by Shaywitz and Shaywitz, 1988; Szatmari et al., 1990).

Evidence from Studies in Humans

Case Reports

No reports have been published in peer-reviewed scientific journals relating pertussis immunization to either learning disability or ADD. One anecdotal report (Coulter and Fisher, 1985) describes a child who was hyperactive and had delayed learning. His problems were attributed to a pertussis immunization that had caused fever and irritability as an infant. Although intelligent (his IQ score was reported as 126), his impulsive behavior was difficult for his parents and the school to tolerate. Few clinical details are provided, but what is available in the chapter suggests that the child would be diagnosed as having ADD. However, there is no basis by which ADD in this case can be attributed to pertussis immunization. No information is provided about the early school history of either parent. This might be relevant since familial influences are by far the most common cause of both learning disability and ADD among a large list of possibly related associations (Shaywitz and Shaywitz, 1989). Although no structural abnormalities have been described for ADD, evidence from several lines of investigation supports the belief that abnormalities in brain neurotransmitter systems, particularly brain catecholaminergic mechanisms, may be related to the emergence of ADD. A recent report suggests abnormalities in cerebral glucose utilization in young adults with a history of ADD as children (Zametkin et al., 1990).

Six cases of hyperactivity (ICD 9 code 314.01) and no cases of learning disability (ICD 9 code 215.2) occurring within 28 days of DPT immunization were reported through the CDC's MSAEFI system from 1978 to 1990, a period in which approximately 80.1 million doses of DPT vaccine were administered through public mechanisms in the United States (J. Mullen, Centers for Disease Control, personal communication, 1990). Of the six cases of hyperactivity, four cases received OPV at the time of DPT immunization and two cases received OPV plus MMR. No follow-up of the cases was made, and a physician's diagnosis was not required. However, a diagnosis of either learning disability or ADD would not be expected to be made until the child was of school age.

Controlled Epidemiologic Studies

The relation between early immunization and later learning and attention was investigated by Butler and colleagues (1982), who examined a cohort of 13,135 children at age 5 years who had received routine DPT immuniza

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tions in infancy. The cohort was part of the National Childhood Development Study, which followed approximately 95 to 99 percent of all children born in Great Britain during a 1-week period in April 1970 (Chamberlain et al., 1975). Five years later, parents of 13,135 (approximately 80 percent) of the original group (excluding cases in Northern Ireland) were interviewed, and "several simple tests were administered" to the child by health visitors (Butler et al., 1982). Analysis gave no indication that the children who had been immunized against pertussis were developmentally disadvantaged. In fact, the children with no immunization against pertussis more frequently had poor scores on the various tests or were rated as intellectually abnormal. However, these results may have been biased because the sample children who were not immunized against pertussis were of lower socioeconomic class than those who were immunized. Many studies have indicated that school performance is directly associated with socio-educational variables such as the mother's level of education (Broman et al., 1985). In addition, it is not clear what measures were used to assess learning and attention. The authors reported a subsequent follow-up of a subset of 1,057 children at age 10 years in which the children's teachers rated each child's behavior and administered achievement tests of reading and arithmetic. No findings from the 10-year follow-up specific to pertussis immunization were reported.

Summary

The body of evidence concerning the possible relation between vaccination with DPT or its pertussis component and learning disabilities or ADD is limited to one published case report, six cases reported through the CDC's MSAEFI system, and one follow-up report at age 5 of children enrolled in the National Childhood Development Study. The last study demonstrated improved intellectual outcome in children who had been immunized against pertussis compared with those who had not been immunized. However, this finding may reflect confounding owing to the fact that the sample children who were immunized against pertussis were of higher socioeconomic class than those who were not immunized, a factor associated with better school performance. The varied definitions, difficulty in diagnosis, and incomplete understanding of the causation of learning disabilities and ADD limit both the ability to ascertain that exposure to DPT vaccine truly preceded the event and the specificity of the putative association with pertussis vaccine. There are no data bearing on a possible biologic mechanism.

Conclusion

There is insufficient evidence to indicate a causal relation between DPT vaccine or the pertussis component of DPT vaccine and the development of learning disabilities or ADD.

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PROTRACTED INCONSOLABLE CRYING AND SCREAMING

Clinical Description

Persistent crying has been commonly noted after DPT immunization and appears to be a reaction to vaccination. The usual course of events is as follows: the child receives the immunization and cries briefly in association with the vaccination. The crying following immunization is short-lived and the child returns to normal behavior. Then, sometime later, usually within 2 to 8 hours, the child starts to cry. The crying is persistent and frequently inconsolable. Occasionally, the cry is episodic in nature throughout a 24-hour period. Crying of this nature is common in infancy, and many causes are suspected.

A more unusual, high-pitched crying also has been reported after DPT immunization. This cry has been characterized as screaming or "a cerebral cry," and parents identify it by saying they "never heard their child cry like this before." There is no unanimity of what constitutes a scream or a cerebral cry (Cherry et al., 1988). Subjectivity in reporting high-pitched crying makes it difficult to develop reliable estimates of its frequency (Cody et al., 1981). In the following summary, the committee is necessarily relying on the verbal descriptions of the authors; these vary by study and include such different terms as *crying; persistent* or *protracted crying; screaming;* and *prolonged, persistent,* or *high-pitched unusual screaming.*

Descriptive Epidemiology

No population-based incidence rates were identified for the pediatric population.

Evidence from Studies in Humans

Case Reports and Case Series

Barkin and Pichichero (1979) surveyed parents of all children receiving DPT vaccine in one of four private practices in Denver, Colorado, between July 1977 and February 1988. Questionnaires were returned by 1,232 (85 percent) of the parents. Crying occurred after DPT immunization in 432 (35 percent) of the children; prolonged (duration not specified) screaming occurred in 159 (13 percent). There were marked differences by DPT series number in the number of children exhibiting crying and prolonged screaming, with the fewest reactions occurring after booster immunizations.

Coulter and Fisher (1985) reported one case of persistent crying and high-pitched screaming associated with subsequent mental and motor retardation. The child exhibited high fever, with crying and high-pitched screaming

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of 3 days' duration following the first DPT shot at age 3.5 months. The second DPT shot 2 months later produced a similar clinical picture, but of shorter duration (duration not specified). Mental and motor retardation were diagnosed at age 21 months and persisted.

Approximately 2,531 cases of "screaming" (ICD 9 code 799.8) occurring within 28 days of DPT immunization were reported through the CDC's MSAEFI system from 1978 to 1990, a period in which approximately 80.1 million doses of DPT vaccine were administered through public mechanisms in the United States (J. Mullen, Centers for Disease Control, personal communication, 1990). Of these, 1,864 (73.6 percent) cases received at least one other vaccine at the time of DPT immunization. No follow-up of the cases was made, and a physician's diagnosis was not required.

Controlled Epidemiologic Studies

A number of studies have examined rates of protracted crying and screaming in children following DPT immunization. In one of the larger controlled studies conducted to date, Cody and colleagues (1981) compared reactions occurring in children, ages 0 to 6 years, in the first 48 hours following 15,752 injections of DPT vaccine and 784 injections of DT vaccine. Crying was noted following 488 (3.1 percent) injections of DPT vaccine and 5 (0.7 percent) injections of DT vaccine. Not only was the event significantly ($p = 0.0003$) more frequent following DPT immunization, it was also of significantly longer duration (p value not given). No DT recipient cried for longer than 2 hours, whereas injections were associated with persistent crying for 3 to 21 hours following immunization. High-pitched, unusual crying (duration not specified) was reported following 17 (0.1 percent) DPT immunizations and following no DT immunizations; however, the difference was not statistically significant ($p = 0.36$) given the small number of cases observed.

Baraff and colleagues (1984) reported significant differences in the rates of persistent crying longer than 30 minutes by immunization site, by vaccine manufacturer, and by vaccine dose. With respect to immunization site, the percentage of recipients with persistent crying was 11, 8, and 7 percent for injections given in the buttock, upper lateral thigh, and mid-anterior thigh, respectively. Three percent of children receiving a full dose of DPT vaccine exhibited persistent crying; none of the children receiving a half-dose of vaccine did.

In a subsequent study comparing reaction rates following 9,920 DPT immunizations from 25 vaccine lots, Baraff and colleagues (1989) reported no differences in rates of screaming (duration not specified) by amount of endotoxin in the vaccine or by pertussis vaccine potency. There was a positive association of screaming with percent mouse weight gain ($p = 0.001$), a test of pertussis vaccine toxicity (see Appendix C for description);

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the proportion of children exhibiting this symptom increased from 1.3 to 3.2 percent with increasing percent mouse weight gain. The finding of a positive association between screaming and percent mouse weight gain is surprising, given that percent mouse weight gain is inversely associated with toxicity. The finding was not explained.

Pollock and colleagues (1984) analyzed data from the North West Thames region of England, where an intensified effort had been undertaken to identify all severe adverse events of immunization occurring between 1975 and 1981. The authors studied a sample of individuals attending routine immunization clinics in Hertfordshire in which 6,004 children started primary immunization with DPT and 4,024 with DT. The DPT group was further divided into those receiving plain versus those receiving adsorbed vaccine. A total of 25,643 doses of vaccine were given: 1,125 of plain DPT, 13,917 of adsorbed DPT, and 10,601 of adsorbed DT. Crying occurred slightly more frequently (p value not given) in children receiving three doses of adsorbed DPT vaccine than in those receiving three doses of adsorbed DT vaccine (19.1 percent versus 14.4 percent, respectively). Similarly, a bout of screaming beginning within 12 hours of immunization and continuing for longer than an hour occurred slightly more frequently (p value not given) in children receiving three doses of adsorbed DPT vaccine than in those receiving three doses of adsorbed DT vaccine (1.9 percent versus 1.2 percent, respectively). Persistent crying for more than 5 hours and high-pitched screaming occurred with similar frequencies (0.9 percent after DPT versus 0.7 percent after DT) in the two groups.

Blumberg and colleagues (1988), in a surveillance study conducted in Los Angeles County in 1986, identified six children who cried persistently for more than 3 hours following DPT immunization. A physical examination and medical history were conducted on and blood samples were collected from each child. Results were compared with those for 16 control children, ages 4 to 6 years, who had no reactions following DPT immunization. Acute leukocytosis (average total white cell count, 9,400 cells/mm^3) was observed in both cases and controls on the day following DPT immunization; no abnormalities were noted in plasma insulin or serum glucose. Five of the six children with persistent crying had severe local reactions, suggesting that localized inflammation may be a cause of persistent crying.

Long and colleagues (1990) assessed the rates of adverse events following pertussis vaccination in 538 children randomized to the standard four-dose immunization schedule or to a three-dose schedule with a saline injection substituted for DPT at age 6 months. In all, 1,553 doses of DPT vaccines were given. Prolonged crying (i.e., crying for more than 30 minutes) was reported following 6 percent of DPT immunizations and 0.5 percent of placebo vaccinations ($p < 0.0001$). Prolonged crying persisted for more than 3 hours following 0.9 percent of DPT immunizations. High-

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pitched, unusual crying was reported after 3 percent of DPT immunizations; no cases occurred following the placebo vaccination ($p < 0.0001$). Of the 89 children who had prolonged crying or high-pitched, unusual crying, or both following DPT immunization, 77 had follow-up evaluations after age 2 years (mean age at evaluation, 3 years, 5 months). The nature of the follow-up, personnel, and tests used were not reported. No child was found to have a neurologic abnormality. One child had a delay in speech development of unknown etiology.

Summary

The body of evidence concerning the possible relation between vaccination with DPT or its pertussis component and protracted inconsolable crying or screaming includes case reports, case series, and several controlled epidemiologic studies. Evidence of sufficient quality pertinent to this question can be summarized as follows. The evidence of controlled studies indicates a direct association, with rates of crying ranging from 3 to 19 percent in DPT recipients versus 1 to 14 percent in DT recipients; rates of persistent crying ranging from 1 to 6 percent in DPT recipients versus approximately 0 percent in DT recipients and 0.5 percent in placebo recipients; and rates of high-pitched, unusual crying ranging from 0.1 to 3 percent in DPT recipients versus approximately 0 percent in DT recipients. These results are generally consistent across studies, although comparison of study findings is complicated by the subjectivity in reporting certain of these events, particularly high-pitched crying, and by the variety of terms used to describe simple crying or screaming or high-pitched, unusual crying. Results from one study (Baraff et al., 1984) demonstrate a direct dose-response relation, with 3 percent of children receiving a full dose of DPT vaccine exhibiting persistent crying but with none of the children receiving a half-dose of the vaccine exhibiting crying. The obvious clinical presentation of crying, its timing, and the duration of persistent crying and high-pitched crying indicate that the exposure truly preceded the onset of the condition. It is reasonable to conclude that crying and screaming can occur in response to the pain, local reaction, and fever often observed after receipt of DPT vaccine.

The evidence concerning a possible relation between protracted, inconsolable crying or screaming and chronic residua such as mental or motor retardation is limited to a few case reports and one randomized controlled study (Long et al., 1990). The latter study reported no association between high-pitched or unusual crying following DPT immunization and a subsequent neurologic abnormality at age 3 years. However, it is not surprising that an event as infrequent as chronic neurologic damage was not detected given the study's small sample. There are no experimental data concerning

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biologic mechanisms that support a causal association between DPT vaccine and chronic neurologic damage.

Conclusions

The evidence indicates a causal relation between the pertussis component of DPT vaccine and protracted, inconsolable, or high-pitched crying or screaming. Incidence rates are estimated to range from 0.1 to 6 percent of recipients of a DPT injection and vary with the type and dose of vaccine and with the immunization site.

Evidence is insufficient to indicate whether pertussis vaccine-associated protracted, inconsolable, or high-pitched crying or screaming does, or does not, lead to chronic neurologic damage.

REYE SYNDROME

Clinical Description

In 1963, Reye and coworkers described the clinical and pathologic features of a syndrome that occurred in 21 Australian children. The findings included prodromal illness, most commonly influenza, chickenpox (varicella), or gastroenteritis, followed by the onset of protracted vomiting. Initially, the patients were oriented, but irritable and lethargic. Subsequently, their level of consciousness varied from no loss of consciousness (Cincinnati Coma Grade I) to a deep comatose state with decerebrate and decorticate posturing, flaccid paralysis, loss of voluntary ventilatory control, and hyperpyrexia (Cincinnati Coma Grade V) (Heubi et al., 1987; Reye et al., 1963).

The case definition of Reye syndrome, according to the CDC, consists of (1) acute noninflammatory encephalopathy demonstrated by either the presence of less than 8 white blood cells per ml in the CSF or cerebral edema without perivascular or meningeal inflammation on histologic sections of the brain, associated with (2) fatty metamorphosis of the liver, diagnosed either by biopsy or autopsy, or (3) a serum glutamic-oxaloacetic transaminase level greater than three times normal and a high blood ammonia level, and (4) no more reasonable explanation for the cerebral or hepatic abnormalities. Major studies on Reye syndrome and medications (Hurwitz et al., 1985, 1987; Pinsky et al., 1988) have confirmed prior reports (Halpin et al., 1982; Starko et al., 1980; Waldman et al., 1982) of an association between ingestion of aspirin during antecedent viral illness and subsequent development of Reye syndrome.

The pathogenesis of Reye syndrome remains incompletely defined. The onset of emesis is considered to be the first sign of encephalopathy. Increasing metabolic derangements including elevated serum free fatty acids,

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elevated serum ammonia, hypoglycemia, and decarboxylic acidemia are noted. Coincident with these changes, the intracranial pressure may become elevated, which precludes effective cerebral perfusion, leading to brain damage or death (Heubi et al., 1987). Morphologic and biochemical studies reveal the presence of an hepatic mitochondrial damage that is characteristic of the hepatic pathology of Reye syndrome.

Descriptive Epidemiology

A number of reports indicate that the incidence of Reye syndrome in the United States increased in the 1970s, with the incidence rate in Olmsted County, Minnesota, in persons under age 18 years, for example, rising from 1.1 per 100,000 person-years in 1970 to 1975 to 1.7 per 100,000 person-years in 1976 to 1981 (Nicolosi et al., 1985). The estimated incidence rate of Reye syndrome in Great Britain for the years 1976 to 1979 obtained in the NCES was 0.7 per 100,000 children age 2 to 36 months per year (Bellman et al., 1982). Since 1980, however, incidence rates have declined, with the annual number of Reye syndrome cases reported to the CDC's National Reye Syndrome Surveillance System falling from 555 (0.9 per 100,000 U.S. population under age 18 years) in 1980 to 20 in 1988 (Centers for Disease Control, 1989). The decline in Reye syndrome cases since late 1980 coincides with the decreased frequency and dose of aspirin-containing medication used in treating children with influenza-like illness (Barrett et al., 1986; Remington et al., 1986).

Evidence from Studies in Humans

Controlled Epidemiologic Study

In the NCES, a total of 37 cases of Reye syndrome were reported (a rate of 0.7 per 100,000 children per year). Only one of these cases occurred within 7 days of DPT immunization (Bellman et al., 1982). The case, a previously normal child, subsequently died; no cause of death was specified. Aspirin exposure in the child is unknown.

Case Reports and Case Series

Linnemann and colleagues (1974) reported on a cluster of 24 cases of Reye syndrome admitted to Children's Hospital Medical Center in Cincinnati in early 1974. The epidemic of Reye syndrome coincided with an epidemic of influenza in the immediate area. All recent immunizations were reviewed; only one child had been immunized (with OPV) within the previous month.

Corey and colleagues (1976) described 379 cases of confirmed Reye

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syndrome reported to the CDC in late 1973 and early 1974. Five cases were reported to have received an immunization within the month prior to hospitalization; all five had an antecedent upper respiratory infection. Two of the five cases had received MMR in the week before hospitalization, one had received DPT 2 days before hospitalization, and two had received OPV in the month before hospitalization. No patient had a history of recent influenza vaccination.

Seven cases of Reye syndrome (ICD 9 code 331.8) occurring within 28 days of DPT immunization were reported through the CDC's MSAEFI system from 1978 to 1990, a period in which approximately 80.1 million doses of DPT vaccine were administered through public mechanisms in the United States (J. Mullen, Centers for Disease Control, personal communication, 1990). Of these, five cases received OPV at the time of DPT immunization and one case received OPV plus MMR. No follow-up of the cases was made, and a physician's diagnosis was not required.

Summary

Only 1 of the 37 cases of Reye syndrome identified in the NCES and none of the 24 cases in Linnemann and colleagues' series had received DPT vaccine within 7 days of onset. The lack of evidence of an association between DPT vaccine and Reye syndrome in these two defined populations, as well as the strong epidemiologic evidence linking aspirin intake with Reye syndrome, including the virtual disappearance of the disease in the United States coincident with the recommended proscription of aspirin in children, argues against a significant contribution of DPT vaccine to this disorder. There are no experimental data that bear on a biologic mechanism by which DPT vaccination might cause Reye syndrome.

Conclusion

The evidence does not indicate a causal relation between DPT vaccine or the pertussis component of DPT vaccine and Reye syndrome.

SHOCK AND "UNUSUAL SHOCK-LIKE STATE" WITH HYPOTONICITY, HYPORESPONSIVENESS, AND SHORT-LIVED CONVULSIONS, USUALLY FEBRILE

Clinical Description

Shock or shock-like state, collapse, and *hypotonic, hyporesponsive episodes* (HHE) are terms that are used interchangeably in the literature to refer to an unusual reaction consisting of an acute diminution in sensory

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awareness or loss of consciousness accompanied by pallor and muscle hypotonicity. As described, the syndrome has its onset between 1 and 12 hours after immunization. Most children are initially irritable and febrile. They then become pale, limp, and unresponsive or hyporesponsive. Respirations are shallow and cyanosis is frequently noted. The duration can be as short as a few minutes and as long as 36 hours (Cody et al., 1981; Siddiqui et al., 1989). The pathophysiology of this entity has not been well described.

At least some of the cases of HHE (as the syndrome is referred to in this report) may be due to anaphylaxis. Both HHE and anaphylaxis can occur within a few minutes to a few hours after injection of DPT. Both are accompanied by tachycardia, although most infants diagnosed with HHE have had fever, which increases the heart rate. Accompanying symptoms of urticaria or angioedema, especially of the larynx, would indicate anaphylaxis (by definition), not HHE. Shallow respirations and cyanosis might occur with either entity. It is possible that at least some cases of HHE represent atonic seizures, which consist of sudden loss of postural tone and consciousness, perhaps triggered by fever (Huttenlocher, 1987).

Descriptive Epidemiology

No population-based incidence rates were identified for the pediatric population.

Evidence from Studies in Humans

Case Reports and Case Series

Although Madsen in 1933 and Werne and Garrow in 1946 reported four deaths from apparent shock following pertussis vaccination, HHE was not systematically described until 1961, when Hopper surveyed 52 parents reporting illnesses in their children following vaccination. Six cases of "collapse" were described, with onset from 1 to several hours after vaccination. All cases recovered with no long-term sequelae noted.

Subsequent case reports of HHE following pertussis vaccination were published over the next 15 years (e.g., Aicardi and Chevrie, 1975; Forrester, 1965; Haire et al., 1967; Hannik and Cohen, 1979; Stewart, 1977; Strom, 1967).

Feery and colleagues (1985) compared the incidence and type of adverse events following administration of plain or adsorbed DPT vaccines in a masked prospective study of 2,041 vaccinations in 1,075 infants receiving routine childhood immunization. In all, 558 infants received a total of 1,031 doses of plain DPT vaccine and 517 infants received a total of 1,010

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doses of adsorbed DPT vaccine. Three recipients of plain vaccine and one of adsorbed vaccine suffered HHE or collapse, giving HHE incidence rates of 291 and 99 cases per 100,000 injections of plain and adsorbed DPT vaccine, respectively.

Coulter and Fisher (1985) described several cases of shock or collapse following pertussis vaccination, some with subsequent death (p. 97) or disability, including learning disabilities (p. 118), hyperactivity (p. 125), and epilepsy (p. 125).

Baraff and colleagues (1989) prospectively studied 9,920 infants and children immunized with DPT from 25 different vaccine lots. HHE was rare (0 to 0.4 percent across lots; absolute numbers were not reported). There were insufficient cases for comparison of rates by vaccine potency, endotoxin content, or percent mouse weight gain. No information on long term outcome of the HHE cases was provided.

Siddiqui and colleagues (1989) identified nine cases of HHE that occurred within 28 days of DPT vaccination in the state of Maryland in 1987. Approximately 259,000 doses of DPT vaccine were administered in Maryland during this time, representing an incidence rate of approximately 3.5 cases per 100,000 vaccinations. No information on long-term case outcome was provided.

Blumberg and colleagues (in press) examined physician and nurse reports from the Los Angeles area to identify severe adverse events following DPT vaccination. Cases were considered eligible for study if the onset of the adverse event was within 48 hours of immunization and if the study staff was able to evaluate the child within 24 hours of symptom onset. Eleven cases of HHE were identified, 10 following immunization with whole-cell vaccine and 1 following receipt of the Takeda acellular pertussis vaccine. Laboratory tests offered no evidence that altered insulin or glucose metabolism or biologically active pertussis toxin was related to HHE onset.

Eight hundred eighty-five cases of HHE (ICD 9 code 785.9) occurring within 28 days of DPT immunization were reported through the CDC's MSAEFI system from 1978 to 1990, a period in which approximately 80.1 million doses of DPT vaccine were administered through public mechanisms in the United States (J. Mullen, Centers for Disease Control, personal communication, 1990). Of these, 634 cases (71.6 percent) received at least one other vaccine at the time of DPT immunization. No follow-up of the cases was made, and a physician's diagnosis was not required.

Controlled Epidemiologic Studies

Cody and colleagues (1981) compared reactions occurring in children, ages 0 to 6 years, in the first 48 hours following 15,752 injections of DPT vaccine and 784 injections of DT vaccine (Table 6-1). Nine cases of HHE

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TABLE 6-1 Controlled Studies of Shock and "Unusual Shock-Like State"[a]

Reference	Years	Age	Vaccine	Children (No.)	Immunizations (No.)	HHE (No.)	RR (95% CI)[b]	Power[c] 50%	Power[c] 80%
Cody et al., 1981	1978-1979	0-6 years	DPT	15,752	15,752	9	1.0 (0.1-7.4)	7.8	18.9
			DT	784	784	0			
Pollock and Morris, 1983[d]	1979	<2 years	DPT	134,700	404,100	8	4.0 (1.0-16.0)	4.1	7.5
			DT	135,500	406,500	2			
			DPT	~17,000	~21,000	NR[e]			
			DT	~18,000	~24,000	NR[e]			
Pollock et al., 1984	1978-1980	3 months-1 year	DPT	6,004	13,917[f]	5	1.0 (0.3-3.3)	3.5	5.9
			DT	4,024	10,601	4			
Long et al., 1990	1984-1985	2-20 months	DPT	538	1,553	0	0.1 (0.0-2.3)	16.0	52.7
			Placebo[g]	218	218	0			

[a]Shock and "unusual shock-like state" defined in report as hypotonic, hyporesponsive episodes (HHE).
[b]RR (95% CI), Estimated relative risk (95 percent confidence interval).
[c]"Power" denotes the probability that a statistical test based on a sample of the same size as the one in the study cited would find a statistically significant increased risk (with alpha = 0.05), given that the true RR in the population being studied is the number stated in the table. The numbers tabulated are the RRs such that the powers are 50 and 80 percent, respectively.
[d]First study based on voluntary reporting; second study based on systematic hospital activity analysis.
[e]NR, Not reported.
[f]Excludes 1,125 doses of plain DPT.
[g]Saline injection substituted for the fourth DPT dose at age 6 months.

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were reported following DPT vaccine for a rate of 57 per 100,000 injections. No cases of HHE were observed following DT vaccines. The difference in rates was not statistically significant (the RR was 1.0 and the 95 percent CI was 0.1 to 7.4), but the power of this study was very low. For instance, the RR would have to be 7.8 for the test to have 50 percent power. All cases occurred within 10 hours of immunization and usually within 4 hours, with episodes lasting from 10 minutes to 36 hours. Cases were associated with the primary immunization series only and occurred in infants aged 2 to 18 months. None of the affected infants had a past history of neurologic problems, convulsions, or developmental delay, and all returned to normal activities or were normal when evaluated by the investigators. The association of HHE with primary immunization has also been reported elsewhere (Health Council of The Netherlands, 1987, 1988).

A subsequent evaluation of the nine cases of HHE identified by Cody and colleagues (1981) was undertaken approximately 7 years later by Baraff and coworkers (1988). Eight of the nine children were contacted and six were given a complete neurologic and psychometric evaluation, the latter consisting of the Wechsler Intelligence Scale for Children—Revised. Two of the children exhibited low verbal IQ scores (i.e., less than 85 or more than 1 standard deviation below the mean). One of these demonstrated an articulatory deficit upon neurologic examination; the patient also had a history of familial speech problem. The authors concluded that there was no evidence that any of the nine cases of HHE suffered chronic neurologic damage as a result of their HHE.

Eight cases of anaphylaxis or collapse after DPT immunization were reported in the North West Thames study (Pollock and Morris, 1983; see section on Anaphylaxis for study description) in approximately 134,700 children receiving complete courses of three injections. Two similar cases were observed in 133,500 children receiving complete courses of three DT injections. Although the relative risk of HHE following DPT compared with that following DT vaccine is 4.0 (95 percent CI = 1.0 to 16.2), the authors note that the increased estimated relative risk could be an artifact of the voluntary reporting system. Symptoms of anaphylaxis or collapse varied in character and severity, and many occurred within a few minutes of the injection. In six cases, the predominant features were pallor, limpness, and apnea, which is consistent with the diagnosis of HHE.

A subsequent study by Pollock and colleagues (1984) compared rates of adverse events in 10,028 infants, of whom 6,004 started primary immunization with DPT vaccine and 4,024 with DT vaccine. The DPT group was further divided into those receiving plain versus those receiving adsorbed vaccine. The first vaccine dose for each child was scheduled at age 3 months, the second 6 to 8 weeks later, and the third, final dose 4 to 6 months following the second dose. A total of 25,643 doses of vaccine were given: 1,125 of plain DPT, 13,917 of adsorbed DPT, and 10,601 of adsorbed

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DT. Rates of pallor and cyanosis, i.e., "hypotonia," were similar (40 per 100,000 doses) in both the adsorbed DPT (5 cases) and DT (4 cases) groups. The RR for HHE following DPT compared with that following DT vaccine is 1.0 with a 95 percent CI of 0.3 to 3.3. The power of this test, like those in the other controlled studies of HHE, was low: 50 percent for an RR of 3.5 and 80 percent for an RR of 5.9. Four cases occurred after plain DPT, but the major difference in the preparation of this vaccine makes comparisons difficult. All 13 children recovered quickly, and there were no sequelae.

Because each of these three studies had relatively low power, the committee combined the evidence from all three using the methods of meta-analysis described in Appendix D. The pooled RR was 1.6 with a 95 percent CI of 0.6 to 4.2 (under both the random- and fixed-effects models). Thus, the meta-analysis provides little evidence of a significantly increased risk of HHE following DPT compared with that following DT vaccine.

Blumberg and colleagues (1988), in a surveillance study conducted in Los Angeles County in 1986, identified five children who had HHE following DPT immunization. A physical examination and medical history were conducted on and blood samples were collected from each child. Results were compared with those for 16 control children, ages 4 to 6 years, who had no reactions following DPT immunization. Acute leukocytosis (average total white cell count, 9,400 cells/mm^3) was observed in both cases and controls on the day following DPT immunization; no abnormalities were noted in plasma insulin or serum glucose. Follow-up at 1 month postimmunization revealed no persistent neurologic abnormalities in the five cases of HHE.

Long and colleagues (1990) prospectively assessed the rates of adverse events, including HHE, following pertussis vaccination in 538 children randomized to the standard four-dose immunization schedule or to a three-dose schedule with a saline injection substituted for DPT at age 6 months. In all, 1,553 doses of DPT vaccine were given. No cases of HHE were observed following DPT vaccination. However, it is not surprising that an event as infrequent as HHE was not detected given the study's relatively small sample size and, therefore, the study provides little information on the presence or absence of an association between DPT immunization and HHE.

Summary

The body of evidence concerning the possible relation between vaccination with DPT or its pertussis component and HHE includes case reports, case series, and several controlled epidemiologic studies. Incidence rates of HHE vary widely, from 3.5 to 291 per 100,000 injections. Epidemiologic evidence of sufficient quality pertinent to this question can be summarized as follows. Two of the three controlled studies comparing children immunized with DPT or DT (Cody et al., 1981; Pollock et al., 1984) found no association between HHE and DPT compared with that between HHE and

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DT vaccine, and the other study (Pollock and Morris, 1983) found a significantly increased risk that the authors ascribed to the voluntary reporting system (Table 6-1). Dose-response relations cannot be evaluated from the available data. The easily visualized presentation of HHE suggests that exposure truly preceded the onset of the condition among the exposed cases.

The pathophysiologic basis of HHE is not understood. The clinical presentation of this adverse event includes a spectrum of signs, ranging from decreased responsiveness to shock, and in some reports, HHE is not differentiated from anaphylaxis. However, no clinical signs of allergy have been reported and no laboratory evidence for an immunologic reaction or any other mechanism has been presented. The clinical picture in some cases resembles a seizure, but there is no evidence for this possibility. Nevertheless, a clinical presentation that could be classified as HHE has been widely observed and reported. Thus, the evidence for causality rests here on the typical clinical presentation that occurs within a few hours after administration of the vaccine.

The evidence concerning a possible relation between HHE and chronic neurologic damage such as mental or motor retardation includes case reports, case series, and controlled epidemiologic studies. A few case reports have raised the possibility that HHE might be associated with permanent sequelae, but the three controlled studies that have examined this issue indicate no such relation. However, the relatively small number of HHE cases (27) followed up in these three studies would suggest that the likelihood that these studies would detect a rare sequela like chronic neurologic damage would be small. In addition, the difficulty in confirming a clear date of onset for certain types of chronic neurologic damage such as mental and motor retardation limits the ability to establish temporal priority of exposure among the few exposed cases reported.

Conclusion

The evidence is consistent with a causal relation between DPT vaccine and HHE. The available evidence does not implicate the pertussis component specifically.

Evidence is insufficient to indicate a causal relation between HHE following DPT immunization and the subsequent development of permanent neurologic damage.

THROMBOCYTOPENIA

Clinical Description

The term *thrombocytopenia* indicates decreased platelet numbers in the blood. Thrombocytopenia may stem from failure of platelet production,

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splenic sequestration of platelets, increased platelet destruction, increased platelet utilization, or dilution of platelets. If thrombocytopenia is severe enough, petechiae and subcutaneous hemorrhages (purpura) may occur. The cause of idiopathic thrombocytopenic purpura, a common form of thrombocytopenia, is not understood. Immunologic mechanisms may be responsible for thrombocytopenia, as described earlier for hemolytic anemia.

Descriptive Epidemiology

Thrombocytopenia is associated with a variety of causes and is not uncommon in pediatric practice. No population-based incidence or prevalence rates were identified for the pediatric population.

Evidence from Studies in Humans

Case Reports and Case Series

Hennessen and Quast (1979) reported on 149 infants experiencing adverse events following pertussis vaccination. All cases were reported to vaccine manufacturers in Switzerland or Germany. Two cases of thrombocytopenia were reported on the same day by one physician 4 weeks after vaccination of two infants.

A 16-month-old girl was hospitalized with thrombocytopenic purpura days after receiving a booster injection of DPT and OPV (Champsaur et al., 1982). The authors concluded after virologic, immunologic, and animal studies that the purpura was caused by a concomitant coxsackievirus B 5 infection.

Thirteen cases of thrombocytopenia (ICD 9 codes 287.3 and 287.5) following DPT vaccination were reported through the CDC's MSAEFI system from 1978 to 1990, a period in which approximately 80.1 million doses of DPT vaccine were administered through public mechanisms in the United States (**J.** Mullen, Centers for Disease Control, personal communication, 1990). Both cases of thrombocytopenia also received OPV at the time of DPT vaccination, and of the 11 cases of thrombocytopenic purpura, 6 cases also received OPV, 1 received MMR, and 4 received OPV plus MMR. No follow-up of the cases was made, and a physician's diagnosis was not required.

Summary

Information concerning the possible relation between vaccination with DPT or its pertussis component and thrombocytopenia is limited to 3 published cases and 13 additional cases reported through the CDC's MSAEFI

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system. The clinical presentation of thrombocytopenia limits the ability to establish whether exposure preceded the condition among these exposed cases. The specificity of association is also unestablished, given the multiple possible causes of thrombocytopenia. An immunologic basis might be proposed, but no experimental data exist to support an immunologic or other causal association.

Conclusion

There is insufficient evidence to indicate a causal relation between DPT vaccine or the pertussis component of DPT vaccine and thrombocytopenia.

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7

Evidence Concerning Rubella Vaccines and Arthritis, Radiculoneuritis, and Thrombocytopenic Purpura

ARTHRITIS

Clinical Description and Pathologic Aspects

Symptoms referable to the musculoskeletal system are among the most common side effects of rubella and of rubella vaccine. The general term for these symptoms, *arthropathy,* refers to any abnormality of the joints. Arthropathy encompasses arthralgia (subjective pain in a joint or joints), stiffness (with arthralgia, commonly referred to as rheumatism), and arthritis (objective findings of swelling, redness, heat, or limitation of motion). Arthralgia is more common than arthritis following natural rubella, with both being more common in adults than in children (Lee et al., 1960). Joint symptoms related to natural rubella or rubella vaccine usually begin within 1 week of the appearance of rash in wild-type rubella infection or within 10 to 28 days after immunization. The joints involved, in order of decreasing frequency, are fingers, knees, wrists, elbows, ankles, hips, and toes. The symptoms are frequently of sudden onset and can consist of prominent stiffness and pain only; however, warmth, redness, and effusions occur, especially in the knees, fingers, and wrists (Smith et al., 1987).

The subjective nature of arthralgia makes it a difficult entity to study. Evaluation of reports of arthritis as a possible adverse consequence of rubella vaccine is complicated by the fact that arthritis and arthralgia are commonly subsumed under the heading arthropathy or "joint manifestations."

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Descriptive Epidemiology

The prevalence of self-reported arthritis and arthralgia (rheumatism), without regard to cause, in the United States has been estimated from a number of national surveys, including the 1960-1962 National Health Examination Survey (National Center for Health Statistics, 1964), the 1971-1975 National Health and Nutrition Examination Survey (National Center for Health Statistics, 1973, 1978), and the 1987 and 1988 National Health Interview Surveys (National Center for Health Statistics, 1988, 1989). According to the 1988 National Health Interview Survey, approximately 13 percent of respondents surveyed reported currently having "arthritis of any kind or rheumatism." Prevalence rates increased with age, with approximately 0.2 percent of persons under age 18 years and 5.3 percent between ages 18 and 44 years reporting arthritis of any kind or arthralgia. Prevalence rates were higher in women of all ages, with 4.3 percent under age 45 years reporting these conditions in contrast to 2.5 percent of men in the same age group. Rates for whites and blacks under age 45 years—both sexes combined—are 3.7 and 2.4 percent, respectively. The combining of arthralgia and arthritis of any kind and the cross-sectional and self-reported nature of National Health Interview Survey data do not permit accurate assessment of the prevalence of chronic or recurrent arthritis in the U.S. population.

History of an Association with Rubella Vaccines

Acute arthralgia and arthritis following vaccination have been noted since the earliest studies of rubella vaccines (Barnes et al., 1972; Cooper et al., 1969; Horstmann et al., 1970; Lerman et al., 1971; Spruance and Smith, 1971; Thompson et al., 1971). These acute events have been associated to various degrees with all rubella vaccine strains and occur more frequently in adult women than in adult men or prepubertal children of either sex (Plotkin, 1988; Polk et al., 1982). Reports of chronic arthropathies following rubella vaccination have been fewer. In 1972, Spruance and colleagues reported recurrent joint symptoms in a group of children receiving one strain of rubella vaccine; however, it was not until the 1980s that more systematic investigation of the possible association of rubella vaccines with chronic arthritis was undertaken (e.g., Cunningham and Fraser, 1985; Tingle et al., 1983, 1985, 1986). The lack of controlled studies, coupled with continued anecdotal reports of chronic arthritis following rubella vaccination (ABC News "20/20" report; J. Hatem, York, Pennsylvania, personal communication, 1990; A. J. Tingle, University of British Columbia, personal communication, 1990), have maintained a level of concern over this possible association.

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Evidence from Studies in Humans

Acute Arthropathy and Arthritis

Case Series and Controlled Epidemiologic Studies There is a substantial body of evidence, both from controlled and noncontrolled studies in humans, relating rubella vaccine to acute arthropathy and arthritis. The earliest evidence derives from noncontrolled retrospective and prospective studies conducted in the late 1960s and early 1970s, the former generally designed to test the efficacy of various rubella vaccine strains, rather than their side effects, and the latter as part of the routine administration of the vaccine in population-based immunization campaigns (e.g., Austin et al., 1972; Balfour et al., 1976, 1980; Barnes et al., 1972; Cooper et al., 1969; Dudgeon et al., 1969; Fox et al., 1976; Freestone et al., 1971; Grand et al., 1972; Kilroy et al., 1970; Lerman et al., 1971; Monto et al., 1970; Rowlands and Freestone, 1971; Spruance and Smith, 1971; Swartz et al., 1971; Wallace et al., 1972; Weibel et al., 1972, 1980). The vaccines examined in these studies were the HPV-77 strain (no longer in use), developed in simian tissue culture and then grown for production in dog kidney (DK) culture or in duck embryo (DEV) culture; the Cendehill strain (in limited use now), developed in rabbit kidney tissue culture; and the RA 27/3 strain (most commonly used now), developed in human diploid cells (WI38).

These and more recent studies (e.g., Peltola and Heinonen, 1986; Polk et al., 1982; Valensin et al., 1987) provide generally consistent findings with respect to the acute arthropathy and arthritis observed following rubella immunization. These include the observation that arthropathy and, less commonly, arthritis occur rarely in children but occur in 10 to 40 percent of susceptible (seronegative for rubella at the time of immunization) postpubertal women. Occurrence of these reactions increases with age, and they are less frequent in men and prepubescent children. Rates of acute arthropathy and arthritis following rubella immunization differ by vaccine strain, with the HPV-77 (DK) variant producing the most joint manifestations in all age groups (Barnes et al., 1972; Spruance and Smith, 1971; Wallace et al., 1972). The HPV-77 (DEV) and RA 27/3 strains have also been observed to produce joint symptoms, but the symptoms are more akin to the reaction following natural disease, and the arthropathy is more likely to occur in adults than in children (Polk et al., 1982; Swartz et al., 1971; Weibel et al., 1972).

In one of the few double-masked controlled studies of joint reactions to rubella vaccine conducted to date, Polk and colleagues (1982) compared reactions in 112 adult, seronegative female employees of a Boston hospital receiving either the HPV-77 (DEV) or the RA 27/3 strain in response to a rubella outbreak. Allocation to the vaccines was haphazard, because the

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supply of the initial HPV-77 (DEV) vaccine was depleted midway through the immunization program and the RA 27/3 vaccine was substituted in its place. Fifty-nine of the 112 women received HPV-77 (DEV) vaccine and 53 received the RA 27/3 vaccine. Sixty women served as controls—that is, they received one or the other vaccine, but were seropositive for rubella at the time of vaccination. In the HPV-77 group, 29 percent (17 of 53) reported onset of joint manifestations and 15 percent (9 of 53) reported onset of arthritis within the first 6 weeks following vaccination. In the RA 27/3 group, 26 percent (14 of 53) reported joint manifestations and 11 percent (6 of 53) reported arthritis with onset within 6 weeks after vaccination. Among the controls, 3 percent (2 of 60) reported joint manifestations and none reported arthritis. Joint manifestations in the HPV-77 (DEV) group occurred later and lasted longer than those in the RA 27/3 group, but all cases recovered without sequelae. There were 8 days missed from work in the HPV-77 group, in contrast to 3 days in the RA 27/3 group. Using data from this study and from 22 studies published elsewhere, the authors estimated the frequencies of joint symptoms following administration of the four different vaccine strains to be as shown in Table 7-1.

The relationship of acute joint manifestations to age must be emphasized. Rubella vaccine-associated arthropathies occur rarely in prepubertal children. In one study of the HPV-77 (DEV) vaccine, none of 31 vaccinees under age 13 years experienced joint manifestations, whereas 25 percent (4 of 16) of women in their 20s and 50 percent (9 of 18) of those aged 25 to 33 had such symptoms (Swartz et al., 1971). A later study of the same vaccine strain in a larger number of subjects (Weibel et al., 1972) revealed similar results. None of 276 cases of acute joint manifestations occurred in persons under age 12 years, whereas 4 percent (6 of 157) of persons between ages

TABLE 7-1 Frequencies of Joint Symptoms in Adult Females Following Administration of Four Vaccine Strains

	Proportions (%) of Adult Females Developing Acute Arthritis or Arthralgia		
Vaccine	Pooled Proportion	95% Confidence Interval	No. of Studies Cited
HPV-77 (DK)	49	35-63	2
HPV-77 (DEV)	30	27-33	13
Cendehill	9	8-10	15
RA 27/3	14	13-15	9

SOURCE: Adapted from Polk et al. (1982).

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12 and 16, 9 percent (12 of 130) of persons between ages 16 and 20, 9 percent (6 of 65) of persons between ages 20 and 25, and 56 percent (14 of 25) of persons older than 25 years did. This study, unlike the previous one by Swartz and colleagues (1971), distinguished between acute arthritis and arthralgia and indicated that the former was rarer, did not occur before age 16 years, and was manifest in only 4 percent (7 of 178) of persons ages 16 through 25 years. Above age 25 years, however, acute arthritis was common, occurring in 46 percent (11 of 24) of women immunized.

In summary, these studies provide consistent evidence that acute arthropathy and, more rarely, acute arthritis can occur following rubella vaccination and that incidence rates are higher in women than in men and increase with age. None of these studies showed an association of rubella vaccines with chronic arthropathies or arthritis, but their generally limited sample sizes and lengths of study follow-up make it unlikely that if there were such an association it could have been detected. Only a few such studies have been conducted to date, and these are described below.

Chronic Arthritis

Case Reports and Case Series A case of acute arthritis following natural rubella that progressed to chronic arthritis was reported in 1968 by Martenis and colleagues, and it has been suggested that wild-type rubella virus might play a role in juvenile rheumatoid arthritis (Hart and Marmion, 1977; Martenis et al., 1968; Ogra et al., 1975). These suggestions have raised concern that a possible similar progression of acute to chronic arthritis following rubella immunization might also occur.

Lerman and colleagues (1971) reported a case of persistent arthritis 1 year after vaccination with HPV-77 (DE) strain, and Spruance and colleagues (1972) reported on 11 children suffering recurrent episodes of knee stiffness, sometimes referred to as "catcher's crouch" syndrome, 8 months after receiving HPV-77 (DK) vaccine. This syndrome has been considered to be caused by radiculoneuritis, rather than arthritis, as described later in this chapter. However, follow-up of the children 11, 48, and 66 months after vaccination indicated that 8, 4, and 3 (with 2 lost to follow-up), respectively, of the original 11 children continued to exhibit episodic morning stiffness in the knees (Spruance et al., 1977). One of the cases was evaluated by arthroscopy, and the synovium was found to be hypertrophied posteriorly; culture for rubella virus was negative. Eleven children with recurrent arthritis 36 months after vaccination with HPV-77 (DK) were reported by Thompson and colleagues in 1973, and other cases have been reported since then, some after immunization with the RA 27/3 strain (Tingle et al., 1979a,b, 1984, 1985, 1986; A. Tingle, British Columbia Children's Hospital, personal communication, 1990). Arthritis occurring first within 12 to

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21 days after rubella vaccination has been reported to persist for 4 to 7 years after receipt of the HPV-77 (DE) strain, for 2 years in one woman after receipt of the RA 27/3 strain (Tingle et al., 1985), and for 3.5 years in a second woman (Tingle et al., 1984). Two additional young adult women had recurrent arthritis or arthralgia (not otherwise defined) for 18 to 24 months after receipt of the RA 27/3 strain (Tingle et al., 1986).

As part of studies that began about a decade ago into the pathogenesis of the acute arthropathy following rubella immunization and the natural disease, Tingle and colleagues (1983) attempted to correlate arthropathy with specific antibodies to rubella. Seven women with recurrent arthritis were studied retrospectively, and 24 hospital personnel were studied prospectively. The standard assay for assessment of antibodies in the IgG and IgM fractions, hemagglutination inhibition (HAI), and a more sensitive enzyme linked immunosorbent assay (ELISA) were used to study antibody at 6 weeks and 6 months after immunization. There were no differences between those recipients who experienced joint manifestations and those who did not. Later, in 10 of 37 adult women volunteers who were seronegative by HAI testing and who developed acute arthritis after RA 27/3 vaccination, Tingle and colleagues (1983) detected prevaccination antibodies by the ELISA. On the assumption that the standard test (HAI) failed to detect antibodies in some preimmune individuals who tested positive by the more sensitive ELISA, the authors suggested that the acute arthropathy could be the result of a reinfection rather than a primary infection. Pursuing this hypothesis, Tingle and colleagues studied six women with recurrent chronic arthropathy, manifested by polyarticular arthritis beginning 12 days to 3 weeks after the immunization. Chronic arthritis was noted 2 years after vaccination in one woman receiving the RA 27/3 strain and 4 to 7 years after vaccination in three women receiving the HPV-77 (DE) strain. Another woman reported chronic arthralgia more than 6 years following receipt of the HPV-77 (DE) strain. Prevaccination sera of three women in this group were positive by ELISA; the sera of the other women were negative (Tingle et al., 1985).

In a later prospective study, Tingle and colleagues (1986) compared incidence rates in two groups: the first consisted of 23 women and 23 men, ages 11 to 54 years (mean age, 19.2 years), who had natural infection with wild-type rubella virus in 1983, all of whom underwent seroconversion. Arthritis (joint effusion, limitation of movement, heat, or erythema) and arthralgia, both acute and chronic, occurred more frequently following infection with wild-type rubella virus than it did following vaccination. In the women who had the natural infection, 52 percent (12 of 23) had acute arthritis and 13 percent (3 of 23) had arthralgia only. Among the men, 65 percent (15 of 23) had some joint manifestations, 9 percent (2 of 23) had arthritis, and 48 percent (11 of 23) had arthralgia only. These signs and symptoms became manifest within 7 to 10 days after the onset of the rash. Eighteen months

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later, 30 percent (7 of 23) of the women had joint manifestations; of these 7 women, 4 had arthritis and 3 had arthralgia. Among the men, 8 percent (2 of 23) had joint manifestations; of these 2 men, 1 each had arthritis or arthralgia. The second group consisted of 44 women students, ages 17 to 33 years (mean age, 23.1 years), given the RA 27/3 vaccine. They were examined at weekly intervals. Within 4 weeks after vaccination, 14 percent (6 of 44) had acute arthritis and 41 percent (18 of 38) had arthralgia only, for a total of 55 percent (24 of 44) of joint manifestations. Eighteen months later, 5 percent (2 of 44) had joint manifestations; it was not specified whether it was arthritis or arthralgia.

In a study of the 1985 epidemic of rubella, Tingle (A. J. Tingle, University of British Columbia, personal communication, 1991) examined 191 seroconverters, of whom 103 were men and 88 were women. Forty-four percent of the women (39 of 88) and 7 percent (7 of 103) of the men had acute arthritis. Twenty-four months later, 30 percent of the women still had joint manifestations; it was not specified whether it was arthritis or arthralgia.

In a retrospective analysis of vaccine reactions to the measles-mumps-rubella (MMR) vaccine administered to 700,000 children in Sweden, Taranger and Wiholm (1984) reported only one case of chronic arthritis. The patient was a 12-year-old boy who developed "juvenile rheumatoid arthritis" 2 years after receiving the vaccine. His HLA haplo-type was B27, which has been associated with chronic arthritis. The authors concluded that this case of arthritis was not causally related to the vaccine, but rather was coincidental.

Two hundred eighteen cases of arthritis (ICD 9 code 716.9) occurring within 28 days of immunization with rubella monovalent, measles-rubella (MR), or MMR vaccine were reported through the CDC's MSAEFI system from 1978 to 1990, a period in which approximately 28.8 million doses of rubella vaccines were administered through public mechanisms in the United States (J. Mullen, Centers for Disease Control, personal communication, 1990). Confirmation of these cases in the form of a physician's diagnosis was not required. Of these 218 cases, 43 (20 percent) cases received at least one other vaccine at the time of rubella immunization. One year after immunization, 13 (6 percent) of the original 218 cases were reported as "not recovered"[1]; an additional 15 cases were lost to follow-up at year 1.

[1] Caution is needed in interpreting this category, because cases of arthritis with a comorbidity for example, otitis media—reported at the time of initial immunization and persisting at 1 year would have been labeled "not recovered," even if the arthritis had resolved. Review of an earlier set of acute arthritis cases subsequently labeled "not recovered" at 1 year indicated that the majority were due to a persisting morbidity other than arthritis (J. Mullen, Centers for Disease Control, personal communication, 1991).

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Controlled Epidemiologic Study Polk and colleagues (1982), in the doublemasked, controlled comparison of joint reactions in 112 seronegative women receiving HPV-77 (DEV) or RA 27/3 vaccine described above, reported no cases of chronic or recurrent arthritis or arthralgia. However, the average length of study follow-up was only 6 weeks, and thus, recurrent cases might not have been detected.

Evidence from Studies in Animals

Data from experimental studies in animals are not available, since it has not been possible to develop an animal model for rubella infection.

Possible Mechanisms

A suggestion that joint involvement is somehow related to stage of the menstrual cycle has been made, but there is no evidence in support of this hypothesis (Best et al., 1974; Lerman et al., 1971; Swartz et al., 1971).

Pathogenesis of the joint involvement is apparently direct infection of the synovial membrane, inasmuch as the virus has been recovered from the joint fluid of patients with repeated episodes of arthritis for up to 3 to 4 months after vaccination with the HPV-77 strain (Ogra and Herd, 1971). This has also been true in cases of rubella caused by the wild-type strain of the virus (Ogra et al., 1975). Chantler, Tingle, and colleagues have isolated rubella virus from peripheral blood mononuclear leukocytes of several patients with persistent post-rubella vaccine arthritis (Chantler et al., 1981, 1982; Tingle et al., 1985). Two of these patients had received the RA 27/3 strain. In one study, rubella virus was grown from the leukocytes of five of six women with arthritis for up to 5 years after receiving the HPV-77 (DEV) vaccine (Chantler et al., 1982). In a separate study, rubella virus was isolated from mononuclear leukocytes from blood, synovial fluid, or both in 7 of 19 children with chronic arthritis of unknown cause (Chantler et al., 1985). There was no history of recent rubella infection or rubella vaccination, although most of the patients had received HPV-77 (DEV) rubella vaccine in the past. The infecting rubella strain (vaccine versus wild type) was not identified and has not been identified in the other subjects reported to have arthropathy after rubella vaccination.

The role of circulating immune complexes (CICs) in the pathogenesis of rubella arthritis has been suggested in one study, in which 11 of 33 (33 percent) children with postvaccinal arthritis had CICs containing rubella antigen, in contrast to only 3 of the 19 (16 percent) who did not experience arthralgia (Coyle et al., 1982). In a study of adults—44 women vaccinated with the RA 27/3 strain and 23 men and 23 women convalescing from wild-

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type rubella infection—no statistically significant differences were found in the CICs between those who had joint manifestations and those who did not. The authors concluded that their data "do not support a direct role for raised CIC levels in the pathogenesis of rubella-associated arthritis or arthralgia" (Singh et al., 1986, p. 115).

Blood lymphocytes from 15 children who had *acute* arthralgia or arthritis after rubella vaccination exhibited depressed transformation responses to rubella virus compared with the responses of lymphocytes from controls who had no complications following vaccination. This finding suggests that arthritis could result from a selective depression in the subject's cell-mediated immunity at the time of the initial encounter with the virus (Chiba et al., 1976). On the other hand, the lymphocyte responses to rubella antigen in six adult women who had had *recurrent* arthritis for at least 9 months after HPV-77 (DEV) rubella vaccination were relatively elevated (Ford and Tingle, 1980; Tingle et al., 1983). The antigens used in the two populations may have differed. However, the two reports are not necessarily at variance, because normal or accentuated cell-mediated immunity to the virus would be expected over the course of an intermittent, recurrent infection in an otherwise normal individual. In any event, it is not clear at this time whether patients who develop arthritis, acute or persistent, after rubella vaccination have a specific immune system defect that prevents their systems from clearing the virus normally.

Summary

Acute Arthropathy and Arthritis

The body of evidence concerning the possible relation between rubella vaccine and acute joint manifestations includes a number of case series and experimental studies comparing different rubella vaccine strains. These studies indicate a consistent, direct relation of all rubella vaccine strains both to acute arthropathy and to acute arthritis, with the discontinued HPV-77 vaccines being associated with the highest reaction rates. Incidence rates following administration of the current RA 27/3 vaccine strain to adult women average 13 to 15 percent. Average rates are much lower in children, increase with age, and are higher in women than in men. Both acute arthropathy and acute arthritis are conditions whose diagnoses are reasonably reliable; thus, the vaccine exposure probably truly preceded onset of these adverse events in most cases. Although acute joint manifestations can result from a number of different causes, their association with natural rubella infection and the recovery of rubella virus from the joint fluid of persons experiencing acute arthropathy or arthritis support the biologic plausibility of a relation with attenuated rubella virus vaccine.

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Chronic Arthritis

The body of evidence concerning the possible relation between vaccination with MMR vaccine or its rubella component and chronic arthritis is limited. There are several case reports and case series, one comparative case series, and one double-masked controlled study. Most of the patients described in these publications had received the HPV-77 (DEV) strain of vaccine. Three or four cases of chronic arthritis following immunization with the RA 27/3 strain have been reported in the literature. A large number of unconfirmed cases of chronic arthritis following administration of RA 27/3 strain have been reported to a single institution. All of the cases were adult females.

In the comparative case series, Tingle and colleagues (1986) reported incidence rates of joint manifestations in 67 young adult women following either natural infection with wild-type rubella virus or receipt of the RA 27/ 3 strain. They reported recurrent arthropathy more than 18 months after either natural infection or vaccination, with incidence rates of 30 and 5 percent (two patients), respectively. The latter two patients had "arthritis or arthralgia" that were not otherwise described (Tingle et al., 1986, p. 113). In a double-masked study of 112 women receiving one of two rubella vaccine strains, Polk and colleagues (1982) reported no cases of chronic or recurrent arthritis or arthralgia. However, the length of the follow-up was only 6 weeks, and cases that might have recurred later would not have been detected. In both studies, the nature of the comparison groups precludes estimation of relative risks for exposed versus nonexposed groups.

One of the women with chronic arthritis after vaccination with the RA 27/3 strain had rubella virus isolated from blood mononuclear cells and from breast milk 7 to 9 months postvaccination. A second woman who reported recurrent arthralgia 2 years and 9 months after receipt of the RA 27/3 vaccine also had rubella virus isolated from peripheral blood leukocytes (Tingle et al., 1985).

The current lack of understanding of the natural history and multiple causes of arthritis and the lack of distinction between cases of arthralgia and arthritis in some reports diminish the specificity of the putative association. It is also difficult to establish whether the vaccination truly preceded the adverse event in many cases. The association of chronic arthritis with natural rubella infection and the recovery of a rubella virus from leukocytes from peripheral blood and synovial fluid of women with prolonged arthritis following rubella vaccination suggest, however, a biologically plausible relation between rubella vaccine and chronic arthritis. Moreover, a few cases have been documented in which arthritis, which was ultimately judged to be chronic, began 2 to 3 weeks after vaccination, which is the incubation period of natural rubella and the time period in which the vaccine strain can be isolated (beginning about 1 week after injection).

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Conclusions

The evidence indicates a causal relation between the currently used rubella vaccine strain (RA 27/3) and acute arthritis. Incidence rates are estimated to average 13 to 15 percent among adult women following RA 27/3 immunization with much lower levels noted among children, adolescents, and adult men.

The evidence is consistent with a causal relation between the currently used rubella vaccine strain (RA 27/3) and chronic arthritis in adult women, although the evidence is limited in scope and confined to reports from one institution.[2] Prospective, double-masked, controlled trials in which subjects are followed for at least 12 months after rubella vaccination are needed to establish this biologically plausible relation. Additional elements of a definitive study would include attempts to isolate rubella virus from the synovial fluid of affected joints of cases of arthropathy and arthritis and molecular-genetic analysis to determine whether the isolated strain is the one that was injected, a strain derived from the injected strain, or an unrelated strain.

RADICULONEURITIS AND OTHER NEUROPATHIES

Clinical Description

Radiculoneuritis is a convenient term used to describe a combination of peripheral neuropathy with dorsal root (spinal nerve) pain. The "catcher's crouch" syndrome, which is knee pain that is somewhat relieved by crouching, has been suggested as an example. This and other related conditions, including polyneuropathy, paresthesias, and carpal tunnel syndrome, occur sporadically in association with natural rubella infection (Bailey, 1962; Brodribb, 1963; Courtenay, 1962; Haire and Hadden, 1970; Heathfield, 1962; Hodges, 1940; Moylan-Jones and Penny, 1962; Witney, 1940).

Descriptive Epidemiology

Radiculoneuritis is uncommon, but it can occur at any age. Incidence rates of related neurologic conditions have been published for defined populations (Beghi et al., 1982, 1985; Stevens et al., 1988).

[2] When all rubella vaccine strains, including the discontinued HPV-77 (DK) and HPV-77 (DEV) strains, are considered as a group, the evidence indicates a causal relation with chronic arthritis in adult women.

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Evidence from Studies in Humans

Case Reports and Case Series

There have been reports of cases of paresthesias (Chin et al., 1971; MortonKute, 1985; Tingle et al., 1985) and pain involving the arms and the knees, the latter giving rise to the "catcher's crouch" syndrome (Deinard et al., 1973; Spruance et al., 1972; Thompson et al., 1971) following rubella vaccination. Three of these occurred after receipt of the RA 27/3 strain (MortonKute, 1985; Tingle et al., 1985). Other related conditions, reported in individual cases, are carpal tunnel syndrome following both HPV-77 (DK) strain (Chin et al., 1971; Thompson et al., 1971) and RA 27/3 strain (Tingle et al., 1985), two cases of optic neuritis following administration of the HPV-77 vaccine in one case (Kazarian and Gager, 1978) and an unstated rubella vaccine in the other (Kline et al., 1982), three cases of transverse myelitis after Cendehill vaccine, a vaccine of unknown rubella strain, and one unstated vaccine (Behan, 1977; Holt et al., 1976), and two cases of Guillain-Barrè syndrome after MMR vaccine that included the HPV-77 (DEV) strain (Gunderman, 1973).

A case of peripheral neuropathy following rubella immunization was reported in 1984 by Taranger and Wiholm (1984). The issue of peripheral neuropathies related to rubella vaccines was reviewed in an article by Schaffner and colleagues (1974), who examined reports of 299 cases. The study concentrated on 32 children with neuropathies who were followed for up to 32 months. Twenty of these children recovered fully and had no recurrences; 10 had minor complaints that persisted during the follow-up period, and 2 developed recurrences of the "catcher's crouch" syndrome after 32 and 33 weeks, respectively. The majority of the 299 total cases and the 32 cases reviewed in detail followed administration of the HPV-77 (DK) vaccine. The authors estimated the rate of these complications to be 2.2 per 1,000 doses and 0.1 per 1,000 doses for the HPV-77 (DK) and the HPV-77 (DEV) strains, respectively.

One case of radiculitis (ICD 9 code 723.4) occurring within 28 days of immunization with MR vaccine was reported through the CDC's MSAEFI system from 1978 to 1990, a period in which approximately 28.8 million doses of rubella-containing vaccine were administered through public mechanisms in the United States (J. Mullen, Centers for Disease Control, personal communication, 1990). No follow-up of the case was made, and a physician's diagnosis was not required.

Summary

The body of evidence concerning the possible relation between immunization with monovalent rubella or MMR vaccine and radiculoneuritis and

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other neuropathies is limited to case reports and case series. Frequencies of peripheral neuropathies have been estimated from case series to be 2.2 and 0.1 per 1,000 doses of HPV-77 (DK) and HPV-77 (DEV) vaccines, respectively. The lack of comparison groups in these studies precludes estimation of the relative risks of neuropathies in relation to these strains. For the RA 27/3 strain currently in use in the United States, rates of radiculoneuritis and other neuropathies following its receipt are not available. Three cases have been reported after administration of this vaccine strain. Evidence for biologic plausibility consists of the observation that radiculoneuritis and other neuropathies can occur, though uncommonly, after natural infection with wild-type rubella virus.

Conclusion

There is insufficient evidence to indicate a causal relation between the currently used rubella vaccine (RA 27/3) and radiculoneuritis and other neuropathies.

THROMBOCYTOPENIC PURPURA

Clinical Description

Thrombocytopenic purpura presents as petechiae, purpura, or mucosal bleeding secondary to decreased numbers of platelets in the blood. It has been reported in association with congenital and acquired rubella (Heggie and Robbins, 1969; Morse et al., 1966). The estimated incidence is 1 case of thrombocytopenia in 3,000 cases of natural rubella (Bayer et al., 1965). This complication is not unique to natural rubella, because it is estimated that 70 percent of cases of thrombocytopenia follow various viral illnesses (Cohn, 1976). Possible mechanisms for virus-induced thrombocytopenic purpura include generation of antibodies to a viral antigen that cross-react with some similar antigen on the platelet, resulting in platelet destruction (Baldini, 1966). The virus itself or immune complexes that include the virus might damage or otherwise modify the platelet surface, making it susceptible to removal by the spleen. The contribution of antibody-mediated platelet dysfunction to bleeding in patients with idiopathic thrombocytopenic purpura, however, remains to be established (George and Shattil, 1991).

Descriptive Epidemiology

Thrombocytopenic purpura can occur at any age. No population-based incidence or prevalence rates were identified.

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Evidence from Studies in Humans

Case Reports

Evidence for thrombocytopenic purpura following rubella immunization is rarer than that for natural infection and is limited to isolated case reports. Bartos (1972) described a case of thrombocytopenic purpura in a 26-year-old female immunized with a monovalent vaccine. Four other cases of thrombocytopenic purpura have been reported in a 1-year-old girl (Sharma, 1973), a 16-month-old boy and a 16-month-old girl, both of whom received the RA 27/3 strain (Azeemuddin, 1987), and an 18-month-old girl (Neiderud, 1983) following administration of the combined MMR vaccine. All five patients, who were asymptomatic for viral illness prior to immunization, developed petechiae, purpura, or mucosal bleeding 10 days to 3 weeks postimmunization. Platelets were markedly reduced, but peripheral red and white blood cell counts and morphology were normal. In the patients tested, megakaryocytes were usually increased, with an otherwise normal bone marrow. In all cases, the postimmunization thrombocytopenia was transient. No virus-containing immune complexes or anti-platelet antibodies were demonstrated in these cases.

Twenty-six cases of thrombocytopenic purpura occurring within 28 days of immunization with rubella-containing vaccines were reported through the CDC's MSAEFI system from 1978 to 1990, a period in which approximately 28.8 million doses of rubella vaccine were administered through public mechanisms in the United States (J. Mullen, Centers for Disease Control, personal communication, 1990). They were reported as idiopathic (ICD 9 code 287.3). All but 1 of the 26 cases received at least one other antigen at the time of rubella immunization. No follow-up of the cases was made, and a physician's diagnosis was not required.

The report "Compensation for Vaccine-Related Injuries" (Office of Technology Assessment, 1980) lists thrombocytopenia as a "possible" adverse event after immunization, but cites no reference or evidence for this conclusion. The Meruvax II (Rubella Virus Vaccine Live, Merck Sharp & Dohme) package insert states, "In view of the decreases in platelet counts that have been reported, thrombocytopenic purpura is a theoretical hazard," but it also cites no evidence for this statement (Merck Sharp & Dohme, West Point, Pennsylvania).

Summary

The body of evidence concerning the possible relation between vaccination with the RA 27/3 rubella vaccine strain and thrombocytopenic purpura is limited to two or three cases reported in the literature and unconfirmed

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cases reported through the CDC's MSAEFI system. The unambiguous clinical presentation of thrombocytopenic purpura would suggest that the vaccine exposure truly preceded the event. The relation is biologically plausible because thrombocytopenic purpura is believed to occur rarely as a complication of natural rubella infection.

Conclusion

There is insufficient evidence to indicate a causal relation between the currently used rubella vaccine (RA 27/3) and thrombocytopenic purpura.

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Afterword on Research Needs

In the course of its review, the committee found many gaps and limitations in knowledge bearing directly and indirectly on the safety of vaccines. Such shortcomings relate, for example, to pathologic mechanisms of specific infectious agents, the molecular basis of vaccine injury, and the natural history of conditions such as encephalopathy, mental retardation, and chronic arthritis. Many of the reports of case series suffer from inadequate or inconsistent case definitions, variable details about cases, inclusion of nonrepresentative case groups, and failure to consider potential confounding variables or biases. In addition, existing surveillance systems of vaccine injury have limited capacity to provide persuasive evidence of causation. Many of the population-based epidemiologic studies are too small or have inadequate lengths of follow-up to have a reasonable chance of detecting true adverse effects, unless these effects are large or occur promptly and consistently after vaccination. If research capacity and accomplishment in this field are not improved, future reviews of vaccine safety will be similarly handicapped.

The committee found few experimental studies published in relation to the number of epidemiologic studies published. As noted in Chapter 2, withholding of vaccines can be regarded as unethical. Although the committee was not charged with, and has not attempted, full consideration of the kinds of studies that would be both ethical and especially informative, either in the areas of vaccines that it has been charged to study or more

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generally, it recognizes, nevertheless, that opportunities may exist for informative experiments in human populations that take advantage of the possibility of using alternative schedules for administration of vaccines.

A careful review is needed to identify what sorts of questions might be best answered by further investigations and which kinds of studies could be carried out economically. The availability and introduction of new forms of pertussis vaccine, for example, could offer valuable opportunities for comparison of vaccine safety as well as efficacy. The committee is not in a position to make specific recommendations, but its experience points to fresh possibilities and to the need for such a review.

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Glossary of Terms

B

Adsorbed vaccine.	See Vaccine, pertussis v., adsorbed [USP].
Anaphylaxis.	Generalized anaphylaxis is an acute, often explosive, systemic reaction characterized by pruritus, generalized flush, hives, respiratory distress, and vascular collapse and, occasionally, by seizures, vomiting, abdominal cramps, and incontinence. It occurs in a previously sensitized person who again receives the sensitizing antigen.
Arthralgia.	Pain in a joint or joints.
Arthritis.	Inflammation of a joint or joints detectable as swelling, redness, and tenderness.
Arthropathy.	Any joint disease.
Aseptic meningitis.	An inflammation of the meninges with typical changes in the cerebrospinal fluid, including increased numbers of white blood cells, normal glucose, and absence of bacteria on examination and culture. The most common causes include viral infection and noninfectious causes such as lead poisoning.
Attention deficit disorder (ADD).	ADD is a neurobehavioral disorder in children characterized by three cardinal symptoms: inattention, hyperactivity, and impulsivity. Many children with ADD also exhibit symptoms of a learning disability, and many children with reading disabilities also exhibit evidence of ADD.

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Attributable fraction (exposed). The attributable fraction among exposed individuals is the proportion by which the incidence rate of the outcome among those exposed would be reduced if the exposure were eliminated. It is assumed that causes other than the one under investigation have had equal effects on exposed and unexposed groups and that the effects of exposures are additive.

Attributable fraction (population). The attributable fraction in the population is the proportion by which the incidence rate of the outcome in the entire population would be reduced if the exposure were eliminated. It is assumed that causes other than the one under investigation have had equal effects on the exposed and unexposed groups and that the effects of exposure are additive.

Attributable risk (exposed). The rate of a disease or other outcome in exposed individuals that can be attributed to the exposure. This measure is estimated by subtracting the rate of the outcome (usually incidence or mortality) among unexposed individuals from the rate among exposed individuals. It is assumed that causes other than the one under investigation have had equal effects on exposed and unexposed groups and that the effects of different causes are additive. This term is often used, incorrectly, to denote the attributable fraction among exposed individuals and in the population.

Autism. The condition of being dominated by subjective, self-centered trends of thought or behavior that are not subject to correction by external information. One form, *infantile autism,* is a condition of the early years of life characterized by failure to relate in the usual way to people and situations and by repetitive activities, developmental language disorders, and a marked inability to adjust socially.

Bias. Deviation of results or inferences from the truth, or processes leading to such deviation. Any trend in the collection, analysis, interpretation, publication, or review of data that can lead to conclusions that are systematically different from the truth. Not to be confused with *prejudice* or *partisan point of view,* as is the conventional usage.

Case-comparison study. (Syn: case-control study). A study that starts with the identification of persons with the disease or condition (adverse event) of interest and a suitable control (comparison) group of persons without the disease. The relation of an attribute (e.g., immunization) to the disease is examined by comparing the diseased and nondiseased groups with regard to how frequently the attribute is present, or if quantitative, the levels of the attribute, in each of the groups.

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Cohort study. (Syn: prospective, follow-up study). A 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 probability of occurrence of a given disease (adverse event) or other outcome. The essential feature of the cohort design is observation of the population for a sufficient length of time to generate reliable incidence or mortality rates.

Controlled study. Controlled studies are studies that use a comparison group that differs from the subjects of the study in either disease experience (outcome) or allocation to a regimen (exposure). Allocation to a regimen can be random, as in a randomized clinical trial or study, or nonrandom, as in an observational cohort study or a case-control study.

DPT vaccine. See Vaccine, DPT v.

DTP vaccine. See Vaccine, DTP v.

Encephalopathy. Refers to a variety of conditions affecting the brain resulting in alterations in the level of consciousness, ranging from stupor to coma. At times, febrile seizures, afebrile seizures, and epilepsy have been considered components of encephalopathy (see Chapter 4).

Erythema multiforme. An inflammatory eruption characterized by symmetrical erythematous, edematous, or bullous lesions of the skin or mucous membranes.

Experimental study. A study in which a population is selected for a planned trial of a regimen (e.g., immunization) whose effects are measured by comparing the outcome of the regimen in the experimental group with the outcome of another regimen in a control group. Allocation of individuals to experimental or control groups is ideally by randomization.

Guillain-Barrè syndrome. An acute, usually rapidly progressive form of polyneuropathy characterized by muscular weakness and mild distal sensory loss.

Hemolytic anemia. Anemia caused by lysis of red blood cells, which leads to shortened in vivo survival of red blood cells, and an inability of the bone marrow to compensate for their decreased life span.

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Hyperactivity (hyperkinesis). See Attention deficit disorder (ADD). Hypotonicity, hypotonia. Decreased muscle tone.

Hypsarrhythmia. An electroencephalographic (EEG) abnormality observed in infants, with random, high-voltage slow waves and spikes that arise from multiple foci and spread to all cortical areas. This abnormal EEG pattern may be manifested clinically by spasms or quivering spells (myoclonus) and may be associated with mental retardation.

Immunization. The process of rendering a subject immune or of becoming immune. In this report the term has been accepted to be synonymous with *vaccination.* See Vaccination.

active i. Inoculation with a specific antigen to induce an immune response.

passive i. The conferral of specific immunity by the administration of sensitized lymphoid cells or serum from immune individuals.

Infantile spasms. A condition characterized by sudden flexion of the arms, forward flexion of the trunk, and extension of the legs. The attacks last only a few seconds but may be repeated many times a day. They are restricted to the first 3 years of life, often to be replaced by other forms of seizures.

Juvenile diabetes. An autoimmune disease characterized most frequently by low or absent levels of circulating endogenous insulin (more properly called *insulin-dependent diabetes mellitus*).

Learning disability. A developmental disability defined by the discrepancy between a child's ability and his or her achievement. Learning disability may occur in any domain, but it is most commonly observed in reading. The terms *reading disability* and *dyslexia* are often used interchangeably.

Masked study. (Syn: blind or blinded study). A study in which an observer(s) and/or subjects are kept ignorant of the group to which subjects are assigned, as in an experiment, or of the population from which the subjects come, as in a nonexperimental study. When both observer and subjects are kept ignorant, the study is referred to as a *double-masked study.* The intent of masking is to keep subjects and/or investigators unaware of knowledge that might introduce bias and, thus, eliminate the possible effects of bias.

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Monitoring System for Adverse Events Following Immunization (MSAEFI).	A passive surveillance system designed and monitored by the Centers for Disease Control for the purpose of collecting nationwide data on adverse events temporally associated with receipt of vaccines purchased with federal, state, or local government funds.
MSAEFI.	See Monitoring System for Adverse Events Following Immunization.
Noncontrolled study.	Noncontrolled studies are those that do not use a comparison group that differs from the subjects of the study in either disease experience (outcome) or allocation to a regimen (exposure). Examples include individual and comparative case series, case reports, and anecdotes.
Odds ratio (OR).	In studies of adverse events following immunization, the OR generally refers to the exposure-odds ratio, which, for a set of case-comparison data, is the ratio of the odds in favor of exposure among the cases to the odds in favor of exposure among noncases. Under certain circumstances, usually met in the study of vaccine-related adverse events, the OR is considered a good estimate of the relative risk.
Parapertussis.	An infectious disease caused by *Bordetella parapertussis* , a coccobacillus closely resembling *Bordetella pertussis.* Parapertussis is clinically indistinguishable from pertussis, but it is usually milder and less often fatal.
Peripheral mononeuropathy.	A syndrome of sensory, motor, reflex, and vasomotor symptoms, singly or in any combination, produced by disease of a single peripheral nerve.
Pertussis (whooping cough).	An infectious disease caused by *Bordetella pertussis,* a small, nonmotile, gram-negative coccobacillus. The disease is characterized by catarrh of the respiratory tract and peculiar paroxysms of cough, ending in a prolonged crowing, or whooping, respiration. The disease is most frequently encountered in children, is much more prevalent in cold weather, and is very contagious.
Radiculoneuritis.	A combination of peripheral neuropathy with dorsal root (spinal nerve) pain.
Relative risk (RR).	The ratio of the risk of disease or death among the exposed to the risk among the unexposed. Generally derived from cohort studies.

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Reye syndrome. An acute and often fatal childhood syndrome of encephalopathy and fatty degeneration of the liver, marked by rapid development of brain swelling, hepatomegaly, and altered levels of consciousness.

Rubella (German measles). A mild viral infection caused by an RNA virus classified as a togavirus. The infection is characterized by a pink, discrete, and confluent macular exanthem and is usually preceded by rhinorrhea, sore throat, and bulbar and, occasionally, palpebral conjunctivitis. Arthralgia is common, and monarticular arthritis occurs in 20 percent of patients, more so adults than children. Transplacental infection of the fetus in the first trimester produces developmental abnormalities of the heart, eyes, brain, bone, and ears in up to 40 percent of cases.

Sudden infant death syndrome (SIDS). The unexpected and unexplained death of an apparently well, or virtually well, infant. SIDS is the most common cause of death of infants between ages 2 weeks and 1 year, accounting for one-third of all deaths in this age group.

Thrombocytopenia. A decrease in the number of platelets, the cells involved in clotting. Thrombocytopenia may stem from failure of platelet production, splenic sequestration of platelets, increased platelet destruction, increased platelet utilization, or dilution of platelets.

Thrombocytopenic purpura. Severe thrombocytopenia characterized by mucosal bleeding and bleeding into the skin in the form of multiple petechiae, most often evident on the lower legs, and scattered small ecchymoses (bruises) at sites of minor trauma. In children, idiopathic thrombocytopenic purpura is usually self-limiting and follows a viral infection.

Vaccination. Inoculation with a vaccine for the purposes of inducing immunity. In this report the term has been accepted to be synonymous with immunization. See Immunization.

Vaccine. A material containing live attenuated or killed microorganisms, or constituents of microorganisms, capable of eliciting protection against infection.

DPT v. A trivalent vaccine containing diphtheria, pertussis, and tetanus.

DTP v. See DPT vaccine.

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MMR v.	A sterile, lyophilized trivalent vaccine containing attenuated measles (rubeola), mumps, and rubella viruses.
pertussis v. [USP].	A sterile bacterial fraction or suspension, in a sodium chloride solution or other suitable diluent, of killed pertussis bacilli of a strain or strains selected for high antigenic efficiency. It is an active immunizing agent against pertussis.
pertussis v., adsorbed [USP].	A sterile bacterial fraction or suspension, in a suitable diluent, of killed pertussis bacilli of a strain or strains selected for high antigenic efficiency and precipitated or adsorbed by the addition of aluminum hydroxide or aluminum phosphate and resuspended. It is an active immunizing agent against pertussis.
rubella v.	A sterile preparation of live attenuated rubella virus.

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Appendixes

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A

Strategies For Gathering Information: Adverse Effects of Pertussis and Rubella Vaccines

LITERATURE SEARCHES

Electronic Data Bases

Because an important aspect of this study was to examine available information about specific adverse effects of pertussis and rubella vaccines, the committee undertook an extensive search of relevant data bases. Searches were conducted in data bases available through Dialog, a data base vendor. Eighteen data bases were searched in all. Six of these were primarily biomedical: Medline, EMBase, BIOSIS, Life Sciences Collection, Clinical Abstracts, and De Haen Drug Data. Two were industry oriented: Pharmaceutical News Index and International Pharmaceutical Abstracts. Two others were primarily agricultural but included world health materials: AGRICOLA and Agris International. Six were either business or general news data bases: ABI/Inform, Trade & Industry Index, Magazine Index, Courier Plus, Newspaper Index, and New search. The final two data bases covered legal and regulatory material: Diogenes and the Legal Resource Index. Each data base was searched in its entirety.

The first step was a broad, but targeted, search of the National Library of Medicine's Medline. A simple combination of the descriptors (subject headings) *pertussis vaccine* or *rubella vaccine* and the subheading *adverse effects* produced 589 articles on pertussis vaccine and 363 articles on rubella vaccine. Comparable searches were then done in the other 17 data bases, using

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using search strategies most appropriate for each. The exact choice of terms depended on the particular data base, but all terms related to the concepts of vaccines and adverse effects. For example, "whooping cough" might have been used instead of (or in addition to) "pertussis," or "reactions" might have been used instead of (or in addition to) "adverse effects."

To further ensure inclusion of relevant material, the two medical files (Medline and EMBase) were searched using combinations of the vaccine terms with various specific medical terms or conditions. For pertussis vaccine, these terms were *anemia, hemolytic; spasms, infantile; Reye syndrome; peripheral nerve disease; sudden infant death; meningitis, aseptic; diabetes mellitus; autism; learning disorders* or *dyslexia; hyperkinesis; brain; convulsions; encephalitis;* and *epilepsy.* For rubella vaccine, the specific terms used were *polyradiculoneuritis* and *arthritis.*

Searches were later conducted for the adverse events added to the committee's charge after the project was under way. For pertussis vaccine, the added adverse events were *anaphylaxis; erythema multiforme* or other rash; *Guillain-Barrè syndrome,* including *mononeuropathy* and *polyneuropathy;* protracted inconsolable *crying* or *screaming; thrombocytopenia;* and *shock* or *"unusual shock-like state"* with *hypotonicity, hyporesponsiveness,* and short-lived *convulsions,* usually *febrile.* For rubella vaccine, the additional adverse event was *thrombocytopenic purpura.* These searches were conducted in a manner similar to those described above.[1]

For the searches in the two medical data bases, where the structure of the data base makes it possible, items found were sorted according to whether they dealt with human or animal subjects. Review articles were also noted.

As lists of citations were generated by computer literature searches, staff, committee members, or both examined them and ordered abstracts of any that concerned the issues or conditions being examined by the committee. Upon receiving the abstracts, a further determination was made by staff and committee as to whether a particular article might contain information pertinent to the committee's task. Articles were then obtained for each selected abstract, and copies were distributed to the appropriate committee members.

OTHER SOURCES

Other sources of information were used by the committee. These included reference lists; presentations to the committee at its public meeting,

[1] A more detailed document entitled "Searches of Electronic Data Bases: Adverse Events Following Pertussis and Rubella Vacination" is available from the National Technical Information Service, 5285 Port Royal Road, Springfield, Virginia 22161 (703-487-4650). Resumès of the librarian who carried out the searches and of the manager of the National Research Council Library are included.

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workshop, and committee meetings; and individuals representing organizations with a special interest in the committee's task.

Reference Lists

Additional information sources included the reference lists of the articles obtained by the committee and staff. The procedures for obtaining abstracts and subsequent pertinent articles was the same as that described above. Particular attention was paid to citations in review articles, in books and reports with extensive reference lists (e.g., *DPT: A Shot in the Dark* [Coulter and Fisher, 1985, New York: Harcourt Brace Jovanovich] and *Vaccine Supply and Innovation* [Institute of Medicine, 1985, Washington, DC: National Academy Press]) and in papers submitted by presenters at the committee's public meeting on January 10, 1990, and its workshop on May 14, 1990 (see boxes).

Presentations

Public Meeting (January 10, 1990)

The committee held a public meeting, Adverse Consequences of Pertussis and Rubella Vaccines, on January 10, 1990, in Washington, D.C. Notices of the meeting were sent to more than 800 people. Fifteen individuals made presentations at the public meeting (see box), which was attended by approximately 150 people.

Workshop (May 14, 1990)

The committee held a workshop, Possible Adverse Consequences of Pertussis and Rubella Vaccines, on May 14, 1990, in Washington, D.C. Approximately 100 people attended. Eleven invited speakers made presentations at the workshop (see box).

Committee Meeting (May 15, 1990)

On May 15, 1990, the committee heard a presentation from Jeanette Wilkins, Professor of Pediatrics and Orthopedics, University of Southern California School of Medicine, entitled "Is Pertussis Whole-Cell Vaccine a Direct Toxin?" Dr. Wilkins followed up her presentation by sending the committee an extensive bibliography of citations on pertussis vaccine and its possible adverse effects.

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BOX 1

Presentations Made to the Committee, Public Meeting, January 10, 1990.

Phillip S. Berry, attorney, Oakland, California. Statement of Phillip S. Berry and Ralph A. Cohen to Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines.

Richard V. Colan, Wauwatosa, Wisconsin. Presentation to the National Academy of Sciences, Institute of Medicine Committee on the Nature and Rates of Adverse Reactions to Pertussis and Rubella Vaccines.

Harris L. Coulter. On Ascertaining the Prevalence of Vaccine Damage (statement submitted to committee prior to public meeting but not presented in person).

Charles A. Dinarello, Tufts University School of Medicine, Boston. Biological Effects of Endotoxin.

Mark R. Geier, medical/legal consultant, Silver Spring, Maryland. Endotoxin in DPT Vaccines.

Marjorie Grant, Determined Parents to Stop Hurting Our Tots (DPTSHOT), Beaver Dam, Wisconsin. Statement at Public Meeting for Comments on Pertussis and Rubella Vaccines.

Rajesh K. Gupta, National Institute of Child Health and Human Development, Bethesda, Maryland. Adverse Reactions After Injection of Adsorbed Diphtheria-Pertussis-Tetanus (DPT) Vaccine Are Not Due Only to Pertussis Organisms or Pertussis Components in the Vaccine.

Erik L. Hewlett, University of Virginia, Charlottesville. Pertussis Vaccine Encephalopathy.

Michael Hugo, attorney, Boston. Statement at Institute of Medicine Public Meeting, January 10, 1990.

Edward A. Mortimer, Jr., Case Western Reserve University School of Medicine, Cleveland. The Epidemiologic Evidence Relating DTP to Acute Encephalopathy, Infantile Spasms and the Sudden Infant Death Syndrome.

Georges Peter, Rhode Island Hospital, Providence. Possible Adverse Consequences of Pertussis Vaccine: Seizures and Epilepsy.

Stanley A. Plotkin, Children's Hospital of Philadelphia. Presentation at Institute of Medicine, January 10, 1990.

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Jeffrey H. Schwartz, attorney, Washington, D.C. Testimony on Behalf of Dissatisfied Parents Together (DPT) before the Institute of Medicine Committee on Adverse Consequences of Childhood Vaccines, January 10, 1990.

Mark E. Thoman, Iowa Poison Control Center, Des Moines. The Clinical Composite of Severe Pertussis Vaccine Reactions Following DPT Vaccine Inoculation(s).

Arthur C. Zahalsky, Southern Illinois University, Edwardsville. Scientific Basis for Including Tests of Acute Phase Reaction Products in Clinical Protocols Designed to Investigate the Cause of Adverse Reactions Following Inoculation (s) in Infants with DTP (ads.) Vaccine.

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BOX 2

Presentations Made to the Committee Workshop, May 14, 1990

Thomas P. Bleck, Rush Memorial Hospital, Chicago. Time Course of Adverse Events Following Exposure to Known Neurotoxic and Immunotoxic Agents.

Marie Valdes Dapena, School of Medicine, University of Miami. Evidence Linking Pertussis Vaccines to Sudden Infant Death Syndrome (SIDS).

Darryl DeVivo, Columbia Presbyterian Medical Center. Evidence Linking Pertussis Vaccines to Irreversible Encephalopathy (Permanent Brain Damage).

Ronald Gabriel, University of California, Los Angeles. School of Medicine, Evidence Linking Pertussis Vaccines to Irreversible Encephalopathy (Permanent Brain Damage).

Mark R. Geier, medical/legal consultant, Silver Spring, Maryland. Implications for Evaluating Possible Neurotoxic Consequences of Pertussis or Rubella Vaccination.

Stanley Plotkin, Children's Hospital of Philadelphia. Evidence Linking Rubella Vaccines to Chronic Arthritis.

Keith Redhead, National Institute for Biologic Standards and Control, United Kingdom. Variations in Pertussis and Rubella Vaccine Composition and Implications for Evaluating Adverse Events Following Vaccination.

Noel R. Rose, Johns Hopkins School of Hygiene and Public Health. Implications for Evaluating Possible Immunotoxic Consequences of Pertussis or Rubella Vaccination.

John Sladky, Children's Hospital of Philadelphia. Evidence Linking Rubella Vaccines to Radiculoneuritis/Peripheral Neuropathy.

Aubrey Tingle, British Columbia Children's Hospital, Vancouver. Evidence Linking Rubella Vaccines to Chronic Arthritis.

Alexander Walker, Harvard School of Public Health. Evidence Linking Pertussis Vaccines to Sudden Infant Death Syndrome (SIDS).

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Additional Individuals and Organizations Who Provided Information

In addition to the formal literature searches and presentations, evidence on adverse events following pertussis or rubella vaccination was received from the following sources or individuals:

Bell of Atri, Inc., College Park, Maryland. Letter from J. Anthony Morris to Dean A. Blumberg, October 19, 1990; and Comments on published material.

Center for Empirical Medicine, Washington, D.C. Contribution to the discussion of a connection between childhood vaccinations and neurologic disease.

Centers for Disease Control. Selected reported adverse events following immunization, U.S., 1978-1990; and Case reports from the Monitoring System for Adverse Events Following Immunization (MSAEFI).

Chronic Rubella Viremia Support, Cataldo, Idaho. Newsletters and informational material.

Determined Parents to Stop Hurting Our Tots, Beaver Falls, Wisconsin. Case reports and published material.

Dissatisfied Parents Together, Vienna, Virginia. Comments on proposed vaccine information materials on diphtheria-tetanus-pertussis vaccine (letters and attachments to the Centers for Disease Control).

Mr. and Mrs. Donny Epps, Athens, Georgia. Case report.

Mark R. Geier, Silver Spring, Maryland. Articles and unpublished material on pertussis vaccine.

Joanne M. Hatem, York Gastroenterology, York, Pennsylvania. Review of prelicensing studies of RA 27/3 vaccine.

Institute of Medicine. Background materials and presentations for a Workshop on the National Childhood Encephalopathy Study, November 1989.

National Vaccine Information Center, Vienna, Virginia. Case reports submitted to Dissatisfied Parents Together between May 1990 and October 1990; and Newsletters dated Spring 1990, November 1990, and March 1991.

Study of Neurologic Illness in Children, Seattle, Washington. Case reports provided by James Gale.

Dirk Teuwin, SmithKline Biologicals, Rixensart, Belgium

Aubrey Tingle, University of British Columbia, Vancouver

Jeanette Wilkins, University of Southern California, Los Angeles. Bibliographic material on pertussis vaccine.

Arthur Zahalsky, Southern Illinois University, Edwardsville. Unpublished papers on pertussis toxin and pertussis vaccine.

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Review of Interim Bibliography

Midway through the project (December 1990), an interim bibliography of more than 1,000 citations bearing on the topics under examination by the committee was circulated to 17 individuals representing a range of views on the topic of adverse events following pertussis and rubella vaccination. These individuals were asked to identify the pertinent sources of information missing from the bibliography to ensure that no important information was overlooked by the committee.

ABSTRACTION OF DATA FROM CASE REPORTS, CASE SERIES, AND CONTROLLED STUDIES

Rationale

The committee decided early in the project to abstract key data from two general sources: (1) case series and case reports published in the peer-reviewed literature or obtained from parents or other sources and (2) controlled studies in humans published in the peer-reviewed literature. Abstracted data were used to evaluate both the extent and completeness of current case series, case report, and controlled study data. In addition, controlled study data were used to characterize the quality of individual controlled studies, to assess the feasibility of pooling study data for meta-analysis, and to identify gaps in knowledge.

Procedures for Abstraction and Adjudication of Study Data

Case series and case reports were identified from a variety of sources: the published literature; parents or affected individuals; organizations such as Dissatisfied Parents Together and its National Vaccine Information Center; reports from the Centers for Disease Control's Monitoring System for Adverse Events Following Immunization (MSAEFI); and reports from the Study of Neurologic Illness in Children (SONIC), sponsored by the Centers for Disease Control at the University of Washington in Seattle. The form used for abstracting case reports and case series was developed by the committee and was pretested by Bennett Shaywitz of the committee. Case series and case reports were abstracted by John Bailey, Michael Katz, or Bennett Shaywitz of the committee. (The Case Report Review Form appears later in this appendix.)

The form used for abstracting data from reports of controlled studies in humans was developed and pretested by Linda Cowan and Darwin Labarthe of the committee, who also evaluated the evidentiary base to identify appropriate studies for abstracting. Data from each controlled study were ab

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stracted independently by two upper-level doctoral students under the supervision of Linda Cowan and Darwin Labarthe. Completed pairs of questionnaires were then reviewed by Darwin Labarthe, Linda Cowan, or Christopher Howson (project director) for consistency of response. In the case of discordant responses, the original article was checked and the response was adjudicated by the reviewer. (The Controlled Study Review Form appears later in this appendix.)

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CASE REPORT REVIEW FORM

Reviewer Name: _____ **Date:** _____

Citation/Source of report:
(code type and print citation)

Reference_____

Case no. _____

1. Peer-reviewed journal
2. CDC report
3. Parents' groups
4. Pharmaceutical company report
5. Other

____

Other identifiers _____

I. Characteristics of Exposure and Subject

A. Type of vaccine:

1. DTP
2. DT
3. Rubella
4. Pertussis
5. MMR
6. OPV
7. Other (Specify): _____

____

B. Source of vaccine (pharmaceutical house): _____

C. Age (mos/yrs)_____

D. Sex 1 = Male 2 = Female ____

E. Race 1 = White 2 = Non-white 9 = Not reported ____

F. Calendar year of adverse event: 19 ____

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II. Clinical Features of Subject

A. Prior illness or condition 1 = Yes 2 = No 3 = Unknown ____

(e.g., low birth weight, meningitis)

If yes, specify: _____

B. Coexisting illness or condition 1 = Yes 2 = No 3 = Unknown ____

If yes, specify: _____

_____

C. Family history of associated diseases?
1 = Yes 2 = No 3 = Unknown ____

D. Duration of follow-up after adverse event: (days/mos/yrs) _____

E. Immunization number in which this event occurred: ____

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III. Clinical Characteristics of Adverse Event

A. For each immunization, indicate with a check mark which of the following events were reported to have occurred.

	Immunization Number			
	1	2	3	4
1. Fever				
2. Protracted inconsolable crying or screaming				
3. Alterations in level of consciousness				
4. Seizure				
Afebrile				
Febrile				
5. Shock and unusual shock-like state with hypotonicity, hyporesponsiveness				
6. Cough, stridor, alterations in breathing				
7. Erythema multiforme or other rash				
8. Vomiting				
9. Motor dysfunction, including weakness, paralysis, spasticity, transverse myelitis				
10. Neuropathies, including mono- and polyneuropathies, Guillain-Barré syndrome, radiculoneuritis, cranial nerve involvement				
11. Anaphylaxis				
12. Thrombocytopenia				
13. Arthralgia				
14. Joint swelling, redness, or tenderness				
15. Other Specify:				

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B. Considering the event described in this case report, for each symptom mentioned, indicate the time of onset after immunization and the duration of the symptom.

	Time from immuniz. to onset / Duration (hours/days)
1. Fever	_____
2. Protracted inconsolable crying or screaming	_____
3. Alterations in level of consciousness	_____
a. Irritability	_____
b. Stupor	_____
c. Coma	_____
4. Seizures	_____
a. Generalized tonic-clonic	_____
b. Focal or partial	_____
c. Minor motor (petit mal)	_____
5. Shock and unusual shock-like state with hypotonicity, hyporesponsiveness	_____
6. Cough, stridor, alterations in breathing	_____
7. Erythema multiforme or other rash	_____
Specify type: _____	_____
8. Vomiting	_____
9. Motor dysfunction, including weakness, paralysis, spasticity, transverse myelitis	_____
a. Upper extremities	_____
b. Lower extremities	_____
10. Neuropathies, including mono- and polyneuropathies, Guillain-Barré syndrome, radiculoneuritis, cranial nerve involvement	_____

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11. Anaphylaxis _____

12. Thrombocytopenia _____

13. Arthralgia _____

14. Joint swelling, redness, or tenderness _____

15. Other
Specify: _____ _____

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C. Laboratory measures: Indicate by a check mark whether tests were done coincident or after the onset of symptoms of the adverse event and whether the results were normal or abnormal.

	Coincident/After	Normal/Abnormal
1. CSF cells		
2. CSF protein		
3. CSF glucose		
4. EEG		
5. Brain imaging		
a. Skull X-ray		
b. PEG		
c. Angiography		
d. CT		
e. MRI		
6. Rubella virus isolation		
Specify source:		
7. Antibody titers		
8. Hematologic and clotting indices		
a. Hemotocrit		
b. Hemoglobin		
c. White blood count		
d. Platelet count		
e. PT/PTT		
f. Bleeding time		
g. Other Specify: _____		

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IV. Permanent Sequelae

For each condition in the report considered to be a chronic, late outcome of immunization, indicate whether the condition was coincident with or had its onset after the acute adverse event, the interval from immunization to onset of the chronic outcome, and the duration of the condition.

	Coincident /After	Onset post-immuniz. (days/mos)	Duration (days/mos)
1. Alterations in level of consciousness			
a. Irritability			
b. Stupor			
c. Coma			
2. Seizures			
a. Generalized tonic-clonic			
b. Focal or partial			
c. Minor motor (petit mal)			
3. Motor dysfunction, including weakness, paralysis, spasticity, transverse myelitis			
a. Upper extremities			
b. Lower extremities			
4. Neuropathies, including mono- and polyneuropathies, Guillain-Barré syndrome, radiculoneuritis, cranial nerve involvement			
5. Developmental delay or mental retardation			
Also indicate:			
a. Age diagnosed _____(mos/yrs)			
b. Method of diagnosis:			
Clinical			
Psychometric testing			
c. Severity:			
Mild			
Moderate			
Severe			
Profound			

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	Coincident /After	Onset post-immuniz. (days/mos)	Duration (days/mos)
6. Chronic medication use Specify types:			
7. Chronic arthritis			
8. Chronic arthralgia			
9. Thrombocytopenia or thrombocytopenic purpura			
10. Death			
11. Other Specify:			
12. No permanent sequelae			

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V. Source of Funding of the Report

1. Government ____
2. Pharmaceutical industry
3. Other
4. None
9. Unknown

VI. Degree of Detail Provided in Report

1. Clinical synopsis ____
2. Table
3. Synopsis and table
4. Other, specify: _____

VII. Estimated Reliability of Report

1. Very reliable ____
2. Reliable
3. Somewhat reliable
4. Not reliable

VIII. Reviewer's Best Estimate of Acute Diagnosis

1. Encephalopathy ____
2. Encephalitis
3. Febrile seizures
4. Mental retardation
5. Epilepsy
6. Infantile spasms
7. Shock and unusual shock-like state with hypotonicity, hyporesponsiveness
8. Motor dysfunction, including weakness, paralysis, spasticity, transverse myelitis
9. Neuropathies, including mono- and polyneuropathies, Guillain-Barré syndrome, radiculoneuritis, cranial nerve involvement
10. Other neurological event
    Specify: _____
11. Not a neurological event of any kind
12. SIDS

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13. Arthralgia
14. Arthritis
15. Other musculoskeletal events
    Specify: _____
16. Erythema multiforme or other rash
17. Anaphylaxis
18. Thrombocytopenia or thrombocytopenic purpura
19. Other
    Specify: _____
20. Normal

IX. Reviewer's Best Estimate of Chronic, Long-Term Diagnosis

1. Encephalopathy ——
2. Encephalitis
3. Febrile seizures
4. Mental retardation
5. Epilepsy
6. Infantile spasms
7. Shock and unusual shock-like state with hypotonicity, hyporesponsiveness
8. Motor dysfunction, including weakness, paralysis, spasticity, transverse myelitis
9. Neuropathies, including mono- and polyneuropathies, Guillain-Barré syndrome, radiculoneuritis, cranial nerve involvement
10. Other neurological condition
    Specify: _____
11. Not a neurological condition of any kind
12. SIDS
13. Arthralgia
14. Arthritis
15. Other musculoskeletal condition
    Specify: _____
16. Erythema multiforme or other rash
17. Anaphylaxis
18. Thrombocytopenia or thrombocytopenic purpura
19. Other
    Specify: _____
20. Normal

X. Summary Comment(s)

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CONTROLLED STUDY REVIEW FORM

NOTE: PLEASE ANSWER EACH QUESTION USING INFORMATION REPORTED *ONLY* IN THIS ARTICLE AND *NOTE* IN THE SPACES PROVIDED THE PAGE (P), COLUMN (C), PARAGRAPH (PG), AND LINE[S] (L) IN WHICH IT APPEARS. INFORMATION FROM ABSTRACTS, FOOTNOTES, TABLES OR FIGURES SHOULD BE NOTED AS: P/Abs/L; P/FN/L; P/T#; AND P/F# RESPECTIVELY. IF LARGE AMOUNTS OF INFORMATION, SUCH AS THE CONTENTS OF A TABLE, ARE REQUIRED TO ANSWER A QUESTION, PHOTOCOPY THE TABLE AND ATTACH IT TO THE ABSTRACT.

IF THERE IS NO INFORMATION IN THE ARTICLE WITH WHICH TO ANSWER A SPECIFIC QUESTION, NOTE THIS ON THE ABSTRACT AS N/I. IF THE QUESTION IS NOT APPLICABLE, NOTE THIS ON THE ABSTRACT AS N/A.

This protocol is divided into eight sections. Sections A-F and Section H should be answered for all articles. Section G is appropriate only for some articles. Please look over this list of the sections to determine which sections are appropriate for your current article.

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READER: _____ DATE: _____

CITATION: _____

Section A
General Information

P/C/PG/L

1. What specific question(s) was this study designed to address?

2. What study design was used (e.g., case report, case series, case-control, prospective, ecological comparison, randomized controlled trial, nonrandomized trial, cross-sectional, etc.)?

3. Where was the study done (i.e., geographic location)?

4. What calendar years were covered by the study?.

5. What are the baseline incidence, prevalence, mortality or morbidity rates of the endpoints in the population studied?

Section B
Description of Vaccine

P/C/PG/L

6. Which vaccines are included in the study?
(Check all that apply.)

DPT ____ Pertussis ____

DT ____ MMR ____

Rubella ____ Other ____ Specify:

7. What is the schedule of immunization (i.e., ages, frequency)?
(If more than one type, list separately for each.)

8. What is the dose of the vaccine?
(If more than one type, list separately for each.)

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Section C
Disease or Condition

P/C/PG/L

9. Which of the following endpoints were included in the study? (Check all that apply.)

Arthritis	___	Hypsarrhythmia	___
Aseptic meningitis	___	Infantile spasms	___
Autism	___	Juvenile diabetes (IDDM)	___
"Brain damage"	___	Learning disabilities	___
Encephalitis	___	Mental retardation	___
Encephalopathy	___	Motor handicap	___
Epilepsy	___	Reye syndrome	___
Febrile seizures	___	SIDS	___
Hemolytic anemia	___	Other	___
Hyperactivity (hyperkinesis)	___	Specify:	___
Hypotonic/hyporesponsive	___		___

10. How were the endpoints defined?

11. What was the time frame for the endpoints considered?

___ Acute? Specify intervals: _____

_____

___ Long-term (chronic)? Specify follow-up time: _____

Section D
Subject Selection and Data Collection

P/C/PG/L

12. What are the criteria for subjects' inclusion in the study (i.e., age, gender, disease/condition, severity of illness)?

13. What are the exclusion criteria for subjects in this study?

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14. How were the study subjects selected (i.e., consecutive sample, all survivors, geographic catchment area, etc.)?

15. What comparison group was used, and what were its characteristics?

16. How many subjects were in the study? (Give total and number in each subgroup, if relevant, e.g., cases and controls, exposed and unexposed, etc.)

17. What are the alternative vaccines discussed in the paper?

18. Were explicit comparisons among vaccines included?

19. How was the information collected (telephone, in person, trained interviewer, record review, someone other than the patient, blinded observers or evaluators, etc.)?

    On Vaccination:

    On Endpoint:

Section E
Data Analysis

P/C/PG/L

20. How many subjects were lost to follow-up, if applicable?

21. How were withdrawals (nonrespondents/refusals/dropouts) handled, if applicable (e.g., eliminated from the study; considered an end result in the group to which they were originally assigned; changed groups and considered an end result in a new group?)

22. What statistical methods were applied to analyze the data? (Name specific tests, techniques, or computer programs used.

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23. Was there adjustment for covariates? If so, which ones?

24. Did the investigators discuss type II error?

Section F
Results

P/C/PG/L

25. What percentage of exposed and unexposed patients experienced endpoints, or what percentage of cases and controls were exposed?

26. What were the results of any comparative analyses?

Section G
Randomized Controlled Trials

P/C/PG/L

27. What method of randomization was used?

28. Was blinding used with respect to treatment?

Single-blind? Double-blind?

29. Were observers or other evaluators of response variables blinded to the ongoing results of the study?

30. Which, if any, prerandomization balancing methods were used (i.e., stratified sampling, weighted samples)?

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Section H
Conclusions

P/C/PG/L

31. What were the investigators' conclusions? (Please copy their statement either from the abstract, summary, conclusion, or discussion section.)

32. To whom do the investigators generalize their findings?

33. What are the limitations of this study? (List only those mentioned by the author.)

34. What other studies, if any, are mentioned in comparison with the present one? (Include only the names or a brief description of [and reference for] the studies to which the authors compared their results. It is not necessary to repeat the reference list.)

35. If the paper contained information we should have asked about but did not, please tell us what it was.

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ID LINK: FIRST AUTHOR (LAST NAME)_____
(PRINT)
JOURNAL (USE ACCEPTED ABBREV.)_____

VOLUME NO. _____ YEAR _____ FIRST PAGE _____

DATA ENTRY SUMMARY:

I. PRIMARY VACCINE STUDIED: OTHERS STUDIED:

Codes:			
	DPT	1	1st _____
	DT	2	
	Pertussis	3	2nd _____
	Rubella	4	
	MMR	5	3rd _____
	Other	6	
	Specify: _____		4th _____

II. STUDY TYPE:

Codes:

Randomized clinical trial	1
Controlled prospective study	2
Case-control study	3
Case report/case series	4
Other noncontrolled observation	5
Non-random experiment/humans	6
Animal study	7
Other controlled study	8
Other laboratory observation	9
Other	10

Specify: _____

_____

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III. CONDITIONS STUDIED (enter major endpoints first):

Codes:

Arthritis	1	Hypsarrhythmia	12
Aseptic meningitis	2	Infantile spasms	13
Autism	3	Juvenile diabetes (IDDM)	14
"Brain damage"	4	Learning disabilities	15
Encephalitis	5	Mental retardations	16
Encephalopathy	6	Motor handicap	17
Epilepsy	7	Reye syndrome	18
Febrile seizures	8	SIDS	19
Hemolytic anemia	9	Other	20
Hyperactivity (hyperkinesis)	10	Specify: _____	
Hypotonic/hyporesponsive	11		

IV. REPORTED RELATIONS OF EXPOSURE AND ENDPOINT(S):
(Code each association)

Codes: 1 = Yes 2 = No

No Association _____

Positive Association _____

Negative Association _____

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B

Pertussis and Rubella Vaccines: A Brief Chronology

PERTUSSIS VACCINES

1906

Jules Bordet and Octave Gengou of the Pasteur Institute of Brussels are able to grow the pertussis bacterium in artificial media. The bacterium, originally called *Haemophilus pertussis,* is found to be sufficiently different from *Haemophilus* to be classified as a new genus. It becomes known as *Bordetella pertussis* in honor of Bordet. When the description of the Bordet-Gengou technique is published, numerous researchers begin to experiment with vaccines made from killed whole-cell *B. pertussis.* In ensuing years, such vaccines are developed, and used in children, by Bordet and Gengou in 1912, Charles Nicolle of the Pasteur Institute in Tunis in 1913, and Thorvald Madsen of the Danish State Serum Institute in Copenhagen in 1914, among others (Chase, 1982).

1914

Pertussis vaccine is listed in the American Medical Association publication *New and Nonofficial Remedies* (Council on Pharmacy and Chemistry, 1914, 1931).

1925

Madsen is the first to describe the use of whole-cell pertussis vaccine on a large scale (Madsen, 1925, 1933). Although his vaccine successfully controls two outbreaks in the Faroe Islands,

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his 1933 account reports two deaths within 48 hours of immunization, the first published report of serious adverse effects after pertussis vaccination. In the same year, Louis Sauer of Northwestern University Medical School, Chicago, describes minor reactions to a whole-cell pertussis vaccine being used in the United States (Sauer, 1933a,b).

1930s-1940s

Pearl Kendrick of the State of Michigan Health Department further refines and uses whole-cell pertussis vaccines in children (Kendrick, 1942, 1943; Kendrick and Eldering, 1936, 1939). In 1942, she and colleagues combine her improved killed vaccine with diphtheria and tetanus toxoids to produce the diphtheria-tetanus-pertussis (DTP, also known as DPT) combination vaccine. In 1944, the Committee on Infectious Diseases of the American Academy of Pediatrics suggests routine use of pertussis vaccine and, in 1947, recommends its use in the form of the DPT combination (American Academy of Pediatrics, 1944; Cherry, 1984). In the United States, vaccination of children against pertussis becomes a routine procedure and is made compulsory in some states.

1947-1948

The first published reports appear of irreversible brain damage after whole-cell pertussis vaccine (Brody and Sorley, 1947; Byers and Moll, 1948). Although the Brody and Sorley report describes one case only, it leads to the first warnings that pertussis vaccine should not be administered to those with a known neurologic disorder.

1948

Approximately a dozen companies are manufacturing DPT vaccine (Coulter and Fisher, 1985).

1959

The Parke-Davis Quadrigen vaccine (DPT combined with the Salk polio vaccine) is licensed. The vaccine is alleged to be particularly reactive because of the effect of the preservative on the pertussis component. Several lawsuits ensue. The vaccine is withdrawn from the market in 1968 (Coulter and Fisher, 1985).

1965

By the mid-1960s, many states have passed laws requiring that all children be immunized with DPT vaccine prior to entering school (Coulter and Fisher, 1985).

1974

In Great Britain, questions about the safety of whole-cell pertussis vaccines are widely publicized in the popular press after news

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paper accounts of a study (Kulenkampff et al., 1974) suggesting adverse reactions. The Association of Parents of Vaccine Damaged Children is formed (Alderslade et al., 1981). Between 1974 and 1978, the proportion of children vaccinated against pertussis falls from 80 to 30 percent (and as low as 9 percent in some areas) (British Medical Journal, 1981).

1975

Japan temporarily stops using pertussis vaccine after publicity about deaths following vaccination. Later in the year, pertussis vaccination is reinstituted in children age 2 years and above. The proportion of immunized children drops from 70 percent in 1974 to 20 to 40 percent in the following years. Reported cases of pertussis increase from 393 with no deaths in 1974 to more than 13,000 with 41 deaths in 1979 (Coulter and Fisher, 1985).

1976

The government-funded National Childhood Encephalopathy Study (NCES) begins in Great Britain, largely as a result of rising public concern about the safety of pertussis vaccine. The study is case-control in design and runs for 3 years (Alderslade et al., 1981).

1977-1979

An epidemic of pertussis occurs in Great Britain. More than 100,000 cases and 36 deaths are reported (Koplan and Hinman, 1987).

1978

In the United States, public health clinics using federally purchased vaccines are required to have parents sign an "important information statement" before their child can be vaccinated (Coulter and Fisher, 1985).

The Monitoring System for Illness Following Immunization (MSIFI) is established by the Centers for Disease Control (CDC). The system is an outgrowth of the monitoring of adverse events following the swine flu vaccine incident.

1978

Two lawsuits are filed in U.S. courts alleging that children were harmed by pertussis vaccine (Koplan and Hinman, 1987).

1979

1979

Meetings are held at the Food and Drug Administration (FDA) Bureau of Biologics and at the CDC to discuss reports of sudden infant death syndrome (SIDS) in Tennessee following pertussis vaccination. No evidence of a causal relationship is found. Wyeth Laboratories, the manufacturer, withdraws the questioned vaccine lot nonetheless (Coulter and Fisher, 1985).

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FDA funds a study to evaluate adverse reactions to DPT vaccines. The study is to be carried out at the University of California, Los Angeles (UCLA).

The Vaccine Damage Payment Act is passed in Great Britain. The act provides a mechanism for government compensation to those with vaccine-associated injuries (Griffith, 1989).

Sweden stops using whole-cell pertussis vaccine because of reported reactions and a lack of vaccine efficacy. The number of pertussis cases increases (Coulter and Fisher, 1985).

1981

The findings of the FDA-sponsored UCLA study are published (Cody et al., 1981). The rate of minor reactions and serious short-term reactions following DPT is found to be higher than that following DT.

The British "Blue Book" (Department of Health and Social Security, 1981) is published. It includes the findings of the NCES (Alderslade et al., 1981) and reports from several panels. The NCES concludes that both DPT and measles vaccines can cause acute neurologic reactions and permanent brain damage but that the latter is a very rare complication. The attributable risk (see Glossary of Terms) of serious neurologic illness in the 7 days following pertussis vaccination is estimated to be 1 in 110,000 immunizations, and that of persistent neurologic damage after 1 year is estimated to be 1 in 310,000 immunizations (with wide confidence limits in both cases).

1982

The television program "DPT: Vaccine Roulette," first broadcast by NBC affiliate WRC-TV in Washington, D.C., is widely publicized. The program depicts children with severe injuries reported to be associated with pertussis vaccine (Griffith, 1989; Koplan and Hinman, 1987).

An advocacy group, Dissatisfied Parents Together, is formed in the United States. Its members call for research toward a safer pertussis vaccine and mandatory reporting of adverse reactions. Some in the group call for a cessation of use of the whole-cell vaccine (Coulter and Fisher, 1985; Koplan and Hinman, 1987).

The Senate Subcommittee on Investigations and General Oversight, chaired by Senator Paula Hawkins, holds hearings "to examine adverse drug reactions from immunization, federal efforts in preventive medicine, and characteristics of certain diseases" (Coulter and Fisher, 1985; Gonzalez, 1982).

The British Child Health and Education Study is published (Butler et al., 1982). The study compares immunization rates,

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hospitalization rates, neurologic illness, and school performance among a cohort of more than 13,000 children followed up at age 5. Long-term neurologic problems are not found to be related to pertussis immunizations.

1983

The Task Force Report on Pertussis is submitted to the U.S. Senate Labor and Human Resources Committee by the U.S. Department of Health and Human Services (DHHS). The committee holds hearings on the report.

The American Academy of Pediatrics and Dissatisfied Parents Together conduct more than 8 months of discussions to develop recommendations for a federal compensation program for children with vaccine-related illnesses and injuries (Coulter and Fisher, 1985). The National Childhood Vaccine Injury Compensation Act (S-2117) is introduced in the U.S. Senate by Senators Paula Hawkins and Orrin Hatch.

The Communicable Diseases Surveillance Centre Study, or North West Thames Study, is published by Pollock and Morris (1983). The study, which followed a large group of children after pertussis vaccination, finds no convincing evidence relating DPT vaccine to neurologic damage.

1984

Senate hearings are held by Senator Paula Hawkins on the National Childhood Vaccine Injury Compensation Act.

Wyeth Laboratories discontinues its marketing of whole-cell pertussis vaccine. Only two pharmaceutical companies in the United States continue to sell pertussis vaccines.

The National Childhood Vaccine Injury Compensation Act is introduced in the U.S. House of Representatives by Representative Henry Waxman.

1985

A total of 219 lawsuits are filed in U.S. courts alleging harm to a child from pertussis vaccine. The average amount of compensation sought (when specified) is $26 million (Koplan and Hinman, 1987).

The book *DPT: A Shot in the Dark* is published. Authors Harris L. Coulter and Barbara Loe Fisher (a founder of Dissatisfied Parents Together) describe numerous case histories of children reportedly injured or killed by the DPT vaccine. The book criticizes laws requiring vaccination, calls for further research on and testing of acellular pertussis vaccines, and urges additional research to identify children at particular risk of reacting to vaccines.

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The Oversight and Investigations Subcommittee of the House Committee on Energy and Commerce conducts hearings on vaccine development as part of a series of hearings on biotechnology. Some witnesses call for better coordination of vaccine activity at the federal level.

1986

Public Law 99-660, the National Childhood Vaccine Injury Act, is passed by the U.S. Congress. The law calls for the establishment of the National Vaccine Program (NVP) ("to achieve optimal prevention of human infectious diseases through immunization and to achieve optimal prevention against adverse reactions to vaccines"); the National Vaccine Advisory Committee (NVAC) to advise the director of the NVP; the National Vaccine Injury Compensation Program (VICP) to evaluate claims of injury from vaccines and provide compensation where justified; and the Advisory Commission on Childhood Vaccines (ACCV) to advise the Secretary of DHHS and the VICP on vaccine policy. It also mandates a scientific review of possible adverse effects of whole-cell pertussis vaccine by the Institute of Medicine (IOM) of the National Academy of Sciences.

1987

The NVP, established under Public Law 99-660, begins operation. The NVP Director is the Assistant Secretary for Health of DHHS.

The Study of Neurologic Illness in Children (SONIC) begins at the University of Washington in Seattle. The CDC-sponsored study includes the states of Washington and Oregon and consists of two population-based case-control pilot studies to determine the risk and frequency of serious acute neurologic illness and a sample survey to estimate the number of doses of vaccine given during the surveillance period.

1988

The NVAC, established under Public Law 99-660, is appointed in April and meets for the first time in June. As specified in the law, the IOM is consulted during the appointment process. The committee reports to the Assistant Secretary for Health of DHHS and is administered by staff of the NVP.

Two important legal cases are decided: the Loveday judgment in Great Britain's High Court of Justice, Queen's Bench Division (Stuart-Smith, 1988), and the Rothwell judgment in the Supreme Court of Ontario, Canada (Osler, 1988). In both cases, the justices rule that there is insufficient evidence to demonstrate that pertussis vaccine can cause permanent brain damage

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in children. Both are considered as "test cases" in their respective jurisdictions, meaning that other lawsuits claiming permanent neurologic effects from pertussis vaccine are effectively excluded.

1989

The ACCV, established under Public Law 99-660, is appointed early in the year and meets for the first time in March. The commission reports to the Secretary of DHHS and is administered by staff of the Health Resources and Services Administration, DHHS.

The VICP begins operation. It is administered by the Secretary of DHHS through the staff of the Health Resources and Services Administration. By the end of the year, it has received 201 petitions for compensation, of which 165 are related to DPT vaccine.

The National Vaccine Information Center sponsors a workshop on the neurologic complications of pertussis and pertussis vaccination (Menkes and Kinsbourne, 1990).

The IOM holds a CDC-sponsored workshop on the National Childhood Encephalopathy Study (Marcuse and Wentz, 1990).

1990

The IOM Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines is appointed in December 1989 and meets for the first time in January 1990. In the same month, the committee sponsors a public meeting in Washington, D.C., to solicit medical and other scientific data and comments on the nature, frequency, and circumstances of adverse events following pertussis and rubella vaccines. In May, it sponsors a workshop, Possible Adverse Consequences of Pertussis and Rubella Vaccines. The IOM study, mandated by Public Law 99-660, is sponsored by a consortium of federal agencies through the National Institute of Allergy and Infectious Diseases.

The Sixth International Symposium on Pertussis is held in Bethesda, Maryland (Manclark, 1990a,b).

RUBELLA VACCINES

1914

A. F. Hess suggests that rubella is caused by a filtrable virus (Chase, 1982).

1938

Y. Hiro and S. Tasaka succeed in transmitting rubella by inoculating healthy nonimmune children with filtrates taken from children

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with active cases of rubella. The causative agent remains unidentified (Chase, 1982).

1941

Norman McAlister Gregg, an Australian ophthalmologist, notes after a rubella epidemic that women who have had rubella during pregnancy seem unusually likely to give birth to children with cataracts and other birth defects (Gregg, 1941). He finds confirmation of his observations in a survey of other physicians in Australia. The defects described include cataracts, deafness, congenital heart disease, microcephaly, cerebral palsy, and mental retardation. Similar reports from other countries ensue. World War II interferes with research to follow up on these observations (Chase, 1982). Studies of Australian census and disease records later suggest that congenital damage from rubella during pregnancy had occurred for at least 40 years before being recognized (Burnet and White, 1972).

1948

Macfarlane Burnet and colleagues use gamma globulin from patients with rubella to confer short-term passive immunity on pregnant women recently exposed to rubella (Chase, 1982). The practice becomes common in a number of industrialized countries.

1960-1961

The rubella virus is isolated by Thomas Weller at the Harvard School of Public Health and, independently, byPaul Parkman and colleagues at the Walter Reed Army Institute of Research (Chase, 1982).

1963-1964

One of the worst rubella outbreaks in U.S. history occurs. Rubella is not, at that time, a notifiable disease, so it is not known with certainty how many people contract the disease or how many children suffer congenital or developmental damage caused by prenatal infection. It is estimated that 20,000 children suffer prenatal damage caused by rubella infections during the epidemic and that the cost of their rehabilitation 5 years after the epidemic ends is $1.5 billion to $2 billion in 1969 U.S. dollars. The epidemic and its aftermath lend impetus to the search for a rubella vaccine and are instrumental in the initial approval of Title XIX (the Medicaid provisions) of the Social Security Act of 1965 and in subsequent amendments to Title XIX, the Early and Periodic Screening, Diagnosis, and Treatment program. The latter make comprehensive pediatric care, including necessary vaccinations, the "mandated birthright" of every child regardless of ability to pay (Chase, 1982).

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1965-1967

Several vaccines made from attenuated rubella strains are developed and tested in clinical trials (Plotkin, 1988).

1969-1970

Three rubella vaccines are licensed in the United States: HPV-77 (grown in dog kidney), HPV-77 (grown in duck embryo), and Cendehill (grown in rabbit kidney). Many states add rubella vaccines to the list of immunizations required for school entry. RA 27/3, a human diploid fibroblast vaccine developed in the United States, is licensed in several European countries (Plotkin, 1988).

1969-1976

Reports of possible serious adverse events following rubella vaccination begin to be published. Two types of events are reported: neuropathies (Gilmartin et al., 1972; Grand et al., 1972; Kilroy et al., 1970; Schaffner et al., 1974) and acute and chronic arthralgia and arthritis (American Journal of Diseases of Children, 1969; Barnes et al., 1972; Fox et al., 1976; Freestone et al., 1971; Horstmann et al., 1970; Lerman et al., 1971; Rowlands and Freestone, 1971; Spruance and Smith, 1971; Spruance et al., 1972; Swartz et al., 1971; Weibel et al., 1972). Because the HPV-77 dog kidney vaccine appears to be associated with a higher proportion of such adverse events, that vaccine is withdrawn from the market in the United States and other countries.

1979

The human diploid cell culture, RA 27/3, is licensed in the United States. The last U.S. manufacturer of the HPV-77 duck embryo vaccine replaces it with RA 27/3, which becomes the only rubella vaccine available in the United States (Plotkin, 1988).

1979-1980s

Systematic investigations are undertaken of the possible association between rubella vaccines and chronic arthritis or arthropathies, leading to an increased level of concern on the part of some investigators and others (Cunningham and Fraser, 1985; Tingle et al., 1979, 1983, 1985, 1986, 1989).

1986

Public Law 99-660, the National Childhood Vaccine Injury Act, is passed by the U.S. Congress (see description above in the section on pertussis vaccines). The law mandates a scientific review of possible adverse effects of rubella vaccines by the IOM of the National Academy of Sciences.

1987

The NVP begins operation. The NVP Director is the Assistant Secretary for Health for DHHS.

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1988

The NVAC meets for the first time in June. The committee reports to the Assistant Secretary for Health of DHHS and is administered by staff of the NVP.

1989

The Advisory Commission on Childhood Vaccines meets for the first time in March. The commission reports to the Secretary of DHHS and is administered by staff of the Health Resources and Services Administration, DHHS.

The National Vaccine Injury Compensation Program begins operation. It is administered by the Secretary of DHHS through the staff of the Health Resources and Services Administration, DHHS. By the end of the year, it has received 201 petitions for compensation, of which 11 are related to measles-mumps-rubella vaccine.

1990

The IOM Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines meets for the first time in January. In the same month, the committee sponsors a public meeting in Washington, D.C., to solicit medical and other scientific data and comments on the nature, frequency, and circumstances of adverse events following pertussis and rubella vaccines. In May, it sponsors a workshop on Possible Adverse Consequences of Pertussis and Rubella Vaccines.

The ABC News program "20/20" presents a report entitled "Why Am I So Sick?," detailing the chronic and disabling symptoms reported by some women after rubella immunization.

A randomized, double-blind, placebo-controlled trial of rubella vaccine and chronic arthritis begins in Vancouver, British Columbia, Canada.

1991

As of April, the CDC is considering issuing a request for proposals for a study of chronic arthritis following rubella vaccination that would include laboratory studies of participants.

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C

Animal Models for the Study of Whooping Cough and the Testing of Vaccine Materials

ANIMAL MODELS FOR THE STUDY OF WHOOPING COUGH

Bordetella pertussis does not naturally cause disease in animals. Nevertheless, experiments in animals have made important contributions to the present, although incomplete, understanding of pertussis. Mice, rats, rabbits, dogs, ferrets, and primates have been used. The respiratory colonization of mice by *B. pertussis* mimics that of humans, but mice do not cough, and so the infection is not spread from mouse to mouse (Pittman et al., 1980). Among experimental animals, only primates have been found to develop a paroxysmal cough and mucus production; they do transmit the infection from one animal to another (Weiss and Hewlett, 1986). However, adult primates can become resistant to pertussis, so that newborn animals are needed for use in experiments, and this is impractical. Rats are very hard to infect with *B. pertussis,* and rabbits carry the organism for months without showing signs of disease (Ashworth et al., 1982; Weiss and Hewlett, 1986).

Most of the information about pertussis gained from animal models has come from the study of mice. Three sites of infection have been used: intraperitoneal, respiratory, and intracerebral. Mice can rapidly kill *B. pertussis* when the organism is injected intraperitoneally. But, given enough bacteria by this route, they will die of apparent toxemia in 1 to 3 days (Pittman, 1970; Proom, 1947). These responses do not represent a model of whooping cough. Unlike the situation in humans, virulence by the intraperitoneal route in mice is inversely related to intracerebral virulence (Pittman, 1970),

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an observation that illustrates the difficulties of using animal models to represent human disease.

Older mice are relatively resistant to respiratory infection; infant or suckling mice have reproducible symptoms and mortality from pertussis pneumonia, and the disease resembles the disease in humans (Pittman et al., 1980; Sato and Sato, 1988; Sato et al., 1981). Infection induced by intranasal inoculation (Pittman et al., 1980) has been reported to be less reproducible than that induced by aerosol inhalation (Sato and Sato, 1988). The strain of mice used can affect the results (Pittman et al., 1980). Survivors of a sublethal dose of organisms can develop a chronic infection that lasts for weeks or months (Dolby et al., 1961; Sato et al., 1981; Weiss et al., 1984).

Using intranasal inoculation of infant mice, Weiss and colleagues (1983, 1984) showed that mutant strains of *B. pertussis* lacking pertussis toxin (PT) or extracytoplasmic adenylate cyclase were much less virulent than the wild-type (naturally occurring) organism. A mutant deficient in filamentous hemagglutinin was nearly as virulent as the wild-type strain. The results obtained with these carefully engineered strains raise a question about the contribution of filamentous hemagglutinin to virulence. Such a contribution had been suggested by data from other models. These and other considerations warrant reservations about the general applicability of the results obtained with this or the other models to the disease in humans.

Mice infected intracerebrally have been the most widely used animal model for pertussis. To achieve this model, anesthetized mice are injected with various numbers of organisms, in some cases after immunization with bacteria or bacterial products (usually given intraperitoneally). Only one strain of *B. pertussis,* strain 18-323, works well in the model, which raises further questions regarding the applicability of this model to the natural disease in humans. In fact, analysis of isoenzyme patterns suggests that this bacterial strain is genetically more closely related to *Bordetella bronchiseptica* than it is to other strains of *B. pertussis* (Musser et al., 1986). In mice, the bacteria attach to the ciliated cells of the ependymal lining of the ventricles (Berenbaum et al., 1960), which simulates attachment to the respiratory cilia in humans with whooping cough. However, this infection within the skull otherwise deviates rather markedly from the presentation of the disease in humans. Despite these obvious differences from the infection in humans, protection in this model has correlated with vaccine efficacy in humans (Medical Research Council, 1959; Standfast, 1958).

STANDARDIZED ANIMAL TESTS OF VACCINE MATERIALS

The intracerebral mouse protection test (Kendrick et al., 1947, 1949) has served importantly in the progress in vaccine development that has been made to date. The test uses a standardized strain of bacteria (strain 18-323)

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stored in liquid nitrogen (Cameron, 1988), standardized mice (strain HSFS/ N) (Manclark et al., 1976), a freeze-dried reference vaccine (Armitage and Perry, 1957), and an interval between immunization and injection of 14 to 17 days (Cameron, 1988).

The intranasal mouse protection test has been improved by use of a standardized system for delivery of bacteria by aerosol (Sato and Sato, 1988). This test has been used for the study of the role in pathogenesis of bacterial adherence proteins, for example, the 69-kilodalton outer membrane protein (Shahin et al., 1990).

The toxicities of vaccines have been studied by the mouse weight gain test. This test depends on the observation that intraperitoneal injection of vaccine into young mice leads to a weight loss within hours, followed by total recovery of weight within the next 7 days (Cameron, 1988). The causes of toxicity (manifested as poor weight gain) in the test are not well understood; the test is not very sensitive to endotoxin (Cameron, 1977). Results of the test have been shown to vary with the adjuvant or absorbent used with the vaccine, mouse strain, diet, size of cage, ambient temperature, and duration of exposure to light (Cameron, 1988). These vagaries further illustrate the difficulty of generalizing to humans the results obtained from studies in animals.

A sensitive assay for the particularly important toxin PT and for anti-PT has been developed by using Chinese hamster ovary (CHO) cells (Gillenius et al., 1985; Hewlett et al., 1983). In the presence of PT, CHO cells undergo a characteristic clumping, which can be blocked with antibody to PT. The test can detect PT at levels one-fiftieth those of the next most sensitive assay (Cameron, 1988).

In summary, *B. pertussis* is a complex organism, multiple factors having been proposed as possible contributors to its virulence. Their role in whooping cough has not been clearly established. Without better understanding of the organism and the human disease, it cannot be concluded with confidence that data from animal models relate to findings in humans.

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D

Technical Details of Power Calculations and Meta-Analyses

POWER CALCULATIONS

Many of the adverse events related to pertussis and rubella vaccines share the characteristic of rareness. Most of the events in question are infrequent to begin with, and the excess risk that may be associated with vaccination is small. As mentioned in Chapter 3, it is often difficult in such situations to distinguish scientifically between *no excess risk* and *no detected excess risk.* Because of the committee's focus on fairly characterizing the uncertainty in the available data, special attention was given to power analysis, a statistical tool that can help to distinguish between these two possibilities. This appendix describes and illustrates the power calculation methods used by the committee to take account of the diverse statistical methods used in the studies on which the analyses are based.

The results of epidemiologic studies are generally reported in terms of *relative risks* (RRs) or *odds ratios.* Because the odds ratio was considered to be an estimate of the RR in the context of this report (see Chapter 3), the term RR is used in the descriptive text to refer to both measures in the report of power analyses. For the purpose of these calculations, it was assumed that, in every study, the sampling distribution of the logarithm of the odds ratio or RR (noted as Y) has a normal distribution with a standard deviation equal to the estimated standard error (Fleiss, 1981, pp. 61-67). In order to calculate power statistics from published results, the committee took the following two steps.

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First, where possible, standard errors for Y were derived from confidence intervals reported by original investigators. In this way, variance reduction techniques such as matching of cases and controls are accurately reflected in the estimated standard error. In particular, if the reported odds ratio or RR is *R*, and the upper limit of its 95 percent confidence interval is *U*, the standard error was estimated as $\sigma = \ln(U/R)/1.96$. For studies in which no confidence interval was calculated by the original authors, the committee calculated an RR as appropriate and an associated confidence interval using standard methods for 2 x 2 tables (Fleiss, 1981, pp. 61-67) and applied the same procedure described above to estimate the standard error.

Second, 50 and 80 percent power levels for the RR were calculated as follows. Under the null hypotheses of no association, the expected value of Y, E (Y), is 0.0 and the critical point for a two-sided test with $\alpha = 0.05$ is 1.96σ. If E (Y) were equal to 1.96σ, there would be a 50 percent chance that the test would detect an elevated risk; thus, the RR for which there is 50 percent power was calculated as $e^{1.96s}$ To achieve 80 percent power, E(Y) must be 0.84σ above the critical point, or 2.80σ. Thus, the RR for which there is 80 percent power was calculated as $e^{2.80s}$.

To illustrate this approach, Table D-1 shows the results of these calculations for the SONIC study relating DPT use to afebrile seizures (Gale et al., 1990; see also Table 4-5). The estimated RRs range from 0.5 to 0.8, and the upper confidence limits range from 1.1 to 1.5. On the basis of these results, the power calculations show that the SONIC study had a 50 percent chance of detecting an RR for afebrile seizures within 7 days of 3.0 and an 80 percent chance of detecting an RR within 7 days of 4.8. Thus, a relatively large increase in the risk of afebrile seizures could have gone unde

TABLE D-1 Power Calculations for the SONIC Study Relating DPT Use to Afebrile Seizures

				Power[c]	
Time Period	RR	Upper CI[a]	σ[b]	50%	80%
Within 7 days	0.5	1.5	0.56	3.00	4.80
Within 14 days	.08	1.5	0.32	1.88	2.45
Within 28 days	0.6	1.1	0.31	1.83	2.38

[a] CI, Confidence interval.

[b] σ , Standard error.

[c] "Power" denotes the probability that a statistical test based on a sample of the same size as the one in the study cited would find a statistically significant increased risk (with alpha = 0.05), given that the true RR in the population being studied is the number stated in the table. The numbers tabulated are the RRs such that the powers are 50 and 80 percent, respectively.

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tected in a study of this size. The committee could only conclude that this study provided no evidence of a large effect.

A different approach was taken to calculate the power of the statistical tests used in a retrospective epidemiologic study by Shields and colleagues (1988). As described in Chapters 4 and 5 of this report, Shields and colleagues ascertained the age distribution of cases of SIDS and of a number of neurologic disorders in Denmark during two time periods with different vaccination schedules. During the 1967-1968 time period, DPT was given at ages 5, 6, 7, and 15 months; in 1972-1973, DPT was given at ages 5 and 9 weeks and 10 months. Shields and colleagues recorded the number of adverse events occurring in the following age intervals: 1 to 3, 4 to 8, 9 to 11, 12 to 14, 15 to 19, and 20 to 23 months. Although Shields and colleagues tested whether the entire distributions of cases differed between the two time periods, the committee's power calculations were based on a comparison of the proportions in two noncontinuous age groups.[1] Group 1 was defined as age 4 to 8 months and age 12 or more months, so that a possible increase in the number of cases consistent with the 1967-1968 vaccination schedule could be detected. Group 2 was defined as ages 1 to 3 months and 9 to 11 months, so that a possible increase in the number of cases consistent with the 1972-1973 vaccination schedule could be detected.

The power calculations are based on the assumption that if there is an increase in the risk of the adverse event shortly following DPT vaccination, the proportion of cases in the time period in which most of the vaccinations take place should increase. More precisely, define p_i as the expected number of cases in age group 1 in time period i, p_0 as the expected proportion of non-vaccine-associated cases in the same group (independent of time period), and qi as the proportion of vaccinations in the same age group and time period. Furthermore, suppose that a proportion k/(+ k) of the adverse events in an age-period group are caused by the vaccines so that the expected value of pi equals $(p_0 + q_i \text{ k})/(1 + k)$. Under these assumptions, given qi and the number of vaccinations administered in each time period as reported by Shields and colleagues (1988), one can calculate the expected difference between the two time periods in the proportion of cases in age group 1, p_2 - p_1, its standard deviation, and thus the power of the test for a given value of k. Such calculations were performed for a range of appropri

[1] A more general version of the power calculations involving more than two groups was developed by Frederick Mosteller and Elizabeth Burdick of Harvard University (personal communication, 1991), and formed the mathematical basis of the simplified model used by the committee. The more complete model requires computer simulations for evaluation and is, thus, more complicated to implement. It was found, however, to yield results similar to those of the simplified model used here.

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ate values of *k,* and the values of *k* for which 50 and 80 percent powers were achieved were reported.

META-ANALYSES

Formal Analysis

As reported in Chapter 3, the committee found nine studies that offer some information on the timing of SIDS relative to vaccination. The following section describes in detail the methods used by the committee to perform a meta-analysis of these data. Part of the approach relies on standard methods for meta-analysis of clinical and epidemiologic data developed by DerSimonian and Laird (1986). But, because only four of the studies correct for the age pattern of SIDS (which would lead one to expect more SIDS cases in the first few days after vaccination than a uniform distribution would predict), an additional step was needed to adjust data from the poorly controlled studies.

The adjustment for the age pattern of SIDS was based on three studies that have proper controls for the age pattern of SIDS and roughly similar divisions of the time between vaccination and death: Griffin et al. (1988), Solberg (1985), and Walker et al. (1987). These studies indicate the number of observed and expected cases in three subdivisions of the (roughly) first month after vaccination: "early" is 0 to 3 days, "mid" is 4 to 7 days, and "late" is the rest of the month (which varies from 28 to 30 days). The study by Hoffman and colleagues (1987) has appropriate controls but is given in time intervals with breakpoints at 24 hours and 14 days, so it was not used in this part of the analysis.

In order to estimate an adjustment factor for the age pattern of SIDS, the fraction of expected cases in each period was compared to the fraction that would be expected if the SIDS deaths were uniformly distributed over time. The result is as expected: there are more deaths among the controls in the early and mid periods than a uniform distribution would predict. The ratios vary across the three studies, but all are in the predicted direction. The simple averages of the three ratios are as follows: early = 1.05, mid = 1.15, and late = 0.96.

These average ratios were then used to correct the five studies (Baraff et al., 1983; Bernier et al., 1982; Pollock et al., 1984; Taylor and Emery, 1982; Torch, 1982) that did not have appropriate controls, as follows. For each study, the number of cases that would have been expected in each interval under the uniform distribution was calculated first. Note that the "early" period is 0 to 2 days in one study, and the end of the "late" period ranges from 21 to 42 days. The average ratios from the first three studies were then applied to calculate an adjusted expected number of cases in each period.

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To summarize these results in a meta-analysis, the committee chose to use the DerSimonian and Laird (1986) approach to analyzing log odds ratios with appropriate sensitivity analyses for the major assumptions. The basic steps in this approach include (1) calculating an odds ratio for each study, comparing the proportion of deaths in the early period between cases and controls; (2) calculating a weighted average of the log odds ratios in which the weights reflect the variance of the individual estimates of the log odds ratios; and (3) calculating an additional weighted average based on a random-effects model, that is, assuming that the observed odds ratios are chosen at random from a population of odds ratios that would be obtained in similar studies. The DerSimonian and Laird approach also produces standard errors and confidence intervals for each weighted average. Because a number of statistical assumptions are possible, an analysis was performed to assess the sensitivity of the qualitative results to the assumptions.

The meta-analysis was based on the odds ratios that compared the number of deaths in the early period to the number in the early and late periods combined. Deaths in the mid period were excluded from the analysis because (1) the study of Hoffman and colleagues had no mid period, and (2) it was not clear whether mid-period deaths in the other studies should be aggregated into the early or late periods.

Because sample sizes in the studies of Taylor and Emery and Pollock and colleagues are so small (1 and 0 observed cases, respectively, in the early period), these two studies were not included in the analysis. Three alternative assumptions were made about the study of Hoffman and colleagues, which has two different control groups as well as a very different set of time breakpoints: (1) the results with both control groups are included as two separate studies, (2) only the results from the more highly matched control group B are included in the meta-analysis, and (3) no data from Hoffman and colleagues are included.

In four of the studies (Baraff et al., 1983; Bernier et al., 1982; Solberg, 1985; Torch, 1982) the expected numbers of cases are based on calculated distributions rather than on a sample of controls. In these cases, the committee assumed that only the observed proportion in the early period contributed to the standard error. This means that the confidence intervals from these studies understate the true uncertainty by an unknown amount. For the other three studies, the committee calculated standard errors without taking into account the matching and other variance reduction techniques that were actually used in the study. This implies that the resulting confidence intervals overstate the true uncertainty, again by an unknown amount.

The odds ratios for the individual studies, as shown in Figure D-l, range from 0.60 to 3.36. As Figure D-1 shows, the 95 percent confidence intervals for these odds ratios differ markedly from study to study. Some of the

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confidence intervals do not overlap, suggesting that a random-effects model is appropriate.

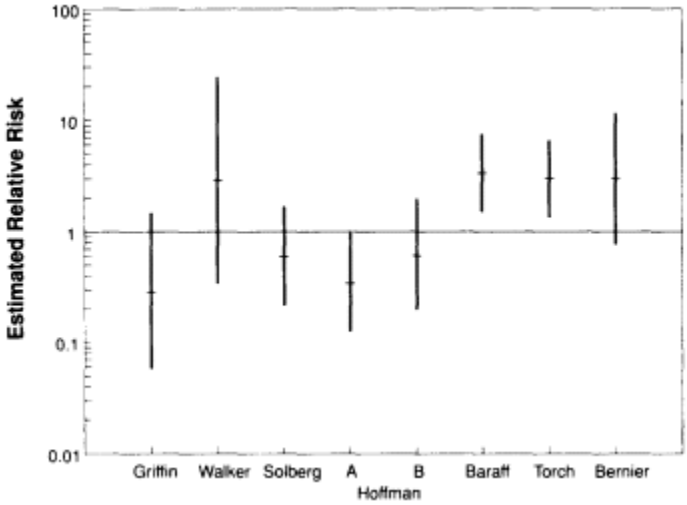

FIGURE D-1 Odds ratios and 95 percent confidence intervals for the risk of SIDS in the early period postvaccination for the seven studies included in the meta-analysis.

The results of the meta-analyses, shown in Figure D-2a, reflect the three assumptions about the study of Hoffman and colleagues laid out above and show the impact of choosing a fixed-effects or random-effects approach. Both assumptions have an impact on the calculations, but not enough to change the qualitative results. The decision to include or exclude the three less well controlled studies has somewhat more of an impact; if only the well-controlled studies are included in the meta-analysis, there is an almost significant inverse association between the vaccine and SIDS in the early period.

Figure D-2b shows the results of altering the categorization of deaths by time period. In the three studies that report on deaths after the first month, these are aggregated into the late period. The resulting meta-analyses differ little from those represented in Figure D-2a.

The committee also experimented with different adjustments for the age pattern of SIDS by varying the *E/U* ratio for the early period from 1.0 to 1.2 for the three studies with no internal controls. This change made very little difference in the results.

Thus, although the results depend somewhat on the statistical assumptions, in no case is there a significantly elevated average odds ratio for the

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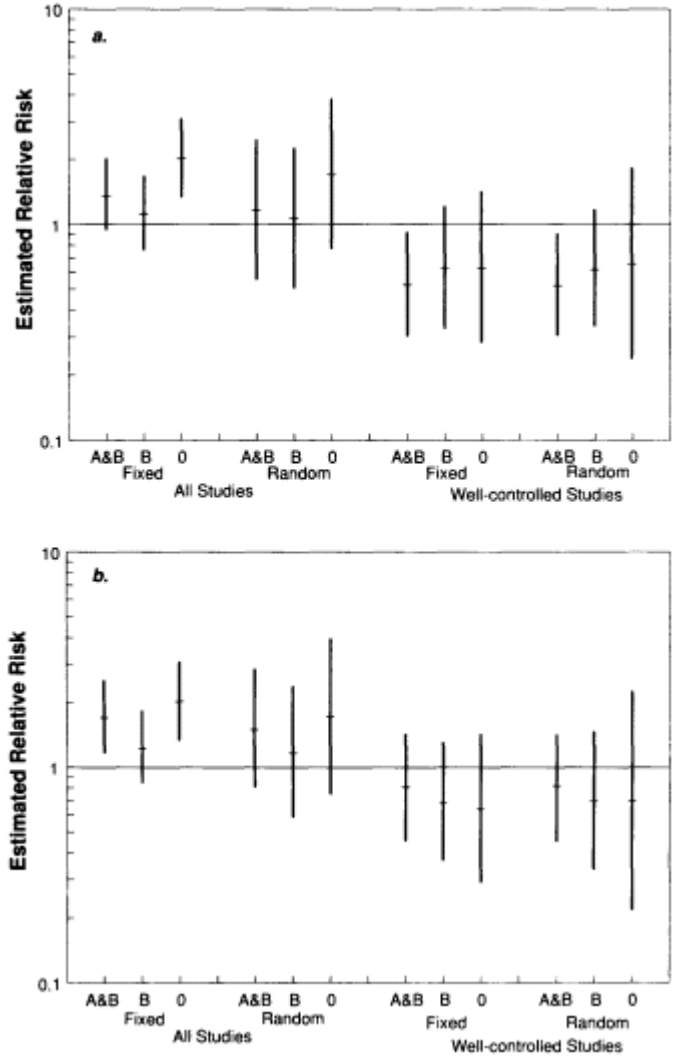

FIGURE D-2 a. Meta-analysis results comparing the estimated risk of SIDS in the early period postvaccination with that in the late part of the first month, under various assumptions: (1) whether all studies or only well-controlled studies are included in the meta-analysis, (2) whether a fixed- or a random-effects model is assumed, and (3) whether the meta-analysis includes results from the study of Hoffman et al. (1987) based on age-matched controls (A) and age-, race-, and birth-weight-matched controls (B), on B alone, or on neither (0). For each set of assumptions, the mean and 95 percent confidence interval from the meta-analysis are shown on a logarithmic scale. b. Similar results comparing SIDS deaths in the early period with deaths in the late period plus deaths after the end of the first month postvaccination.

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early period. Including the less well controlled studies, the average odds ratio is close to 1.0. Inclusion of only the well-controlled studies leads to a lower average odds ratio, under 0.6.

Informal Analysis

The committee felt that a formal meta-analysis as described above was not appropriate for the data on encephalopathy because of the relatively few cases recorded in studies other than the NCES. The committee did, however, make the following calculations to assess the consistency of data on encephalopathy from the other studies with those from the NCES.

Table D-2 lists the eight studies in which a number of vaccinated children in a defined population were monitored subsequent to vaccination. The number of children monitored and the number of encephalopathies recorded within 2 days (or 1 week, as explained in footnote a) are shown. The estimate of the total incidence in the 2 days postvaccination based on the data in all eight studies is 6.57 cases/864,041 children = 7.6 cases per million vaccinated children.

To determine the relative and attributable risks of encephalopathy following DPT immunization, the background incidence rate was estimated as follows. The four studies listed in Table 4-4 provide information on the total number of encephalopathy cases occurring in children of various ages.

TABLE D-2 Pooled Data for Encephalopathy Calculation

Reference	No. Children	No. Cases
Studies in defined populations		
Cody et al. (1981)	15,752	0
Pollock and Morris (1983)		
Self-reports	134,700	4
Hospital reports	17,000	0
Pollock et al. (1984)	6,004	1
Strom (1967)	516,276	1
Long et al. (1990	538	0
Controlled studies		
Walker et al. (1988)	26,600	0
Griffin et al. (1990)	38,171	0
Gale et al. (1990)	109,000	0.57[a]
Total	864,041	6.57

[a] There were two cases reported within I week of vaccination. Assuming a uniform distribution over the week, 2 x 2/7 = 0.57 cases were estimated to have occurred in the first 2 days.

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Because Beghi and colleagues (1984) found that the incidence of encephalopathy was higher in the first year of life than in the second or third years, these data could not be combined without taking into account the differences in the ages of the children. Assuming that the ratio of incidence in the first year life to the incidence in the second and third years as estimated in the study by Beghi and colleagues (22/15.8, or 1.4) is correct, each year of observation beyond the first birthday is equivalent to 1/1.4, or approximately 0.7 years of experience before the first birthday. By using this figure, adjusted background incidence rates were calculated for each study in Table 4-4 and for the four studies together by dividing the number of cases recorded outside of the immediate postvaccination interval by the number of first-year-equivalent years of observation. By pooling the results of the four studies in Table 4-4, the estimated background incidence rate for encephalopathy is estimated to be 78 per million children per year, or 0.43 per million children per 2-day period.

By comparing the estimated total incidence in the 2 days postvaccination derived from all eight studies listed in Table D-2 with the estimated background incidence rate during this same period, the RR in the 2 days postvaccination can be estimated at 7.6 per million divided by 0.43 per million = 17.7. The attributable risk for encephalopathy is the difference between the total incidence and the background incidence: 7.6 per million - 0.43 per million = 7.2 per million. Assuming that children, on average, receive three immunizations, the estimated attributable risk of encephalopathy is 2.4 per million immunizations.

If the studies of Pollock and Morris (1983) and Strom (1967), which relied on spontaneous reports for ascertainment, are excluded, the RR estimate is 17.1 and the attributable risk estimate is 2.3 per million immunizations. Relying only on the data in controlled studies of well-defined populations (Gale et al., 1990; Griffin et al. 1990; Walker et al., 1988), the total incidence in the week following vaccination is 2 cases per 173,771 children = 11.5 cases per million vaccinated children. Using a background rate of 0.43 x 7/2 per million = 1.5 per million, the RR estimate is 7.6 and the attributable risk estimate is 3.3 per million immunizations.

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E

Possible Involvement of Aluminum Salts in Erythema Multiforme, Encephalopathy, or Other Adverse Events After Pertussis Immunization

DPT vaccine preparations regularly contain aluminum salts (aluminum hydroxide, aluminum potassium sulfate, or aluminum phosphate) that are intended to serve as adjuvants (British National Formulary, 1988; Physicians' Desk Reference, 1989). Orlans and Verbov (1982) suggested that DPT-associated rashes could be due to aluminum hydroxide. Other more significant local reactions including nodules at the site of injection, itching, eczema, and circumscribed hypertrichosis over nodules have been observed more frequently following administration of aluminum hydroxide-adsorbed DPT vaccine than after administration of unadsorbed DPT vaccine (Pembroke and Marten, 1979).

Interest has developed recently in the potential health effects of aluminum, particularly in the setting of chronic renal failure, in which aluminum is not excreted from the body normally (Alfrey, 1984; Monteagudo et al., 1989). A severe, often fatal encephalopathy found in patients undergoing long-term dialysis was attributed to aluminum deposition in the brain (Alfrey et al., 1976). Reduction of aluminum in dialysate has largely eliminated this condition, but dialysis patients may still have subtle psychomotor defects that may be due to aluminum toxicity (Altmann et al., 1989). Animal studies have shown that aluminum can increase the rate of transmembrane diffusion across the blood—brain barrier (Banks and Kastin, 1989), which could possibly permit greater access of toxins to the brain.

Patients receiving long-term injections of aluminum-containing allergenic

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extracts had slightly increased levels of serum and urinary aluminum compared with those in age-matched controls receiving aqueous extracts, but aluminum levels in these patients did not fall outside the broad range of normal values (Glinert and Burnatowska-Hledin, 1988). Patients were estimated in this study to receive, on average, about 2.5 mg of aluminum per injection, with injections being given every 2 to 4 weeks for a period of 3 to 5 years. The DPT vaccines used in the United States are reported to contain not more than 0.25 to 0.8 mg of aluminum per 0.5-ml injection (Physicians' Desk Reference, 1989). One study suggested that use of aluminum-adsorbed DPT was associated with fewer febrile reactions than use of unabsorbed DPT vaccine was (Waight et al., 1983).

The possibility has been raised that the aluminum content of DPT vaccines might play a role in some of the adverse events that occur, or that are suspected to occur, in association with DPT immunization, particularly encephalopathy. However, there are no data to indicate that such a relationship exists.

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F

Committee and Staff Biographies

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JOHN C. BAILEY is Director of the Bear River District Health Department in Logan, Utah. He is Adjunct Professor of Public Health at Utah State University. He received his M.D. from the University of Utah School of Medicine. He is board certified in public health by the American Board of Preventive Medicine and is a fellow of the American College of Preventive Medicine. He currently serves on the Board of Directors for the National Association of County Health Officials. He has also been on several

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advisory bodies to the Utah State Health Department, including one on the development and administration of public immunization policy.

MARY LUZ COADY is Director of the Department of Pediatrics at Bryn Mawr Hospital, Bryn Mawr, Pennsylvania; Clinical Instructor in Pediatrics at the Temple University School of Medicine, Philadelphia; and a board-certified pediatrician in private practice in Bryn Mawr, Pennsylvania. Dr. Coady received an M.D. from the Women's Medical College of Pennsylvania and completed residencies in pediatrics at Children's Hospital of San Francisco and St. Christopher's Hospital for Children in Philadelphia. She is a fellow of the American Academy of Pediatrics and a member of the Pennsylvania Medical Society.

LINDA D. COWAN is Associate Professor in the Department of Biostatistics and Epidemiology, College of Public Health, at the University of Oklahoma, where she has been a faculty member since 1983. Dr. Cowan received her Ph.D. degree in epidemiology in 1979 from The Johns Hopkins University School of Hygiene and Public Health. After completing her degree, she was a postdoctoral fellow in neuroepidemiology at Children's Hospital, Boston, and the Harvard School of Public Health. From 1980 to 1983, Dr. Cowan was Assistant Member at the Oklahoma Medical Research Foundation where she worked on the national, collaborative Lipid Research Clinics Program. Dr. Cowan's research focuses on cardiovascular disease in adults, especially studies to elucidate gender differences in risk, and on the epidemiology of neurological disorders in infants and children, especially childhood epilepsy. Dr. Cowan has served as a member of the Epidemiology and Disease Control Study Section for the National Institutes of Health, is on the Editorial Board of *Brain and Development,* and is a member of the American Epidemiologic Society. She is currently on sabbatical at the Department of Pediatrics, New York University Medical Center.

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his undergraduate and medical education at Vanderbilt University and his postgraduate training at Children's Hospital, Boston, and Harvard Medical School. He has been chairman of the Department of Pediatrics at the National Jewish Center for Immunology and Respiratory Medicine and at the University of Pennsylvania. He is board certified in pediatrics and serves as a clinical immunologist for children. His clinical and research interests center about host defense against infection; his research involves the biochemical basis for the killing of invading microorganisms by phagocytic cells. He presently chairs the Advisory Committee for Vaccines and Related Biological Products for the Food and Drug Administration.

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