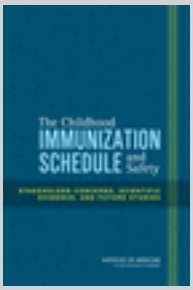

# The Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies

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Committee on the Assessment of Studies of Health Outcomes Related to the Recommended Childhood Immunization Schedule; Board on Population Health and Public Health Practice; Institute of Medicine

# The Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies

**Committee on the Assessment of Studies of Health Outcomes Related to the Recommended Childhood Immunization Schedule**

**Board on Population Health and Public Health Practice**

INSTITUTE OF MEDICINE
*OF THE NATIONAL ACADEMIES*

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



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# COMMITTEE ON THE ASSESSMENT OF STUDIES OF HEALTH OUTCOMES RELATED TO THE RECOMMENDED CHILDHOOD IMMUNIZATION SCHEDULE

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*Until August 2012

# REVIEWERS

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

**Ann Bostrom,** University of Washington
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**Kenneth McIntosh,** Harvard University
**Arthur Reingold,** University of California, Berkeley

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **Bradford H. Gray,** the *Milbank Quarterly*, the Urban Institute, and **Donald M. Steinwachs,** Johns Hopkins University. Appointed by the National Research Council and the Institute of Medicine, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

# Acknowledgments

The committee thanks colleagues both within and outside the National Academies who provided expertise and time to inform the committee and enhanced the quality of the report. Numerous individuals and organizations shared their knowledge and expertise with the committee during information-gathering sessions held on February 9, March 8, and May 29, 2012. These sessions were intended to assist the committee in collecting information on the safety and study of current and past vaccine schedules in the United States and abroad to inform the committee's understanding and vision in completing its task. These individuals are listed in Appendix E.

Of particular note, Martin Kulldorff provided a commissioned paper on study designs that could be considered to assess the safety of the immunization schedule (see Appendix D). Both draft and revised versions of the paper were posted on the study's website to receive public comments to inform the committee's work. In total, the committee reviewed more than 900 public comments. The commissioned paper and public submissions were critical to ensuring fruitful discussions among the members of the committee.

Committee members Alfred Berg and Elena Fuentes-Afflick graciously hosted committee meetings near their respective institutions. The committee thanks the numerous staff members of the Institute of Medicine (IOM), the National Research Council, and the National Academies Press who contributed to the development, production, and dissemination of the report, including study staff Karen Helsing, Suzanne Landi, Chelsea Frakes, Rose Marie Martinez, and Hope Hare. In addition, the study received valuable contributions from Christine Stencel (Office of News and Public Information), Daniel Bethea, Marton Cavani, Laura Harbold DeStefano, and Diedtra Henderson (IOM Office of Reports and Communication), and Doris Romero (IOM Office of Financial Administration). Clyde Behney, Katharine Bothner and Sarah Ziegenhorn (IOM Deputy Executive Office) provided guidance on best practices throughout the study. Michael Hayes served as the editor for the report.

# Contents

# Abstract

The charge to the Committee on the Assessment of Studies of Health Outcomes Related to the Recommended Childhood Immunization Schedule was to (1) review scientific findings and stakeholders concerns related to the safety of the recommended childhood immunization schedule and (2) identify potential research approaches, methodologies and study designs that could inform this question, considering strengths, weaknesses as well as ethical and financial feasibility of each approach. As reviewed by prior Institute of Medicine studies, a substantial literature exists on adverse effects of individual vaccines, but few studies have focused on elements of or on the recommended childhood immunization schedule as a whole. The lack of conclusive evidence linking adverse events to multiple immunizations or other "schedule" exposures suggest that the recommended schedule is safe. There are concerns from some stakeholders that merit exploration through research if epidemiological signals are detected and an indication of biological plausibility is available. However, the committee concludes that it is not ethical to implement any study requiring that some children receive fewer vaccines than recommended as part of the childhood immunization schedule because this would needlessly endanger children's lives. The committee concludes that data from existing surveillance systems, such as the Vaccine Safety Datalink, could be used and offers the best means for ongoing research efforts regarding the safety of the schedule. In recognition of this, future federal research approaches should

- collect and assess evidence regarding public confidence in and concerns about the entire childhood immunization schedule, with the goal to improve communication with health care professionals, and between health care professionals and the public regarding safety;
- standardize definitions of key elements of the schedule, and relevant health outcomes;
- establish research priorities on the basis of epidemiological evidence, biological plausibility, and feasibility; and
- continue to fund and support the Vaccine Safety Datalink project to study the safety of the recommended immunization schedule.

# Summary

## BACKGROUND

Vaccines are among the most effective and safe public health interventions available to prevent serious disease and death. As the incidence of vaccine-preventable diseases has declined because of the widespread use of immunizations, potential adverse effects of the vaccines themselves have taken on greater saliency among stakeholders. The U.S. Advisory Committee on Immunization Practices (ACIP) has created a schedule of vaccines that should be administered at various intervals. ACIP recommends immunization with vaccines that protect young children (age 6 years and under) against 14 pathogens (see Appendix A) and strives to protect children at the youngest age necessary to shield them from diseases when they are the most vulnerable. The childhood immunization schedule (defined in this report as the immunization schedule covering children from birth through age 6 years) immunizes children in a manner consistent with demonstrated efficacy, safety, and feasibility but also permits some degree of flexibility to accommodate individual preferences and logistics.

With the current schedule, children may receive up to 24 immunizations by age 2 years and up to 5 injections in a single visit. Although the number of vaccines has increased over the years to protect against a greater number of diseases, because of technological advances, children now receive fewer antigens, which are the components of vaccines that stimulate the immune system.

In the United States, manufacturers extensively test new vaccine products and then the federal government undertakes a formal process of review and approval before vaccines are made publicly available. Each new vaccine considered for inclusion in the immunization schedule is tested within the context of the existing schedule and reviewed by clinical researchers, who analyze the balance of demonstrated benefits and risks. Thus, each new vaccine is approved on the basis of a detailed evaluation of both the vaccine itself and the immunization schedule. Every year, the Centers for Disease Control and Prevention (CDC) issues guidance on the vaccines to be administered and immunization schedules for children, adolescents, and adults, based on recommendations from ACIP.

To recommend new vaccines, ACIP uses a process in which it reviews a comprehensive set of data associated with the vaccine, including illnesses and deaths associated with the disease and specific high-risk groups; the results of clinical trials, including indicators of safety, efficacy, and effectiveness; cost-effectiveness; information on vaccine use provided by the manufacturer in the product's labeling or package insert; and the feasibility of incorporation of the vaccine into the existing immunization schedule.

Ongoing surveillance systems are the primary source of data on vaccine safety postmarketing. CDC maintains three major postmarketing surveillance systems: the Vaccine

Adverse Event Reporting System, which is jointly managed with the Food and Drug Administration (FDA); the Vaccine Safety Datalink (VSD); and the Clinical Immunization Safety Assessment Network. In addition to the surveillance systems managed by CDC, FDA has established the Sentinel Initiative, a supplementary mechanism for monitoring vaccine safety.

Immunization coverage among children entering kindergarten currently exceeds 90 percent for most recommended vaccines. However, concerns about vaccine safety have contributed to increases in the delay or refusal of immunization, which have, in turn, contributed to a reemergence of vaccine-preventable illnesses. For example, measles and pertussis (whooping cough) outbreaks have occurred in areas where higher proportions of children are unimmunized.

Vaccines—like all drugs or medical interventions—are neither 100 percent risk-free nor 100 percent effective. Additionally, population-wide prevention of vaccine-preventable diseases relies on community immunity, also commonly referred to as herd immunity, which is the shared protective effect conferred on unimmunized individuals when a sufficiently large proportion of the population is immunized against infectious diseases. This phenomenon is achieved when too few people who are vulnerable to development of a disease remain in the population to maintain the chain of disease transmission. Community immunity is waning, however, in places with increasing numbers of unimmunized, incompletely immunized individuals and/or individuals with waning immunity.

Even though children are required to be immunized to enter school and child care, medical exemptions are allowed in all states, and almost all states allow immunization exemptions for people who have religious beliefs against them. Furthermore, 20 states permit exemptions for those who object to immunizations because of personal, moral, or other beliefs.

## THE COMMITTEE

The National Vaccine Program Office (NVPO) of the U.S. Department of Health and Human Services (HHS) asked the Institute of Medicine (IOM) to convene a committee of experts in pediatrics, neurology, medical ethics, immunology, statistics, epidemiology, and public health to identify feasible study designs to explore the safety of the U.S. childhood immunization schedule. A 14-member committee was assembled to address the statement of task. The committee's charge is independent of the charges for previous IOM vaccine studies, and committee members were selected to avoid any real or perceived biases or conflicts. Strict criteria for membership prevented members from having financial ties to vaccine manufacturers or their parent companies, previous service on federal vaccine advisory committees, or having delivered expert testimony or written publications on vaccine safety. The committee's charge is detailed in Box S-1.

**BOX S-1**
**Statement of Task**

The Institute of Medicine will convene an expert committee to

1. Review scientific findings and stakeholder concerns related to the safety of the recommended childhood immunization schedule.
2. Identify potential research approaches, methodologies, and study designs that could inform this question, including an assessment of the potential strengths and limitations of each approach, methodology and design, as well as the financial and ethical feasibility of doing them.
3. Issue a report summarizing their findings.

## COMMITTEE PROCESS

To complete its charge, the committee held three information-gathering meetings in two locations. Before the first meeting and throughout the committee's deliberations, the committee gathered information on public perspectives and reviewed the scientific literature on the safety of the recommended childhood immunization schedule. At the public forums, the committee heard presentations by pediatricians, representatives of federal and state agencies and public health agencies in other countries, vaccine safety researchers, advocacy groups, vaccine manufacturers, and methodological experts. The committee invited comments (both written and oral) from the general public and representatives from numerous organizations with an interest in vaccine safety.

The committee held 5 deliberative meetings over 6 months. To address its charge, the committee requested a commissioned paper on study designs that could be used to assess the safety of the immunization schedule from consultant Martin Kulldorff (see Appendix D). The paper was intended to provide methodological input to the committee but the paper does not necessarily reflect the committee's views. To solicit stakeholders' feedback, the commissioned paper was posted on the committee's website.

## STAKEHOLDERS' CONCERNS

A review of the scientific literature, as well as a detailed review of the oral and written public comments, revealed that among the various stakeholder groups,[1] parents, health care providers, and public health officials share the sentiment that there is insufficient communication between providers and parents about the schedule's safety. Even though the vast majority of parents adhere to the ACIP-recommended immunization schedule, some parents are concerned

[1]Stakeholder groups include researchers; advocacy groups; federal agencies and advisory committees; the general public (including parents); the health care system and providers; international organizations; media; nongovernmental organizations; philanthropic organizations; state, local, and tribal government agencies; industries, such as travel and vaccine manufacturing industries; vaccine distributors; and investors in vaccine manufacturers.

that the schedule may present unnecessary risks because of the timing and number of vaccinations.

Some parents request variations in the immunization schedule, such as a delay of one or more immunizations or the administration of fewer vaccinations at each visit. Some parents also refuse immunizations entirely on the basis of the premise that their children's risks from vaccine-preventable diseases are less than the risks of adverse events associated with immunizations. Such decisions may reflect, in part, the significant and sustained decline in vaccine-preventable diseases that immunization policy has achieved in the past several decades and against which the risk of even extremely rare adverse events may be seen as not worth taking. Some parents are concerned about their child's risk of complications after immunization on the basis of a family history or the child's medical condition and thereby decide to delay or omit immunizations. Other parents express a general lack of confidence in U.S. government decisions about the safety and benefits of the childhood immunization schedule.

The committee understands that these parental concerns are an expression of concern and a way to care for their children's health and well-being. However, the committee also recognizes that a delay or refusal to immunize their children has already contributed to outbreaks of disease across the United States that pose a risk to the health of many people, particularly those with compromised immune systems.

The committee's review of the literature also focused on factors that affect public trust in vaccination campaigns and information on vaccines. Improved communication between public health authorities and parents will require improvements to the clarity of information as well as the building of trust and the use of a systematic approach to elicit public concerns. Further research into questions that parents seek to answer by use of the scientific methods of social, behavioral, and decision science is indicated.

## HEALTH OUTCOMES

The committee searched for, assembled, and summarized evidence on the association between the immunization schedule and specific health conditions that was already published in the peer-reviewed literature. The health outcomes that the committee chose to review were selected on the basis of an examination of the peer-reviewed literature, previous IOM vaccine safety studies, and public presentations at open meetings of this committee. The number of studies that addressed aspects of the immunization schedule varied; for some outcomes, several studies had examined the cumulative effects of vaccines and adjuvants or preservatives, whereas very few studies could be found for other outcomes.

The committee's literature searches and review were intended to identify health outcomes associated with some aspect of the childhood immunization schedule. Allergy and asthma, autoimmunity, autism, other neurodevelopmental disorders (e.g., learning disabilities, tics, behavioral disorders, and intellectual disabilities), seizures, and epilepsy were included as search terms. Furthermore, the committee reviewed papers on immunization and premature infants.

In summary, few studies have comprehensively assessed the association between the entire immunization schedule or variations in the overall schedule and categories of health outcomes, and no study has directly examined health outcomes and stakeholder concerns in precisely the way that the committee was charged to address in its statement of task. No studies

have compared the differences in health outcomes that some stakeholders questioned between entirely unimmunized populations of children and fully immunized children. Experts who addressed the committee pointed not to a body of evidence that had been overlooked but rather to the fact that existing research has not been designed to test the entire immunization schedule.

The committee believes that although the available evidence is reassuring, studies designed to examine the long-term effects of the cumulative number of vaccines or other aspects of the immunization schedule have not been conducted. Nevertheless, in its literature review, the committee found useful designs for studies to measure exposures and outcomes and identified strategies for expanding or adapting conventional study designs to clearly address whether any adverse health outcomes are associated with the overall immunization schedule.

## METHODOLOGICAL APPROACHES

Moving from an analysis of stakeholders' concerns and the limited scientific evidence about the association between the immunization schedule and adverse events to recommendation of specific research methods and study designs to address that association is an ambitious task, in light of the complexity and changing nature of the recommended immunization schedule. Variables such as number of doses, age of administration, and amount of time between doses permit the examination of a large number of potential research questions. Among the many questions about the current immunization schedule that could be posed, the committee parsed the phrase "this question" in Part 2 of the statement of task (Box S-1) into four broad research questions of interest to stakeholders. These are identified in Box S-2.

The committee broadly considered several general research strategies that might be used to address these questions: randomized controlled trials (RCTs), prospective and retrospective observational studies, animal models, and secondary analyses of existing data.

**BOX S-2**

**Leading Research Questions of Interest to Select Stakeholders**

1. How do child health outcomes compare between those who receive no vaccinations and those who receive the full currently recommended immunization schedule?
2. How do child health outcomes compare between (a) those who receive the full currently recommended immunization schedule; and (b) those who omit specific vaccines?
3. For children who receive the currently recommended immunization schedule, do short- or long-term health outcomes differ for those who receive fewer immunizations per visit (e.g., when immunizations are spread out over multiple occasions), or for those who receive their immunizations at later ages but still within the recommended ranges?
4. Do potentially susceptible subpopulations—for example, children from families with a history of allergies or autoimmune diseases—who may experience adverse health consequences in association with immunization with the currently recommended immunization schedule exist?

### Randomized Controlled Trials

When it is possible to randomize study participants, the RCT is widely acknowledged to be the preferred study design for determining cause and effect. RCTs are currently used as part of the FDA approval process to evaluate the safety and effectiveness of individual vaccines in the context of the recommended immunization schedule. Although this is the strongest type of study design, the committee concluded that costs, the large number of participants that would be required, ethical concerns, and other factors make it an inappropriate design for addressing the research questions at hand.

RCTs require participants to be randomly assigned to a study group. However, the random placement of children into a study group in which they would receive less than the full immunization schedule or no vaccines would not be ethical because they would be exposed to a greater risk for the development of diseases and community immunity would be compromised. Furthermore, parents who reject vaccination likely would not allow their children to be randomized to the group that receives full immunization. Additionally, health care professionals serving participants placed in the group to receive fewer or no vaccines would have to go against professional medical guidelines that call on them to encourage patients to follow the recommended schedule.

Even the use of a dispersed immunization schedule that is still within the accepted ACIP time frame for vaccinations as a trial arm would require an increased number of clinic visits, often in rapid succession over a period of a few weeks, which could prove difficult and costly for both the clinics and participating families and may be unacceptable to insurers if its improved effectiveness—measured as a decreased rate of adverse outcomes—was negligible. Although the use of a different schedule that still conforms to the ACIP vaccination time frame is unobjectionable ethically, the committee cannot endorse this method as a feasible option.

The conduct of an RCT would require thousands of participants to be of sufficient size to answer questions about the outcomes of different immunization schedules, and the study would have to span at least 6 to 10 years, meaning that it would likely cost the nation tens of millions of dollars. The risks to participants' health, the cost and time involved, and the ethical challenges all make the conduct of an RCT unsuitable for addressing the research questions, at least until further work with secondary data has been conducted.

### Initiation of New Prospective Observational Studies

Observational studies are another form of clinical research that can provide useful insights and information that may be used to answer research questions. The committee reviewed opportunities to study groups that choose not to vaccinate using a prospective cohort study design. However, such a study would not conclusively reveal differences in health outcomes between unimmunized and fully immunized children for two main reasons. First, to be informative, cohort studies require sufficiently large numbers of participants in each study group and the sample populations often suggested for use in a comparison of vaccinated and unvaccinated children (such as some religious groups) are too small to adequately power a comparative analysis, particularly in the case of rare adverse health outcomes. Because meaningful comparisons require thousands of participants in each study group and less than 1 percent of the U.S. population refuses all immunizations, the detection of enough unvaccinated children would be prohibitively time-consuming and difficult.

Such a study would also need to account for the many confounding variables that separate some populations from the average U.S. child, including lifestyle factors and genetic variables. To be useful, a comparison would require children matched by age; sex; geographic location; rural, urban, or suburban setting; socioeconomic group; and race/ethnicity.

The committee acknowledges that large-scale, long-term studies of infants through adulthood would be informative for evaluating health outcomes associated with immunization. A new research initiative, the National Children's Study, is a multicenter, congressionally funded effort that meets these criteria. Although such studies would be the optimal design for evaluating long-term health outcomes associated with the childhood immunization schedule, they would require considerable time and funding, and the committee did not find adequate epidemiological evidence to recommend investment in this type of research at this time.

### Secondary Analyses with Existing Data

The most feasible approach to studying the safety of the childhood immunization schedule is through analyses of data obtained by VSD. VSD is a collaborative effort between CDC and 9 managed care organizations that maintain a large database of linked data for monitoring immunization safety and studying potential rare and serious adverse events. VSD member sites include data for more than 9 million children and adults receiving vaccinations on a variety of immunization schedules. However, children who are vaccinated on alternative schedules (including those who are not vaccinated) may differ in meaningful ways. Although this confounding can be minimized through matching and controlling for variations, differences in nonrandomly constructed cohorts cannot be fully accounted for by the use of these data.

The committee discussed several potential modifications that could be introduced into this system that would enable new analyses of the key research questions (Box S-2), including collection of additional data on the participants. The committee found that secondary analyses within VSD would advance knowledge of the safety of the immunization schedule and identified enhancements to improve the data in VSD.

### Animal Models

The committee also reviewed the potential for animal studies to be used to study the childhood immunization schedule. Given the committee's recognition of the complexity of the immunization schedule, the importance of family history, the role of individual immunologic factors, and the complex interaction of the immunization schedule with the health care system, the committee determined that it was more appropriate to focus future research efforts on human research.

### Population Impacts of Alternative Schedules

The committee agreed that evaluations of the recommended immunization schedule need to be attentive to effects at the population level as well as the individual level. Attempts to quantify the relative safety of contrasting immunization schedules need to take into account at least two separate health outcomes: adverse events after the administration of specific vaccines and the overall immunization schedule and the respective impacts of alternative schedules on the

circulation of vaccine-preventable diseases and the consequent adverse outcomes associated with infection.

The intimate association between immunization and age-specific disease incidence needs to be addressed. Specifically, any changes in the immunization schedule that lead to an increase in exposure to preventable disease will increase the spread of the pathogens responsible for these diseases. The population-level impacts of such an outcome would be a simultaneous rise in the incidence of infectious diseases and a reduction in the age at which these illnesses are contracted. Thus, not only is the risk of exposure to preventable diseases increased, but the severity of infection, which is age dependent, is also likely to increase.

### Conclusions About Stakeholders' Concerns

The committee identified concerns among some parents about the number, frequency, and timing of immunizations in the overall immunization schedule. These concerns were not expressed by clinicians, public health personnel, or policy makers in the committee's review. Among the last three groups, the childhood immunization schedule is considered one of the most effective and safest public health interventions available to prevent serious disease and death. Furthermore, the committee's review of the literature did not find high quality evidence supporting safety concerns about the immunization schedule.

In its role to ensure vaccine safety, the federal government has emphasized the engagement of stakeholders in multiple activities. However, an effective national vaccine program will require a more complete and systematic collection of information about stakeholders' concerns about vaccine safety, the severity of vaccine-preventable diseases, individual- and population-level immunization rates, the efficacy of immunization, and the delivery and supply of vaccines recommended in the childhood immunization schedule.

To more effectively implement immunization programs, a robust communication and engagement strategy is needed which includes careful study of safety concerns. Currently, the designs used in most studies of immunizations do not permit a detailed analysis of the impact of parental concerns on the decision to immunize their children. Most concerns about safety are expressed by parents, but multiple stakeholders should be included in NVPO efforts. For example, even health care providers with much knowledge about individual vaccines may have less information about the effects of administering multiple vaccines at a single visit or the timing of the immunizations.

**Recommendation 4-1: The committee recommends that the National Vaccine Program Office systematically collect and assess evidence regarding public confidence in and concerns about the entire childhood immunization schedule, with the goal to improve communication with health care professionals, and between health care professionals and the public regarding the safety of the schedule.**

## CONCLUSIONS ABOUT SCIENTIFIC FINDINGS

The committee encountered two major issues in its review of the findings in the scientific literature. First, the concept of the immunization "schedule" is not well developed. Most vaccine-

related research focuses on the outcomes of single immunizations or combinations of vaccines administered at a single visit. Although each new vaccine is evaluated in the context of the overall immunization schedule that existed at the time of review of that vaccine, elements of the schedule are not evaluated once it is adjusted to accommodate a new vaccine. Thus, key elements of the entire schedule—the number, frequency, timing, order, and age at administration of vaccines—have not been systematically examined in research studies.

The second major issue that the committee encountered was uncertainty over whether the scientific literature has addressed all health outcomes and safety concerns. The committee could not tell whether its list was complete or whether a more comprehensive system of surveillance might have been able to identify other outcomes of potential significance to vaccine safety. In addition, the conditions of concern to some stakeholders, such as immunologic, neurologic, and developmental problems, are illnesses and conditions for which etiologies, in general, are not well understood.

Finally, the committee found that evidence assessing outcomes in subpopulations of children who may be potentially susceptible to adverse reactions to vaccines (such as children with a family history of autoimmune disease or allergies or children born prematurely) was limited and is characterized by uncertainty about the definition of populations of interest and definitions of exposures and outcomes.

In summary, to consider whether and how to study the safety and health outcomes of the entire childhood immunization schedule, the field needs valid and accepted metrics of the entire schedule (the "exposure") and clearer definitions of health outcomes linked to stakeholder concerns (the "outcomes") in rigorous research that will ensure validity and generalizability.

**Recommendation 5-1: To improve the utility of studies of the entire childhood immunization schedule, the committee recommends that the National Vaccine Program Office develop a framework that clarifies and standardizes definitions of**

- **key elements of the schedule,**
- **relevant health outcomes, and**
- **populations that are potentially susceptible to adverse events.**

## CONCLUSIONS ABOUT RESEARCH METHODS

Vaccine safety is critically important, but a determination of safety is ultimately a value judgment. For example, some might believe that a serious adverse event that occurs once in 1 million doses is "safe enough" relative to the benefit of preventing a serious disease, whereas others may consider that risk unacceptably high. The committee did not set a specific numerical target or goal for what should be considered "safe enough." Instead, the committee made a judgment based on the literature that failed to link adverse effects to schedule exposures or multiple immunizations, concluding that there is no evidence that the schedule is not safe.

The committee identified four broad research questions of interest to stakeholders (Box S-2) and discussed general research approaches that could be used to address these questions. Setting of priorities for research will be challenging. The committee proposes a process for setting research priorities that incorporates epidemiological and other evidence (formal

systematic reviews), biological plausibility, feasibility, and stakeholder concerns. Before HHS agencies, such as CDC, FDA, the National Institutes of Health, and NVPO, initiate further research on the entire immunization schedule, a thorough review of the biological plausibility of the association of a particular outcome with an aspect of the immunization schedule should be conducted.

**Recommendation 6-1: The committee recommends that the Department of Health and Human Services incorporate study of the safety of the overall childhood immunization schedule into its processes for setting priorities for research, recognizing stakeholders' concerns and establishing the priorities on the basis of epidemiological evidence, biological plausibility, and feasibility.**

The decision to initiate further studies should depend on the evaluation of three considerations that the committee identified through its review of stakeholder concerns and scientific findings:

1. epidemiological evidence of potential adverse health outcomes associated with elements of the immunization schedule (such as postmarketing signals or indications of an elevated risk from observational studies);
2. biological plausibility supporting hypotheses linking specific aspects of the immunization schedule with particular adverse health outcomes; and
3. expressed stakeholder concerns about immunization schedule's safety, which should initiate efforts to explore the previous two considerations.

The committee acknowledges the evidence that reduced immunization coverage is associated with increases in the incidence of vaccine-preventable disease and found ad hoc, inconsistent, and anecdotal evidence to imply that the recommended immunization schedule is not safe. Moreover, existing adverse event detection systems provide confidence that the existing childhood immunization schedule is safe, and the committee recognizes that the federal government invests considerable resources to ensure vaccine safety. However, some stakeholders have suggested that further research is warranted, such as a comparison of vaccinated children with unvaccinated children or children immunized on alternative schedules.

It is possible to make this comparison through analyses of patient information contained in large databases such as VSD, but it would be unethical and infeasible to conduct an RCT, as summarized above and detailed in Chapter 6. Because an RCT would increase the risk of preventable diseases in individuals and in the community and entail significant amounts of time, money, and other resources, the committee concludes that new RCTs of the childhood immunization schedule are not justified at this time.

**Recommendation 6-2: The Department of Health and Human Services should refrain from initiating randomized controlled trials of the childhood immunization schedule that compare safety outcomes in fully vaccinated children with those in unvaccinated children or those vaccinated by use of an alternative schedule.**

The committee concludes that secondary analyses of existing data are more promising approaches to examination of the research questions identified by the committee in future studies of the childhood immunization schedule. VSD is a useful collaborative project for conducting both postmarketing surveillance and longer-term targeted research. The ability to augment the routinely collected administrative data in VSD with parent interviews and reviews of medical records for selected study populations is an important strength.

VSD is currently the best available system for studying the safety of the immunization schedule in the United States. VSD should strive to improve its generalizability to the U.S. population by enhancing the quality of its demographic information or by expanding its scope to include more diversity in its study populations. Secondary analyses with data from other existing databases could also be feasible, ethical, and cost-effective in investigating several of the research questions that the committee identified.

The committee recognizes that the currently funded managed care organizations' commitment to VSD studies needs to remain high to continue and build on existing efforts. The committee concludes that VSD is a valuable component of the federal research infrastructure and will be the best-suited source of data for studying the childhood immunization schedule. VSD's utility will be expanded with the addition of more detailed demographic data and family medical histories.

**Recommendation 6-3: The committee recommends that the Department of Health and Human Services (HHS) and its partners continue to fund and support the Vaccine Safety Datalink project to study the safety of the recommended immunization schedule. Furthermore, HHS should consider expanding the collaboration with new health plan members and enhancing the data to improve its utility and generalizability.**

## CONCLUDING OBSERVATIONS

The committee's efforts to identify priorities for recommended research studies did not reveal an evidence base suggesting that the childhood immunization schedule is linked to autoimmune diseases, asthma, hypersensitivity, seizures, child developmental disorders, learning disorders or developmental disorders, or attention deficit or disruptive behavior disorders. Although stakeholders' concerns should be one of the elements used to drive searches for scientific evidence, these concerns alone, absent epidemiological or biological evidence, do not warrant the initiation of high-cost research studies. The committee concludes that the use of existing data from database systems to conduct observational studies offers the best means for ongoing research efforts about the immunization schedule's safety.

The committee found no significant evidence to imply that the recommended immunization schedule is not safe. Furthermore, existing surveillance and response systems have identified known adverse events associated with vaccination. The federal research infrastructure is a strong system. A key component is the VSD project, which with ongoing support will be able to feasibly address the committee's research questions identified in Box S-2. Although the committee concluded that protecting children from vaccine-preventable diseases is of higher importance than testing alternative immunization schedules without epidemiological or

biological evidence indicating a safety problem, VSD should continue to examine the health outcomes of people who choose alternative schedules.

Looking to the future, the committee supports the work of the federal research infrastructure to ensure that stakeholders are involved in all stages of the development, implementation, evaluation, and dissemination of the immunization schedule. As electronic medical records become more commonly used, they may provide an opportunity to capture complete immunization data linked with hospital discharge records, which will be useful to future studies. Newer initiatives such as the National Children's Study and the Post-licensure Rapid Immunization Safety Monitoring (PRISM) program also hold promise in providing further study opportunities.

The childhood immunization schedule may become more complex over time as scientific advances are made and new vaccines are developed and incorporated into the schedule. Feasible research approaches to study potential adverse health outcomes will emerge only with sustained and substantial federal commitment to research on vaccine safety.

# 1

# Introduction

Vaccines have significantly contributed to worldwide reductions in morbidity and mortality by reducing the incidence of serious infectious diseases (IOM, 2012). Today, people all over the world experience the benefits of immunizations, beginning in infancy. Most adults in the United States have not witnessed first-hand the devastating illnesses against which vaccines offer protection, for example, polio, diphtheria, and *Haemophilus influenzae* meningitis. However, as the incidence of vaccine-preventable disease has declined, many do not appreciate the potential of these diseases to reemerge, and the potential adverse effects of the vaccines themselves take on greater saliency among certain stakeholders. Indeed, vaccine safety concerns exist among a diverse range of individuals, institutions, and formal and informal networks worldwide.

Healthy individuals are immunized with immunogenic materials that induce immunity to serious pathogens. A "schedule" is a tool that is used to ensure that the recommended immunizations are provided to shield both children and adults from disease when they are the most vulnerable. In the United States, schedules recommended by the Advisory Committee on Immunization Practices (ACIP) (schedules for children from birth to age 6 years, children and adolescents ages 7 through 18 years, and adults) are based on the immunogenicity of vaccines and the burden and timing of disease (CDC, 2011a). The schedule is designed and updated yearly on the basis of new evidence (see Appendix A). This report focuses on the vaccines that protect young children under age 6 years against 14 different pathogens because that time period is when multiple inoculations are given (see Appendix A).

Children may receive as many as 24 injections by 2 years of age and up to 5 injections in a single visit (see Appendix A). Immunization schedules vary around the world, however, with the variability being due in part to the different patterns of disease that exist globally (Lopalco et al., 2009; WHO, 2012). Additionally, levels of antigens and immunization timing and number differ. Some countries also have differing approaches to postmarketing surveillance systems, as will be described in Chapter 3.

Although the number of vaccinations recommended is greater than ever before, the vaccines used in the current immunization schedule actually have fewer antigens (inactivated or dead viruses and bacteria, altered bacterial toxins, or altered bacterial toxins that cause disease

and infection) because of developments in vaccine technology (Offit et al., 2002). For example, the vaccines to prevent whooping cough used before 1991 contained 3,000 different potentially antigenic proteins (IOM, 2002). From 1980 to 2000, the immunization schedule's total number of antigens decreased by approximately 96 percent (from 3,041 to 123-126) (Offit et al., 2002).

Ever since vaccines were introduced in the 18th century, questions and concerns about their safety have been voiced. However, the protection against feared, deadly diseases that vaccines offer encourages the majority of health care professionals and laypeople to support immunization (Stern and Markel, 2005). Although research on the adverse effects of individual vaccines is robust and a required part of the approval process by ACIP, questions about the safety of the entire recommended immunization schedule for children persist. Moreover, how safety is interpreted varies according to the severity of an adverse event and the benefit of the vaccine. For example, some might believe that one serious adverse event that occurs once in 1 million doses is "safe enough" compared with the benefit of prevention of serious disease, whereas others may consider that risk unacceptably high.

As the number of recommended vaccines has increased in recent years, some parents and advocacy groups have expressed the concern that the immunization schedule is too crowded and complex because of the increasing number of vaccines administered during the first 2 years of a child's life (Offit et al., 2002). In addition to the complexity of vaccine delivery, some people have raised questions about the potential for adverse health outcomes as a consequence of the simultaneous or sequential administration of childhood vaccines (Gregson and Edelman, 2003). Even though the current childhood immunization schedule offers flexibility for administration of recommended vaccines (see Appendix A), some parents elect not to follow the recommended schedule (Dempsey et al., 2011).

Analysis of current U.S. data shows that the vaccination rate of among children entering kindergarten exceeds 90 percent for most recommended vaccines (CDC, 2012b). However, increases in the prevalence of delay or refusal of recommended vaccines have contributed to the emergence of vaccine-preventable illnesses across the country. For example, measles and pertussis outbreaks have occurred in recent years in geographic areas with higher concentrations of unimmunized children (Felkin et al., 2000). States with easy procedures for granting exemptions were associated with a 90% higher incidence of pertussis in 2011 (Omer et al., 2006). Some vaccine-preventable diseases can be fatal and have caused morbidity and mortality in infants and people with compromised immune systems. The impacts on disease prevention that vaccines have had in the United States are illustrated in Table 1-1.

**TABLE 1-1** Comparison of Pre-Vaccine Annual Incidence and Current Morbidity for Vaccine-Preventable Diseases

| Disease | 20th Century Annual Morbidity (No. of Cases)[a] | No. of Cases Reported in 2011[b] | Percent Decrease |
|---|---|---|---|
| Congenital rubella syndrome | 152 | 0 | 100 |
| Diphtheria | 21,053 | 0 | 100 |
| *Haemophilus influenzae* (<5 years of age) | 20,000[c] | 14[d] | >99 |
| Measles | 530,217 | 220 | >99 |

| | | | |
|---|---|---|---|
| Mumps | 162,344 | 404 | >99 |
| Pertussis | 200,752 | 18,719 | 89 |
| Polio (paralytic) | 16,316 | 0 | 100 |
| Rubella | 47,745 | 4 | >99 |
| Smallpox | 29,005 | 0 | 100 |
| Tetanus | 580 | 36 | 98 |

[a] SOURCE: Roush et al., 2007.
[b] SOURCE: CDC, 2012a.
[c] Estimated.
[d] *Haemophilus influenzae* type b among children <5 years of age.

Vaccinations—like all medical procedures—are neither 100 percent free of risk nor 100 percent effective. Vaccines, in rare cases, can cause illness. Most children who experience an adverse reaction to immunization have a preexisting susceptibility. Some predispositions may be detectable prior to vaccination; others, at least with current technology and practice, are not (IOM, 2012, p. 82). The U.S. Department of Health and Human Services (HHS), through its agencies responsible for vaccine safety, supports such research and surveillance, including studies addressing concerns and fears over the current childhood immunization schedule. The system in the United States designed to ensure vaccine safety is detailed in Chapter 3. While immunization may be one of the greatest achievements in public health, the complex interactions between populations, health care systems, families, children, and so forth that are affected by the immunization schedule cannot be ignored.

## STUDY BACKGROUND

On June 2, 2009, the National Vaccine Advisory Committee (NVAC) reviewed the nation's vaccine safety system and endorsed the recommendation of the NVAC Safety Working Group for an external expert committee, such as a committee convened by the Institute of Medicine (IOM), "with broad expertise in research methodologies, study design, and the ethical conduct of research to consider the strengths and weaknesses, ethical issues and feasibility including timelines and cost of various study designs to examine outcomes in unvaccinated, vaccine-delayed and vaccinated children and report back to the NVAC" (CDC, 2011b, p. 72).

The recommendation by the NVAC Safety Working Group was based on a series of meetings and discussions on the U.S. childhood immunization schedule in which individuals raised concerns that the schedule could potentially harm children because of immunological or neurodevelopmental adverse effects. Furthermore, in the minds of some parents, concerns about potential harms outweigh the well-documented benefits of immunization for the prevention of morbidity and mortality, with the resulting being that their children are less than fully immunized (NVAC, 2009).

After years of debate, some people continue to advocate for a study to compare health outcomes among vaccinated and unvaccinated children. The NVAC report stated that "the strongest study design, a randomized clinical trial that includes a study arm receiving no vaccine or vaccine not given in accord with the current recommended schedule, is not ethical, would not pass Institutional Review Board (IRB) review, and cannot be done" (NVAC, 2009, p. 38).

(Chapter 6 discusses some of the ethical considerations in detail.) Furthermore, it may be impossible to draw unbiased results from an observational study of this issue because of potential differences in baseline health and social characteristics of populations and subgroups.

## COMMITTEE ON THE ASSESSMENT OF STUDIES OF HEALTH OUTCOMES RELATED TO THE RECOMMENDED CHILDHOOD IMMUNIZATION SCHEDULE

The National Vaccine Program Office of HHS asked the IOM to convene a diverse committee of experts in pediatrics, neurology, medical ethics, immunology, statistics, epidemiology, and public health to identify study designs feasible to address questions about the safety of the United States' childhood immunization schedule. A 14-member committee was selected to complete a study addressing the statement of task (see Box 1-1). The committee's charge was independent of the charges for previous IOM studies of vaccines, and committee members were carefully selected to avoid real or perceived biases or conflicts of interest. Strict criteria for membership prevented any members from having financial ties to vaccine manufacturers or their parent companies, previous service on federal vaccine advisory committees, or delivered expert testimony or written publications on issues of vaccine safety.

Biographical sketches of the members of committee can be found in Appendix F. The committee's charge is detailed in Box 1-1.

## COMMITTEE PROCESS

To complete its charge, the committee held three information-gathering meetings in two different locations. Before the first meeting and throughout the committee's deliberations, the committee gathered information on public perspectives and reviewed the scientific literature on the safety of the recommended childhood immunization schedule. At the public forums held in February, March, and May 2012, the committee heard presentations from clinicians, representatives of U.S. federal and state agencies and public health agencies in other countries, vaccine safety researchers, advocacy groups, vaccine manufacturers, and methodological experts. During the public forums, the committee invited comments (both written and oral) from the general public and representatives from numerous organizations with an interest in vaccine

**BOX 1-1**
**Statement of Task**

The Institute of Medicine will convene an expert committee to

1. Review scientific findings and stakeholder concerns related to the safety of the recommended childhood immunization schedule.
2. Identify potential research approaches, methodologies, and study designs that could inform this question, including an assessment of the potential strengths and limitations of each approach, methodology, and design, as well as the financial and ethical feasibility of doing them.
3. Issue a report summarizing their findings.

safety. Additionally, the committee received and reviewed written correspondence from the public throughout the duration of the study.

The committee held 5 deliberative meetings over 6 months between February and August 2012. To fully address its charge, the committee identified a consultant who prepared a commissioned paper on study designs that could be used to assess the safety of the immunization schedule (see Appendix D). The paper, written by Martin Kulldorff, was intended to provide methodological input to the committee, but the paper does not necessarily reflect the committee's views or deliberations. To solicit stakeholders' interest and feedback, a draft version of the commissioned paper was posted on the committee's website on May 14, 2012, and comments on the paper were invited from the public. The comment period extended to May 31, 2012, and approximately 230 individuals provided written feedback. After a review of these comments and committee discussion, the committee requested revisions from the consultant. The commissioned paper was finalized on July 3, 2012, and again posted online for comment. The committee reviewed an additional 700 comments.

## PREVIOUS IOM VACCINE STUDIES

Since the late 1970s, the IOM has conducted 60 studies on vaccination (see Appendix G). Each IOM study has relied on scientific evidence as the basis for its findings, conclusions, and recommendations. Committee members reviewed the summaries of 18 IOM studies that focused on vaccine safety. Reexaminations of safety are often prompted by new scientific findings and rising concerns usually in relationship to an individual vaccine and a possible adverse health outcome. However, the study of the present IOM committee is unique in that its focus is on the complete childhood immunization schedule.

This report follows a series of eight reports on vaccine safety that appeared between 2001 and 2004. The eighth report in this series examined the evidence about a possible link between autism and vaccines. That examination of the evidence found no association. A striking element described in each of these IOM reports is society's sustained interest in vaccines (Fineberg, 2011).

The 2012 IOM committee report *Adverse Effects of Vaccines* examined 158 pairs of vaccines and putative adverse effects and was the IOM's most recent study of vaccine safety (IOM, 2012). No evidence to support a link between a vaccine and adverse events was found for the majority of adverse events, but this was often due to the rarity of the adverse event and the lack of evidence in general to support or reject a causal link. However, the committee concluded that very few health problems are caused by or are clearly associated with vaccines.

## ORGANIZATION OF THE REPORT

This report is organized into seven chapters and seven appendixes. Chapter 2 provides background on how vaccines are developed and recommended for U.S. children. Chapter 3 details existing surveillance and data systems for evaluating vaccine safety. Chapter 4 reports on the committee's review of stakeholder concerns. Chapter 5 describes the methods used to perform and the results of a literature review on the scientific findings of studies of selected health outcomes and the recommended immunization schedule. Chapter 6 presents several

methodological approaches for future studies. Chapter 7 summarizes the committee's findings, conclusions, and recommendations. The appendixes include ACIP's 2012 recommended immunization schedule for children (Appendix A), a glossary (Appendix B), a list of acronyms used in this report (Appendix C), the commissioned paper by Martin Kulldorff (Appendix D), agendas from public meetings held by the committee (Appendix E), biographical sketches of the committee members (Appendix F), and a chronological list of the IOM's vaccine publications (Appendix G).

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# 2

# Determination of the Immunization Schedule

The immunization schedule recommended by the Advisory Committee on Immunization Practices (ACIP) is determined through consideration of numerous factors and the cooperation of numerous federal agencies in an extensive federal research infrastructure that includes the National Institutes of Health, the Food and Drug Administration (FDA), and the Centers for Disease Control and Prevention (CDC). This chapter provides an overview of some of these factors and the processes in place to help ensure that the immunization schedule benefits the recipients.

## IMMUNE SYSTEM RESPONSES

The biology of the immune system response to pathogens and foreign substances is complex and was reviewed in a 2012 Institute of Medicine report. A broad overview of how vaccines work to protect the human body against disease is first presented as a prelude to consideration of the safety of the aggregate of vaccines that are part of the immunization schedule from the perspective of immune system responses.

The fundamental goal of vaccination is to prepare the immune system to defend the host against disease by intentionally exposing the body to all or part of an infectious agent, in an effort to confer long-term protective immunity against future infection and to protect the most vulnerable individuals against disease.

Immunity protects the body against infectious diseases mainly through the production of specialized protein molecules known as “antibodies” or “immunoglobulins,” once the immune system has been stimulated by the presence of foreign substances, called “antigens,” from, for example, pathogens or vaccines (CDC, 2012d; Siegrist, 2008). In addition to immunoglobulins, other parts of the immune system also contribute to protection, including lymphocytes (specialized white blood cells), antigen-presenting cells (which recognize the foreign elements of the vaccine or the virus or bacterium that is the cause of an infectious disease and which help initiate the steps involved in protection), the spleen, and the skin itself, which serves as a protective barrier against bacteria and viruses.

For a vaccine to be efficacious and reduce the incidence of vaccine-preventable diseases, it must elicit the production of high-quality antibodies against the pathogen responsible for disease. Certain vaccines are able to generate an immunologic memory similar to that generated by natural infection, which often confers lifelong protection, whereas other vaccines may require boosters over time to maintain immunity.

The immune response is largely dependent upon the properties of the antigen used to develop the vaccine and on the route of administration. Live attenuated vaccines contain viruses or bacteria that are weakened versions of the naturally occurring infectious agent, whereas inactivated vaccines contain either antigens that are grown in laboratory culture media and inactivated by the use of heat or chemicals, altered bacterial toxins (toxoids) that when administered do not result in natural disease, or antigens that are produced artificially to mimic the surface properties of the pathogen.

Vaccines containing live, attenuated antigens confer a stronger immune response because the antigen is more similar to that encountered during natural infection; however, in rare cases, the virus may replicate uncontrollably in immunocompromised individuals and lead to a severe or fatal reaction. In an inactivated vaccine, the virus or bacterium is not alive and is not able to cause an infectious disease through unintended replication.

The type of vaccine is one factor that determines where the vaccine appears in the recommended immunization schedule. For example, the measles-mumps-rubella (MMR) virus vaccine is a live attenuated vaccine that for most recipients confers immunity after just one dose. Children following the recommended immunization schedule receive one dose of MMR at between 12 and 15 months of age and a second dose after age 4 years to ensure immunity. An inactivated vaccine such as diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (DTaP), which contains diphtheria and tetanus toxoids combined with a subunit of the bacterium that causes pertussis, does not confer full immunity until after the second or third dose and requires later booster doses to remain immunologically effective, as the antibody titers that maintain immunity diminish with time.

Adjuvants can provide improved immunity by delaying the absorption of the antigens or by arousing or boosting the immune system response (IOM, 2012; Melvold, 2009). The immunoglobulin M (IgM) isotype is the primary immunoglobulin generated after immunization, quickly followed by the IgG isotype. To demonstrate the immunogenicity of a vaccine, serum antivaccine (or antigenic marker) IgG antibodies are measured. For example, in studies of immunization with pandemic swine influenza A virus (H1N1) vaccines, detection of antibodies demonstrating inhibition of hemagglutination at a serum titer of 1:40 or greater provides evidence of seroprotection to the individual (Liang et al., 2010). These antibodies reduce infection by blocking the interaction between the influenza virus antigen, hemagglutinin, and cell surface receptors that it will use to enter the cell (Reddy et al., 2011). For the group of subjects studied, after a single immunization of 7.5 μg of a nonadjuvant split-virion formulation of the H1N1 vaccine in children ages 3 to <12 years, the increase in the hemagglutination titer over the baseline titer by 3 weeks postimmunization was robust (from a baseline mean titer of 6 to a postimmunization titer of 178) (Liang et al., 2010). When the titers are presented as geometric means to account for the distribution of responses, the baseline geometric mean titer was 5.3 and the postimmunization geometric mean titer was 178, a

32-fold response achieved by 3 weeks postimmunization . In adolescents (individuals ages 12 to <18 years), the geometric mean titers increased even more over the first 3 weeks postimmunization, from a baseline of 7 to 578, an 82-fold change (Liang et al., 2010).

The response to vaccination can be blunted in individuals who lack critical components of the immune system. For example, the responses to influenza immunization can be nonexistent or poor in patients who have received rituximab, which is an antibody to CD20, a membrane surface marker on B cells, present from early to full maturation of B cells and plasma cells, which secrete immunoglobulins (Bedognetti et al., 2011). Rituximab is useful therapeutically for the treatment of multiple conditions, including forms of lymphoma and collagen vascular diseases. However, the number of B ($CD19^+$) cells can be reduced for 6 months or longer after discontinuation of rituximab in patients who are in remission from lymphoma. Treatment with rituximab was found to greatly reduce the number of memory B cells characterized as $CD27^+$ and was associated with a poor or absent response to influenza immunization (Bedognetti et al., 2011). Although the patients had detectable $CD4^+$ and $CD8^+$ lymphocytes, they did not have $CD19^+$ B cells and did have reduced numbers of $CD27^+$ memory B cells, a condition which was associated with failure to mount a protective response after immunization (Bedognetti et al., 2011).

Another factor used to determine where a vaccine appears in the immunization schedule is vulnerability to the vaccine-preventable disease by age. This determination requires some knowledge of the pattern of disease in the community, which may differ by region of the world. As the immunity afforded by maternal antibodies at birth wanes, infants become more susceptible to pathogens, many of which may lead to serious or fatal infections. Therefore, to be effective, a vaccine should be administered early enough to protect the infant or child against preventable diseases.

The age range for which a childhood vaccine is developed and recommended as part of the immunization schedule takes into account the age at which the immune system can tolerate vaccine components, potential interference with the immune response from maternal antibodies, and the age at which a child is most at risk for disease transmission and mortality. ACIP recommends vaccines "for members of the youngest age group at risk for experiencing the disease for which efficacy and safety have been demonstrated," and its recommendations are based on the best evidence available (CDC, 2011a, p. 4).

## IMMUNIZATION AT THE POPULATION LEVEL

For immunizations to adequately protect individuals and the individuals in the communities in which they live against outbreaks of vaccine-preventable diseases, a high proportion of vaccinated individuals needs to be maintained in the general population. The success of vaccination to preserve low levels of disease incidence depends on the population level of "community immunity," also commonly known as herd immunity, which refers to the immunity of a group that is afforded when a high proportion of individuals are not susceptible to infection. Community immunity is maintained by vaccination against communicable diseases, and this concept is expertly discussed in other sources (Fine, 1993; Fine et al., 2011).

It is possible to quantify the fraction of the population that needs to be protected to prevent disease spread on the basis of the epidemiological traits of the pathogen in question (such as its transmissibility and duration of infectivity). The calculation requires an understanding of the so-called basic reproduction ratio, or $R_0$, which quantifies the maximum transmission potential of an infectious disease. It is strictly defined as the number of secondary cases generated by a typical primary case in a fully susceptible population. If $R_0$ is >1, then the pathogen is predicted to transmit to more than one other person and successfully invade the population. For the major childhood infectious diseases, such as measles, mumps, rubella, chickenpox, and polio, a variety of methods have been devised to estimate $R_0$ from longitudinal incidence reports, outbreak data, and age-stratified serology (Anderson and May, 1982, 1992; Becker, 1989; Keeling and Rohani, 2008).

The quantity $R_0$ has been used to guide vaccination policy with recognition that it is defined when the entire population is susceptible to the pathogen. That is, the number of susceptible individuals ($S$) is equal to the population size ($N$). To determine the size to which the pool of susceptible individuals needs to be reduced (via immunization) to control the infection, researchers consider the following expression: $R_0 \times S/N$. This quantity takes into account both the fundamental transmission potential of the pathogen (quantified by the use of $R_0$) and the fraction of the population that is susceptible ($S/N$). The aim of vaccination is therefore to ensure that $R_0 \times S/N$ remains less than 1; that is, less than one transmission will result from an infection. To achieve this goal, immunization needs to reduce the proportion of the population unprotected ($S/N$) to less than $1/R_0$, which implies that the fraction of the population that needs to be immunized is $1 - 1/R_0$ (Fine et al., 2011). This principle is illustrated in Figure 2-1.

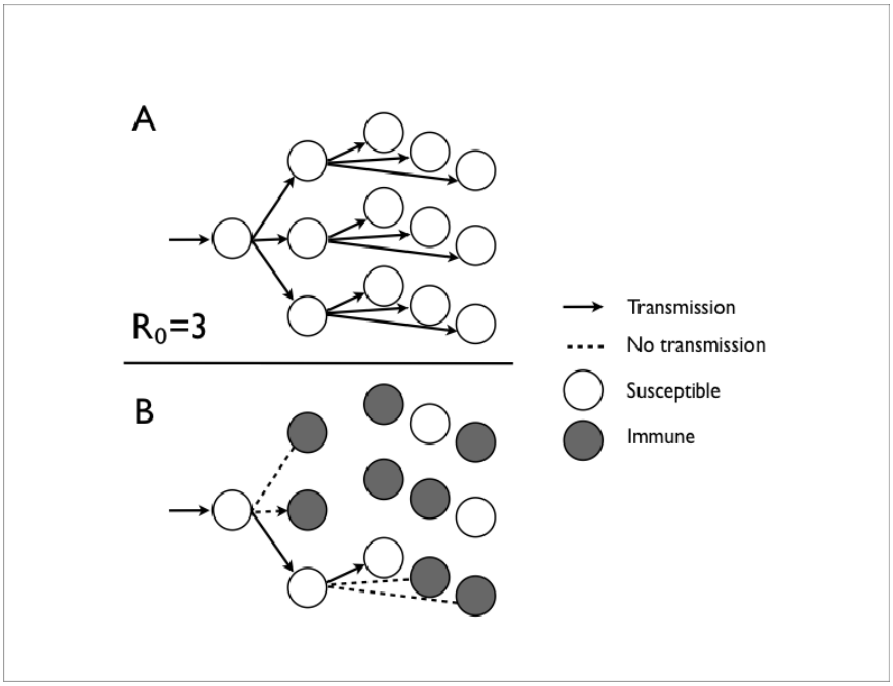


**FIGURE 2-1** Different transmission outcomes with immunization when $R_0$ is equal to 3. (A) With the entire population susceptible, successive generations lead to one, three, and,

eventually, nine transmissions. (B) When $1 - 1/R_0$ is equal to 2/3 of the population protected by immunization, each infected individuals will infect only one other individual.
SOURCE: Committee on the Assessment of Studies of Health Outcomes Related to the Recommended Childhood Immunization Schedule.

The relationship between the estimated $R_0$ and the targeted vaccination coverage is illustrated in Figure 2-2. This calculation has been of practical use in guiding the setting of immunization targets, albeit with the recognition that for any infectious disease, $R_0$ is likely to change in different settings and is determined by population density, contact patterns, and access to health care (Anderson and May, 1982). The gray regions translate ranges of the estimated $R_0$ into vaccination targets. For instance, on the basis of historical records, the estimated $R_0$ values for mumps and chickenpox in North America prevaccination were 8 to 10, leading to a vaccination target threshold of 87.5 to 90 percent of the population. Similarly, for measles and pertussis in England and Wales before the introduction of immunization, $R_0$ values ranged from 16 to 18 (Anderson and May, 1992), leading to a vaccination target of between 93.75 and 94.4 percent of the population.

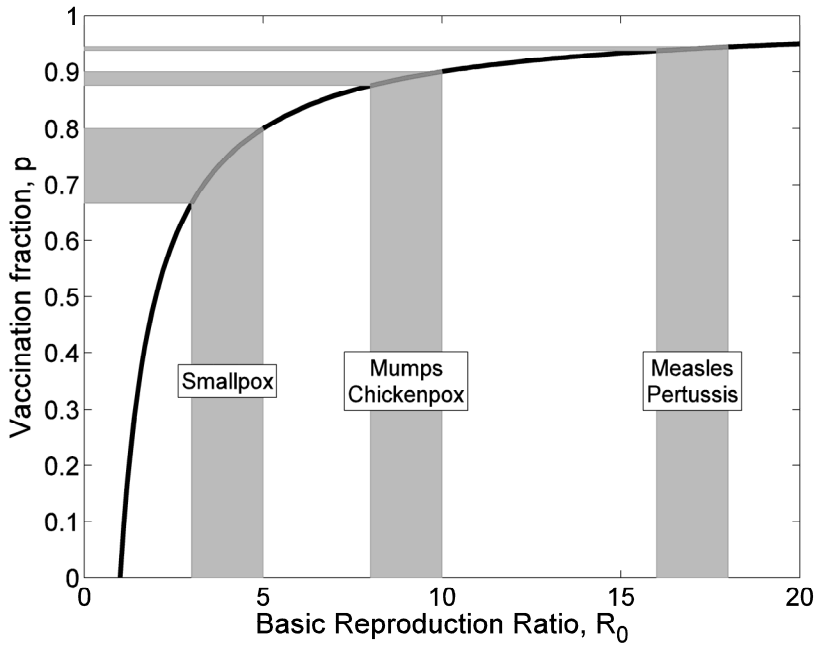


**FIGURE 2-2** Relationship between the estimated $R_0$ and the immunization target (solid black line). The gray regions translate ranges of the estimated $R_0$ into the vaccination target.
SOURCE: Adapted and reprinted by Committee on the Assessment of Studies of Health Outcomes Related to the Recommended Childhood Immunization Schedule.

## IMMUNIZATION LICENSURE AND POLICY

Vaccines are held to the highest possible standard of safety, in part because they are provided to healthy individuals with the purpose of preventing illness (Chen et al., 2005). In the United States, before a vaccine is introduced into the population as part of the recommended childhood immunization schedule, it must undergo careful analysis and evaluation, principally by FDA and ACIP. The review examines the immunologic properties of the vaccine and its probable effect on population health.

Each new vaccine is tested within the context of the existing immunization schedule, for example, by identification of the biologically optimal time during childhood when the immunization should be received and then testing of the new vaccine by incorporation of the vaccine into the existing schedule within that time frame. Selection of a particular moment within that biologically appropriate time frame is done mainly on the basis of considerations of safety and effectiveness (i.e., it should not be administered too early, when a child cannot generate an effective immune response, yet it should be administered soon enough to protect the child against the disease) (Siegrist, 2008).

Logistics and feasibility also need to be considered; for example, a vaccine could be scheduled for administration at times when a child is already likely to be visiting a provider for a normal periodic health care visit based on conventional guidelines (CDC, 2011a). Thus, approval of each new vaccine is premised on evaluation of the vaccine itself and of the entire schedule within which it is situated.

Although this process results in an evaluation of whether the observed benefits outweigh the observed risks for the new vaccine and, by extension, for the schedule, it does not include studies specifically designed to test variations in the schedule in an effort to identify the optimal schedule. Chapter 5 reviews researchers' efforts in testing variations in immunization schedules. An overview of the licensure and recommended practice review is discussed below.

## VACCINE DEVELOPMENT AND APPROVAL SPECIFICS

### Role of FDA

Since 1902, the U.S. government has exercised increasingly strict control over the development, manufacture, and sale of vaccines (Baylor and Midthun, 2004). At present, all vaccines marketed in the United States must be licensed by FDA. The licensing requirement provides the means by which FDA exercises authority over the testing and approval of new vaccines, as well as the manufacture, labeling, and continued safety and effectiveness of approved vaccines (Baylor and Midthun, 2004; FDA, 2010).

The clinical development of a vaccine in the United States begins when a sponsor submits the required Investigational New Drug (IND) application to FDA. The IND application includes information on the vaccine's safety and immunogenicity in animal trials, its manufacturing details, and the proposed protocol of clinical trials for testing in humans.

When the FDA accepts an IND application, manufacturers proceed with premarketing Phase I, II, and III clinical trials (Baylor and Midthun, 2004). Phase I and II clinical trials enroll less than 1,000 participants and are designed to draw conclusions about the vaccine's components, dosing effectiveness and the need for booster doses, and route of administration and to evaluate common reactions. The results of these trials may influence the choice of the candidate vaccine to be used in subsequent studies, such as additional Phase I or II trials or after Phase III trials. Sample sizes for Phase III trials are determined to evaluate a vaccine's efficacy, and therefore, such trials have larger sample sizes (up to 100,000 participants in some rare cases) than Phase I or II trials for vaccines or other premarketing trials for therapeutic drugs. Because Phase III trials are primarily powered for determination of efficacy (Hudgens et al., 2004), conclusions about vaccine safety derived from these trials are limited and may best extrapolate to common adverse events (Chen and Orenstein, 1996; Chen et al., 2005).

Throughout this process, FDA has the authority to request additional information about the clinical trials or to interrupt the clinical trials if concerns about safety or effectiveness emerge. If the clinical trials demonstrate that a vaccine is safe and effective, the licensing procedures begin with the submission of a Biologics License Application and a review of the immunization benefits and risk demonstrated by the clinical evidence. If FDA's Center for Biologics Evaluation and Research is convinced that the vaccine's benefits significantly outweigh potential risks for use in the general population, the vaccine is licensed and will undergo further evaluation of product safety through activities such as periodic facility inspections (FDA, 2010). Manufacturers may be asked to undergo Phase IV studies, which include a larger population and are used to assess less common adverse events or the length of time for which the vaccine induces immunity (Baylor and Midthun, 2004). Following vaccine licensure, manufacturers are required by 21 CFR 600.80 to report to the FDA serious or unexpected adverse events within 15 days of the event occurring, and to report other adverse events quarterly for the first 3 years after the vaccine is licensed, and then once per year thereafter (Baylor and Midthun, 2004; Farizo, 2012; FDA, 2010). Postmarketing surveillance efforts that are coordinated as part of the federal research infrastructure are discussed in detail in Chapter 3.

### Role of ACIP

In the United States, immunization policy is developed and implemented through collaborations among federal partners, state and local governments, professional medical associations, and other relevant organizations. These organizations are represented on ACIP, which is the federal advisory committee that provides expert external advice and guidance on the use of FDA-licensed vaccines and related agents in the U.S. population to the director of CDC and the secretary of the U.S. Department of Health and Human Services.

Each year CDC issues recommendations on the use of vaccines and immunization schedules for children, adolescents, and adults (Kroger et al., 2011; NVAC, 2011). A number of liaison organizations, such as the American Academy of Pediatrics (AAP), the American College of Physicians, and the American Academy of Family Physicians (AAFP), issue recommendations on the immunization schedule that are harmonized to the greatest extent possible with the annual recommendations from CDC (NVAC, 2011;

Smith, 2010; Smith et al., 2009). A representative from ACIP serves as a liaison on the National Vaccine Advisory Committee, which is the federal advisory committee responsible for advising the National Vaccine Program Office (NVPO) on priorities of vaccine supply and enhancing vaccine safety and efficacy (HHS, 2012).

In the process of making recommendations for new vaccines, ACIP first reviews a wide range of data associated with the vaccine, including the rates of morbidity and mortality from the disease that the vaccine protects against in the general U.S. population and specific high-risk groups; cost-effectiveness; the results of clinical trials, including indicators of safety, efficacy, and effectiveness; information on vaccine use provided by the manufacturer in the product's labeling or package insert; and the feasibility of incorporating the vaccine into the existing immunization program. Expert opinions from voting members and other experts may also be incorporated into the deliberations (NVAC, 2011; Smith, 2010; Smith et al., 2009).

As of October 2010, ACIP has adopted an evidence-based framework, Grading of Recommendations Assessment, Development, and Evaluation (GRADE), which it uses when making new recommendations or substantial revisions of vaccination recommendations. The GRADE framework is a method for ACIP to systematically assess the type or quality of evidence about the health outcomes after immunization with a vaccine. The evidence that ACIP reviews is grouped into four categories that reflect the reviewers' level of confidence in the estimated effect of vaccination on health outcomes on the basis of the strength of the design of the study used to provide the evidence considered. The GRADE categories are as follows (CDC, 2012b):

1. Randomized controlled trials or overwhelming evidence from observational studies;
2. Randomized controlled trials with important limitations or exceptionally strong evidence from observational studies;
3. Observational studies or randomized controlled trials with notable limitations; and
4. Clinical experience and observations, observational studies with important limitations, or randomized controlled trials with several major limitations.

Recommendations from ACIP are also categorized into Category A or B recommendations, although the distinction does not reflect the quality of the evidence reviewed. Category A recommends vaccination for all people in a particular age group or for a group at increased risk for vaccine-preventable diseases. Category B recommendations do not apply to all members of a group; rather, they are intended to provide guidance to a clinician when determining if vaccination is appropriate for an individual. After review, if CDC accepts the recommendations of ACIP, they are published in *Morbidity and Mortality Weekly Reports* (MMWR) (Smith, 2010; Smith et al., 2009).

## PAST AND PRESENT IMMUNIZATION SCHEDULES

The current schedule of recommended immunizations for infants and children from birth through age 6 years comprises vaccines that prevent 14 infectious diseases, a remarkable achievement compared with the schedule in 1948, when immunizations against only diphtheria, tetanus, pertussis, and smallpox were available and recommended for administration for protection. In 1955, the polio vaccine was licensed and added to the recommended immunizations to eliminate yearly outbreaks. Over the next 40 years, vaccines were added to the recommended schedule as they were licensed, including MMR, the hepatitis B vaccine, and the *Haemophilus influenzae* type B vaccine (Hib). Smallpox vaccine was removed from the U.S. recommended schedule in 1972, as the disease had been eliminated as a result of great public health efforts.

It became increasingly evident that as the schedule became more complex, providers would benefit from annual updates with detailed information about new vaccines, who should receive each vaccine, the age(s) at the time of receipt, the dose, and the use of combination vaccines in their practices. In 1995, CDC, AAP, and AAFP created a harmonized immunization schedule. Since then, the ACIP-recommended schedule has been adopted by the CDC and both professional associations, along with others (CDC, 2012c). Today, combination vaccines deliver immunizations against up to five separate diseases in a single injection, including DTaP-Hib-inactivated poliovirus vaccine (IPV) and DTaP-hepatitis B virus vaccine-IPV.

Immunization rates for children in the United States are generally high, with some variation occurring depending on geography and the specific vaccine. The majority of children are fully immunized with the recommended component of vaccines (not including influenza and hepatitis A virus vaccines) by age 3 years. According to the National Immunization Survey (NIS), less than 1 percent of U.S. children aged 19 to 35 months receive no vaccinations at all (CDC, 2011c). However, not every vaccine on the schedule has equal coverage in this population. In the NIS study population for children born between January 2008 and May 2010, vaccines with higher coverage included the poliovirus vaccine (93.9 percent), MMR (91.6 percent), the hepatitis B vaccine (91.1 percent), and the varicella vaccine (90.8 percent). In contrast, the rotavirus vaccine was received by only 67.3 percent of children, and just 80.7 percent of children received the full series of the Hib vaccine, which is an increase from previous years during which a shortage of the vaccine was experienced (CDC, 2012a). A review of data from the 2003 NIS revealed that more than one in three children were undervaccinated (missing age-appropriate doses from the recommended immunization schedule) during the first 24 months of life and that only 18 percent of U.S. children received all vaccinations at the recommended times or acceptably early (Luman et al., 2005). Immunizations are recommended to protect children when they are most vulnerable to vaccine-preventable diseases, and delays in timely immunization leave children susceptible to disease.

For some children, vaccination on the recommended schedule may be contraindicated, either permanently or temporarily, and the CDC offers guidelines on conditions that may require that vaccination with certain vaccines be postponed or avoided altogether (CDC, 2011b).

Most health care providers encourage adherence with the recommended immunization schedule for children; however, a compelling motivator to see that children receive their full immunizations is their requirement to attend school. Since the early 1980s, all 50 states have made policy decisions to require immunizations for school entry. These immunization requirements were originally enacted to prevent and control frequent outbreaks of vaccine-preventable diseases. Furthermore, during outbreaks, officials have removed unvaccinated children from school, which has proved to be a successful control measure (Omer et al., 2006).

Because school-based immunization requirements are determined on a state-by-state basis, differences in age requirements, processes for adding new vaccines, and exemptions to immunizations exist across the country. Exemptions may be medical in nature, such as exemptions for delayed or skipped immunization if the child has a condition that contraindicates immunization with the vaccine, as referenced above.

Currently, every state law covering immunization requirements has a provision that allows medical exemptions. Parents may also request an exemption on religious grounds, and such exemptions are permitted in 48 states. Exemptions because of personal beliefs, which include religious, philosophical, or other nonmedical beliefs, are granted in 20 states, including Colorado and Washington, two states that saw localized outbreaks of pertussis in 2012 (Omer et al., 2006).

Although rates of medical exemptions are relatively constant nationwide, rates of nonmedical exemptions vary considerably (CDC, 2010, 2011d). For example, from 2006 to 2007, the average nonmedical exemption rate in the state of Washington was 6 percent, although some counties had exemption rates as high as 27 percent (Omer et al., 2006).

## Adverse Effects of Vaccines

Parents may be what is referred to as vaccine-hesitant (refusing, delaying, or feeling unsure about some immunizations) because vaccines, like other drugs and biologicals, can in some cases be associated with adverse events (Opel et al., 2011). Vaccines that are commonly associated with serious adverse events are never licensed. Likewise, if a serious or frequent adverse event is discovered during postmarketing surveillance, the vaccine is taken off the schedule (e.g., the first rotavirus vaccine).

Most adverse events are mild or self-limited, for example, fever after measles vaccine or a sore, swollen injection site after the tetanus booster. Many events may occur in the days and weeks following vaccination, however, typically few are a result of vaccination, and most are coincidental. Ongoing research continues to examine such adverse events (IOM, 2012).

In the 1980s, the United States experienced an increase in civil lawsuits filed against vaccine manufacturers for injury compensation, which led to hesitancy on the part of the manufacturers to produce enough vaccines to keep the supply stable at a reasonable price. To streamline the legal process and maintain the vaccine supply, the U.S. Congress enacted the National Childhood Vaccine Injury Act in 1986 to establish a no-fault system for compensating individuals for vaccine-related injuries, the National Vaccine Injury Compensation Program (VICP). Individuals or parents of children who experience a vaccine-related injury must first file their petition with VICP before pursuing a civil case.

As a no-fault system, the possible negligence of the manufacturer or physician is not considered in determination of compensation, which is funded by an excise tax on vaccines.

VICP covers all vaccines routinely administered to children as part of the recommended childhood immunization schedule and all injuries listed in its injury table. A claimant who seeks compensation for an adverse event that has not been established and placed in this table has the option of providing evidence to establish causation (Cook and Evans, 2011). The National Childhood Vaccine Injury Act also established the Vaccine Adverse Event Reporting System to track adverse events and created NVPO to coordinate immunization-related activities among federal agencies (Cook and Evans, 2011).

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# 3

# Existing Data Sources and Systems

While the Advisory Committee on Immunization Practices (ACIP) is tasked with making recommendations on vaccine usage, the National Vaccine Advisory Committee (NVAC) directs research priorities on vaccine development, efficacy, and safety. Included in the membership of NVAC are a number of ex officio representatives from federal agencies engaged in vaccine safety monitoring. Several systems that are part of the federal research infrastructure provide postmarketing data on vaccines that are used for immunization safety surveillance, to determine immunization coverage, and to assess the effects of vaccines on vaccine-preventable diseases. In turn, vaccine safety research is often conducted using data obtained from ongoing surveillance. This chapter reviews these systems and discusses how data from these systems are used to help assess the safety of cumulative immunizations, the timing of immunizations, and other aspects of the immunization schedule.

## IMMUNIZATION SAFETY SURVEILLANCE

A number of systems for ongoing monitoring and study of the safety of vaccines recommended for use are in place in the United States (and other nations as well), where the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and vaccine manufacturers have systems in place for postmarketing surveillance and research.

CDC manages a number of postmarketing activities, including surveillance of vaccine-preventable diseases, monitoring of adverse events following immunization, tracking of vaccine coverage and issuance of guidance on vaccine shortages. Although vaccine safety is rigorously assessed during prelicensing clinical trials, this postmarketing monitoring is important because the sample sizes in prelicensing clinical trials may not have been adequate to detect rare adverse events, the prelicensing study population may not have been monitored for long-term adverse events, and populations may not have been heterogeneous (Baggs et al., 2011; Chen et al., 2000). Consequently, postmarketing evaluation of vaccine safety is needed to assess rare, delayed, or unusual reactions and in general provides a fuller understanding of the safety of vaccines recommended in the immunization schedule (Chen et al., 1997).

Ongoing surveillance systems serve as the primary resource for information and research on postmarketing vaccine safety. The CDC Immunization Safety Office (ISO) maintains three major postmarketing surveillance systems: the Vaccine Adverse Event Reporting System (VAERS; jointly managed with FDA), the Vaccine Safety Datalink (VSD), and the Clinical Immunization Safety Assessment (CISA) Network. Most CDC immunization activities are located in the National Center for Immunization and Respiratory Diseases. Since 2005, the ISO was moved to the National Center for Emerging and Zoonotic Infectious Diseases as its mission is clearly distinct from other immunization programs within the agency. This organizational change ensures the separation at CDC between vaccine promotion and safety. In addition to the surveillance systems managed by CDC, FDA has established a supplementary mechanism for monitoring vaccine safety called the Sentinel Initiative.

### Vaccine Adverse Event Reporting System

VAERS is a passive reporting surveillance system that is jointly managed by CDC and FDA and serves as a warning system for potential adverse events and side effects from a recommended vaccine that may not have been detectable in clinical trials (NVAC, 2011). Anyone, including parents and providers, may submit voluntary, spontaneous reports of adverse events observed after administration of licensed vaccines. Reports received by VAERS are analyzed and recorded for possible follow-up (CDC and FDA, 2012).

Although VAERS is useful for the early detection of signals of adverse events, the data obtained from the system have limitations. The reports received may not be fully documented, or the adverse event attributed to the vaccine may, in actuality, be a case not caused by the vaccine on the basis of background rates of clinical events. In addition, data on the number of doses of vaccine administered or number of vaccinated people do not exist and are thus not available for use as the denominator, so researchers cannot calculate what proportion of individuals were affected by an adverse event for comparison with the background rate of the event in the general population. Because no denominator data are available, VAERS cannot be used to evaluate causality. The VAERS data are useful, however, for the development of adverse event signals and the formation of related hypotheses that can be further tested and validated by more robust methods.

### Vaccine Safety Datalink

One system better suited to the testing of hypotheses about vaccine safety is VSD. The VSD project was formed in the 1990s as a collaborative effort between CDC and a group of managed care organizations (MCOs) to maintain a large linked database for monitoring immunization safety and studying potential rare and serious adverse events. The number of VSD member sites has increased over the years and now includes nine MCOs that enroll approximately 9.5 million children and adults, or about 3 percent of the U.S. population. VSD sites are located at geographically diverse locations in California, Colorado, Georgia, Hawaii, Massachusetts, Michigan, Minnesota, Oregon, and Washington (Frank DeStefano, CDC, personal communication, October 18, 2012). Because the data in the database are generated as a by-product of the routine administration of health care and the system does not rely on voluntary adverse event reporting (as VAERS does), the problems of underreporting and recall bias are reduced.

The VSD is a useful system that includes demographic data and information on the medical services that have been provided to those enrolled in the health plans, such as age and gender; vaccinations; hospitalizations; outpatient clinic, emergency department, and urgent care visits; mortality data; and additional birth information (e.g., birth weight) (Baggs et al., 2011). Automated pharmacy and laboratory data as well as information on diagnostic procedures (e.g., radiography and electroencephalography) that the patient has undergone are also included (Chen et al., 2000). Data on adverse events, including deaths (from probabilistic matching of death files), are routinely collected (Chen et al., 1997). Covariates used to control for potential confounders include birth certificates and variables from the decennial census at the zip code level, in addition to demographic data from the health plans.

Each site collects data on vaccinations (the type, date, and concurrent vaccinations), medical outcomes (diagnoses and procedures associated with outpatient, inpatient, and urgent care visits), and birth and census data. To ensure compliance of federal regulations and to protect confidentiality, each person within the VSD is assigned a unique random VSD study identification number which is not linked their MCO member identification number. These VSD study identification numbers can be used to link data on demographics and medical services (Baggs et al., 2011).

Since 2001, VSD has used a distributed data model, whereby each MCO assembles and maintains its computerized files on a secure server at the site. This distributed data model has permitted the creation of dynamic data files that permit the ongoing capture of near real-time event-based MCO administrative data. This includes data on vaccinations, hospitalizations, emergency department and clinical care visits, and certain demographic characteristics. While most files are updated weekly with new data from each MCO, some files are updated less frequently (Baggs et al., 2011). This organization of the data enables near real-time postmarketing surveillance to be conducted and enhances the timeliness of certain studies.

*Surveillance and Research*

The VSD has been used to conduct rigorous epidemiological studies on a wide range of immunization safety topics. Strategic priorities for research and surveillance are developed and updated regularly. The following priorities reported in 2011 (Baggs et al., 2011):

- Evaluate the safety of newly licensed vaccines.
- Evaluate the safety of new immunization recommendations for existing vaccines.
- Evaluate clinical disorders after immunization.
- Assess vaccine safety in particular populations at high risk.
- Develop and evaluate methodologies for vaccine safety assessment.

The enhancements in data transfer and updating permit near real-time postmarketing surveillance. Adverse events identified in the VSD system are analyzed by use of an active surveillance system called Rapid Cycle Analysis. Every week, the Rapid Cycle Analysis team determines the rates of adverse events associated with newly licensed or recommended vaccines in the study population. This information allows VSD researchers to compare the rates of adverse events in similar groups of people to determine if an event is related to the vaccine. If an increased risk is detected, VSD project scientists implement a formal, population-based epidemiological study to test the hypothesis of a causal relationship.

VSD data are also used in conjunction with data from VAERS, to determine, for example, whether the number of adverse events reported to VAERS exceeds the background occurrence of the events shown in VSD.

VSD has been used to conduct rigorous studies on a wide range of topics on vaccine safety, as well as studies on immunization coverage, disease incidence, research methodologies, cost-effectiveness, and medical informatics (Baggs et al., 2011; DeStefano, 2001). For example, VSD has been used to study immunization safety concerns, such as the risk of seizures following receipt of the whole-cell pertussis vaccine or the measles-mumps-rubella (MMR) vaccine, and to evaluate the safety of thimerosal-containing vaccines (Barlow et al., 2001; CDC, 2011b; Verstraeten et al., 2003).

Importantly, in selected studies, the automatically collected administrative data in VSD have been supplemented with information from other sources to test selected hypotheses on vaccine safety. For example, in a study examining the hepatitis B vaccine and the risk of autoimmune thyroid disease, cases were initially identified through VSD and then validated through a review of the medical records. Telephone interviews were then conducted with the parents to confirm the child's hepatitis B vaccination status (Yu et al., 2007).

As another example, in a study of early thimerosal exposure and neuropsychological outcomes, mercury exposure was determined from VSD medical, and personal immunization records and interviews with parents. The study also used the results of standardized tests that assessed 42 neuropsychological outcomes (Thompson et al., 2007).

*Studying the Safety of the Immunization Schedule*

Some characteristics of VSD lend themselves to the study of the safety of the immunization schedule. The fact that MCOs have different vaccination policies (after the first year of life), along with deviations in the immunization schedule due to variations in clinical practice, vaccine shortages, problems with access, or intentional denial of vaccine coverage, yields differences in vaccine exposure in this large cohort (Chen et al., 1997). These differences have been leveraged to examine the safety of aspects of the immunization schedule (Chen et al., 1997; see Appendix D). Because relatively few children are completely unvaccinated, study designs do not rely on comparison groups of children but instead use case-only methods such as self-controlled case-series designs (Baggs et al., 2011; see Appendix D).

*Limitations of VSD*

The MCOs that make up the VSD are largely private plans; thus, the population, although large, is not demographically representative of the children in the United States. Safety outcomes or other medical consequences may not vary on the basis of income or insurance status; but other information collected by the VSD, such as the completeness of the immunization schedule, immunization delays, or the amount of time that an individual receives immunizations off of the immunization schedule, may be related to such socioeconomic factors (Luman et al., 2005).

Furthermore, because beneficiaries move between plans because of choice, a job change, or other factors, the ability to monitor children for an extended period may be limited. Although the average time spent in the VSD is not known, more than half of the children born in 2001 and included in the system at that time are still in the system (Frank DeStefano, personal communication). Although studies have used the VSD to select the cohort and have augmented

VSD data with data from other sources, the committee was not aware of any studies have monitored a VSD cohort outside the health plan structure over time. This sort of longer-term follow-up may be important to the study of the safety of the immunization schedule, and if such follow-up is undertaken, ethical and confidentiality issues will need to be explored.

### Sentinel Initiative

The Sentinel Initiative program, established by FDA, is designed to build and implement a national electronic system to monitor the safety of FDA-approved drugs and other medical products. The pilot project for this initiative, the Mini-Sentinel, is currently collecting data from 17 collaborating institutions with databases containing health care data collected from 2000 to 2011 from 126 million participants and data on more than 345 million person-years of observation time (Mini-Sentinel Coordinating Center, 2011).

The Mini-Sentinel is an active surveillance system that uses a distributed database design, which means that the data remain in their existing secure environments at collaborating institutions rather than centralized into one database. When it is fully implemented, the Sentinel Initiative will complement the existing passive surveillance system, VAERS, in capturing reports of adverse events after immunization and will enable FDA to use existing electronic health care data to perform near real-time analyses (NVAC, 2011).

FDA's Post-License Rapid Immunization Safety Monitoring Program similarly captures claims data from the Mini-Sentinel sites to establish a large cohort with which to analyze vaccine exposure and adverse events with a high degree of statistical power. This active surveillance system, which is updated quarterly, has the capacity to link claims data from collaborating health insurers to immunization registries. To date, the program has been used to conduct various epidemiological analyses, such as an investigation of postmarketing adverse events after administration of the 2009 pandemic H1N1 influenza vaccine which evaluated vaccine safety data for over 38 million individuals (Nguyen et al., 2012; see Appendix D). Although PRISM's database is larger than that of the VSD, PRISM is newer and less able to rapidly conduct medical record review to confirm suspected outcomes of interest initially identified in claims data. Though neither Mini-Sentinel nor any of the other existing surveillance systems described above have yet been used to evaluate health outcomes associated with the entire recommended childhood immunization schedule, there is great potential in these large database initiatives to monitor rare adverse events potentially associated with the childhood immunization schedule.

### Clinical Immunization Safety Assessment Network

CDC also maintains the CISA Network to perform clinical research on biological mechanisms of adverse events, which are often hypothesized on the basis of reports to VAERS. The CISA Network is network of six U.S. academic medical centers with experts in vaccinology and vaccine safety who collaborate in discussions about adverse events (CDC, 2011c). Although VSD researchers conduct population-based research on vaccine safety, experts in the CISA Network investigate the pathophysiological basis for an adverse event to counsel clinicians on individual variations in reactions to vaccines and to help policy makers determine precaution and contraindication criteria for vaccines. CISA investigators have performed causality assessments on reports received from VAERS, including a recent assessment of serious neurologic adverse events following immunization with the H1N1 influenza vaccine (Williams et al., 2011). The

CISA Network also maintains for future study a repository of biological samples obtained from individuals who have experienced unusual adverse events (NVAC, 2011).

### National Institutes of Health

The National Institutes of Health (NIH) have an important role in maintaining the safety of vaccines, from basic biological study that leads to new vaccine development through supporting research to address ongoing vaccine safety and efficacy. Two recent initiatives from the NIH are particularly relevant to the study of the recommended childhood immunization schedule. Several NIH institutes, including the National Institute of Allergy and Infectious Diseases (NIAID) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development have collaborated with the CDC to announce a funding opportunity entitled Research to Advance Vaccine Safety. Researchers from eligible institutions are invited to propose research on topics including but not limited to "evaluation of existing childhood immunization schedules to optimize safe and long-term protective immune memory" (Curlin et al., 2011) and "comparison of the immunologic and physiologic effects of different combinations of vaccines and different schedules" (Curlin et al., 2011). In addition, research topics can include studies that seek to determine genetic susceptibility to serious adverse events following vaccination, and research that attempts to identify the molecular basis for differential immune responses to vaccination when an underlying health condition is present (Curlin et al., 2011).

Similarly, the Human Immunology Project Consortium (HIPC) program was developed by the NIAID in 2010 to further understanding of the human immune system and its regulation. HIPC researchers are using innovative technologies to profile human responses and provide new biological evidence to help determine if there is a relationship between short-term adverse events following vaccination and long-term health issues (HIPC, 2012). Although the HIPC offers a promising approach to studying health outcomes of the childhood immunization schedule, researchers will require data on the effects of age, environment, infectious exposures, lifestyle, and many other possibly confounding variables before any conclusions can be drawn (Hackett, 2012). Thus, it is critical to continue epidemiological study of vaccines through systems like VAERS, the VSD, and the Sentinel Initiative, as well as study of biological mechanisms through CISA and NIH.

## DATABASES USED TO ASSESS COVERAGE

Data from another set of databases are used to assess immunization coverage, including the population-based National Immunization Survey (NIS) telephone survey and the state-level immunization registries.

### National Immunization Survey

The surveillance systems described above are tools to monitor vaccine safety. Ensuring that vaccines are safe and present minimal health risks to individuals is an important part of keeping the majority of the population immunized and preserving community immunity. Furthermore, because no vaccine alone is 100 percent effective at preventing disease for any individual, sustaining a low incidence of vaccine-preventable diseases in the United States requires a population-based effort. As such, it is important to have tools to examine populations

that may not be adequately immunized and to monitor trends in vaccine coverage. The National Center for Immunization and Respiratory Diseases and the National Center for Health Statistics jointly operate the NIS for this purpose.

The NIS is a large random-digit-dialing telephone survey that collects data on immunization coverage for U.S. children aged 19 to 35 months. The survey sampling methodology provides both national and state-level estimates of coverage. State-level estimates can be used to compare immunization rates among states; the national estimates can be used to compare rates by race/ethnicity or other subpopulation. The survey is conducted in two parts: a telephone interview is conducted with the parents or caregivers in the household, and if the parents or caregivers consent, a subsequent survey is mailed to the child's immunization provider to verify the parental report of immunizations. Providers are asked to fill out a list of all immunizations, the dates when they were given to the child, and whether the immunizations were given in that or another medical practice. In addition to immunization history, providers are asked about other characteristics of the practice, such as the type of facility, the number of physicians working at the practice, vaccine ordering, and whether the practice reported any of the child's immunizations to the community or state registry (CDC, 2011a).

Using this method, the NIS obtains data for more than 17,000 U.S. children in all 50 states and selected territories and urban areas. The combined surveys produce coverage data for children in the United States by individual vaccine, as well as immunization schedule completion indicators, such as completion of the 4:3:1:3:3:1:4 seven-vaccine series (four or more doses of diphtheria-tetanus-pertussis vaccine, three or more doses of poliovirus vaccine, one or more doses of MMR vaccine, three or more doses of *Haemophilus B influenzae*, vaccine, three or more doses of hepatitis B vaccine, one or more doses of varicella vaccine, and four doses of seven-valent pneumococcal conjugate vaccine). In addition to immunization information, the surveys also obtain information for other variables, such as poverty status; provider facility; race and ethnicity; participation in programs such as Vaccines for Children or the Women, Infants, and Children food program; and a history of breast-feeding.

Scientists often use data from the NIS to track trends in immunization coverage over time and to compare groups of children by demographic characteristics and immunization coverage to formulate hypotheses about what factors may be causing significant differences in immunization coverage (CDC, 2011a).

### State Immunization Registries

CDC supports a network of immunization information systems (IISs), formerly called immunization registries, which consist of computerized, population-based databases that confidentially collect and consolidate immunization records from partnering vaccine providers. The 50 states, the District of Columbia, and 5 cities receive CDC grants to maintain their IISs. Providers are able to use the IISs to determine appropriate patient vaccinations, manage their vaccine inventories, and generate reminder and recall messages. The percentage of children whose immunization records are entered into an IIS varies widely by grantee: in 2010, the Connecticut Immunization Registry and Tracking System reported that 75 percent of eligible children in Connecticut participated, whereas Maryland's IIS participation rate was only 42 percent (CDC, 2012a). The IISs count children as participants only if they have received at least

two immunizations from a reporting vaccination provider, and reporting requirements vary between grantees (CDC, 2012c; Hedden et al., 2012).

IISs are primarily useful for tracking vaccine coverage, and those with a high participation rate and comprehensive data are potentially well-suited to evaluate postmarketing vaccine effectiveness (Cortese et al., 2011; Guh and Hadler, 2011). However, as electronic health records become more widely available in the United States, the opportunities for linking immunization history with other health data may increase.

IISs offer some benefits over systems in private health care plans, such as the VSD, for measuring immunization coverage. The systems are established in more than 50 geographic locations and receive data from a larger variety of immunization providers, including providers in private and public health care systems. In 2010, 11,536 public and 36,512 private providers reported participation in the IISs (CDC, 2012c). Nevertheless, children receive immunizations in a number of settings that may not report to an IIS.

The utility of immunization registries is likely to increase, as the provisions of the American Reinvestment and Recovery Act for the meaningful use of interoperable electronic health records require the linkage of a region's IIS to an electronic health record to qualify for incentives (CDC, 2012b).

## DATABASES EXAMINING ADVERSE EVENTS AFTER IMMUNIZATION FOR VACCINE-PREVENTABLE DISEASES

A set of national and state databases with data on hospital discharges can be used to monitor events requiring medical attention that occur after immunization with selected vaccines. Data from state-level claims databases and surveys assessing the characteristics of office visits can be used in the same way. If adverse events have a specific diagnosis code, these can be monitored as well.

One such family of health care databases is the Agency for Healthcare Research and Quality-sponsored Healthcare Cost and Utilization Project (HCUP). Through a partnership between industry and government at the state and federal levels, HCUP has the largest collection of longitudinal data on hospital care in the United States, with these data dating back to 1988. All data collected in HCUP are obtained at the encounter level from patients of all payment types (all payers), including uninsured individuals. Some of the HCUP databases most relevant to the examination of immunization outcomes include the following (AHRQ, 2009):

- The Nationwide Inpatient Sample, which collects inpatient data from more than 1,000 hospitals in the United States, is the largest database of its kind in the United States.
- The Kids' Inpatient Database (KID), which also collects hospital inpatient data for children and adolescents ages 20 years and younger, is the only all-payer database with this kind of information.
- The Nationwide Emergency Department Sample captures the records for emergency department encounters from approximately 1,000 community hospitals.

A similar database for hospital discharges (the National Hospital Discharge Survey) is sponsored by the National Center for Health Statistics. It is not part of a family of databases like those described above, but it is also widely used.

Because the HCUP family of databases includes all discharges at the state level and a large sample at the national level, data from those databases can be used to detect rare events, such as adverse reactions. These data have been used, for example, to examine intussusception rates before and after the introduction of rotavirus vaccination to determine whether increases occurred (Simonsen et al., 2001; Tate et al., 2008; Yen et al., 2011). These analyses generally use data from the universal state-level inpatient databases of several states. Analyses like these require specific diagnosis codes for the adverse events and, in addition, require a causal chain that links the adverse event to vaccines. This is the case for rotavirus and intussusception but is less frequent for adverse events with other vaccines.

In addition, data from these databases can be used to assess the burden of disease for a variety of vaccine-preventable diseases. For example, Ma et al. (2009) used data from the Kids' Inpatient Database to assess the burden of hospitalizations for rotavirus infections in children receiving Medicaid compared with that in children not receiving Medicaid. Fischer et al. (2007) used data from these databases to establish the rate of diarrhea- and rotavirus infection – associated hospitalizations before the introduction of a new rotavirus vaccine, including baseline rates, trends, and risk factors.

Finally, because they are longitudinal, data from the databases can be used to track the effects of the introduction of a vaccine on the incidence of the disease that it is intended to prevent. For example, these databases have been used to show the reduction in hospitalizations for pneumococcal pneumonia, all-cause pneumonia, and pneumococcal meningitis after introduction of the seven-valent pneumococcal conjugate vaccine (PCV7) for all children and for children with sickle cell disease (Grijalva et al., 2007; McCavit et al., 2012; Simonsen et al., 2011; Tsai et al., 2008). Databases have been used in the same manner to show reductions in the numbers of hospitalizations for acute gastroenteritis after introduction of a rotavirus vaccine (Curns et al., 2010).

A similar database (the National Hospital Discharge Survey, sponsored by the National Center for Health Statistics) has been used, in combination with estimates of vaccine effectiveness, to predict the reduction of the disease burden after introduction of a vaccine against that disease (Curns et al., 2009). Among the limitations of studies like these are that they generally do not rely on laboratory-confirmed disease, and because they are observational, researchers are not able to control the exposures in the population, and thus may not be able to clearly identify if the disease is a direct result of the vaccine.

### State-Level Medicaid Claims and Related Local Databases

Data from state-level Medicaid and health plan databases have been used to assess the disease burden overall and in specific regions or for specific payers (Poehling et al., 2003). Data from these local claims databases have also been used to examine reductions in the incidence of disease after introduction of a vaccine, for example, the reduction in the incidence of otitis media after the introduction of PCV7 (Poehling et al., 2003, 2007). Furthermore, data from these state-level Medicaid or plan-level claims databases have also been used to assess the effectiveness of local immunization campaigns as seen from reductions in the incidence of disease. For example,

data from local claims databases in Tennessee were used to assess the effectiveness of school-based influenza campaigns (Grijalva et al., 2010a,b).

### National Ambulatory Care Databases

CDC sponsors both the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Care Survey. The National Ambulatory Medical Care Survey is a national survey of visits to nonfederal office-based physicians who are primarily engaged in direct patient care; the National Hospital Ambulatory Care Survey is a national survey of visits to emergency department doctors and the outpatient departments of general and short-stay hospitals. Both surveys collect data on the use and provision of ambulatory medical care services. Physicians also provide information about themselves and their practices. Data from these databases have been used to examine the effect of vaccine introduction on ambulatory care visits of a given type, such as examination of reductions in the rates of visits for otitis media after the introduction of PCV7 mentioned earlier (Grijalva et al., 2006).

## IMMUNIZATION DATA SYSTEMS IN OTHER COUNTRIES

A number of other countries have in place data systems that are successfully used to investigate vaccine safety and coverage. Although these systems and those in place in the United States have key differences, starting with differences in the recommended immunization schedules, other countries may be well-equipped to provide data on safety concerns with the immunization schedule identified by the committee. Descriptions of immunization data systems from three countries, including Canada, with populations similar to the population in the United States are presented below.

### United Kingdom

Residents of the United Kingdom (England, Northern Ireland, Scotland, and Wales) access health care through the taxpayer-funded National Health Service (NHS), which issues to each resident a unique identifying NHS number. Residents receive immunizations from their general practitioners, who serve as the initial point of access for all primary care provided by the NHS. General practitioners also issue referrals for elective or acute secondary care, although patients can seek care at a hospital emergency room at any time.

Like many other countries, including the United States, the United Kingdom has a spontaneous reporting system that passively collects data on suspected adverse events after the receipt of vaccines and other drugs. This system is known as the “Yellow Card scheme,” so named because yellow cards were historically used for reporting in the British National Formulary. The Yellow Card passive surveillance system was introduced in 1965 and is currently operated by the pharmaceutical licensing authority in the United Kingdom, the Medicines and Healthcare Products Regulatory Agency. Today, UK health care professionals and patients can also report potential adverse events electronically or by phone. In addition, vaccine manufacturers have more recently been required to conduct postmarketing pharmacovigilance for adverse events after immunization or to undertake special studies when appropriate.

The Medicines and Healthcare Products Regulatory Agency also cosponsors the United Kingdom's Clinical Practice Research Datalink (CPRD) with the NHS National Institute for Health Research. The CPRD was introduced in March 2012 and contains observational data that build on the data collected for its predecessor, the General Practice Research Database (GPRD). The GPRD is a primary care database that contains anonymous records on consultations, secondary care referrals, prescriptions, and vaccinations for about 5 percent of the population of the United Kingdom. The CPRD aims to maximize the linkages that can be made between the data that the GPRD collects and data from other disease registries or from health care databases maintained in the United Kingdom (CPRD, 2012).

The Health Protection Agency (HPA) is an independent body in the United Kingdom with functions analogous to those of CDC in the United States. Among the HPA's responsibilities are a number of vaccine safety activities, including performing clinical trials, surveillance for vaccine-preventable diseases, and mathematical modeling and economic analyses; maintaining adequate vaccine coverage; and monitoring the safety and efficacy of the vaccines provided by the NHS.

The HPA conducts analytical studies on adverse event signals that arise from the Yellow Card system. HPA researchers also often use the GPRD to investigate health concerns, but the study population is not large enough to examine the rare adverse events associated with vaccines (Miller, 2012). The Hospital Episode Statistics (HES) database contains records for all hospital admissions in the United Kingdom, along with the individual's NHS number for each admission. Using the NHS number, researchers can contact an individual's general practitioner to obtain immunization records and link those data to any hospital admission from the HES.

England and Wales maintain national child health databases that routinely collect immunization records and can likewise be linked with the HES by use of an NHS number and specified approvals. This method has been used to investigate adverse event signals, such as a suspected increased risk of purpura or convulsions from the meningococcal group C conjugate vaccine and a potential association between MMR and idiopathic thrombocytopenic purpura (Andrews et al., 2007; Miller et al., 2001).

### Denmark

Denmark is uniquely positioned to build and maintain large cohorts for the evaluation of vaccine safety, thanks to the Danish Civil Registration System (CRS) and national health care system. The CRS was established in 1968 and registered every living person in Denmark at that time. Every living resident in Denmark, including noncitizens, is issued a unique personal identification number; and the CRS collects data on each individual's gender, date of birth, place of birth, place of residence, citizenship status, and parents and spouses and continuously updates vital statistics (Pedersen et al., 2006).

Linking a personal identification number to the data collected by the CRS makes it possible to track demographic trends and vital statistics for Danish residents over time. This identifier is also used to link individuals with data collected by Denmark's many health care registries. The National Board on Health administers registries on the incidence of specific diseases (e.g., the National Diabetes Register and the Danish Cancer Register), and since 1990, Denmark has maintained a registry containing information on all vaccinations administered to children aged 18 years and younger. General practitioners report incidences of vaccination to a

state-based administrative registry and are in turn reimbursed by the national health insurance system (Thygesen et al., 2011).

Epidemiological research on vaccine safety is conducted with data from these registries by the Department of Epidemiology Research at the Statens Serum Institut, one of Denmark's largest health research institutions (Statums Serum Institut, 2012). Because each health-related registry records the resident's CRS, it is possible to link the data collected by separate registries. Therefore, much of the formative research on vaccine safety has been conducted in Denmark with registry linkages. These linkages of data between the childhood vaccination registry and other disease-specific registries provide data that can be used to evaluate hypotheses on vaccine safety for large cohorts of Danish residents (often, more than 500,000). For example, the cohort study design has been used to investigate associations between MMR and autism, childhood vaccinations and type 1 diabetes, and thimerosal-containing vaccines and autism (Hviid et al., 2003, 2004; Madsen et al., 2002).

## Canada

Canada's health care system has some similarities with those in countries such as Denmark and the United Kingdom, including the provision of primary care health services without cost sharing. Unlike those countries, Canada's health care system is provincial, rather than federal, meaning that coverage varies across the 13 separate provinces. The determination of an immunization schedule is no exception: each province is given authority to create its own immunization schedule, although evidence of vaccine safety and efficacy is still reviewed by the National Advisory Committee on Immunization. Nevertheless, provinces may have very similar schedules for one vaccine; for example, the only province that does not recommend immunization with MMR at 12 months of age is Prince Edward Island, which recommends the vaccine's first administration 3 months later at age 15 months. For another vaccine, that for hepatitis B, the differences are more striking: the province of Prince Edward Island recommends administration of the first dose in infancy, whereas its provincial neighbor, Nova Scotia, does not recommend administration of the first dose until grade 8 (Macdonald and Bortolussi, 2011).

Canada also has a spontaneous reporting system for suspected adverse events related to vaccines, the Vaccine Associated Adverse Event Reporting System, which was established in 1987. Today, the passive surveillance system is called the Canadian Adverse Events Following Immunization Surveillance System and is maintained by the Public Health Agency of Canada. Health care professionals in Canada can submit reports of suspected adverse events to their local public health authority. Unlike in the United States, however, Canada has no system for the general public to report events without a health professional, who must submit the required form. In the provinces of Manitoba, New Brunswick, Nova Scotia, Ontario, Quebec, and Saskatchewan, reporting of adverse events after immunization is required by law (Public Health Agency of Canada, 2006).

To supplement its passive surveillance system, Canada implemented the Immunization Monitoring Program, Active (IMPACT) in 1991. The IMPACT network is based in 12 pediatric hospitals and is maintained by the Canadian Paediatric Society. In IMPACT, a nurse monitor and clinical investigator regularly review admission records at network hospitals. Any suspected adverse events are reported to the vaccinee's local public health authorities and the Public Health Agency of Canada (Public Health Agency of Canada, 2006). IMPACT data have been used in

studies of suspected adverse events after immunization, including studies of the risk of seizures or encephalopathy after implementation of acellular pertussis-containing vaccines (Scheifele et al., 2003).

### International Collaborations

In addition to country-specific data systems, some international collaborations seek to improve assessments of vaccine safety. The Brighton Collaboration is a global research network comprising more than 300 vaccine safety experts from 124 countries, including the United States. The focus of their work to enhance vaccine safety falls into five categories: capacity building, clinical assessments, communication, data linkages, and research standards. Included in their activities is an effort to standardize case definitions of adverse events after immunization (Brighton Collaboration, 2012).

In addition, the Brighton Collaboration operates the Vaccine Adverse Event Surveillance and Communication network of data linkages in Europe, which is funded by the European Centre for Disease Prevention and Control (VAESCO, 2010). To date, this network of investigative centers has conducted a five-country distributed case-control study to evaluate the risk of Guillain-Barré syndrome after administration of the pandemic influenza (H1N1) vaccine and the incidence of idiopathic thrombocytopenic purpura after immunization with MMR in a combined sample from Denmark and the United Kingdom (Dieleman et al., 2011; Madsen et al., 2002).

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# 4

# Stakeholders' Concerns Related to the Safety of the Immunization Schedule

Immunizations represent a unique health intervention because they simultaneously affect the health of individuals and the health of their communities. The success of vaccination programs in reducing the human reservoir of infectious diseases requires the collaboration and participation of a complex system of stakeholders in which each plays a specific role. These stakeholders include but are not limited to the parents of children who receive vaccines, the physicians and other health care professionals who deliver inoculations, and public health professionals who ensure vaccine delivery and safety. The concerns that surround the immunization schedule are equally complex and diverse.

Concerns about vaccines have historically had a significant impact on the immunization system. Decreases in measles-mumps-rubella (MMR) vaccine coverage in the United Kingdom are largely attributed to parental fears of autism linked to immunization with MMR following publication of the discredited Wakefield paper, which falsely claimed to demonstrate this association and was subsequently retracted years later from *the Lancet* (Brown et al., 2012; Madsen and Vestergard, 2004; Taylor et al., 1999). In the 1970s, concerns about adverse effects from the whole-cell pertussis vaccine contributed to a decrease in uptake and halted pertussis vaccination programs in some countries. From this controversy came innovation that created the acellular pertussis vaccine, which has fewer observed adverse effects, as well as policy changes in the United States with the enactment of the National Childhood Vaccine Injury Act (IOM, 1992; Noble et al., 1987).

The committee recognized the challenge and importance of identifying and understanding the range of stakeholder concerns about the childhood immunization schedule and its safety. To gain a fuller understanding of this system, the committee developed a strategy to gather and analyze stakeholder concerns, which included a review of the existing literature, listening to public testimony, and soliciting comments on a commissioned paper.

## IDENTIFICATION OF STAKEHOLDERS

Given the committee's charge, the first step was to identify stakeholders whose concerns focused on the safety of the immunization schedule rather than the safety of individual vaccines or nonsafety issues such as cost or convenience. To begin, the committee consulted the list of stakeholders from the 2008 Institute of Medicine (IOM) report *Initial Guidance for an Update of the National Vaccine Plan: A Letter Report to the National Vaccine Program Office* (IOM, 2008), which is also referenced in the 2010 National Vaccine Plan of the U.S. Department of Health and Human Services. As a second step, the committee categorized the extensive list of stakeholders by their general interest in immunization (Box 4-1).

**BOX 4-1**
**Stakeholders in the U.S. National Vaccine System**

- Academic researchers
- Advocacy groups
- Federal government agencies, departments, and federal advisory committees
- General public (including parents)
- Health care system and providers
- International organizations
- Media
- Nongovernmental organizations
- Philanthropic organizations
- State, local, and tribal governments and public health agencies
- Travel industry
- Vaccine distributors
- Vaccine industry
- Vaccine investors

SOURCES: IOM (2008) and adapted from the 2010 National Vaccine Plan (http://www.hhs.gov/nvpo/vacc_plan/2010 percent20Plan/appendix5.pdf).

## INFORMATION GATHERING

After identifying key stakeholders, the committee reviewed the most frequently expressed concerns related to the safety of the immunization schedule from three primary sources of information: the current literature, online postings, and public testimony.

The committee reviewed all the information that interest groups, individuals, and researchers provided through the online submissions and in public testimony at the committee meetings and throughout the study period. Even before the first committee meeting, the committee received online testimony as well as many e-mail messages. The committee held three public meetings that included information-gathering sessions and a session during which it heard public testimony. During the three public meetings, the final hour was reserved for stakeholders to share their concerns related to the committee's charge. Throughout the study, the committee also reviewed media coverage and scientific

articles related to the safety of the immunization schedule. However, the committee based its review of the safety of the immunization schedule on information reported in the scientific literature.

The literature review focused on the recommended childhood immunization schedule and yielded an extensive body of scientific articles, reports in the popular media, reviews, and summaries. Because the committee's study period was limited (no longer than 12 months), the committee established priorities to identify and review the most common and noteworthy stakeholder concerns about the safety of the childhood immunization schedule.

## LITERATURE SEARCH

The committee used the Ovid MEDLINE database to search the scientific literature published within the past 10 years (2002 to 2012). Multiple comprehensive searches were used to identify references that described stakeholders' concerns and analyzed health outcomes after immunization according to the recommended childhood immunization schedule. The committee focused on articles published in the past 10 years because the childhood immunization schedule has been modified several times as new vaccines have been approved and incorporated into the schedule. Concerns related to the 2001 recommended childhood immunization schedule are likely to be different from concerns related to 2012's schedule, which recommends additional immunizations for children. Because the committee's task was to assess the safety of the immunization schedule rather than the safety of individual vaccines, the literature searches did not include articles that focused on a single vaccine. The committee's review included peer-reviewed publications such as scientific articles, reviews, commentaries, and editorials. The committee used medical subject heading searches to identify references, using the terms "immunization" (which includes "immunization schedule"), "vaccines," "attitude to health," and "attitude of health personnel."

The initial literature search yielded 421 articles. To further refine the search, the committee reviewed the titles and abstracts (when available) and removed articles that met any of following three exclusionary criteria. First, from the beginning of the study period, the committee noted that the childhood immunization schedule spans the entire period of childhood (birth to age 18 years). The committee found that the most prominent safety concerns about the immunization schedule are related to vaccinations received during infancy and early childhood. Thus, the committee focused its review on the body of literature that addressed concerns about the short- and long-term effects of the schedule of vaccinations given to young children (birth to age 6 years) and excluded studies that focused on the immunization schedule for older children and adolescents (age >6 years). Second, the committee excluded studies that focused on individual vaccines or combination immunizations rather than the entire childhood immunization schedule. Finally, the committee excluded studies of non-U.S. populations, unless the study focused on the Advisory Committee on Immunization Practices (ACIP)-recommended immunization schedule for young children.

After the committee applied these criteria, it retained 85 published articles for comprehensive review. Two-thirds of these articles were categorized as studies of

parental concerns about either safety ($n$ = 26) or communication between providers, public health authorities, and parents ($n$ = 31). Several articles that the committee reviewed did not meet the study criteria (largely owing to having an older publication date) but were frequently cited in the literature and added to the committee's knowledge base.

An iterative review of the literature as well as oral and written public comments revealed that among the primary stakeholders (parents, health care providers, public health officials), a subset of parents were the group with the most concerns about the safety of the immunization schedule. The review also revealed that parents, providers, and public health officials all believe that effective communication about these safety concerns remains a challenge.

## PARENTAL CONCERNS IN THE SCIENTIFIC LITERATURE

Parental concerns about the safety of vaccines and the immunization schedule have been well publicized but are not well understood by all health care professionals. A number of recent studies have described the challenges associated with research into the safety of the immunization schedule and defined the methods that can be used to elicit and quantify parental concerns (Dempsey et al., 2011; Freed et al., 2010; Gust et al., 2005; Kennedy et al., 2011a; Niederhauser et al., 2001; Salmon et al., 2004).

In 2000, Gellin et al. reported that the two most common concerns that parents expressed about childhood immunizations were that too many vaccines were being administered to infants and children and that childhood vaccines may weaken the immune system (Gellin et al., 2000). The 2002 IOM report *Immunization Safety Review: Multiple Immunizations and Immune Dysfunction* determined that no biological or epidemiological evidence for such concerns was available and that infants receive more antigenic exposures from the natural world, including exposures to infections for which no vaccine is provided. The report noted, however, that "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 further challenges for immunization policy-making" (IOM, 2002, p. 12)

A recent study of the concerns stated by parents with young children (<7 years) in the 2010 HealthStyles survey revealed a number of vaccine-related attitudes and concerns (Kennedy et al., 2011b). The concerns that 376 respondents reported the most frequently are listed in Table 4-1.

**TABLE 4-1** Vaccine-Related Concerns, 2010

| Vaccine-Related Concern | Percentage of Responses |
|---|---|
| It is painful for children to receive so many shots during one doctor's visit | 38 |
| My child is getting too many vaccines in one doctor's visit | 36 |
| Children get too many vaccines during the first 2 years of life | 34 |

SOURCE: Kennedy et al., 2011b.

Similar results were found in the 2002 HealthStyles and ConsumerStyles surveys of a nationally representative sample of 697 parents, although the rank order of their concerns was slightly different (Gust et al., 2005). Despite documented parental concerns about vaccines, most parents still have their children receive the recommended immunizations. In fact, the 2010 National Immunization Survey reported that less than 1 percent of toddlers had received no vaccines at all (CDC, 2012).

A 2011 article focused on the relationship between parents' attitudes toward childhood immunizations and the decision to delay or decline immunizations (Smith et al., 2011). Using data from the 2009 National Immunization Survey (NIS), the researchers reviewed 11,206 parents' reports of immunization delays and refusals. Approximately 60 percent of parents with children aged 24 to 35 months neither delayed nor refused immunizations, 26 percent only delayed immunizations, 8 percent refused immunizations, and approximately 6 percent both delayed and refused immunizations. Concerns were aggregated into categories such as a lack of trust that vaccines are safe, suspicions that vaccines might produce serious side effects, concerns that too many vaccines can overwhelm a child's immune system, and the general sense that their children are immunized with too many vaccines (Smith et al., 2011).

Safety concerns have led some parents to prefer alternative immunization schedules that may involve delaying specific immunizations or omitting some or all immunizations. A recent review of the literature on the growing trend of following alternative immunization schedules produced a summary of parental concerns, such as concerns about vaccine safety, efficacy, and necessity; distrust of vaccine advocates' motivation; and insufficient information with which to make an informed decision (Dempsey et al., 2011). Health care providers reported that parents' requests for an alternative schedule may be based on a specific immunization schedule or may reflect parental concerns about an individual vaccine rather than the entire schedule.

A recent cross-sectional, Internet-based survey of a representative sample of parents of young children (ages 6 months to 6 years) reported that less than 10 percent of parents indicated that they follow an alternative immunization schedule (Dempsey et al., 2011). The study identified the four vaccines that were the most commonly refused: the H1N1 influenza, seasonal influenza, rotavirus, and varicella vaccines. In general, newer vaccines were more likely to be declined than established vaccines. Parents who requested a delay for a specific vaccine most commonly (more than 40 percent) requested a delay in receiving MMR and the varicella vaccine.

In 2009, Freed et al. conducted an online survey and reported that the varicella and meningococcal vaccines were the most commonly refused (Freed et al., 2009). An analysis of responses to the NIS in 2003 and 2004 also reported that the varicella vaccine was the one that prompted the most concerns among parents who declined immunizations for their children (Gust et al., 2008).

Although parents have various reasons for declining or delaying immunizations, a 2011 study also reported that a large proportion of parents who requested an alternative immunization schedule understood and acknowledged that undervaccination increases the risk of infection and spread of disease in the community (Dempsey et al., 2011). Despite

recent increases in the popularity of alternative immunization schedules, their use remains infrequent (Dempsey et al., 2011; Robison et al., 2012).

Analysis of the data from the 2003-2004 NIS revealed that parents of underimmunized children articulated their concerns about the safety of the immunization schedule in the popular media more forcefully than parents of fully immunized children (Gust et al., 2004). Results of a later iteration of the NIS in 2009 found that parents of fully immunized children reported concerns about vaccines, but their concerns did not preclude immunization of their children (Kennedy et al., 2011a).

In their public testimony during the committee meetings, parents provided a range of concerns about the immunization schedule; the committee received limited public testimony from parents who endorse the recommended schedule, despite evidence that the majority of U.S. parents support and follow ACIP's recommendations (CDC, 2012).

The 2004 NIS reported that parental concerns about vaccine safety were associated with underimmunization, which is further associated with adverse health outcomes for individuals and their communities, including increases in the prevalence of vaccine-preventable diseases (Gust et al., 2004). Furthermore, the designs used in most studies of immunizations do not permit a detailed analysis of the impact of parental concerns on parents' decision to immunize their children (Kennedy et al., 2011b); and although many research studies have focused on parental concerns about vaccine safety, they have not adequately explored parental knowledge of the protective benefits of immunizations.

The committee identified a need for further study of parental attitudes and concerns about immunization. Based on the committee's review of the literature and public testimony, the committee strongly endorses research to understand parents' knowledge, beliefs, and concerns about vaccines and vaccine-preventable diseases, which is a key component of the 2010 National Vaccine Plan.

## PUBLIC CONCERNS PRESENTED TO THE COMMITTEE

The public testimony presented to the committee highlighted concerns about the quality and strength of existing research on vaccine safety in the United States. Some individuals who provided public testimony focused on the lack of research on vaccine safety for subpopulations that may be potentially susceptible to adverse events. For example, children with family histories of adverse vaccine events, autoimmune diseases, allergies, and neurological diseases were described to be underrepresented in prelicensure and clinical trials of childhood immunizations.

Furthermore, public testimony to the committee described the speculation that children with a family history of autoimmune disease or allergies and premature infants may be additional subpopulations at increased risk for adverse effects from immunizations. The 2012 IOM report *Adverse Effects of Vaccines: Evidence and Causality* supports the fact that individuals with certain characteristics (such as acquired or genetic immunodeficiency) are more likely to suffer adverse effects from particular immunizations, such as MMR and the varicella vaccine (IOM, 2012).

During each of the three public sessions held in conjunction with committee meetings, the testimony of many individuals and organizational representatives revealed a lack of trust in the quality and thoroughness of vaccine safety research. Several individuals recommended that the committee review the scientific studies that have compared health outcomes among fully vaccinated, partially vaccinated, and unvaccinated children as well as children who have been vaccinated according to alternative schedules.

The comments that were submitted through an online questionnaire in response to the committee's commissioned paper (see Appendix D) echoed many of the concerns and suggestions that were articulated during the three public sessions. The sentiments largely focused on the concern that the recommended immunization schedule bombards children's immune systems with an excessive number of antigens at an early age and may not be as safe as possible.

## PATIENT-PROVIDER COMMUNICATION

As indicated by the high rates of vaccination coverage, most American parents believe that vaccinations are an effective way to protect their children from serious infectious diseases (CDC, 2012). Despite this strong support, parents have concerns, questions, and misperceptions about childhood immunizations (Kennedy et al., 2011b). Parents seek information about vaccine safety from a multitude of sources: public health authorities, pediatricians, other child health care professionals, professional organizations' websites, personal blogs, celebrities, and advocacy groups (Freed et al., 2011a).

With such a wide range of sources of information about immunizations, the committee recognized the likelihood that parents could receive conflicting information that could exacerbate their concerns and confusion about the safety of vaccines. The committee also noted the many high-quality websites and materials that have recently been produced, including Vaccines.gov and materials produced by the American Academy of Pediatrics (AAP) and available on the AAP website. However, findings from an online survey conducted as part of an ongoing study of 2,521 parents and nonparents demonstrated that although websites from doctors' groups, such as AAP, and government websites were trusted by the greatest proportion of surveyed parents (27 and 7 percent, respectively), a larger proportion did not view or use these resources at all (29 and 38 percent, respectively) (Freed et al., 2011b).

Apart from the confusion associated with conflicting sources of information about childhood vaccines (Freed et al., 2011a), the committee's review of the scientific literature and the public testimony identified the lack of parental trust in vaccines and vaccine safety to be an important concern. Overall, a large majority of parents rely on the professional advice that they receive from their child's doctor or health care provider, and they report high levels of trust in their doctor's advice (Freed et al., 2011a). However, a recent study reported that 26 percent of parents trusted celebrities as a reliable source of information on the safety of vaccines (Freed et al., 2011b). Thus, although the relationship between the parent and the child's health care provider is a strong determinant of decision making about childhood vaccines, some parents rely on

nonprofessional sources of information to make the same decisions (Gust et al., 2008; Serpell and Green, 2006).

In some cases, pediatricians may dismiss parents from their practice if the parents decline vaccines, delay vaccinations, or base their decisions on unscientific information (Flanagan-Klygis et al., 2005). For example, a 2011 study reported that more than 30 percent of Connecticut pediatricians have dismissed families because of their refusal to immunize their children (Leib et al., 2011). AAP discourages the dismissal of parents on the basis of their refusal to immunize their children (Diekema and the AAP Committee on Bioethics, 2005). Furthermore, AAP believes that providers should maintain a relationship with families that decline immunizations so that children continue to receive appropriate medical care. In addition to the value of that care, the continuing relationship provides an opportunity for the pediatrician to encourage parents to consider immunization of their children in the future (Diekema and the AAP Committee on Bioethics, 2005). The committee also notes that the dismissal of families from pediatric practices could further erode trust in the health care system.

A recent study of 209 pediatricians in Washington State reported that parental requests for alternative immunization schedules are not uncommon (Wightman et al., 2011). Overall, 61 percent of these pediatricians agreed that they were comfortable using different schedules if the parents made this request. The three vaccines that most pediatricians were willing to delay were the hepatitis B vaccine (69 percent), varicella vaccine (53 percent), and inactivated poliovirus vaccine (45 percent) (Wightman et al., 2011).

Based on the literature review and public testimony, the committee noted the importance of providers' knowledge of vaccine safety. Furthermore, the committee found it to be essential that providers use a communication style that elicits parents' concerns and encourages respectful dialogue to address divergent opinions. Even though health care providers may focus on the benefits of childhood immunizations, they may not adequately discuss the anticipated, higher-prevalence side effects or the potential events that are significantly more rare and severe. Therefore, based on the review of the scientific literature and the public input, the committee believes that all health care providers who immunize children should receive training in communication with the goal of improving provider-parent communication of immunization issues (Gust et al., 2008).

Apart from the need for training in communication, the committee reviewed several recent studies that identified the need for improved communication about vaccine safety by the scientific community and public media (Levi; Gust and Campbell; Gust and Weber). Gust and Campbell suggested that enhanced communication training for providers should increase their willingness to engage parents in discussions of vaccine and immunization issues.

Studies are also under way to develop techniques to identify categories of vaccine hesitancy and develop tools to assist providers as they communicate with parents who express concerns about vaccines (Diekema, 2012). The IOM report *Immunization Safety Review: Multiple Immunizations and Immune Dysfunction* recommended that an appropriate panel of multidisciplinary experts be convened to "develop a comprehensive research strategy for knowledge leading to the optimal design and evaluation of vaccine

risk-benefit communication approaches" (IOM, 2002, p. 16). Furthermore, the 2010 IOM study described in the report *Priorities for the National Vaccine Plan* emphasized that communication must reflect current research and strategies (IOM, 2010).

Government agencies and professional organizations play a key role in providing parents with information on vaccines and immunizations. However, the public erosion of trust in government and the suboptimal effectiveness of public health campaigns on immunizations in particular highlight the challenges of mounting an effective strategy of communication about the childhood immunization schedule. This challenge is exacerbated by the fact that public decision making as it applies to vaccines is driven not only by scientific and economic evidence but also by political, psychological, and sociocultural factors.

## CONCLUSIONS

From the literature review and the comments received online and during the public sessions, the committee determined that although the majority of parents adhere to the ACIP-recommended immunization schedule for their children, many parents remain concerned that their children may face unnecessary risks because of the timing and number of vaccinations.

The decisions that parents make about the risk of disease versus the risk of immunization are attributable, in part, to the significant and sustained declines in most vaccine-preventable diseases that have resulted in the community immunity (also known as herd immunity) that vaccination policy has achieved. Although some parents may not fully understand the concept of community immunity, at some level, many parents understand that widespread efforts to immunize children protect both vaccinated and unvaccinated children. The protection offered by community immunity may mislead some parents who decline all immunizations and allow them to believe that childhood vaccines are unnecessary, when vaccination in the community has actually shielded their children from serious infectious diseases (Chen et al., 2005). Finally, some parents are concerned about their child's risk of complications of immunization with a vaccine on the basis of family history or the child's medical conditions and decide to delay or omit immunizations. Children with certain predispositions are more likely to suffer adverse events from vaccines than those without that risk factor, such as children with immunodeficiencies that are at increased risk for developing invasive disease from a live virus vaccine (IOM, 2012). The committee recognizes that while the CDC has identified persons with symptoms or conditions that should not be vaccinated, some stakeholders question if that list is complete. Potentially susceptible populations may have an inherited or genetic susceptibility to adverse reactions and further research in this area is ongoing.

Thus, the committee understands that parental concerns are an expression of concern over and a way to care for their children's health and well-being. However, the committee also recognizes that a growing pattern of delaying or declining all or some vaccines has already contributed to outbreaks of vaccine-preventable diseases and mortality across the United States. These disease outbreaks place children and adults at risk, including children who are only partially immunized or experience waning immunity. Immunized children and adults in the community represent another group of

stakeholders, and the committee recognizes the concern about declining community immunity as well.

Research from telephone surveys and other methods reviewed in this chapter typically provide information about what participants think, but such surveys usually cannot probe into why respondents think the way they do. To develop an effect risk-benefit communication strategy, more detailed research is warranted. The committee concludes that parents and health care professionals would benefit from the availability of more comprehensive and detailed information with which to address parental concerns about the safety of the vaccines in the immunization schedule. Such information should clearly address vaccine-preventable diseases, the risks and benefits of immunizations, and the safety of the vaccines in the immunization schedule.

At present, as described in Chapter 5, relatively few studies have directly assessed the immunization schedule. Although health care professionals have a great deal of information about individual vaccines, they have much less information about the effects of immunization with multiple vaccines at a single visit or the timing of the immunizations. Providers are encouraged to explain to parents how each new vaccine is extensively tested when it is approved for inclusion in the recommended immunization schedule. However, when providers are asked if the entire immunization schedule has been tested to determine if it is the best possible schedule, meaning that it offers the most benefits and the fewest risks, they have very few data on which to base their response. Furthermore, although the 2010 National Vaccine Plan addresses the need to provide health care providers with more timely, accurate, and transparent information about the benefits and risks of vaccines, providers are not singled out in specific strategies offered by the U.S. Department of Health and Human Services.

Although the committee identified several studies that reviewed the outcomes of studies of cumulative immunizations, adjuvants, and preservatives (see Chapter 5), the committee generally found a paucity of information, scientific or otherwise, that addressed the risk of adverse events in association with the complete recommended immunization schedule, even though an extensive literature base on individual vaccines and combination immunizations exists. The committee also acknowledges that the public health community has in place monitoring systems that work very well for the detection adverse events that occur in the short term after immunization and that could be enhanced for the detection of longer-term outcomes, as discussed in Chapters 3 and 6. The continuation of studies looking at immune phenotyping, such as those of the National Institutes of Health's Human Immunology Project Consortium, is also important in the identification of populations that are potentially susceptible to adverse events (HIPC, 2012).

To achieve the goal of giving health care providers and parents information that addresses the concerns that correlate with delaying or declining childhood immunizations, the committee developed a list of priority areas in which more information or clear communication of existing research is needed. The committee summarizes the priority concerns into the following topics:

1. Immune system overload. As several parents asked, are children given too many vaccines? Do immunizations start when babies are too young? Are immunizations administered too frequently?
2. Immunization schedule. What is the evidence that the ACIP-recommended immunization schedule is better than other schedules? Could the health outcomes among children who are vaccinated according to the recommended schedule be compared with those among unimmunized children? Likewise, could the health outcomes among children vaccinated on the recommended schedule be compared with those among children vaccinated on alternative schedules?
3. Are subpopulations of children potentially susceptible to adverse reactions to vaccines, such as children with a family history of autoimmune disease or allergies or children born prematurely?

The committee recognizes not only that additional information is needed to address parental concerns but also that other factors will affect parental decision making. For example, in the testimony and online comments, the committee identified skepticism about (1) the quality of vaccine research (prelicensure and postmarketing), (2) the influence of pharmaceutical companies on scientific research, and (3) the influence of the governmental entities that oversee vaccine research. In addition, as stated earlier, clear and effective parent-provider communication is essential to convey accurate information and foster mutual trust.

The committee's review of the determinants of public trust in vaccination campaigns and information on vaccines identified three types of concerns raised by stakeholders:

- knowledge and expertise,
- openness and honesty, and
- concern and care.

Thus, improved communication between public health authorities and parents requires improvements to the clarity of the information and the effectiveness with which the information is conveyed as well as the building of trust and the use of a systematic approach to elicit public concerns. Further research into the impact of parental perceptions about risk on their decisions about immunizing their children is indicated, and that research should be performed by methods that use decision and social science (Larson et al., 2011).

The committee acknowledges that parents and providers are not the only stakeholders who are concerned about the safety of the immunization schedule. The committee listened to presentations from a range of stakeholders whose concerns focused on providing immunizations to preserve community immunity and prevent the reemergence of vaccine-preventable diseases, which ultimately requires the cooperation and trust of parents in immunizing their children. These other groups and individuals who also have a vested interest in providing children with a safe and effective immunization schedule include pharmaceutical companies; federal, state, and local governments; health

insurers; the many health care providers who oversee administration of vaccines; and many others in the health care system.

The committee also acknowledges that the low rate of many infectious diseases may encourage parents to focus on the risks of immunizations rather than the risk of vaccine-preventable diseases. These low rates of infectious diseases may reinforce parents' reliance on community immunity to protect their child rather than choose immunizations.

The vaccine safety activities of the federal government are prioritizing the engagement of stakeholders in multiple activities, detailed in the 2010 National Vaccine Plan and implementation efforts, as well as the Scientific Agenda of the Centers for Disease Control and Prevention's Immunization Safety Office. However, an effective national vaccine program will require better-quality information on stakeholder concerns about the safety of vaccines, the severity of vaccine-preventable diseases, individual and population-level immunization, vaccine efficacy, and the delivery and supply of vaccines recommended in the childhood immunization schedule. To effectively implement immunization programs, a state-of-the-art communication plan is needed.

**Recommendation 4-1: The committee recommends that the National Vaccine Program Office systematically collect and assess evidence regarding public confidence in and concerns about the entire childhood immunization schedule, with the goal to improve communication with health care professionals, and between health care professionals and the public regarding the safety of the schedule.**

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# 5

# Review of Scientific Findings

Previous reports from the Institute of Medicine (IOM) have reviewed the evidence regarding individual immunizations and adverse health outcomes. The most recent comprehensive report was *Adverse Effects of Vaccines: Evidence and Causality* (IOM, 2012). Most IOM reviews of vaccine safety have examined the association between adverse events and individual vaccines. One prior IOM review examined the evidence for an association between three adverse outcomes and the overall recommended childhood immunization schedule: increased susceptibility to heterologous infection; autoimmunity, as reflected in type 1 diabetes; and allergy, as reflected in asthma (IOM, 2002). The statement of task for the present IOM committee requests a review of the available data on the relationship between the overall immunization schedule and health effects that might be of concern to stakeholders, including parents, health care providers, and the public health community.

To complete its task, the committee reviewed research on the health outcomes and safety of the immunization schedule. It sought to identify study designs for analysis of health outcomes following immunization and ways to define the health outcomes used in recent studies reviewing aspects of the immunization schedule. Finally, it sought to provide guidance on ways to define exposures and health outcomes in the study designs that the committee may propose.

The committee did not have the time or the resources to conduct formal reviews meeting all criteria for systematic reviews for each question of interest, nor did it find substantial evidence to conduct a quantitative synthesis (IOM, 2011). Therefore, the committee searched for, assembled, and summarized information on the association between aspects of the immunization schedule and specific health conditions already available in the peer-reviewed literature. The health outcomes that the committee chose to review were selected on the basis of its examination of the peer-reviewed literature, previous IOM vaccine safety studies, and public presentations at open meetings of the committee. The number of studies of aspects of the schedule varied; for some outcomes, several studies examining the cumulative effects of vaccines and adjuvants or preservatives were found; for other outcomes, very few studies were found. The committee's methods and reviews are briefly summarized below.

## LITERATURE SEARCH METHODS

The committee members and IOM staff conducted searches of the English-language literature published in the past 10 years (2002 to 2012) for children ages 0 to 18 years using the medical subject headings (MeSH) "immunization" or "vaccines," combined with the following terms for health outcomes of interest:

- "autoimmune diseases" (which captures "diabetes mellitus, yype 1"),
- "asthma,"
- "hypersensitivity,"
- "seizures" or "epilepsy" or "febrile seizures,"
- "child developmental disorders, pervasive" (which captures "autistic disorders"),
- "learning disorders" or "communications disorders" or "intellectual disability" or "developmental disorders,"
- "attention deficit and disruptive behavior disorders," and
- "tics" or "Tourette's syndrome."

The literature published in the past 10 years was chosen to fill the gap since the 2002 IOM review and because several changes to the immunization schedule have been made since 2000 (e.g., addition of the pneumococcal and rotavirus vaccines). Studies more than 10 years old would be of outcomes that occurred after use of an immunization schedule with less resemblance to the current one.

All searches were run against the Ovid MEDLINE database (1950 to present). The search excluded reviews, commentaries, editorials, and similar publications. The conventional electronic searches were supplemented with articles identified by committee members and staff and articles that were noted during committee discussions and public presentations at open meetings. Commentaries and reviews were reviewed but not analyzed in the same detail as original research papers. The searches initially yielded 748 references. This number was further reduced to 143 by exclusion of articles that reviewed vaccines not included in the current or recent childhood immunization schedule or included vaccines for adolescents, such as the human papillomavirus vaccine, and by elimination of references duplicated in more than one category. The number of articles reviewed was further reduced by limitation of the search to articles describing studies that examined at least one health outcome and at least one of the following elements of the schedule, including

- number of vaccines,
- frequency of administration,
- spacing between doses,
- cumulative doses,
- age of the recipient, and
- order of vaccine administration.

Though the committee did not undertake a formal systematic review, the quality of individual articles was judged by the validity of the study design, the method by which the research was conducted, and the transparency of methods. In the end, 37 articles were chosen, and these, organized by category of health outcome, are briefly summarized below.

A second search was performed by use of the MeSH heading "immunization schedule" without predefined headings to investigate specific diseases or conditions. This search was conducted to ensure that the committee's review adequately addressed any demonstrated associations between components of the immunization schedule and adverse health outcomes. Again, the search was limited to articles published in the past 10 years and excluded reviews, commentaries, editorials, and similar publications. After application of the exclusionary criteria, 1,235 abstracts were reviewed, and this number was narrowed to 56 that were considered potentially relevant to the committee's charge. The committee concluded that only four of these research papers covered aspects of the childhood immunization schedule and safety. Two were considered not helpful to an evaluation of safety. (One was an economic evaluation of the childhood immunization schedule and did not examine safety; the second had serious limitations and was not considered for this chapter.) Two of the papers provided useful information, so summaries are included under the appropriate outcome section below (one is included under allergy/atopy; the second is included under neurological outcomes).

A third search was done to examine studies of immunization in infants born prematurely. Although prematurity is not a "health outcome," the committee's efforts included collection of data on premature infants because of concerns about this vulnerable population. The search included the English-language literature published in the past 10 years (2002 to 2012) and used the previously mentioned MeSH terms "vaccines" and "immunization," combined with "infant, premature," and "premature birth." The search was further reduced to include only research on children 0 to 18 years of age and infants from birth to 23 months of age. The initial results yielded 143 abstracts. The committee reviewed the only seven articles that contained relevant data and that met the quality criteria.

## LITERATURE SUMMARY

### Allergy and Asthma

The Ovid MEDLINE literature search identified 40 references to articles on the relationship between immunizations or vaccines and asthma or hypersensitivity. (Although "atopy" and "allergy" were not search terms, many papers identified by use of the search term "asthma" or "hypersensitivity" included "atopy" or "allergy" as outcomes.) After an initial review, a team of two reviewers determined that 13 papers focused on some aspect of the immunization schedule. The committee's second search provided a 14th paper for review, described below. A number of studies reported in the past 10 years have addressed the association between various aspects of the immunization schedule and asthma, atopy, or allergy. As one author noted (McKeever et al., 2004), it is necessary to have a detailed understanding of the relationship between allergic disease and vaccination, because the effectiveness of the immunization program may be adversely impacted by a perception that vaccination is harmful.

The following summary categorizes papers into groups: (1) studies examining an entire immunization schedule, (2) studies examining pertussis-containing vaccines, and (3) ecological studies (defined in Appendix B) and other studies that do not fit into one of the other two categories. Several papers reported on cohort follow-up studies with asthma, allergy, or atopy as the outcome and cumulative immunizations (the entire schedule for the country and time of the study) as the independent variable.

A longitudinal cohort in Australia was examined for the association between early childhood infection and immunization with the development of allergic diseases, including asthma (Thomson et al., 2010). The cohort included 620 allergy-prone children enrolled in 1989 and monitored from birth to 6 years of age. All data, including immunizations (diphtheria and tetanus toxoids and acellular pertussis [DTP] vaccine adsorbed or diphtheria and tetanus toxoids absorbed [DT], oral poliovirus [OPV] vaccine, and measles-mumps-rubella [MMR] vaccine), were collected by telephone interviews. There was no relationship between cumulative immunizations and asthma. Administration of DT in the first year of life but not the second year of life was associated with asthma and eczema. The study was limited by the self-report nature of the data and the small sample size.

Matheson and colleagues (2010) reported on atopy in the most recent follow-up study of 5,729 adults in the Tasmanian Longitudinal Health Study cohort of 1968 in Australia. This most recent follow-up of 44-year-olds was done by use of a mailed survey and explored the effects of immunization on atopic conditions. Only DTP, polio, and smallpox immunizations were in use in the cohort in 1968. The study is limited by the self-reported nature of the information on atopy. Nevertheless, the long-term follow-up demonstrated no association between immunization and asthma or atopic conditions into middle age.

A small study in France examined the association between vaccines received before age 6 months and asthma, allergic rhinitis, and eczema (Martignon et al., 2005). This was a retrospective cross-sectional study of 718 adolescents. Data on the three vaccines that were received before age 6 months were obtained from the pediatric record: Bacille Calmette-Guérin (BCG), diphtheria-tetanus-poliomyelitis, and pertussis vaccines. Live and inactivated vaccines were administered separately. Vaccinated adolescents were significantly less likely to have asthma, allergic rhinitis, and eczema than those who were not vaccinated. Although no association was found between an increase in cases of asthma, allergy, or eczema and immunization with the vaccines, the sample may have been too small to account for confounders, such as exposure to environmental tobacco smoke.

Benke et al. (2004) studied 4,500 young adults enrolled in a study in Australia in 1992 to determine whether childhood vaccines were associated with atopy and asthma in the cohort. Data on symptoms and vaccinations (including MMR, DTP, OPV, the hepatitis B [HepB] vaccine, and BCG) were collected by a mailed questionnaire. Atopy was measured directly by a skin test. Recall bias due to the collection of data via a mailed questionnaire was a limitation of this study. Overall, this study found no significant association between cumulative vaccinations and asthma.

McKeever et al. (2004) reported on a study of the relationship between vaccination and allergic disease, including asthma and wheezing, in the United Kingdom in individuals born from 1988 to 1999. The study had a retrospective observational cohort design and used the United Kingdom's General Practice Research Database (GPRD). The cohort included 29,238 children ages 0 to 11 years with at least a single visit to a general practitioner in the first 6 months of life. Outcomes examined were asthma, wheeze, and eczema. The analysis controlled for the frequency of physician visits ("consulting frequency"). They examined groups of vaccines and also the total number of vaccines in the recommended immunization schedule. Children diagnosed with allergy before full vaccination was completed were excluded from part of the analysis. The authors found no relationship between age at the time of the first immunization with DTP or MMR and asthma or eczema and no relationship between the total number of immunizations and allergic diseases. A relationship was explained by ascertainment

bias rather than a biological effect for the children with from zero to six office visits, who appeared to have a higher risk of a diagnosis of asthma. The study was limited by the small numbers of unvaccinated children and possible ascertainment bias (number of office visits). No association between vaccinations and allergic disease, including asthma, was found.

Gruber and colleagues (2003) conducted a prospective investigation of atopy among 7,609 infants born in Germany in 1990 and monitored to age 5 years. The objective was to determine prospectively if the number (percentile) of childhood immunizations was associated with atopy in 5-year-olds who had been identified to be a high-risk cohort (at least two family members had atopy and a detectable immunoglobulin E concentration of >0.9 kU/L at birth). Atopy was confirmed by clinical diagnosis. Vaccination history was by parental report. The study analyzed exposure to individual vaccines and the cumulative use of vaccines containing aluminum. Overall, the study reported a negative correlation between atopy and the cumulative number of vaccine doses received, including pertussis vaccine. The principal limitation was the self-reporting of vaccination history. However, the committee believes that this was a well-constructed and well-reported study and may serve as one example of a means by which the U.S. immunization schedule could be studied.

*Four Studies of Pertussis Vaccine-Containing Vaccines*

Spycher et al. (2009) studied the development of wheezing and asthma among 6,811 children born in the United Kingdom from 1993 to 1997 and monitored to 2003 in a population-based cohort study. Immunization data were obtained from the National Health Service database. Data on the outcomes of wheezing and asthma were collected from repeated questionnaire surveys. The analysis compared children with complete, partial, or no vaccination against pertussis with children who were immunized with the whole-cell pertussis vaccine included in DTP at the time. Limitations included the self-reported nature of the outcomes data by questionnaires and the fact that 96.9 percent of the children were fully immunized: very few children were not vaccinated or incompletely vaccinated. Overall, the authors found no association between vaccination against pertussis and asthma by age 7 years.

A retrospective, longitudinal study in Manitoba, Canada, reported in 2008 (McDonald et al., 2008), examined an association between the timing of immunization with DTP and the development of childhood asthma by age 7 years. The study used data on asthma risk from health administration records and income data from Canada Census by neighborhood. Manitoba switched from the use of DTP to the use of diphtheria and tetanus toxoids acellular pertussis vaccine adsorbed (DTaP) in 1997; most of the approximately 14,000 children in that study had received DTP and not DTaP. The study reported a decrease in the incidence of asthma for each month of delay in the time of vaccination with the first dose of DTP. A similar but weaker association between the incidence of asthma and each month of delay was also found for the second dose of DTP. The study was limited by potential ascertainment bias: variations in the number of doctor visits, nonrandom reasons for a delay in DTP administration (e.g., because of fever, an infection might promote a T-helper type 1 response [antiviral] over a T-helper type 2 response [proallergy/asthma]), and variations in socioeconomic status. A prospective study of DTaP would be needed to confirm whether these findings can be repeated with DTaP.

A second longitudinal study in the United Kingdom (Maitra et al., 2004) examined the association between pertussis immunization and asthma or atopy by age 7.5 years in a large birth cohort of 13,971 children as part of the Avon Longitudinal Study of Parents and Children. The

study used three approaches (symptoms, a doctor's diagnosis, and questionnaires) to identify children with asthma (symptoms reported by the parent or a doctor) via questionnaires. The aspect of the schedule covered in this study was immunization with DTP; and the study differentiated between full, partial (diphtheria and tetanus toxoids [DT] but not pertussis vaccine), and no immunization. No association between asthma and pertussis immunization was found in children with a high cumulative prevalence of asthma.

Nilsson et al. (2003) reported on allergic disease in Sweden among 538 children at the age of 7 years after pertussis vaccination during infancy. This analysis was based on a follow-up study of a randomized controlled trial of three vaccines. The objective was to assess prospectively sensitization rates and the development of allergic diseases in a follow-up of children included in a randomized controlled trial of the pertussis vaccine. The group analyzed data from three randomized controlled trials evaluating differences in outcomes by age 7 years after immunization with DT or DT plus pertussis vaccine in a study with four arms: a two-component experimental pertussis vaccine, a five-component pertussis vaccine, a whole-cell pertussis vaccine, or no pertussis vaccine arm. All vaccines had aluminum phosphate as an adjuvant. Rigorous definitions of allergic disease were used, and skin tests of the children were used to demonstrate atopy. Compared with the DT vaccine, none of the three pertussis vaccines was a risk factor for the development of allergy in the first 7 years of life. The two-component pertussis experimental vaccine was associated with increased allergic symptoms after booster vaccination. This vaccine was not subsequently used. No relationship between pertussis vaccines and atopic diseases was detected in children with a history of allergies.

*Four Studies That Used Other Methods*

One ecological study was done to examine trends in asthma prevalence and the recommended number of childhood immunizations (Enriquez et al., 2007). The group used National Health Interview Survey (NHIS) data on asthma, the timing of immunization, and the number of recommended immunizations by age 2 to determine whether increases in asthma prevalence paralleled trends in the number of immunizations recommended; however, the increase in the incidence of asthma reported in NHIS preceded the increase in the recommended number of vaccines. This information did not support a relationship between the recommended number of childhood immunizations and the increase in the prevalence of asthma and, in fact, provided evidence of no association.

Mullooly et al. (2007) used a case-control study of 6- to 16-year-olds in an allergy clinic with proven new allergic conditions to determine whether the receipt of immunizations or oral antibiotics in the first 2 years of life affected the odds that they would have atopy (measured by skin test). Compared with the control subjects, atopy cases received fewer antigen doses and fewer different antigens, had less exposure to *Haemophilus influenzae* type b conjugate vaccine (HiB), and received fewer doses of the HiB and mumps and rubella vaccines during the first 2 years of life. The study was limited by the fact that data on immunizations and other variables (e.g., family history of atopy, smoking in the home) were collected by retrospective medical record review. Their power to detect associations was also limited by the fact that only 21 percent of eligible allergy patients could be classified as non-atopic, leaving 79 percent as atopic study subjects. Finally, there was limited variation in vaccine exposure further reducing the power to detect differences. Nevertheless, despite limited statistical power, this study found no association between atopy and vaccine exposure.

Maher et al. (2004) conducted a follow-up of a cohort previously enrolled in a study performed by a U.S.-managed care organization (MCO) as part of the Vaccine Safety Datalink (VSD) project. The analysis examined the association between immunizations and asthma among 1,778 children enrolled from 1991 to 1994. The original study used a matched-pair case-control method. Five vaccines were included: HepB, whole-cell pertussis vaccine, HiB, OPV, and MMR. The analysis was limited by the high rate of vaccine coverage and the small sample size. Childhood immunizations were not associated with asthma by age 5 years, but asthma was related to wheezing episodes in infancy. This study provides useful evidence of no association between vaccinations and asthma.

Bremner et al. (2005) examined the association between allergic rhinitis ("hay fever") and MMR, DTP, and BCG immunization. The study used a case-control design and data from GPRD and the Doctors Independent Network primary care database in the United Kingdom. Children who had been immunized with MMR and DTP did not have greater odds of being diagnosed with hay fever than those who were unvaccinated. Slightly decreased odds of a diagnosis of hay fever in association with delayed DTP administration were detected, however. The researchers suggested that it is possible that an immunization delay in some children is associated with febrile illness. Infectious illness in early childhood could potentially protect against the development of atopy, and the association with delayed immunization with DTP needs further investigation. The small number of children who received BCG had slightly increased odds of having hay fever. The study was limited by the source of the outcomes data, which were based on medical records in which the International Classification of Diseases, revision 9, code for allergic rhinitis was used and medicines commonly prescribed for hay fever were listed. The study has limited value for interpretation of the safety of the U.S. immunization schedule, as the researchers were examining the association between allergic rhinitis and separate vaccines, and neither DTP nor BCG is currently recommended for U.S. children.

In summary, research examining the association between the cumulative number of vaccines received and the timing of vaccination and asthma, atopy, and allergy has been limited; but the findings from the research that has been conducted are reassuring. No data have demonstrated harm (an increased risk of atopy) from immunizations. Indeed, the opposite may be the case. No evidence is available from studies that have directly examined the current immunization schedule (most studies enrolled children in the 1990s, and most were not conducted in the United States), but no studies suggest harm (e.g., an accelerated or increased likelihood of the development of asthma or atopic diseases). The single study finding an association between age at the time of immunization with the first whole-cell pertussis-containing vaccine and a later diagnosis of asthma (McDonald et al., 2008) has not been extended to examine acellular pertussis vaccine. One publication (Thomson et al., 2010) noted the importance of confounding infectious episodes, especially gastroenteritis, suggesting that childhood infections (a target for future effective vaccines) and not childhood immunizations are associated with asthma.

### Autoimmune Diseases

Fifty papers describing studies of a relationship between immunization or vaccines and autoimmune diseases were identified in the initial search. This list was reduced to six papers after the exclusion criteria described above were used. After further review, four of the papers

were believed to focus on some aspect of the immunization schedule and were selected for a more in-depth review.

A study of five U.S. MCOs involving 1.8 million children evaluated the risk of development of immune thrombocytopenic purpura (ITP) after immunization with childhood vaccines other than MMR (O'Leary et al., 2012). The study involved a self-controlled case series and was able to confirm an association between ITP and MMR. It found no increased risk of ITP after immunization with vaccines other than MMR in young children but did find an association between ITP and immunization with HepA; tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine adsorbed; and varicella vaccine in older children. However, because of the small numbers of reports of ITP and potential confounders, the researchers concluded that further investigation is needed. A limitation of this study was that ITP is a rare adverse event, and it is difficult to examine the risk of ITP in association with immunization with other vaccines independently when these vaccines are routinely given at the same time as MMR, which has been determined to be one possible cause of rare cases of ITP (IOM, 1994).

Yong et al. (2010) used data from the United Kingdom GPRD to assess the incidence of ITP in the pediatric population in the United Kingdom and to compare the incidence of ITP in children with that in adults in a large population-based study. The researchers examined the evidence of infection and a history of immunization among pediatric patients with ITP, focusing on infections recorded within 8 weeks and immunizations recorded within 6 weeks before the first recorded diagnosis of ITP. A limitation of this study was that the investigators identified cases of infection through computerized records instead of the questionnaires used in other studies, which may have failed to capture a number of mild infections that did not lead to prompt contact with a physician.

Hviid and colleagues (2004) evaluated whether a link exists between childhood vaccinations and the development of type 1 diabetes using data from a cohort of children born between 1990 and 2000. The researchers used Danish data and estimated rates of type 1 diabetes according to vaccination status, including the type and number of doses, among all children and a subgroup of children who had a sibling with type 1 diabetes. Rate ratios were also estimated for the period from 2 to 4 years after vaccination. During the time period of the study, the schedule varied with the introduction of Hib from 1993 to 1995, when it was administered at 5, 6, and 16 months of age, but administration of Hib was then changed to 5, 6, and 15 months of age starting in 1996 and 3, 5, and 12 months of age starting in 1997. The combined diphtheria, tetanus, and inactivated poliovirus vaccine was given at ages 5, 6, and 15 months until 1996, and a whole-cell pertussis vaccine was given separately at 5 weeks (half-dose), 9 weeks, and 10 months of age. In 1997, the pertussis vaccine was modified to the acellular pertussis vaccine, which was incorporated into the diphtheria, tetanus, and inactivated poliovirus vaccine. The schedule of the combined vaccine was modified to be given at 3, 5, and 12 months of age. Boosters of oral polio vaccine were given at 2, 3, and 4 years of age. The study evaluated 739,694 children for 4,720,517 person years of follow-up. Overall, 681 cases of type 1 diabetes were identified from the Danish National Hospital Register, 26 of whom (4,208 person years) had a sibling with type 1 diabetes. This study found no association between childhood vaccination and the development of type 1 diabetes, even among children who had a sibling with diabetes. A limitation noted by the authors was the use of the Danish National Hospital Register rather than the National Diabetes Registry, which goes back only to 1996, to make sure that they had large enough numbers of children for analysis. A strength of the study is that it was a nationwide cohort with

longitudinal, individual-level information on vaccinations and type 1 diabetes incidence, minimizing selection and recall bias.

Verstraeten and colleagues (2008) performed an integrated analysis of studies performed internationally to assess the safety of vaccines containing the AS04 adjuvant according to the incidence of adverse events of potential autoimmune etiology, particularly in adolescents and young adults. The study compared recipients who received vaccines with the AS04 adjuvant and a control group who received nonadjuvanted vaccine (i.e., control), vaccines with aluminum adjuvant, or aluminum hydroxide alone. Overall, the rate of reporting of autoimmune disorders was low, with an event rate of approximately 0.5 percent which did not differ between the groups receiving vaccines with the AS04 adjuvant and the control groups

The distribution of the reports by category did not suggest unusual patterns of autoimmune disorders. The authors concluded that these analyses do not suggest any statistically significant association between the development of autoimmune disorders and immunization with AS04-adjuvanted vaccines. This conclusion reinforces other reports in the literature concluding that no evidence exists for an association between autoimmune disorders and most vaccines. Limitations of the analysis mainly included a lack of validation of each diagnosis, which relied on investigator reports, and variability in the collection of adverse event data between studies (Verstraeten et al., 2008).

In summary, the literature that the committee found to examine the relationship between the overall immunization schedule and autoimmunity was limited. The evidence from a single large Danish study for diabetes is reassuring because it did not detect a relationship between the immunization schedule and autoimmunity. Evidence for ITP confirms prior evidence of an association with immunization with MMR and is not clear about immunization with other vaccines.

### Autism

The initial literature search identified 32 papers on the relationship between immunizations or vaccines and pervasive developmental disorder (PDD), which includes the diagnoses autistic spectrum disorder, autism, and Asperger's syndrome. After an initial review, a team of two IOM committee members determined that 12 papers focused on some aspect of the immunization schedule. Three of the papers either addressed only one vaccine or had methodological limitations. The other nine studies examined the association between thimerosal and autism and other neurodevelopmental problems (Andrews et al., 2004; Fombonne et al., 2006; Geier and Geier, 2003, 2004a,b, 2006; Hviid et al., 2003; Madsen et al., 2003; Young et al., 2008). Five of the studies had serious methodological limitations and were not helpful with examination of the association between thimerosal and vaccines. Each of the other four papers might help with a study of the schedule.

Fombonne et al. (2006) examined the prevalence of PDD in relation to two aspects of the immunization schedule in Canada: cumulative thimerosal dose and a change in the MMR schedule from one to two doses in birth cohorts from 1987 to 1998. Thimerosal was eliminated in 1996, and a second MMR (administered at age 18 months) was added to the schedule in 1996. Data on autism were from school records. Vaccine data were in part from a registry and in part from provider records. The dose of thimerosal was calculated from the recommended immunization schedule by year (not the dose received by individual children). A continuous

increase in the incidence of PDD occurred over time, despite the elimination of thimerosal, and a decrease in MMR coverage was also detected. The increased rate of PDD was the same before and after the addition of a second required dose of MMR. The study was limited by reliance on administrative codes for the diagnosis of PDD. The study was also conducted in one school board (district), and some PDD cases may have moved into that board, which would have inflated the numbers. This was an ecological study, but the data were interpreted carefully and the differences in appropriate trends were noted.

Andrews et al. (2004) used the United Kingdom GPRD to evaluate the risk of a variety of neurodevelopmental disorders, including autism, tics, speech and language delay, attention deficit disorder, and other developmental delays, in association with the calculated cumulative exposure to thimerosal to up to 4 months of age in more than 100,000 children born between 1988 and 1997. The retrospective cohort study found no evidence for an increased risk of neurodevelopmental disorders, with the possible exception of tics, in association with thimerosal exposure. For general developmental disorders, unspecified developmental delay, and attention deficit disorder, increasing thimerosal exposure had an apparent protective effect. Although the study was limited by an inability to adjust for several confounding factors, such as socioeconomic status and other medical conditions, in general, it had a sound methodology. GPRD is a good source of linked data that may be used to look at other aspects of the vaccination schedule in the United Kingdom. The aspect of the schedule covered by this study included the cumulative doses of thimerosal received by children immunized with DTP and DT and whether these were received, for example, on time or late.

Two studies examined aspects of the Danish immunization schedule. Hviid et al. (2003) studied the relationship between cumulative thimerosal exposure via the whole-cell pertussis vaccine and autistic spectrum disorder. The study included a cohort of children with a diagnosis of autistic spectrum disorder born between 1990 and 1996. The diagnoses were taken from the Danish Psychiatric Central Research Registry and linked with the immunization history of each child. The study covered a period (1990 to 1992) when only one thimerosal-containing vaccine was in use. The study found no association between a diagnosis of autism and the presence of thimerosal but noted that the incidence of autism may have been underascertained, especially in earlier birth cohorts. This study did not demonstrate a relationship between thimerosal administration via the pertussis vaccine and the development of autism in a small country (Denmark) with high immunization rates and a good system of record keeping. The only aspect of the schedule covered was thimerosal exposure specifically via the pertussis vaccine.

The other Danish study evaluating an association between immunization and PDD (Madsen et al., 2003) also used data from the Danish Psychiatric Central Research Registry. The authors sought to evaluate the vaccine history for all Danish children identified with autism between 1971 and 2000 to assess the incidence of autism among children between 2 and 10 years of age before and after the removal of thimerosal from vaccines in 1992. The annual incidence of autism increased rapidly starting in 1990 and continued to do so through 1999, even though thimerosal was eliminated from DTP in 1992. The study was limited, as was the study by Hviid et al. (2003), by the fact that before 1995, diagnoses of autism were made only for hospitalized patients, whereas after 1995, outpatient diagnoses of autism were included. This study failed to demonstrate a correlation between the discontinuation of thimerosal in DTP and the incidence of autism in Danish children. This was an ecological study and so it cannot confirm an association. The paper provided no real information about the immunization schedule.

In summary, the evidence of an association between autism and the overall immunization schedule is limited both in quantity and in quality and does not suggest a causal association. The committee found the literature to be most useful in suggesting study designs that might be adapted and extended for the committee's core task of suggesting further research.

### Other Neurodevelopmental Disorders

Forty-one papers concerning a relationship between immunizations, immunization schedule, or vaccines and learning disorders, communication disorders, developmental disorders, intellectual disability, attention deficit disorder, disruptive behavior disorders, tics, and Tourette's syndrome were identified via an Ovid MEDLINE database search. This list was reduced to eight papers after use of the exclusion criteria described above, including exclusion of papers on vaccines not currently recommended for administration to children under age 6 years. After an initial review, five of the papers were believed to focus on some aspect of the immunization schedule and were selected for more in-depth review. Each of these five studies focused on possible adverse effects of thimerosal (given via different schedules). Importantly, with the exception of the influenza vaccine, since 2001 thimerosal has been either removed from or substantially reduced in amount in vaccines given to U.S. children under 6 years of age. Although thimerosal is no longer a component of U.S. childhood vaccines, these studies may suggest methods to study variations due to use of alternative schedules, or to changes to the recommended immunization schedule made over time. The committee identified a sixth study through its second search effort.

A study conducted by Tozzi et al. (2009) in Italy also evaluated the effects of different doses of thimerosal during infancy on neurodevelopmental outcomes. These investigators conducted a late follow-up evaluation at 10 to 12 years of age of subjects who were initially enrolled in a study of the efficacies of two formulations of pertussis vaccine that contained different amounts of thimerosal. Twenty-four neurodevelopmental outcomes were measured via 11 standardized tests. Only two statistically significant differences, which were believed not to have been clinically significant, were noted in the female subjects. Specifically, girls with higher thimerosal exposure had lower mean scores in the Boston Naming Test and on finger tapping with the dominant hand. Given the large number of comparisons, these significant differences could be attributable to chance. In this study, the cumulative dose of thimerosal was low compared with the doses that had been used in the United States.

In a cohort study of 1,047 subjects enrolled in three MCOs as part of the VSD, Thompson et al. (2007) evaluated the effects of cumulative exposure to thimerosal on 42 neurodevelopmental outcome measures (excluding autism). The subjects were between 7 and 10 years of age. Immunization status was retrospectively assessed, and the assessment included exposure to thimerosal both prenatally (via maternal immunization or immunoglobulin administration) and then during the first 7 months of life. Few significant associations between cumulative thimerosal exposure and a particular neurodevelopmental outcome were noted. These associations were few in number and were equally divided between positive and negative effects. Most were gender specific. For example, in boys, higher exposure to thimerosal prenatally was associated with a higher score on the Stanford-Binet copying test and a lower score on the Wechsler Intelligence Scale for Children III (WISC-III) digit-span test of backward recall. In girls, higher thimerosal exposure at between birth and 7 months of age was associated with a better performance on the Grooved Pegboard Test in the nondominant hand as well as on the

WISC-III digit-span test of backward recall. Although this study was limited by only a 30 percent participation rate, which may have resulted in selection bias, it failed to demonstrate a causal association between early exposure to mercury via thimerosal-containing vaccines or immunoglobulins and neurodevelopment.

Smith and Woods (2010) used secondary data from the VSD cohort study of Thompson et al. (2007) to determine if on-time immunization by 1 year of age was associated with neuropsychological outcomes. The researchers performed two analyses using immunization and outcomes data from the VSD. The first analysis compared children who had received all vaccinations on time with those who had not. Complete immunization was defined as having received within 30 days of the recommended age at least two doses of HepB, three doses of DTaP, three doses of Hib, and two doses of polio vaccine (referred to as the 2:3:3:2 series) during the first year of life. The second analysis stratified children into five groups by age at the time of completion of the 2:3:3:2 series. Children with on time immunizations consisted of those who received at least 10 vaccinations in the first 7 months of life, whereas the least vaccinated group comprised those who had received less than seven vaccine doses of any type during the same time period. Using the outcomes data obtained from the research of Thompson et al. (2007), Smith and Woods (2010) found that children who had received their immunizations on time and also those who had received at least 10 doses did not have better neuropsychological outcomes in this study than those who had received fewer doses, and no significant differences were found between those who received the least vaccines and those with the greatest vaccine exposure during the first 7 months of life.

In a cohort study conducted in Brazil, Marques et al. (2007) evaluated the effects of thimerosal exposure during the neonatal period on neurodevelopment measured by use of the Gesell battery of tests at 6 months of age. In their study, 84 infants were immunized with a thimerosal-containing HepB either on the day of birth or later in the neonatal period (between days 2 and 4 of life). Before the neurodevelopmental assessments at 6 months of age, these infants also received additional doses of vaccines containing thimerosal (two doses of HepB and three doses of DTP). The researchers did not report any difference in neurodevelopmental measures between the two groups. In addition to the small sample size, this research focused on a minimal alteration in the immunization schedule that may have been so minor that an effect on neurodevelopment would not be expected.

In a longitudinal study of 14,000 infants in the United Kingdom, Heron et al. (2004) evaluated the relationship between cumulative exposure to thimerosal and several neurodevelopmental outcomes, including behavioral difficulties, tics, deficits in speech and fine motor development, and other "special needs." At the time of this study, thimerosal-containing vaccines were administered in the United Kingdom at 2, 3, and 4 months of age, which represents an accelerated schedule of exposure compared with the schedule used in the United States. This study evaluated 69 specific behavioral and developmental outcomes via questionnaires that were sent to the parents of children born over a 15-month interval during 1991 and 1992. Only one outcome (poor prosocial behavior) was found to be associated with cumulative thimerosal exposure at 3 months of age. Interestingly, this study demonstrated that adverse neurodevelopmental outcomes were less likely in children who had higher thimerosal exposures.

In another VSD study, Verstraeten et al. (2003) also evaluated the association between the cumulative exposure to thimerosal at 1, 3, and 7 months of age and neurodevelopmental

disorders such as autism, other speech and language disorders, disorders of attention, and tics. This was a large retrospective cohort study of subjects from three MCOs that participated in the VSD. In Phase 1 of the study, data from two MCOs were analyzed. A positive association between cumulative thimerosal exposure and the development of tics was found for subjects from one MCO, whereas a positive association with language delay was found for subjects from the other MCO. In Phase 2 of the study, the most common associations seen in Phase 1 were evaluated in a third MCO, and no significant associations were demonstrated. Therefore, no consistent significant association between cumulative thimerosal exposure and neurodevelopmental outcomes was found. Importantly, in no instance was a significant risk of cumulative thimerosal exposure and either autism or disorders of attention detected. This study was limited, as the investigators evaluated thimerosal only as opposed to the type of vaccine. Neurodevelopmental outcomes for the subjects were determined only by medical record designations (codes) and not by a review of the results of formal neuropsychological assessments.

In summary, the evidence regarding an association between the overall immunization schedule and other neurodevelopmental disorders is limited in quantity and of limited usefulness because of its focus on a preservative no longer used in the United States.

### Seizures, Febrile Seizures, and Epilepsy

Fifty-eight papers of studies of the association between immunizations, immunization schedule, or vaccines and seizures, epilepsy, or febrile seizure were identified via an Ovid MEDLINE search. This list was then reduced to 14 papers. After an initial review, four of the papers were believed to focus on some aspect of the immunization schedule and were selected for a more in-depth review.

A study from Denmark by Sun and colleagues (2012) determined the risk of cumulative doses of combined DTaP-inactivated poliovirus vaccine (IPV)-Hib on the development of both febrile seizures and the later development of epilepsy as well as the risk of these adverse events after pneumococcal vaccine was added to the combined DTaP-IPV-Hib. This was a self-controlled case series study based on children with febrile seizures during follow-up of the cohort. In Denmark, DTaP-IPV was introduced in 1997, Hib was added in September 2002, and pneumococcal vaccine was added in October 2007. Data were collected from January 1, 2003, to December 31, 2008, and the immunization schedule that was evaluated included vaccine administration at 3, 5, and 12 months of age. The analysis did not include the 5-year booster immunization. Compared with a reference cohort of children who were not within 0 to 7 days of receiving an immunization, the increased risk of febrile seizure on the day of immunization only (but not between days 0 and 7 after immunization) was minimal after the first or second dose of combined DTaP-IPV-Hib vaccine but not after the third dose. The overall incidence of febrile seizures in these cohorts was small. The vaccinated group had a lower risk of developing epilepsy in the first 15 months of life than the reference cohort of children, whereas the risk of epilepsy later in life was unchanged. The estimates did not change when pneumococcal vaccine was added to the vaccination program. It is not clear why the immunized children had a decreased risk of epilepsy. This may have been due to unmeasured confounding factors, as the investigators did not address whether children with a high risk of developing febrile seizures or epilepsy (such as children with preexisting neurological disorders) were less likely to have been vaccinated.

A VSD surveillance study by Klein et al. (2010) evaluated the risk of development of febrile seizures after children received the combined measles, mumps, rubella, and varicella vaccine (MMRV), MMR plus the varicella vaccine, MMR alone, or the varicella vaccine alone. The investigators compared the incidence of evaluations for seizures in the emergency department or hospital and for fever in the clinic that occurred in patients at between 12 and 23 months of age within 42 days of receiving any "measles-containing vaccine" as well as the varicella vaccine (either as a component of the measles vaccine, at the same time as the measles vaccine, or at a different time). The investigators determined that both MMRV and MMR, but not the varicella vaccine alone, are associated with increased outpatient visits for fever and seizures 7 to 10 days after vaccination, with MMRV increasing the risk of fever and seizures twice as much as MMR plus the varicella vaccine. A limitation of this study was that the cases of febrile seizure were determined by the presence of *International Classification of Diseases, Ninth Revision,* codes for febrile seizure within the medical record. This may have somewhat overestimated the risk of this adverse event.

Another VSD study (Tse et al., 2012) investigated the risk of febrile seizures that followed the receipt of trivalent inactivated influenza vaccine (TIV) which was administered during the 2010-2011 influenza season. The investigators conducted surveillance of adverse events in children between the ages of 6 and 59 months of age who had received a first dose of TIV. Cases of febrile seizures were identified through the analysis of ICD-9 codes and chart review, specifically for patients presenting to emergency departments or those who were hospitalized. In mid November 2010, a signal was detected that indicated an increased risk of febrile seizures occurring between 0 and 1 days following the first dose of TIV. However, further analysis demonstrated that the risk of febrile seizure was higher after the concomitant administration of both TIV and 13-valent pneumococcal conjugate vaccine (PCV13) compared with the additive risk of febrile seizure after receiving either TIV or PCV13 alone. This risk was highest in children vaccinated at 16 months of age which is not surprising as studies of the natural history of febrile seizures indicate that the background risk is greatest around this age and progressively falls off in older children. Limitations of this study were that the investigators did not evaluate the possible effects of the concomitant administration of other vaccines (such as DTaP), and due to limited information about attributable causes, the investigators were not able to exclude cases who had intercurrent infections as the cause of the febrile seizure. Importantly, given the results of this study, the vaccine information statement for TIV was updated for the 2011-2012 influenza season to include a statement about the possible increased risk of febrile seizure in young children who concomitantly receive both TIV and PCV13 (CDC, 2012).

A study conducted in The Netherlands (David et al., 2008) evaluated the frequency of adverse events that occurred after infants received pertussis vaccine. In The Netherlands, infants receive this vaccine at 2, 3, 4, and 11 months of age. The study compared the adverse events that occurred after patients received whole-cell pertussis vaccine, acellular pertussis vaccine, or acellular pertussis vaccine along with pneumococcal vaccine. The data were acquired from 28,796 of approximately 53,000 questionnaires distributed to parents. The risks of prolonged crying, pallor, high fever, and "fits and jerks" were significantly reduced when the whole-cell pertussis vaccine was replaced by the acellular vaccine. The authors point out that although "fits and jerks" was meant to be an indicator for "seizures," upon review of their data, it was apparent that this category mainly included chills, shivering, jitteriness, and myoclonus. Possible febrile seizures were noted only after the fourth dose of vaccine, with only two cases occurring in the group receiving the whole-cell pertussis vaccine and one case occurring in the group receiving

the acellular pertussis vaccine. This was not a statistically significant finding. The addition of pneumococcal vaccine to the schedule did not change the risk of any adverse events. This study was limited by the 54 percent questionnaire return rate, with a probable bias of an increased rate of return from parents of children who had had reactions. In addition, some at-risk children (children of mothers with hepatitis B) received HepB at the same time as pertussis vaccine, but this clinical feature was not factored into the analysis.

In summary, the literature associating the overall immunization schedule with seizures, febrile seizures, and epilepsy is limited and inconclusive. With the exception of the study suggesting the increased risk of febrile seizure after concomitant TIV and PCV13 immunization (Tse et al., 2012), there is no suggestion of a causal relationship between the administration of multiple vaccines and a single seizure or the later development of epilepsy.

### Immunization of Premature Infants

The committee reviewed six papers on the immunization of premature infants published since 2002. Five papers examined postvaccination cardiorespiratory events, and two papers examined C-reactive protein levels following the immunizations at 2 months of age. All papers included at least some very premature infants (≤32 weeks of gestation), all examined aspects of the vaccines scheduled to be delivered at 2 months of age, and two reviewed longer-term effects. Because small numbers of infants were monitored for short periods of time, it is challenging to draw conclusions from this review. An increased risk of cardiorespiratory events after vaccination may exist, especially in infants with prior septicemia and the need for continuous positive airway pressure for a longer period of time earlier in their lives. The authors of several papers proposed that some infants be monitored in hospital after the first and perhaps the second round of immunizations, but the authors had no consensus on how to identify which infants born prematurely are the most likely to benefit from monitoring. They did note, however that risk factors include lower birth weight, ongoing complications, and underlying medical conditions.

## CONCLUSIONS

The committee conducted a review directed by conventional electronic searches of the peer-reviewed literature, findings from searches conducted by committee members, committee member expertise, committee discussions, and information from public presentations at open committee meetings.

The committee's review confirmed that research on immunization safety has mostly developed around studies examining potential associations between individual vaccines and single outcomes. Few studies have attempted more global assessments of entire sequence of immunizations or variations in the overall immunization schedule and categories of health outcomes, and none has squarely examined the issue of health outcomes and stakeholder concerns in quite the way that the committee was asked to do in its statement of task. None has compared entirely unimmunized populations with those fully immunized for the health outcomes of concern to stakeholders.

Queries of experts who addressed the committee in open session did not point toward a body of evidence that had been overlooked but, rather, pointed toward the fact that the research

conducted to date has generally not been conceived with the overall immunization schedule in mind.

The available evidence is reassuring, but it is also fragmentary and inconclusive on many issues. Nevertheless, the committee found in its literature review useful perspectives on how to define exposures and outcomes and how conventional study designs might be expanded and adapted to more clearly address the question of health outcomes after immunization with the overall immunization schedule.

A challenge to the committee in its review of the scientific literature was uncertainty whether studies published in the scientific literature have addressed all health outcomes and safety concerns. The field needs valid and accepted metrics of the entire schedule (the "exposure") and clearer definitions of the health outcomes linked to stakeholder concerns (the "outcomes") in research that is sufficiently funded to ensure the collection of a large quantity of high-quality data.

**Recommendation 5-1: To improve the utility of studies of the entire childhood immunization schedule, the committee recommends that the National Vaccine Program Office develop a framework that clarifies and standardizes definitions of**

- **key elements of the schedule,**
- **relevant health outcomes, and**
- **populations that are potentially susceptible to adverse events.**

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# 6

# Methodological Approaches to Studying Health Outcomes Associated with the Current Immunization Schedule: Options, Feasibility, Ethical Issues, and Priorities

The current immunization schedule recommended by the Advisory Committee on Immunization Practices (ACIP) was developed after consideration of the safety and effectiveness of the component vaccines and the burden of the infectious diseases on the population targeted by each vaccine. The Food and Drug Administration's (FDA's) current protocol for approval of new vaccines requires an evaluation of the effect of administration of a new vaccine along with other vaccines within the preexisting schedule. Therefore, the burden of disease and evidence of adequate immunogenicity when vaccines are administered together with existing recommended vaccines are established at the time of FDA approval and development of a recommendation by the ACIP. Although the committee's review of the available scientific evidence revealed that no potential adverse health outcomes that may occur after immunization with the recommended immunization schedule rose to a level of concern or biological plausibility sufficient to justify a strong recommendation for immediate study, the committee was asked to recommend methodological approaches that could be implemented should the need arise.

To fulfill its appointed charge, the committee deliberated on five distinct topics to meet the requirements of its statement of task: (1) factors that should be used to determine that new research is needed, (2) major stakeholder concerns that the committee identified, (3) epidemiological evidence on the health effects of the current schedule, (4) major stakeholder concerns and available epidemiological evidence recast into testable research questions, and (5) possible research approaches to address priority research questions.

## CONSIDERATIONS TO DETERMINE NEED FOR INITIATION OF NEW STUDIES

As discussed in Chapter 5, the committee noted that limited published data do not provide evidence that the recommended immunization schedule is associated with safety or health risks. Indeed, the available epidemiological data repeatedly indicate the health benefits associated with the recommended schedule (e.g., reduced infections and hospitalizations).

To undertake new studies on the immunization schedule beyond analyses with existing data from surveillance systems, researchers will need to carefully consider the current evidence, both epidemiological and biological, that supports the plausibility of their hypotheses. The decision to initiate further studies should depend on the results of an evaluation of three considerations that the committee identified through its review of stakeholder concerns and scientific findings:

1. epidemiological evidence of potential adverse health outcomes associated with elements of the immunization schedule (such as postmarketing signals or indications of an elevated risk from observational or experimental studies);
2. biological plausibility supporting hypotheses linking specific aspects of the immunization schedule with particular adverse health outcomes; and
3. expressed concerns from some stakeholders about the immunization schedule's safety, which should support efforts to evaluate the previous two considerations.

Currently, the U.S. Department of Health and Human Services (HHS) considers these criteria before initiating new studies through the Vaccine Safety Datalink (VSD). As discussed in Chapter 3, the Vaccine Adverse Event Reporting System (VAERS) allows parents and providers to report suspected adverse events after immunization. If an association is suspected on the basis of these signals, medical experts in the Clinical Immunization Safety Assessment (CISA) Network evaluate the pathophysiological basis of the suspected event. Researchers may also conduct, using VSD, population-based epidemiological studies on the basis of signals reported through VAERS and conclusions about biological plausibility reported by the CISA Network.

The committee concluded that stakeholder concerns have a role in guiding the research priorities of the Centers for Disease Control and Prevention (CDC), FDA, the National Institutes of Health, and the National Vaccine Program Office because they may point to potential research questions that need to be validated from their epidemiological signals and the plausibility of the suggested biological pathways. Given the safeguards already in place, stakeholder concerns alone are not sufficient reason to embark on costly clinical research, such as new randomized controlled trials (RCTs) or prospective cohort studies, without the existence of supporting signals or evidence of biological plausibility.

**Recommendation 6-1: The committee recommends that the Department of Health and Human Services incorporate study of the safety of the overall childhood immunization schedule into its processes for setting priorities for research, recognizing stakeholders' concerns and establishing the priorities on the basis of epidemiological evidence, biological plausibility, and feasibility.**

### Animal Models

Animal models play a critical role in preclinical studies during development of all medications, including vaccines (Kanesa-thasan et al., 2011). For example, rats and mice are used for investigations into fundamental basic science issues to establish ranges of dosing, explore immunogenicity, and even provide perspectives on some clinical outcomes. Studies of acute toxicity, tolerability, and causes of fever have been performed in guinea pigs and rabbits (Kanesa-thasan et al., 2011). Subsequent studies of safety may be carried out in rats or primates, as appropriate (Kanesa-thasan et al., 2011). Animal models may also be useful for studies exploring novel vaccines, the extent of interference with vaccine immunogenicity by

concurrently administered vaccines, and the bactericidal qualities of antibodies. In its review of the existing evidence of the immunization schedule and safety, the committee did not explicitly review mechanistic evidence for any health outcomes, such as case studies or existing animal models, and instead points to the excellent work of previous committees in their reviews of individual vaccines (IOM, 2002, 2012). However, various stakeholders expressed interest in the potential use of animal models, and the committee therefore also considered the potential of studies with animal models of disease to advance knowledge of the biological mechanisms by which the childhood immunization schedule might be associated with adverse events.

To use animal models for the biological study of the recommended immunization schedule, however, many challenges must be overcome and limitations must be appreciated. For example, if one is interested in events that are purported to occur long after vaccine administration, such as asthma or food allergy, one must establish the generalizability of animal models of those diseases to the human context. Furthermore, spontaneously occurring models of diseases in animals would have to be developed before studies exploring the safety of the aggregate immunization schedule could be performed.

To the committee's knowledge, realistic animal models that could provide information on the potential of long-term health outcomes of the full immunization schedule in humans are not available. Furthermore, an assessment of the long-term effects of multiple immunizations in, for example, rats 3 months after they receive those immunizations would not be applicable to humans because the onset of such chronic diseases takes years to arise in humans.

An example of an animal model is the model of allergic hypersensitivity to dust mites and *Ascaris* in monkeys, which has resulted in studies of asthma (Hogan et al., 1994). However, few such primate colonies with relevance to asthma in humans exist. Furthermore, the cost to establish and maintain a primate colony is extremely high, and the availability of allergic monkeys is therefore extremely limited.

In the absence of animal models of the spontaneous onset of chronic diseases such as Guillain-Barré syndrome, studies of the effects of multiple vaccinations on aspects of airway hyperreactivity in mice or monkeys could be performed, but such studies would be limited in their ability to answer questions about the aggregate immunization schedule.

The key limitation to the use of animal models for evaluation of the immunization schedule therefore is not the availability of science or resources but is the limited ability of models to produce results generalizeable to the human experience. Given the committee's recognition of the complexity of the immunization schedule, the importance of family history, the role of individual immunologic factors, and the complex interaction of immunization with the health care system, the committee determined that it would be more appropriate to focus future research efforts on human research rather than research involving animal models.

In summary, it is not possible to recommend studies with animals to inform the notion that the aggregate childhood immunization schedule results in the onset of chronic diseases. The committee also recognized the role of animal models in understanding neurological diseases, which have made important contributions to the understanding of disease processes that affect the brain in terms of structural or motor changes, such as seizures. In addition to the limitations described above in relation to chronic diseases, the study of neurological diseases such as autism has limited use for animal models, since "no animal embodies the repertoire of behaviors seen in the human, and in particular, no animal has language equivalent to that of the human" (IOM,

2012, p. 86). Thus, there are sizable barriers in using animal models to assess such neurological outcomes following administration of the childhood immunization schedule.

## POTENTIAL RESEARCH QUESTIONS OF INTEREST

The complexity of the current immunization schedule, which includes variables such as the number of doses, the age of administration, and the time between doses, permits the examination of a large number of potential research questions. Nevertheless, the committee noted a general lack of consistent and integrated theories of biological mechanisms or pathways that link specific elements of the immunization schedule to specific health conditions in the vaccinated child.

Perhaps the most compelling hypothesis is that introduction of an excess of immune-stimulating agents into an immature or dysregulated immune system might result in a cascade of adverse immunological processes culminating in asthma, allergies, autoimmune disorders, and the like. Nevertheless, the biological evidence to support this line of reasoning was examined by an Institute of Medicine committee in 2002 as part of the *Immunization Safety Review* series, and that examination found no more than weak justification for such a hypothesis (IOM, 2002).

Likewise, the committee's review of existing epidemiological studies of the immunization schedule was complicated by the effectively infinite number of variations for delivery of the recommended childhood immunization schedule that could be investigated. The literature summarized in Chapter 5 reflects the range of approaches that have been used to characterize departures from the recommended schedule, and no single approach prevailed across multiple investigations.

The committee struggled in its efforts to identify research questions that could be posed to evaluate the health outcomes after immunization with the recommended childhood immunization schedule because of a lack of well-defined exposures and biologically plausible outcomes. Thus, the primary research questions of interest that the committee identified and that are listed below are broad and most likely too general to be readily translated into new research studies, unless biologically plausible hypotheses emerge.

Among the many questions about the current immunization schedule that could be posed, the committee identified what it viewed to be the leading research questions of interest on the basis of a review of stakeholders' concerns. The committee parsed the phrase "this question" in Part 2 of the statement of task into four broad research questions. These questions are listed in Box 6-1.

**BOX 6-1**
**Leading Research Questions of Interest to Select Stakeholders**

1. How do child health outcomes compare between those who receive no vaccinations and those who receive the full currently recommended immunization schedule?
2. How do child health outcomes compare between (a) those who receive the full currently recommended immunization schedule and (b) those who omit specific vaccines?
3. For children who receive the currently recommended immunization schedule, do short- or long-term health outcomes differ for those who receive fewer immunizations per visit (e.g., when immunizations are spread out over multiple occasions)?
4. Do potentially susceptible subpopulations—for example, children from families with a history of allergies or autoimmune diseases—who may experience adverse health consequences in association with immunization with the currently recommended immunization schedule exist?

The committee identified other potential gaps in research on the larger health care delivery system and policy-setting procedures that influence parents' knowledge of and decisions about their immunization choices for their children. For example, several stakeholders identified the need for additional research on effective provider-patient communications on the risks and benefits of vaccinations. Others suggested the value of additional research on patient barriers to obtaining vaccinations. Although the committee acknowledges that these subjects are of interest and indeed are merely two examples of a large number of potential questions about the system of delivery of the immunization schedule that research could evaluate (see Chapter 4), they are beyond the scope of this committee's task. Therefore, the committee makes no recommendations regarding further research aimed at addressing such concerns; however, the committee encourages HHS to make continued efforts to identify populations facing barriers to immunization and consider stakeholder concerns on the safety, efficacy, and delivery of the immunization schedule and communication about the immunization schedule, as detailed in Recommendation 4-1.

This chapter focuses on potential health benefits or concerns about the recommended schedule at the individual level (e.g., the vaccinated child) and population-level considerations, including monitoring of community immunity (also called "herd immunity," which is the indirect protection afforded to unimmunized individuals, e.g., infants too young to be vaccinated against pertussis, when a sufficient fraction of the population is vaccinated), that are necessary for study of the recommended immunization schedule.

The next section focuses on research questions that directly address the individual health benefits and risks of the recommended immunization schedule for the vaccinated child and describes a number of research approaches that could be pursued. The chapter then highlights the critical point that the consequences of individual vaccination choices can be considered only in light of the level of immunization in the larger population, to which the individual is invariably linked.

The committee recognized the vital importance of considering the population health impacts of any studies of the childhood immunization schedule. As the immunization schedule

exists within a complex system consisting of individual-level protection and community immunity, studies that require any variations to the immunization schedule may have a profound impact on broader population health. After the discussion of methods to study individual health outcomes, the committee describes methods to monitor and maintain community immunity.

## GENERAL RESEARCH APPROACHES TO ADDRESS PRIMARY RESEARCH QUESTIONS OF INTEREST

Each of the primary research questions of interest to stakeholders concerned about the safety of the immunization schedule described in Box 6-1 could be investigated by a range of study methods that vary considerably according to their cost, feasibility, and ethical propriety. At the one end are secondary analyses of existing data sets that could be initiated immediately; at the other end are primary research efforts involving the collection of new data, most notably, large, new RCTs.

This section describes the range of research approaches that could be pursued to investigate the leading questions of interest, with attention given to each approach's potential according to cost, feasibility, and anticipated scientific yield and utility. The research strategies broadly include

- initiation of new RCTs,
- initiation of new observational studies, and
- secondary analyses of data from current vaccine safety surveillance systems in the United States (such as VSD) and comparable international systems.

Each of these approaches has some potential to advance knowledge of the four primary research questions identified. The following sections discuss the strengths, limitations, cost, and feasibility of each approach.

### Overview of Major Study Design Options

*Randomized Controlled Trials*

It is widely acknowledged that when it is possible to randomize study participants, the RCT is the preferred design for evaluating the effectiveness and safety of health interventions. Data obtained from RCTs are often touted as the "gold standard" for clinical evidence, and results from a properly conducted clinical trial are considered to be of superior quality and reliability to evidence from most observational studies. The committee deliberately considered the form that an RCT of the immunization schedule could take and explored whether such a design would be both ethical and practical.

The critical advantage of the RCT is its ability to randomly assign participants to follow one of two or more different immunization schedules. Such a design would enable researchers to be reasonably certain that any observed difference in outcomes would be free of bias that could result from unequal allocation to treatment groups and would create reasonably comparable groups. The outcomes observed in a well-conducted RCT thus should accurately reflect an actual causal effect of treatment, rather than results that could arise from population differences (Friedman et al., 2010).

Although it is well established that vaccines prevent a vast burden of disease among both immunized individuals and un- or underimmunized people via community immunity, data suggest that some children continue to receive no vaccinations. One could argue that it would be ethical to recruit this population to an RCT comparing a group that receives the standard vaccination schedule with a group that receives no immunization. Because participants would be randomly placed in one of these study arms, at least half of the participating children, who otherwise would receive no vaccination, would receive all or part of the recommended immunization schedule. The other half would receive no benefit, except for a possible improvement in community immunity that would increase their chances of avoiding vaccine-preventable diseases. They would also avoid any hypothetical risk of receiving immunizations according to the ACIP-recommended schedule.

The committee considered and rejected this logic, on the basis that any child, even the child of a parent who staunchly rejects vaccination, who is randomized to a no-vaccination arm is essentially consigned to an elevated risk of severe illness and even possible death should the child contract a vaccine-preventable disease. Moreover, should a child in the no-vaccination arm contract a preventable disease, the risk to other unprotected people in the community would increase. Randomization of such a child would also place the child's pediatrician in the position of having to go against professional medical guidelines. Likewise, parents of intentionally unvaccinated children are unlikely to allow their children to be randomized to receive vaccines. Similarly, the committee believes that any study stipulating that some children receive less than the recommended immunization schedule would not be ethical. The ethics of human experimentation always trump scientific and other considerations, and no study that needlessly endangers children is acceptable. As the committee did not find evidence to suggest that the current schedule is unsafe, the committee concludes that any RCT comparing the current schedule with an alternative schedule that does not provide full and timely coverage of all the currently recommended vaccines would offer an unacceptable risk of vaccine-preventable diseases in individuals and in the population.

The committee believes that it may be ethical to use the RCT design to evaluate the third research question, which seeks to determine how health outcomes differ for those who receive the full recommended schedule in unconventional ways. A potential schedule that might be feasible as a comparative intervention is one that would disperse the vaccinations within the recommended window so that children are visiting their health care providers more often but receiving fewer doses at each visit. An example of such a study would be one that (e.g., compares the health of infants who receive their five immunizations at the 4-month visit during one encounter with a health care provider with the health of infants who receive the same immunizations after age 4 months over the course of five separate visits. Because such a dispersed vaccination schedule would require an increased number of visits, often in rapid succession over a period of a few weeks, such a study would add substantial costs to both parents and providers and, moreover, may be unacceptable to insurers if its effectiveness—measured as a decreased rate of adverse outcomes—is negligible. Although it is unobjectionable ethically, the committee considered the time and financial strains resulting from immunization on a dispersed schedule to be too prohibitively costly to recommend pursuing this line of research and, thus, does not endorse this method as a feasible option for studying the recommended immunization schedule.

Certain segments of the population, including premature infants, children born into families with histories of autoimmune disease, and children with genetic traits not yet identified that confer an increased chance of developing diseases having autoimmune features, could be vulnerable both to putative harmful effects of vaccination and, conversely, to the absence of protection from vaccine-preventable diseases should they not be vaccinated. The benefits of immunization to such possibly vulnerable populations could surpass those to children in nonvulnerable groups, allowing them to avoid vaccine-preventable diseases that, although mild for others, could be severe for them. One might hypothesize, however, that the risk of a severe adverse effect of immunization is elevated in this group if, for example, administration of several vaccines causes an immune overload that precipitates the onset of an immunological disease.

If observational data suggest that a particular element of the schedule is associated with a particular adverse outcome in an identifiable subgroup, it could be ethical to conduct a randomized trial of the schedule with such a population, if such a trial does not require some children to receive a reduced schedule that would put them at risk for vaccine-preventable disease. However, as both the potential risks and the benefits are elevated and, moreover, the research community does not currently have a sound idea of the magnitudes of those risks and benefits, it is premature to propose RCTs to evaluate differences in outcomes between these hypothesized groups.

*General Feasibility Issues*

As detailed in Chapter 3, RCTs to evaluate the introduction of individual vaccinations are conducted within the context of the currently recommended childhood immunization schedule. The committee found no evidence that a trial has ever been conducted to evaluate the entire immunization schedule, for example, to compare administration of the recommended schedule of vaccines with administration of an alternative schedule. To conduct such a trial would require careful consideration of multiple factors. For instance, it has been established that some vaccines are associated with fevers, febrile convulsions, anaphylaxis, and other syndromes, which in some cases are similar to the symptoms of the diseases that they are intended to prevent. These adverse reactions are mostly rare. For example, febrile seizures occur for only 1 of every 3,000 measles, mumps, and rubella (MMR) vaccine doses (IOM, 2012), but a sufficiently large study of the safety of a schedule that omits or delays MMR would likely show an increased risk of seizures in the group receiving the regular doses of MMR. Unless researchers somehow accounted for the occurrence of the more serious preventable diseases, it may appear that nonvaccination is "safer" in this respect. To further complicate matters, the rare unvaccinated child in an otherwise heavily vaccinated area will benefit from community immunity and may thus appear to have done better than his or her peers, some of whom will develop adverse effects, such as fever.

Because vaccination in the United States essentially begins at birth, an RCT of the immunization schedule would have to randomize children either before birth or shortly thereafter. In addition to the many practical difficulties that this raises, randomization before birth means that the trial cannot be conducted solely through interactions with child healthcare providers, as pregnant women will typically be seeing pregnancy care provider in the months preceding delivery. Such a trial would also require parents to adhere to their child's assigned schedule for at least 6 years and to avoid catch-up immunizations in the years that follow to evaluate hypothesized long-term health outcomes, all of which would likely add up to an

impractically long study commitment, likely much longer than 10 years. Compliance with this study protocol may prove difficult for parents over this length of time.

Clinical trials commonly mask participants and evaluators to the identity of the randomized treatments to prevent bias in the evaluation of treatment effects. In an RCT comparing the recommended schedule with an alternative schedule, masking of subjects would involve administration of placebo injections at the recommended vaccination times (for the alternative arm) and at the alternative times (for the recommended arm). Such a scheme would be cumbersome and difficult to implement, potentially causing errors in treatment administration and discouraging good compliance. It would also be unacceptable to parents, who would object to their children being repeatedly injected.

One key limitation of RCTs, which was discussed in Chapter 2 in the context of RCTs already performed to evaluate vaccine safety, is that they generally require large sample sizes to have adequate power. The power critically depends on the incidence rate of the adverse outcome in question. For example, a 90 percent power to detect a halving of the rate of an adverse event that occurs in 8 percent of children would require a relatively small sample size, likely no more than 2,000 participants. With disorders that are less common, for example, those that occur in only 1 percent of a population, one would need about 15,000 subjects to achieve a 90 percent power of detection. For events that occur very rarely, for example, in 0.25 percent of children, a trial would need upward of 50,000 participants to have the same level of power. Given the weak biological justification for the association of the immunization schedule with any adverse outcome, an RCT would have to include tens or hundreds of thousands of participants to be powered to look for a range of outcomes simultaneously, including those that are very rare (see Appendix D).

Only if observational studies suggest specific hypotheses to address could researchers use smaller sample sizes in follow-on RCTs. Given the large number of participants that would be required, the cost of such trials would also be prohibitive. Tens of millions of dollars would likely be required to adequately study the identified hypotheses. A federal investment in an RCT of the immunization schedule would therefore be infeasible, and unless further epidemiological evidence of safety problems from observational studies reveals a safety problem, such an investment could be considered wasteful.

Overall, the committee recognizes the value of the RCT in providing definitive data on the potential effects of the immunization schedule on adverse outcomes and asserts that the RCT should have a role in the overall research program on the safety of the schedule. Even though RCTs on individual and combination vaccines are part of the federal research infrastructure, in the absence of data to suggest that the current schedule is unsafe, the committee must reject on ethical grounds any RCT design that compares the current schedule with an alternative that does not involve full vaccination within the permitted time windows. The committee believes that if clearly defined, biologically plausible hypotheses emerge from observational studies—either studies based on current resources, such as VSD, or studies with newly recruited cohorts—then these could serve as the basis for further research by the use of studies with the RCT design. Before HHS initiates further research on the entire immunization schedule, a thorough review of the biological plausibility of the association of a particular outcome with an aspect of the schedule should be conducted.

**Recommendation 6-2: The U.S. Department of Health and Human Services should refrain from initiating randomized controlled trials of the childhood immunization schedule that compare safety outcomes in fully vaccinated children with those in unvaccinated children or those vaccinated by use of an alternative schedule.**

## New Observational Studies

Observational studies are the cornerstone of epidemiological science and are often used to evaluate associations between exposures and outcomes in situations in which randomization to a treatment arm would be unethical or in which it would not be feasible, because of either costs or other factors, to directly assign and monitor an intervention in the study population. Observational studies can involve either primary data, in which new data are obtained by the investigators to examine study hypotheses, or secondary data analysis, in which instances investigators analyze data that have been previously collected. In its consideration of the use of observational methods to address the four research questions of interest to stakeholders concerned about the safety of the immunization schedule identified in Box 6-1, the committee discussed potential options and challenges for studies with both primary in this section, and secondary data in the section that follows.

### *Prospective Cohort Studies*

Prospective cohort studies, which monitor forward in time populations selected on the basis of their exposure status, would be the most ambitious primary data collection options involving primary data collection to address research questions, such as comparison of the health outcomes between children who receive no vaccinations and those who receive the full, currently recommended immunization schedule. As was mentioned earlier in this report, a small percentage of the U.S. population receives no recommended childhood immunizations for reasons ranging from religious or philosophical beliefs, such as followers of Christian Science and some in U.S. Amish communities, to health reasons, such as children with certain conditions, to personal convictions about the safety of vaccines. Given the above-average proportion of unimmunized children in these populations, ranging from 4 to 16 percent in surveys of different communities (Smith et al., 2004; Wenger et al., 2011), it has been suggested that such a population could serve as a naturally occurring unimmunized group in designing a new prospective cohort study. However, such a study would have limited utility to accurately assess differences in health outcomes between unimmunized and fully immunized children. Firstly, there are questions regarding the potential size and resulting statistical power for such a study. As with RCTs, sufficiently large numbers of participants would need to be recruited for each study arm — those who are unimmunized and those who are fully immunized. Because some Amish communities and other potential naturally occurring unimmunized populations have relatively so few unvaccinated children, the sample population of unimmunized children who could be recruited would likely be too small to provide adequate statistical power, particularly for very rare outcomes (see Appendix D).

Furthermore, the study would need to account for the many confounding variables that distinguish distinct sub-groups of naturally occurring unimmunized populations from the rest of the U.S. population, including lifestyle factors and known genetic variables that may play a role in the development of allergies, asthma, and other conditions. For example, data from the National Immunization Survey have shown that unimmunized children are characteristically

different from children who are underimmunized or fully immunized on the basis of race, gender, socioeconomic status, and parental concerns (Smith et al., 2004). For all these reasons, the committee does not recommend the pursuit of prospective cohort studies with distinct subgroups of naturally occurring unimmunized populations (such as those who decline immunizations due to membership in specific religion or cultural groups).

One option warranting additional investigation would involve embedding a new prospective cohort study of nonvaccinated and fully vaccinated families within the VSD surveillance system. If adequate numbers of fully unvaccinated children were included within VSD, it might be possible to identify comparable, well-matched, fully vaccinated children and actively monitor both groups over time with direct assessments of health functioning. In contrast to a study of, for instance, Amish families only, this study would likely include a more diverse and less highly-selective group of unimmunized children (with reduced potential for confounding) and with a larger sample size.

Further investigation of the number and characteristics of fully unvaccinated children or children vaccinated by use of alternative schedules within VSD appears warranted. It would be important to ensure an adequately comparable comparison group of fully vaccinated children. The committee raised some concerns that differences between the comparison groups of interest might constrain the utility of such a study, for reasons discussed below in regards to secondary analyses.

Furthermore, to be of sufficient scientific quality, such a study would require considerable effort to retain study participants. Additional consideration should be given to the feasibility of assessing of long-term health outcomes for participants in the VSD and the cost of doing so. This information would be essential to adequately assess the feasibility and cost of initiating a new prospective cohort study nested within the VSD.

In addition to studies focused on existing unimmunized populations, the committee recognized that other longitudinal cohort studies of infants and children could be informative for evaluating long-term health outcomes after immunization, if a large sample size was available and accurate recording of immunization coverage was possible. One such opportunity is the National Children's Study (NCS), which is funded by both the U.S. Congress and the National Institutes of Health through the Children's Health Act of 2000 and which received total funding of $744.6 million from fiscal years 2007 to 2011. The budgetary request for fiscal year 2013 is $165 million, which will fund the continuation of the pilot study and introduction of data collection for the main study (National Children's Study, 2012).

The main NCS will be a multicenter effort that will examine the effect of a child's environment—including variables such as air and water quality, diet, family dynamics, and cultural influences—on his or her general health and well-being from birth through age 21 years. With a target population of 100,000 children, the NCS will be adequately powered to evaluate rare health outcomes and will aim to prioritize the investigation of environmental determinants of neurodevelopmental disorders and asthma, among other outcomes. Once begun, the main study will actively collect immunization histories. NCS therefore affords an opportunity to study potential health outcomes among children with a range of immunization histories, and the committee encourages such efforts through NCS and other similar cohorts to create a rich set of data for continued research.

Given the opportunity available through NCS, the limits of studying distinct sub-groups of naturally occurring unimmunized populations, and the high cost of pursuing prospective data collection, the committee does not consider the initiation of new prospective cohort studies to be the most feasible or fruitful approach to studying the recommended immunization schedule at this time.

*Case-Control Studies*

Although they are less demanding in time and cost than a cohort study, the committee concluded that studies with case-control designs are unlikely to advance knowledge and provide answers to the four primary research questions of interest to concerned stakeholders presented in Box 6-1. The main reasons for this conclusion are that (1) the major variations in immunization history of interest are relatively uncommon, necessitating the enrollment of a large number of affected cases and unaffected study participants, and (2) it is not clear how accurately investigators would be able to retrospectively reconstruct details of the child's vaccination history. In addition, case-control studies can be used only if the adverse event of interest is known (see Appendix D for further discussion). Additional methodological work designed to determine the accuracy of retrospective ascertainment of vaccine histories and known adverse events, may well be warranted.

**Secondary Analyses of Existing Databases**

*U.S. Databases*

Unlike prospective observational studies, which require the collection of new data, secondary analyses of accumulated data, such as retrospective cohort or case-control studies, are traditionally less resource intensive because they generally rely largely on information previously or routinely collected in existing databases. Given the comprehensive state of immunization data systems in the United States, the committee considered secondary analyses with data from existing data sets to be the most feasible option for the study of the safety of the childhood immunization schedule. In particular, a number of questions about variations in the current immunization schedule could be further investigated by the use of VSD.

VSD is the premier electronic health record (EHR)-based vaccine safety data system in the United States (Baggs et al., 2011; Chen et al., 1997; DeStefano, 2001). As noted in Chapter 3, VSD is a collaboration between the Centers for Disease Control and Prevention (CDC) and nine health plans that serve about 9.5 million members and that have an annual birth cohort of more than 100,000. In recent years, funding for VSD has totaled approximately $9 million per year, with additional funding being provided for special projects, making VSD a relatively low-cost and effective data system for investigating immunization safety (Frank DeStefano, CDC, personal communication, September 25, 2012).

VSD could be valuable for answering the research questions that the committee identified in Box 6-1 because it includes information on the immunization histories of participants that can be used to identify

1. individuals vaccinated according to some alternative immunization schedules;
2. variations in immunization schedules because of different immunization policies in the participating health plans, variations in clinical practice, vaccine shortages, problems with access, or parental decisions to delay vaccinations;

3. multiple outcomes, including adverse events, diagnoses, and procedures as well as mortality;
4. covariates, including race, age, gender, and zip code – level demographics; and
5. global indices of shorter-term child health and service utilization, including numbers of days hospitalized, numbers of emergency room visits, and so forth.

Accordingly, secondary analyses of the data in VSD databases would add to current knowledge and help answer the four primary research questions listed in Box 6-1. For example, in a review of alternative immunization schedules in the Kaiser Permanente Colorado system, VSD researchers initiated a retrospective matched cohort study to examine patterns and trends for children defined as undervaccinated at ages 2 to 24 months and compared the health care utilization rates between undervaccinated children and children vaccinated at the appropriate age.

Eight sites in the VSD participated in this study. Of 323,247 children born (within the participating managed care organization sites) between 2004 and 2008, 48.71 percent were considered undervaccinated for at least 1 day before age 24 months. The prevalence and specific patterns of undervaccination significantly increased across the study duration. In a matched cohort analysis, undervaccinated children had a significantly lower outpatient visit rate (11 percent) than children who were vaccinated in an age-appropriate manner. In contrast, undervaccinated children had significantly greater (25 percent more) inpatient hospital admission rates than children vaccinated at the appropriate age.

In a second matched cohort analysis, children who were undervaccinated because of parental choice had fewer outpatient visits and emergency room encounters than children vaccinated at the appropriate age. In this second matched cohort analysis, no significant detectable difference in inpatient visit rates was detected between the two groups. Among children considered undervaccinated for any reason, 1,399 instances of undervaccination (variations in immunization history that could indicate alternative schedules) were detected. Among children undervaccinated because of parental choice, 756 distinct instances of undervaccination were detected (Glanz et al., in press). More study will clearly be needed to draw conclusions from these early results, but the potential of this study addressing alternate schedules and of other VSD research is promising.

As already mentioned, families electing different immunization schedules presumably differ in meaningful ways (e.g., according to their access to health care providers, attitudes toward vaccines, health care utilization, and sociodemographic factors). Although these differences may not affect reported incidence of adverse events or the presence of disease, they could be related to individual beliefs or to access to health care. Although confounding can ultimately be reduced by explicit adjustment for covariates, it cannot be fully addressed through analysis of existing study variables.

Moreover, the VSD system has limitations, including a population limited to children in private health care plans and therefore not representative of the entire U.S. population, loss of children to follow-up when families move or switch insurers, and an occasional need for additional data not routinely collected by VSD. These limitations may be addressed by the collection of supplementary data, including through patient interviews or medical record reviews.

To address the adequacy of long-term follow-up data, the magnitude of patient attrition from VSD would need to be fully investigated. For example, preliminary evidence suggests that

VSD lost approximately half of its population over a 10-year period, or an average of 5 percent of its population per year (Frank DeStefano, CDC, personal communication, August 28, 2012).

*Collection of Additional Data on VSD Participants*

One potential enhancement to VSD would be to collect additional demographic and, possibly, family history data for current participants. Basic information on vaccination history, child gender, race/ethnicity, and birth status (e.g., gestational age or birth weight) could be systematically collected for all participants. New approaches to the collection of additional data on a family history of allergies, autoimmune disorders, neurological disorders, and the like should be considered. These data would permit analyses of the fourth research question (about potentially susceptible subpopulations) that cannot be readily conducted at this time.

Collection and banking of blood samples with appropriate informed consent from VSD participants would support subsequent analyses of subpopulations that are potentially susceptible to adverse events according to genetic and epigenetic characteristics.

A more costly enhancement to the current system would be to attempt to capture additional data on child health, possibly including additional data on participants' use of health care services that are not already in the database.

Finally, it might be conceivable to conduct direct assessments of subgroups of interest (e.g., those who receive no vaccinations and a comparable group that receives the full immunization schedule). This option is discussed further below, but it is more feasible to study children who have had incomplete immunizations by a specified age than to identify children considered vaccine refusals because the population which falls into the latter category is generally very small.

*Extending the Length of Follow-Up of VSD Patients*

A limitation of VSD is that it includes data only from individuals in the nine participating health plans. Families with young children may move and switch health plans, resulting in limited follow-up information after their immunizations. This shortcoming is largely overcome in comparable systems in Scandinavia and the United Kingdom because of their universal health care systems and patient registries that contain information on medical services received from primary care providers. The use of strategies to collect health care utilization data through EHRs or provider reports after a participant has left the original health plan may warrant consideration.

*Increasing the Number and Variety of VSD Participants*

With an annual birth cohort of more than 100,000 participants, the total number of children monitored through VSD is substantial. However, national estimates derived from a representative sample of all U.S. children, including those in public health plans, suggest that less than 1 percent of children receive no vaccines. Unpublished data from VSD (Jason Glanz, University of Colorado–Denver, personal communication) suggest that the number of unvaccinated children within VSD is generally consistent with national values. Approximately 1.23 percent of children participating in VSD had no vaccinations recorded by age 1 year, and 1 percent of children had no vaccinations recorded by age 2 years. These estimates are limited to children who were born between 2004 and 2008 and who had a minimum period of enrollment in

VSD of 12 months and a maximum enrollment of 36 months. It is not clear how commonly other variations of the recommended immunization schedule occur among the children in VSD.

In addition, the diversity of the participants represented in VSD is limited by the fact that managed care organizations in the Southwest and rural South are not currently among the managed care organizations participating in VSD. Furthermore, because VSD does not now include any public insurance plans, its population has fewer low-income and minority individuals than the number in the U.S. population as a whole. Options to broaden the diversity of VSD participants would enhance the utility of this system to address the primary research questions of interest and increase the generalizability of research results.

Further discussion would be required to assess the feasibility and cost of such efforts. The committee noted that although VSD represents the most promising system for investigating outcomes after immunization with the recommended childhood immunization schedule, other resources discussed in Chapter 3, such as VAERS, the National Immunization Survey, and immunization information systems, are highly valued resources for monitoring vaccine safety and coverage as well. The Post-licensure Rapid Immunization Safety Monitoring (PRISM) program, which has been used to evaluate vaccine safety in a larger cohort than the VSD, may have the capability to monitor rare adverse events potentially associated with the childhood immunization schedule. However, the data are not yet well-characterized.

Analyses of comparable international immunization surveillance systems in countries including Denmark, the United Kingdom, and Canada have historically been better suited for these purposes for the reasons described below. Although consideration of international immunization surveillance systems was not central to the committee's task, analyses in Denmark, the United Kingdom, Canada, and other countries also hold considerable promise for advancing knowledge about the health outcomes associated with the immunization schedule. First, as discussed in Chapter 3, these countries often collect and maintain full immunization histories for the entire population, greatly increasing the total sample size and the number of children immunized with less common combinations of vaccines (including no vaccines). Second, many of these countries have comprehensive health and educational registries permitting linkage to longer-term and less severe child outcomes. Third, these systems include a richer set of variables on sociodemographic characteristics and family history, permitting analyses of potentially susceptible subpopulations.

The committee considered but does not recommend cross-national comparisons because of the potential bias and lack of generalizability from results that must account for different environments, vaccine antigens, or immunization schedules. The U.S. population differs from the populations in other countries in important ways, including on the basis of genetics and health care history. Even vaccine efficacy can vary among populations, as has been demonstrated in separate studies of a *Haemophilus influenzae b* vaccine in two different populations (Eskola et al., 1990; Ward et al., 1990). A cross-national comparison to study child health outcomes related to recommended childhood immunization schedules would require careful and extensive consideration of the possible covariates, many of which may not be known at this time. Ecological comparisons may be useful for monitoring disease trends and detecting epidemiological signals; however, the information gathered from such studies could not be extrapolated to inferences of individual risk of adverse events related to each immunization schedule, and thus would not be useful for shaping U.S. immunization policy.

The major limitations of U.S. surveillance systems to address the primary research questions identified in this report are (1) the potentially limited number of families included in these systems who will have used the major alternative immunization schedules of interest, (2) potentially high rates of migration from the participating health care organizations, resulting in varying and often short-term follow-up after vaccination, (3) limits on how much information on less severe health outcomes is collected from participating children, and (4) limited ancillary information routinely collected about participating children, such as premature birth or a family history of allergies.

Despite these limitations, VSD is currently the best available system for the study of the safety of the immunization schedule in the United States and holds tremendous promise for advancement, including the potential for future prospective cohort studies. Furthermore, continuing to move toward the increased use of EHRs, as encouraged by federal funding, which are what allow VSD to capture and link large amounts of immunization and health data on children, will help the United States establish richer data sets that are more comparable to those in other high-income countries.

To further enhance the data collected by VSD, the system should strive to obtain complete demographic information to strengthen its functions and generalizability to the whole U.S. population. Secondary analyses with data from other existing databases similar to VSD would be feasible, ethical, and a lower-cost approach to investigating the research questions that the committee identified, including research on alternative immunization schedules. To date, the data obtained from VSD have already been used to study health outcomes of children with incomplete immunizations or who may follow alternative schedules, as described above. In addition, the VSD system has a large enough proportion of unvaccinated children to investigate differences in health outcomes of unvaccinated and vaccinated children. Increased efforts to collect information on individual medical histories could lead to a fruitful source of data for studying which populations are potentially susceptible to vaccine adverse events. The committee recognizes that the currently funded managed care organizations' commitment to VSD studies needs to remain high to continue and build upon existing efforts. Additionally, VSD's utility will be expanded with the addition of more detailed demographic data and family medical histories.

**Recommendation 6-3: The committee recommends that the Department of Health and Human Services (HHS) and its partners continue to fund and support the Vaccine Safety Datalink project to study the safety of the recommended immunization schedule. Furthermore, HHS should consider expanding the collaboration with new health plan members and enhancing the data to improve its utility and generalizability.**

## METHODS TO MONITOR COMMUNITY IMMUNITY AND MEASURE POPULATION-LEVEL IMPACTS OF STUDIES OF THE IMMUNIZATION SCHEDULE

If large numbers of children avoided immunization, community immunity would be eroded and this protective effect would disappear for those who are not or who cannot be fully vaccinated. Thus, any analysis of vaccine safety data needs to consider the community immunity

aspect of the milieu in which the study is conducted. Such complications would affect both clinical trials and observational studies.

### Consideration of Population Impacts of Alternative Schedules

Attempts to quantify the relative safety of contrasting immunization schedules need to take into account at least two separate health outcomes: (1) adverse events related to the administration of specific vaccines and the overall immunization schedule and (2) the respective impacts of alternative schedules on the circulation of vaccine-preventable diseases and the consequent adverse outcomes associated with infection. Secondary effects (such as longer waiting times and the greater cost of care if more visits are needed for immunization) and potential medical errors in provider offices accustomed to the routine schedule would also have to be measured.

Previously, high-profile analyses have focused on calculation of the number of serious reactions either per vaccine or over the immunization schedule compared with the per child risk of hospitalization associated with vaccine-preventable diseases (Sears, 2011). Although such analyses are intuitively appealing, they overlook the intimate association between immunization and age-specific disease incidence. Specifically, any shifts in the immunization schedule that lead to a net increase in the time spent vulnerable to these diseases will inevitably increase the circulation of these pathogens. The population-level impacts of such an outcome will be a simultaneous rise in the incidence of the affected infectious diseases and a reduction in the age at which they are contracted. Thus, not only is the risk of exposure to vaccine-preventable diseases increased but so is the likely severity of infection, which may be most acute in younger children (Heiniger et al., 1997).

A clear manifestation of the dual impact of immunization on the incidence and age distribution of vaccine-preventable diseases has been documented in Sweden, where the pertussis vaccine was removed from the national pediatric immunization schedule in 1979 because of concerns over the reactogenicity of the whole-cell vaccine (Gangarosa et al., 1998; Romanus et al., 1987). After a 17-year hiatus, the acellular pertussis vaccine was added to the immunization schedule in 1996 (Carlsson and Trollfors, 2009). Analyses of age-stratified incidence reports highlighted both a sharp decline in the incidence and a marked increase in the age distribution of pertussis cases as a result of the resumption of immunization against pertussis (Rohani et al., 2010). Importantly, Swedish data also illustrate the concept of community immunity.

A pattern similar to that seen in Sweden has been observed in England and Wales, where declines in the uptake of MMR after controversy instigated by a subsequently retracted paper questioning the vaccine's safety were associated with a rise in measles notifications and a shift in the incidence of measles toward younger age groups (Jansen et al., 2003).

### Predicting Changes to Community Immunity

As outlined in the commissioned paper (see Appendix D), a variety of designs may be used to compare the safety of alternative schedules. It is, unfortunately, difficult predict the long-term population-level consequences of disease transmission as a result of changes to the immunization schedule. It is possible, however, to use mathematical and computational models to predict the impacts of changes in the administration of any one specific vaccine on the incidence of the infectious disease affected by that vaccine. This process involves three distinct

steps: model formulation, parameterization, and model validation. These and other elements of the models are described below.

*Model Formulation*

The development of a disease-specific transmission model begins with determination of the model structure and key processes, which are informed by the known immunology and epidemiology of the system. For instance, a loss of immunity may be a necessary ingredient for a model of pertussis transmission, whereas a latent carrier stage may be appropriate for varicella (Anderson and May, 1992; Keeling and Rohani, 2008). The model also needs to explicitly consider age-dependent heterogeneities in contact rates, susceptibility to complications, and reporting.

A number of age-specific models have been proposed for many of the key childhood infections, including measles (Anderson and May, 1992; Schenzle, 1984), pertussis (Hethcote, 1998; Rohani et al., 2010), *Streptococcus pneumoniae* infection (Cobey and Lipsitch, 2012), rubella (Metcalf et al., 2011), and chickenpox (Ferguson et al., 1996).

*Parameterization and Model Validation*

The usefulness of any model and the reliability of its predictions depend on its veracity. Thus, models need to be carefully based on ground truths, a process that is made particularly challenging for high-dimensional age-structured models because a fundamental challenge to the effective parameterization of age-specific models is determination of the appropriate patterns of contact by age. It is fortunate that recent studies have addressed this problem, and detailed information on the typically age-stratified patterns of contact in the United States (Del Valle et al., 2007) and a number of European countries (Mossong et al., 2008) is now available. Synthesis of this information together with historical incidence data to formulate validated transmission models is made possible by the use of modern inference techniques, including sequential Monte Carlo methods for hypothesis testing (Ionides et al., 2006). An example is the age-structured pertussis model developed by Rohani et al. (2010) and parameterized with data from incidence reports from Sweden.

*Data Needs*

The production of fully validated transmission models requires access to age-specific incidence reports. This is often a critical bottleneck in such an endeavor, as public health agencies (e.g., CDC) do not routinely provide such complete data via, for instance, the National Notifiable Diseases Surveillance System (Goldwyn and Rohani, 2012). When detailed incidence reports, stratified by age, county, and immunization status (e.g. through the Supplementary Pertussis Surveillance System), do become available, requests for access to such data are not always granted in a timely manner, and may be answered with the provision of data that was not obtained using the best-available methods (Thacker et al., 2012).

*Quantifying Uncertainty and Sensitivity*

The predictions of any formal modeling analyses need to be evaluated within the context of their inherent variability and should be subject to extensive sensitivity analyses (Blower et al., 2000). Uncertainty in predictions can be quantified by use of a wide array of rigorous probabilistic approaches to model execution, whereby the system of equations is translated into a

Markov chain process (Gibson and Bruck, 2000; Gillespie, 1977; Keeling and Rohani, 2008). Such an approach would permit a detailed situational analysis, whereby the model could provide policy makers with information on the most likely (i.e., the median) outcome, for example, the size of the focal vaccine-preventable disease outbreak given a specific change in the immunization schedule. This approach would also provide information about extreme outcomes or the 95th percentile of predicted outbreak sizes (Park et al., 2009; Rohani et al., 2009). Examination of sensitivity involves extensive repetition of the model simulation as a critical parameter of interest (e.g., the efficacy of the first dose of diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed administered at 3 months of age) is systematically varied.

The development, appropriate parameterization, and scrutiny of mechanistic transmission models have been adopted by a number of governmental agencies; and this process has been influential for determination of the implementation of specific immunization practices in countries such as the United Kingdom. In 2002, for example, Edmunds et al. used an approach similar to that outlined here to examine the potential cost-effectiveness of introduction of an acellular pertussis booster vaccine to the schedule in England and Wales (Edmunds et al., 2002). Similarly, Jit et al. (2008) carried out extensive analyses of detailed transmission models to inform the policy decision of the government of the United Kingdom on the effectiveness of routine vaccination of 12-year-old schoolgirls against human papillomavirus. Other examples include identification of the optimal targeting of age groups to contain the influenza pandemic (Medlock and Galvani, 2009), as well as pinpointing the most effective immunization schedule for meningococcal serogroup C (Trotter and Edmunds, 2006).

## CONCLUSIONS

The committee deliberated on many potential research approaches and worked to determine which were feasible, ethical, and cost-effective. The commissioned paper in Appendix D helped identify methods that could be considered. Many questions can be answered by use of the methods described above, although they are not currently well integrated.

Chapter 7 summarizes the committee's judgment on its statement of task. Setting of priorities for research will be challenging. For example, the committee does not recommend a study comparing the recommended immunization schedule and no immunization at this time because a high-quality randomized trial is not ethical and a prospective observational study could be complex, lengthy, and expensive and would potentially provide inconclusive results about key health outcomes after immunization. Thus, the committee proposes establishment of a process for setting priorities incorporating epidemiological and other evidence (on the basis of formal systematic reviews), biological plausibility, feasibility, and stakeholder concerns.

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# 7

# Conclusions and Recommendations

## COMMITTEE RESPONSE TO ITS STATEMENT OF TASK

This final chapter highlights selected findings and conclusions and presents recommendations for each section of the committee's statement of task. The preceding chapters, especially Chapter 6, include many assessments that may be construed as the committee's preferences among the alternatives presented but that fall short of formal recommendations.

Vaccine safety is critically important, but a determination of safety is ultimately a value judgment. For example, some might believe that a serious adverse event that occurs once in 1million doses is "safe enough" relative to the benefit of preventing a serious disease, whereas others may consider that risk unacceptably high. The committee did not set a specific numerical target or goal for what should be considered "safe enough." Instead, the committee made a judgment based on the literature that failed to link adverse effects to schedule exposures or multiple immunizations, concluding that there is no evidence that the schedule is not safe.

The committee recognized that final decisions about research studies must await knowledge of further evidence including, biological plausibility and/or epidemiological evidence, feasibility, cost, and the exact circumstances of stakeholders' concerns, before the planning and conduct of specific research projects. In turn, the committee believes that it would be inappropriate to make unqualified recommendations without this knowledge. The committee notes that stakeholders' concerns may be used to drive a search for scientific evidence (biological or epidemiological), although such concerns would not be sufficient motivation to embark on costly clinical research, such as new randomized controlled trials or cohort studies.

The committee thus decided to make five general recommendations. Three recommendations focus on improvements to understanding stakeholders' concerns, harmonizing research methods, and sequencing the process for selecting research questions. Two recommendations focus on research methods, including randomized controlled trials and data systems that would enable ongoing and improved observational studies.

Statement of Task (Part I): Review scientific findings and stakeholder concerns related to the safety of the recommended childhood immunization schedule.

## Summary of Stakeholders' Concerns

The committee's findings and conclusions about stakeholders' concerns are presented in Chapter 4. Although the committee identified the concerns of some parents about the number, frequency, and timing of immunizations in the overall immunization schedule, the committee did not find in its literature review that clinicians, public health personnel, or policy makers have similar safety concerns. Among the latter groups, the childhood immunization schedule is considered to be among the most effective and safe of the public interventions available to prevent serious disease and death. However, although health care professionals have much information about individual vaccines, they have much less information about the effects of administration of multiple vaccines at a single visit or the timing of the immunizations. Additionally, health care professionals cited concerns include efficacy of certain vaccines as well as appropriate delivery and communication regarding the recommended childhood immunization schedule.

Although the 2010 National Vaccine Plan addresses the need to provide health care providers with more timely, accurate, and transparent information about the benefits and risks of vaccines, the Plan does not specifically address strategies to assist providers with questions about the safety of the immunization schedule (HHS, 2010). The committee concluded that parents and health care professionals would benefit from more comprehensive and detailed information with which to address parental concerns about the safety of the immunization schedule. Such information should clearly address vaccine-preventable diseases, the risks and benefits of immunizations, and the safety of the immunization schedule.

The committee's literature review highlighted the lack of high-quality evidence supporting stakeholders' concerns (the priority stakeholders are listed in Box 4-1) about the immunization schedule. In its role to ensure vaccine safety, the federal government has already prioritized the engagement of stakeholders in multiple activities, as detailed in the 2010 National Vaccine Plan and implementation efforts, as well as the Centers for Disease Control and Prevention's Immunization Safety Office scientific agenda (CDC, 2011; HHS, 2010). However, an effective national vaccine program will require more complete information on stakeholders' concerns about the safety of the immunization schedule, the severity of vaccine-preventable diseases, individual- and population-level immunization rates, vaccine efficacy, and the delivery and supply of vaccines recommended in the childhood immunization schedule. Improved communication between public health authorities and parents requires improvements to the clarity of the information provided, as well as the building of trust and the use of a systematic approach to elicit public concerns. Further research into the type of questions that parents seek to answer by the use of the scientific methods of social, behavioral, and decision science is indicated.

On the basis of the committee's literature review and public testimony, the committee strongly endorses the need for research to understand the public's knowledge, beliefs, and concerns about vaccines and vaccine-preventable diseases in particular, which is a key strategy

in the 2010 National Vaccine Plan (HHS, 2010). It must be acknowledged that the methods used in most immunization studies do not permit a detailed analysis of the impact of parental concerns on the decision to immunize their children. Although the committee found that the largest safety concerns exist among a subset of parents, the concerns of multiple stakeholders should be included as part of the efforts of the National Vaccine Program Office (NVPO). For example, health care providers have much knowledge about individual vaccines but less information about the effects of administering multiple vaccines at a single visit or the timing of the immunizations.

**Recommendation 4-1: The committee recommends that the National Vaccine Program Office systematically collect and assess evidence regarding public confidence in and concerns about the entire childhood immunization schedule, with the goal to improve communication with health care professionals, and between health care professionals and the public regarding the safety of the schedule.**

## Summary of Scientific Findings

The committee's findings and conclusions about the safety of the immunization schedule on the basis of the information in the scientific literature are presented in Chapter 5. The committee encountered two major issues. First, the concept of the immunization "schedule" is not well developed in the scientific literature. Most vaccine research focuses on the health outcomes associated with single immunizations or combinations of vaccines administered at a single visit. Even though each new vaccine is evaluated in the context of the overall immunization schedule that existed at the time of review, individual elements of the schedule are not evaluated once it is adjusted to accommodate a new vaccine. Key elements of the immunization schedule—for example, the number, frequency, timing, order, and age at the time of administration of vaccines—have not been systematically examined in research studies.

The second major issue that the committee encountered during the review of the scientific literature was uncertainty over whether the scientific literature has addressed all health outcomes and safety concerns. The committee could not determine whether its list of health outcomes was complete or whether a more comprehensive system of surveillance might identify other outcomes of potential safety significance. In addition, the conditions of concern to some stakeholders, such as immunological, neurological, and developmental problems, are illnesses and conditions for which the etiology, in general, is not well understood. Further research on these conditions may clarify their etiologies.

Finally, the committee found that evidence from assessments of health outcomes in potentially susceptible subpopulations of children who may have an increased risk of adverse reactions to vaccines (such as children with a family history of autoimmune disease or allergies or children born prematurely) was limited and is characterized by uncertainty about the definition of populations of interest and definitions of exposures and outcomes. Most children who experience an adverse reaction to immunization have a preexisting susceptibility. Some predispositions may be detectable prior to vaccination; others, at least with current technology and practice, are not (IOM, 2012, p. 82).

In summary, to consider whether and how to study the safety and health outcomes of the entire childhood immunization schedule, the field needs valid and accepted metrics of the entire immunization schedule (the "exposure") and clearer definitions of health outcomes linked to

stakeholders' concerns (the "outcomes") in rigorous research that will ensure validity and generalizability.

**Recommendation 5-1: To improve the utility of studies of the entire childhood immunization schedule, the committee recommends that the National Vaccine Program Office develop a framework that clarifies and standardizes definitions of**

- **key elements of the schedule,**
- **relevant health outcomes, and**
- **populations that are potentially susceptible to adverse events.**

Statement of Task (Part 2): Identify potential research approaches, methodologies, and study designs that could inform this question, including an assessment of the potential strengths and limitations of each approach, methodology, and design, as well as the financial and ethical feasibility of doing them.

## Summary of Methodological Issues

The committee's findings and conclusions about research approaches are presented in Chapter 6. The committee parsed the phrase "this question" in Part 2 of the statement of task into four broad research questions in Box 7-1

**BOX 7-1**
**Leading Research Questions of Interest to Stakeholders**

1. How do child health outcomes compare between those who receive no vaccinations and those who receive the full currently recommended immunization schedule?
2. How do child health outcomes compare between (a) those who receive the full currently recommended immunization schedule and (b) those who omit specific vaccines?
3. For children who receive the currently recommended immunization schedule, do short- or long-term health outcomes differ for those who receive fewer immunizations per visit (e.g., when immunizations are spread out over multiple occasions)?
4. Do potentially susceptible subpopulations—for example, children from families with a history of allergies or autoimmune diseases—who may experience adverse health consequences in association with immunization with the currently recommended immunization schedule exist?

The committee then discussed general research approaches with the potential to answer these questions: ongoing research with data from existing data systems, research with enhanced data from existing data systems, prospective observational studies, and randomized controlled trials. The committee also recognized that to advance the knowledge about the safety of the immunization schedule, certain enhancements to the research infrastructure will be needed, as detailed in Chapter 6.

The committee recognizes that the establishment of priorities for research will be a challenge. Thus, the committee proposes a process for setting priorities that recognizes

stakeholders' concerns and establishes these priorities on the basis of epidemiological and other evidence (based on formal systematic reviews), biological plausibility, and feasibility.

Before the U.S. Department of Health and Human Services (HHS) initiates further research on the entire immunization schedule through its agencies, most notably CDC, FDA, the National Institute of Health, and NVPO, the biological plausibility of the association of a particular outcome with an aspect of the immunization schedule must be thoroughly reviewed. Along these lines, previous IOM vaccine safety committees have assessed the mechanisms by which vaccines potentially cause adverse events by identifying and evaluating the clinical and biological evidence (from human, animal, and in vitro studies) for individual vaccines. Furthermore, the recent IOM Committee to Review Adverse Effects of Vaccines developed categories for a mechanistic assessment of the weight of the evidence. Each assessment considers clinical information from case reports and clinical and experimental evidence from other sources (IOM, 2012).

**Recommendation 6-1: The committee recommends that the Department of Health and Human Services incorporate study of the safety of the overall childhood immunization schedule into its processes for setting priorities for research, recognizing stakeholders' concerns and establishing the priorities on the basis of epidemiological evidence, biological plausibility, and feasibility.**

The decision to initiate further studies should be based on an evaluation of three considerations that the committee identified through its review of stakeholders' concerns and scientific findings:

1. epidemiological evidence of potential adverse health outcomes associated with elements of the immunization schedule (such as postmarketing signals or indications of elevated risk from observational studies);
2. biological plausibility supporting hypotheses linking specific aspects of the immunization schedule with particular adverse health outcomes; and
3. concern about the immunization schedule's safety expressed by stakeholders, which should initiate efforts to explore the two previous considerations.

The committee acknowledges the evidence that reducing vaccine coverage is associated with increases in vaccine-preventable disease and found only ad hoc, inconsistent, and anecdotal evidence to imply that the recommended immunization schedule is not safe. Furthermore, existing systems for the detection of adverse events provide confidence that the existing childhood immunization schedule is safe, and the committee recognizes that the federal government invests considerable resources to ensure vaccine safety. Nevertheless, some stakeholders have suggested that further work is warranted, such as a comparison of vaccinated children with unvaccinated children or children receiving immunizations on alternative immunization schedules.

The committee supports the National Vaccine Advisory Committee Safety Working Group statement that "the strongest study design, a prospective, randomized clinical trial that includes a study arm receiving no vaccine or vaccine not given according to the current recommended schedule, would be unethical and therefore cannot be done" (National Vaccine Advisory Committee, 2009, p. 38). In Chapter 6, the committee presents the formidable ethical and feasibility problems associated with the conduct of randomized controlled trials of children

who receive all recommended immunizations and children who receive none of them and randomized controlled trials of children who receive all recommended immunizations and children who receive the recommended immunization on an alternative schedule. There are very low observed rates of adverse events with vaccination which is another factor effecting feasibility of a randomized controlled trial. Because of these problems, the committee concludes that a randomized controlled trial comparing the recommended schedule with any alternative schedule would be unethical and infeasible and could increase the risk of vaccine-preventable diseases in individuals and in the community.

Furthermore, the committee found that a trial of a modified version of the ACIP schedule—one that would disperse the timing of vaccinations so that children are visiting health care professionals more often but receiving fewer shots at each visit—would be ethical; however, it would add substantial costs to both parents and providers and, moreover, may be unacceptable to insurers if its effectiveness—measured as a decreased rate of adverse safety outcomes—was negligible. This modified schedule would provide immunizations within the time intervals approved by ACIP and would address the concern about immunization with too many vaccines at one office visit, but the committee did not view this option to be feasible for study.

In light of the ethical and feasibility requirements and the available evidence, the committee concludes that new randomized controlled trials of the childhood immunization schedule are not justified at this time.

**Recommendation 6-2: The Department of Health and Human Services should refrain from initiating randomized controlled trials of the childhood immunization schedule that compare safety outcomes in fully vaccinated children with those in unvaccinated children or those vaccinated by use of an alternative schedule.**

The committee also reviewed opportunities to study groups that choose not to vaccinate their children by use of a prospective cohort study design. However, such a study would not conclusively reveal differences in health outcomes between unimmunized and fully immunized children for two main reasons. First, the sample populations often suggested for study (such as some religious populations) may be too small to adequately power such a comparative analysis, particularly for very rare adverse health outcomes. Such a study would also need to account for the many confounding variables that separate these naturally occurring unimmunized populations from the average U.S. child, including lifestyle factors and genetic variables.

The committee finds that secondary analyses of existing systems are more promising approaches to examination of the research questions that the committee identified in future studies of the childhood immunization schedule. The Vaccine Safety Datalink (VSD) is a useful collaborative project that could conduct both postmarketing surveillance and longer-term targeted research. The ability to augment routinely collected administrative data in VSD with data from parent interviews and reviews of medical records for a selected study population is an important strength.

VSD is currently the best available system for studying the safety of the immunization schedule in the United States. VSD should strive to improve the generalizability of its data to the U.S. population as a whole by enhancing the quality of its demographic information and by expanding its scope to include more diversity in its study populations. Secondary analyses with data from other existing databases (that might be modeled on VSD) could be a feasible, ethical,

and cost-effective means of investigating several research questions that the committee identified. The committee recognizes that the commitment to VSD studies by the managed care organizations currently receiving funding through VSD needs to be sustained to continue to build on existing efforts. The committee concludes that VSD is a valuable component of the federal research infrastructure and will be the best-suited source of data for studying the childhood immunization schedule. Its utility will be expanded with the addition of more detailed demographic data and family medical histories.

**Recommendation 6-3: The committee recommends that the Department of Health and Human Services (HHS) and its partners continue to fund and support the Vaccine Safety Datalink project to study the safety of the recommended immunization schedule. Furthermore, HHS should consider expanding the collaboration with new health plan members and enhancing the data to improve its utility and generalizability.**

## CONCLUDING OBSERVATIONS

The committee's efforts to identify priorities for recommended research studies did not reveal a base of evidence suggesting that the childhood immunization schedule is linked to autoimmune diseases, asthma, hypersensitivity, seizures or epilepsy, child developmental disorders, learning disorders or developmental disorders, or attention deficit or disruptive behavior disorders. While the committee found that there is no scientific evidence to justify the majority of safety concerns, perceptions dictate parental support and actions. Therefore further study of the full immunization schedule as well as further study to understand stakeholder perceptions and how they are formed may help improve awareness and education efforts. Stakeholders' concerns should be one of the elements used to drive searches for scientific evidence, but these concerns alone, absent epidemiological or biological evidence, do not warrant the initiation of new high-cost randomized controlled trials. The committee concludes that data from existing data systems may be used to conduct observational studies and offer the best means for ongoing research efforts of the immunization schedule's safety.

The committee found no significant evidence to imply that the recommended immunization schedule is not safe. Furthermore, existing surveillance and response systems have identified adverse events known to be associated with vaccination. The federal immunization research infrastructure is strong. A key component is the VSD project, which with ongoing support will be able to feasibly address the committee's identified key research questions. Although the committee concludes that protection of children from vaccine-preventable diseases is of higher importance than testing of alternative immunization schedules without epidemiological or biological evidence indicating a safety problem, VSD should continue to examine the health outcomes of people who choose alternative schedules.

Looking to the future, the committee supports the work of the federal research infrastructure in ensuring that stakeholders are involved in all stages of development, implementation, evaluation, and dissemination of the immunization schedule. As electronic medical records become more commonly used, they may provide an opportunity to capture complete immunization data linked with hospital discharge records that will be useful to future studies. Further, the Post-licensure Rapid Immunization Safety Monitoring (PRISM) program

may have the capability to monitor rare adverse events potentially associated with the childhood immunization schedule. Initiatives such as the National Children's Study also hold promise; it will be one of the most comprehensive research efforts focused on studying children's health and development.

The childhood immunization schedule may become more complex over time as scientific advances are made and new vaccines are developed. Feasible research approaches to study potential adverse health outcomes will emerge only with a sustained and substantial federal commitment to research on vaccine safety.

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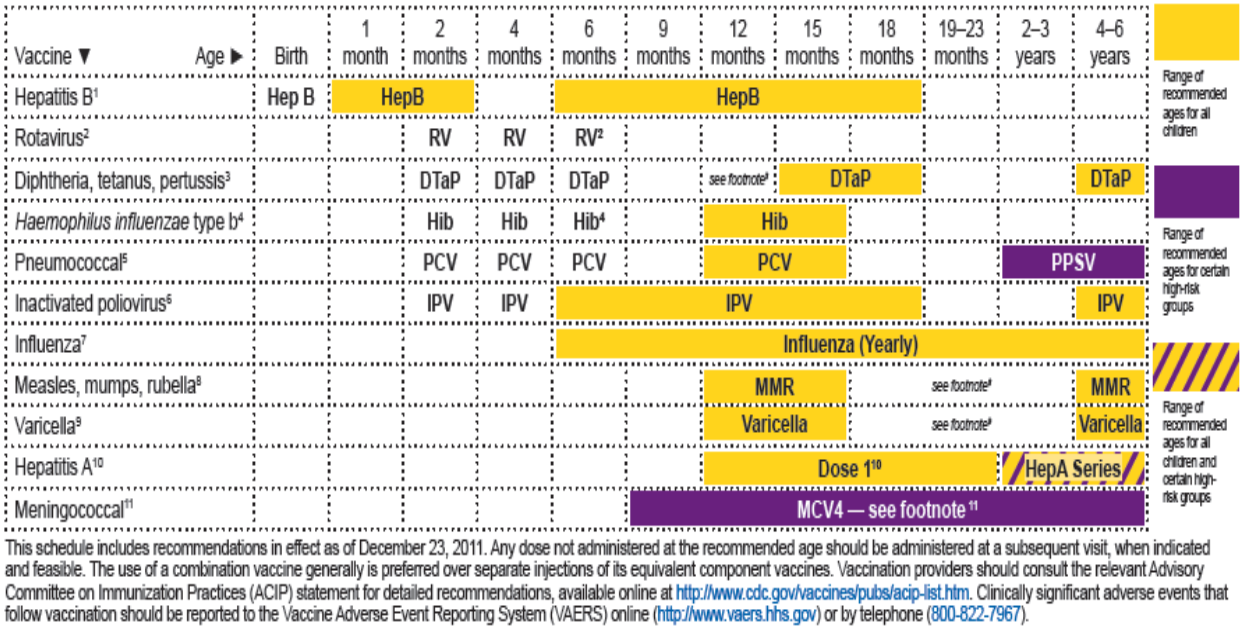
# Appendix A

# 2012 Advisory Committee on Immunization Practices' Recommended Immunization Schedule for Children

## 0-6 YEARS SCHEDULE




This schedule includes recommendations in effect as of December 23, 2011. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Vaccination providers should consult the relevant Advisory Committee on Immunization Practices (ACIP) statement for detailed recommendations, available online at http://www.cdc.gov/vaccines/pubs/acip-list.htm. Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) online (http://www.vaers.hhs.gov) or by telephone (800-822-7967).

**FIGURE A-1** Recommended immunization schedule for individuals aged 0 through 6 years, United States, 2012.

SOURCE: CDC (Centers for Disease Control and Prevention). 2012. *Immunization schedules.* Atlanta, GA: Centers for Disease Control and Prevention. http://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html.

**1. Hepatitis B (HepB) vaccine.** (Minimum age: birth) **At birth:**
• Administer monovalent HepB vaccine to all newborns before hospital discharge.

• For infants born to hepatitis B surface antigen (HBsAg)–positive mothers, administer HepB vaccine and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth. These infants should be tested for HBsAg and antibody to HBsAg (anti-HBs) 1 to 2 months after completion of at least 3 doses of the HepB series, at age 9 through 18 months (generally at the next well-child visit).
• If mother's HBsAg status is unknown, within 12 hours of birth administer HepB vaccine for infants weighing ≥2,000 grams, and HepB vaccine plus HBIG for infants weighing <2,000 grams. Determine mother's HBsAg status as soon as possible and, if she is HBsAg-positive, administer HBIG for infants weighing ≥2,000 grams (no later than age 1 week).

**Doses after the birth dose:**

• The second dose should be administered at age 1 to 2 months. Monovalent HepB vaccine should be used for doses administered before age 6 weeks.
• Administration of a total of 4 doses of HepB vaccine is permissible when a combination vaccine containing HepB is administered after the birth dose.
• Infants who did not receive a birth dose should receive 3 doses of a HepBcontaining vaccine starting as soon as feasible (see Figure A-2).
• The minimum interval between dose 1 and dose 2 is 4 weeks, and between dose 2 and 3 is 8 weeks. The final (third or fourth) dose in the HepB vaccine series should be administered no earlier than age 24 weeks and at least 16 weeks after the first dose.

**2. Rotavirus (RV) vaccines.** (Minimum age: 6 weeks for both RV-1 [Rotarix] and RV-5 [Rota Teq])

• The maximum age for the first dose in the series is 14 weeks, 6 days; and 8 months, 0 days for the final dose in the series. Vaccination should not be initiated for infants aged 15 weeks, 0 days or older.
• If RV-1 (Rotarix) is administered at ages 2 and 4 months, a dose at 6 months is not indicated.

**3. Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine.** (Minimum age: 6 weeks)

• The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose.

**4. *Haemophilus influenzae* type b (Hib) conjugate vaccine.** (Minimum age: 6 weeks)

• If PRP-OMP (PedvaxHIB or Comvax [HepB-Hib]) is administered at ages 2 and 4 months, a dose at age 6 months is not indicated.
• Hiberix should only be used for the booster (final) dose in children aged 12 months through 4 years.

**5. Pneumococcal vaccines.** (Minimum age: 6 weeks for pneumococcal conjugate vaccine [PCV]; 2 years for pneumococcal polysaccharide vaccine [PPSV])

• Administer 1 dose of PCV to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.
• For children who have received an age-appropriate series of 7-valent PCV (PCV7), a single supplemental dose of 13-valent PCV (PCV13) is recommended for:
—— All children aged 14 through 59 months
—— Children aged 60 through 71 months with underlying medical conditions.
• Administer PPSV at least 8 weeks after last dose of PCV to children aged 2 years or older with certain underlying medical conditions, including a cochlear implant. See *MMWR* 2010:59(No. RR-11), available at http://www.cdc.gov/mmwr/pdf/rr/rr5911.pdf.

**6. Inactivated poliovirus vaccine (IPV).** (Minimum age: 6 weeks)

• If 4 or more doses are administered before age 4 years, an additional dose should be administered at age 4 through 6 years.
• The final dose in the series should be administered on or after the fourth birthday and at least 6 months after the previous dose.

**7. Influenza vaccines.** (Minimum age: 6 months for trivalent inactivated influenza vaccine [TIV]; 2 years for live, attenuated influenza vaccine [LAIV])

• For most healthy children aged 2 years and older, either LAIV or TIV may be used. However, LAIV should not be administered to some children, including
(1) children with asthma, (2) children 2 through 4 years who had wheezing in the past 12 months, or (3) children who have any other underlying medical conditions that predispose them to influenza complications. For all other contraindications to use of LAIV, see *MMWR* 2010; 59(No. RR-8), available at http://www.cdc.gov/mmwr/pdf/rr/rr5908.pdf.
• For children aged 6 months through 8 years:

—— For the 2011–12 season, administer 2 doses (separated by at least 4 weeks) to those who did not receive at least 1 dose of the 2010–11 vaccine. Those who received at least 1 dose of the 2010–11 vaccine require 1 dose for the 2011–12 season.
—— For the 2012–13 season, follow dosing guidelines in the 2012 ACIP influenza vaccine recommendations.

**8. Measles, mumps, and rubella (MMR) vaccine.** (Minimum age: 12 months)

• The second dose may be administered before age 4 years, provided at least 4 weeks have elapsed since the first dose.
• Administer MMR vaccine to infants aged 6 through 11 months who are traveling internationally. These children should be revaccinated with 2 doses of MMR vaccine, the first at ages 12 through 15 months and at least 4 weeks after the previous dose, and the second at ages 4 through 6 years.

**9. Varicella (VAR) vaccine.** (Minimum age: 12 months)

• The second dose may be administered before age 4 years, provided at least 3 months have elapsed since the first dose.
• For children aged 12 months through 12 years, the recommended minimum interval between doses is 3 months. However, if the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.

**10. Hepatitis A (HepA) vaccine.** (Minimum age: 12 months)

• Administer the second (final) dose 6 to18 months after the first.
• Unvaccinated children 24 months and older at high risk should be vaccinated. See *MMWR* 2006; 55(No. RR-7), available at http://www.cdc.gov/mmwr/pdf/rr/rr5507.pdf.
• A 2-dose HepA vaccine series is recommended for anyone aged 24 months and older, previously unvaccinated, for whom immunity against hepatitis A virus infection is desired.

**11. Meningococcal conjugate vaccines, quadrivalent (MCV4).** (Minimum age: 9 months for Menactra [MCV4-D], 2 years for Menveo [MCV4-CRM])

• For children aged 9 through 23 months (1) with persistent complement component deficiency; (2) who are residents of or travelers to countries with hyperendemic or epidemic disease; or (3) who are present during outbreaks caused by a vaccine serogroup, administer 2 primary doses of MCV4-D, ideally at ages 9 months and 12 months or at least 8 weeks apart.
• For children aged 24 months and older with (1) persistent complement component deficiency who have not been previously vaccinated; or (2) anatomic/functional asplenia, administer 2 primary doses of either MCV4 at least 8 weeks apart.
• For children with anatomic/functional asplenia, if MCV4-D (Menactra) is used, administer at a minimum age of 2 years and at least 4 weeks after completion of all PCV doses.
• See *MMWR* 2011; 60:72–76, available at http://www.cdc.gov/mmwr/pdf/wk/mm6003. pdf, and Vaccines for Children Program resolution No.6/11-1, available at http://www. cdc.gov/vaccines/programs/vfc/downloads/resolutions/06-11mening-mcv.pdf, and *MMWR* 2011; 60:1391–1392, available at http://www.cdc.gov/mmwr/pdf/wk/mm6040. pdf, for further guidance, including revaccination guidelines.

## CATCH-UP SCHEDULE

| Persons aged 4 months through 6 years | | | | | |
|---|---|---|---|---|---|
| Vaccine | Minimum Age for Dose 1 | Minimum Interval Between Doses | | | |
| | | Dose 1 to dose 2 | Dose 2 to dose 3 | Dose 3 to dose 4 | Dose 4 to dose 5 |
| Hepatitis B | Birth | 4 weeks | 8 weeks<br>and at least 16 weeks after first dose; minimum age for the final dose is 24 weeks | | |
| Rotavirus[1] | 6 weeks | 4 weeks | 4 weeks[1] | | |
| Diphtheria, tetanus, pertussis[2] | 6 weeks | 4 weeks | 4 weeks | 6 months | 6 months[2] |
| *Haemophilus influenzae* type b[3] | 6 weeks | 4 weeks<br>if first dose administered at younger than age 12 months<br>8 weeks (as final dose)<br>if first dose administered at age 12–14 months<br>No further doses needed<br>if first dose administered at age 15 months or older | 4 weeks[3]<br>if current age is younger than 12 months<br>8 weeks (as final dose)[3]<br>if current age is 12 months or older and first dose administered at younger than age 12 months and second dose administered at younger than 15 months<br>No further doses needed<br>if previous dose administered at age 15 months or older | 8 weeks (as final dose)<br>This dose only necessary for children aged 12 months through 59 months who received 3 doses before age 12 months | |
| Pneumococcal[4] | 6 weeks | 4 weeks<br>if first dose administered at younger than age 12 months<br>8 weeks (as final dose for healthy children)<br>if first dose administered at age 12 months or older or current age 24 through 59 months<br>No further doses needed<br>for healthy children if first dose administered at age 24 months or older | 4 weeks<br>if current age is younger than 12 months<br>8 weeks (as final dose for healthy children)<br>if current age is 12 months or older<br>No further doses needed<br>for healthy children if previous dose administered at age 24 months or older | 8 weeks (as final dose)<br>This dose only necessary for children aged 12 months through 59 months who received 3 doses before age 12 months or for children at high risk who received 3 doses at any age | |
| Inactivated poliovirus[5] | 6 weeks | 4 weeks | 4 weeks | 6 months[5]<br>minimum age 4 years for final dose | |
| Meningococcal[6] | 9 months | 8 weeks[6] | | | |
| Measles, mumps, rubella[7] | 12 months | 4 weeks | | | |
| Varicella[8] | 12 months | 3 months | | | |
| Hepatitis A | 12 months | 6 months | | | |
| **Persons aged 7 through 18 years** | | | | | |
| Tetanus, diphtheria/ tetanus, diphtheria, pertussis[9] | 7 years[9] | 4 weeks | 4 weeks<br>if first dose administered at younger than age 12 months<br>6 months<br>if first dose administered at 12 months or older | 6 months<br>if first dose administered at younger than age 12 months | |
| Human papillomavirus[10] | 9 years | Routine dosing intervals are recommended[10] | | | |
| Hepatitis A | 12 months | 6 months | | | |
| Hepatitis B | Birth | 4 weeks | 8 weeks<br>(and at least 16 weeks after first dose) | | |
| Inactivated poliovirus[5] | 6 weeks | 4 weeks | 4 weeks[5] | 6 months[5] | |
| Meningococcal[6] | 9 months | 8 weeks[6] | | | |
| Measles, mumps, rubella[7] | 12 months | 4 weeks | | | |
| Varicella[8] | 12 months | 3 months<br>if person is younger than age 13 years<br>4 weeks<br>if person is aged 13 years or older | | | |

**FIGURE A-2** Catch-up immunization schedule for persons aged 4 months through 18 years who start late or who are more than 1 month behind-United States, 2012. The figure provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses.

SOURCE: CDC. 2012. *Immunization schedules.* http://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html.

**1. Rotavirus (RV) vaccines (RV-1 [Rotarix] and RV-5 [Rota Teq]).**
• The maximum age for the first dose in the series is 14 weeks, 6 days; and 8 months, 0 days for the final dose in the series. Vaccination should not be initiated for infants aged 15 weeks, 0 days or older.
• If RV-1 was administered for the first and second doses, a third dose is not indicated.
**2. Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine.**
• The fifth dose is not necessary if the fourth dose was administered at age 4 years or older.
**3. *Haemophilus influenzae* type b (Hib) conjugate vaccine.**
• Hib vaccine should be considered for unvaccinated persons aged 5 years or older who have sickle cell disease, leukemia, human immunodeficiency virus (HIV) infection, or anatomic/functional asplenia.
• If the first 2 doses were PRP-OMP (PedvaxHIB or Comvax) and were administered at age 11 months or younger, the third (and final) dose should be administered at age 12 through 15 months and at least 8 weeks after the second dose.
• If the first dose was administered at age 7 through 11 months, administer the second dose at least 4 weeks later and a final dose at age 12 through 15 months.
**4. Pneumococcal vaccines.** (Minimum age: 6 weeks for pneumococcal conjugate vaccine [PCV]; 2 years for pneumococcal polysaccharide vaccine [PPSV])
• For children aged 24 through 71 months with underlying medical conditions, administer 1 dose of PCV if 3 doses of PCV were received previously, or administer 2 doses of PCV at least 8 weeks apart if fewer than 3 doses of PCV were received previously.
• A single dose of PCV may be administered to certain children aged 6 through 18 years with underlying medical conditions. See age-specific schedules for details.
• Administer PPSV to children aged 2 years or older with certain underlying medical conditions. See *MMWR* 2010:59(No. RR-11), available at http://www.cdc.gov/mmwr/pdf/rr/rr5911.pdf.
**5. Inactivated poliovirus vaccine (IPV).**
• A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months after the previous dose.
• In the first 6 months of life, minimum age and minimum intervals are only recommended if the person is at risk for imminent exposure to circulating poliovirus (i.e., travel to a polio-endemic region or during an outbreak).
• IPV is not routinely recommended for U.S. residents aged 18 years or older.
**6. Meningococcal conjugate vaccines, quadrivalent (MCV4).** (Minimum age: 9 months for Menactra [MCV4-D]; 2 years for Menveo [MCV4-CRM])
• See Figure 1 ("Recommended immunization schedule for persons aged 0 through 6 years") and Figure 2 ("Recommended immunization schedule for persons aged 7 through 18 years") for further guidance.
**7. Measles, mumps, and rubella (MMR) vaccine.**
• Administer the second dose routinely at age 4 through 6 years.
**8. Varicella (VAR) vaccine.**
• Administer the second dose routinely at age 4 through 6 years. If the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.
**9. Tetanus and diphtheria toxoids (Td) and tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccines.**
• For children aged 7 through 10 years who are not fully immunized with the childhood DTaP vaccine series, Tdap vaccine should be substituted for a single dose of Td vaccine in the catch-up series; if additional doses are needed, use Td vaccine. For these children, an adolescent Tdap vaccine dose should not be given.

• An inadvertent dose of DTaP vaccine administered to children aged 7 through 10 years can count as part of the catch-up series. This dose can count as the adolescent Tdap dose, or the child can later receive a Tdap booster dose at age 11-12 years.

**10. Human papillomavirus (HPV) vaccines (HPV4 [Gardasil] and HPV2 [Cervarix]).**

• Administer the vaccine series to females (either HPV2 or HPV4) and males (HPV4) at age 13 through 18 years if patient is not previously vaccinated.

• Use recommended routine dosing intervals for vaccine series catch-up; see Figure 2 ("Recommended immunization schedule for persons aged 7 through 18 years," http://www.cdc.gov/vaccines/schedules/downloads/child/7-18yrs-schedule-pr.pdf).

# Appendix B

# Glossary

**Acellular vaccine:** a vaccine containing partial cellular material as opposed to complete cells.*

**Adjuvant:** a substance (e.g., aluminum salt) that is added during production to increase the body's immune response to a vaccine.*

**Adverse event:** undesirable experiences occurring after immunization that may or may not be related to the vaccine.*

**Allergic rhinitis:** rhinitis (inflammation of the mucous membrane of the nose marked especially by rhinorrhea, nasal congestion and itching, and sneezing) caused by exposure to an allergen. ‡

**Allergy:** a condition in which the body has an exaggerated response to a substance (e.g. food or drug). Also known as hypersensitivity.*

**Anaphylaxis:** an immediate and severe allergic reaction to a substance. Symptoms of anaphylaxis include breathing difficulties, loss of consciousness and a drop in blood pressure. This condition can be fatal and requires immediate medical attention.*

**Antibody:** a protein found in the blood that is produced in response to foreign substances (e.g., bacteria or viruses) invading the body. Antibodies protect the body from disease by binding to these organisms and destroying them.*

**Antigens:** foreign substances (e.g., bacteria or viruses) in the body that are capable of causing disease. The presence of antigens in the body triggers an immune response, usually the production of antibodies.*

**Arthritis:** inflammation of joints due to infectious, metabolic, or constitutional causes. ‡

**Asperger syndrome:** a developmental disorder resembling autism that is characterized by impaired social interaction, by repetitive patterns of behavior and restricted interests, by normal language and cognitive development, and often by above average performance in a narrow field against a general background of deficient functioning—also called *Asperger's disorder.*‡

**Asthma:** a disorder that causes the airways of the lungs to swell and narrow, leading to wheezing, shortness of breath, chest tightness, and coughing.†

**Atopy:** a genetic disposition to develop an allergic reaction (as allergic rhinitis, asthma, or atopic dermatitis) and produce elevated levels of IgE upon exposure to an environmental antigen and especially one inhaled or ingested.‡

**Attention deficit disorder (ADD):** a syndrome of disordered learning and disruptive behavior that is not caused by any serious underlying physical or mental disorder and that has several subtypes characterized primarily by symptoms of inattentiveness or primarily by symptoms of hyperactivity and impulsive behavior (as in speaking out of turn) or by the significant expression of all three.‡

**Attenuated vaccine:** a vaccine in which live virus is weakened through chemical or physical processes in order to produce an immune response without causing the severe effects of the disease. Attenuated vaccines currently licensed in the United States include measles, mumps, rubella, polio, yellow fever and varicella. Also known as a *live vaccine*.*

**Autism:** a developmental disorder that appears in the first 3 years of life, and affects the brain's normal development of social and communication skills.†

**Autoimmune Diseases Disorder:** a condition that occurs when the immune system mistakenly attacks and destroys healthy body tissue. There are more than 80 different types of autoimmune disorders.†

**Bacille Calmette-Guérin (BCG):** an attenuated strain of tubercle bacillus developed by repeated culture on a medium containing bile and used in preparation of tuberculosis vaccines.‡

**Bias:** systematic deviation of results or inferences from truth; processes leading to such deviation. An error in the conception and design of a study—or in the collection, analysis, interpretation, reporting, publication, or review of data—leading to results or conclusions that are systematically (as opposed to randomly) different from the truth.Δ

**Case-control study:** the observational epidemiological study of persons with the disease (or another outcome variable) of interest and a suitable control group of persons without the disease (comparison group, reference group). The potential relationship of a suspected risk factor or an attribute to the disease is examined by comparing the diseased and nondiseased subjects with regard to how frequently the factor or attribute is present (or, if quantitative, the levels of the attribute) in each of the groups (diseased and nondiseased).Δ

**Cohort study:** the analytic epidemiological study in which subsets of a defined population can be identified who are, have been, or in the future may be exposed or not exposed, or exposed in different degrees, to a factor or factors hypothesized to influence the occurrence of a given disease or other outcome. The main feature of cohort study is observation of large numbers over a long period (commonly years), with comparison of incidence rates in groups that differ in exposure levels. The alternative terms for a cohort study (i.e., follow-up, longitudinal, and prospective study) describe an essential feature of the method, which is observation of the population for a sufficient number of person-years to generate reliable incidence or mortality rates in the population subsets. This generally implies study of a large population, study for a prolonged period (years), or both. The denominators used for analysis may be persons or person-time.Δ

**Community immunity:** a situation in which a sufficient proportion of a population is immune to an infectious disease (through vaccination and/or prior illness) to make its spread from person to person unlikely. Even individuals not vaccinated (such as newborns and those with chronic

illnesses) are offered some protection because the disease has little opportunity to spread within the community. Also known as herd immunity.*

**Confounding:** loosely, the distortion of a measure of the effect of an exposure on an outcome caused by the association of the exposure with other factors that influence the occurrence of the outcome. Confounding occurs when all or part of the apparent association between the exposure and outcome is in fact accounted for by other variables that affect the outcome and are not themselves affected by exposure.[Δ]

**Contraindication:** a condition in a recipient which is likely to result in a life-threatening problem if a vaccine were given.*

**Convulsion:** see Seizure.

**Cross-sectional study:** a study that examines the relationship between diseases (or other health-related characteristics) and other variables of interest as they exist in a defined population at one particular time. The presence or absence of disease and the presence or absence of the other variables (or, if they are quantitative, their level) are determined in each member of the study population or in a representative sample at one particular time. The relationship between a variable and the disease can be examined (1) in terms of the prevalence of disease in different population subgroups defined according to the presence or absence (or level) of the variables and (2) in terms of the presence or absence (or level) of the variables in the diseased versus the nondiseased. Note that disease prevalence rather than incidence is normally recorded in a cross-sectional study. The temporal sequence of cause and effect cannot necessarily be determined in a cross-sectional study.[Δ]

**Diabetes:** a chronic health condition where the body is unable to produce insulin and properly breakdown sugar (glucose) in the blood. Symptoms include hunger, thirst, excessive urination, dehydration and weight loss. The treatment of diabetes requires daily insulin injections, proper nutrition and regular exercise. Complications can include heart disease, stroke, neuropathy, poor circulation leading to loss of limbs, hearing impairment, vision problems and death.*

**Diphtheria:** a specific infectious disease due to the bacterium *Corynebacterium diphtheriae* and its highly potent toxin; marked by severe inflammation that can form a membranous coating, with formation of a thick fibrinous exudate, of the mucous membrane of the pharynx, the nose, and sometimes the tracheobronchial tree; the toxin produces degeneration in peripheral nerves, heart muscle, and other tissues, diphtheria had a high fatality rate, especially in children, but is now rare because of an effective vaccine.[Π]

**Ecological study:** a study in which the units of analysis are populations or groups of people rather than individuals. Conclusions of ecological studies may not apply to individuals; thus caution is needed to avoid the ecological fallacy. Ecological studies can reach valid causal inferences on causal relationships at the ecological level-i.e., on causal processes that occur at the group level of among groups. Ecological studies are necessary for decisions that affect entire groups.[Δ]

**Eczema:** an inflammatory condition of the skin characterized by redness, itching, and oozing vesicular lesions which become scaly, crusted, or hardened.[‡]

**Encephalopathy:** a general term describing brain dysfunction. Examples include encephalitis, meningitis, seizures, and head trauma.*

**Epilepsy:** any of various disorders marked by abnormal electrical discharges in the brain and typically manifested by sudden brief episodes of altered or diminished consciousness, involuntary movements, or convulsions.‡

**Febrile seizures:** a febrile seizure is a convulsion in a child triggered by a fever. Febrile seizures occur most often in otherwise healthy children between ages 9 months and 5 years. Toddlers are most commonly affected. Febrile seizures often run in families. Most febrile seizures occur in the first 24 hours of an illness and may not occur when the fever is highest. Ear infections or any cold or viral illness may trigger a febrile seizure.†

**Guillain-Barré syndrome (GBS):** an acute, immune-mediated disorder of peripheral nerves, spinal roots, and cranial nerves, commonly presenting as a rapidly progressive, areflexive, relatively symmetric ascending weakness of the limb, truncal, respiratory, pharyngeal, and facial musculature, with variable sensory and autonomic dysfunction; typically reaches its nadir within 2–3 weeks, followed initially by a plateau period of similar duration, and then subsequently by gradual but complete recovery in most cases.Π

**Haemophilus influenzae type b (Hib):** a bacterial infection that may result in severe respiratory infections, including pneumonia, and other diseases such as meningitis.*

**Hepatitis:** inflammation of the liver, due usually to viral infection but sometimes to toxic agents.Π

**Hepatitis A:** a viral disease with a short incubation period (usually 15–50 days), caused by hepatitis A virus, a member of the family Picornaviridae, often transmitted by fecal-oral route; may be inapparent, mild, severe, or occasionally fatal and occurs sporadically or in epidemics, commonly in school-age children and young adults; necrosis of periportal liver cells with lymphocytic and plasma cell infiltration is characteristic, and jaundice is a common symptom.Π

**Hepatitis B:** a viral disease with a long incubation period (usually 50–160 days), caused by a hepatitis B virus, a DNA virus and member of the family Hepadnaviridae, usually transmitted by injection of infected blood or blood derivatives or by use of contaminated needles, lancets, or other instruments or by sexual transmission; clinically and pathologically similar to viral hepatitis type A, but there is no cross-protective immunity; $HB_sAg$ is found in the serum and the hepatitis delta virus occurs in some patients. May lead to acute or chronic liver disease.Π

**Human papillomavirus (HPV):** an icosahedral DNA virus, 55 nm in diameter, of the genus *Papillomavirus*, family Papovaviridae; certain types cause cutaneous and genital warts; other types are associated with severe cervical intraepithelial neoplasia and anogenital and laryngeal carcinomas.Π

**Immune thrombocytopenic purpura (ITP):** a systemic illness characterized by extensive ecchymoses and hemorrhages from mucous membranes and very low platelet counts; resulting from platelet destruction by macrophages due to an antiplatelet factor; childhood cases are usually brief and rarely present with intracranial hemorrhages, but adult cases are often recurrent and have a higher incidence of grave bleeding, especially intracranial. Also known as *idiopathic thrombocytopenic purpura*.Π

**Immunoglobulins:** see “antibody”

**Inactivated vaccine:** a vaccine made from viruses and bacteria that have been killed through physical or chemical processes. These killed organisms cannot cause disease.*

**Influenza:** an acute infectious respiratory disease, caused by influenza viruses, which are in the family Orthomyxoviridae, in which the inhaled virus attacks the respiratory epithelial cells of those susceptible and produces a catarrhal inflammation; characterized by sudden onset, chills, fever of short duration (3-4 days), severe prostration, headache, muscle aches, and a cough that usually is dry and may be followed by secondary bacterial infections that can last up to 10 days.[Π]

**Live vaccine:** a vaccine in which live virus is weakened (attenuated) through chemical or physical processes in order to produce an immune response without causing the severe effects of the disease. Attenuated vaccines currently licensed in the United States include measles, mumps, rubella, shingles (herpes zoster), varicella, and yellow fever. Also known as an attenuated vaccine.*

**Measles:** an acute exanthematous disease, caused by measles virus (genus Morbillivirus), a member of the family Paramyxoviridae, and marked by fever and other constitutional disturbances, a catarrhal inflammation of the respiratory mucous membranes, and a generalized dusky red maculopapular eruption; the eruption occurs early on the buccal mucous membrane in the form of Koplik spots, a manifestation useful in early diagnosis; average incubation period is from 10-12 days.[Π]

**Meningitis:** inflammation of the membranes of the brain or spinal cord.[Π]

**Mumps:** an acute infectious and contagious disease caused by a mumps virus of the genus Rubulavirus and characterized by fever, inflammation and swelling of the parotid gland, and sometimes of other salivary glands, and occasionally by inflammation of the testis, ovary, pancreas, or meninges.[Π]

**Myoclonus:** irregular involuntary contraction of a muscle usually resulting from functional disorder of controlling motor neurons.‡

**Nested case-control study:** an important type of case-control study in which cases and controls are drawn from the population in a fully enumerated cohort. Typically, some data on some variables are already available about both cases and controls; thus concerns about differential (biased) misclassification of these variables can be reduced (e.g., environmental or nutritional exposures may be analyzed in blood from cases and controls collected and stored years before disease onset). A set of controls is selected from subjects (i.e., noncases) at risk of developing the outcome of interest at the time of occurrence of each case that arises in the cohort.[Δ]

**Observational study:** a study that does not involve any intervention (experimental or otherwise) on the part of the investigator. A study with random allocation is inherently experimental or nonobservational. Observations are not just a haphazard collection of facts; in their own way, observational studies must apply the same rigor as experiments. Many important epidemiological, clinical, and microbiological studies are completely observational or have large observational components.[Δ]

**Otitis Media:** a viral or bacterial infection that leads to inflammation of the middle ear. This condition usually occurs along with an upper respiratory infection. Symptoms include earache, high fever, nausea, vomiting and diarrhea. In addition, hearing loss, facial paralysis and meningitis may result.*

**Pertussis:** an acute infectious inflammation of the larynx, trachea, and bronchi caused by Bordetella pertussis; characterized by recurrent bouts of spasmodic coughing that continues until

the breath is exhausted, then ending in a noisy inspiratory stridor (the "whoop") caused by laryngeal spasm.[Π]

**Pneumonia:** inflammation of the lung parenchyma characterized by consolidation of the affected part, the alveolar air spaces being filled with exudate, inflammatory cells, and fibrin.[Π]

**Poliomyelitis:** an acute infectious virus disease caused by the poliovirus, characterized by fever, motor paralysis, and atrophy of skeletal muscles often with permanent disability and deformity, and marked by inflammation of nerve cells in the ventral horns of the spinal cord—called also *infantile paralysis, polio.*[‡]

**Randomized controlled trial (RCT):** an epidemiological experiment in which subjects in a population are randomly allocated into groups, usually called study and control groups, to receive or not receive an experimental preventive or therapeutic procedure, maneuver, or intervention. The results are assessed by rigorous comparison of rates of disease, death, recovery, or other appropriate outcome in the study and control groups. RCTs are generally regarded as the most scientifically rigorous method of hypothesis testing available in epidemiology and medicine. Nonetheless, they may suffer serious lack of generalizability, due, for example, to the nonrepresentativeness of patients who are ethically and practically eligible, chosen, or consent to participate.[Δ]

**Retrospective study:** a research design used to test etiological hypotheses in which inferences about exposure to the putative causal factor(s) are derived from data relating to characteristics of the persons under study or to events or experiences in their past. The essential feature is that some of the persons under study have the disease or other outcome condition of interest, and their characteristics and past experiences are compared with those of other, unaffected persons. Persons who differ in the severity of the disease may also be compared. It is no longer considered a synonym for case-control study.[Δ]

**Rotavirus:** a group of viruses that cause diarrhea in children.*

**Rubella:** an acute but mild exanthematous disease caused by rubella virus (Rubivirus family Togaviridae), with enlargement of lymph nodes, but usually with little fever or constitutional reaction; a high incidence of birth defects in children results from maternal infection during the first trimester of fetal life (congenital rubella syndrome).[Π]

**Seizure:** a violent spasm or series of jerkings of the face, trunk, or extremities. Also known as convulsions.[Π]

**Self-controlled case series study:** the method, like the case-crossover method, uses cases as their own controls. However, the similarity stops there, as the case series method derives from cohort rather than case-control logic. In particular, ages at vaccination are regarded as fixed, and the random variable of interest is the age at adverse event, conditionally on its occurrence within a pre-determined observation period.[Φ]

**Socioeconomic status (SES):** descriptive term for a person's position in society, which may be expressed on an ordinal scale using such criteria as income, level of education attained, occupation, value of dwelling place, etc.[Δ]

**Stroke:** any acute clinical event, related to impairment of cerebral circulation, that lasts longer than 24 hours.[Π]

**Sudden death:** unexpected death that is instantaneous or occurs within minutes or hours from any cause other than violence.‡

**Surveillance:** systematic and continuous collection, analysis, and interpretation of data, closely integrated with the timely and coherent dissemination of the results and assessment to those who have the right to know so action can be taken. It is an essential feature of epidemiologic and public health practice. The final phase in the surveillance chain is the application of information to health promotion and to disease prevention and control. A surveillance system includes functional capacity for data collection, analysis, and dissemination linked to public health programs.[Δ]

**Tetanus:** a disease marked by painful tonic muscular contractions, caused by the neurotropic toxin (tetanospasmin) of *Clostridium tetani* acting upon the central nervous system.[Π]

**Thimerosal:** thimerosal is a mercury-containing preservative used in some vaccines and other products since the 1930's. There is no convincing evidence of harm caused by the low concentrations of thimerosal in vaccines, except for minor reactions like redness and swelling at the injection site. However, in July 1999, the Public Health Service agencies, the American Academy of Pediatrics, and vaccine manufacturers agreed that thimerosal should be reduced or eliminated in vaccines as a precautionary measure. Today, all routinely recommended childhood vaccines manufactured for the U.S. market contain either no thimerosal or only trace amounts with the exception of some flu vaccines. There are thimerosal-free influenza vaccines available.*

**Thrombocytopenia:** a condition in which an abnormally small number of platelets is present in the circulating blood.[Π]

**Toxoid vaccines:** toxoid vaccines contain a toxin or chemical made by the bacteria or virus. They make you immune to the harmful effects of the infection, instead of to the infection itself. Examples are the diphtheria and tetanus vaccines.[†]

**Type 1 diabetes:** diabetes of a form that usually develops during childhood or adolescence and is characterized by a severe deficiency of insulin secretion resulting from atrophy of the islets of Langerhans and causing hyperglycemia and a marked tendency toward ketoacidosis—called also *insulin-dependent diabetes, insulin-dependent diabetes mellitus, juvenile diabetes, juvenile-onset diabetes, type 1 diabetes mellitus.*‡

**Vaccine:** immunobiological substance used for active immunization by introducing into the body a live modified, attenuated, or killed inactivated infectious organism or its toxin. The vaccine is capable of stimulating an immune response by the host, who is thus rendered resistant to infection. The word *vaccine* was originally applied to the serum from a cow infected with vaccinia virus (cowpox; from Latin *vacca*, "cow"); it is now used of all immunizing agents.[Δ]

**Vaccine Adverse Event Reporting System (VAERS):** a database managed by the Centers for Disease Control and Prevention and the Food and Drug Administration. VAERS provides a mechanism for the collection and analysis of adverse events associated with vaccines currently licensed in the United States. Reports to VAERS can be made by the vaccine manufacturer, recipient, their parent/guardian, or health care provider. For more information on VAERS call (800) 822-7967.*

**Vaccine Safety Datalink Project (VSD):** to increase knowledge about vaccine adverse events, the Centers for Disease Control and Prevention have formed partnerships with nine large health management organizations (HMOs) to continually evaluate vaccine safety. The project contains

data on more than 9 million people. Medical records are monitored for potential adverse events following immunization. The VSD project allows for planned vaccine safety studies as well as timely investigations of hypotheses.*

**Vaccination:** injection of a killed or weakened infectious organism in order to prevent the disease.*

**Varicella:** an acute contagious disease, usually occurring in children, caused by the Varicella-zoster virus genus, Varicellovirus, a member of the family Herpesviridae, and marked by a sparse eruption of papules, which become vesicles and then pustules, like that of smallpox although less severe and varying in stages, usually with mild constitutional symptoms; incubation period is about 14-17 days.[Π]

SOURCES:

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# Appendix C

# Acronyms

| | |
|---|---|
| AAFP | American Academy of Family Physicians |
| AAP | American Academy of Pediatrics |
| ACIP | Advisory Committee on Immunization Practices |
| BCG | bacillus Calmette-Guérin |
| CDC | Centers for Disease Control and Prevention |
| CISA | Clinical Immunization Safety Assessment |
| CMS | Centers for Medicare & Medicaid Services |
| CPRD | Clinical Practice Research Datalink (United Kingdom) |
| CRS | Danish Civil Registration System |
| DT | diphtheria and tetanus toxoids absorbed |
| DTaP/DTP | diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed |
| EHR | electronic health record |
| EMR | electronic medical record |
| FDA | Food and Drug Administration |
| GPRD | General Practice Research Database (United Kingdom) |
| GRADE | Grading of Recommendations Assessment, Development, and Evaluation |
| HCUP | Healthcare Cost and Utilization Project |
| HES | Hospital Episode Statistics |
| HHS | U.S. Department of Health and Human Services |
| Hib | *Haemophilus influenzae* type B conjugate vaccine |
| HPA | Health Protection Agency |
| IgM | immunoglobulin M |
| IIS | immunization information systems |
| IMPACT | Immunization Monitoring Program, Active (Canada) |

| | |
|---|---|
| IND | Investigational New Drug |
| IOM | Institute of Medicine |
| IPV | inactivated poliovirus vaccine |
| ITP | immune thrombocytopenic purpura |
| KID | Kids' Inpatient Database |
| MeSH | medical subject headings |
| MMR | measles, mumps, and rubella vaccine |
| MMRV | measles, mumps, rubella, and varicella (chickenpox) vaccine |
| MMWR | *Morbidity and Mortality Weekly Reports* |
| NCS | National Children's Study |
| NHIS | National Health Interview Survey |
| NHS | National Health Service (United Kingdom) |
| NIS | National Immunization Survey |
| NVAC | National Vaccine Advisory Committee |
| NVPO | National Vaccine Program Office |
| OPV | oral poliovirus vaccine |
| PCV7 | pneumococcal conjugate vaccine (7-valent) |
| PCV13 | Pneumococcal conjugate vaccine (13-valent) |
| PDD | pervasive developmental disorder |
| PRISM | Post-Licensure Rapid Immunization Safety Monitoring |
| RCT | randomized controlled trial |
| TIV | Trivalent inactivated influenza vaccine |
| VAERS | Vaccine Adverse Event Reporting System |
| VAESCO | Vaccine Adverse Event Surveillance and Communication Network |
| VICP | Vaccine Injury Compensation Program |
| VSD | Vaccine Safety Datalink |
| WHO | World Health Organization |
| WISC-III | Wechsler Intelligence Scale for Children III |

# Appendix D

# Study Designs for the Safety Evaluation of Different Childhood Immunization Schedules

*Martin Kulldorff*[1]

**SUMMARY**

To date, there have been few comparative studies evaluating the safety of different vaccine schedules. A few of the existing studies have shown that there are cases in which the risk of adverse events can depend on the vaccination schedule used. Hence, it is both a feasible and important area of study. As a relatively new field of investigation, the big question is what types of study designs will be most fruitful for evaluating different childhood vaccine schedules. A number of possible study designs are presented in this review to evaluate different features or components of the vaccine schedule. These include the timing of individual vaccines, the timing between doses of the same vaccine, the interaction effect between vaccines and concurrent health conditions or pharmaceutical medications, the interaction effects of different vaccines given on the same day, the ordering of different vaccines, and the effect of cumulative summary metrics such as the total number of vaccines or the total amount of some vaccine ingredient. Study designs for the comparative evaluation of one or more complete schedules are also considered. Methods are presented both for adverse events with an

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early onset, which are the easiest to study, and for adverse events with a late onset, including serious chronic conditions. It is concluded that a wide variety of different vaccine schedule components can be studied.

## INTRODUCTION

Before approval by the Food and Drug Administration (FDA), vaccines are evaluated for efficacy and safety using large Phase III randomized controlled trials. For childhood vaccines, the number of children enrolled in these trials is typically in the thousands. That is sufficient to detect common but not rare adverse events. For the latter, there exist several postmarketing vaccine safety surveillance systems using observational data on children who receive the vaccines as part of their general care. In the United States, these include the Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD), and the Clinical Immunization Safety Assessment Network, all sponsored by the Centers for Disease Control and Prevention (CDC), as well as the Post-licensure Rapid Immunization Safety Monitoring System (PRISM), which is part of the FDA-sponsored Mini-Sentinel Initiative. Internationally, there are other important vaccine safety surveillance systems such as the Epidemiology Vaccine Research Program at the National Institute for Health Data and Disease Control in Denmark; the Vaccine Adverse Event Surveillance and Communication Network (VAESCO), coordinated by the European Center for Disease Control; the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring ; and the Immunization Division at the Communicable Disease Surveillance Centre in England. All these vaccine safety systems have proven to be very useful and important. They have detected unsuspected adverse events leading to revisions in vaccine recommendations and, in other cases, established the safety of vaccines for which important safety concerns existed. Throughout their existence, there has been continuous and rapid development with respect to the types of questions studied and the epidemiological and statistical methods used. For example, for every new childhood vaccine approved by the FDA, VSD now conducts near real-time safety surveillance using weekly data feeds from electronic health records (Lieu et al., 2007; Yih et al., 2011). The credit for these continuously improved vaccine safety surveillance systems goes both to the devoted scientists that are building the systems and using them for many important studies, to the government agencies supporting this work, and to the vaccine safety advocacy groups that are the key public voice for improved and expanded vaccine safety surveillance.

Most postmarketing studies evaluate the general question as to whether or not a vaccine causes an adverse event. Very few postmarketing studies have evaluated whether the risk of adverse events depends on the scheduling of the vaccines. For example, few postmarketing studies have evaluated whether the risk of adverse events depends on the age at which a vaccine is given, on the relative timing of two different vaccines, or on a combined cumulative effect generated by the timing of dozens of different vaccines. These are all different components of the vaccine schedule, and any one of these could potentially be related to the number and severity of adverse events. When evaluating the safety of different vaccine schedules, it is hence important to study the whole range of

issues, from the timing of a single vaccine to summary metrics based on the timing of dozens of vaccines.

The paper presented in this appendix was commissioned by the Institute of Medicine Committee on the Assessment of Studies of Health Outcomes Related to the Recommended Childhood Immunization Schedule. The paper considers different types of potential questions and concerns about the safety of vaccine schedules and describes different epidemiological study designs and statistical methods that can be used to answer such questions in a scientifically rigorous manner. The core of this paper is a set of proposals for the type of study designs and methods that would be appropriate for the comparative evaluation of vaccine adverse events under different vaccine schedules, and the paper is written in the context of the many difficulties raised by the speakers at the committee meetings held in February and March of 2012. Note, though, that it is neither a synthesis, an evaluation, nor a review of the many excellent presentations made at those meetings. Instead, it should be viewed as complementary information. Note also that the paper does not say anything about the advantages or disadvantages about specific vaccines or vaccine schedules. Rather, the focus is on potential study designs and methods and their ability, or inability, to answer such questions.

## DEFINITIONS OF KEY TERMS

*Component of the vaccine schedule:* some specific feature of the vaccine schedule, such as the age at which one of the vaccines is given or the total amount of immune-stimulating content received from all vaccines in the schedule. Not to be confused with different components of a single vaccine.

*Early onset*: an adverse event that manifests itself and can be detected within a few weeks after vaccination.

*Late onset*: an adverse event that does not manifest itself and/or cannot be detected until a few months or years after vaccination.

*Potential adverse event*: a health event under evaluation in a vaccine safety study, in order to determine if it is caused by the vaccine(s) or not.

## VACCINE SCHEDULES, ADVERSE EVENTS, AND DATA SETS

### Vaccine Schedules and Their Components

To study the safety of different childhood vaccine schedules is an important but complex task. With dozens of vaccines, many of which have multiple doses, there are an almost infinite number of possible vaccine schedules that can be used. To scientifically evaluate the safety of different vaccine schedules, it is necessary to look at specific components of the schedule. Some such components are as follows:

*Timing of Specific Vaccines*

- The age at which a specific vaccine is given, such as the age at the first dose of the hepatitis B vaccine.
- The relative timing of different doses of the same vaccine, such as the number of months between the first and second doses of the 7-valent pneumococcal conjugate vaccine (PCV7).
- The interaction between the timing of a specific vaccine and time-varying health events or health status, such as a vaccination given to a child taking a temporary or seasonal medication.

*Relative Timing of Two or More Different Vaccines*

- The interaction between different vaccines given on the same day, such as the effect of giving the measles, mumps, and rubella (MMR) vaccine and varicella vaccines at the same health care visit or different health care visits.
- The order in which different vaccines are given, such as whether measles vaccine is given a few months before or after the diphtheria-tetanus-pertussis vaccine (DTP).

*Summary Metrics of a Vaccine Schedule*

- The total number of vaccinations given to the child before a certain age, such as the sixth birthday.
- The average age at which the vaccines were given.
- The cumulative amount of immune-stimulating content present in all vaccines received.

In addition to specific components of the vaccine schedule, one can also try to compare complete vaccine schedules.

*Comparison of Complete Vaccine Schedules*

- Whether or not the child has approximately followed the CDC-recommended vaccine schedule.
- The comparative safety of a specific alternative vaccine schedule, such as Dr. Bob's (Sears, 2007), versus the one recommended by CDC.

The study design and statistical methods used depend on which vaccine schedule component is being evaluated. As they are quite different, each component of Components (a) to (e) is dealt with in separate sections of this paper. For cumulative summary metrics, the methods are similar irrespective of what component of the vaccine schedule the metric is designed to measure. Components (f) to (h) are treated together. Methods for comparing different complete vaccine schedules are discussed, and one vaccine schedule with completely unvaccinated children is evaluated. More general methodological issues and financial and ethical considerations are also discussed.

The different types of studies should not be done in isolation from each other. If it is found that one complete vaccine schedule has an excess number of adverse events compared to another, we do not know which component of the schedule caused the difference. Hence, it is not recommended that studies comparing complete schedules be conducted without also evaluating specific components of those schedules. Likewise, when a specific component is studied, results may be confounded by other components of the vaccine schedule. For example, a child receiving vaccine A at an early age may be more likely to also receive vaccine B at an early age, and the timing of vaccine A will then be correlated with the number of adverse events even if it is the timing of vaccine B that is the culprit. It could also be that there are two different vaccine schedule components that cause adverse events but that they cancel each other out when one looks at the difference between two complete schedules, making it impossible to detect the problem if only the complete schedules are studied.

Another reason for studying specific components of the vaccine schedule is that, if a problem is found, we need to know how to revise the schedule in order to reduce the number of adverse events. Just because one complete vaccine schedule is found to cause more adverse events than another, we do not necessarily have to revise all components of that schedule.

## Adverse Events with Early Versus Late Onset

In vaccine safety studies, the goal is to evaluate if there is a causal relationship between the vaccine(s) and some health event of interest. The latter is denoted as a potential adverse event, as it may or may not be an actual adverse event caused by the vaccine(s). The type of health event under study determines the appropriate methodological methods for vaccine safety studies. This paper considers two main types. The first type consists of potential adverse events with an early onset that can be detected soon after the onset. The event itself could be either acute and of a passing nature without any permanent damage, such as a febrile seizure, or chronic, lasting many years, such as a stroke. The second type consists of potential adverse events with a late onset several months or years after vaccination and events with an early or a gradual onset that cannot be detected until long after vaccination. For simplicity, all of these are denoted ”late onset.” These potential adverse events can also be either acute or chronic in nature.

The most suitable study designs and analysis methods are greatly dependent on whether the potential adverse event has an early or late onset, and in the description below, separate methods are proposed for the two outcome types. This is a little bit of a simplification, since there are, of course, also potential adverse events that fall somewhere in between on this spectrum. It should also be pointed out that an early-onset chronic condition can be studied by use of either of the methods described for early or late onset, but the early-onset methods are in most cases preferable.

Another key issue is whether there is a clear time at which the potential adverse event happened, as with, for example, a seizure, or whether the disease evolves more gradually, without a single clearly defined day of onset, as with, for example, narcolepsy or autism. This does not affect the study design as much as the time of onset, but it is an important consideration when defining and collecting the data.

For most potential adverse events, we are interested only in incident diagnoses, that is, the first time that a particular diagnosis has been made. For example, if a child is diagnosed with asthma at age 2 years and then has a follow-up visit for his/her asthma at age 4 years, we do not want to attribute the asthma to a vaccination given at age 3 years. Depending on the potential adverse event under study, one can define an incident diagnosis as a diagnosis that has not occurred during the previous *D* days. The value of *D* will depend on the adverse event, but a typical value is about 1 year.

The potential adverse event studied either can be very specific, such as febrile seizures or autism, or can be more general, such as all-cause outpatient physician visits, emergency department visits, or hospitalizations. The latter set of events may seem more desirable, as it includes the combined effect of the vaccine schedule on all important health events, but the opposite is true. Such general definitions are more prone to biases, and they are therefore more difficult to study. This is because people that follow the CDC-recommended vaccine schedule may be different from those that do not, in terms of their health care-seeking behavior. For example, parents that are more prone to take their children to the doctor when the child is sick may also be more prone to take their children to the well care visits during which most vaccines are given.

## Data Sets for Postmarketing Vaccine Safety Studies

To facilitate the understanding of the study designs and methods described in subsequent sections, a brief background is first given concerning some of the data sets that are available and currently used for postmarketing vaccine safety studies.

### *Premarketing Randomized Trials*

Phase III randomized trials are primarily designed to evaluate the efficacy of vaccines. They are also able to find common adverse events, but their sample size is typically not large enough to evaluate rare but serious adverse events. Their primary use for postmarketing vaccine safety surveillance is to generate study hypotheses. For example, a single case of Kawasaki disease in the vaccine arm of a Phase III randomized trial is not evidence that the vaccine causes Kawasaki disease, since it could be pure coincidence, but it may warrant a postmarketing safety evaluation.

### *Spontaneous Reporting Systems*

Most countries in the world have a vaccine safety surveillance system based on spontaneous reports. These are linked together through the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden, so that it is possible to combine data from multiple countries. In the United States, CDC and FDA are joint sponsors of VAERS.

These systems contain spontaneous reports of suspected vaccine adverse events sent in by physicians, nurses, patients, parents, manufacturers, and others. The gender and age of the vaccinated person are some of the variables collected. There is often information about multiple vaccines given on the same day. Analyses are done by the use of proportional reporting ratios (Evans et al., 2001) and similar methods. For example, if 1.5 percent of all vaccine-related adverse event reports are for seizures and there are

1,000 reports for vaccine A, then we would expect 15 seizure reports for vaccine A. If, in reality, there are 45 such reports, the proportional reporting ratio is 3. That is more than what one would expect, and it may indicate that there is an excess risk of seizures after vaccination. Actual analyses are more complex, since it is necessary to adjust for age and other variables. There are also other more sophisticated methods used (Bate et al., 1998; DuMouchel, 1999; Rothman, 2006).

The major advantage of VAERS is that it receives reports from the whole country. The two major disadvantages are that there is underreporting and that there are no reliable denominator data. That is, while we have information about a number of vaccinated children with the potential adverse event of interest, we do not know the total number of children that were vaccinated, how many unvaccinated children had the same type of event, or how many vaccinated children had the event without it being reported.

Some reports to VAERS are studied further in the Clinical Immunization Safety Assessment Network. Among other things, this network aims to "improve the scientific understanding of vaccine safety at the individual patient level" by obtaining and evaluating detailed genetic and other information from each patient (LaRussa et al., 2011).

*Electronic Medical Records*

For 2011, it is estimated that 57 percent of office-based physicians used electronic medical records (EMRs), up from 24 percent in 2005 (Hsiao et al., 2011). The EMRs most useful for medical research are the ones from large health plans, as they contain medical records for a well-defined member population, including both inpatient and outpatient encounters. The VSD project is the premier EMR-based vaccine safety system in the United States (Baggs et al., 2011; Chen et al., 1997; DeStefano and the Vaccine Safety Datalink Research Group, 2001). Led by CDC, it is a collaboration with 10 health plans: Group Health in the State of Washington; Harvard Pilgrim/Atrius Health in Massachusetts; HealthPartners in Minnesota; Kaiser Permanente in Colorado, Georgia, Hawaii, Northern California, Oregon, and Southern California; and Marshfield Clinic in Wisconsin. Together, these health plans have about 9.5 million members and an annual birth cohort of more than 100,000. The VSD system is used both for retrospective studies and for near real-time vaccine safety surveillance with weekly analyses of newly approved vaccines. Similar systems exist in a few other countries, including the Epidemiology Vaccine Research Program at the National Institute for Health Data and Disease Control (Seruminstitutet) in Denmark.

The major advantage with EMR systems is that denominator data are available, as all vaccinated children can be identified. It is then possible to compare the number of adverse events in vaccinated and unvaccinated children or vaccine-exposed and unexposed time periods within the same child. A disadvantage is that the data are registered for purposes other than research, and there is sometimes miscoding of health events. Depending on the health outcome, manual chart review is therefore sometimes warranted.

*Health Insurance Claims Data*

Health insurance companies have medical information for millions of insured members and their families, which they receive when doctors and hospitals file their financial reimbursement claims. One such system in the United States is the PRISM program, run by FDA as part of its Mini-Sentinel project (Nguyen et al., 2012). Claims data are more limited than EMRs but can be used in much the same way for postmarketing vaccine safety studies. The major advantage is the large sample size that can be achieved. The major disadvantage is that some health conditions are not captured. Depending on the potential adverse event under study and the confounders that need to be adjusted for, this may or may not be a problem.

Because of their similarities, EMRs and health insurance claims data will be treated as the same type of data in this appendix under the name "health plan data."

*Study-Specific Data Collection*

Sometimes, new data are collected specifically for vaccine safety studies, such as a self-controlled case series, a case-control study, a cohort study, or a postmarketing randomized trial. An intermediate option is to obtain some of the data from health plans, disease registries, and/or vaccine registries, while the remaining data are collected from study-specific patient surveys or measurements. The available options are too many to provide a detailed description of each.

## TIMING OF SPECIFIC VACCINES

In a randomized childhood vaccine trial, the age at which the vaccine is given is tightly controlled by the study design, to correspond to the future planned vaccine schedule. This is appropriate, but once a vaccine is on the market, it is also given at a wide variety of other ages, for a variety of reasons. There are two scenarios in which it is of great interest to evaluate the risk of a vaccine as a function of the age at which the vaccine was given. (i) If a vaccine safety study has shown that there is a statistically significant excess risk of an adverse event, we want to know if the excess risk varies by the age at which the vaccine was given. (ii) Even if a general safety study covering all age groups has not shown a statistically significant excess risk of the adverse event, there could still be an excess risk if the vaccine is given at certain ages outside the recommended schedule. Such a safety problem could be masked by the noneffect among the most populous age group, and a special study looking at age-specific risks would be warranted.

### Known Adverse Events with Early Onset

*Background*

Some vaccines have been shown to cause an acute adverse event within a few weeks after vaccination. Examples include intussusception 3 to 7 days after vaccination with rotavirus vaccine (RotaShield) (Kramarz et al., 2001; Murphy et al., 2001) and febrile seizure 7 to 10 days after vaccination with MMR and the measles, mumps, and rubella-varicella (MMRV) vaccine (Klein et al., 2010). There are also several such

examples of less severe adverse events like fever and rash. The adverse event may be serious enough to warrant the withdrawal of the vaccine from the market, as with the rotavirus vaccine, or it may be mild enough to keep using the vaccine, as with MMR. A midlevel alternative option is to revise the vaccination schedule to minimize the number of adverse events or to contraindicate the vaccine in a certain age group. Knowledge of the relative and attributable risk of the adverse event as a function of age is one important component when deciding between these options, together with other important factors, such as how the immunogenicity varies by age. This paper discusses only methods for obtaining knowledge about the former and not how to weight different sources of information to arrive at a final decision.

*Examples*

In two different studies, Gargiullo et al. (2006) and Rothman et al. (2006) evaluated the effect of age on the excess risk of intussusceptions after vaccination with the rotavirus vaccine (RotaShield). In a more recent study, Rowhani-Rahbar et al. (2012) evaluated the effect of age on the risk of febrile seizures after vaccinations with MMR and MMRV. All three studies found that the risk of the adverse event varied greatly by age.

*Data*

EMRs from health plans and health insurance claims from health plans are ideally suited for studying this question. It is also possible to use data from a case-control study. VAERS data cannot easily be used since VAERS does not contain information about the age distribution of vaccinated children. Too few data are available from premarketing randomized because such trials are too small and typically do not include individuals over a wide enough range of ages. In light of existing observational data, specifically designed postmarketing randomized trials could be unethical, depending on the nature of the known adverse event.

*Methods*

The first key step is to determine the time between the vaccination and the adverse event as precisely as possible. Some children will, just by chance, have the adverse event soon after vaccination. To maximize the precision of our age estimates, we want to exclude as many of them as possible, by counting only the adverse events occurring in the true risk window. An efficient way to determine the appropriate risk window is to use a temporal scan statistic. For a cohort of vaccinees with a subsequent event of interest, record the number of days from vaccination to the event. Ignore events that occur on the same day as the vaccination, as they may have a different background rate, as well as those that occur beyond an upper limit, such as 70 days after vaccination. If there is no relationship between the vaccine and the adverse event, we expect the adverse events to be uniformly distributed during the [1,70]-day period. The temporal scan statistic scans the time period for any cluster of events, without any assumptions about their location or length. The method determines the statistical significance of such clusters, adjusting for the multiple testing inherent in the hundreds of overlapping time periods evaluated. As an example, temporal scan statistics were used to determine that

the excess risk of seizures after vaccination with MMRV is confined to the 7- to 10-day postvaccination period (Klein et al., 2010).

The second step is to evaluate the relationship between age at vaccination and excess risk of the adverse event. The simplest and most common way to do this is to divide age into different groups, such as 6 to 12 months and 12 to 24 months, and compare the risk. It is unrealistic to assume that the risk suddenly jumps at a particular age, and for greater precision, it is better to model risk as a continuous function of age. This can be done by the use of either regression with first-, second-, and higher-degree polynomials or regression splines (Rothman et al., 2006).

In these analyses, it is important to take the underlying natural age-related risk into account. For example, the incidence of intussusceptions is very low immediately after birth, after which it gradually increases until about 5 months of age, after which it gradually decreases (Eng et al., 2012). There are a number of possible ways to adjust for this, depending on the exact study design. In a cohort study of vaccinated individuals, one can use historical data to estimate the age curve, using a polynomial function, and then use that as an offset term in the regression model. An alternative approach is to use both a risk and control interval for each individual, in a self-controlled analysis, evaluating whether the relative risk in these intervals varies by age of vaccination. Note, though, that if the natural incidence rate for the adverse event varies greatly by age in weeks rather than years, it is still necessary to incorporate an offset term based on the natural age curve even when a self-controlled analysis is conducted. In a case-control study, matching by age ensures that the age-based incidence curve is adjusted for.

### Vaccine Risk for Specific Age Groups: Early-Onset Adverse Events

*Background*

Most childhood vaccines are given according to the recommended schedule, but some children may get the vaccine at a much earlier or a much later age. There are many potential reasons for this, including a high risk of exposure due to a current disease outbreak or because family members have the disease, or due to missed well care visits, shortages of the vaccine, parental or physician concerns about the recommended vaccine schedule, misunderstanding of the recommended schedule, or medical errors, etc. As an example, while the first dose of MMR is recommended at age 12 to 15 months, in one health plan, 22 percent of children were recorded to have received it later and 0.7 percent to have received it before their first birthday, with 0.3 percent receiving it before 6 months of age. Nationwide, even half a percent adds up to a fairly large number, and it is important to evaluate the safety of the vaccine for those children, so that a contraindication warning can be issued if there is a major safety problem.

*Example*

After the 2004 recommendation to give influenza vaccines to 6- to 23-month-old children, Hambidge et al. (2006) used data from VSD to conduct an influenza vaccine safety study specific to this age group, looking at a wide variety of potential adverse events.

*Data*

Health plan data capture all vaccinations at whatever age they occurred, so such data are useful not only for evaluating the safety of vaccines in special age groups but also for characterizing the real-world age distribution of vaccinated children.

With its national coverage, VAERS data can also be used to monitor vaccine safety in specific age groups. While no denominator data are directly available, a large number of adverse event reports in children outside the recommended age range could be the first indication that an age-specific problem exists.

If a change in the recommended age that a vaccine should be given is anticipated, a randomized trial may be warranted. For that to occur, there needs to be some uncertainty as to whether the currently recommended time is safe and some evidence, based on, for example, observational data, that an alternative age is safer. If the question is simply whether the vaccine should be contraindicated for certain age groups or whether the vaccine is also safe outside the recommended age of vaccination, without any evidence of harm at the recommended age, then a randomized trial would not be ethical.

*Methods*

For health plan data, there are a few different analysis options. For early-onset events, a self-controlled risk interval design can be used. First, decide on a risk window, such as 1 to 21 days after vaccination, and a control window, such as 22 to 42 days after vaccination. For each vaccinated child in the age group of interest, count how many of them had an adverse event in the risk and control windows, respectively. Suppose that the two windows are of the same length and that there are a total of $n$ adverse events in the two windows combined. The number of adverse events in the risk window then has a binomial distribution with parameters $n$ and $p = ½$.

Since this is a self-controlled analysis, it is only time-varying confounders that may need to be adjusted for, and there is no need to worry about gender, genetics, stable environmental factors, study site, etc. For some adverse events where the incidence rate changes rapidly from one week of age to the next, an age adjustment must be made. If the age distribution of the disease is know, this can easily be done by use of an offset term in a logistic regression model. The same is true if there are strong seasonal trends in the incidence rate. An alternative way to adjust for seasonality is to use a case-centered approach, as proposed by Fireman et al. (2009).

The choice of risk and control windows depends on the vaccine and the adverse event. Sometimes, it is worthwhile to have a washout period between the two windows. To avoid day-of-week effects, the two windows should have the same number of days in any modulus of seven. For example, the risk window may be 1 to 14 days and the control window 22 to 70 days or the risk window may be 1 to 2 days and the control window days 8 to 9 together with days 15 to 16. Theoretically, it is also possible to use a comparison window before vaccination, but that can introduce confounding by indication or contraindication.

In VAERS data, the age of the vaccinated child is one of the variables collected. To evaluate whether a vaccine is safe outside the recommended schedule, it is hence possible to look at specific predefined age groups. This can be done by the same methods

that are used for all age groups combined, such as proportional reporting ratios (Evans et al., 2001).

## TIME BETWEEN VACCINE DOSES

### Background

Almost all childhood vaccines are given in multiple doses a few months or years apart. It is conceivable that the length of the time interval between vaccine doses could increase or decrease the risk of adverse events.

### Example

Using a randomized trial, Pitman (2002) showed that the risk of adverse events was reduced if the second dose of subcutaneous anthrax vaccine, adsorbed, is given 4 months rather than 2 weeks after the first dose.

### Early-Onset Adverse Events

*Data*

The use of electronic health data is suitable for vaccine doses that are at most a few years apart. If the time between doses is too long, health plan data are less suitable, as only some members will have been enrolled long enough to have information about all the doses of interest.

*Methods*

For simplicity's sake, first consider the situation where we want to evaluate the length of the time interval between the first two doses of the vaccine with respect to early-onset adverse events after the second dose. First, identify a cohort of children who received the first two doses of the vaccine. Exclude children that do not have a sufficiently long enrollment in the health plan to ensure that these are truly the first two doses. Note the number of days between the doses and whether they had an adverse event during a prespecified risk window after the second dose. For the statistical analysis, use logistic regression. The dependent variable is whether the potential adverse event was present in the risk window or not. The independent variable of interest is the number of days between the two doses. Adjust for gender, age at the second dose, calendar year, seasonality, study site, and any other potential confounders by including these as additional independent variables.

When one is looking at early-onset adverse events after the third dose, the same methods can be used for evaluating the length between the first and third dose or between the second and third dose. A single logistic regression can be used to evaluate both the time from the first to the third dose and the time from the second to the third dose, by including both of them as two separate independent variables. The same applies for early-onset adverse events after subsequent doses.

If an excess risk is found, it is not clear from this design whether it is an excess risk due to the time length between the vaccinations or if there is an excess risk driven purely by the first dose and where the timing of the adverse event is such that it happens soon after the second dose in children that receive the second dose sooner. By estimating the temporal function of any excess risk due to dose number 1 alone, this can be adjusted for by including it either as an offset term or as an additional variable in the regression model, which then also may include children who never received dose two. An alternative, simpler approach is to limit the study to children where the doses are given at least *x* days apart, where *x* is chosen to be large enough that it is unlikely that there is any excess risk beyond that time that is purely due to the first dose.

If there is some evidence from the observational study that there is a differential risk depending on the time between vaccinations but it is not conclusive, then a randomized trial could be conducted. For example, in a study of a rotavirus vaccine, children may be randomized to receive the three doses at age 2, 4, and 6 months of age, according to the CDC-recommended vaccine schedule, plus a placebo dose at age 9 months, versus three doses at age 2, 6, and 9 months, plus a placebo dose at age 4 months. The results from the observational study, with its wide variety of schedules, can be used to inform the definition of the study arms in the randomized trial. Note, though, that if the adverse event is rare, a randomized trial is not a feasible approach, as the required sample size would be very large, and hence, the cost of the trial would be prohibitively expensive.

## Late-Onset Adverse Events

*Data*

The use of electronic health data is suitable for late-onset adverse events that occur within a few years after the last dose and for vaccines for which all doses of interest are given within a year or two. For late-onset events and longer times between doses, health plan data may be less suitable, as only some members will have been enrolled long enough to be informative.

*Methods*

The same methods used for early-onset events can be used for late-onset adverse events, with some modifications. Most importantly, rather than defining adverse events in terms of a predefined risk window after the last dose, it is more suitable to define them according to a predefined age range. For example, the study may include only children who had all the doses of interest before 18 months of age and would consider only adverse events for which the incident diagnosis occurred between ages 2 and 6 years. That will prevent bias due to age-varying incidence rates.

If suitable health plan data are not available, a case-control approach can be used instead. The first step is then to select children with an incident diagnosis during a predefined age range, together with a set of controls matched by age, gender, calendar month, study site, and other covariates of interest. The next, more challenging step is to obtain the vaccination history of each of the children. This could be done by contacting

all the health plans or all the pediatricians that the child has had. The dose interval length is then compared between those children with and without the adverse event.

## INTERACTION EFFECTS BETWEEN VACCINES AND HEALTH CONDITIONS

### Background

Several vaccines are contraindicated for children with specific health problems. For example, live attenuated influenza vaccine should not be given to 2- to 4-year-old children who have had wheezing during the past 12 months (CDC, 2012). This means that the vaccine schedule may have to be modified for some children on the basis of their personal disease history. To know if and when that is necessary, one needs to study the interaction effects between vaccines and preexisting health conditions.

The study of interaction effects between vaccines and health conditions is especially important when there is a known excess risk of an adverse event. If it is possible to pinpoint that the adverse events are due to an interaction effect, then the number of adverse events can be reduced by contraindicating the vaccine for children with the health condition in question. For example, if the risk of seizures after vaccination with MMR is higher among children with a recent well-defined disease episode, then MMR may potentially be postponed by 3 months for those children.

### Early-Onset Adverse Events

*Data*

Electronic health plan data are suitable for early-onset adverse events.

*Methods*

First consider the scenario in which there is a known increased risk of the adverse event in the population as a whole and we want to know if the excess risk is more severe among children in a specific group. By use of the temporal scan statistic, first determine the true risk window for the adverse event, as described above. Suppose that we have an excess risk in the 7 to 10 days after vaccination. We now define the study population as those who received the vaccine and who had an adverse event in some longer time period, such as 1 to 42 days after vaccination. In a logistic regression model, the dependent variable is whether they had the adverse event inside or outside the true risk window. The independent variables are the various health status variables that we want to examine as potential risk modifiers. Several of these can be included in the same logistic regression, but doing several univariate analyses may be a suitable first step. As long as the baseline risk for the adverse event is fairly constant over the longer time period, it is not necessary to adjust for age. Note that since all subjects had the vaccine and all subjects had the adverse event, there is no actual interaction term in the logistic regression model.

If we do not have a known adverse event but still want to evaluate possible vaccine-health status interaction terms, we can still use the same approach with a

reasonable guess of a wider risk interval. For example, the risk interval may be 1 to 42 days, while the comparison interval is 43 to 84 days.

### Late-Onset Adverse Events

The approach described above cannot be used to study late-onset adverse events. Instead, we first determine if a vaccinated child had the health condition of interest at the time of vaccination. We then compare the number of late-onset events between the children that did and those that did not. This design is more prone to bias than the self-controlled design described above. One way to partially adjust for this is to include only children that had both the vaccine and the potential adverse event of interest, at any time, and compare the children who had the vaccination at the same time as the health event with those that had them at different times.

## VACCINE-VACCINE INTERACTION

### Background

In the CDC-recommended vaccine schedule, many different vaccines are given on the same day. It is plausible that two vaccines, if given separately from each other, do not increase the risk of adverse events, but if they are given on the same day, there is a vaccine-vaccine interaction effect, leading to increased risk. It could also be that one or both of the vaccines, when given separately, lead to a modest excess risk of the adverse event but, when given together, lead to a much higher excess risk.

### Example

With data from VSD and separate self-controlled risk interval analyses, it was found that there was an increased risk of seizures 0 to 1 days after trivalent inactivated influenza vaccine (TIV) and also that there was an increased risk of seizures 0 to 1 days after the 13-valent pneumococcal conjugate vaccine (PCV13). To tease apart the effects from the two different vaccines and to evaluate the interaction between the two, the author of this paper suggested the approach mentioned below and worked out the formulas for the analysis. It was found that both vaccines had caused an excess risk of seizures 0 to 1 days after vaccination, irrespective of the presence of the other vaccines, and that the effects were independent of each other (Tse et al., 2012). This means that there was a positive additive interaction but no multiplicative interaction. Hence, the estimates obtained indicated that it is safer to give the two vaccines on separate days rather than on the same day.

### Early-Onset Adverse Events

*Data*

Both VAERS and electronic health plan data can be used to evaluate early-onset adverse events due to vaccine-vaccine interaction.

*Methods*

For spontaneous reporting systems, Almenoff et al. (2003) have developed a proportionality-based version of DuMouchel's (1999) empirical Bayes multi-item gamma Poisson shrinker. Pairs of two drugs are treated as a separate unique drug, different from individual drug users. To signal a possible interaction-induced adverse event, the lower 5th percentile of the empirical base geometric mean estimate must be larger than the upper 95th percentile of the empirical base geometric mean estimate for both of the individual drugs. This approach makes sense in a data-mining context, where it is necessary to have some form of formal or informal adjustment for the multiple testing.

Two other methods for evaluating interaction effects in spontaneous reports have been proposed by Thakrar et al. (2007) and Norén et al. (2008). Both of these, as well as the previously described method by Almenoff et al. (2003), were proposed for drug-drug interactions, but they can also be used for vaccines.

For electronic health plan data, a different methodological approach is needed. With a self-controlled risk interval analysis, it is possible to evaluate the effect of a vaccine on an adverse event by comparing the number of adverse events in a risk interval right after the vaccine is given with the number in a control interval long after vaccination. Now, suppose we have two vaccines, such as PCV13 and trivalent inactivated influenza vaccine (TIV), and we want know to if there is an increased risk of seizure 1 to 2 days after vaccination. We can then do a self-controlled risk interval analysis for TIV and another one for PCV13, ignoring any other vaccines given on the same day. Suppose that we see an excess risk in both analyses. Since these particular vaccines are often given on the same day, it then is not clear if

- TIV causes an excess risk and PCV13 is just an innocent bystander with no excess risk.
- PCV13 causes an excess risk and TIV is just an innocent bystander with no excess risk.
- both vaccines cause an increased risk of seizures independently of each other.
- there is either a positive or a negative interaction effect between the two vaccines.

To better understand the importance of different interaction effects, a few examples are given. Assume that TIV alone causes a twofold excess risk and that PCV7 alone also causes a twofold excess risk:

- If, when taken together, they also cause a twofold excess risk, then there is a negative interaction and it is safer to take the two vaccines on the same day.
- If, when taken together, there is a threefold excess risk, then there is a negative multiplicative interaction, while there is no additive interaction. In this scenario, it is equally safe to take the two vaccines on the same day or on separate days. This is because a threefold excess risk has twice as many excess cases than a twofold excess risk but there is only one rather than two times of exposure, which evens out the excess risk.
- If, when taken together, there is a fourfold excess risk, then the two vaccines act independently on a multiplicative scale (i.e., TIV doubles the risk and then PCV7 doubles the risk on top of that), while there is a positive interaction on an additive

scale. In this scenario, it is safer to give the two vaccines on separate days, since one time period with a fourfold excess risk is worse than two time periods with twofold excess risk.

- If, when taken together, there is a fivefold excess risk, then there is a positive interaction on both the multiplicative and the additive scales, and again, it is safer to take the vaccines on separate days.

While it is possible to do three separate self-controlled risk interval analyses for the vaccines when given alone and when given together, the best approach is to combine all the information into one logistic regression model that includes both the main effects and the interaction terms. This can be done, and it is then possible to formally test for a multiplicative interaction effect.

## VACCINE ORDER

### Background

While not a common concern, it has occasionally been suggested that the order in which vaccines are given may be influence the risk of adverse events. Here, we are not thinking of vaccines given a couple of minutes apart at the same health care visit but of vaccines given a few days, weeks, or months apart. For example, in a study of DTP and the measles vaccine in a low-income African country, Aaby et al. (2004) hypothesized that "DTP as the last vaccine received may be associated with slightly increased mortality." Veirum et al. (2005) suggested that "it might be examined whether provision of BCG [bacilleCalmette-Guérin] or measles vaccine shortly after the last dose of DTP could secure specific protection and prevent the negative immune stimulation associated with having received DTP," and that "different sequences of vaccinations" might have to be considered.

### Example

In a three-arm randomized vaccine trial with a total of 1,027 children, Leonadri et al. (2011) compared both immunogenicity and safety for different orders of vaccination with MMRV and PCV7. In the study, MMRV was given either 6 weeks prior to, on the same day, or 6 weeks after the fourth dose of PCV7. The incidence of local and systemic adverse events was comparable between the groups, while no serious adverse events were reported in either group.

*Data*

Electronic health plan data are ideally suited to study this question. Alternatively, children with the outcome of interest could be identified by the use of, for example, hospital data or data from a disease registry, followed by a vaccination history survey to their parents.

## Late-Onset Adverse Events

*Methods*

The following is a study design for comparing the order of vaccines A and B with health plan data. For simplicity, this description assumes a single dose of each vaccine, but it can be generalized to multiple doses. First, identify children with the purported adverse event outcome of interest. Include only those children that had both vaccines A and B at least *x* days prior to the onset of the disease, except those that had both vaccines on the same day. With health plan data, the comparison group will be all other children. For each child with the purported adverse event, (i) note the exact age at disease onset, (ii) calculate how many of the comparison children of the same gender that also had both vaccines A and B at least x days before that age but not on the same day, and (iii) note the proportion of those that had vaccine A before vaccine B. Under the null hypothesis of no effect of vaccine order, this proportion is the estimated probability that the study child had vaccine A before vaccine B. The analysis is adjusted for age and gender, and other covariates can be adjusted for in the same way as gender.

The reason for excluding children that had one of the vaccines less than *x* days before the adverse event is to remove the effect of vaccine-specific early-onset adverse events that is caused by one of the vaccines independently of the presence of the other. The value of *x* will depend on the vaccines and adverse event studied. To avoid bias, it should be large enough so that any adverse events caused by one vaccine independently of the other do not vary in time on the basis of the number of days after vaccination.

An alternative is to use a case-control design. First, the children with the adverse event are selected as before. Second, identify a comparison group of children who did not have the adverse event outcome, matched by age, gender, and any other variables, and with the same inclusion criteria with respect to vaccination history. Then compare how many of the cases and how many of the controls had vaccine A before vaccine B, and vice versa.

## Early-Onset Adverse Events

*Methods*

The above-described design cannot be used for acute adverse events because of the bias mentioned above. Instead, the following design can be used. By the use of health plan data, select children that had vaccine A at any time. Separate them by whether they have had vaccine B prior to vaccine A or not. Then compare these two groups in term of how many of them had the adverse event of interest on the 1 to *D* days after they received vaccine A. The value of *D* defines the risk window and will depend on the vaccines and adverse event studied. The analysis can be performed using unconditional logistic regression, adjusting for covariates such as age at vaccination, gender, calendar years, and study site.

This study design cannot in itself distinguish between an effect due to the order of the vaccines and an interaction effect, where the risk increases with the same amount after the second vaccine irrespective of their order. By collection of the above-described data both for vaccine A and then, in the corresponding manner, for vaccine B, it is

possible to compare the two risk estimates. If the increased risk is due to vaccine-vaccine interaction but not the order of the vaccination, these estimates should be the same.

## CUMULATIVE SUMMARY METRICS OF THE VACCINE SCHEDULES

### Background

It is conceivable that it is neither the timing of individual vaccines nor the interaction between vaccines that is responsible for adverse events but, rather, some more general component of the vaccine schedule, such as the total number of vaccines given or the cumulative amount of immune-stimulating content, immunogenic adjuvants, or preservatives in all vaccines received. Similar study designs and statistical methods can be used for most of these types of summary measures or metrics of the vaccine schedule, so they are considered together.

### Examples

The total amount of immunogens that a child has been exposed to is being used in studies of autism (DeStefano et al., 2012) and neuropsychological outcomes (Iqbal and DeStefano, 2012).

### Cumulative Summary Metrics for General Features of Vaccine Schedules

The first and most critical step is to define one or more suitable metrics reflecting the general feature of the vaccine schedule that should be evaluated. The number of options is large. Here are some examples:

- The total number of vaccines received before the child's 6th birthday.
- The total number of health care visits before the child's 6th birthday on which the child received at least one vaccine.
- The total amount of immunogens (antibody-stimulating proteins and polysaccharides) that a child was exposed to from all vaccines combined (DeStefano, 2012).
- The total amount of immunogenic adjuvants that a child was exposed to from all vaccines combined.
- The total amount of the thimerosal preservative that a child was exposed to from all vaccines combined (Price et al., 2010).

For all the metrics listed above, completely unvaccinated children will have a value of zero. These children are at one end of the exposure spectrum, and together with the fully vaccinated children at the other end, they provide the most informative data points for statistical analyses. Hence, they should be included in these types of studies in order to ensure the highest possible statistical power.

All of the above metrics are continuous or ordinal in nature. Each one could be dichotomized into a 0/1 variable. For example, in the first example mentioned above, the

children could be split into those receiving at least 10 vaccines and those receiving less than 10 vaccines. Such dichotomization is not recommended. If there is a difference in risks between receiving 9 and 10 vaccines, there is also probably a difference between 5 and 9 vaccines and between 10 and 15 vaccines. Such information is thrown away when the data are dichotomized, and hence, statistical power is lost. It may be tempting to compare only fully vaccinated and completely unvaccinated children, but that is not recommended either. By excluding the children in between, statistical power is lost, as they provide valuable information about the intermediate group. It also makes it impossible to look for a dose-response relationship, as described below.

*Data*

Electronic health plan data provide one of the best opportunities to study the safety of vaccine schedules with respect to cumulative summary metrics. As the complete vaccination history is needed to calculate the metric of interest, population-based studies will be limited to children with a sufficiently long enrollment in the same health plan. In some European countries with a national health care system, such as Denmark, these studies are easier to conduct, as only a small percentage of children immigrate to or emigrate from the country. From the U.S. perspective, a drawback of doing these types of studies in foreign countries is, of course, that their recommended vaccine schedule is different from ours.

*Methods*

Once the outcome definition has been decided, the methods that one can use for these more general vaccine schedule components are very similar to those described above concerning the time between vaccine doses. With health plan data, first classify each child according to one or more of the metrics indicated above. Include only children with a sufficiently long enrollment period. As the next step, determine if they have the adverse event of interest during some predefined age period. For the statistical analysis, use logistic regression with the potential adverse event as the dependent variable and the vaccine schedule metric as the independent variable. More than one metric for the vaccine schedule can be included in the same regression model, by which it is possible to try to tease apart the relative influence of each one on the adverse event. Gender, calendar year, study site, and other covariates can be adjusted for by also including them as independent variables in the logistic regression.

To include as many children as possible in the study, irrespective of their length of enrollment, a survival analysis model could be used instead of logistic regression. Children leaving the health plan are then censored at the time of departure. Note, though, that the enrollment period must still be long enough to determine their vaccine schedule in sufficient detail to calculate the metric of interest. It is only the follow-up period that can be sensored.

The key strength of health plan data is the availability of detailed longitudinal vaccination and disease histories for millions of children. They do not contain all potential information of interest, though. If some of the exposure history is unavailable, such as the particular brand of a vaccine, one can instead conduct a case-control study. If the potential adverse event is rare, cases can be identified through the health plan data,

together with a set of matched controls. Chart review can then be conducted on this limited population to obtain more detailed information about each of the vaccines given, about the exact nature of the potential adverse event, or about various potential confounders.

There is not necessarily a linear dose-response relationship between the metric of choice and the risk of a potential adverse event, but a linear function can be used in the regression model as a test for trend. Quadratic and other nonlinear functions can then be explored and formally tested for statistical significance in order to get a better understanding about the dose-response curve.

When doing these types of studies, it is important to look for a dose-response relationship in which an excess risk observed is a monotonically increasing or decreasing function of the summary metric being evaluated. If it instead is, for example, a U-shaped function with a high risk among the least and most vaccinated and a low risk among the middle group, it is likely to be something else responsible for the differences, rather than the cumulative metric under study.

## VACCINE SCHEDULE SUMMARY METRICS, INDEPENDENT OF VACCINES RECEIVED

A fundamentally different set of metrics compares children who receive the same set of vaccines, but through different schedules. The question is then exclusively focused on how the vaccinations are scheduled, and we want to adjust away any differences due to the different sets of vaccines received.

The number of potential vaccine schedule summary metrics is large. Here are some examples:

- The maximum number of vaccines received on a single day.
- The maximum amount of immunogens received on a single day (DeStefano, 2012).
- The maximum amount of adjuvants received on a single day.
- The average number of vaccines given at each visit. For example, if one child had 15 vaccines spread out over five visits, the average is 3. If another child had only 3 vaccines in total, all given at the same visit, the average is also 3.
- The number of days undervaccinated (Glanz et al., 2012). For each vaccine, calculate the number of days between the recommended age and the actual age of vaccination and then sum over all vaccines. For a perfectly compliant child, the value is zero.
- The age at which a certain portion of the recommended vaccine schedule was completed. For example, one could take the set of vaccines that CDC recommends for the first 18 months and determine the age at which all of them have been given.
- Average age at which vaccines were given.

None of these definitions is the "right" one, but they serve as examples of what could be used rather than recommendations of what should be used. The choice will and must depend on the scientific hypothesis that the scientist is evaluating.

*Data*

Electronic health plan data are the most suitable for studying vaccine schedule metrics. Since the complete vaccination history is needed to calculate the metric of interest (such as average age at vaccinations), a sufficiently long enrollment in the same health plan is needed.

*Methods*

The methods described in the previous section can be used for these types of studies as well, with one critical modification. To truly evaluate the metric of the vaccine schedule and not the collection of vaccines received, the latter must be adjusted for. This can be done by classifying the children by the set of vaccines received and then conditioning the analysis on these sets. In this way, children are compared only with other children that received the same set of vaccines. All children who received at least one vaccine can be included in the same study, maximizing the statistical power. Children who did not receive any vaccines are not informative in this type of study and must be excluded.

## COMPARISON OF COMPLETE VACCINE SCHEDULES

### Background

Some parents have consciously decided to follow a specific alternative vaccine schedule other than the one recommended by the CDC. Hence, there is a natural interest in comparing the safety of these complete schedules as discrete entities rather than through the various components of the schedule, as discussed in previous sections. For example, one may compare the number of potential adverse events in (i) children that have followed the CDC-recommended vaccine schedule, (ii) children that have followed one of Dr. Bob's recommended schedules (Sears, 2007), and (iii) children that have not received any vaccines at all. The statistical methods are the same irrespective of which vaccination schedules are compared or whether vaccinated children are compared to completely unvaccinated children. Hence, we treat them together in this section.

### Examples

In a pioneering study on vaccine schedules, Glanz et al. (2012) used a matched cohort design where children on the CDC-recommended vaccine schedule were matched with children not on that schedule. It was then evaluated whether there were any differences in a few different outcomes: pertussis, upper respiratory infections, fever, sinusitis, outpatient physician visits, and hospitalizations. The data used were from VSD. In a companion study, Hambidge et al. (2012) used the same data to look at febrile seizures.

*Data*

From a purely scientific perspective, the best design would be a double-blind placebo-controlled randomized trial with an intention-to-treat analysis where children are randomized to one of several vaccination schedules and/or no vaccinations at all. There are major financial, logistical, and ethical issues with conducting such trials, as discussed below.

To avoid ethical issues, observational health plan data can be used as an alternative to randomized trials. As in the previous section, complete vaccination histories are required to classify children into alternative vaccine schedules, so the length of enrollment must be long enough for a sufficiently large number of children.

*Methods*

Very few children are 100 percent compliant with any one particular schedule. Hence, the first challenge with these studies is to define some criteria of how divergent they can be from the schedule and still be considered compliant. For example, one could require that all the recommended vaccines have been received and that the average temporal divergence from the schedule is at most 1 month, taken over all the vaccines. Alternatively, one could require that the sum of the temporal divergences, taken over all vaccines, is at most, say, 1 year. If the criteria are too strict, the sample size will be too low and the statistical power will suffer. If the criteria are too wide, many of the children will not be appropriate representatives of the schedule that they are set to represent. In that case, the study is not actually evaluating the vaccines schedules that it is meant to evaluate.

Children with an incomplete vaccination history must be excluded from the study, together with children whose vaccine schedule is too divergent from either of the schedules being studied.

Once children in the health plan have been classified by the vaccine schedule, a variety of potential adverse events can be studied. A key difficulty here is to define the time period during which the events will be counted. The cleanest option is to make the vaccine schedule classification based on data up to a certain age and consider only potential adverse events that occur after this age. This ensures that there is no bias if the adverse event studied causes subsequent changes in the vaccination schedule. It is not an ideal solution, though, since we must ignore either the adverse events occurring early during the vaccination schedule or the possible effect of later parts of the vaccination schedule. If the potential adverse event under study is such that there is little risk that its presence will change any aspect of the vaccination schedule, then one could include adverse events that occur before the end of the vaccine schedule considered, but such an approach is risky.

Since different children will have different lengths of follow-up, time-to-event data will best be analyzed by survival analysis methods, adjusting for possible confounders. When two alternative schedules are compared, an alternative way to adjust for covariates is to use a matched cohort design (Glanz, 2012), where each child with the recommended schedule is matched with a child with the alternative schedule having the same age, gender, study site, and calendar year of immunization. This is especially useful

if additional health data that are not available in the health plan data sets are to be gathered from the children, since it is typically infeasible to collect such data for all children in a health plan.

To use observational health plan data to compare complete vaccination schedules, there must be enough children in the health plan that follow each schedule under study. That may be a problem if one of the comparison groups consists of followers of a very specific alternative schedule or of completely unvaccinated children. It may then be necessary to include a larger number of health plans or health plans with a larger number of members.

## ADDITIONAL METHODOLOGICAL ISSUES

### Bias and Confounding

The observational study designs described above are, like all observational studies, prone to various sources of bias. The type of bias is often different for different designs, and it is hence often wise to use multiple study designs for the same question. Of special concern in these types of studies is confounding due to the innocent bystander effect. This is when an adverse event that is seemingly due to one component of the vaccine schedule under study is actually due to another component that is correlated with the first one.

As a first step, it is natural to do a study considering a single component of the vaccine schedule, adjusting only for demographic variables. If a significant relationship is observed, though, it is sometimes important to consider other aspects of the schedule as possible confounders. This is especially true for late-onset events. This can be tackled in one of several ways. As a second step, additional studies evaluating other components of the vaccine schedule can be conducted. One way to do this is to incorporate multiple components in the same regression model. For example, one regression model may include variables representing the age at which each vaccine was given, the total number of vaccines given, the total exposure to immune-stimulating content, and the total exposure to adjuvants. Such a design will provide information as to whether the component that is suspected of being the culprit still has a statistically significant relationship with the outcome after adjustment for other components of the schedule. It is important to note, though, that with many different correlated components in the same schedule, none may be statistically significant after adjustment for all the others. This does not mean that the risk of the adverse events does not depend on the vaccine schedule. It just means that it is not possible to determine which component is responsible, and that is important information.

### Combining Health Plan Data with Study-Specific Data Collection

In the data sections presented above, health plans are often recommended as the best source of data to use. There are some potential adverse events that are not fully captured in the electronic health plan data, though, such as neuropsychological performance or immune function. Such outcomes must be measured specifically for a

research study, but that can obviously not be done for all members of a health plan. Depending on the outcome, there are at least three different ways to go about doing this:

- Select a random sample of children from the health plan, measure the outcome of interest for each one, and evaluate the relationship between the relevant component of the vaccine schedule and the outcome measurement values. This is the simplest approach.
- Select a nonrandom sample of children from the health plan, oversampling children on both end of the metric used in the study. For example, if the variable of interest is the timing of the first dose of the hepatitis B vaccine, children who received it long after birth would be oversampled. After that, proceed as described above. This design will in many cases increase the statistical power. It is important that the probability of selection be unrelated to other health events.
- Select a nonrandom sample of children from the health plan, on the basis of a health outcome that is present in the health plan data and that is correlated with the outcome of interest. The goal here is to get a larger variance in the health outcome being measured, thereby increasing the statistical power. It is important that the probability of selection be unrelated to any aspect of the vaccine schedule. After the study population has been selected, proceed as described for the first scenario.

### Vaccine-Specific Versus General Components of Vaccine Schedules

The more general components of the vaccine schedule described above, as well as the comparison between complete schedules discussed earlier, are considerably more difficult to study than the more vaccine-specific components described above. There are several reasons for this.

First and foremost, there are many alternative vaccine schedules, and slightly different schedules have to be lumped together in the same comparison group. For the cumulative summary metrics, many different vaccination schedules will have the same value, for example, the average age at vaccination. If one vaccine schedule is safer than an alternative vaccine schedule in terms of a specific outcome but they both have the same average age at vaccination, then the effect size will be attenuated and go undetected.

If a statistically significant excess number of adverse events is found, a second problem with these designs is that it can be hard to know which aspect of the schedule caused the excess or reduced risk. Is it the timing of one specific vaccine, is it an interaction between two or more vaccines, or is it something else? Hence, any statistically significant findings will have to be followed up with studies concerning more specific vaccine schedule components.

A third issue is confounding. While confounding is present in all observational studies, it is likely to be a greater problem when complete vaccine schedules are studied. For example, children for whom most of the vaccines are delayed from the recommended schedule may be different in terms of both health care utilization and socioeconomic factors. This may bias the results, and the bias may exist whether the delayers are deliberately following an alternative schedule or not, and the bias may go in different

directions for these two groups. The same type of confounding can be present when one is looking at more specific components of the vaccine schedule, but it is likely to be less strong, as such individual components are likely to have more random and less systematic variability than a complete schedule. A way to intuitively see this is to note that whatever it is that causes a general parental tendency to delay vaccinations, that will likely be more correlated with the average timing of all vaccinations than with the timing of a single vaccination.

To date, there have been few comparative studies evaluating the safety of different vaccine schedules. For the above-mentioned reasons, it is suggested that, initially, the majority of such studies focus on the most vaccine-specific components of the vaccine schedule described earlier, as well as the content-defined components mentioned above. Information from such studies will greatly facilitate the design and understanding of subsequent studies evaluating the more general components discussed earlier as well as the comparison of complete vaccines schedules described above.

### Cross-National Comparisons

Different countries have different recommended vaccine schedules, so it may seem natural to do cross-national studies to compare the safety of the schedules in an ecological study design. Unfortunately, this is very difficult to do well and generally not recommended. The problem is that the incidence of most diseases varies by geographical region for reasons other than the vaccine schedule, such as genetics, diet, physical exercise, or other environmental factors. Any such cross-national study may hence be heavily biased. This does not mean that one cannot do studies that include data from multiple countries or regions, as long as each one has a range of different exposures in each place. In such studies, the geographical region can easily be adjusted for in the analysis, in order to take the differential disease incidences into account.

### Time Trend Evaluations

Another ecological study design is to take a particular country or region and compare time trends in disease incidence with temporal changes in the vaccination rate or vaccination schedule. This is also not recommended. In addition to vaccinations, there are many other reasons why the reported disease incidence may increase or decrease over time, including changes in environmental risk factors and changes in health care practice and diagnosis. Hence, an apparent temporal correlation between increasing disease incidence and increasing vaccine usage could be completely spurious. It should be pointed out that the bias can also go in the other direction. Even if there is no temporal correlation between disease incidence and vaccinations, a true relationship can be hidden by a compensatory effect from an unknown confounder.

### Near-Real-Time Safety Surveillance:

In what is called “rapid-cycle analysis,” the VSD project has pioneered near real-time vaccine safety surveillance (Lieu et al., 2007; Yih et al., 2011). For newly approved vaccines and selected adverse events, weekly data feeds are received from the health plans and the data are analyzed by continuous sequential statistical methods (Kulldorff et

al., 2011). If there are specific concerns regarding the newly revised vaccine schedule, such rapid-cycle analysis can also be implemented for many of the study designs described above.

### Data Mining

Most vaccine safety studies evaluate a specific vaccine-event pair. For VAERS data, data mining methods are also used, where thousands of potential vaccine and adverse event pairs are evaluated simultaneously, without there being any prior hypothesis about their being an excess risk of the event. This is done to cast the net as wide as possible. Recently, data mining methods are also started to be used for health plan data. As vaccine safety data mining develops further, it may also be used to study questions regarding the vaccine schedule.

### Disease-Causing Complications Versus Adverse Events

It should be noted that in these types of studies, it is not always clear what is an adverse event and what is not. For example, a child may have a febrile seizure that was caused by one or more of the vaccines or a febrile seizure caused by a disease, where the child got the disease because he or she was not immunized against it. Hence, an excess risk of seizures due to a particular vaccine schedule could be due either to vaccines given at a certain time when the child is more sensitive to adverse events or to vaccines not given at a certain time when the child needed the vaccine protection.

If the same type of health event is caused by the vaccine among one group of children as an adverse event and by the disease among the same or another group of children as a complication, then the vaccine may be found to cause an excess number of the adverse events in a vaccinated population, since the nonvaccinated children benefit from herd immunity. Hence, findings about the risk to individuals in a mostly vaccinated population cannot necessarily be generalized to the population level.

### Vaccine Efficacy and Effectiveness

This paper covers only the study of potential adverse events after vaccination. If a study does not find an excess risk, all is fine and there is no need to worry about vaccine efficacy. On the other hand, if a true differential risk of adverse events is found with respect to some component of the vaccine schedule, vaccine efficacy and effectiveness must also be considered when contemplating a revised vaccine schedule. Some vaccines, such as MMR, have a different immune response depending on the age of the child, and vaccine efficacy therefore depends on the vaccine schedule. The timing of a vaccination also influences the time period during which the child is protected from the disease and the herd immunity of the population at large. Herd immunity can also be affected if a parent refuses future vaccinations after his or her child has had an adverse event vaccine that could have been avoided with a different schedule. While such an analysis is outside the scope of this paper, all these factors must be considered in a joint cost-benefit analysis before the recommended vaccine schedule is revised, if and when there is a finding of a vaccine schedule-dependent adverse event.

## FINANCIAL CONSIDERATIONS

When deciding what to study and what study design to use, cost is an important consideration. The study designs mentioned in this paper range from very cheap to very expensive. For some designs, the cost depends on how common the potential adverse event is. While we cannot do any precise sample size calculations, we will for illustrative purposes consider three classes of health outcomes: common, moderately rare, and very rare. Common events are those that affect more than 1 out of every 100 children, such as allergies and some learning disorders. Moderately rare outcomes are those that affect more than 1 out of 100 but less than 1 in 10,000, such as intussusception. Very rare outcomes are those affecting less than 1 in 10,000, such as Guillain-Barré syndrome,

The least expensive studies are those using VAERS data. Since those data are already collected, only the investigator's time needs to be covered. Unfortunately, VAERS data are of limited use when one is studying vaccine schedules. The cost is independent of the adverse event.

The second least expensive study designs are the ones based on fully automated health plan data. While they involve no new data collection, the extraction of data from large administrative databases is a complex activity involving detailed knowledge of the database structure and content, sophisticated computer programming, and thorough data quality control. To set up a new system from scratch is very costly, but the marginal cost of additional studies in existing systems is not. In most cases, the cost is independent of the potential adverse event under study. For common and medium-rare outcomes, a VSD-size study population of about 100,000 annual births should be enough for most study designs. For very rare outcomes, data from more and larger health plans may be needed in order to achieve sufficient power, resulting in additional expenses. Bigger datasets may also be needed for common events and moderately rare adverse events when complete vaccination schedules are evaluated, if only a small proportion of health plan members follow the particular schedule of interest. In summary, the cost of these types of studies is similar to the cost of current vaccine safety studies conducted in VSD, PRISM, and similar systems.

With most health plan data, vaccine information has a high positive predictive value, but that is usually not the case for disease outcomes. For such adverse events, it is often necessary to conduct chart reviews to confirm whether or not a patient actually had the health event of interest, and that will increase the cost. For very rare adverse events, it is not a major additional cost, but for medium-rare and common adverse events, it can be. One way to reduce this cost is to first do a study on fully automated data and do chart review only when that study shows an excess risk of adverse events, to confirm or dismiss that finding.

The next level of cost is incurred by study designs that combine health plan data with specially collected outcome data that are not available as part of the EMRs. The cost will depend on the type of data collected but will in most situations be very high. For medium-rare and very rare outcomes, a very large number of health plan enrollees will have to be enrolled, potentially making such studies prohibitively expensive.

Randomized trials are the most expensive study design. For medium-rare and very rare adverse events, the study needs to have a very large sample size to detect a potential problem. For example, if a vaccine causes a specific adverse event in 1 of every 1,000 children, that is not something that can be detected in a randomized trial with 4,000 children in each arm, for a total of 8,000, even if the baseline rate of the event is very rare. To see this, suppose that there are four adverse events in the vaccinated arm and none in the control arm receiving the placebo. Under the null hypothesis, the probability of all four being in the vaccinated arm is $(1/2)^4 = 0.0625$, which is not statistically significant, and hence, we cannot conclude that it was the vaccine that caused the adverse events. So, for medium-rare and very rare adverse events, we need data with tens or hundreds of thousands of vaccinated children, and for such sample sizes, randomized trials are prohibitively expensive. A cost advantage of randomized trials over case-control studies is that multiple potential adverse events can be evaluated within the same study.

Irrespective of the design, studies evaluating late-onset events are more expensive than those evaluating early-onset events, since the individuals must be followed for a much longer time. With health plan data, this requires larger population sizes since many children will be lost to follow-up. When health plan data are augmented with specially collected data on health outcomes, children must be tracked and monitored for a longer time, which is costly. The same is true for randomized trials.

## ETHICAL CONSIDERATIONS

As with all medical research, ethical considerations are very important when one is designing vaccine safety studies. With observational studies with health plan data, the key ethical issue is patient confidentiality, which can be ensured through existing research practices.

For randomized trials, ethical considerations play a much more important role. Depending on the vaccine component of interest, a randomized trial can sometimes be conducted in a way so that both arms fall within the recommended vaccination schedule, in which case there are no ethical concerns. An example of such a trial would be whether to give children two vaccines on the same day or a week apart. At the other extreme, it would be unethical to do a randomized trial where children in one arm are completely unvaccinated, since the scientist will then knowingly put some of the children at increased risk for vaccine-preventable diseases, some of which may result in death. Somewhere in between these two extremes there is a gray zone where randomized trials may or may not be ethical, depending on the vaccine schedules being compared and on the available strength of the evidence regarding efficacy and potential adverse events. Experts on medical ethics should then be consulted.

For more common adverse events, randomized trials have a potential role to play in postmarketing vaccine safety studies. There is little reason to use them to evaluate the general safety of a particular vaccine, since that evaluation is already covered by the Phase III trials. Questions for which randomized trials may be used include the order in which different vaccines are given, the exact timing between doses of the same vaccine, and whether two different vaccines are given on the same day or a week apart.

If a randomized trial is conducted, it is important to consider the effect on herd immunity. If the two arms differ by delaying one or more vaccines by at most a few weeks, it is not a major issue. If vaccination in one arm is delayed for a much longer time period or not given at all, it may reduce herd immunity. This may put children that are not participating in the study at increased risk for the disease, and this can be especially serious for immune-compromised children for which a vaccination is contraindicated. To minimize the negative effect on herd immunity, such randomized trials should be spread out geographically, so that there are at most a few additional unvaccinated children in any given location. In that way, nonparticipating children will not be at an increased risk of the disease, and equally important, those children randomized to the delayed vaccination will still have some protection against the disease from herd immunity.

## CONCLUSIONS

Randomized trials are the "gold standard" for scientific studies, and premarketing Phase III randomized trials play an important role in the evaluation of vaccine-related adverse events. Because of their limited sample size, rare adverse events may not be detected, though. For financial and ethical reasons, the utility of randomized trials is more limited for postmarketing vaccine safety studies.

On the basis of utility and cost, health plan – based study designs are the most promising for the safety evaluation of different vaccine schedules. This is definitely true for medium-rare and very rare adverse events that cannot be detected in Phase III randomized trials, but such data can also be used to study common adverse events. The key is to always consider potential problems with confounding, and it is often a good idea to use different study designs with different potential biases for the same research question.

Hypotheses about potential adverse events may come from Phase III trials or from observational postmarketing studies with data from health plans or spontaneous reporting systems.

The comparative safety evaluation of different vaccine schedules is a complex and multifaceted task, and all aspects of the vaccine schedule are currently understudied with regards to potential adverse events. A number of different study designs and methods can be used to evaluate different components of the schedule. For all known and most potential adverse events, it is recommended that a wide variety of vaccine schedule components be evaluated. Direct evaluation of complete vaccine schedules is more difficult and probably less fruitful, but it is not impossible. Such studies are most useful when conducted in parallel with studies of specific components of the schedule. This is especially important when there is a significant adverse event finding, since it is otherwise impossible to know which of the many features of the complete schedule are actually causing the adverse events.

This paper should not be utilized as a cookbook where definite study designs and methods are obtained and used for different classes of problems in a black box – type approach. Each study is unique, depending on the vaccine(s) under study, the potential adverse event(s) of interest, the data used, and the scientific research question. All those

aspects need to guide the methodology. The goal of this paper is simply to show that a wide variety of study designs and methods are available to study the comparative safety of different vaccine schedules, and the hope is that some of the proposed methods can serve as a starting point when thinking about the most suitable designs and statistical methods to use for different studies.

This paper does not present an exhaustive list of study designs and methods that can be used for the comparative evaluation of potential adverse events due to different childhood vaccination schedules. As more such studies are performed, additional designs and methods will surely be developed and used. The paper should not be interpreted as a recommendation to use all of the study designs and statistical methods mentioned. The scientific question should drive which designs and methods are used, and while some of them may become widely used, others may not be used at all.

What the paper attempts to show is that the comparative safety evaluation of vaccine schedules is complex and multifaceted and that a wide variety of study designs and statistical methods are available to a scientist who wishes to conduct such studies.

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# Appendix E

# Agendas of Public Meetings Held by the Committee

**February 9, 2012**

**The PEW Charitable Trusts**
**901 E Street, NW**
**Washington, DC 20004**

Welcome and Overview

Ada Sue Hinshaw, Ph.D., R.N.

*Committee Chair*

Presentation of the Charge from the National Vaccine Program Office

Bruce Gellin, M.D., M.P.H.

*Deputy Assistant Secretary for Health*

*Director, National Vaccine Program Office, U.S. Department of Health and Human Services*

Review of the IOM Committee to Review Adverse Effects of Vaccines

Ellen Wright Clayton, J.D., M.D.

*Chair of the IOM Committee to Review Adverse Effects of Vaccines*

*Craig-Weaver Professor of Pediatrics, Vanderbilt University*

National Vaccine Information Center Perspectives

Barbara Loe Fisher

*Co-Founder and President, National Vaccine Information Center*

Provider Perspectives

Gary Freed, M.D., M.P.H.

*Professor, Department of Health Management and Policy, University of Michigan School of Public Health*

*Director, Division of General Pediatrics*
*The Percy and Mary Murphy Professor of Pediatrics and Child Health Delivery*

The Use of Clinical Trials for Childhood Vaccines
Susan Ellenberg, Ph.D.
*Professor of Biostatistics and Associate Dean for Clinical Research*
*Perelman School of Medicine at the University of Pennsylvania*

Ethical Issues in Clinical Trials
Robert (Skip) Nelson, M.D., Ph.D.
*Senior Pediatric Ethicist/Lead Medical Officer, Food and Drug Administration*

National Center for Immunization and Respiratory Diseases (NCIRD), Centers for Disease Control and Prevention (CDC)
Melinda Wharton, M.D., M.P.H.
*Deputy Director, NCIRD, CDC*
*Captain, U.S. Public Health Service*

Immunization Safety Office (ISO), CDC
Frank DeStefano, M.D., M.P.H.
*Director, ISO, CDC*

Data and Approaches in National and International Immunization Studies
Saad Omer, Ph.D., M.P.H., M.B.B.S.
*Assistant Professor, Hubert Department of Global Health Epidemiology, Emory University Rollins School of Public Health*
*Assistant Professor, Emory Vaccine Center*

Immune Profiling Research
Chuck Hackett, Ph.D.
*Deputy Director, Division of Allergy, Immunology, and Transplantation*
*National Institute of Allergy and Infectious Diseases*

OPEN SESSION—Opportunity for Attendee Comments

Adjourn

**March 8, 2012**

**Talaris Conference Center**
**4000 NE 41st Street**
**Seattle, Washington 98105**

Welcome and Overview

Ada Sue Hinshaw, Ph.D., R.N.
*Committee Chair*

Welcome from Washington State Department of Health

Mary Selecky
*Secretary of Health, Washington State Department of Health*

Maxine Hayes, M.D., M.P.H.
*State Health Officer, Washington State Department of Health*

Washington State's Immunization Programs

Janna Bardi, M.P.H.
*Office Director, Immunization and Child Profile Office*
*Washington State Department of Health*

Findings on Alternative Immunization Schedule Practices

Douglas Opel, M.D., M.P.H.
*Assistant Professor of Pediatrics, Adjunct Assistant Professor of Bioethics and Humanities*
*University of Washington*
*Treuman Katz Center for Pediatric Bioethics*
*Seattle Children's Research Institute*

Assessing the Safety of Vaccines at the FDA: Pre- and Postlicensure Evaluations

Marion F. Gruber, Ph.D. (by phone)
*Acting Director, Office of Vaccines Research and Review*
*Center for Biologics Evaluation and Research*
*Office of Medical Products and Tobacco*
*Food and Drug Administration*

Karen Farizo, M.D. (by phone)
*Acting Associate Director for Medical Policy and Safety*
*Office of Vaccines Research and Review*

*Center for Biologics Evaluation and Research*
*Office of Medical Products and Tobacco*
*Food and Drug Administration*

Issues Leading to Vaccine Hesitancy
Douglas Opel, M.D., M.P.H.
*Assistant Professor of Pediatrics, Adjunct Assistant Professor of Bioethics and Humanities*
*University of Washington*
*Treuman Katz Center for Pediatric Bioethics*
*Seattle Children's Research Institute*

Process for Immunization Schedule Recommendations
Edgar Marcuse, M.D., M.P.H.
*Professor of Pediatrics, Adjunct Professor of Epidemiology, University of Washington*
*Associate Medical Director, Quality Improvement, Seattle Children's Hospital*

Decision Making at Advisory Committee on Immunization Practices in Response to Unanticipated Adverse Event Detection
Jeffrey Duchin, M.D.
*Chief, Communicable Disease Epidemiology and Immunization Section*
*Public Health*
*Seattle and King County, Washington*

Provider Self-Efficacy and Tools to Improve Immunization Rates
David Grossman, M.D., M.P.H.
*Medical Director, Preventive Care*
*Group Health Cooperative*

Group Health Research Institute and the Vaccine Safety Datalink
Michael L. Jackson, Ph.D., M.P.H.
*Assistant Scientific Investigator*
*Group Health Research Institute*

OPEN SESSION—Opportunity for Attendee Comments

Adjourn

**May 29, 2012**

**The PEW Charitable Trusts**
**901 E Street, N.W.**
**Washington, D.C. 20004**

Welcome and Overview
Ada Sue Hinshaw, Ph.D., R.N.
*Committee Chair*

U.S. Childhood Immunization Schedule Decisions
Margaret B. Rennels, M.D.
*Professor of Pediatrics, University of Maryland School of Medicine (retired)*
*Independent Consultant*

Question and Answer

Vaccine Policy and Safety Surveillance in the United Kingdom
Elizabeth Miller (by phone)
*Head, Immunization Division*
*Communicable Disease Surveillance Centre*
*Health Protection Agency, Colindale, United Kingdom*

Question and Answer

Vaccine Decisions: Policy Making and Priority Setting in Canada
Charlotte Moore Hepburn, M.D., F.R.C.P.C., F.A.A.P.
*Lead, Child Health Policy Initiative*
*Assistant Professor, University of Toronto School of Medicine*
*Staff Paediatrician, Division of Paediatric Medicine, The Hospital for Sick Children*

Question and Answer

Advisory Committee on Immunization Practices Decision-Making
Melinda Wharton, M.D., M.P.H.
*Deputy Director, National Center for Immunization and Respiratory Diseases*
*Centers for Disease Control and Prevention*
*Captain, U.S. Public Health Service*

Question and Answer

Alternative Immunization Schedules: A Feasibility Study for Evaluating Vaccine Safety and the Risk of Pertussis

Jason Glanz, Ph.D.
*Epidemiologist, Institute for Health Research*
*Kaiser Permanente Colorado*

Question and Answer

Study Designs for the Safety Evaluation of Different Childhood Immunization Schedules

Martin Kulldorff, Ph.D.
*Professor, Biostatistician, Department of Population Medicine,*
*Harvard Medical School and Harvard Pilgrim Health Care Institute*

Question and Answer

Commentary on Commissioned Paper and Other Committee Considerations

Michael A. Stoto, Ph.D.
*Professor of Health Systems Administration and Population Health*
*Georgetown University School of Nursing and Health Studies*

Question and Answer

OPEN SESSION—Opportunity for Attendee Comments

Adjourn

# Appendix F

# Biographical Sketches of Committee Members

**Ada Sue Hinshaw, R.N., Ph.D. (chair),** is a professor and dean at the Graduate School of Nursing of the Uniformed Services University of the Health Sciences as well as a professor and dean emeritus of the University of Michigan's School of Nursing. She received her Ph.D. and master of arts in sociology from the University of Arizona, a master of nursing sciences from Yale University, and a bachelor of science from the University of Kansas. She is a member of the Institute of Medicine, a leader in nursing education and research, and a widely published scholar. Throughout her career, Dr. Hinshaw has conducted nursing research that focuses on the areas of quality of care, patient outcomes, measurement of those outcomes, and building positive work environments for nurses. Dr. Hinshaw was the first permanent director of the National Center for Nursing Research and the first director of the National Institute of Nursing Research at the National Institutes of Health. She led the institute in its support of disease prevention, health promotion, acute and chronic illness, and the environments that enhance nursing patient care outcomes. Dr. Hinshaw's awards include the Midwest Nursing Research Society Lifetime Achievement Award, the United States Public Health Service's Health Leader of the Year Award, the Elizabeth McWilliams Miller Award for Excellence in Nursing Research from Sigma Theta Tau, and the Nurse Scientist of the Year Award from the American Nurses Association. In addition, she has received 13 honorary doctorate degrees from universities in the United States and Canada.

**Tomás J. Aragón**, **M.D., Dr.P.H.,** is the health officer of the city and county of San Francisco, California, director of population health and prevention at the San Francisco Department of Public Health, and medical director of the Center for Infectious Diseases and Emergency Readiness at the University of California, Berkeley, School of Public Health. He specializes in the epidemiology and control of infectious diseases, population and community health, public health preparedness, and epidemiological computing. In San Francisco, he oversees disease control and prevention, public health laboratory, and environmental health. At the University of California, Berkeley, he teaches epidemiology and conducts research.

**Alfred Berg, M.D., M.P.H.,** is a professor in the Department of Family Medicine at the University of Washington School of Medicine, Seattle. Dr. Berg received his professional education in family medicine and general preventive medicine and public health at Washington

University, St. Louis, Missouri; the University of Missouri; and the University of Washington and was elected to the Institute of Medicine in 1996. Dr. Berg's research has focused on clinical epidemiology in primary care settings. He has been active on many expert panels using evidence-based methods to develop clinical guidance, including chair of the United States Preventive Services Task Force, cochair of the Otitis Media Panel convened by the Agency for Health Care Policy and Research (now the Agency for Healthcare Research and Quality), chair and moderator of the Centers for Disease Control and Prevention's (CDC's) Sexually Transmitted Disease Treatment Guidelines panel, a member of the American Medical Association/CDC panel producing Guidelines for Adolescent Preventive Services, and founding chair of CDC's Evaluation of Genetic Applications in Practice and Prevention working group. He was recently appointed to the Methodology Committee of the Patient Centered Outcomes Research Institute. Dr. Berg has served on the Institute of Medicine's Immunization Safety Review Committee (member), the Committee on the Treatment of Post Traumatic Stress Disorder (chair), the Committee on Standards for Systematic Reviews of Clinical Effectiveness Research (chair), and the Committee on Preventive Services for Women (member) and is currently on the Committee on the Governance and Financing of Graduate Medical Education.

**Stephen L. Buka**, **M.S., M.A., Sc.D.,** is a professor in and chair of the Department of Epidemiology at Brown University and also directs Brown's Center for Population Health and Clinical Epidemiology and Center for the Study of Human Development. He received a Sc.D. in epidemiology from the Harvard School of Public Health in 1988 and was a faculty member in its Departments of Maternal and Child Health, Epidemiology, and Society, Human Development and Health before moving to Brown in 2005. With training in epidemiology and developmental psychology, his research focuses on the causes and prevention of major psychiatric and cognitive disorders. Current studies include investigations of prenatal risks for schizophrenia, attention deficit disorder, learning disabilities, and addictive disorders; work on the long-term effects of maternal smoking on offspring health and behavior; community-level influences on youth substance use and delinquency; and community-based strategies for the prevention of adolescent drinking and drug use. He has served on multiple panels for the National Institutes of Health and other federal organizations.

**R. Alta Charo, J.D.,** is the Warren P. Knowles Professor of Law and Bioethics at the University of Wisconsin at Madison (UW), where she is on the faculty of the Law School and the Department of Medical History and Bioethics at the medical school. She also serves on the faculty of the UW Masters in Biotechnology Studies program and lectures in the master's of public health program of the Department of Population Health Sciences. Alta Charo (B.A. biology, Harvard, 1979; J.D. Columbia, 1982) is an elected member of the World Technology Network (2004) and the Wisconsin Academy of Sciences, Arts and Letters (2005). In 2006 she was elected to membership in the National Academies' Institute of Medicine. Professor Charo served on President Obama's transition team, where she was a member of the U.S. Department of Health and Human Services review team, focusing her attention particularly on transition issues related to the National Institutes of Health (NIH), the Food and Drug Administration (FDA), bioethics, stem cell policy, and women's reproductive health. She was on leave from 2009 to 2011 to serve as a senior policy advisor on emerging technology issues in the Office of the Commissioner at FDA. Professor Charo offers courses on public health law, bioethics, biotechnology law, food and drug law, reproductive rights, torts, and legislative drafting. In

addition, she has served on the UW Hospital clinical ethics committee, the University's Institutional Review Board for the protection of human subjects in medical research, and the University's Bioethics Advisory Committee. Professor Charo's advisory committee service for the federal government includes the 1994 NIH Human Embryo Research Panel and President Clinton's National Bioethics Advisory Commission (1996 to 2001), where she participated in drafting its reports *Cloning Human Beings* (1997), *Research Involving Persons with Mental Disorders that May Affect Decisionmaking Capacity* (1998), *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance* (1999), *Ethical Issues in Human Stem Cell Research* (1999); *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries* (2001), and *Ethical and Policy Issues in Research Involving Human Participants* (2001). From 2001 to 2008 she was a member of the Board on Life Sciences of the National Academy of Sciences and the National Academies. She served as its liaison to the Committee on Research Standards and Practices to Prevent Destructive Applications of Biotechnology as well as its committee to develop national voluntary guidelines for stem cell research. She also served as a member of the Institute of Medicine's Committee on Smallpox Vaccination Program Implementation, and since 2006 she has served on the Board on Population Health and Public Health Practice of the Institute of Medicine. In 2005 and 2006, she was a member of the committee to review FDA and the U.S. national system for the assurance of drug safety.

**Gerry Fairbrother**, **Ph.D.,** is a senior scholar at AcademyHealth, an adjunct professor of health policy at the George Washington University, and professor of pediatrics at the University of New Mexico and the University of Cincinnati. Dr. Fairbrother's research areas include measuring quality of care, the impact of churning in Medicaid and the Children's Health Insurance Program, and effects of health information technology on health care outcomes. She is currently examining the impact of health information technology on performance in the Cincinnati Beacon Communities Project and the impact of an improvement intervention in School-Based Health Centers as part of one demonstration projects of the Children's Health Insurance Program Reauthorization Act. She has led investigations on gaps and patterns of enrollment in child health insurance, barriers and cost to enroll in these programs, the impact of Medicaid managed care on preventive screening for children, and the impact of financial incentives on physician behavior. Dr. Fairbrother holds a Ph.D. from The Johns Hopkins University, is a fellow of the New York Academy of Medicine and of the Ambulatory Pediatric Association, and is a member of the National Association of Social Insurance. She serves on the Centers for Medicare & Medicaid Services (CMS) Technical Expert Panel on National Impact Assessment of CMS Quality Measures and on the National Policy Advisory Committee of the National Institute of Children's Healthcare Quality. In recognition of her work, she received the Best Ohio Health Policy Award for Independent Scholar or Practitioner from the Health Policy Institute of Ohio.

**Elena Fuentes-Afflick**, **M.D., M.P.H.,** is professor of pediatrics, epidemiology, and biostatistics and Vice Dean for Academic Affairs in the School of Medicine at the University of California, San Francisco (UCSF). Dr. Fuentes-Afflick completed her residency and chief residency in pediatrics at UCSF, followed by training in epidemiology and health policy. Dr. Fuentes-Afflick joined the faculty at UCSF in 1993. Dr. Fuentes-Afflick has served on the National Advisory Council of the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the Agency for Healthcare Research and Quality as well as the National

Advisory Committee of the Robert Wood Johnson Foundation's Clinical Scholars Program. In 2009 she was president of the Society for Pediatric Research. Her research focuses on Latino health, with a specific interest in the impact of acculturation, immigration status, perinatal outcomes, and body mass. Dr. Fuentes-Afflick was elected to the Institute of Medicine in 2010.

**Sidney M. Gospe, Jr., M.D., Ph.D.,** holds the Herman and Faye Sarkowsky Endowed Chair and is the head of the Division of Pediatric Neurology at the University of Washington and Seattle Children's Hospital. Prior to joining the faculty of the University of Washington in 2000, he served on the faculty of the University of California, Davis, for 13 years. Dr. Gospe received his undergraduate education at Stanford University and M.D. and Ph.D. degrees from Duke University. He completed his postgraduate medical education in both pediatrics and child neurology at the Baylor College of Medicine. Dr. Gospe's laboratory research has focused on neurotoxicology, in particular, the neurodevelopmental effects of maternal exposure to certain toxicants during pregnancy. He has conducted studies designed to help determine the effects of exposure to environmental tobacco smoke on brain development and whether the fetal brain is more vulnerable during certain periods of development. His earlier work focused on the effects of maternal exposure to the organic solvent toluene on fetal growth and development. Dr. Gospe's clinical research concerns pyridoxine (vitamin $B_6$)-dependent epilepsy (PDE), a rare familial cause of infantile seizures and associated developmental disability. He collaborates in biochemical and molecular studies of patients with PDE and has established a national registry for patients with this uncommon inherited disorder.

**Paul A. Greenberger**, **M.D.,** is an attending physician at Northwestern Memorial Hospital and professor of medicine in the Division of Allergy-Immunology, Department of Medicine, Northwestern University Feinberg School of Medicine. He served as Fellowship Program Director from 1992 to 2007 and has helped oversee the postgraduate education for 128 allergy-immunology fellows over the past 33 years. Dr. Greenberger received an undergraduate degree from Purdue University with highest distinction and a medical degree from Indiana University in Indianapolis, where he did his internship at the Methodist Hospital. He completed an internal medicine residency at the Jewish Hospital of St. Louis, Washington University. He was a fellow in allergy-immunology at Northwestern University, where he has been a faculty member since 1977. Dr. Greenberger's research interests include reduction of allergic antibody reactivity utilizing the neuropeptide substance P, idiopathic anaphylaxis, drug allergy, severe and fatal asthma, and allergic bronchopulmonary aspergillosis. Dr. Greenberger has published 260 original articles and 90 reviews and book chapters. He is coeditor of *Patterson's Allergic Diseases* and all three editions of the Northwestern University Allergy-Immunology Syllabus: Residents and Students and Drug Allergy and Protocols for Management of Drug Allergies. Dr. Greenberger reviews manuscripts for many journals and was co-editor-in-chief of *Allergy and Asthma Proceedings* for 12 years. He has contributed to various practice parameters in the field of allergy-immunology and served as chair of the Allergy-Immunology Residency Review Committee of the Accreditation Council on Graduate Medical Education. Dr. Greenberger is a recipient of the Special Recognition and Distinguished Service Award of the American Academy of Allergy, Asthma and Immunology, of which he served as president during 2009 and 2010.

**Daniel F. Heitjan**, **Ph.D., M.Sc.,** is professor of biostatistics and statistics and director of the Biostatistics Core Facility in the Abramson Cancer Center at the University of Pennsylvania. After earning a Ph.D. in statistics from the University of Chicago in 1985, he served on the faculties of the University of California, Los Angeles, (1985 to 1988), Pennsylvania State University (1988 to 1995), and Columbia University (1995 to 2002) before moving to the University of Pennsylvania. He was the 1994-1995 Stanley S. Schor Visiting Scholar at Merck & Co., Inc., and was elected a fellow of the American Statistical Association in 1997 and a fellow of the Institute of Mathematical Statistics in 2012. Dr. Heitjan is an associate editor of *Statistics in Biopharmaceutical Research* and *Clinical Trials* and a statistical editor of the *Journal of the National Cancer Institute*. He was formerly a member of the Agency for Healthcare Research and Quality Healthcare Technology and Decision Sciences study section and is a regular reviewer of grants for the National Institutes of Health, Susan G. Komen for the Cure, and other agencies. He was program chair of the 2005 Joint Statistical Meetings, the largest annual statistical conference in the world; was 2009 chair of the American Statistical Association's Biometrics Section, the largest and oldest of the American Statistical Association's sections; and is currently president-elect of the Eastern North American Region of the International Biometric Society. Dr. Heitjan's research interests include the theory and methodology of statistical analysis with incomplete data, clinical trial design, Bayesian statistics, health economics, and statistical methods for smoking cessation studies. His recent research in smoking cessation involves microsimulation modeling of the cost-effectiveness of smoking cessation treatment strategies, statistical methods for the analysis of rounded daily cigarette counts, comparison of cigarette counts recorded by time line follow back and electronic momentary assessment, and statistical modeling of time-to-event data on repeated smoking quits and lapse.

**Annette C. Leland**, **M.B.A.,** graduated from Occidental College in 1980 with an A.B. in economics with an emphasis in econometrics. She received an M.B.A. in 1984 from the University of Southern California. Ms. Leland began her career as an economic forecaster at General Telephone before returning to graduate school. She subsequently held leadership roles in marketing for Redken Laboratories and for the Nutrition Counseling Institute, a start-up nutrition/weight-loss venture, where she coordinated with various local hospitals, developed a marketing campaign, and marketing materials. Ms. Leland then moved on to work as a liaison between Clinique Cosmetics and the Kaufmanns Department Store chain, overseeing branch performance, training new employees, and coordinating special events. In 1989, Ms. Leland had her first child and made the choice to be a stay-at-home parent. In 1995, her family moved to the Washington, DC, area and she became active in volunteering as a reading and art class assistant at the local elementary school and volunteering in several capacities at the Washington Waldorf School. Her second child required intensive occupational, speech, and vision therapies, which inspired Ms. Leland to dedicate her time to learning more about these issues. Ms. Leland continued to be involved in her children's schools as the family moved to Connecticut, to Italy, and then back to Washington, DC. Since returning to Washington, DC, Ms. Leland has graduated from the Northern Virginia Institute Waldorf Teacher Training program while continuing to volunteer extensively at the Washington Waldorf School, both in and out of the classroom. She has continued to actively educate herself on the medical challenges that her children encounter. Her youngest child has participated in a 2-year clinical drug trial for type 1 diabetes at the Children's Hospital of Pennsylvania, and she has dedicated significant time to learning about the disease and how clinical drug trials operate. Currently, she serves as Annual

Bazaar Chairperson, Parent Organization Steering Committee Chair, and 2nd Grade Class Reading Assistant for the Washington Waldorf School.

**Pejman Rohani, Ph.D.,** is a professor of ecology and evolutionary biology, epidemiology and complex systems at the University of Michigan. His training was in mathematics (BSc, University of Manchester, Manchester, United Kingdom) and population ecology (PhD, Imperial College, London, United Kingdom). He has held posts at the University of Georgia (2002 to 2009) and was a Royal Society University Research Fellow at the University of Cambridge (1996 to 2002). His research focuses on the population biology of infectious diseases, with a strong emphasis on the use of mathematical, computational, and statistical approaches to the elucidation of host-pathogen interactions. Currently, research in his lab focuses on the epidemiology and evolution of pertussis, dengue viruses, polio, and avian influenza viruses. He has published more than 75 papers, including 4 in *Science*, 1 in *Nature*, 2 in the Proceedings of the National Academy of Sciences of the United States of America, and 1 in *Lancet*. He has also coauthored a book on modeling infectious disease published by Princeton University Press. He has worked on numerous occasions in an advisory capacity with the World Health Organization's Quantitative Analysis of Vaccine Related Research and served on the scientific advisory board of the Center for Zoonotic, Vector-Borne and Enteric Diseases at the Centers for Disease Control and Prevention.

**Lainie Friedman Ross**, **M.D., Ph.D.,** is the Carolyn and Matthew Bucksbaum Professor of Clinical Medical Ethics; professor in the Departments of Pediatrics, Medicine, and Surgery and the College; associate director of the MacLean Center for Clinical Medical Ethics; and codirector of the Clinical and Translational Science Award at the University of Chicago. Dr. Ross has published two books on pediatric ethics: *Children, Families and Health Care Decision Making* (Oxford University Press, 1998) and *Children in Medical Research: Access Versus Protection* (Oxford University Press, 2006). She has also published more than 100 articles in peer-reviewed journals in the areas of pediatric ethics, transplantation ethics, research ethics, and genetics and ethics. Dr. Ross earned an A.B. from the Woodrow Wilson School at Princeton University (1982), an M.D. from the University of Pennsylvania School of Medicine (1986), and a Ph.D. in philosophy from Yale University (1996). She did her residency at the Children's Hospital of Philadelphia (1986 to 1988) and at Columbia University (1988 to 1989). She currently serves as the chair of the Executive Committee of the American Academy of Pediatrics Section on Bioethics and is a member of the U.S. Department of Health and Human Services Secretary's Advisory Committee on Human Research Protections.

**Pauline A. Thomas**, **M.D., F.A.A.P.,** is associate professor in the Department of Preventive Medicine and Community Health at the New Jersey Medical School (NJMS) and in the School of Public Health of the University of Medicine and Dentistry of New Jersey. She is codirector of the NJMS Preventive Medicine Residency. Previously, Dr. Thomas spent 23 years at the New York City Department of Health and Mental Hygiene (DOHMH), where she served as director of AIDS Surveillance, director of the Immunization Program, and assistant commissioner for surveillance. Her work at DOHMH included development of the World Trade Center Health Registry, studying the health effects of more than 70,000 people exposed to the aftermath of the disaster at the World Trade Center on September 11, 2001. Dr. Thomas received undergraduate

and medical degrees from Yale University. She completed a residency in pediatrics at the University of Rochester and after her residency joined the Centers for Disease Control and Prevention's Epidemic Intelligence Service. She is chair of the Epidemiology Section of the American Academy of Pediatrics (AAP). She recently served on the Institute of Medicine Adverse Effects of Vaccines Committee. Dr. Thomas has authored more than 60 journal articles and maintains a small part-time private pediatric practice in a multispecialty medical group in New Jersey.

# Appendix G

# Institute of Medicine Publications on Vaccines

- *Adverse Effects of Vaccines: Evidence and Causality* (2012)
- *Ranking Vaccines: A Prioritization Framework: Phase I: Demonstration of Concept and a Software Blueprint* (2012)
- The 2009 H1N1 Influenza Vaccination Campaign: Summary of a Workshop Series (2010)
- The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic: Global Challenges, Global Solutions: Workshop Summary (2009)
- *Live Variola Virus: Considerations for Continuing Research* (2009)
- *Priorities for the National Vaccine Plan* (2009)
- Initial Guidance for an Update of the National Vaccine Plan: A Letter Report to the National Vaccine Program Office (2008)
- *Battling Malaria: Strengthening the U.S. Military Malaria Vaccine Program* (2006)
- John R. La Montagne Memorial Symposium on Pandemic Influenza Research: Meeting Proceedings (2006)
- *The Smallpox Vaccination Program: Public Health in an Age of Terrorism* (2005)
- *Vaccine Safety Research, Data Access, and Public Trust* (2005)
- *Immunization Safety Review: Vaccines and Autism* (2004)
- *Immunization Safety Review: Influenza Vaccines and Neurological Complications* (2004)
- *Financing Vaccines in the 21st Century: Assuring Access and Availability* (2003)
- *Immunization Safety Review: Vaccinations and Sudden Unexpected Death in Infancy* (2003)
- Review of the Centers for Disease Control and Prevention's Smallpox Vaccination Program Implementation, Letter Report 1 (2003)
- Review of the Centers for Disease Control and Prevention's Smallpox Vaccination Program Implementation, Letter Report 2 (2003)

- Review of the Centers for Disease Control and Prevention's Smallpox Vaccination Program Implementation, Letter Report 3 (2003)
- Review of the Centers for Disease Control and Prevention's Smallpox Vaccination Program Implementation, Letter Report 4 (2003)
- Review of the Centers for Disease Control and Prevention's Smallpox Vaccination Program Implementation, Letter Report 5 (2003)
- Review of the Centers for Disease Control and Prevention's Smallpox Vaccination Program Implementation, Letter Report 6 (2003)
- Setting the Course—A Strategic Vision for Immunization. Part 3: Summary of the Los Angeles Workshop (2003)
- Setting the Course—A Strategic Vision for Immunization. Part 4: Summary of the Washington, DC, Workshop (2003)
- *The Anthrax Vaccine: Is It Safe? Does It Work?* (2002)
- *An Assessment of the CDC Anthrax Vaccine Safety and Efficacy Research Program* (2002)
- *Considerations for Viral Disease Eradication: Lessons Learned and Future Strategies* (2002)
- *Immunization Safety Review: Hepatitis B Vaccine and Demyelinating Neurological Disorders* (2002)
- *Immunization Safety Review: Multiple Immunizations and Immune Dysfunction* (2002)
- *Immunization Safety Review: SV40 Contamination of Polio Vaccine and Cancer* (2002)
- *Protecting Our Forces: Improving Vaccine Acquisition and Availability in the U.S. Military* (2002)
- Scientific and Policy Considerations in Developing Smallpox Vaccination Options: A Workshop Report (2002)
- Setting the Course—A Strategic Vision for Immunization Finance. Part 1: Summary of the Chicago Workshop (2002)
- Setting the Course—A Strategic Vision for Immunization. Part 2: Summary of the Austin Workshop (2002)
- Presidential Address
- *Immunization Safety Review: Measles-Mumps-Rubella Vaccine and Autism* (2001)
- *Immunization Safety Review: Thimerosal-Containing Vaccines and Neurodevelopmental Disorders* (2001)
- Statement from the IOM Council on Vaccine Development (2001)
- An Assessment of the Safety of the Anthrax Vaccine: A Letter Report (2000)
- *Calling the Shots: Immunization Finance Policies and Practices* (2000)

- Urgent Attention Needed to Restore Lapsed Adenovirus Vaccine Availability: A Letter Report (2000)
- *Vaccines for the 21st Century: A Tool for Decisionmaking* (2000)
- *Preliminary Considerations Regarding Federal Investments in Vaccine Purchase and Immunization Services: Interim Report on Immunization Finance Policies and Practices* (1999)
- *Assessment of Future Scientific Needs for Live Variola Virus* (1999)
- Detecting and Responding to Adverse Events Following Vaccination: Workshop Summary (1997)
- Research to Identify Risks for Adverse Events Following Vaccination: Biological Mechanisms and Possible Means of Prevention. Workshop Summary (1997)
- Risk Communication and Vaccination Workshop Summary (1997)
- Options for Poliomyelitis Vaccination in the United States: Workshop Summary (1996)
- *Vaccines Against Malaria: Hope in a Gathering Storm* (1996)
- The Children's Vaccine Initiative: Continuing Activities (summary of two workshops) (1995)
- *Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality* (1994)
- *DPT Vaccine and Chronic Nervous System Dysfunction: A New Analysis* (1994)
- Research Strategies for Assessing Adverse Events Associated with Vaccines (summary of a workshop) (1994)
- *The Children's Vaccine Initiative: Achieving the Vision* (1993)
- *Adverse Effects of Pertussis and Rubella Vaccines* (1991)
- The Potential Value of Research Consortia in the Development of Drugs and Vaccines Against HIV Infection and AIDS (report of a workshop) (1989)
- *An Evaluation of Poliomyelitis Vaccine: Policy Options* (1988)
- Prospects for Vaccines Against HIV Infection (report of a conference) (1988)
- Temperature-Stable Vaccines for Developing Countries: Significance and Development Strategies (summary of a workshop) (1987)
- *New Vaccine Development: Establishing Priorities. Volume II, Diseases of Importance in Developing Countries* (1986)
- *New Vaccine Development: Establishing Priorities. Volume I, Diseases of Importance in the United States* (1985)
- *Vaccine Supply and Innovation* (1985)
- *Evaluation of Poliomyelitis Vaccines* (1977)