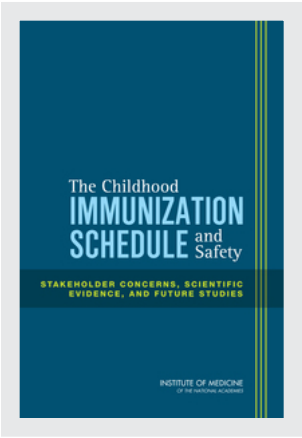

The Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies (2013)

DETAILS

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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.

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

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.

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 five deliberative meetings over 6 months. To address its charge, the committee requested from consultant Martin Kulldorff a commissioned paper on study designs that could be used to assess the safety of the immunization schedule (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.

STAKEHOLDER 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 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

[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.

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 stakeholder 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 the number of doses, the age of administration, and the 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.

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.

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?

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.

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.

Second, 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 of 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 immu-

nization 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 STAKEHOLDER 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 stakeholder 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 that includes careful study of safety concerns is needed. 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, based on the literature, the committee made a judgment 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 stakeholder 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 the 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 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 stakeholder 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.