Immunization Safety Review

Vaccinations and Sudden Unexpected Death in Infancy

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

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Kathleen Stratton, Donna A. Almario, Theresa M. Wizemann, and Marie C. McCormick, *Editors*

Immunization Safety Review Committee
Board on Health Promotion and Disease Prevention

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Willing is not enough; we must do."
—Goethe

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

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recom-

mendations nor did they see the final draft of the report before its release. The review of this report was overseen by **Robert Lawrence, M.D.**, The Johns Hopkins University. Appointed by the National Research Council and Institute of Medicine, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Foreword

Vaccines are among the greatest public health accomplishments of the past century. In recent years, however, a number of concerns have been raised about both the safety of and the need for certain immunizations. Indeed, immunization safety is a contentious area of public health policy, with discourse around it having become increasingly polarized and exceedingly difficult. The numerous controversies and allegations surrounding immunization safety signify an erosion of public trust in those responsible for vaccine research, development, licensure, schedules, and policy making. Because vaccines are so widely used—and because state laws require that children be vaccinated to enter daycare and school, in part to protect others—immunization safety concerns should be vigorously pursued in order to restore this trust.

It is in this context that the Institute of Medicine (IOM) was approached more than a year ago by the Centers for Disease Control and Prevention and the National Institutes of Health to convene an independent committee that could provide timely and objective assistance to the Department of Health and Human Services in reviewing emerging immunization safety concerns.

The IOM was chartered by the National Academy of Sciences in 1970 to serve as an adviser to the federal government on issues affecting the public's health, as well as to act independently in identifying important issues of medical care, research, and education. The IOM thus brings to this mission three decades of experience in conducting independent analyses of significant public health policy issues. In particular, as described in more detail in this report, the IOM has a long history of involvement in vaccine safety. The IOM published its first major vaccine safety report in 1977, followed by a subsequent report in 1988; both

focused on the safety of polio vaccines. Two subsequent major reports, published in 1991 and 1994, examined the adverse events of childhood vaccines. Since then, the IOM has conducted several smaller studies and workshops focused on various vaccine safety topics. These studies were all well received by both the public and policy makers, and previous IOM committees on vaccine safety issues have been viewed as objective and credible.

Given the sensitive nature of the present immunization safety review study, the IOM felt it was especially critical to establish strict criteria for committee membership. These criteria prevented participation by anyone with financial ties to vaccine manufacturers or their parent companies, previous service on major vaccine advisory committees, or prior expert testimony or publications on issues of vaccine safety.

The rationale for imposing these stringent criteria was twofold. First, given growing public concern about vaccine safety and the public scrutiny surrounding this committee's work, it was important to establish standards that would preclude any real or perceived conflict of interest or bias on the part of the committee members. While the committee members all share a belief in the benefits of vaccines to the public health, none of them has any vested interest in any of the vaccine safety issues that will come before them. Second, the IOM wanted to ensure consistency in the committee membership and to avoid having members recuse themselves from the deliberations because they had participated in the development or evaluation of a vaccine under study.

Thus, the IOM has convened a distinguished panel of 15 members who possess significant breadth and depth of expertise in a number of fields, including pediatrics, neurology, immunology, internal medicine, infectious diseases, genetics, epidemiology, biostatistics, risk perception and communication, decision analysis, public health, nursing, and ethics. The committee members were chosen because they are leading authorities in their respective fields, are well respected by their colleagues, and have no conflicts of interest. This committee brought a fresh perspective to these critically important issues and approached its charge with impartiality and scientific rigor.

The IOM does not propose the use of the criteria it has laid out above in selecting members for federal vaccine advisory committees. The IOM committee was convened for a very different purpose from the usual federal vaccine advisory committees and, as such, required different standards.

As with all reports from the IOM, the committee's work was reviewed by an independent panel of experts. The purpose of the review process is to enhance the clarity, cogency, and accuracy of the final report and to ensure that the authors and the IOM are creditably represented by the report published in their names. The report review process is overseen by the National Research Council's (NRC) Report Review Committee (RRC), comprised of approximately 30 members of the National Academy of Sciences, National Academy of Engineering, and IOM. The IOM, in conjunction with the RRC, appoints a panel of reviewers with a

diverse set of perspectives on key issues considered in the report. Unlike the selection criteria for committee membership (discussed above), many reviewers will have strong opinions and biases about the report topic. The composition of the review panel is not disclosed to the committee until after the report is approved for release. While the committee must consider and evaluate all comments from reviewers, it is not obligated to change its report in response to the reviewers' comments. The committee must, however, justify its responses to the reviewers' comments to the satisfaction of the RRC's review monitor and the IOM's review coordinator. A report may not be released to the sponsors or the public, nor may its findings be disclosed, until after the review process has been satisfactorily completed and all authors have approved the revised draft.

This report represents the unanimous conclusions and recommendations of that dedicated committee whose members deliberated a critical health issue. The report's conclusions and recommendations should be of value to all concerned about these important matters.

Harvey V. Fineberg
President, Institute of Medicine

Acknowledgments

The committee would like to acknowledge the many speakers and attendees at its open meeting held on October 28, 2002, at the Beckman Center in Irvine, CA. The discussions were informative and helpful. The committee would also like to thank those people who submitted information to the committee through the mail or via e-mail. Finally, the committee would like to thank the IOM staff for their dedication to this project. Without their commitment, attention to detail, creativity, sensitivity, and hard work, this project would be unworkable.

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Executive Summary

ABSTRACT

With current recommendations calling for infants to receive multiple doses of vaccines during their first year of life and with sudden infant death syndrome (SIDS) the most frequent cause of death during the postneonatal period, it is important to respond to concerns that vaccination might play a role in sudden unexpected infant death. A death that occurs suddenly and unexpectedly in the first year of life, whether or not there is an underlying disorder that predisposes to death, has been referred to by the term "sudden unexpected death in infancy" (SUDI). SUDI includes deaths that can be attributed to identifiable causes and deaths for which the causes remain uncertain. SIDS is the diagnosis most commonly given to the deaths of uncertain cause. The committee reviewed epidemiologic evidence focusing on three outcomes: SIDS, all SUDI, and neonatal death (infant death, whether sudden or not, during the first 4 weeks of life). Based on this review, the committee concluded that the evidence favors rejection of a causal relationship between some vaccines and SIDS; and that the evidence is inadequate to accept or reject a causal relationship between other vaccines and SIDS, SUDI, or neonatal death. The evidence regarding biological mechanisms is essentially theoretical, reflecting in large measure the lack of knowledge concerning the pathogenesis of SIDS. Anaphylaxis related to vaccination has been discussed in detail in previous IOM reports and is reexamined in the report; the committee observed that anaphylaxis is known to be a rare but causally-related adverse event following the administration of some vaccines. Fatal anaphylaxis in infants is extraordinarily rare. The committee found no basis for a review of current immunization policies, but saw a clear need for continued research on adverse events following vaccination and on the biological basis for sudden unexpected infant deaths. See Box ES-1 for a summary of all conclusions and recommendations.

Immunization to protect children and adults from many infectious diseases is one of the greatest achievements of public health. Immunization is not without risks, however. Given the widespread use of vaccines, state mandates requiring vaccination of children for entry into day care, school, or college, and the importance of ensuring that trust in immunization programs is justified, it is essential that safety concerns receive assiduous attention.

The Immunization Safety Review Committee was established by the Institute of Medicine (IOM) to evaluate the evidence on possible causal associations between immunizations and certain adverse outcomes, and to then present conclusions and recommendations. The committee's mandate also includes assessing the broader societal significance of these immunization safety issues. While the committee members all share the view that immunization is generally beneficial, none of them has a vested interest in the specific immunization safety issues that come before the group.

The committee reviews three immunization safety review topics each year, addressing one at a time. In this sixth report in the series, the committee examines the hypothesis that infant vaccination is associated with an increased risk of sudden unexpected death during the first year of life.

The committee is charged with assessing both the scientific evidence regarding the hypotheses under review and the significance of the issues for society:

- The *scientific* assessment has two components: an examination of the epidemiologic and clinical evidence regarding a possible *causal relationship* between exposure to the vaccine and the adverse event; and an examination of theory and experimental evidence from human or animal studies regarding biological *mechanisms* that might be relevant to the hypothesis.
- The *significance* assessment addresses such considerations as the burden of the health risks associated with the vaccine-preventable disease and with the adverse event. Other considerations may include the perceived intensity of public or professional concern, or the feasibility of additional research to help resolve scientific uncertainty regarding causality.

The findings of the scientific and significance assessments provide the basis for the committee's recommendations regarding the public health response to the issues. In particular, the committee addresses needs for a review of immunization policy, for current and future research, and for effective communication strategies.

For its evaluation of the hypothesis that vaccinations given to infants may produce an increased risk of sudden unexpected death during the first year of life, the committee held an open scientific meeting in October 2002 to hear presentations on issues germane to the topic. These presentations are available in electronic form (audio files and slides) on the project website (www.iom.edu/imsafety). In addition, the committee reviewed an extensive collection of mate-

rial, primarily from the published, peer-reviewed scientific and medical literature. A list of the materials reviewed by the committee, including many items not cited in this report, can be found on the project's website.

THE FRAMEWORK FOR SCIENTIFIC ASSESSMENT

Causality

The Immunization Safety Review Committee has adopted the framework for assessing causality developed by previous IOM committees (IOM, 1991; 1994a, b), convened under the congressional mandate of P.L. 99-660 to address questions of immunization safety. The categories of causal conclusions used by the committee are as follows:

1. No evidence
2. Evidence is inadequate to accept or reject a causal relationship
3. Evidence favors rejection of a causal relationship
4. Evidence favors acceptance of a causal relationship
5. Evidence establishes a causal relationship.

Assessments begin from a position of neutrality regarding the specific vaccine safety hypothesis under review. That is, there is no presumption that a specific vaccine (or vaccine component) does or does not cause the adverse event in question. The committee does not conclude that the vaccine does not cause the adverse event merely if the evidence is inadequate to support causality. Instead, it concludes that the "evidence is inadequate to accept or reject a causal relationship."

Biological Mechanisms

Evidence considered in the scientific assessment of biological mechanisms[1] includes human, animal, and *in vitro* studies related to biological or pathophysiological processes by which immunizations could cause an adverse event. When other evidence of causality is available, biological data add supportive evidence but they cannot prove causality on their own.

The committee has established three general categories of evidence on biological mechanisms:

1. *Theoretical.* A reasonable mechanism can be hypothesized that is commensurate with scientific knowledge and does not contradict known physical and

[1]For a discussion of the evolution of the terminology concerning biological mechanisms, see the committee's earlier reports (IOM, 2001a,b; 2002a,b).

biological principles, but it has not been demonstrated in whole or in part in humans or in animal models.

2. *Experimental.* A mechanism can be shown to operate in *in vitro* systems, animals, or humans. But, experimental evidence often describes mechanisms that represent only a portion of the pathological process required for expression of disease. Showing that multiple portions of a process operate in reasonable experimental models strengthens the case that the mechanisms could possibly result in disease in humans.

3. *Evidence that the mechanism results in known disease in humans.* For example, the wild-type infection causes the adverse health outcome, or another vaccine has been demonstrated to cause the same adverse outcome by the same or a similar mechanism.

If the committee identifies evidence of biological mechanisms that could be operational, it will offer a summary judgment of that body of evidence as weak, moderate, or strong. The summary judgment of the strength of the evidence also depends both on the quantity (e.g., number of studies or number of subjects in a study) and quality (e.g., the nature of the experimental system or study design) of the evidence.

Sudden Unexpected Death in Infancy

A death that occurs suddenly and unexpectedly in the first year of life, whether or not there is an underlying disorder that predisposes to death, has been collectively termed "sudden unexpected death in infancy" (SUDI). It includes deaths that can be attributed to an identifiable cause as well as deaths for which the cause remains uncertain.

The committee looked widely for all possible associations between immunization and SUDI. Sudden infant death syndrome (SIDS) is the diagnosis most commonly given to infant deaths of uncertain cause and, as such, the committee focused largely on SIDS. After assessing other distinct contributors to SUDI the committee chose to also focus on inborn errors of metabolism (IEM) and anaphylaxis.

The committee acknowledges that vaccines protect against diseases that contribute to infant mortality. The committee's charge, however, was to examine sudden unexpected infant death, not all-causes of death.

SIDS is defined as "the sudden death of an infant under 1 year of age, which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history" (Willinger et al., 1991). SIDS deaths have been observed to peak at 2 to 4 months of age and to be somewhat higher in the fall and winter months (Adams et al., 1998; Sullivan and Barlow, 2001). SIDS mortality rates are higher for male infants than for female. SIDS deaths occur among all socioeconomic, racial, and

ethnic groups, but the rates vary widely. By definition, the cause or causes of SIDS are unknown, but a variety of often-interrelated risk factors—including maternal characteristics, prenatal factors, and postnatal conditions—have been identified. No agreement yet exists on the pathologies or mechanisms associated with the risk factors for SIDS. Several researchers have proposed variations on a "triple-risk" hypothesis, suggesting that SIDS can occur through the interaction of three factors: (1) an infant with an underlying vulnerability, (2) a critical developmental period, and (3) exposure to an exogenous stressor (Filiano and Kinney, 1994; Rognum and Saugstad, 1993; Wedgewood, 1972).

Inborn errors of metabolism (IEM) include over 400 genetically transmitted conditions that involve deficiencies of specific enzymes or transport proteins (McInnes and Clarke, 2002). One set of these disorders is related to fatty acid oxidation (FAO). Oxidation of fatty acids in the mitochondria is a key source of energy for the heart and skeletal muscles and plays an essential role in energy production during periods of fasting, or when illness or stress require higher energy consumption (McInnes and Clarke, 2002; Rinaldo et al., 1999; 2001). FAO defects can result in cardiomyopathy, acute metabolic crisis, or skeletal myopathy (Mathur et al., 1999), and they pose a particular risk of sudden death in infancy (Bennett and Powell, 1994; Mathur et al., 1999; McInnes and Clarke, 2002; Strauss et al., 1995). It is hypothesized that approximately 1 to 5 percent of all cases of sudden death in infancy are the result of an FAO disorder (Boles et al., 1998; Rinaldo et al., 1999). Some disorders can be detected through newborn screening programs. Over 35 IEM, including some FAO disorders, can now be identified through analysis of blood or bile specimens using a process of tandem mass spectrometry (Chace and Naylor, 2002). Such analysis is sometimes conducted as part of a "metabolic autopsy" in cases of sudden unexpected infant death (Wilcox et al., 2002).

Anaphylaxis is a type I, immediate-hypersensitivity immunologic reaction that can range from mild allergic rhinitis such as that triggered by pollens, to wheal and flare skin reactions following an insect bite, to severe and potentially fatal systemic anaphylaxis. An immediate reaction generally occurs within minutes of exposure to an antigen in a person who has been "sensitized" through a previous exposure to that antigen (Parham, 2000). A second, much more slowly evolving "late phase" hypersensitivity reaction is also possible, 4 to 8 hours after the immediate reaction subsides.

The biological mechanism underlying anaphylactic reactions to a foreign antigen (e.g., a food, drug, or environmental allergen) is well elucidated. When anaphylaxis occurs, it generally does so within a few hours of exposure to the antigen. The vast majority of these reactions can be readily resolved if medical treatment is received in a timely manner, but when treatment is not received, anaphylactic reactions can lead to death (although this occurs rarely).

Vaccines Routinely Administered During Infancy

Current recommendations call for children to receive multiple doses of seven different vaccines over the course of their first year of life. These include the combination diphtheria-tetanus-acellular pertussis vaccine (DTaP) and individual vaccines against *Haemophilus influenzae* type b (Hib), hepatitis B (HepB), polio (IPV), and pneumococcus (PCV). Often, several vaccines are administered at the same time.

HepB is the only vaccine routinely administered during the neonatal period. The others are given at about 2 months of age, with possible additional doses at 4 and 6 months. The timing of these vaccine doses coincides with the period of peak incidence of SIDS.

SCIENTIFIC ASSESSMENT

Causality

The committee's review of the epidemiologic evidence on the association between exposure to vaccines and SUDI focused on three outcomes: SIDS, sudden unexpected death (all SUDI), and neonatal death.

One causal relationship established in reviews by previous IOM committees—myocarditis as a consequence of infection with the vaccine-strain poliovirus used in oral polio vaccine (OPV)—was not reexamined for the present report (IOM, 1991, 1994a, b). Current U.S. immunization recommendations do not call for administration of any live-virus vaccines during the first year of life.

Sudden Infant Death Syndrome (SIDS)

The committee reviewed data on any relationship between SIDS and the individual diptheria–tetanus–whole-cell pertssis (DTwP), DTaP, HepB, Hib, and polio vaccines, and specific combinations of vaccines or any combination of vaccines.

Both the 1991 and 1994 IOM vaccine safety committees concluded from their reviews that the evidence favored rejection of a causal relationship between DTwP vaccine and SIDS (IOM, 1991, 1994b). Given that no additional analytical studies are available, **the present committee finds no basis for a change in the prior conclusion that the evidence favors rejection of a causal relationship between DTwP vaccine and SIDS**.

The epidemiologic evidence regarding the relationship between SIDS and receipt of DTaP vaccine consists of one uncontrolled observational study. **The committee concludes that the evidence is inadequate to accept or reject a causal relationship between DTaP vaccine and SIDS**. However, given that DTaP is associated with fewer adverse reactions than is DTwP, and that the

constituents of DTaP are relatively refined compared with those of DTwP, the committee found no reason to suspect that a causal relationship might exist between DTaP and SIDS when the evidence indicates that none exists with DTwP.

The committee concludes the evidence is inadequate to accept or reject causal relationships between SIDS and the individual vaccines Hib, HepB, OPV, and IPV. Since the 1991 and 1994 IOM reports, no additional epidemiologic studies have been published. The limited data available are drawn from Vaccine Adverse Event Reporting System (VAERS) case reports, which alone are insufficient to establish any causal link.

In the four controlled observational studies reviewed by the committee, exposure to multiple vaccines was not associated with an elevated risk of SIDS deaths. The committee notes that most of the studies reviewed were on multiple vaccines since most vaccines are usually administered in combination with other vaccines. These studies were subject to limitations resulting from a possible selection bias because of inclusion of SUDI cases in some of the analyses, controls whose immunization records could not be located, or parents who could not be interviewed or did not agree to participate in the study. Nevertheless, findings from studies in three different countries produced consistent results, and one study suggested a protective effect, but was not statistically significant (Fleming et al., 2001). The committee also reviewed an uncontrolled cohort study, an ecologic study, and a report on VAERS (Vaccine Adverse Event Reporting System) data. The findings in these studies contribute little to the assessment of causality, but provide no signals of risks. **The committee concludes that the evidence favors rejection of a causal relationship between exposure to multiple vaccines and SIDS.**

Sudden Unexpected Death

The committee reviewed two published studies that examined the association between exposure to multiple vaccines and all sudden unexpected death in infants. The committee considered only one of these studies (Fleming et al., 2001) to be methodologically strong. Thus, based on one methodologically strong study, **the committee concludes that the evidence is inadequate to accept or reject a causal relationship between exposure to multiple vaccines and sudden unexpected death in infancy, other than SIDS.**

The committee examined deaths caused by anaphylaxis (severe, immediate type I hypersensitivity reaction) after receipt of a vaccine, and it reexamined the conclusions from the previous IOM committees that reviewed this relationship.

A causal relationship had been established by previous IOM committees between DTwP[2] vaccine and anaphylaxis (IOM, 1991), and between tetanus-

[2]In infants and children.

toxoid-containing[3] and hepatitis B vaccines[4] and death from anaphylaxis (IOM, 1994a). Although very rare, anaphylaxis from any cause (e.g., food, drug, environmental allergen) can lead to sudden unexpected death. However, death of infants from anaphylaxis following vaccination has been reported in only one well-documented case report (of identical twin infants following administration of the second dose of a DwP vaccine; Werne and Garrow, 1946). **The present committee concludes that the evidence favors acceptance of a causal relationship between diphtheria toxoid-and whole cell pertussis vaccine and death due to anaphylaxis in infants.** It should be noted, however, that despite the more than 50 years subsequent to the publication of that case report and despite the widespread use of vaccines in infants, the committee could not identify in the medical literature any additional reports of death in infants due to vaccine-related anaphylaxis. This lack of data probably reflects two things: the relatively rare occurrence of anaphylaxis in response to vaccines, and the availability of an effective treatment for anaphylaxis that resolves the condition.

Neonatal Death

Only HepB vaccine is administered during the neonatal period. The committee reviewed data on neonatal death following receipt of HepB vaccine from one unpublished controlled observational study and from one published report describing VAERS data. Given the limitations of these data sources for assessing causality, **the committee concludes that the evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and neonatal death.**

Biological Mechanisms

Most sudden unexpected deaths in infancy are diagnosed as SIDS, a diagnosis that is reached specifically because all other known causes have been eliminated. This lack of a clear understanding of the causal pathways in SIDS complicates the task of identifying any mechanisms by which vaccination might be thought to contribute. For guidance, the committee looked to the various lines of research on SIDS, as reflected in the triple-risk models, and focused on vaccination as a potential source of stressors.

Considering both explained and unexplained infant deaths, the committee reviewed the evidence regarding biological mechanisms that might be related to vaccination in terms of three possible pathways: neuroregulatory abnormalities (including homeostatic and autonomic functions), inborn errors of metabolism,

[3]In children and adults. No data were available for infants.

[4]In children and adults. No data were available for infants.

and adverse immune responses. The committee's assessment included consideration of certain widely recognized, generally self-limited reactions to vaccination, particularly fever and decreased appetite, that are relevant to those pathways.

Neuroregulatory Abnormalities

Some hypotheses regarding SIDS link exogenous stimuli (e.g., prone positioning or tobacco smoke) to neuroregulatory abnormalities. Such interactions might involve the respiratory or cardiovascular systems, or both, and a failure of compensatory mechanisms (e.g., inability to restore vascular tone and normalize blood pressure; Harper, 2000). Vaccination might be thought to pose the risk of producing reactions—fever, listlessness, or altered sleep patterns, for example—that could serve as the exogenous stimuli for provoking abnormal neuroregulatory responses in vulnerable infants.

The committee considered evidence for two biological mechanisms that might link vaccination and neuroregulatory abnormalities—impaired respiratory responses and impaired arousal—but none was available. **In the absence of experimental or human evidence regarding the ability of common side effects of immunization, including fever and anorexia, to trigger sudden unexpected death in infants with underlying neuroregulatory abnormalities, the committee concludes that this mechanism is only theoretical.**

Inborn Errors of Metabolism

IEM involve deficiencies of specific enzymes or transport proteins, and those disorders—which are related to defects in fatty acid oxidation (FAO)— have been linked to sudden unexpected infant deaths (e.g., Bennett and Powell, 1994; Mathur et al., 1999; Strauss et al., 1995). Deaths from FAO disorders generally occur under circumstances such as illness or fasting that limit the supply of glucose and increase fat metabolism. Fever or anorexia following vaccination might be thought to induce metabolic responses similar to illness or fasting in infants with undiagnosed FAO disorders, thus posing a risk of sudden death.

In the absence of experimental or human evidence regarding the ability of common side effects of immunization, including fever and anorexia, to trigger an acute metabolic crisis in patients with IEM, the committee concludes that this mechanism for vaccine-related sudden unexpected infant death is only theoretical.

Adverse Immune Responses

Although some studies suggest that SIDS may result from an inappropriate immune response to common respiratory pathogens, data are not available to

show whether vaccination triggers the production of inflammatory cells or cytokines like those found in SIDS cases or whether those cells and cytokines are causally related to SIDS. **In the absence of experimental or human evidence demonstrating the ability of vaccines to stimulate an abnormal inflammatory response in the lung leading to sudden unexpected infant death, the committee concludes that this mechanism is only theoretical.**

Previous IOM reports considered cases of anaphylaxis occurring within 4 hours after immunization (IOM, 1991; 1994a). The present committee identified one case report of identical twin-infants (Werne and Garrow, 1946), in which symptoms began before 4 hours and progressed to death at 16 and 20 hours, respectively. Post-mortem analysis was consistent with an immediate-phase accompanied by a late-phase type I hypersensitivity reaction. In this case, the initial non-specific signs of an immediate-hypersensitivity (i.e., anaphylactic) reaction appear to have been initially unrecognized and progressed to death. The inflammatory infiltrates found in SIDS cases by standard autopsy techniques most likely result from infection, but it is not possible to exclude a contribution of late-phase allergic responses to these infiltrates in some cases. **Although a type I hypersensitivity reaction leading to death could possibly be missed both clinically and at post-mortem examination, and therefore misdiagnosed as SIDS, the committee concludes that this possibility is only theoretical.**

SIGNIFICANCE ASSESSMENT

Vaccines have made a substantial and an undeniable contribution to reductions in the toll of illness and death from several major infectious diseases. Nevertheless, vaccines are not completely free of risks, including a risk of fatal adverse events. To ensure that vaccines are as safe as possible and the value of vaccines is not undermined by fears about their use, it is essential to understand and minimize such risks. In the United States, current immunization recommendations call for vaccination of infants to begin at birth, with additional vaccines and vaccine doses given at 2, 4, and 6 months of age. Infants are among the most vulnerable members of society, and protecting them from avoidable health risks is a responsibility that parents share with physicians, nurses, others who provide health care, vaccine manufacturers, and officials who shape and implement health policies. Although the death of an infant from *any* cause is a grave loss to a family, infant deaths that might result from efforts to protect health must be a source of special concern.

Many of those who question the safety of vaccines include SIDS as a possible adverse outcome. Fears related to vaccination and SIDS must, in the committee's judgment, be considered a significant concern that deserves further attention. But investigating a possible relationship between vaccination and SIDS is complicated by at least three factors. First, research has yet to determine the cause or causes of SIDS, by definition, making it difficult to know what biologi-

cal mechanisms are relevant, with or without regard to vaccination. Second, epidemiologic investigations covering the past 10 to 15 years must take into account several changes in the vaccines administered to infants and the effects of SIDS-prevention efforts. Third, controlled prospective cohort studies to assess possible vaccine-related risks are difficult to conduct because SIDS deaths are increasingly rare and because most children in the United States are vaccinated.

RECOMMENDATIONS FOR PUBLIC HEALTH RESPONSE

Policy Review

The committee does not recommend a policy review of the recommended childhood vaccination schedule by any of the national or federal vaccine advisory bodies on the basis of concerns about sudden unexpected death in infancy.

Research

Surveillance and Epidemiological Studies

At the committee's meeting of October 2002, two recent studies on infant deaths were presented, based on the work of the Vaccine Safety Datalink (a government-HMO collaboration). Because of the attention to the VSD datasets paid by vaccine safety advocates and the potential contributions of the studies to the vaccine safety literature, **the committee urges prompt publication of these and all other VSD results.**

Basic and Clinical Science

The committee recommends continued research on the etiology and pathology of SIDS. It notes that the National Institute of Child Health and Human Development (NICHD, 2001) is targeting five areas of research: (1) the brain and homeostatic control, (2) autonomic development and function, (3) infant care and the sleep environment, (4) infection and immunity, and (5) genetics.

The committee makes its recommendation for further research recognizing that it has no basis for judging whether the results of such research will alter the balance of evidence that led to its conclusions in this report. Any research that helps to elucidate the mechanisms underlying SIDS would help future investigations of the potential association between sudden unexpected infant death and vaccines or any other hypothesized trigger.

The committee recommends that a comprehensive postmortem workup, including a metabolic analysis, be done on all infants who die suddenly and unexpectedly. For SIDS cases for which metabolic analyses, such as those that

use the tandem mass spectrometry method, were not done at birth, it may be useful to conduct such analyses with samples obtained at autopsy or, if available, using stored blood samples (bloodspots) originally obtained for newborn screening tests.

The committee encourages efforts by the Centers for Disease Control and Prevention (CDC), the American Academy of Pediatrics (AAP), and others to promote the development and consistent use throughout the United States of national guidelines for investigation, diagnosis, and reporting of SIDS cases. The committee notes the development of various resources in the United States and internationally to aid in standardizing approaches to the diagnosis of SIDS. In the United States, the accepted definition of SIDS specifies "the sudden death of an infant under 1 year of age which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history" (Willinger et al., 1991). The definition agreed to at more recent international consensus conferences does not restrict SIDS to infants under 1 year of age (Byard et al., 1996; Sullivan and Barlow, 2001).

Guidance from CDC (1996) and the AAP (1999; 2001) emphasizes the importance of post-mortem examinations and thorough investigation of death scenes to rule out other causes, especially child abuse, before deaths are attributed to SIDS. Also available is an international standardized protocol for autopsies in cases of sudden unexpected infant death (Krous, 1996). In the United States, however, requirements for investigation of unexpected infant deaths are officially established by state and local statutes (CDC, 1996).

The committee recommends the development of standard definitions and guidance for diagnosis and reporting of SUDI for research purposes. SUDI, unlike SIDS, is not a single, officially recognized cause of death. It can include deaths that are attributed to many different causes but that are linked by being sudden and unexpected. Despite the heterogeneity of SUDI, it is a useful concept for research on infant deaths following vaccination.

Consistent application of the criteria related to SIDS and SUDI will aid interpretation of reports of vaccine-related deaths and enhance the comparability of results from surveillance, epidemiological, and biological investigations.

BOX ES-1 Committee Conclusions and Recommendations

SCIENTIFIC ASSESSMENT

Causality Conclusions

There is no basis for a change in the prior conclusions that the evidence favors rejection of a causal relationship between DTwP vaccine and SIDS.

The evidence is inadequate to accept or reject a causal relationship between DTaP vaccine and SIDS.

The evidence is inadequate to accept or reject causal relationships between SIDS and the individual vaccines Hib, HepB, OPV, and IPV.

The evidence favors rejection of a causal relationship between exposure to multiple vaccines and SIDS.

The evidence is inadequate to accept or reject a causal relationship between exposure to multiple vaccines and sudden unexpected death in infancy, other than SIDS.

The evidence favors acceptance of a causal relationship between diphtheria toxoid-and whole cell pertussis vaccine and death due to anaphylaxis in infants.

The evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and neonatal death.

Biological Mechanisms Conclusions

In the absence of experimental or human evidence regarding the ability of common side effects of immunization, including fever and anorexia, to trigger sudden unexpected death in infants with underlying neuroregulatory abnormalities, the committee concludes that this mechanism is only theoretical.

In the absence of experimental or human evidence regarding the ability of common side effects of immunization, including fever and anorexia, to trigger an acute metabolic crisis in patients with inborn errors of metabolism, the committee concludes that this mechanism for vaccine-related sudden unexpected infant death is only theoretical.

In the absence of experimental or human evidence demonstrating the ability of vaccines to stimulate an abnormal inflammatory response in the lung leading to sudden unexpected infant death, the committee concludes that this mechanism is only theoretical.

The committee concludes that immediate type I hypersensitivity reactions to vaccines can cause SUDI within 24 hours of vaccine administration. Although a

continued

BOX ES-1 continued

type I hypersensitivity reaction leading to death could possibly be missed both clinically and at post-mortem examination, and therefore misdiagnosed as SIDS, the committee concludes that this possibility is only theoretical.

PUBLIC HEALTH RESPONSE RECOMMENDATIONS

Policy Review

The committee does not recommend a policy review of the recommended childhood vaccination schedule by any of the national or federal vaccine advisory bodies on the basis of concerns about sudden unexpected death in infancy.

Surveillance and Epidemiological Studies

The committee urges prompt publication of all Vaccine Safety Datalink results.

Basic and Clinical Science

The committee recommends continued research on the etiology and pathology of SIDS.

The committee recommends that a comprehensive postmortem workup, including a metabolic analysis, be done on all infants who die suddenly and unexpectedly.

The committee encourages efforts by the Centers for Disease Control and Prevention, American Academy of Pediatrics, and others to promote the development and consistent use throughout the United States of national guidelines for investigation, diagnosis, and reporting of SIDS cases.

The committee recommends the development of standard definitions and guidance for diagnosis and reporting of SUDI for research purposes.

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Immunization Safety Review: Vaccinations and Sudden Unexpected Death in Infancy

Immunization to protect children and adults from many infectious diseases is one of the greatest achievements of public health. Immunization is not without risks, however. It is well established, for example, that the oral polio vaccine can on rare occasion cause paralytic polio, that some influenza vaccines have been associated with a risk of Guillain-Barré syndrome, and that vaccines sometimes produce anaphylactic shock. Given the widespread use of vaccines, state mandates requiring vaccination of children for entry into school, college, or day care, and the importance of ensuring that trust in immunization programs is justified, it is essential that safety concerns receive assiduous attention.

The Immunization Safety Review Committee was established by the Institute of Medicine (IOM) to evaluate the evidence on possible causal associations between immunizations and certain adverse outcomes, and then to present conclusions and recommendations. The committee's mandate also includes assessing the broader significance for society of these immunization safety issues.

In this sixth report in a series, the committee examines the hypothesis that infant vaccination is associated with an increased risk of sudden unexpected death during the first year of life.

THE CHARGE TO THE COMMITTEE

Challenges to the safety of immunizations are prominent in public and scientific debate. Given these persistent and growing concerns about immunization safety, the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) recognized the need for an independent, expert group

to address immunization safety in a timely and objective manner. The IOM has been involved in such issues since the 1970s. (A brief chronology can be found in Appendix C.) In 1999, because of IOM's previous work and its access to independent scientific experts, CDC and NIH began a year of discussions with IOM to develop the Immunization Safety Review project, which would address both emerging and existing vaccine safety issues.

The Immunization Safety Review Committee is responsible for examining a broad variety of immunization safety concerns. Committee members have expertise in pediatrics, neurology, immunology, internal medicine, infectious diseases, genetics, epidemiology, biostatistics, risk perception and communication, decision analysis, public health, nursing, and ethics. While all the committee members share the view that immunization is generally beneficial, none of them has a vested interest in the specific immunization safety issues that come before the group. Additional discussion of the committee composition can be found in the Foreword written by Dr. Harvey Fineberg, President of the IOM.

The committee is charged with examining three immunization safety hypotheses each year during the three-year study period (2001–2003). These hypotheses are selected by the Interagency Vaccine Group (IAVG), whose members represent several units of the Department of Health and Human Services: the National Vaccine Program Office, the National Immunization Program, and the National Center for Infectious Diseases at CDC; the National Institute for Allergy and Infectious Diseases at NIH; the Food and Drug Administration; the National Vaccine Injury Compensation Program at the Health Resources and Services Administration; and the Centers for Medicare and Medicaid Services (formerly the Health Care Financing Administration). The IAVG includes representation from the Department of Defense and the Agency for International Development as well.

For each topic, the Immunization Safety Review Committee reviews relevant literature and submissions by interested parties, holds an open scientific meeting, and directly follows the open meeting with a 1- to 2-day closed meeting to formulate its conclusions and recommendations. The committee's findings are released to the public in a brief consensus report 60 to 90 days after its meeting.

The committee is charged with assessing both the scientific evidence regarding the hypotheses under review and the significance of the issues for society.

- The *scientific* assessment has two components: (1) an examination of the epidemiologic and clinical evidence regarding a possible *causal relationship* between exposure to the vaccine and the adverse event; and (2) an examination of theoretical, experimental, and observational evidence from *in vitro*, animal, or human studies regarding biological *mechanisms* that might be relevant to the hypothesis.
- The *significance* assessment addresses such considerations as the burden of the health risks associated both with the vaccine-preventable disease and the

adverse event. Other considerations may include the perceived intensity of public or professional concern, or the feasibility of additional research to help resolve scientific uncertainty regarding causality.

The findings of the scientific and significance assessments provide the basis for the committee's recommendations regarding the public health response to the issue. In particular, the committee addresses needs for a review of immunization policy, for current and future research, and for effective communication strategies. See Figure 1 for a schematic representation of the committee's charge.

THE STUDY PROCESS

The committee held an initial organizational meeting in January 2001. CDC and NIH presented the committee's charge at the meeting, and the committee then conducted a general review of immunization safety concerns. At this initial meeting, the committee also determined the basic methodology to be used for assessing causality in the hypotheses to be considered at subsequent meetings. A website (www.iom.edu/imsafety) and a listserv were created to provide public access to information about the committee's work and to facilitate communication with the committee. The conclusions and recommendations of the committee's reports thus far (see Box 1) are summarized in Appendix A.

For its evaluation of the potential role of vaccination in sudden unexpected death in infancy, the committee held an open scientific meeting in October 2002 (see Appendix B) to hear presentations on issues germane to the topic. These presentations are available in electronic form (audio files and slides) on the project website (www.iom.edu/imsafety). In addition, the committee reviewed an extensive collection of material, primarily from the published, peer-reviewed scientific and medical literature. A list of the materials reviewed by the commit-

BOX 1
Previous Reports by the Immunization Safety Review Committee

Immunization Safety Review: Measles-Mumps-Rubella Vaccine and Autism (IOM, 2001a)
Immunization Safety Review: Thimerosal-Containing Vaccines and Neurodevelopmental Disorders (IOM, 2001b)
Immunization Safety Review: Multiple Immunizations and Immune Dysfunction (IOM, 2002b)
Immunization Safety Review: Hepatitis B Vaccine and Demyelinating Neurological Disorders (IOM, 2002a)
Immunization Safety Review: SV40 Contamination of Polio Vaccine and Cancer (IOM, 2002c)

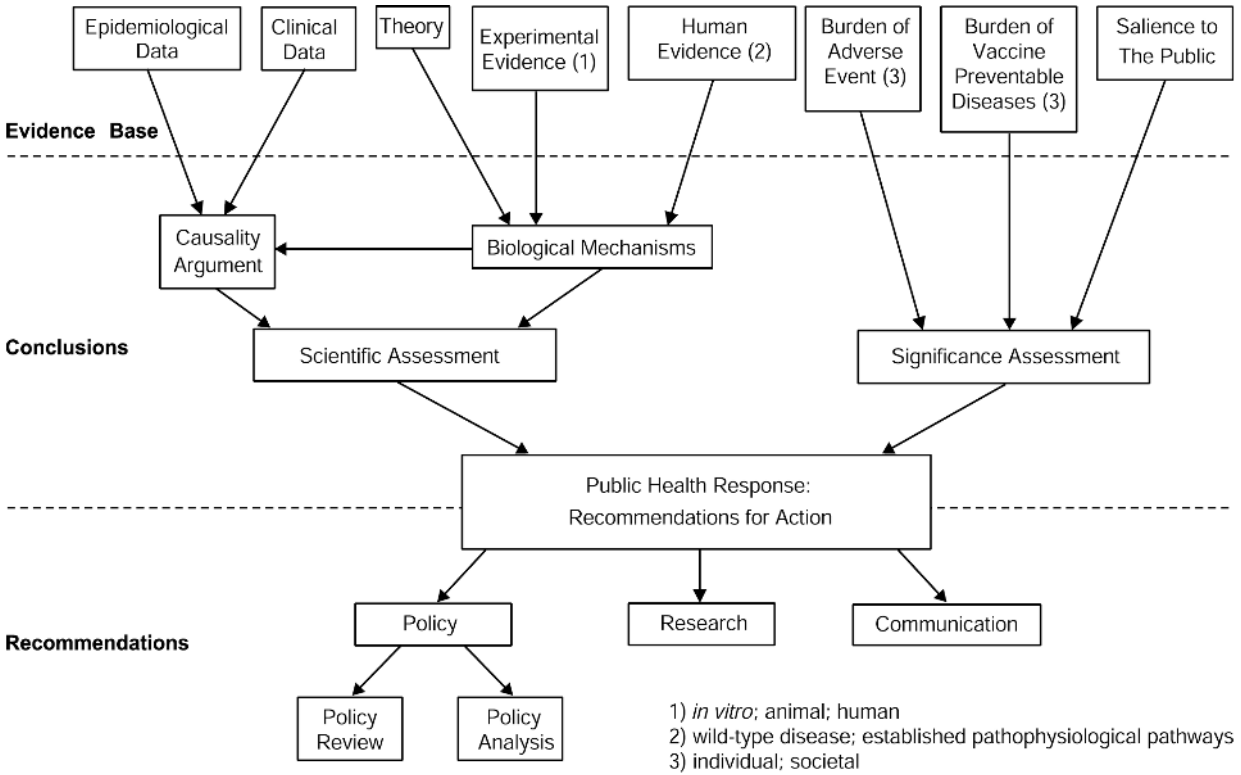


FIGURE 1 Committee charge.

tee, including many items not cited in this report, can be found on the project's website.

THE FRAMEWORK FOR SCIENTIFIC ASSESSMENT

Causality

The Immunization Safety Review Committee has adopted the framework for assessing causality developed by previous IOM committees (IOM, 1991; 1994a,b), convened under the congressional mandate of P.L. 99-660 to address questions of immunization safety. The categories of causal conclusions used by the committee are as follows:

1. No evidence
2. Evidence is inadequate to accept or reject a causal relationship
3. Evidence favors rejection of a causal relationship
4. Evidence favors acceptance of a causal relationship
5. Evidence establishes a causal relationship.

Assessments begin from a position of neutrality regarding the specific vaccine safety hypothesis under review. That is, there is no presumption that a specific vaccine (or vaccine component) does or does not cause the adverse event in question. The weight of the available clinical and epidemiologic evidence determines whether it is possible to shift from that neutral position to a finding for causality ("the evidence favors acceptance of a causal relationship") or against causality ("the evidence favors rejection of a causal relationship"). The committee does not conclude that the vaccine does not cause the adverse event merely if the evidence is inadequate to support causality. Instead, it maintains a neutral position, concluding that the "evidence is inadequate to accept or reject a causal relationship."

Although no firm rules establish the amount of evidence or the quality of the evidence required to support a specific category of causality conclusion, the committee uses standard epidemiologic criteria to guide its decisions. The most definitive category is "establishes causality," which is reserved for those relationships in which the causal link is unequivocal, as with the oral polio vaccine and vaccine-associated paralytic polio or with anaphylactic reactions to vaccine administration (IOM, 1991; 1994a). The next category, "favors acceptance" of a causal relationship, reflects evidence that is strong and generally convincing, although not firm enough to be described as unequivocal or established. "Favors rejection" is the strongest category in the negative direction. (The category of "establishes no causal relationship" is <u>not</u> used because it is virtually impossible to prove the absence of a relationship with the same surety that is possible in establishing the presence of one.)

If the evidence is not reasonably convincing either in support of or against causality, the category "inadequate to accept or reject a causal relationship" is used. Evidence that is sparse, conflicting, of weak quality, or merely suggestive—whether toward or away from causality—falls into this category. Under these circumstances, some authors of similar assessments use phrases such as "the evidence does not presently support a causal association." The committee believes, however, that such language does not make the important distinction between evidence indicating that a relationship does not exist (category 3) and evidence that is indeterminate with regard to causality (category 2).

The category of "no evidence" is reserved for those cases in which there is a complete absence of clinical or epidemiologic evidence.

The sources of evidence considered by the committee in its scientific assessment of causality include epidemiologic and clinical studies directly addressing the question at hand. That is, the data are specifically related to the effects of the vaccine(s) under review and the adverse health outcome(s) under review— in this report, the effects of vaccination on the risk for sudden unexpected death in infancy.

Epidemiologic studies carry the most weight in a causality assessment. These studies measure health-related exposures and outcomes in a defined set of subjects and then make inferences about the nature and strength of associations between exposures and outcomes in the overall population from which the study sample was drawn. Epidemiologic studies can be categorized as observational or experimental (clinical trial), and as uncontrolled (descriptive) or controlled (analytic). Among the various study designs, experimental studies generally have the advantage of random assignment to exposures and are therefore the most influential in assessing causality. Uncontrolled observational studies are important but are generally considered less definitive than controlled studies. In uncontrolled observational studies, where observations are made over time, confounding factors such as changing case definitions or improving case detection may affect the apparent incidence and prevalence of the adverse outcomes studied.

Case reports and case series are generally inadequate by themselves to establish causality. Despite the limitations of case reports, the causality argument for at least one vaccine-related adverse event (the relationship between vaccines containing tetanus toxoid and Guillain-Barré syndrome) was strengthened most by a single, well-documented case report on recurrence of the adverse event following re-administration of the vaccine, a situation referred to as a "rechallenge" (IOM, 1994a).

Biological Mechanisms

The committee's causality assessments must be guided by an understanding of relevant biological processes. Evidence considered in the scientific assessment

of biological mechanisms[1] includes human, animal, and *in vitro* studies related to biological or pathophysiological processes by which immunizations could cause an adverse event.

When convincing statistical or clinical evidence of causality is available, biological data add support. But this committee is often faced with circumstances in which the epidemiologic evidence is judged inadequate to accept or reject a causal association between a vaccine exposure and an adverse event of concern. It is then left with the task of examining proposed or conceivable biological mechanisms that might be operating *if* an epidemiologically sound association could be shown between a vaccine exposure and an adverse event. The biological data alone cannot be invoked as proof of causality, however.

The committee has established three general categories of evidence on biological mechanisms:

1. Theoretical. A reasonable mechanism can be hypothesized that is commensurate with scientific knowledge and does not contradict known physical and biological principles, but has not been demonstrated in whole or in part in humans or in animal models. Postulated mechanisms by which a vaccine might cause a specific adverse event but for which no coherent theory exists would not qualify for this category. Thus, "theoretical" is not a default category, but one that requires thoughtful and biologically meaningful suppositions.

2. Experimental. A mechanism can be shown to operate in *in vitro* systems, animals, or humans. But, experimental evidence often describes mechanisms that represent only a portion of the pathological process required for expression of disease. Showing that multiple portions of a process operate in reasonable experimental models strengthens the case that the mechanisms could possibly result in disease in humans.

Some experimental evidence is derived under highly contrived conditions. For example, achieving the results of interest may require extensive manipulation of the genetics of an animal system, or *in vivo* or *in vitro* exposures to vaccine antigen that are extreme in terms of dose, route, or duration. Other experimental evidence is derived under less contrived conditions. For example, a compelling animal or *in vitro* model might demonstrate a pathologic process analogous to human disease when a vaccine antigen is administered under conditions similar to human use. Experimental evidence can also come from studies in humans. In any case, biological evidence is distinct from the epidemiologic evidence obtained from randomized controlled trials and other population-based studies that are the basis for the causality assessment.

3. Evidence that the mechanism results in known disease in humans. For example, the wild-type infection causes the adverse health outcome associated

[1]For a discussion of the evolution of the terminology concerning biological mechanisms, see the committee's earlier reports (IOM, 2001a,b; 2002a,b,c).

with the vaccine, or another vaccine has been demonstrated to cause the same adverse outcome by the same or a similar mechanism. Data from population-based studies of the risk of adverse outcomes following vaccination constitute evidence regarding causality, not biological mechanisms.

If the committee identifies evidence of biological mechanisms that could be operating, it will offer a summary judgment of that body of evidence as weak, moderate, or strong. Although the committee tends to judge biological evidence in humans as "stronger" than biological evidence from highly contrived animal models or *in vitro* systems, the summary judgment of the strength of the evidence also depends on the quantity (e.g., number of studies or number of subjects in a study) and quality (e.g., the nature of the experimental system or study design) of the evidence. Obviously, the conclusions drawn from this review depend both on the specific data and scientific judgment. To ensure that its own summary judgment is defensible, the committee intends to be as explicit as possible regarding the strengths and limitations of the biological data.

The committee's examination of biological mechanisms reflects their opinion that available information on possible biological explanations for a relationship between immunization and an adverse event should influence the design of epidemiologic studies and analyses. Similarly, the essential consideration of confounders and effect modifiers in epidemiologic studies depends on an understanding of the biological phenomena that could underlie or explain the observed statistical relationship. The identification of sound biological mechanisms can also guide the development of an appropriate research agenda and aid policymakers, who frequently must make decisions without having definitive information regarding causality.

In addition, investigating and understanding possible biological mechanisms is often of value even if the available epidemiologic evidence suggests the absence of a causal association. A review of biological data could give support to the negative causality assessment, for example, or it could prompt a reconsideration or further investigation of the epidemiologic findings. If new epidemiologic studies were to question the existing causality assessment, the biological data could gain prominence in the new assessments.

Published and Unpublished Data

Published reports carry the most weight in the committee's assessment because their methods and findings are laid out in enough detail to be assessed. Furthermore, those published works that undergo a rigorous peer review are subject to comment and criticism by the entire scientific community. In general, the committee cannot rely heavily on unpublished data in making its scientific assessments (regarding either causality or biological mechanisms) because they usually lack the comment and criticism provided by peer review and must there-

fore be interpreted with caution. The committee also relies on editorial and peer-review procedures to ensure the disclosure of potential conflicts of interest that might be related to the source of funding for the research study. The committee does not investigate the source of funding of the published research reports it reviews, nor does the funding source influence the committee's interpretation of the evidence.

Unpublished data and other reports that have not undergone peer review do have value, however, and are often considered by the committee. They might be used, for example, in support of a body of published, peer-reviewed literature with similar findings. If the committee concluded that the unpublished data were well described, had been obtained using sound methodology, and presented very clear results, the committee could report, with sufficient caveats in the discussion, how the unpublished data fit with the entire body of published literature. Only in extraordinary circumstances, however, could an unpublished study refute a body of published literature.

The Immunization Safety Review Committee's scope of work includes consideration of clinical topics for which high-quality experimental studies are rarely available. Many other panels making clinical recommendations using evidence-based methods are able to require that randomized trials be available to reach strong conclusions, but, the IOM committee was convened specifically to assess topics that are of immediate concern yet for which data of any kind may just be emerging. Given the unique nature of this project, therefore, the committee deemed it important to review and consider as much information as possible, including unpublished reports. The committee does not perform primary or secondary analyses of unpublished data, however. In reviewing unpublished material, the committee applies generally accepted standards for assessing the quality of scientific evidence, as described above. (All unpublished data reviewed by the committee and cited in this report are available—in the form reviewed by the committee—through the public access files of the National Academies. Information about the public access files is available at 202-334-3543 or www.nationalacademies.org/publicaccess.)

UNDER REVIEW: VACCINATIONS AND SUDDEN UNEXPECTED DEATH IN INFANCY

Infant Mortality: Rates and Causes of Death

Infant mortality refers to deaths that occur between birth and 1 year of age. In 2000, there were approximately 28,000 infant deaths in the United States, and the infant mortality rate was 6.9 deaths per 1,000 live births (Miniño et al., 2002). This rate in 2000 is the lowest ever recorded in the United States and is 25 percent lower than the rate of 9.2 in 1990. The decline in the infant mortality rate during the 1990s is attributed in part to the use of surfactants and other medical interven-

tions that improved the survival of premature and low-birth-weight infants, and, in part to reductions in sudden infant death syndrome (SIDS) that resulted from the spreading adoption of recommendations that prone positions be avoided for infant sleep.

Various characteristics of infants or their mothers are associated with differences in the infant mortality rate (Mathews et al., 2002). The rate is higher for male infants (7.2) than for female infants (6.0). Low birth weight and premature birth are associated with especially high rates of infant mortality; in 2000, the mortality rate for infants born weighing less than 1,500 grams was 244.3 per 1,000 births, compared with 2.5 for infants who weighed 2,500 grams or more at birth. Low birth weight and prematurity contribute to an even higher mortality rate in multiple births (Branum, 2002). Higher infant mortality rates are also associated with lack of prenatal care, births to teenage mothers, and maternal smoking during pregnancy.

Among racial and ethnic groups in 2000, the lowest infant mortality rate was 3.5, seen for children born to mothers of Chinese origin. For children of non-Hispanic white mothers, the rate was 5.7. The overall rate for infants born to Hispanic mothers was 5.6, but within the Hispanic population it was highest for children of Puerto Rican mothers (8.2). For children born to American Indian mothers, the rate was 8.3. Infant mortality was highest for the non-Hispanic black population, with 13.6 deaths per 1,000 live births (Branum, 2002; Mathews et al., 2002). Some of the difference among racial and ethnic groups is accounted for by their differences in rates of low birth weight.

About two-thirds of infant deaths occur within 27 days of birth, a period designated as neonatal. In 2000, approximately 80 percent of neonatal deaths occurred within the early part of the neonatal period—the first 6 days of life—and most early neonatal deaths occurred less than 24 hours after birth (Branum, 2002; Mathews et al., 2002). For 2000, the neonatal mortality rate was 4.6 deaths per 1000 births (Mathews et al., 2002). The postneonatal mortality rate—deaths at ages 28 days to 1 year—was 2.3.

Most deaths occurring during the neonatal period are related to problems arising during gestation or delivery. The five leading causes of neonatal mortality in 2000 were (1) disorders related to short gestation and low birth weight, (2) congenital anomalies, (3) effects of maternal complications of pregnancy, (4) effects of pregnancy complications related to the cord or placenta, and (5) respiratory distress (Branum, 2002).

In contrast to the neonatal period, the leading causes of infant death during the postneonatal period reflect the impact of social and environmental factors, as well as biological ones. The five leading causes of postneonatal infant mortality in 2000 were (1) SIDS, (2) congenital anomalies, (3) unintentional injuries, (4) diseases of the circulatory system, and (5) assault (Branum, 2002).

Sudden Unexpected Death in Infancy

A death that occurs suddenly and unexpectedly in the first year of life, whether or not there is an underlying disorder that predisposes the infant to death, has been referred to collectively by the term "sudden unexpected death in infancy" (SUDI). It includes deaths that can be attributed to an identifiable cause as well as deaths for which the cause remains uncertain. SIDS is the diagnosis most commonly given to the deaths of uncertain cause.

No generally accepted list of causes of death has been established to define SUDI. As a result, it is difficult to assess the national rate of SUDI in the population from vital statistics data. However, special investigations examining deaths in infants less than a year old in Quebec (Cote et al., 1999) and in several regions in the United Kingdom (Leach et al., 1999) found that about 80% of the SUDI cases in the study sample could be attributed to SIDS.

The committee acknowledges that vaccines protect against diseases that contribute to infant mortality. The committee's charge, however, was to examine sudden unexpected infant death, not all-causes of death. For purposes of this report, the committee looked widely for all possible associations with SUDI but focused particularly on three distinct contributors to sudden unexpected death in infants—SIDS, inborn errors of metabolism, and anaphylaxis—in considering possible links to immunization.

Sudden Infant Death Syndrome

SIDS is defined as "the sudden death of an infant under 1 year of age, which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history" (Willinger et al., 1991). Although this definition calls for an autopsy and other investigation of the death before a diagnosis of SIDS is made, Sullivan and Barlow (2001) note that autopsy rates and protocols for investigation of infant deaths vary among countries and among regions within countries.

In the United States in 2000, the 2,523 deaths from SIDS accounted for 9 percent of all infant deaths (Anderson, 2002). Of those deaths, 2,319 occurred in the postneonatal period, representing 25 percent of all postneonatal deaths. SIDS deaths have been observed to peak at 2 to 4 months of age and to be somewhat higher in the colder fall and winter months than in spring and summer (Adams et al., 1998; Sullivan and Barlow, 2001). Also characteristic of SIDS is higher mortality rates for male infants than for female infants. In 2000, the postneonatal SIDS mortality rate in the United States was 67.6 per 100,000 live births for males and 46.2 for females.

SIDS deaths occur among all socioeconomic and racial and ethnic groups, but the rates vary widely. For non-Hispanic African-American infants in 2000, the postneonatal mortality rate from SIDS was 122.9 per 100,000 births, com-

pared with 51.4 for non-Hispanic white infants and 34.7 for Hispanic infants (Anderson, 2002). Postneonatal mortality rates for SIDS were also high for American Indian/Alaskan Native infants (103.2). The lowest rate was for infants who were classified as Asian or Pacific Islander (19.9).

By definition, the cause or causes of SIDS are unknown, but a variety of often interrelated risk factors have been identified. From their review of the research literature, Sullivan and Barlow (2001) point to maternal characteristics, prenatal factors, and postnatal conditions. Factors related to the mother that increase the risk of SIDS include lower socioeconomic status, less education, and a first pregnancy before age 20. Maternal smoking appears to be an important SIDS risk factor for infants. The risks associated with prenatal versus postnatal exposure (to smoking by the mother or others in the household) remain unclear (Sullivan and Barlow, 2001), however, a survey of the published data examining the risk of SIDS from paternal smoking, where the mother is a non-smoker, suggests that the increased SIDS risk may be predominately due to *in utero* exposure of the fetus rather than postnatal environmental smoke (Mitchell and Milerad, 1999). Infants who are premature or have a low birth weight are also at increased risk for SIDS. Some researchers note that risk factors of SIDS are common to those of explained deaths (Leach et al., 1999).

Many postnatal risk factors for SIDS are linked to infant care practices (Sullivan and Barlow, 2001). Most notably, babies who are put to sleep on their stomachs are at substantially increased risk. Sleeping on soft surfaces that may obstruct breathing such as cushions or foam pads, sheepskin rugs, waterbeds, and loose bedding also appear to increase the risk of SIDS (Gilbert-Barness et al., 1991). Overwrapping an infant, which can possibly result in overheating, may also be a risk factor. Sullivan and Barlow (2001) note mixed findings regarding the risk to an infant who shares a bed with an adult, but they point to clearer indications that sharing a room with an adult has a beneficial effect.

No agreement yet exists on the pathologies or mechanisms associated with the risk factors for SIDS. Some investigations suggest that abnormalities in the brainstem or other areas of the brain might impair ventilatory or circulatory responses during sleep or to conditions such as a lack of oxygen or an excess of carbon dioxide (e.g., Harper, 2001; Kinney et al., 2001). Others report evidence of an abnormal inflammatory response in some SIDS deaths (e.g., Howat et al., 1994; Vege and Rognum, 1999). Chronic hypoxemia has been suggested as a final common pathway to SIDS. Studies have demonstrated elevated levels of fetal hemoglobin in postmortem blood samples from SIDS infants compared to age-matched living and deceased control infants (Cochran-Black et al., 2001; Fagan and Walker, 1992; Gilbert-Barness et al., 1993; Perry et al., 1997). It has also been suggested that cardiac arrhythmias and congenital long-QT syndrome may be responsible for some cases of SIDS (Schwartz et al., 1998; 2000). One study demonstrated spontaneous mutations in cardiac ion channels in approxi-

TABLE 1 Triple Risk Hypotheses in Sudden Infant Death Syndrome

Triple Risk Model Filiano and Kinney, 1994	Fatal Triangle Rognum and Saugstad, 1993	Triple Risk Hypothesis Wedgewood, 1972
A vulnerable infant (e.g., an underlying brain abnormality)	Predisposing factors (e.g., astrogliosis, genetic make-up)	General factors that increase the probability of death from any cause (e.g., poverty, prematurity, gender, and race)
A critical developmental period in homeostatic control (e.g., regulation of sleep and wake patterns, breathing, and temperature)	A vulnerable developmental stage of central nervous system and mucosal immunity	Age-specific risks related to an infant's developmental status
An exogenous stressor (e.g., infection, hyperthermia, sleep position)	A trigger event (e.g., infection)	Precipitating factors (e.g., sleep state, position, and infection)

SOURCE: Guntheroth and Spiers, 2002; Filiano and Kinney, 1994.

mately 2 percent of the SIDS cases in the cohort evaluated (Ackerman et al., 2001).

Several researchers have proposed variations on a "triple-risk" hypothesis to try to account for the pathogenesis of at least a portion of SIDS deaths (Filiano and Kinney, 1994; Rognum and Saugstad, 1993; Wedgewood, 1972). According to these models, SIDS can occur through the interaction of three factors: (1) an infant with an underlying vulnerability, (2) a critical developmental period, and (3) exposure to an exogenous stressor (see Table 1).

The widely used Filiano and Kinney model is currently cited on the CDC website (www.cdc.gov/nip/vacsafe/concerns/sids/default.htm) and reflected in the strategic plan on SIDS from the National Institute of Child Health and Human Development at NIH (NICHD, 2001). Guntheroth and Spiers (2002), however, question the contribution of these triple-risk models to the overall understanding of the pathogenesis of SIDS. In particular, they assert that abnormalities in neurotransmitter systems found in the brains of some infants who died of SIDS cannot be proven to have had a prenatal rather than a postnatal origin.

Some deaths given a diagnosis of SIDS undoubtedly represent cases of misdiagnosis. For example, investigators have found indications of underlying metabolic disorders in a small percentage of infant deaths diagnosed as SIDS (e.g., Bennett and Powell, 1994; Boles et al., 1998). Also, the American Academy of Pediatrics (2001) cites reports that in the past up to 5 percent of SIDS deaths might have been the result of child abuse.

Inborn Errors of Metabolism

Inborn errors of metabolism (IEM) include over 400 genetically transmitted conditions involving deficiencies of specific enzymes or transport proteins (McInnes and Clarke, 2002). One set of these disorders is related to fatty acid oxidation (FAO). Oxidation of fatty acids in the mitochondria is a key source of energy for the heart and skeletal muscles, and it plays an essential role during periods of fasting or when illness or stress require higher energy consumption (McInnes and Clarke, 2002; Rinaldo et al., 1999; 2001).

FAO defects can result in cardiomyopathy, acute metabolic crisis (hepatic encephalopathy with hypoketotic hypoglycemia), or skeletal myopathy (Mathur et al., 1999), and they pose a particular risk of sudden unexpected death in infancy (Bennett and Powell, 1994; Mathur et al., 1999; McInnes and Clarke, 2002; Strauss et al., 1995). Deaths from these metabolic disorders generally occur during periods of increased fat metabolism, including birth, illness, and fasting. It is estimated that approximately 1 to 5 percent of all cases of sudden unexpected death in infancy are the result of an FAO disorder (Boles et al., 1998; Rinaldo et al., 1999; Wilcox et al., 2002).

If correctly diagnosed, many patients can be successfully treated with simple and inexpensive therapeutic measures such as the avoidance of fasting, careful control of diet, and vigilance during illness. Some disorders can be detected through newborn screening programs; similar techniques are also being used to test postmortem samples for evidence of FAO and other IEM disorders.

FAO disorders are probably the most common form of IEM, with at least 22 different FAO disorders characterized thus far (Rinaldo et al., 1999). Among the more common deficiencies are medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency, carnitine uptake defect (primary carnitine deficiency), carnitine palmitoyltransferase (CPT) deficiencies I and II, carnitine-acylcarnitine translocase deficiency, and glutaric acidemia type II (McInnes and Clarke, 2002).

Over 35 IEMs, including some FAO disorders, can now be identified through analysis of blood or bile specimens using a process of tandem mass spectrometry (Chace and Naylor, 2002). In the United States, four laboratories are currently able to perform such analyses which are sometimes conducted as part of a "metabolic autopsy" in cases of sudden unexpected infant death (Wilcox et al., 2002). Because early detection of IEM can improve the management of these disorders, there is also interest in including metabolic analyses as part of newborn screening programs. Analysis can also be done later, using the dried blood spot on the newborn screening card. Several states already include screening for certain IEMs as part of standard newborn testing, and studies and cost-benefit analyses of the use of tandem mass spectrometry for an expanded program of routine newborn

screening are in progress (Filiano et al., 2002; Naylor and Chace, 1999; Schoen et al., 2002).

Anaphylaxis

Anaphylaxis is a potentially life-threatening allergic response. It occurs when an allergen enters the blood stream, causing widespread activation of tissue mast cells associated with blood vessels. This disseminated mast cell activation causes increased vascular permeability and constriction of smooth muscle in the airways. There can be a loss of fluid from the blood, a drop in blood pressure, and swelling of connective tissue, leading to shock and organ damage (Parham, 2000). Anaphylaxis is a type I, immediate hypersensitivity immunologic reaction. Type I reactions can range from mild allergic rhinitis such as that triggered by pollens, to wheal and flare skin reactions following an insect bite, to severe and potentially fatal systemic anaphylaxis.

An immediate reaction generally occurs within minutes of exposure to an antigen in a person who has been "sensitized" through a previous exposure to that antigen (Parham, 2000). A second, much more slowly evolving "late phase" hypersensitivity reaction is also possible, 4 to 8 hours after the immediate reaction subsides. Whereas immediate reactions are the direct result of activation of mast cells, late phase reactions result from the effects of leukocytes (including eosinophils and type 2 helper T [Th2] cells) recruited to the site and the proinflammatory mediators and cytokines that they release there. (Busse and Lemanske, 2001; Parham, 2000).

Anaphylaxis is known to be a rare but causally related adverse event following the administration of some vaccines. Anaphylaxis related to vaccination has been discussed in detail in previous IOM reports (IOM, 1991; 1994a).

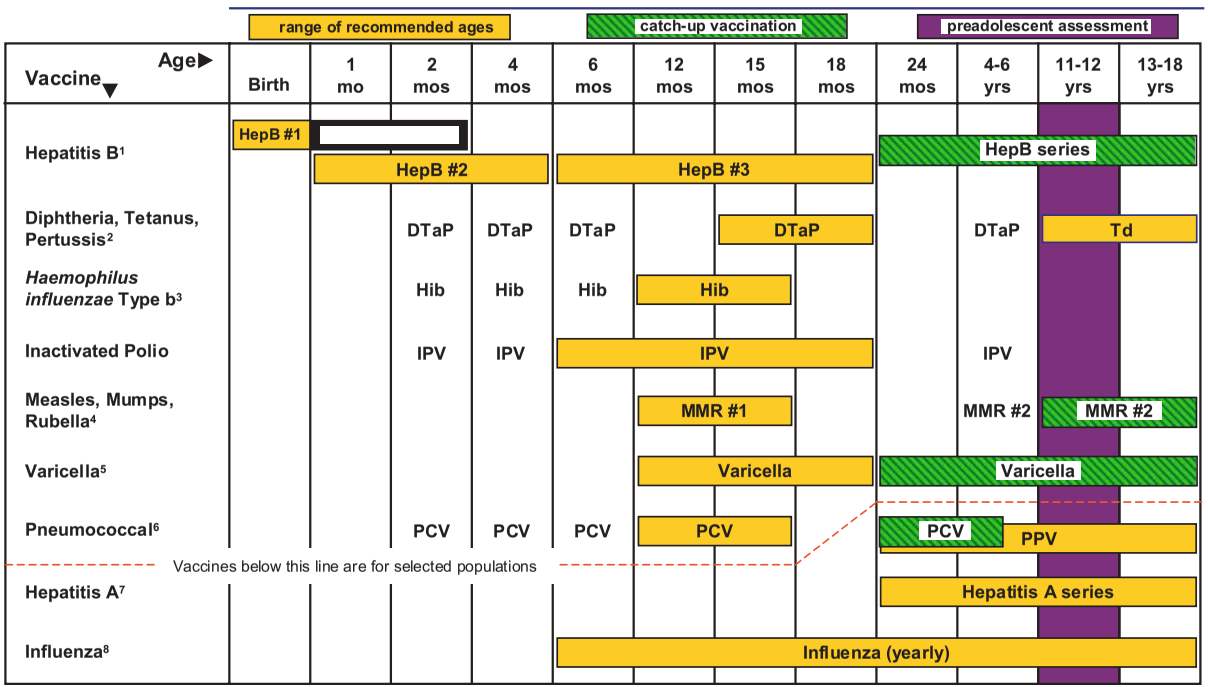
Vaccines Routinely Administered During Infancy

Current recommendations call for children to receive multiple doses of seven different vaccines over the course of their first year of life (see Figure 2). These vaccines are the combination product diphtheria-tetanus-acellular pertussis vaccine (DTaP) and individual vaccines against *Haemophilus influenzae* type b (Hib), hepatitis B (HepB), polio (IPV), and pneumococcus (PCV). Often, several vaccines are administered at the same time.

HepB is administered to many children within 24 hours after birth, making it the only vaccine routinely administered during the neonatal period. Children usually begin receiving the other recommended vaccines at about 2 months of age and receive additional doses of some of the vaccines at 4 and 6 months. The timing of these vaccine doses coincides with the period of peak incidence of SIDS.

Most of the currently recommended vaccines have been added to the child-

FIGURE 2: Recommended Childhood and Adolescent Immunization Schedule—United States, 2003.



This schedule indicates the recommended ages for routine administration of currently licensed childhood vaccines, as of December 1, 2002, for children through age 18 years. Any dose not given at the recommended age should be given at any subsequent visit when indicated and feasible. Indicates age groups that warrant special effort to administer those vaccines not previously given. Additional vaccines may be licensed and recommended during the year. Licensed combination vaccines may be used whenever any components of the combination are indicated and the vaccine's other components are not contraindicated. Providers should consult the manufacturers' package inserts for detailed recommendations.

1. Hepatitis B vaccine (HepB). All infants should receive the first dose of hepatitis B vaccine soon after birth and before hospital discharge; the first dose may also be given by age 2 months if the infant's mother is HBsAg-negative. Only monovalent HepB can be used for the birth dose. Monovalent or combination vaccine containing HepB may be used to complete the series. Four doses of vaccine may be administered when a birth dose is given. The second dose should be given at least 4 weeks after the first dose, except for combination vaccines which cannot be administered before age 6 weeks. The third dose should be given at least 16 weeks after the first dose and at least 8 weeks after the second dose. The last dose in the vaccination series (third or fourth dose) should not be administered before age 6 months.

Infants born to HBsAg-positive mothers should receive HepB and 0.5 mL Hepatitis B Immune Globulin (HBIG) within 12 hours of birth at separate sites. The second dose is recommended at age 1-2 months. The last dose in the vaccination series should not be administered before age 6 months. These infants should be tested for HBsAg and anti-HBs at 9-15 months of age.

Infants born to mothers whose HBsAg status is unknown should receive the first dose of the HepB series within 12 hours of birth. Maternal blood should be drawn as soon as possible to determine the mother's HBsAg status; if the HBsAg test is positive, the infant should receive HBIG as soon as possible (no later than age 1 week). The second dose is recommended at age 1-2 months. The last dose in the vaccination series should not be administered before age 6 months.

2. Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP). The fourth dose of DTaP may be administered as early as age 12 months, provided 6 months have elapsed since the third dose and the child is unlikely to return at age 15-18 months. **Tetanus and diphtheria toxoids (Td)** is recommended at age 11-12 years if at least 5 years have elapsed since the last dose of tetanus and diphtheria toxoid-containing vaccine. Subsequent routine Td boosters are recommended every 10 years.

3. *Haemophilus influenzae* type b (Hib) conjugate vaccine. Three Hib conjugate vaccines are licensed for infant use. If PRP-OMP (PedvaxHIB® or ComVax® [Merck]) is administered at ages 2 and 4 months, a dose at age 6 months is not required. DTaP/Hib combination products should not be used for primary immunization in infants at ages 2, 4 or 6 months, but can be used as boosters following any Hib vaccine.

4. Measles, mumps, and rubella vaccine (MMR). The second dose of MMR is recommended routinely at age 4-6 years but may be administered during any visit, provided at least 4 weeks have elapsed since the first dose and that both doses are administered beginning at or after age 12 months. Those who have not previously received the second dose should complete the schedule by the 11-12 year old visit.

5. Varicella vaccine. Varicella vaccine is recommended at any visit at or after age 12 months for susceptible children, i.e. those who lack a reliable history of chickenpox. Susceptible persons aged 13 years should receive two doses, given at least 4 weeks apart.

6. Pneumococcal vaccine. The heptavalent **pneumococcal conjugate vaccine (PCV)** is recommended for all children age 2-23 months. It is also recommended for certain children age 24-59 months. **Pneumococcal polysaccharide vaccine (PPV)** is recommended in addition to PCV for certain high-risk groups. See *MMWR* 2000;49(RR-9);1-38.

7. Hepatitis A vaccine. Hepatitis A vaccine is recommended for children and adolescents in selected states and regions, and for certain high-risk groups; consult your local public health authority. Children and adolescents in these states, regions, and high risk groups who have not been immunized against hepatitis A can begin the hepatitis A vaccination series during any visit. The two doses in the series should be administered at least 6 months apart. See *MMWR* 1999;48(RR-12);1-37.

8. Influenza vaccine. Influenza vaccine is recommended annually for children age 6 months with certain risk factors (including but not limited to asthma, cardiac disease, sickle cell disease, HIV, diabetes, and household members of persons in groups at high risk; see *MMWR* 2002;51(RR-3);1-31), and can be administered to all others wishing to obtain immunity. In addition, healthy children age 6-23 months are encouraged to receive influenza vaccine if feasible because children in this age group are at substantially increased risk for influenza-related hospitalizations. Children aged 12 years should receive vaccine in a dosage appropriate for their age (0.25 mL if age 6-35 months or 0.5 mL if aged 3 years). Children aged 8 years who are receiving influenza vaccine for the first time should receive two doses separated by at least 4 weeks.

For additional information about vaccines, including precautions and contraindications for immunization and vaccine shortages, please visit the National Immunization Program Website at www.cdc.gov/nip or call the National Immunization Information Hotline at 800-232-2522 (English) or 800-232-0233 (Spanish).

Approved by the Advisory Committee on Immunization Practices (www.cdc.gov/nip/acip), the American Academy of Pediatrics (www.aap.org), and the American Academy of Family Physicians (www.aafp.org).

hood immunization schedule since 1990 (see Appendix C). Between 1963 and 1990, children in the United States generally received only the diphtheria–tetanus–whole-cell pertussis vaccine (DTwP) and an oral polio vaccine (OPV) during their first year of life. Those vaccines were replaced by DTaP and IPV in the mid-1990s. Hib and HepB were added to the childhood immunization schedule in 1991 and 1992, respectively. PCV was added in 2000.

Two other recommended vaccines—measles-mumps-rubella and varicella—have not been considered by the committee for this report because they are usually administered for the first time after the first year of life—at 12 to 15 months of age.

SCIENTIFIC ASSESSMENT

The committee's scientific assessment focuses on epidemiologic evidence regarding a possible association between vaccinations and sudden unexpected death in infancy, as well as on evidence concerning biological mechanisms through which vaccination might contribute to that outcome.

One causal relationship established in reviews by previous IOM committees (IOM, 1991; 1994a) was not reexamined for the present report. This was the relationship for myocarditis as a consequence of infection with the vaccine-strain poliovirus used in OPV (IOM, 1994a). An infant died 4 days after receiving the second dose of OPV and DTP, and postmortem studies isolated vaccine-strain poliovirus from the infant's myocardium. The present committee concluded that further investigation of the role of vaccine-strain infections in infant deaths was not warranted however, because current U.S. immunization recommendations do not call for administration of any live-virus vaccines during the first year of life.

Causality

The committee's review of the epidemiologic evidence on the association between exposure to vaccines and sudden unexpected death in infancy focused on three outcomes: SIDS, SUDI, and neonatal death. Where available, evidence related to a single vaccine is reviewed first, followed by a discussion of evidence related to specific combinations of vaccines or to any combination of vaccines. The committee notes that individual vaccines are usually administered in combination with other vaccines and are rarely, if ever, given individually.

Passive surveillance data from the Vaccine Adverse Events Reporting System (VAERS) on infant deaths following vaccination, including published reports, are briefly described when they are available for a given outcome and vaccine. As discussed in previous IOM reports (IOM, 1991; 1994a,b) and in other published articles (Chen, 2000; Ellenberg and Chen, 1997), such passive surveillance data are of limited value in assessing causality.

Included in the committee's review of the evidence on vaccines and sudden unexpected infant deaths is anaphylaxis (severe, immediate type I hypersensitivity reaction), which on rare occasions can be fatal (CDC, 1996b). The biological mechanism underlying anaphylactic reactions to a foreign antigen (e.g., a food, drug, or environmental allergen) is well elucidated.[2] When anaphylaxis occurs, it generally does so within a few hours of exposure to the antigen. The vast majority of these reactions can be readily resolved if medical treatment is received in a timely manner, but when treatment is not received, anaphylactic reactions can, although rarely, lead to death. To assure that the review of SUDI was comprehensive, the committee examined the evidence on infant death due to anaphylactic reactions. The committee also considered the possibility that SUDI could occur as the result of fatal late-phase anaphylactic reaction following a mild immediate-hypersensitivity reaction that was clinically missed. Such a delayed, unexpected reaction is discussed as a potential biological mechanism later in this report.

The committee notes that for SIDS the focus was on reviewing epidemiologic data that have become available since the completion of previous IOM reports on vaccine safety (1991; 1994a). The approach used in these reports for the review of the earlier epidemiologic evidence was judged comparable to the approach of the present committee. Allowing for a possible concern that SIDS deaths might be missed through misclassification, the committee took note of unpublished data that were presented at its scientific meeting in October 2002. These data, from a study conducted through the Vaccine Safety Datalink (VSD) project, showed no significant association between receipt of any specific vaccines and deaths from all causes within 1 week or 1 month of vaccination for children between ages 1 month and 7 years (Ward, 2002). A detailed review of the evidence concerning vaccination and infant deaths from all causes was judged as falling outside the committee's charge to focus on sudden unexpected infant death.

Sudden Infant Death Syndrome

The committee reviewed data on any relationship between SIDS and the individual DTwP, DTaP, HepB, Hib, and polio vaccines. The committee also reviewed data on any relationship between SIDS and specific combinations of vaccines or any combination of vaccines. The committee notes that individual vaccines are usually administered in combination with other vaccines and are rarely, if ever, given individually.

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[2]For further discussion on anaphylaxis, see the biological mechanisms section of this report, as well as Busse and Lemanske (2001) and Parham (2000).

DTwP Vaccine

Both the 1991 and 1994 IOM vaccine safety committees concluded from their reviews that the evidence favored rejection of a causal relationship between DTwP vaccine and SIDS (IOM, 1991; 1994a). Detailed descriptions of the studies reviewed can be found in the earlier IOM reports. Since the completion of those two reports, no additional epidemiologic studies examining the association between exposure to DTwP vaccine and SIDS have been published. In 1997 DTaP replaced DTwP as the recommended vaccine in the childhood immunization schedule in the United States.

Given that no additional analytical studies are available, the committee found no reason to reconsider the conclusions of the previous committees. **Thus, the committee finds no basis for a change in the prior conclusion that the evidence favors rejection of a causal relationship between DTwP vaccine and SIDS**.

DTaP Vaccine

Germany. In a prospective multicenter trial in Germany, Schmitt and colleagues (1996) examined data on 22,505 infants to assess the safety, reactivity, and immunogenicity of three doses of DTaP vaccine. Subjects were recruited from pediatric outpatient clinics and private practices in six areas of the former West Germany. Excluded from the study were infants with any signs of previous pertussis infection, any other acute or chronic illness, or any indication of a possible allergic reaction to one of the vaccine components. The infants received their first dose of DTaP at 8 to 24 weeks of age, and the second and third vaccine doses after 28- to 35-day intervals. In accordance with the German immunization schedule, infants may also have received Hib vaccine and/or OPV. Researchers reported 95 percent power to detect rare events with an incidence of 1 per 10,000.

Parents were given diaries to record any serious adverse events occurring over the 28 to 35 days after each vaccination. This provided for an observation period of approximately 3 months following receipt of the first dose. Serious adverse events included hospitalizations; events that were fatal, life threatening, or disabling; congenital abnormalities; or the occurrence of malignancies. Also recorded were severe early onset reactions, such as anaphylaxis, and other symptoms considered serious by investigators. Researchers focused their analysis on SIDS, neurologic events, and hypotonic-hyporesponsive episodes.

A total of 153 (0.23%) serious adverse events were reported for the 67,000 vaccine doses administered during the study period. Of these, nine were fatalities of which none were related to exposure to DTaP vaccine, according to the authors. Seven of the deaths were attributed to SIDS: three occurred 8 to 14 days after vaccination, another three occurred 15 to 30 days after vaccination, and one occurred 2 months after vaccination. One sudden unexpected death was reported in a 14-month-old, 10 months after receipt of the third dose. The authors reported

that the observed incidence of SIDS (0.031%) in the study was below the expected annual incidence in the general population (0.1-0.17%).

The study is limited by the lack of a control group. In addition, the basis for the authors' conclusion that the fatalities were not related to vaccination was not made clear in the paper. It was also unclear how the cause of death was assessed. These flaws limit the study's contribution to the committee's causality assessment.

Causality Argument

The epidemiologic evidence regarding the relationship between SIDS and receipt of DTaP vaccine consists of one uncontrolled observational study (see Table 2). The authors of that study (Schmitt et al., 1996) found no indication of an elevated incidence of SIDS in vaccinated infants. The committee also examined a published report (Braun et al., 2000) on passive surveillance data from VAERS for infants who received a pertussis-containing vaccine (DTaP, DTwP, or DTwPH [diphtheria, tetanus, whole-cell pertussis, and Hib vaccine]) between January 1, 1995, and June 30, 1998. Information on SIDS deaths was not provided, but the data appeared to suggest that DTaP was associated with fewer reports of adverse events than was DTwP. The VAERS data appear consistent with clinical trial results where fewer reactions were reported after receipt of DTaP than after receipt of DTwP vaccine (Decker et al., 1995; Decker and Edwards, 1996; Greco et al., 1996).

The committee concludes that the evidence is inadequate to accept or reject a causal relationship between DTaP vaccine and SIDS. However, given the indication that DTaP is associated with fewer adverse reactions than DTwP, the committee found no reason to suspect that a causal relationship might exist between DTaP and SIDS when the evidence indicates that none exists with DTwP.

Other Vaccines

Hepatitis B Vaccine. An earlier IOM committee found no published studies on the relationship between HepB vaccine and SIDS. Only VAERS reports of SIDS following immunization with HepB vaccine were available. Based on those data, the earlier committee concluded that the evidence was inadequate to accept or reject a causal relationship between HepB vaccine and SIDS (IOM, 1994a). The present committee found no epidemiologic studies that examine the association between HepB vaccine and SIDS that had been published since the previous IOM report. Niu and colleagues (1999) describe 18 reports to VAERS between 1991 and 1998 of neonatal deaths following HepB vaccination. Autopsy reports were available for 17 cases, of which 12 were diagnosed as SIDS.[3] Three cases initially attributed to SIDS were assigned other diagnoses following autopsy.

[3]Deaths during the neonatal period are usually not attributed to SIDS, despite a negative investigation.

TABLE 2 Evidence Table: Exposure to DTaP Vaccine and Sudden Infant Death Syndrome

Citation	Design	Population	Assessment of Vaccine Exposure
Schmitt et al. (1996)	Cohort	22,505 infants, each receiving 3 doses of DTaP Germany	First dose of DTaP at age 8 to 24 weeks; 2nd and 3rd doses after 28- to 35-day intervals. Infants may also have received Hib and/or OPV. DTaP doses recorded by investigators as doses were administered.

Hib Vaccine. An earlier IOM vaccine safety committee found no published studies on the relationship between Hib vaccine and SIDS. Only VAERS reports following immunization with Hib vaccine were available. Based on those data, the earlier committee concluded that the evidence was inadequate to accept or reject a causal relationship between Hib vaccine and SIDS (IOM, 1994a). The present committee identified no studies on the relation between Hib and SIDS that had been published since the previous IOM report.

Polio Vaccines. An earlier IOM vaccine safety committee noted that the possible causal relation between polio vaccines and SIDS has rarely been studied. Most studies examined the risk of SIDS after exposure both to DTwP and polio vaccines, and only one study reported the risk estimate for SIDS after receipt of OPV. VAERS reports of SIDS following OPV immunization were also available. A detailed description of the few studies reviewed by that group concerning OPV can be found in its report (IOM, 1994a). Based on the available data, the earlier committee concluded that the evidence was inadequate to accept or reject a causal relationship between polio vaccines and SIDS (IOM, 1994a).

In September 1996, a recommendation was made to use IPV in place of OPV for the first two doses of the childhood polio immunization schedule in the

Outcomes	Results	Comment	Contribution to Causality Argument
Serious adverse events, recorded by parents over 28- to 35-day period after each vaccination or identified by investigators. Researchers focused on SIDS, neurologic events, and hypotonic-hyporesponsive episodes. Children with neurologic events followed for 1 year or longer.	**Serious Adverse Events: 153** Fatalities = 9 SIDS = 7 cases Incidence = 0.031 per 100	Observed SIDS incidence (0.031%) was lower than the annual SIDS incidence in general population (0.1-0.17%). Authors note that fatalities were not related to vaccine, but do not state reasons for this conclusion. Also, no SIDS case definition provided, which may lead to misclassification bias. There were no controls in this study.	The study provides weak evidence of no association between DTaP and SIDS; weaknesses in the study limit its contribution to the causality argument.

United States. These vaccine doses are usually given at ages 2 and 4 months of age.

Since the 1994 report, the present committee found only one published passive surveillance study concerning OPV or IPV and SIDS. Wattigney and colleagues (2001) examined VAERS reports submitted between January 1, 1991 and December 31, 1998 that mentioned receipt of either IPV or OPV. Both vaccines were usually co-administered with other vaccines, including DTaP, Hib, and HepB. The authors note no indication of a marked change in reported adverse events following the recommendation for use of IPV. There were 72 reports of death following receipt of OPV or IPV in 1997 and 70 reports in 1998. A majority of these deaths were attributed to SIDS (44 in 1997 and 45 in 1998). From January 1991 to September 1996, SIDS was mentioned in 8.6 percent of the IPV-related reports and 20.3 percent of OPV-related reports, concerning infants age 1 to 6 months. From October 1996 to December 1998, SIDS was mentioned in 22.2 percent of the IPV-related reports and 22.1 percent of the OPV-related reports in the same age group.

The passive surveillance data available from VAERS do not contribute to assessing causality. Since the 1994 report, the present committee found no addi-

tional epidemiologic studies concerning OPV and SIDS. The committee also notes that as of 2000, OPV is no longer part of the recommended childhood schedule in the United States. Neither the present committee nor the earlier IOM committee found epidemiologic studies that have examined the relationship between IPV and SIDS.

Causality Conclusion

The committee concludes the evidence is inadequate to accept or reject causal relationships between SIDS and the individual vaccines Hib, HepB, OPV, and IPV. Since the 1991 and 1994 IOM reports, no additional epidemiologic studies have been published. The limited data available are drawn from VAERS case reports, which alone are insufficient to establish any causal link.

Multiple Vaccines

Controlled Observational Studies

United Kingdom. Fleming and colleagues (2001) conducted a case-control study to examine the association between immunization status under an accelerated immunization program and SUDI, including SIDS. In 1990, the immunization schedule in the United Kingdom was changed to administer DTwP and OPV at 2, 3, and 4 months, instead of at 3, 5, and 9 months. In 1992, Hib was added to the schedule. The study of immunization status was part of a study of sudden unexpected death in infancy for the Confidential Enquiry into Stillbirths and Deaths in Infancy (the CESDI SUDI study)(CESDI SUDI, 2000).

The cases were infants aged 1 week to 1 year who died suddenly and unexpectedly in various parts of England between February 1993 and January 1995 or April 1995 and March 1996. The study included infants whose deaths were explained and infants whose deaths were unexplained and diagnosed as SIDS. As described in another report on the CESDI SUDI study, infant deaths were identified through a network of professionals and lay organizations (Leach et al., 1999). This method was found to have identified 98.3 percent of SUDI that occurred in the study regions. Each case was matched with four controls on the basis of age, locality, and time of last sleep. The controls for each case were selected from the population served by the health visitor who had been assigned to the infant who died.[4]

Interviews were conducted with the families of case and control infants generally within a week of the index death. For each control, a "reference sleep"

[4]A health visitor is a nurse with special training in community-based child health surveillance (Leach et al., 1999).

was identified that corresponded to the time of death of the matching case. Immunization histories were obtained from parental records. Immunization exposure was based on receipt of any component of the immunization program before a case infant's last sleep or before a control infant's reference sleep. For the case infants, a multidisciplinary team established a cause of death after a full pediatric postmortem examination, conducted according to a standard protocol.

A total of 456 sudden unexpected infant deaths were identified, of which 363 were classified as SIDS. Families of 325 of these infants were interviewed (90%), and immunization histories were available for 303 of the 325 infants (93%). For the remaining 93 explained deaths, 72 families were interviewed (77%), and immunization histories were available for 65 of 72 infants (90%). A total of 1,588 controls were selected; immunization histories were available for 1,515 of the controls (95%). (Analysis of the explained deaths is discussed in the subsequent section on SUDI.)

The infants who died of SIDS were less likely to have been immunized than their matched controls. A univariate analysis gave an odds ratio for SIDS of 0.48 (95% CI 0.36-0.63) for infants who began or completed the immunization program. After adjusting for matching, the odds ratio was 0.23 (95% CI 0.14-0.37). The difference between SIDS infants and control infants was consistent across the different age groups. A multivariate analysis that controlled for possible confounders such as birth weight, infant age, and socioeconomic variables produced an odds ratio of 0.45 (95% CI 0.24-0.85). The protective effect of immunization in relation to SIDS was no longer seen when the analysis controlled for highly significant risk factors in an infant's sleeping environment (OR=0.67, 95% CI 0.31-1.43), but none of the analyses showed an elevated risk for SIDS. The authors concluded that immunization did not lead to SIDS, and that the results were consistent with a possible protective effect from immunization.

France. Jonville-Bera and colleagues (2001) conducted a case-control study to examine the association between SIDS in infants between the ages of 30 and 90 days and exposure to diphtheria-tetanus vaccine, with or without exposure to whole-cell pertussis, polio, or Hib vaccines. Between February 1995 and March 1997, 28 SIDS Centres in France identified 114 cases of SIDS or sudden unexpected death (SUDI) at ages 30 to 90 days for infants with a gestational age of more than 34 weeks. SIDS was defined as the sudden death of any infant or young child that is unexpected by medical history and for which an autopsy fails to demonstrate an adequate cause of death. SUDI was defined as the sudden death of any infant in good health until death for whom investigations failed to show an adequate explanation of death but without an autopsy. Of the 114 deaths, there were 90 SIDS cases (79%); the other 24 cases were categorized as SUDI, but were included in the analysis. (A separate analysis of the SUDI cases is described below.) Additional information on each infant was obtained from an interview with the parents within 3 months of the infant's death.

Three controls were selected for 113 of the cases; one case had only two controls. The controls were matched to cases according to age, sex, and maternity unit of birth. They were recruited by identifying the first 10 infants born after the index case in the same maternity unit; the first three infants whose parents gave consent served as the controls for that case. The consenting parents provided information through a telephone interview.

Immunization histories were obtained from the health and development record. Vaccine exposure consisted of at least one dose of vaccines for diphtheria-tetanus and pertussis, polio, and/or Hib before death for cases and before a comparable age for controls. Other vaccine exposures for some infants included BCG and HepB.

The unadjusted odds ratio for SIDS with exposure to vaccines for diphtheria, tetanus, pertussis, and polio, with or without Hib (DTPP ± Hib), was 0.87 (95% CI 0.43-1.68). For infants who also received BCG vaccine, the odds ratio was 1.85 (95% CI 0.21-42.76); for those who also received HepB, the odds ratio was 0.89 (95% CI 0.19-3.64). Multivariate analysis, using a conditional logistic regression model, controlled for possible confounders, such as illness in the week before death, maternal smoking, birth weight, sleeping position, use of a firm mattress, breastfeeding, and sex. The multivariate odds ratio was 1.08 (95% CI 0.49-2.36). The study had 74 percent power at a 5 percent level of significance to detect a twofold increase in the risk of SIDS. The authors conclude that receipt of DTPP +/-Hib was not a risk factor for SIDS for infants at ages 30 to 90 days.

The authors note possible biases in the study, however. Selection bias in identification of cases was considered minimal because the study included most of the SIDS cases reported on death certificates. Determination of SIDS as a cause of death was considered more accurate for study cases than for death certificates, but misclassification bias could have existed because of the inclusion of the SUDI cases in the analysis. Selection bias could also arise from the exclusion of case or control infants whose parents could not be contacted or who did not agree to participate in the study. Recall bias may have affected cases and controls differently (median time from death to interview was 8.5 days for cases and 110 days for controls), but all immunization data were obtained separately from official records.

Jonville-Bera and colleagues (1995) also conducted an earlier retrospective case-control study to assess the risk for SIDS in infants following exposure to tetravalent diphtheria-tetanus-pertussis (whole-cell)-polio vaccine (Tetracoq or DTCP) or to trivalent diphtheria-tetanus-pertussis (whole-cell) vaccine (DTC) plus polio vaccine.

The cases consisted of 118 SIDS deaths of infants born between January 1, 1983 and December 31, 1987, who were identified through referrals to one of the authors. SIDS was defined as a sudden death not explained by the infant's medical status. The diagnosis was based on a clinical examination, history of death, and an autopsy, when performed. Fourteen additional SIDS cases were excluded

because of lack of data. Two or three controls were selected for each case. The 332 controls in the study were matched to cases by sex, month, and year of birth, and they were seen by a medical practitioner within 2 weeks before or after the death of the matching case. To prevent misclassification bias, any child who died within one month after vaccination was excluded from the control group. The controls were selected from three sources: urban and rural clinics and private pediatric practices.

Cases were considered vaccinated if they had received at least one vaccine dose. Controls were considered vaccinated if they had received at least one vaccine dose by the age at which the matching case died. The article does not indicate whether information on immunizations was obtained from reports by parents or from medical records.

Using a Miettinen X test (a test of independence for a retrospective case-control study) and an estimate of relative risk, the odds ratio for SIDS in vaccinated children was 1.9 (95% CI 0.9-3.9). The authors also commented on an analysis of the SIDS deaths that occurred at less than 3 months of age (68 cases and 191 controls). Six of the SIDS cases had been vaccinated, but none of the controls had. The difference was statistically significant ($\chi = 3.97$, $p < 0.0001$).

The authors cite several possible biases in this study. First, controls who were seen by private pediatricians were significantly more likely to be vaccinated than the controls from the urban or rural clinics. In addition, this group was vaccinated at a younger age than the other control groups. Thus, the usual source of care for the SIDS cases could have influenced their vaccination status, but it was not possible to match cases and controls in terms of source of care. Second, selection bias may also have occurred because cases and controls were not drawn from the same source. Differences between the two groups in terms of socioeconomic status or other factors related to the risk for SIDS could not be assessed. In addition, misclassification bias was possible because autopsies were performed for only 33 of the SIDS cases (28%).

New Zealand. Mitchell and colleagues (1995) conducted a case-control study to examine the association between immunization and SIDS in New Zealand. Data were obtained from the New Zealand Cot Death Study, which included 78 percent of all live births in New Zealand between November 1, 1987 and October 31, 1990. A total of 716 postneonatal deaths were identified, of which 485 were classified as SIDS. Autopsies were performed for 474 (97%) of the SIDS deaths. A total of 1,800 controls was randomly selected from all births in the study regions (except home births). The controls were matched by age and randomly assigned to a time of day to generate a distribution corresponding to the distribution of times of death of the cases. Parents of the SIDS cases were interviewed within one month of the death, and parents of control infants were interviewed within one week of a reference date and time.

Immunization histories were determined on the basis of the health and development record, which is kept by the parents and completed by the general practitioner during check-ups. Infants were considered immunized if they had received any of the vaccines that were appropriate for their age at death (cases) or at the reference date (controls). The New Zealand immunization program includes the following required vaccinations: BCG (at birth for infants at risk), DTwP at 6 weeks, DTwP and polio at 3 and 5 months. Requirements for HepB vaccination changed over the course of the study. Before March 1987, plasma-derived vaccine was given at birth, 6 weeks, and 3 and 15 months to infants born to mothers who were HBeAg and HBsAg positive. From March 1987 through February 29, 1988, HepB was given to infants born to HBsAg-positive mothers and to all infants in selected high-risk regions. After February 29, 1988, all infants received the vaccine. Beginning December 1, 1989, exclusive use of the recombinant vaccine began, with doses given at 6 weeks and at 3 and 15 months.

Data from obstetric records, parental interviews, and immunization records were available for 317 cases and 1,524 controls. Those who were not interviewed were more likely to be Maori[5] and to have smoked during pregnancy. Cases with missing immunization records were more likely to be children of a single Maori parent, who lived in the North Island.

The analysis tested for an association between SIDS and, unlike other studies that examine exposure to immunizations, lack of age-appropriate immunizations. The univariate odds ratio was 0.9 (95% CI 0.7-1.1) at birth, 2.1 (95% CI 1.4-3.1) for immunization status at 6 weeks, 2.5 (95% CI 1.6-4.0) at 3 months, and 2.0 (95% CI 1.1-3.9) at 5 months. A multivariate analysis controlled for potential confounding from sociodemographic characteristics of the family and factors related to the pregnancy, the infant, and the postnatal environment. The adjusted odds ratios for the risk of SIDS were 1.1 (95% CI 0.8-1.6) at birth, 2.1 (95% CI 1.2-3.5) at 6 weeks, 1.3 (95% CI 0.7-2.5) at 3 months, and 2.6 (95% CI 0.9-7.5) at 5 months.

Recognizing the potential for bias because immunization status was unknown for a greater proportion of cases than controls, the researchers further analyzed the data to include cases without an immunization record. With the assumption that all cases with missing immunization records had been immunized (the assumption most likely to provide an indication of any increased risk associated with immunization), no changes in significance were seen in the multivariate odds ratios for birth, 3 months, and 5 months. The odds ratio for not being immunized at 6 weeks was no longer significant (OR = 1.6, 95% CI 1.0-2.7).

A larger proportion of controls than cases were found to have been immunized within 4 days of their reference date or date of death. An analysis of the risk for SIDS within 0 to 9 days of immunization showed no increase in risk for any

[5]Indigenous people of New Zealand.

interval and a significant reduction in risk at 4 days after immunization (OR = 0.5, 95% CI 0.2-0.9). Controlling for confounding factors did not alter the results.

The authors noted some possible limitations of their study. Controls were more likely to have immunization records, possibly contributing to a selection bias. As noted, a sensitivity analysis was performed to test the effect of either full immunization or no immunization among those without records. The assumption of full immunization failed to show a significant risk for SIDS. The authors also acknowledge the possibility of unrecognized confounding from factors related to the risk for SIDS or for immunization. Efforts were made, however, to control for possible confounding from sociodemographic factors, differences in use of health care services, and prior illness. The authors concluded that the findings suggest there is no increased risk of SIDS with hepatitis B immunization or DTwP immunization at 6 weeks of age.

Uncontrolled Observational Study

California. Black and others (1993) examined the safety of the combination vaccine product containing the oligosaccharide conjugate Hib vaccine, diphtheria and tetanus toxoids, and whole cell pertussis vaccine (HbOC-DTwP) compared with HbOC and DTwP given separately. Between November 1, 1990 and July 26, 1991, 2-month-old infants were enrolled in the study from the 13 largest centers of the Kaiser Permanente Medical Care Program (KPMCP), a prepaid health plan with an ethnically and socioeconomically diverse membership of 2.4 million people in Northern California.

A total of 6,644 infants received 18,359 doses of the combined DTwP and Hib vaccine, and 3,913 infants received 10,196 doses of each of the two vaccines in separate injections. The vaccines were given at 2, 4, and 6 months of age. The outcomes studied included SIDS, local and systemic reactions, hospitalizations, and emergency room visits. Nine cases of SIDS were identified: six deaths occurred among infants who received the combined vaccine, and three deaths occurred among those who received the vaccines separately. Autopsies were performed for all of the SIDS deaths. No temporal clustering of SIDS cases was observed. The deaths occurred from 1 to 67 days following receipt of the combined vaccine and from 1 to 51 days after receipt of the two separate vaccines. The authors state that rate of SIDS deaths in the study was compared with rates in the five counties served by KPMCP and among infants enrolled in KCMCP who did not participate in the study. The SIDS rates in those comparison populations were not reported in the article.

Ecologic Study

Scotland. Essery and colleagues (1999) conducted an ecological analysis that compared SIDS rates in Scotland before and after an October 1990 change in

the immunization schedule that called for immunization to begin at 2 months rather than at 3 months. The incidence of SIDS in Scotland for the years 1986–1990 was compared with the rates for 1991–1996, by age at death in months. Rates were lower in the 1991–1996 period for ages 2 to 12 months. The largest differences were seen at ages 2 to 6 months, and the maximum difference was at 4 months (the ratio of 1991–1996 rates to 1986–1990 rates was 0.31). The committee judged that this study contributed little to the causality argument because of its ecological nature and because of the confounding effect on changes in SIDS rates of a "back to sleep" campaign that began in October 1991.

Passive Surveillance Data

VAERS. Silvers and colleagues (2001) reviewed all deaths reported to VAERS from July 1990 through June 1997. FDA physicians reviewed autopsy reports, death certificates, and case histories included in the reports, and they classified the causes of deaths according to the following categories: congenital, infectious, neoplastic, SIDS, other, or unknown. A total of 1,266 fatalities were reported, of which 531 were SIDS. SIDS accounted for 47.6 percent of all deaths reported to VAERS, and 69.5 percent of all reported infant deaths. The majority of SIDS deaths occurred at 2 to 4 months of age (70%). The median interval between immunization and SIDS deaths was 3 days, with 25 percent occurring within 24 hours of vaccination and another 25 percent occurring 1 week or more after vaccination. The five most common vaccine combinations in the pediatric cases were the following: DTP, Hib, and OPV; DTP, Hib, OPV, and Hib; DTP, OPV, and DTPH; Hib and OPV; and DTPH and OPV.

The number of SIDS deaths peaked at 100 cases during the 1992–1993 study year and steadily declined in subsequent years. In 1996–1997, there were 49 reports of SIDS deaths. These changes in the numbers of VAERS reports reflect a broader change in the epidemiology of SIDS as a result of the "Back to Sleep" campaign; moreover, the consistency of these trends would be expected if a substantial proportion of SIDS deaths reported to VAERS were coincidental. Because the data from VAERS are produced by passive surveillance, this study contributes little to the committee's causality argument.

The committee also received summary data from CDC on reports of SIDS received by VAERS from January 1991 through November 2002. A total of 763 unique reports (excluding foreign reports) concerning infants less than 12 months of age mentioned SIDS in conjunction with receipt of multiple vaccines. Approximately 51 percent of the reported deaths occurred within 3 days after vaccination. Cases were identified on the basis of terms (e.g., SIDS) used in the VAERS report, not on a formal medical diagnosis.

Causality Argument

In the four controlled observational studies reviewed by the committee, exposure to multiple vaccines was not associated with an elevated risk of SIDS deaths (see Table 3). The committee notes that most of the studies reviewed were on multiple vaccines since most vaccines are usually administered in combination with other vaccines. These studies are subject to limitations, often related to a possible selection bias because of inclusion of SUDI cases in some of the analyses, controls whose immunization records could not be located, or parents who could not be interviewed or did not agree to participate in the study. Nevertheless, findings from studies in three different countries produced consistent results. One study (Fleming et al., 2001) suggested a protective effect, but not significant, of vaccines against SIDS. The committee also reviewed an uncontrolled cohort study, an ecologic study, and a report on VAERS data. The findings in these latter studies contribute little to the assessment of causality, but provide no signals of risks. **The committee concludes that the evidence favors rejection of a causal relationship between exposure to multiple vaccines and SIDS.**

Sudden Unexpected Death

The committee reviewed data on the association between exposure to multiple vaccines and all sudden unexpected death in infants (SUDI). The section on multiple vaccines and all sudden unexpected death in infants is followed by the section on anaphylaxis. As anaphylaxis is known to be a rare but causally related adverse event following the administration of some vaccines, the committee reviewed evidence regarding anaphylaxis following vaccination in infants.

Multiple Vaccines

Controlled Observational Studies

United Kingdom. Fleming and colleagues (2001) in the case-control study described above examined the association between immunization status under an accelerated immunization program and SUDI. The cases were infants aged 1 week to 1 year who died suddenly and unexpectedly in various parts of England between February 1993 and January 1995 or April 1995 and March 1996. The study included infants whose deaths were explained and infants whose deaths were unexplained and diagnosed as SIDS. The findings on SIDS were discussed in the previous section.

A total of 456 sudden unexpected infant deaths were identified, of which 93 were explained. Interviews were conducted with parents of 72 of the 93 infants (77%), and immunization histories were available for 65 of those 72 infants

TABLE 3 Evidence Table: Exposure to Multiple Vaccines and Sudden Infant Death Syndrome

Citation	Design	Population	Assessment of Vaccine Exposure
Fleming et al. (2001)	Case-control	Cases: sudden unexpected deaths, age 1 week to <1 year, from Feb 1993-March 1996. 303 SIDS 65 explained deaths Controls: 1,515 infants, matched according to age, locality, and time of reference sleep England	At least one dose of DTP, OPV, and/or Hib. Immunization information from parent-held records. Infant considered immunized if received any component of the immunization program prior to last or reference sleep.
Jonville-Bera et al. (2001)	Case-control	Cases: 114 sudden unexpected deaths (90 SIDS, 24 SUD) of infants between ages 30 and 90 days, Feb 1995-March 1997. Controls: 341 infants, matched for sex, gestational age, and born immediately after the case in the same maternity unit France Multi-centre	At least one dose of diphtheria, tetanus ± pertussis, poliomyelitis, or Haemophilus vaccine (DTPP +/-Hib). Other vaccines received: BCG, HepB. Vaccine exposure determined from Health and Development Record.

Outcomes	Results	Comment	Contribution to Causality Argument
Explained or unexplained sudden unexpected deaths (unexplained deaths = SIDS) Multidisciplinary committee established cause of death after full pediatric postmortem examination to a standard protocol. Explained deaths: unrecognized infection, accidental injury, congenital anomalies, non-accidental injury, metabolic disorders, bowel obstruction, bronchopulmonary dysplasia, and cardiomyopathy.	**SIDS vs. Controls OR (95% CI)** **Univariate** 0.48 (0.37-0.63) **Mulitvariate** 0.45 (0.24-0.85) **Adjusted for sleeping environment** 0.67 (0.31-1.43) Explained deaths vs. controls Univariate OR (95% CI) 0.51 (0.21-1.26)	Authors noted that results were consistent with a possible protective effect from immunization.	The study provides strong evidence of no association between exposure to multiple vaccines and SIDS.
SIDS = sudden death, unexpected by history and for which thorough post mortem examination fails to demonstrate an adequate cause of death. SUDI = sudden death of infant in good health until death for whom investigations failed to show adequate explanation; no post mortem examination.	**SIDS** **Univariate OR (95% CI)** DTPP ± Hib: 0.87 (0.43-1.68) Plus: BCG: 1.85 (0.21-42.76) HepB: 0.89 (0.19-3.64) **Multivariate OR (95% CI)** 1.08 (0.49-2.36)	Possible misclassification bias from inclusion of SUDI cases. Possible selection bias from missed cases or from exclusion of cases or controls who could not be located or did not agree to participate. Possible differential recall bias between cases and controls because length of time between death (or reference date) and interview differed by almost 100 days.	The study provides weak evidence of no association between exposure to multiple vaccines and SIDS in early infancy; weaknesses in the study limit its contribution to the causality argument.

continued on next page

TABLE 3 Continued

Citation	Design	Population	Assessment of Vaccine Exposure
Jonville-Bera et al. (1995)	Retrospective case-control	Cases: 118 SIDS deaths of infants born between January 1983-December 1987	At least 1 dose of tetravalent diphtheria-tetanus-pertussis-polio vaccine or trivalent diphtheria-tetanus-pertussis vaccine plus polio vaccine.
		Controls: 332 infants matched according to sex, birth date, and age at death	Source of information on immunization status not reported.
		France	

Outcomes	Results	Comment	Contribution to Causality Argument
SIDS = sudden death not explained by medical status; diagnosis based on clinical examination, history of death and autopsy report, when performed	**OR (95% CI) for SIDS** **All Children** 1.9 (0.9-3.9) **Age < 3 months** No OR reported (Miettinen × test: 3.97, p = 0.0001)	Possible misclassification bias because autopsy performed for only 28% of SIDS cases. Possible health-care-seeking bias because controls from private pediatricians more often vaccinated infants at a younger age. Possible selection bias because cases and controls selected from different populations. Cases were identified from referrals by general practitioners; controls were selected from urban and rural clinics and private practices. Information on possible confounders (e.g., socioeconomic status) unavailable.	The study provides weak evidence of no association between exposure to multiple vaccines and SIDS; weaknesses in the study limit its contribution to the causality argument.

continued on next page

TABLE 3 Continued

Citation	Design	Population	Assessment of Vaccine Exposure
Mitchell et al. (1995)	Case-control	Cases: 317 SIDS deaths, infants aged 28 days to 1 year (postneonatal), from Nov 1987 through Oct 1990. Controls: 1,524 infants born during the study period New Zealand Cot Death Study	At least one dose of BCG, DTP, polio, or HepB at specified ages (birth, 6 weeks, 3 months, 5 months). Immunization status determined from health and development record (HDR), which is kept by parents and completed by the general practitioner.

Outcomes	Results	Comment	Contribution to Causality Argument
SIDS	**OR for SIDS if not immunized (95% CI)** Univariate Birth 0.9 (0.7-1.1) 6 weeks 2.1 (1.4-3.1) 3 months 2.5 (1.6-4.0) 5 months 2.0 (1.1-3.9) Multivariate Birth 1.1 (0.8-1.6) 6 weeks 2.1 (1.2-3.5) 3 months 1.3 (0.7-2.5) 5 months 2.6 (0.9-7.5) Sensitivity analysis Assumed excluded cases with incomplete immunization records were fully immunized: 6 weeks 1.6 (1.0-2.7) for other time periods, OR changed slightly OR for SIDS based on time since immunization (0 to 9 days) 4 days: 0.5 (0.2-0.9) other intervals not significant	Authors note possible selection bias, with immunization records more likely to be missing for cases than controls. Parents of excluded cases tended to be single and Maori. Cases and controls excluded for lack of parent interview were more likely to have been Maori and have a mother who smoked during pregnancy. More cases (35%) than controls (15%) were excluded from the analysis.	The study provides weak evidence of no association between exposure to multiple vaccines and SIDS; weaknesses in the study limit its contribution to the causality argument.

(90%). Each case was matched with four controls on the basis of age, locality, and time of last sleep. A total of 1,588 controls were selected for the entire study; immunization histories were available for 1,515 of the controls (95%). Infant deaths were identified through a network of professionals and lay organizations (Leach et al., 1999). This method was found to have identified 98.3 percent of SUDI in the study regions. Cause of death was established by a multidisciplinary team after a full pediatric postmortem examination, conducted according to a standard protocol. Immunization histories were obtained from health records held by parents. Immunization exposure was based on receipt of any component of the immunization program before a case infant's last sleep or before a control infant's reference sleep.

Of the infants who died of explained causes, 54 percent received some immunization compared with 61 percent of the control infants, a difference that was not statistically significant (univariate odds ratio was 0.51 [95% CI 0.21-1.26]). For those who died of infection, the univariate odds ratio (OR) was 0.44 (95% CI 0.11-1.65). The authors concluded that immunization was not associated with sudden unexpected death in infancy.

France. The risk for sudden unexpected death in immunized infants between the ages of 30 and 90 days was examined by Jonville-Bera and her colleagues (2001) in a case-control study described above in the review of studies on SIDS. Immunized infants were exposed to diphtheria-tetanus vaccine, with or without exposure to whole-cell pertussis, polio, or Hib vaccines. The study identified 114 sudden deaths of 30- to 90-day-old infants who had a gestational age of more than 34 weeks. These deaths occurred between February 1995 and March 1997.

Of the 114 deaths, 24 cases were categorized as SUDI—defined as the sudden death of any infant in good health for whom investigations failed to show an adequate explanation of death but without an autopsy. Controls were matched to cases according to age, sex, and maternity unit of birth. The analysis showed that immunization was not associated with SUDI (OR = 0.42, 95% CI 0.06-1.8).

Causality Argument

The committee reviewed two published studies (see Table 4) that examined the association between exposure to multiple vaccines and sudden unexpected death in infants.[6] The committee relied on the fairly rigorous study by Fleming and colleagues (2001) since the cause of death was determined by a standard examination protocol. In contrast, the Jonville-Bera and colleagues study (2001)

[6]Anaphylaxis was not listed among the outcomes discussed in either study.

was subject to misclassification bias since autopsies were not performed on any of the SUDI cases. Thus, based on only one methodologically strong study, **the committee concludes that the evidence is inadequate to accept or reject a causal relationship between exposure to multiple vaccines and sudden unexpected death in infancy, other than SIDS.**

Anaphylaxis

The present committee examined deaths due to anaphylaxis (severe, immediate type I hypersensitivity reaction) after receipt of a vaccine, and it reexamined the conclusions from previous IOM committees that reviewed this relationship.[7]

In summary, a 1994 IOM committee reviewed fatal anaphylaxis cases in which symptoms began within 4 hours of vaccine administration. Based on two case reports in adults in which death was associated with the administration of tetanus toxoid given as a single antigen (Regamey, 1965; Staak and Wirth, 1973), the committee found a causal relationship between tetanus toxoid containing vaccines and death from anaphylaxis. No epidemiologic studies were available, nor were definitive reports in infants available. The same committee found a causal relationship between HepB vaccine and fatal anaphylaxis. (The 1994 committee noted there was no direct evidence for this, but based its conclusion on the evidence establishing a causal relationship between HepB vaccine and anaphylaxis and on the fact that, in general, anaphylaxis is very rarely fatal.)

Based on case reports, a 1991 IOM committee concluded that the evidence established[8] a causal relation between DTwP vaccine and anaphylaxis. In a review of the literature published since the completion of the 1991 report, the current committee found no additional epidemiologic studies examining the association between exposure to DTwP vaccine and anaphylaxis. It is important to note that the previous committee (1991) did not come to a conclusion on DTwP vaccine and *deaths* from anaphylaxis, nor did it form a conclusion specific to infants. In 1997, DTaP replaced DTwP as the recommended vaccine in the childhood immunization schedule in the United States. Given that no additional analytic studies are available, the present committee finds no basis for a change in

[7]*Adverse events of Pertussis and Rubella Vaccines* (IOM, 1991) provides an in-depth review of the literature concerning the adverse events associated with whole-cell pertussis containing vaccine (DTwP), as well as rubella vaccine. The charge to the Vaccine Safety Committee (IOM, 1994) was to examine adverse events associated with tetanus toxoid as well as with tetanus and diphtheria toxoid combination preparations and other childhood vaccines. It was beyond the 1994(a) committee's charge to form conclusions about pertussis vaccine or DTP. Note that in contrast to the scope of the present study, the charges to the 1991 and 1994 committees were not limited to infants.

[8]The 1991 conclusion is reworded here for consistency with the causality categories established by the 1994 committee.

TABLE 4 Evidence Table: Exposure to Multiple Vaccines and Sudden Unexpected Death in Infancy

Citation	Design	Population	Assessment of Vaccine Exposure
Fleming et al. (2001)	Case-control	Cases: sudden unexpected deaths, age 1 week to <1 year, from Feb 1993-March 1996. 303 SIDS 65 explained deaths Controls 1,515 infants, matched according to age, locality, and time of reference sleep England	At least one dose DTP, OPV, and/or Hib. Immunization information from parent-held records. Infant considered immunized if received any component of the immunization program prior to last or reference sleep.
Jonville-Bera et al. (2001)	Case-control	Cases: 114 sudden unexpected deaths (90 SIDS, 24 SUDI) of infants between ages 30 and 90 days, Feb 1995-March 1997. Controls: 341 infants, matched for sex, gestational age, and born immediately after the victim in the same maternity unit France Multi-centre	At least one dose of diphtheria, tetanus ± pertussis, poliomyelitis, or Haemophilus vaccine (DTPP ± Hib). Other vaccines received: BCG, HepB. Vaccine exposure determined from Health and Development Record.

Outcomes	Results	Comment	Contribution to Causality Argument
Outcomes included both explained or unexplained sudden unexpected deaths (explained deaths were classified as SUDI). Multidisciplinary committee established cause of death after full pediatric postmortem examination to a standard protocol. Explained deaths: unrecognized infection, accidental injury, congenital anomalies, non-accidental injury, metabolic disorders, bowel obstruction, bronchopulmonary dysplasia, and cardiomyopathy.	SUDI, Explained vs. Controls Univariate OR (95% CI) 0.51 (0.21-1.26) Death due to infection Univariate OR (95% CI) 0.44 (0.11-1.65)	Authors noted that results were consistent with a possible protective effect from immunization.	The study provides strong evidence of no association between exposure to multiple vaccines and SUDI; weaknesses in the study limit its contribution to the causality argument.
SUDI = sudden death of infant in good health until death for whom investigations failed to show adequate explanation; no post mortem examination.	**SUDI (OR 95% CI)** DTPP ± Hib: 0.42 (0.06-1.8)	Possible selection bias from missed cases, exclusion of cases, or controls who could not be located or did not agree to participate. Possible differential recall bias between cases and controls because length of time between death (or reference date) and interview differed by almost 100 days.	The study provides weak evidence of no association between exposure to multiple vaccines and SUDI in early infancy; weaknesses in the study limit its contribution to the causality argument.

the prior conclusion that the evidence establishes a causal relation between DTwP and anaphylaxis.

One case report (Werne and Garrow, 1946), discussed in both the 1991 and 1994 reports, described identical twins who died 16 and 20 hours after receipt of the second diphtheria toxoid and pertussis antigen (DwP) vaccine given at 10 months. Autopsies 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 the vaccine, and the injected material was shown to be sterile.) The delayed response was noted by the authors of the study to be atypical of the anaphylactic reactions reported at that time.[9] In an effort to identify any subsequent cases, the present committee reviewed VAERS data provided by CDC on reports of anaphylaxis between January 1991 and November 2002. Of the 36 reports of anaphylaxis in infants less than 1 year of age, one report was for an infant who died. This death occurred outside the United States, following administration of vaccines not previously associated with anaphylaxis. Moreover, CDC notes that these 36 cases were identified on the basis of terms (e.g., anaphylaxis, anaphylactic shock) used in the reports, not as formal medical diagnoses. Thus the cause of death due to anaphylaxis was not verified. As with other passive surveillance data discussed in this report, this individual case is of limited value in assessing causality.

Causality Argument

A causal relationship has been established by previous IOM committees between DTwP[10] vaccine and anaphylaxis (IOM, 1991). They also established causal relationships between tetanus toxoid-containing vaccines[11,12] as well as between hepatitis B vaccines,[13,14] and death from anaphylaxis (IOM, 1994a).

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[9]This case is discussed further in the section on fatal late-phase anaphylactic reactions as a theoretical biological mechanism for SUDI.

[10]In infants and children.

[11]In children and adults. No data were available for infants.

[12]The 1994 IOM committee based its conclusion on two case reports in adults in which death was associated with the administration of tetanus toxoid given as single antigen. One case (Regamey, 1965) was immunized in 1933, and his reaction may have been related to the use of blood components from horses during toxoid production at that time (Ehrengut and Staak, 1973). In the second case (Staak and Wirth, 1973), Spiess and Staak (1973) raised the possibility of inadvertent intravascular injection and Ehrengut and Staak (1973) noted that the vaccine was given "in both arms," suggesting that equine antiserum might have been given in addition to the vaccine.

[13]In children and adults. No data were available for infants.

[14]The 1994 IOM committee noted that there was no direct evidence for a causal relationship between hepatitis B vaccine and fatal anaphylaxis, but based its conclusion on the evidence establishing a causal relationship between hepatitis B vaccine and anaphylaxis and on the fact that in general anaphylaxis is very rarely fatal.

Although very rare, anaphylaxis from any cause (e.g., food, drug, or environmental allergen) can lead to sudden unexpected death. However, death of infants from anaphylaxis following vaccination has been reported in only one well-documented case report from 1946 (of identical twin infants following administration of the second dose of a DwP vaccine, described above. See also Table 5). **The present committee concludes that the evidence favors acceptance of a causal relationship between diphtheria toxoid and whole cell pertussis vaccine and death due to anaphylaxis in infants.** It should be noted however, that despite the more than 50 years subsequent to the publication of the 1946 case report and despite the widespread use of vaccines in infants, the committee could not identify in the medical literature any additional reports of death in infants due to anaphylaxis. This lack of data probably reflects two things: the relatively rare occurrence of anaphylaxis in response to vaccines, and the availability of an effective treatment that resolves the condition for anaphylaxis.

The committee notes that causality is usually addressed by epidemiologic studies, but in their absence, individual case reports and case series are relied upon (provided that the nature and timing of the adverse event following vaccine administration and the absence of likely alternative etiologic candidates gave reasonable certainty that causality could be inferred from one or more case reports) (IOM, 1994a). When such information (particularly concerning timing) is unavailable, it is difficult or impossible to infer causality for that case.

For the present review, the committee felt that the Werne and Garrow case report (1946) provided sufficient evidence to indicate a link between vaccines, anaphylaxis, and infant death. Further support of causality is based on the well-established biologic mechanism that anaphylaxis can occur after exposure to a foreign antigen or drug and by the temporal sequence of observed events following vaccination. On the basis of the case reports, evidence indicates that anaphylaxis can occur after vaccination. However, the very limited number of case reports of fatal vaccine-induced anaphylaxis (one published report involving two deaths, and one case in VAERS) underscores that such an occurrence is an exceedingly rare event. Nonetheless, the timing and the unmistakable classic presentation of anaphylaxis in the Werne and Garrow case report indicate that vaccines can cause anaphylaxis and fatal anaphylaxis in infants.

Neonatal Death

Only HepB vaccine is administered during the neonatal period (the first 27 days of life).

TABLE 5 Evidence Table: Exposure to DwP Vaccine and Fatal Anaphylaxis

Citation	Design	Population	Assessment of Vaccine Exposure
Werne and Garrow (1946)	Case-report of two twins	Identical twins aged 10 months	Second injection of diphtheria toxoid and whole-cell pertussis antigen given at 10 months.

Hepatitis B Vaccine

Controlled Observational Study, Unpublished Report

Vaccine Safety Datalink. At the committee's October 2002 meeting, Ward (2002) presented unpublished data on an analysis of neonatal mortality following hepatitis B vaccination. A total of 1,124 infants who had been enrolled in the Northern and Southern California Kaiser Permanente health plans from 1993 to 1998 and who died of any cause before 29 days of age were included in the study. Exposure to the hepatitis B vaccine was determined by review of computerized files created for the Vaccine Safety Datalink (VSD) project and by medical chart review. Fifty-nine infants received the hepatitis B vaccine, and a total of 159 matched controls who had not received the Hep B vaccine were selected from the cohort of neonatal deaths to serve as controls. The proportion of "unexpected deaths" (the presence or absence of a potentially fatal neonatal or perinatal condition) in the unvaccinated and vaccinated groups was compared. The rate of unexpected mortality was equivalent in the vaccinated and unvaccinated groups, suggesting a lack of association between vaccine and subsequent death. The difference in the distributions was not significant ($p = 0.9$). Because the study is unpublished, the committee did not find that the study contributed to its assessment of causality.

Outcomes	Results	Comment	Contribution to Causality Argument
Fatal anaphylaxis	Infants died 16 and 20 hours after receipt of the second injection of diphtheria toxoid and pertussis antigen.	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 the vaccine. Injected material was shown to be sterile.	The well-documented case report provides evidence of a causal relationship between exposure to DwP vaccine and death due to anaphylaxis in infants.

Passive Surveillance Data

VAERS. As previously described, Niu and colleagues (1999) reviewed reports to VAERS of neonatal deaths following receipt of HepB vaccine. The reports were received between January 1, 1991 and October 5, 1998. There were a total of 18 reports of death, of which 17 had autopsy results. Of those 17 deaths, 12 deaths were attributed to SIDS. Other causes of death included infections, intracerebral hemorrhage, accidental suffocation, and congenital heart disease.

Causality Argument

The committee reviewed data on neonatal death following receipt of HepB vaccine from one unpublished controlled observational study and from one published report describing VAERS data. **Because of the nature of the available case reports and the limited, unpublished epidemiological data, the committee concludes that the evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and neonatal death.**

Biological Mechanisms

Although biological data do not provide an independent basis for evaluating causality, they can help validate epidemiologically based conclusions that are for

or against causal associations. Such data can also guide further investigation when epidemiological evidence is inconclusive.

For this report, the committee's task was to consider the evidence regarding biological mechanisms that might link vaccination during the first year of life with sudden unexpected death in infancy. Some of these deaths can be attributed to various identifiable causes, which provide a basis for identifying and evaluating potential mechanisms that might be related to vaccination.

Most sudden unexpected deaths in infancy, however, are diagnosed as SIDS, specifically because all other known causes have been eliminated, and the lack of a clear understanding of the causal pathways in SIDS complicates the task of identifying any mechanisms by which vaccination might be thought to contribute. For guidance, the committee looked to the various lines of research on SIDS, as reflected in the triple-risk models and focused on vaccination as a potential source of stressors.

Considering both explained and unexplained infant deaths, the committee reviewed the evidence regarding biological mechanisms that might be related to vaccination in terms of three possible pathways: neuroregulatory abnormalities (including homeostatic and autonomic functions), inborn errors of metabolism, and adverse immune responses. The committee's assessment included consideration of certain widely recognized reactions to vaccination, particularly fever and decreased appetite, that are relevant to those pathways. The committee emphasizes that these and several other reactions commonly observed in infants following vaccination (e.g., pain at the injection site, irritability, drowsiness, or sleeplessness) are generally self-limited and not considered a cause for concern by themselves.

Neuroregulatory Abnormalities

Epidemiologic studies have shown that risk factors for SIDS include the prone sleeping position, exposure to pre- and postnatal maternal smoking, and elevated body temperature (Sullivan and Barlow, 2001). The mechanisms through which these risks operate are unknown, but possibilities include rebreathing carbon dioxide entrapped near the face when an infant is prone, upper airway obstruction and compromised airway reflexes, impaired arousal thresholds in the prone position, altered vestibular influences on blood pressure recovery systems, and hyperthermia due to overwrapping or failure of facial heat dissipation while prone.

Some hypotheses regarding SIDS posit an interaction between exogenous stimuli (e.g., prone positioning or tobacco smoke) and neuroregulatory abnormalities. Such a process might involve the respiratory or cardiovascular systems, or both, and a failure of compensatory mechanisms. The abnormalities may involve alteration in neurotransmitter receptors in regions of the brain that are involved in chemoreception and cardiovascular control (Harper, 2000). Vaccina-

tion might be thought to pose the risk of producing reactions—for example, fever, listlessness, or altered sleep patterns—that could serve as exogenous stimuli for abnormal neuroregulatory responses in vulnerable infants.

Research on brains from SIDS cases has shown abnormalities within and above the brainstem. Cerebellar areas appear to play a role in correcting abnormal breathing rates and blood pressure. In particular, some SIDS cases show bradycardia prior to cessation of breathing, which suggest that death might result from an uncompensated blood pressure drop as a consequence of cerebellar or cerebellar-related structural damage and failure of that system to restore perfusion and maintain autonomic control (Harper, 2000, 2002). Other research suggests that a subset of SIDS deaths may result from a developmental abnormality in a medullary network of serotonergic neurons that leads to the failure of protective responses to stressors during sleep (e.g., asphyxia, hypoxia) (Kinney et al., 2001).

The committee considered evidence for the following two biologic mechanisms that might link vaccination and neuroregulatory abnormalities: impaired respiratory responses and impaired arousal.

Impaired respiratory responses. At one time, clinical impressions had suggested that DTP immunization was associated with an increased frequency of prolonged apnea, which was thought to potentially increase the risk for SIDS (Steinschneider et al., 1991). But, two studies failed to demonstrate an association between DTP immunization and increased respiratory abnormality during sleep in children considered at risk for SIDS. One study compared breathing patterns during sleep on the nights before and after DTP immunization for subsequent siblings of SIDS victims, infants with unexplained apnea, and infants in a control group (Keens et al., 1985). None of the groups showed an increase in respiratory abnormalities following vaccination. The second study monitored the occurrence of prolonged apnea or bradycardia following DTP vaccination in a series of 100 subsequent siblings of SIDS cases. No episodes of prolonged apnea or bradycardia occurred during the 10 days before and after vaccination; one episode occurred in the 10- to 20-day period after vaccination (Steinschneider et al., 1991).

However, the possible relationship between apnea and SIDS appears complex. Findings reviewed by Harper and colleagues (2000) show that infants who later succumbed to SIDS had fewer breathing pauses than other infants and that some apnea appears to occur normally in other infants (where it is associated with movement and brief increases in blood pressure and may be a compensatory mechanism to maintain homeostatic control). Thus, the pattern in the infants who later died might suggest underlying abnormalities, possibly neurological in origin, in interactions between respiration and regulation of blood pressure.

Viewed in this context, the study by Keens and colleagues (1985) also shows that the total amount of apnea or periods of briefly interrupted ("periodic") breathing as a percentage of total sleep time before DTP immunization

TABLE 6 Duration of Apnea and Periodic Breathing as Percentages of Total Sleep Time, Before and After DTP Immunization

	Control group (N = 30)		Subsequent siblings of SIDS Cases (N = 33)	
	Pre-DTP	Post-DTP	Pre-DTP	Post-DTP
Total sleep time, min	549±14	528±16	549±15	539±15
Apnea (%)	0.31±0.06	0.18±0.04	0.24±0.05	0.20±0.04
Periodic breathing (%)	1.09±0.59	0.71±0.32	0.41±0.16	0.36±0.12

NOTE: Values are mean ± standard error of measurement.
SOURCE: adapted from Keens et al., 1985.

tended to be lower, though not significantly so, for the subsequent siblings of SIDS cases (apnea: 0.24%±0.05; periodic breathing: 0.41%±0.16) compared with the controls (0.31±0.06; 1.09±0.59). In both groups, the percentages of sleep time with apnea or periodic breathing were lower after immunization but not significantly different from the preimmunization levels or between the two groups (SIDS siblings: apnea: 0.20%±0.04; periodic breathing: 0.36%±0.12); (controls: apnea: 0.18%±0.04; periodic breathing: 0.71%±0.32). The results do not suggest that immunization has an adverse effect on breathing patterns during sleep (see Table 6).

It should be noted that the studies by Keens and colleagues (1985) and by Steinschneider and colleagues (1991) included infants "considered at risk" for SIDS and SIDS siblings and that none of these infants died of SIDS during the course of the study. Caution should be used in interpreting the results of these studies as there is currently no proof that SIDS is familial or has a genetic cause.

Impaired arousal. Concerns about impaired arousal might arise because of an established link between hypotonic-hyporesponsive episodes (HHE)—and receipt of whole-cell pertussis vaccines (DTwP, DTwP-HiB) (IOM, 1991). HHE refers to the sudden onset of limpness, decreased responsiveness, and pallor or cyanosis in a child under the age of 10 years, within 48 hours after an immunization. The episode can last from 1 minute to 48 hours. All three symptoms must be present for a diagnosis of HHE to be confirmed; it is not considered to have occurred if there is urticaria or anaphylaxis during the episode, if normal skin color is maintained during the episode, if the cause of the signs can be identified, or if the child is sleeping (Braun et al., 1998). HHE has also been observed, less frequently, following immunization with DTaP, and some cases have been reported following DT, HiB, and HepB vaccinations (DuVernoy and Braun, 2000; Heijbel et al., 1997).

Studies have not associated HHE with mortality or with any long-term morbidity (Gold, 2002), despite assertions in successful claims under the National Vaccine Injury Compensation Program that HHE led to death (Ridgway, 1998). The evidence points to HHE being a generally benign, self-limited syndrome, with children returning to their prevaccination state within 6 to 24 hours (DuVernoy and Braun, 2000). Although some providers regard HHE as a contraindication to revaccination with pertussis vaccine, the data suggest that the rate of recurrence is low (DuVernoy and Braun, 2000). The current CDC Advisory Committee on Immunization Practices guidelines (ACIP) list HHE as a precaution, but not a contraindication to subsequent vaccinations (CDC, 1997).

Vaccination might also be thought to affect arousal mechanisms in two other ways: through increases in body temperature as a result of fever, or through disruptions in sleeping patterns because of irritability or increased sleepiness. Evidence indicates that the increased sleepiness of ill or feverish patients may be related to changes in the activity of interleukin 1 (IL-1) and tumor necrosis factor (TNF), which appear to be important mediators of sleep regulation (Krueger and Majde, 1995; Krueger et al., 2001). However, evidence from a study of 14 healthy human infants who received DTwP, Hib, and OPV offers no support for an effect of this sort related to immunization. Although the infants' mean core temperature during sleep was significantly higher after immunization, arousal thresholds and sleep patterns were not significantly altered (Loy et al., 1998).

In the absence of experimental or human evidence regarding the ability of common side effects of immunization, including fever and anorexia, to trigger sudden unexpected death in infants with underlying neuroregulatory abnormalities, the committee concludes that this mechanism is only theoretical.

Inborn Errors of Metabolism

As discussed above, IEM involves deficiencies of specific enzymes or transport proteins (McInnes and Clarke, 2002), and those disorders related to defects in FAO have been linked to sudden unexpected infant deaths (e.g., Bennett and Powell, 1994; Mathur et al., 1999; Strauss et al., 1995). Deaths from FAO disorders generally occur under circumstances, such as illness or fasting, that limit the supply of glucose and increase fat metabolism. Fever or anorexia following vaccination might be thought to induce metabolic responses similar to illness or fasting in infants with undiagnosed FAO disorders, thus posing a risk of sudden unexpected death.

The committee found no published reports of studies in humans or animals with known FAO disorders that have examined metabolic responses following vaccination. The committee also found that reports discussing the detection of IEM among deaths initially attributed to SIDS provided no information on the vaccination status of infants found to have IEM or on the timing of those deaths

following vaccination. It is possible that the processes that produce fever following vaccination are not related to those aspects of illness that can induce a metabolic crisis in a susceptible infant.

To learn more about exposure to vaccines among children with metabolic disorders, committee members informally queried clinicians at seven medical centers specializing in the care of such children (Goodman, 2002; Kaback, 2002). At one center, children are generally not vaccinated. However, physicians from the six other centers reported that immunizations are regularly given according to the recommended schedule, with careful observation of the infants but no special precautions to prevent fever (e.g., administration of aspirin or acetaminophen). At one center, infants receive less protein on the day before and the day after immunization. No problems related to vaccination were reported.

In the absence of experimental or human evidence regarding the ability of common side effects of immunization, including fever and anorexia, to trigger an acute metabolic crisis in patients with IEM, the committee concludes that this mechanism for vaccine-related sudden unexpected infant death is only theoretical.

Adverse Immune Responses

Signs in some SIDS cases of recent immunological or inflammatory activity, such as higher levels of immunoglobulins, inflammatory cells, and inflammatory cytokines, provide a basis for a hypothesis that in vulnerable infants SIDS might result from an exaggerated immune response to common respiratory pathogens (Vege and Rognum, 1999). Some also propose that SIDS might be linked to an extreme immune response in the form of anaphylaxis (Buckley et al., 2001). Vaccines might be suspected of contributing to sudden unexpected infant death by provoking exaggerated immune responses like those thought to be related to infection or by provoking allergic responses like anaphylaxis.

The committee examined biological mechanisms related to two types of immune response: inflammatory reactions related to respiratory infections, and anaphylaxis and related hypersensitivity reactions.

Inflammatory reactions related to respiratory infections. In some studies, more than half the infants who died of SIDS have had signs of a minor infection, particularly from respiratory viruses, prior to death (Forsyth, 1999; Vege and Rognum, 1999). However, it is not yet known if such infections are causally related to SIDS, contributory in conjunction with other risk factors, or only coincidental; it is particularly difficult to distinguish between these possibilities because of the high frequency of respiratory tract infections in infancy.

Studies have found various markers of inflammatory activity in SIDS cases. Howat and colleagues (1994) found greater numbers of inflammatory cells, including T lymphocytes, B lymphocytes, and eosinophils, in the lungs of SIDS

cases compared with the lungs of infants in a control group who died without pulmonary inflammation. The researchers suggested that products of eosinophil degranulation could cause epithelial damage and pulmonary edema, which could be associated with the respiratory obstruction and hypoxia observed with SIDS. Other studies have demonstrated elevated levels of the cytokine interleukin-6 (IL-6) in the cerebrospinal fluid of SIDS victims (Vege et al., 1995). IL-6 can induce fever, anorexia, and the acute phase response, and in the context of central nervous system (CNS) inflammatory conditions such as meningitis, IL-6 may contribute to respiratory depression. Although the concentrations of IL-6 in the cerebrospinal fluid of infants with SIDS are in some cases greater than those in controls, they are lower than those found in infants with CNS inflammatory conditions (Vege et al., 1995; Vege and Rognum, 1999). Some have speculated that IL-6 may contribute to respiratory depression in a subset of children who are vulnerable, but there is no direct evidence to support this conjecture.

It has been known for some time that infection can prime the immune system to hyper-respond in such a way that challenge with a normally sublethal dose of endotoxin (a component of gram-negative bacteria) or with another infectious agent can lead to sudden unexpected death from systemic shock (Freudenberg et al., 1998; Galanos and Freudenberg, 1993; Gumenscheimer et al., 2002). A recent study in rats suggests that there may be a period during which the infant's developing immune system may be particularly vulnerable to such priming. Infecting the rats with a nonlethal strain of influenza A virus, followed 1 to 5 days later by a sublethal dose of endotoxin, resulted in unexplained deaths in infant rats that were similar in pathology, organ damage, and vascular collapse (Blood-Siegfried et al., 2002). Although the authors of this report suggest that the pathology is consistent with that seen in SIDS, these findings are not specific. Further, under other conditions this mechanism is operative in adult as well as infant animals. For these reasons and because the amounts of endotoxin needed to induce death were still quite large, the relevance of this model to SIDS is only speculative.

Although some studies suggest that SIDS may result from an inappropriate immune response to common respiratory pathogens, data are not available to show that vaccination triggers the production of inflammatory cells or cytokines like those found in SIDS cases or that those cells and cytokines are causally related to SIDS. **In the absence of experimental or human evidence demonstrating the ability of vaccines to stimulate an abnormal inflammatory response in the lung leading to sudden unexpected infant death, the committee concludes that this mechanism is only theoretical.**

Anaphylaxis and related hypersensitivity reactions. Anaphylaxis and other type I hypersensitivity reactions occur when soluble antigens bind to antigen-specific immunoglobulin E (IgE) on mast cells. This binding triggers the release of preformed inflammatory mediators, such as histamine and TNFα, that

are stored in granules in the mast cell. As described above, a type I reaction is immediate, occurring within seconds to minutes. It may also be followed by a late-phase reaction that is triggered by cytokines and other inflammatory mediators some 4 to 8 hours after the immediate reaction subsides. Whereas immediate reactions are the direct result of activation of mast cells, late-phase reactions result from the synthesis and secretion from activated mast cells of inflammatory mediators (including leukotrienes, chemokines, cytokines, and prostaglandins) and subsequent infiltration of the site by inflammatory cells (including eosinophils and type 2 cytokine producing Th2 T cells) (Busse and Lemanske, 2001; Parham, 2000).

A link between SIDS and anaphylaxis has been proposed. An elevated level of the mast cell enzyme β-tryptase in post-mortem serum samples is thought to be a marker for anaphylaxis (Kemp and Lockey, 2002), and the enzyme has been detected in the blood of SIDS victims (Buckley et al., 2001). An alternative hypothesis, however, is that the increased tryptase levels observed in SIDS cases could be a result of non-IgE-related mast-cell degranulation, possibly due to hypoxia from prone sleeping, rather than an allergic response (Edston et al., 1999; Holgate et al., 1994).

Anaphylaxis and other allergic reactions are known to occur in response to vaccine antigens or to other vaccine components. Previous IOM committees (IOM, 1991, 1994a) have established causal relationships between DTwP,[15] tetanus-toxoid-containing vaccines,[16] and hepatitis B vaccine[17] and anaphylaxis. Although very rare, anaphylaxis from any cause (e.g., food, drug, or environmental allergen) can lead to sudden unexpected death.

The previous IOM reports considered cases of anaphylaxis occurring within 4 hours after immunization (IOM, 1994a). The present committee identified one report of a pair of identical twins following the second administration of diphtheria toxoid and whole-cell pertussis antigen (Werne and Garrow, 1946), described above, in which symptoms began before 4 hours and progressed to death at 16 and 20 hours. Post-mortem analysis revealed edema, vasoconstriction, and in some tissues perivascular mononuclear and eosinophilic infiltrates, which are consistent with an immediate-phase accompanied by a late-phase type I hypersensitivity reaction.

In the case presented by Werne and Garrow (1946), the initial, nonspecific signs of an immediate-hypersensitivity (i.e., anaphylactic) reaction appear to have been initially unrecognized, and it eventually progressed to death. The suggestion has also been made that a small subset of sudden, unexpected deaths in adults is due to clinically unrecognized anaphylaxis (e.g., following a bee sting) (Schwartz et al., 1995).

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[15]In infants and children

[16]In children and adults. No data were available for infants.

[17]In children and adults. No data were available for infants.

The inflammatory infiltrates found in SIDS cases by standard autopsy techniques most likely result from infection, but it is not possible to exclude a contribution of late-phase allergic responses to these infiltrates in some cases. However, if properly performed, standard autopsy techniques are sufficient to exclude the vascular changes characteristic of anaphylaxis, including those found in the delayed anaphylactic deaths in the twin study by Werne and Garrow (1946). **Although a type I hypersensitivity reaction leading to death could possibly be missed both clinically and at post-mortem examination, and therefore misdiagnosed as SIDS, the committee concludes that this possibility is only theoretical.**

Conclusions Regarding Biological Mechanisms

The biological evidence concerning mechanisms that might link vaccination and sudden unexpected infant deaths is limited. The situations and mechanisms discussed above—neuroregulatory abnormalities, inborn metabolic errors, and adverse immune responses—are the circumstances under which the committee considers it theoretically possible that responses to vaccination might contribute to sudden unexpected infant death from SIDS or other causes. In the case of anaphylaxis—a serious, systemic allergic response of the immune system—the biological mechanisms linking foreign antigens (including vaccines) and death are well established. However, the possibility of vaccination leading to a fatal, late-phase anaphylactic reaction (following a clinically missed mild immediate reaction) is only theoretical. Furthermore, without a clear understanding of the biological mechanisms underlying SIDS, it is difficult to make a meaningful assessment of the role that vaccination might play in those deaths.

Thus, aside from a type I hypersensitivity or anaphylactic reaction to a vaccine antigen or to vaccine components administered within 24 hours prior to death, the proposed mechanisms for vaccines to have a causal role in sudden unexpected death in infancy are only theoretical.

SIGNIFICANCE ASSESSMENT

The charge to the Immunization Safety Review Committee includes consideration of the public health response to the immunization safety concerns it examines. Most previous IOM studies on immunization safety, by contrast, were limited to conclusions from causality assessments and to recommendations for future research. The public health response to an immunization safety concern potentially encompasses a broad range of activities, including policy reviews, new research directions, and changes in communication to the public and health care providers about issues of immunization safety. In formulating the breadth and direction of the recommended public health response, the committee considers not only its conclusions regarding causality and biological mechanisms, but

also the significance of the immunization safety issues for society—the context in which policy decisions must be made.

In the present case, the committee considered the concern that vaccinations given during the first year of life might increase the risk of SIDS or other types of sudden unexpected death among infants. Vaccines have made a substantial and an undeniable contribution to reductions in the toll of illness and death from several major infectious diseases (CDC, 1999). Nevertheless, vaccines are not completely free of risks, including a risk of fatal adverse events. For example, the scientific evidence reviewed by the committee supports the possibility that vaccination can occasionally cause anaphylaxis. To ensure that vaccines are as safe as possible and the value of vaccines is not undermined by fears about their use, it is essential to understand and minimize such risks.

In the United States, current immunization recommendations call for vaccination of infants to begin at birth, with additional vaccines and vaccine doses given at 2, 4, and 6 months of age. These recommendations reflect the judgment of public health officials and health professionals that the health of infants and others will benefit. Infants are among the most vulnerable members of society after all, and protecting them from avoidable health risks is a responsibility that parents share with physicians, nurses, others who provide health care, and vaccine manufacturers, as well as officials who shape and implement health policies. But, although the death of an infant from *any* cause is a grave loss to a family, infant deaths that might result from efforts to protect health must be a source of special concern.

Fears related to vaccination and SIDS must, in the committee's judgment, be considered a significant concern that deserves further attention. SIDS is the most common cause of death in the postneonatal period, with the highest incidence seen between the ages of 2 and 4 months (AAP, 2001; Adams et al., 1998), a time when most infants are also receiving many vaccines.

But investigating the possible relationship between vaccination and SIDS is complicated by at least three factors. First, research has yet to determine the cause or causes of SIDS, making it difficult to know what biological mechanisms are relevant, with or without regard to vaccination.

If certain environmental risk factors can trigger SIDS only in a subset(s) of the individuals with specific predisposing genetic factors, then theoretically, epidemiological studies in which all SIDS cases are lumped together might fail to detect causal associations that actually exist. Vaccines could be associated. It is possible that only one subset of SIDS complicates a particular vaccine administration. However, this is simply speculation.

To the extent that SIDS encompasses heterogeneous but still unknown causes of death, isolating any specific component that might be related to vaccination becomes more difficult. Careful postmortem examination is also essential to distinguish SIDS from other known causes of death. Data from the early 1990s indicate that autopsies were performed in more than 90 percent of SIDS deaths

(CDC, 1996a; Overpeck et al., 2002), but national data on autopsy rates have not been available since 1994 (Overpeck et al., 2002). Use of new screening technologies will help in attributing some sudden unexpected infant deaths to causes such as metabolic disorders.

Second, epidemiologic investigations covering the past 10 to 15 years must take into account several changes in SIDS-prevention efforts. Between 1983 and 2000 the SIDS mortality rate fell by almost 60 percent, from 146 deaths per 100,000 births (Overpeck et al., 2002) to 62 deaths per 100,000 births (Anderson, 2002). The AAP recommended in 1992 to avoid infant prone sleeping, and in 1994, a Back to Sleep campaign was initiated as a joint effort of the U.S. Public Health Service, the AAP, the SIDS Alliance, and the Association of SIDS and Infant Mortality Programs (AAP, 2000). Between 1992 and 1998, the proportion of U.S. infants sleeping prone decreased from more than 70 percent to about 20 percent. The committee acknowledges the possibility that SIDS risks associated with the vaccination schedule during this period might be masked by the large reductions in risk associated with changes in infant sleep position. If vaccine-related risks exist, all indications are that they are small.

Third, controlled prospective cohort studies to assess possible vaccine-related risks are difficult to conduct because SIDS deaths are increasingly rare and because most children in the United States are vaccinated. This along with effective SIDS-prevention efforts further complicate the ability to assess the link between vaccines and SIDS. The VSD project, with its access to a large population of HMO members, offers one prospect of assembling a study population of sufficient size to produce statistically meaningful results. At its October 2002 meeting, the committee heard reports on studies of infant death that had been conducted through the VSD (Ward, 2002).

RECOMMENDATIONS FOR PUBLIC HEALTH RESPONSE

With current public health recommendations calling for infants to receive multiple doses of vaccines during the first year of life and with SIDS the most frequent cause of death during the postneonatal period, it is important to respond to concerns that vaccination might play a role in sudden unexpected infant death. The committee's review supported conclusions that the evidence favors rejection of a causal relationship between some vaccines and SIDS and is inadequate to accept or reject a causal relationship between other vaccines and SIDS, SUDI, or neonatal death. Except in the case of an immediate anaphylactic reaction resulting in death, the evidence regarding biological mechanisms was essentially theoretical, reflecting in large measure the lack of knowledge concerning the pathogenesis of SIDS. The committee found no basis for a review of current immunization policies, but it did see a clear need for continued research on adverse events following vaccination and on the biological basis for sudden unexpected infant deaths.

Policy Review

The committee does not recommend a policy review of the recommended childhood vaccination schedule by any of the national or federal vaccine advisory bodies on the basis of concerns about sudden unexpected death in infancy.

Research

Although SIDS is the leading cause of death during the postneonatal period, it is a rare event in epidemiologic terms and its biological basis is not yet fully understood. The biology of other causes of sudden unexpected infant death is better understood than that of SIDS, but such deaths are rarer than SIDS deaths. Because of these factors, research concerning any possible role for vaccination in sudden unexpected infant death faces serious challenges. The committee encourages greater emphasis on population-based surveillance of vaccine recipients as a basis for epidemiologic studies, together with continued basic and clinical research to elucidate the causes of sudden unexpected infant death, including SIDS.

Surveillance and Epidemiologic Studies

The committee emphasizes the need for continuing surveillance for adverse events following vaccination. Careful prospective monitoring of any vaccines added to the recommended infant immunization schedule is particularly important. The relatively small numbers of participants in clinical trials of new vaccines and the limited period of follow-up in those studies mean that the full heterogeneity of the population ultimately receiving the vaccine may not be represented and that rare adverse events may not be detected. The Vaccine Adverse Events Reporting System (VAERS), the national post-marketing surveillance system administered by the FDA and CDC, is one tool for monitoring adverse events. However, reports to VAERS indicate a temporal, but not necessarily causal, relationship between an adverse event and a vaccine. Furthermore, coming as they do from a passive system, VAERS data are subject to a variety of limitations, including underreporting of adverse events and multiple reports of a single event.

Although reports to VAERS have limitations, the committee encourages the continued systematic investigation by FDA of each report of an infant death. The new network of Clinical Immunization Safety Assessment (CISA) centers may also be helpful in this regard. These centers are a collaboration between CDC and clinical academic centers across the United States (Pless et al., 2002). They are specifically intended to serve as a source of clinical expertise for the evaluation of adverse events. The first five centers were funded in October 2001.

The Vaccine Safety Satelink (VSD) is another important resource for sur-

veillance and investigation of adverse events. Because it is a population-based system, the VSD can also support the epidemiologic studies necessary to determine whether a causal relationship exists between an adverse event and a vaccine, even though such studies can be difficult to conduct when that adverse event—such as sudden unexpected infant death—is rare and the published reports are scarce and often based on individual case studies or small groups. The VSD is a collaborative effort between the CDC and seven large HMOs with more than six million members. The project captures information on the vaccines administered to the HMO members and monitors their medical records for adverse events. The results of several VSD-based epidemiologic studies have been published and additional studies are currently under way. (For an overview and bibliography of published studies see Chen et al., 2000; see also www.cdc.gov/nip/vacsafe/vsd/research.htm.)

At the committee's meeting in October 2002, two recent VSD-based studies on infant deaths were presented, one of which examined the association between hepatitis B vaccine and neonatal death. Because of the attention to the VSD datasets paid by vaccine safety advocates and the potential contributions of the studies to the vaccine safety literature, **the committee urges prompt publication of these and all other VSD results.**

The committee notes that in future studies of infant death it would be especially important to identify the timing of death in relation to vaccine administration. Clear distinctions should be made whenever possible between SIDS deaths and sudden unexpected infant deaths with an identifiable cause. In addition, studies should report as much demographic information, including race and ethnicity, as possible; studies of vaccine-related risks for SIDS could be confounded by the risks associated with the sociodemographic characteristics of the infants or their families.

Basic and Clinical Science

Aside from fatal anaphylactic reactions, the biological mechanisms by which vaccines could cause sudden unexpected death in certain susceptible infants are only theoretical. Cases of SUDI, particularly SIDS, make a substantial contribution to infant mortality. Although efforts such as the Back to Sleep campaign, which target recognized risk factors, are credited with substantial reductions in SIDS mortality during the 1990s, the biology of SIDS remains poorly understood. **The committee recommends continued research on the etiology and pathology of SIDS.** It notes that the National Institute of Child Health and Human Development (NICHD, 2001) is targeting five areas of research for this purpose: (1) the brain and homeostatic control, (2) autonomic development and function, (3) infant care and the sleep environment, (4) infection and immunity, and (5) genetics.

The committee makes its recommendation for further research recognizing that it has no basis for judging whether the results of such research will alter the balance of evidence that led to the committee's conclusions in this report. Nevertheless, any research that helps to elucidate the mechanisms underlying SIDS would inform future investigations of the potential association between sudden unexpected infant death and vaccines, or any other hypothesized trigger.

Postmortem evaluation of infants varies widely across the country and the depth of the investigation is often related to the evaluation site, the diagnostic resources available, and the availability of specialists such as pediatric or neonatal pathologists (AAP, 1999). **The committee recommends that a comprehensive postmortem workup, including a metabolic analysis, be done on all infants who die suddenly and unexpectedly.** In SIDS cases for which metabolic analyses (such as those done using the tandem mass spectrometry method discussed above) were not done at birth, it may useful to conduct such analyses using samples obtained at autopsy or, if available, stored blood samples (bloodspots) originally obtained for newborn screening tests.

Basic and clinical research, surveillance and epidemiologic studies, and postmortem investigations would all be strengthened by use of standard definitions of SIDS and SUDI. The committee's efforts to reach conclusions regarding causality were hampered by inconsistencies in the epidemiologic reports in the use of these terms.

The committee notes the development of various resources in the United States and internationally to aid in standardizing approaches to the diagnosis of SIDS. In the United States, the accepted definition of SIDS specifies "the sudden death of an infant under 1 year of age which remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history" (Willinger et al., 1991). The definition agreed to at more recent international consensus conferences does not restrict SIDS to infants under 1 year of age (Byard et al., 1996; Sullivan and Barlow, 2001).

Guidance from CDC (1996a) and the AAP (1999; 2001) emphasizes the importance of postmortem examinations and thorough investigation of death scenes to rule out other causes, especially child abuse, before deaths are attributed to SIDS. Also available is an international standardized protocol for autopsies in cases of sudden unexpected infant death (Krous, 1996). In the United States, however, requirements for investigation of unexpected infant deaths are officially established by state and local statutes (CDC, 1996a). **The committee encourages efforts by CDC, AAP, and others to promote the development and consistent use throughout the United States of national guidelines for investigation, diagnosis, and reporting of SIDS cases.**

SUDI, unlike SIDS, is not a single, officially recognized cause of death. It can include deaths that are attributed to many different causes but that are linked

by being sudden and unexpected. Despite the heterogeneity of SUDI, it is a useful concept for research on infant deaths following vaccination. **The committee recommends the development of standard definitions and guidance for diagnosis and reporting of SUDI for research purposes.**

Consistent application of the criteria related to SIDS and SUDI will aid interpretation of reports of vaccine-related deaths and enhance the comparability of results from surveillance, epidemiologic, and biological investigations.

SUMMARY

With current recommendations calling for infants to receive multiple doses of vaccines during their first year of life and with suddent infant death syndrom (SIDS) the most frequent cause of death during the postneonatal period, it is important to respond to concerns that vaccination might play a role in sudden unexpected infant death. A death that occurs suddenly and unexpectedly in the first year of life, whether or not there is an underlying disorder that predisposes to death, has been referred to by the term "sudden unexpected death in infancy" (SUDI). SUDI includes deaths that can be attributed to identifiable causes and deaths for which the causes remain uncertain. SIDS is the diagnosis most commonly given to the deaths of uncertain cause. The committee reviewed epidemiologic evidence focusing on three outcomes: SIDS, all SUDI, and neonatal death (infant death, whether sudden or not, during the first 4 weeks of life). Based on this review, the committee concluded that the evidence favors rejection of a causal relationship between some vaccines and SIDS; and that the evidence is inadequate to accept or reject a causal relationship between other vaccines and SIDS, SUDI, or neonatal death. The evidence regarding biological mechanisms is essentially theoretical, reflecting in large measure the lack of knowledge concerning the pathogenesis of SIDS. Anaphylaxis related to vaccination has been discussed in detail in previous IOM reports and is reexamined in the report; the committee observed that anaphylaxis is known to be a rare but causally related adverse event following the administration of some vaccines. Fatal anaphylaxis in infants is extraordinarily rare. The committee found no basis for a review of current immunization policies, but saw a clear need for continued research on adverse event following vaccination and on the biological basis for sudden unexpected infant deaths. See Box 2 for a summary of all conclusions and recommendations.

BOX 2 Committee Conclusions and Recommendations

SCIENTIFIC ASSESSMENT

Causality Conclusions

There is no basis for a change in the prior conclusions that the evidence favors rejection of a causal relationship between DTwP vaccine and SIDS.

The evidence is inadequate to accept or reject a causal relationship between DTaP vaccine and SIDS.

The evidence is inadequate to accept or reject causal relationships between SIDS and the individual vaccines Hib, HepB, OPV, and IPV.

The evidence favors rejection of a causal relationship between exposure to multiple vaccines and SIDS.

The evidence is inadequate to accept or reject a causal relationship between exposure to multiple vaccines and sudden unexpected death in infancy, other than SIDS.

The evidence favors acceptance of a causal relationship between diphtheria toxoid-and whole cell pertussis vaccine and death due to anaphylaxis in infants.

The evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and neonatal death.

Biological Mechanisms Conclusions

In the absence of experimental or human evidence regarding the ability of common side effects of immunization, including fever and anorexia, to trigger sudden unexpected death in infants with underlying neuroregulatory abnormalities, the committee concludes that this mechanisms is only theoretical.

In the absence of experimental or human evidence regarding the ability of common side effects of immunization, including fever and anorexia, to trigger an acute metabolic crisis in patients with inborn errors of metabolism, the committee concludes that this mechanism for vaccine-related sudden unexpected infant death is only theoretical.

In the absence of experimental or human evidence demonstrating the ability of vaccines to stimulate an abnormal inflammatory response in the lung leading to sudden unexpected infant death, the committee concludes that this mechanism is only theoretical.

The committee concludes that immediate type I hypersensitivity reactions to vaccines can cause SUDI within 24 hours of vaccine administration. Although a type I hypersensitivity reaction leading to death could possibly be missed both

continued

BOX 2 continued

clinically and at post-mortem examination, and therefore misdiagnosed as SIDS, the committee concludes that this possibility is only theoretical.

PUBLIC HEALTH RESPONSE RECOMMENDATIONS

Policy Review

The committee does not recommend a policy review of the recommended childhood vaccination schedule by any of the national or federal vaccine advisory bodies on the basis of concerns about sudden unexpected death in infancy.

Surveillance and Epidemiological Studies

The committee urges prompt publication of all Vaccine Safety Datalink results.

Basic and Clinical Science

The committee recommends continued research on the etiology and pathology of SIDS.

The committee recommends that a comprehensive postmortem workup, including a metabolic analysis, be done on all infants who die suddenly and unexpectedly.

The committee encourages efforts by the Centers for Disease Control and Prevention, American Academy of Pediatrics, and others to promote the development and consistent use throughout the United States of national guidelines for investigation, diagnosis, and reporting of SIDS cases.

The committee recommends the development of standard definitions and guidance for diagnosis and reporting of SUDI for research purposes.

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Appendix A

Committee Recommendations and Conclusions from Previous Reports

MEASLES-MUMPS-RUBELLA VACCINE AND AUTISM:

Conclusions

The committee concludes that the evidence favors rejection of a causal relationship at the population level between measles-mumps-rubella (MMR) vaccine and autistic spectrum disorders (ASD). However, this conclusion does not exclude the possibility that MMR vaccine could contribute to ASD in a small number of children.

The committee concludes that further research on the possible occurrence of ASD in a small number of children subsequent to MMR vaccination is warranted, and it has identified targeted research opportunities that could lead to firmer understanding of the relationship.

Recommendations

Public Health Response

The committee recommends that the relationship between the MMR vaccine and autistic spectrum disorders receive continued attention.

Policy Review

The committee does not recommend a policy review at this time of the

licensure of MMR vaccine or of the current schedule and recommendations for administration of MMR vaccine.

Research Regarding MMR and ASD

The committee recommends the use of accepted and consistent case definitions and assessment protocols for ASD in order to enhance the precision and comparability of results from surveillance, epidemiological, and biological investigations.

The committee recommends the exploration of whether exposure to MMR vaccine is a risk factor for autistic spectrum disorder in a small number of children.

The committee recommends the development of targeted investigations of whether or not measles vaccine-strain virus is present in the intestines of some children with ASD.

The committee encourages all who submit reports to VAERS of any diagnosis of ASD thought to be related to MMR vaccine to provide as much detail and as much documentation as possible.

The committee recommends studying the possible effects of different MMR immunization exposures.

The committee recommends conducting further clinical and epidemiological studies of sufficient rigor to identify risk factors and biological markers of ASD in order to better understand genetic or environmental causes.

Communications

The committee recommends that government agencies and professional organizations, CDC and the Food and Drug Administration (FDA) in particular, review some of the most prominent forms of communication regarding the hypothesized relationship between MMR vaccine and ASD, including information they provide via the Internet and the ease with which Internet information can be accessed.

THIMEROSAL-CONTAINING VACCINES AND NEURODEVELOPMENTAL DISORDERS

Conclusions

The committee concludes that although the hypothesis that exposure to thimerosal-containing vaccines could be associated with neurodevelopmental disorders is not established and rests on indirect and incomplete information, primarily from analogies with methylmercury and levels of maximum mercury exposure from vaccines given in children, the hypothesis is biologically plausible.

The committee also concludes that the evidence is inadequate to accept or reject a causal relationship between thimerosal exposures from childhood vaccines and the neurodevelopmental disorders of autism, ADHD, and speech or language delay.

Public Health Response Recommendations

Policy Review and Analysis

The committee recommends the use of the thimerosal-free DTaP, Hib, and hepatitis B vaccines in the United States, despite the fact that there might be remaining supplies of thimerosal-containing vaccine available.

The committee recommends that full consideration be given by appropriate professional societies and government agencies to removing thimerosal from vaccines administered to infants, children, or pregnant women in the United States.

The committee recommends that appropriate professional societies and government agencies review their policies about the non-vaccine biological and pharmaceutical products that contain thimerosal and are used by infants, children, and pregnant women in the United States.

The committee recommends that policy analyses be conducted that will inform these discussions in the future.

The committee recommends a review and assessment of how public health policy decisions are made under uncertainty.

The committee recommends a review of the strategies used to communicate rapid changes in vaccine policy, and it recommends research on how to improve those strategies.

Public Health and Biomedical Research

The committee recommends a diverse public health and biomedical research portfolio.

Epidemiological Research

The committee recommends case-control studies examining the potential link between neurodevelopmental disorders and thimerosal-containing vaccines.

The committee recommends further analysis of neurodevelopmental disorders in cohorts of children who did not receive thimerosal-containing doses as part of a clinical trial of DTaP vaccine.

The committee recommends conducting epidemiological studies that compare the incidence and prevalence of neurodevelopmental disorders before and after the removal of thimerosal from vaccines.

The committee recommends an increased effort to identify the primary sources and levels of prenatal and postnatal background exposure to thimerosal (e.g., Rho (D) Immune Globulin) and other forms of mercury (e.g., maternal consumption of fish) in infants, children, and pregnant women.

Clinical Research

The committee recommends research on how children, including those diagnosed with neurodevelopmental disorders, metabolize and excrete metals—particularly mercury.

The committee recommends continued research on theoretical modeling of ethylmercury exposures, including the incremental burden of thimerosal with background mercury exposure from other sources.

The committee recommends careful, rigorous, and scientific investigations of chelation when used in children with neurodevelopmental disorders, especially autism.

Basic Science Research

The committee recommends research to identify a safe, effective, and inexpensive alternative to thimerosal for countries that decide they need to switch from using thimerosal as a preservative.

The committee recommends research in appropriate animal models on the neurodevelopmental effects of ethylmercury.

MULTIPLE IMMUNIZATIONS AND IMMUNE DYSFUNCTION

Conclusions

Scientific Assessment

Causality Conclusions

The committee concludes that the epidemiological evidence favors rejection of a causal relationship between multiple immunizations and an increase in heterologous infection.

The committee concludes that the epidemiological evidence favors rejection of a causal relationship between multiple immunizations and an increased risk of type 1 diabetes.

The committee concludes that the epidemiological evidence is inadequate to accept or reject a causal relationship between multiple immunizations and increased risk of allergic disease, particularly asthma.

Biological Mechanisms Conclusions

Autoimmune Disease

In the absence of experimental or human evidence regarding molecular mimicry or mercury-induced modification of any vaccine component to create an antigenic epitope capable of cross-reaction with self epitopes as a mechanism by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity, the committee concludes that these mechanisms are only theoretical.

The committee concludes that there is weak evidence for bystander activation, alone or in concert with molecular mimicry, as a mechanism by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity.

In the absence of experimental or human evidence regarding loss of protection against a homologous infection as a mechanism by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity, the committee concludes that this mechanism is only theoretical.

In the absence of experimental or human evidence regarding mechanisms related to the hygiene hypothesis as a means by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity, the committee concludes that this mechanism is only theoretical.

Considering molecular mimicry, bystander activation, and impaired

immunoregulation collectively rather than individually, the committee concludes that there is weak evidence for these mechanisms as means by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity.

Allergic Disease

The committee concludes that there is weak evidence for bystander activation as a mechanism by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of allergy.

In the absence of experimental or human evidence regarding mechanisms related to the hygiene hypothesis as a means by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of allergy, the committee concludes that this mechanism is only theoretical.

The committee concludes that there is weak evidence for the existence of any biological mechanisms, collectively or individually, by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of allergy.

Heterologous Infection

The committee concludes that there is strong evidence for the existence of biological mechanisms by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk for heterologous infections.

Significance Assessment

The committee concludes that concern about multiple immunizations has been, and could continue to be, of societal significance in terms of parental worries, potential health burdens, and future challenges for immunization policymaking.

Public Health Response Recommendations

Policy Review

The committee recommends that state and federal vaccine policymakers consider a broader and more explicit strategy for developing recommendations for the use of vaccines.

The committee does not recommend a policy review—by the CDC's Advisory Committee on Immunization Practices (ACIP), the American Academy of

Pediatrics' Committee on Infectious Diseases, and the American Academy of Family Physicians—of the current recommended childhood immunization schedule on the basis of concerns about immune system dysfunction.

The committee does not recommend a policy review by the Food and Drug Administration's Vaccines and Related Biologic Products Advisory Committee of any currently licensed vaccines on the basis of concerns about immune system dysfunction.

Research

Epidemiological Research

The committee recommends exploring the feasibility of using existing vaccine surveillance systems, alone or in combination, to study safety questions related to asthma and other important allergic disorders, as well as to type 1 diabetes and other important autoimmune diseases.

The committee recommends exploring the use of cohorts for research on possible vaccine-related disease risks. Furthermore, the committee recommends that disease registries and research programs for autoimmune and allergic disorders routinely collect immunization histories as part of their study protocol.

Basic Science and Clinical Research

The committee recommends continued research on the development of the human infant immune system.

The committee endorses current research efforts aimed at identifying genetic variability in human immune system development and immune system responsiveness as a way to gain a better understanding of genetic susceptibility to vaccine-based adverse events.

The committee recommends exploring the feasibility of collecting data on surrogate markers for autoimmune and allergic disorders in the vaccine testing and licensing process.

The committee recommends exploring surrogates for allergy and auto-immunity in existing cohort studies of variations in the vaccine schedule.

Communication

The committee recommends that an appropriate panel of multidisciplinary experts be convened by the Department of Health and Human Services. It would develop a comprehensive research strategy for knowledge leading to the optimal design and evaluation of vaccine risk-benefit communication approaches.

HEPATITIS B VACCINE AND DEMYELINATING NEUROLOGICAL DISORDERS

SCIENTIFIC ASSESSMENT

Causality Conclusions

The committee concludes that the evidence favors rejection of a causal relationship between hepatitis B vaccine administered to adults and incident multiple sclerosis.

The committee also concludes that the evidence favors rejection of a causal relationship between hepatitis B vaccine administered to adults and multiple sclerosis relapse.

The committee concludes that the evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and the first episode of a central nervous system demyelinating disorder.

The committee concludes that the evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and ADEM.

The committee concludes that the evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and optic neuritis.

The committee concludes that the evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and transverse myelitis.

The committee concludes that the evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and GBS.

The committee concludes that the evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and brachial neuritis.

Biological Mechanisms Conclusions

The committee concludes that there is weak evidence for biological mechanisms by which hepatitis B vaccination could possibly influence an individual's risk of the central or peripheral nervous system disorders of MS, first episode of CDD, ADEM, or optic neuritis, transverse myelitis, GBS, or brachial neuritis.

SIGNIFICANCE ASSESSMENT

The committee concludes that concerns about the hepatitis B vaccine remain significant in the minds of some parents and workers who are required to take the vaccine because of occupational risk.

PUBLIC HEALTH RESPONSE RECOMMENDATIONS

Policy Review

The committee does not recommend a policy review of the hepatitis B vaccine by any of the national and federal vaccine advisory bodies on the basis of concerns about demyelinating neurological disorders.

The committee recommends continued surveillance of hepatitis B disease and increased surveillance of secondary diseases such as cirrhosis and hepatocellular carcinoma.

Basic and Clinical Science

The committee recommends continued research in animal and in vitro models, as well as in humans, on the mechanisms of immune-mediated neurological disease possibly associated with exposure to vaccines.

Communication

The committee again recommends that government agencies and professional organizations responsible for immunizations critically evaluate their communication services with increased understanding of, and input from, the intended user.

SV40 CONTAMINATION OF POLIO VACCINE AND CANCER

SCIENTIFIC ASSESSMENT

Causality Conclusions

The committee concludes that the evidence is inadequate to accept or reject a causal relationship between SV40-containing polio vaccines and cancer.

Biological Mechanisms Conclusions

The committee concludes that the biological evidence is strong that SV40 is a transforming virus.

The committee concludes that the biological evidence is moderate that SV40 exposure could lead to cancer in humans under natural conditions.

The committee concludes that the biological evidence is moderate that SV40 exposure from the polio vaccine is related to SV40 infection in humans.

SIGNIFICANCE ASSESSMENT

The committee concludes that concerns about exposure to SV40 through inadvertent contamination of polio vaccines are significant because of the seriousness of cancers as the possible adverse health outcomes and because of the continuing need to ensure and protect public trust in the nation's immunization program.

PUBLIC HEALTH RESPONSE RECOMMENDATIONS

Policy Review

The committee does not recommend a policy review of polio vaccine by any of the national or federal vaccine advisory bodies, on the basis of concerns about cancer risks that might be associated with exposure to SV40, because the vaccine in current use is free of SV40.

Policy Analysis and Communication

The committee recommends that the appropriate federal agencies develop a Vaccine Contamination Prevention and Response Plan.

Research

The committee recommends development of sensitive and specific serologic tests for SV40.

The committee recommends the development and use of sensitive and specific standardized techniques for SV40 detection.

The committee recommends that once there is agreement in the scientific community as to the best detection methods and protocols, pre-1955 samples of human tissues should be assayed for presence or absence of SV40 in rigorous, multi-center studies.

The committee recommends further study of the transmissibility of SV40 in humans.

Until some of the technical issues are resolved, the committee does not recommend additional epidemiological studies of people potentially exposed to the contaminated polio vaccine.

Appendix B

Public Meeting Agenda
October 28, 2002

Immunization Safety Review
Potential Role of Vaccinations in Sudden Unexpected Death in Infancy

Auditorium, Beckman Center of the National Academies
Irvine, California

10:00 - 10:15 am	**Welcome and Opening Remarks** *Marie McCormick, MD, ScD, Committee Chair*
10:15 - 10:50 am	**Epidemiology of Infant Deaths** *Amy Branum, MSPH,* *National Center for Health Statistics*
10:50 - 11:25 am	**Investigation of Reports to VAERS of Infant Death** *Robert Ball, FDA, MD, MPH, ScM (presenting via conference call)*

11:25 - 12:00 pm	**VSD Analysis of Mortality Risk Following Vaccination** *Joel Ward, MD, UCLA (presenting via conference call)*
12:00 - 12:30 pm	**Discussion**
12:30 - 1:30 pm	**Lunch**
1:30 - 2:15 pm	**Screening for Inborn Errors of Metabolism** *Edwin Naylor, PhD, MPH, Neo Gen Screening* *Donald Chace, PhD, MSFS Neo Gen Screening* *(presenting via conference call)*
2:15 - 3:00 pm	**Research Strategies for Investigating Inborn Errors of Metabolism** *Stephen Goodman, MD, University of Colorado Health Sciences Center*
3:00 - 3:15 pm	**Discussion**
3:15 - 4:00 pm	**Neuroregulation and Sudden Infant Death** *Ronald Harper, PhD, UCLA Neuroscience Program*
4:00 - 4:30 pm	**Discussion and Public Comment**
4:30 pm	**Adjourn**

Appendix C

Chronology of Important Events Regarding Vaccine Safety

Year	Vaccine Licensure	Legislation and/or Policy Statements	IOM Reports on Vaccine Safety
1955	Inactivated poliomyelitis vaccine (IPV) available		
1963	Oral poliomyelitis vaccine (OPV) available, replaces IPV		
	Measles vaccine available		
1967	Mumps vaccine available		
1969	Rubella vaccine available		
1971	Measles-Mumps-Rubella (MMR) vaccine available		
1977		Mumps vaccination recommended	*Evaluation of Poliomyelitis Vaccines*
1979	Current formulation of rubella vaccine available, replaces earlier versions		
1982	Plasma-derived hepatitis B vaccine available		

Year	Vaccine Licensure	Legislation and/or Policy Statements	IOM Reports on Vaccine Safety
1985	Hib vaccine licensed for children >15 months		
1986		Congress passes Public Law 99-660, the National Childhood Vaccine Injury Act (introduced in 1984) calls for: • est. of NVPO • est. of NVAC • est. of VICP • est. of ACCV IOM review of 1) pertussis and rubella, 2) routine child vaccines	
1988			*Evaluation of Poliomyelitis Vaccine Policy Options*
1990	2 Hib conjugate vaccines licensed for use beginning at 2 months		
1991	Acellular pertussis component licensed for the 4th and 5th doses of the 5-part DTP series in ACEL-IMUNE	Hepatitis B recommended by ACIP for addition to childhood immunization schedule ACIP recommends Hib be added to childhood immunization schedule	*Adverse Effects of Pertussis and Rubella Vaccines*
1992	Acellular pertussis component licensed for the 4th and 5th doses of the 5-part DTP series in Tripedia	Hepatitis B vaccine: Added universal vaccination for all infants, high-risk adolescents (e.g., IV drug users, persons with multiple sex partners)	
1993	Combined DTP and Hib vaccine (Tetramune) licensed		

Year	Vaccine Licensure	Legislation and/or Policy Statements	IOM Reports on Vaccine Safety
1994			*Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality* *DPT and Chronic Nervous System Dysfunction: A New Analysis*
1995	Varicella virus vaccine available (Varivax)		
1996	DTaP vaccine licensed for first three doses given in infancy (Tripedia and ACEL-IMUNE were previously licensed for only the 4th and 5th doses).	ACIP recommends using IPV for the first 2 polio vaccinations, followed by OPV for remaining doses. Intended to be a transitional schedule for 3–5 years until an all-IPV series is available ACIP recommends children 12months – 12 years receive Varicella vaccine	*Options for Poliomyelitis Vaccinations in the United States: Workshop Summary*
1997	Additional DTaP vaccine (Infanrix) licensed for first 4 doses of 5-part series	ACIP recommends DTaP in place of DTP	*Vaccine Safety Forum: Summary of Two Workshops* *Risk Communication and Vaccination: Workshop Summary*
1998	Additional DTaP vaccine (Certiva) licensed for first 4 doses of 5-part series	ACIP updates MMR recommendation, encouraging use of the combined MMR vaccine	
1999		ACIP updates varicella vaccine recommendation, requiring immunity for child care and school entry	

Year	Vaccine Licensure	Legislation and/or Policy Statements	IOM Reports on Vaccine Safety
		ACIP recommends an all-IPV schedule begin January 2000 to prevent cases of vaccine-associated paralytic polio AAP and PHS recommend removal of thimerosal from vaccines Also recommended postponement of hepatitis B vaccine from birth to 2–6 months for infants of hepatitis B surface antigen-negative mothers	
	Additional supply of thimerosal-free hepatitis B vaccine made available	*MMWR* notifies readers of the availability of a thimerosal-free hepatitis B vaccine, enabling the resumption of the birth dose	
2000	Pneumococcal vaccine for infants and young children licensed (Prevnar)	ACIP recommends pneumococcal vaccination for all children 2–23 months, and at-risk children 24–59 months (e.g., immunocompromised)	
2001		October: ACIP drafts statement expressing a preference for use of thimerosal-free DTaP, Hib, and Hep B vaccines by March 2002	*Immunization Safety Review: Measles-Mumps-Rubella Vaccine and Autism* *Immunization Safety Review: Thimerosal-Containing Vaccines and Neuro-developmental Disorders*

Year	Vaccine Licensure	Legislation and/or Policy Statements	IOM Reports on Vaccine Safety
2002			*Immunization Safety Review: Multiple Immunizations and Immune Dysfunction* *Immunization Safety Review: Hepatitis B Vaccine and Demyelinating Neurological Disorders* *Immunization Safety Review: SV40 Contamination of Polio Vaccine and Cancer*

Appendix D

Acronyms

AAP – American Academy of Pediatrics
ACIP – Advisory Committee on Immunization Practices

BCG – Bacillus Calmet-Guerin vaccine

CDC – Centers for Disease Control and Prevention
CI – confidence interval
CPT – carnitine palmitoyltransferase
CESDI– Confidential Enquiry into Stillbirths and Deaths in Infancy
CISA – Clinical Immunization Safety Assessment
CNS – central nervous system

DHHS – Department of Health and Human Services
DTaP – diphtheria-tetanus-acellular pertussis vaccine
DTC – trivalent diphtheria-tetanus-pertussis (whole-cell) vaccine
DTCP – tetravalent diphtheria-tetanus-pertussis (whole-cell)-poli vaccine
DTP or DTwP– diphtheria–tetanus–whole-cell pertussis vaccine
DTPP – diphtheria, tetanus, pertussis, and polio vaccine
DTwPH – diphtheria, tetanus, whole-cell pertussis, and *Haemophilus influenzae* type b vaccine
DwP – diphtheria toxoid and pertussis antigen vaccine

FAO – fatty acid oxidation
FDA – Food and Drug Administration

HBeAg – hepatitis B e antigen
HbOC – oligosaccharide conjugate *Haemophilus influenzae* type b vaccine
HBsAg – hepatitis B surface antigen
HepB – hepatitis B vaccine
HHE – hypotonic-hyporesponsive episode
Hib – *Haemophilus influenzae* type b vaccine
HMO – health maintenance organization
HRSA – Health Resources and Services Administration

IAG – Interagency Vaccine Group
IEM – Inborn errors of metabolism
IgE – immunoglobulin E
IL- 1 – interleukin 1
IL-6 – interleukin 6
IOM – Institute of Medicine
IPV – inactivated polio vaccine

KPMCP – Kaiser Permanente Medical Care Program

LCHAD – long-chain 3 hydroxyacyl CoA dehydrogenase

MCAD – medium-chain Acyl-CoA dehydrogenase

NIAID – National Institute for Allergy and Infectious Disease at NIH
NICHD – National Institute of Child Health and Human Development
NIH – National Institutes of Health
NIP – National Immunization Program
NVPO – National Vaccine Program Office

OPV – oral polio vaccine
OR – odds ratio

PCV – pneumococcus vaccine

SIDS – sudden infant death syndrome
SUDI – sudden unexpected death in infancy

TNF – tumor necrosis factor
TH2 –type 2 helper T-cells

VAERS – Vaccine Adverse Events Reporting System
VLCAD – very-long chain acyl-CoA dehydrogenase
VSD – Vaccine Safety Datalink