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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