Executive Summary

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ABSTRACT

By two years of age, healthy infants in the United States can receive up to 20 vaccinations to protect against 11 diseases. Although most people know that vaccines effectively protect against serious infectious diseases, approximately one-quarter of parents in a recent survey believe that infants get more vaccines than are good for them, and that too many immunizations could overwhelm an infant's immune system. The Immunization Safety Review Committee reviewed the evidence regarding the hypothesis that multiple immunizations increase the risk for immune dysfunction. Specifically, the committee looked at evidence of potential biological mechanisms and at epidemiological evidence for or against causality related to risk for infections, the autoimmune disease type 1 diabetes, and allergic disorders.

There are reasonable theories for how vaccines could cause these effects. However, for allergic disease and type 1 diabetes, the evidence from animal and clinical studies is weak that relevant biological mechanisms operate in humans after receipt of vaccines. The biological mechanisms evidence regarding increased risk for infections is strong. However, the committee found that the epidemiological evidence (i.e., from studies of vaccine-exposed populations and their control groups) favors rejection of a causal relationship between multiple immunizations and increased risk for infections and for type 1 diabetes. The epidemiological evidence regarding risk for allergic disease, particularly asthma, was inadequate to accept or reject a causal relationship.

These immune disorders carry heavy individual and societal burdens, and serious vaccine-preventable disease could increase if parents unnecessarily avoid immunizing their children due to continuing concerns about this issue.

Because vaccines are given to healthy children to protect others in addition to themselves, it is important to understand fully the possible risks of serious adverse consequences of vaccines. Therefore, the committee recommends continued attention in the form of policy analysis, research, and communication strategy development. However, the committee does not recommend a review by national and federal vaccine-related advisory bodies of the licensure or schedule of administration of the vaccines administered to infants in the United States on the basis of concerns about immune dysfunction. See Box ES-1 for a summary of all conclusions and recommendations.

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Immunization to protect infants and children from vaccine-preventable diseases is one of the greatest achievements of public health. Immunization is not without risks, however. It is well established, for example, that the oral polio vaccine can on rare occasion cause paralytic polio.

The Immunization Safety Review Committee was established by the Institute of Medicine (IOM) to evaluate the available evidence on a series of immunization safety concerns. While all of the committee members share the view that immunization is generally beneficial, none of them has a vested interest in the specific immunization safety issues that come before the group.

For each hypothesis to be examined, the committee assesses both the scientific evidence and the significance of the issue for society.

- The *scientific* assessment has two components: an examination of the epidemiological and clinical evidence regarding a possible causal relationship between the immunization and the adverse event, and an examination of experimental evidence for any biological mechanism(s) relevant to the hypothesis.
- The *significance* assessment addresses such considerations as the burden of the health risks associated with the vaccine-preventable disease and with the adverse event in question, as well as the level of public concern about the safety issue.

In this report, the committee examines the hypothesis that receipt of multiple immunizations adversely affects the developing immune system.

The examination of experimental evidence for biological mechanisms has been referred to in previous reports of this committee (IOM, 2001a, 2001b) and others (IOM, 1991, 1994) as an assessment of "biological plausibility." The committee has noted, however, that the term is a source of confusion on at least two fronts. First, it is associated with a particular set of guidelines (sometimes referred to as the Bradford Hill criteria) for causal inference from epidemiological evidence; and second, readers sometimes regard the term with a degree of certainty or precision the committee never intended. For example, a relationship

between immunization and a particular adverse event may be found to be biologically plausible at the same time that the epidemiological evidence is found to be inadequate to accept or reject a causal relationship.

Given the resulting lack of clarity, the committee believes that the adoption of new terminology and a new approach to its discussions of experimental biological data are warranted. The committee will thus review evidence regarding "biological *mechanisms*" that might be consistent with the proposed relationship between immunization and a given adverse event. This biological assessment section of the report is written distinct from any argument regarding the causality of such relationships.

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Beginning with this report, the committee will summarize the biological mechanisms as theoretical only, or as having derived from either experimental evidence in animals or *in vitro* systems or from mechanism-related, biological evidence in humans of response to vaccine or infectious disease antigen. If there is either experimental evidence (e.g., from animals) or evidence in humans for a mechanism, the committee will designate it as weak, moderate, or strong. Though the committee tends to judge biological evidence in humans to be "stronger" than experimental evidence, the strength of the evidence also depends on other factors, such as experimental design and sample size. The conclusions drawn from this review will depend both on evidence and scientific judgment.

UNDER REVIEW

Over the past two decades, the pediatric immunization schedule has grown more complicated. In 1980, infants received immunizations against four diseases (diphtheria, tetanus, pertussis, and polio). Today, a healthy infant immunized in complete accord with the recommended childhood immunization schedule receives up to 15 doses of five vaccines to protect against seven diseases by 6 months of age and up to 20 doses of seven vaccines to protect against 11 diseases by 2 years of age. According to a recent survey, a substantial minority of parents (23–25%) believes that getting too many immunizations weakens a child's immune system and that children get more immunizations than are good for them (Gellin et al., 2000).

The Immunization Safety Review Committee was asked to address the hypothesis that multiple immunizations can adversely affect the developing immune system. One particular concern, for example, is related to increases in the incidence of diseases such as asthma and type 1 diabetes—conditions associated with immune system dysfunctions. Although genetic factors are known to affect the risk of these diseases, increases in their incidence seem more likely to reflect changes in environmental exposures than in the genetic makeup of a population. Immunization has been proposed as one possible adverse environmental modifier of immune function.

To conduct its review, the committee had to establish a clear statement of the question before it, as well as a manageable scope of inquiry. The committee focused on exposure to multiple immunizations during infancy (less than two years of age), a period of active immune system development. The committee included studies of "one vaccine" if it contained antigens against more than one disease or more than one strain of infectious agent. For example, the diphtheria and tetanus toxoids and pertussis vaccine would be considered to represent "multiple immunization." The committee restricted its considerations regarding causality to those vaccines used in the United States.

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Because immune system dysfunction is a broad term—adverse outcomes can result from stimulation of harmful immune responses or suppression of beneficial immune responses—the committee had to define it for the purposes of this study. The scope of the committee's inquiry can be summarized in the following three questions:

1. Do multiple immunizations have adverse short-term effects on the developing infant immune system that are reflected in increased susceptibility to heterologous infection (infections other than those targeted by the immunization)?
2. Does exposure to multiple antigens, as administered in vaccines, directly and permanently redirect or skew the immune system toward autoimmunity, as reflected in type 1 diabetes?
3. Does exposure to multiple antigens, as administered in vaccines, directly and permanently redirect or skew the immune system toward allergy, as reflected in asthma?

The committee was unable to address the concern that repeated exposure of a susceptible child to multiple immunizations over the developmental period may also produce atypical or non-specific immune or nervous system injury that could lead to severe disability or death (Fisher, 2001). There are no epidemiological studies that address this. Thus, the committee recognizes with some discomfort that this report addresses only part of the overall set of concerns of some of those most wary about the safety of childhood immunization.

The committee collected information from several sources. At an open scientific meeting in November 2001 (see Appendix C), academic researchers gave presentations on specific scientific issues germane to the topic. All information presented to the committee at that meeting can be viewed on the project website (www.iom.edu/imsafety). In addition, an extensive review was performed of the published, peer-reviewed scientific and medical literature. (see Appendix D).

Autoimmune Diseases

Collectively, diseases of autoimmunity affect 3 to 5 percent of the population in the United States (Jacobson et al., 1997). Autoimmune diseases are mediated by T cell and/or T cell-dependent B cell responses directed against self-

antigens, and the T cell responses in most autoimmune diseases are dominated by interferon-_ producing CD4 T cells, commonly referred to as Th1 T cells (Marrack et al., 2001). An autoimmune process can target individual organs, such as the central nervous system in multiple sclerosis, or can operate throughout the body, as in systemic lupus erythematosus. For this report, the committee focused on type 1a diabetes, which is associated with an autoimmune-mediated loss of insulin-secreting pancreatic cells. (Type 1b refers to diabetes associated with a loss of insulin secretion, for reasons unknown. Many epidemiological studies do not distinguish between these two types.) Type 2 diabetes is not associated with destruction of insulin-secreting cells. Type 1 diabetes has been referred to as "childhood" or insulin-dependent diabetes, while type 2 diabetes has been referred to as "adult-onset" diabetes. However, the onset of either form of the disease can occur at any age.

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Worldwide, estimates of the incidence of type 1 diabetes in children under 14 years of age range from 0.1 per 100,000 in parts of China and Venezuela to 36.8 per 100,000 in Sardinia and 36.5 per 100,000 in Finland (Karvonen et al., 2000). As reported by Karvonen and colleagues (2000), estimated incidence for the early 1990s in the United States locations range from 11.7 per 100,000 in Chicago to 17.8 per 100,000 in Allegheny County, Pennsylvania.

Allergic Diseases

Allergy is responsible for a variety of acute and chronic health problems, including anaphylaxis, rhinitis, asthma, and allergic eczema. These conditions reflect an overreaction of the immune system to allergens—normally harmless environmental agents such as pollens, dust mites, insect venom, and certain foods. Under certain circumstances, exposure to an allergen primes the immune system for hypersensitivity reactions involving allergen-specific IgE antibodies and Th2 cells.

The committee focused on allergic asthma. Characteristic symptoms of asthma are episodes of shortness of breath, coughing, wheezing, and chest tightness. These symptoms reflect an acute bronchial hyperresponsiveness to specific allergens and other environmental factors, and a chronic inflammation of the airways (IOM, 2000; Parham, 2000).

The prevalence of asthma has increased in the United States and other countries over the past 30 years (Grant et al., 1999). An international study of asthma in children found that prevalence was higher in more developed countries (Asher and Weiland, 1998). In the United States, the prevalence rates of self-reported asthma rose from 3.1 percent in 1980 to 5.4 percent in 1994, an increase of 74 percent (Mannino et al., 1998). For children aged 0 to 4 years, rates increased by 159 percent during this period (from 2.2 percent to 5.7 percent). Increases in asthma prevalence were seen in all race, sex, age, and regional groups in the United States.

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Antigen Load

Central to the concerns about multiple childhood immunizations is whether the recommended schedule overloads an infant's immune system. That is, are there quantitative or qualitative aspects of the antigens to which an infant is exposed through immunization that lead to an inability of the developing immune system to respond appropriately?

Calculations reviewed by the committee (Kollman, 2001; Offit et al., 2002) suggest that the number of antigens contained in the complete set of vaccines that comprise the recommended childhood immunization schedule has actually decreased over the past 20 to 30 years, despite the increased number of vaccines and vaccine doses administered. The removal from the schedule of two vaccines, smallpox and the whole cell pertussis vaccine, accounts for this decrease. Routine use of the smallpox vaccine, which contained approximately 200 distinct and potentially antigenic elements, was discontinued in the United States in 1971. The whole-cell pertussis vaccine was replaced by an acellular vaccine, the first of which was approved by the FDA in 1991. The whole-cell vaccine contained approximately 3,000 distinct and potentially antigenic components, whereas the acellular vaccine contains only 2–5 antigens.

Vaccines added to the immunization schedule over the past 20 years have relatively few antigens. For example, the hepatitis B vaccine contains only one antigen. Therefore, the decrease in vaccine antigens from the removal of smallpox and whole cell pertussis vaccines far exceeds the increase of antigens from the addition of newer vaccines added to the schedule.

Another question is whether infants are capable of responding adequately to the antigens presented by immunization. Although the numbers of different T cell receptors present in human neonates has not been determined directly, their diversity has been shown by several groups to be similar to that of the adults. This is the basis for the notion that human infants have the capacity to respond to the substantial number of foreign molecules (e.g., bacterial antigens) to which they are exposed shortly after birth. This is consistent with the theoretical estimates presented to the committee, which suggest that the capacity of the infant's immune system is at least 1000 times greater than that maximally required to respond to vaccines (Kollman, 2001; Offit et al., 2002).

Over the course of several decades, the antigen load presented to the developing immune system has undergone significant qualitative changes, particularly in the context of the total antigen exposures during infancy and childhood. Approximately a decade ago, researchers interested in the changing epidemiology of several diseases began formulating the "hygiene hypothesis." This hypothesis suggests that the increasingly aseptic environment in which children in developed countries live has led to changes in the development of the immune system, causing an increase in allergic disease (Rook, 2000; Strachan, 2000; Wills-Karp et al., 2001). In keeping with the hygiene hypothesis, factors that

decrease the risk for allergy include the presence of pets, infections through the fecal-oral route, and rural living.

The proposed explanation for an immune system role in these epidemiological observations is that early exposure to infectious diseases and environmental microbes "shapes" the developing immune system toward a Th1[1] cell responsiveness, which is generally considered a protective immune response (i.e., to host defense against intracellular pathogens and allergy). Eliminating these early exposures through hygienic practices and altered behaviors is thought to predispose the immune system toward a Th2[2] cell responsiveness, which is associated with allergy.

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The most recent refinement of the hygiene hypothesis includes regulatory cell imbalance (Rook, 2001; Wills-Karp et al., 2001). This Th2-skewing or regulatory cell imbalance, some theorize, is exacerbated by exposure to vaccines, many of which evoke a Th2 response instead of the Th1 response that would be generated by wild-type infections with the diseases that the immunizations prevent.

Not yet clear is the role vaccines may have in directly altering the development of the immune system, or the relative contribution of immunization-related changes in the context of the hygiene hypothesis. Vaccine-induced immune responses may differ from those resulting from wild-type infection because of differences in context, including differences in their timing, either in terms of age at exposure or of the sequence of antigen exposure. Most certainly, the route of exposures—that is, an injection rather than a respiratory or gastrointestinal exposure—is different from what it had been. Under debate is whether that difference in exposure is associated with adverse health outcomes.

In any case, the number of infections prevented by immunization is actually quite small compared with the total number of infections prevented by other hygienic interventions such as clean water, food, and living conditions.

SCIENTIFIC ASSESSMENT

Causality

Heterologous Infection

The committee reviewed several case-control or cohort studies (Black et al., 1991; Burstein and Fleisher, 1994; Davidson, 1991; Griffin et al., 1992; Kristensen et al., 2000) and a randomized controlled trial (Otto et al., 2000). Vaccine

[1] Th1 (h stands for helper) cells travel to the site of infection and secrete cytokines that mainly activate macrophages. Upon activation, macrophages will phagocytose extracellular pathogens and then kill them.

[2] The primary function of Th2 cells is to stimulate B cells to make antibodies which bind to extracellular bacteria and virus particles. Th2 cells work within secondary lymphoid tissue.

exposure varied among the studies but fit the committee's definition of exposure to "multiple immunizations." The studies examined the effects of adding one vaccine to an existing immunization schedule, of one vaccine dose consisting of antigens from more than one infectious agent or strain of virus (e.g., DTP, OPV, or MMR), or of several vaccines received at the same time. Outcome measures in the studies also varied, with the "disease" group including subjects who had a positive culture to invasive bacterial disease, who had symptoms related to infectious diseases, or who had died. Limitations of the studies included a potential health care utilization bias and high dropout rates. Despite these variations and limitations, the overall findings from the studies consistently demonstrated either no effect or a beneficial effect of multiple immunizations on heterologous disease. **Therefore, the committee concludes that the epidemiological and clinical evidence favors rejection of a causal relationship between multiple immunizations and an increased risk of heterologous infections.**

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Type 1 Diabetes

The committee found five controlled studies (Blom et al., 1991; DeStefano et al., 2001; EURODIAB, 2000; Heijbel et al., 1997; Karvonen et al., 1999) and three ecological studies (Classen, 1996; Hiltunen et al., 1999; Hyoty et al., 1993) that examined this relationship. The studies looked at the effects of adding one vaccine to an existing immunization schedule, of one vaccine dose consisting of antigens from more than one infectious agent or strain of virus (e.g., DTP, OPV, or MMR), or of several vaccines received at the same time. Despite these variations, the overall findings from the studies consistently demonstrated no effect of multiple immunizations on the incidence of type 1a diabetes. **Therefore, the committee concludes that the epidemiological and clinical evidence favors rejection of a causal relationship between multiple immunizations and an increased risk of type 1 diabetes.**

Allergic Disease

The committee reviewed five studies that utilized controls (Farooqi and Hopkin, 1998; Hurwitz and Morgenstern, 2000; Kemp et al., 1997; Wickens et al., 2001), including a randomized controlled trial (Nilsson et al., 1998) and one ecological study (Anderson et al., 2001). Outcomes assessed included allergic symptoms (wheezing) and allergic disorders (hay fever and asthma). All the studies examined exposure to DTaP or DTwP, and other vaccines given concurrently, such as MMR and polio vaccines, but no two studies examined exactly the same exposure.

While many of these studies reported elevated odds ratios linking immunizations to some allergic outcome, some of which were statistically significant, methodological weaknesses within individual studies, as well as the pattern of

results across studies diminish the confidence that the observed associations reflect causal relationships. In the two studies that reported a significant positive effect of DTP or tetanus immunization or the pertussis component of DTwP (Farooqi and Hopkin, 1998; Hurwitz and Morgenstern, 2000), potential sampling bias, caused by substantial losses to follow-up or restriction to subjects with regular medical care, could have distorted the relationship between immunization and allergies.

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A problem in most of the studies was that the number of unvaccinated children was small, limiting the ability to control for potentially confounding factors, which are numerous and strong for the outcomes of asthma and atopy, and particularly complex when considering risk over an entire childhood. Adequate control of confounding is a serious issue for observational designs, particularly in this domain, as nonimmunized children typically differ on baseline characteristics from immunized children in ways that are not always measurable.

Finally, the findings of the studies, taken as a whole, did not show a consistency of findings that would outweigh the concerns about individual studies. While some studies pointed to the pertussis vaccine as a risk factor for allergic syndromes with no effect of MMR, another found that MMR vaccine was the strongest risk factor. The ecological study indicated a protective DPT effect, and the only randomized study indicated minimal or no effect of pertussis vaccines, with a non-significant reduction in risk from the whole-cell vaccine.

Given the design weaknesses in the observational studies, and a randomized trial study that does not support the risk factor most frequently implicated in the observational studies, **the committee concludes that the epidemiological and clinical evidence is inadequate to accept or reject a causal relationship between multiple immunizations and an increased risk of allergic disease, particularly asthma.**

Biological Mechanisms

Although biological data do not provide an independent basis for evaluating causality, they can help validate epidemiologically based conclusions for or against causal associations; such data can also guide further investigation when epidemiological evidence is inconclusive. The mechanisms considered by the committee represent two possible pathways to adverse outcomes: stimulation of harmful immune responses, or suppression of beneficial immune responses. The stimulation of harmful immune responses involves the mechanisms of molecular mimicry,[3] bystander activation, [4] and nonspecific or polyclonal T-cell and/or B-

[3] Molecular mimicry is the antigenic similarity between a pathogen antigen and a cellular antigen which results in the induction of antibodies or T cells that act against the pathogen but also cross-react with the self antigen (Parham, 2000).

cell activation. The suppression of beneficial immune responses is addressed in terms of the hygiene hypothesis and the prevention of potentially protective infections through immunization.

In theory, molecular mimicry, bystander activation, and impaired immunoregulatory mechanisms might act in an additive or synergistic manner to affect the risk of autoimmunity. There is, however, no experimental evidence for molecular mimicry by any of the vaccines in the current routine childhood immunization schedule to create an antigenic epitope[5] capable of cross-reaction with self epitopes. **Therefore, in the absence of experimental or human evidence regarding molecular mimicry or mercury-induced modification of any vaccine component to create an antigenic epitope capable of cross-reaction with self epitopes as a mechanism by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity, the committee concludes that these mechanisms are only theoretical.**

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There is some evidence of a bystander effect associated with immunization, but this effect is 1) relatively modest compared to those resulting from wild-type infection, 2) most evident to co-administered vaccine antigens rather than other environmental antigens or infections and 3) inconsistently shown. Current vaccines have, on balance, weak or no Th1-inducing activities. BCG appears to demonstrate the principle for co-administered antigens. However, BCG is not used in the U.S., so the relevance for this mechanism in the effects of the U.S. recommended schedule is not demonstrated. Viral vaccines carry some potential for bystander activation, but likely would have a small effect, if it occurs at all. The data on DTaP vaccine indicates that Th1 dominance is not prominent. There is also no evidence in humans that vaccine antigens lead to the pathophysiological disease state. The limited evidence from humans that does exist regards surrogates of the disease process, that is, just some components of the events that would need to take place for the appearance of clinically relevant pathophysiology. **Thus, the committee concludes that there is weak evidence for bystander activation, alone or in concert with molecular mimicry, as a mechanism by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity.**

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

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[4] Bystander activation results when an infection creates environmental conditions that allow the activation of self-reactive T and B cells that are normally held in check. It does not require that antigens of the infectious agent be structurally similar to self-antigens.

[5] An epitope is a molecule's specific antigenic site that is bound by an antibody.

this mechanism is only theoretical. On balance, the current recommended childhood immunization schedule in the United States appears less likely to act as an initiator or facilitator of autoimmunity than the schedule of the past.

On a numerical basis, vaccine-preventable infections represent a minute fraction of the overall infectious and microbial exposure in childhood. For immunization to have an impact on autoimmunity under the hygiene hypothesis, it would be necessary for one or more vaccine-preventable diseases to be particularly important for conditioning immunoregulatory immune responses. The gastrointestinal tract is thought to play a particularly critical role in this process, so it would follow that immunizations that affect infection or colonization of the gut would be good candidates, but none of the childhood vaccines currently in use do so. Data from animal models suggest that no one infection is likely to be key, but rather a global reduction in microbial contact could be a factor.

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The theory by which the hygiene hypothesis, originally proposed on the basis of epidemiological data, could explain an increase in incidence of autoimmune (or allergic) disease is substantial, and the biological evidence in support of the hygiene hypothesis is moderate. However, the potential contribution of vaccine-preventable diseases as part of this model is minimal. **Therefore, in the absence of experimental or human evidence regarding mechanisms related to the hygiene hypothesis as a means by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity, the committee concludes that this mechanism is only theoretical.**

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

The biological mechanisms by which immunizations that contain microbial stimuli favor Th1 responses and immunizations containing alum favor Th2 responses are well established. Although the impact of immunization on heterologous allergic responses is unknown, on balance the current routine childhood immunization schedule in the United States is less likely to favor Th1 responses to heterologous antigens and more likely to favor Th2 responses. **The committee concludes that there is weak evidence for bystander activation as a mechanism by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of allergy.**

The theory by which the hygiene hypothesis could explain an increase in incidence of allergic diseases is substantial. However, the potential contribution of vaccine-preventable diseases as part of this hypothesis is minimal. **In the absence of experimental or human evidence regarding mechanisms related to the hygiene hypothesis as a means by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an indi-**

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

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

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SIGNIFICANCE ASSESSMENT

The committee's assessment of the significance of concerns about possible immune system dysfunctions took several factors into consideration: the burden of the possible adverse outcomes of autoimmune diseases such as type 1 diabetes and allergic diseases such as asthma; indications of the extent of the concern about multiple immunizations; and views regarding the framework for immunization policy-making.

Although parents appear to value immunization, a substantial minority (23-25%) believes that multiple immunizations could be harmful (Gellin et al., 2000). Autoimmune and allergic diseases are common in the United States, after all, and the incidence of these conditions appears to be increasing. As represented by type 1 diabetes and asthma, these conditions are life-threatening if not adequately treated and are associated with substantial health care costs.

A better understanding of parents' perceptions of risk and decisionmaking may be necessary in order to prevent decreases in immunization rates and increases in vaccine-preventable disease. Current approaches to immunization policy-making emphasize epidemiological and economic considerations, but a recent paper suggests that these policies may benefit from greater attention to ethical issues, including personal liberty and equity in allocation of the benefits and burdens of immunization (Feudtner and Marcuse, 2001). **Thus, the committee concludes that concern about multiple immunizations has been, and could continue to be, of societal significance in terms of parental worries, potential health burdens, and future challenges for immunization policy-making.**

RECOMMENDATIONS REGARDING PUBLIC HEALTH RESPONSE

With government and professional recommendations calling for young children to receive increasing numbers of immunizations, it is important to respond to concerns about possible increases in risk of allergic or autoimmune diseases. Although the committee's review points to no causal relationship between multiple immunizations and type 1 diabetes or risk of infection, and the

review is inconclusive for asthma, the biological evidence does provide weak support for increased risk of allergy and autoimmunity and strong support for increased risk of infection (see Table ES-1 for summary). Further study of such associations poses difficult scientific challenges, and relevant epidemiological evidence remains limited. Several important scientific and policy issues, therefore, deserve further public health attention.

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Policy Review

The nature of the childhood immunization schedule is likely to change in response to such factors as the development of new vaccines and utilization of novel delivery systems. Changing perceptions of disease risks—derived from antibiotic resistance, threats of bioterrorism, or (re)emerging infectious diseases—could also lead to wider use of existing vaccines not currently included in the immunization schedule. As the array of available vaccines and disease targets expands the current emphasis on universal recommendations and state mandates for vaccine use should be reassessed (Feudtner and Marcuse, 2001). **The committee recommends that state and federal vaccine policymakers consider a broader and more explicit strategy for developing recommendations for the use of vaccines.**

Feudtner and Marcuse (2001) have provided a beginning for such discussion by urging consideration of a range of perspectives (e.g., those of individuals, families, organizations, society) regarding the benefits, risks, and ethical implications of vaccine use and immunization policies. Priorities can be expected to differ among the diverse perspectives, and policymakers must consider how to achieve an equitable balance. These issues require long-term planning and evaluation; a reactive response to the next schedule addition will be much less effective than a proactive assessment and strategy development across-the-board.

As part of this overall effort, the committee encourages an exploration of the merits of accommodating requests for alternative vaccine-dosing schedules and the development of appropriate clinical guidance for any such alternatives. A more flexible schedule might allow for a reduction in the number of vaccines administered at one time. Such a change would respond to some concerns about multiple immunizations; but it would also have disadvantages, such as requiring more health care visits, that might contribute to lower rates of immunization coverage in the population and consequent increases in morbidity and mortality. In addition, such a change would require extensive communication with health-care providers and health plans in order that appropriate immunizations occur and are reimbursed equivalently to those on the "traditional" schedule.

By issuing the recommendation above, the committee does not intend to signal concern about health consequences of the multiple immunizations in the recommended childhood immunization schedule. In fact, **the committee does not recommend a policy review—by the CDC's Advisory Committee on**

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

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

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Research

The committee concluded that the findings available from epidemiological sources and consideration of possible biological mechanisms do not at this time warrant specialized studies of possible associations between multiple immunizations and immune system dysfunction. Instead, the committee encourages epidemiological studies on immunization safety conducted within the framework of ongoing research and surveillance programs on allergy, autoimmune disease, and vaccine safety; it also encourages additional basic research on the immune system and on allergy and autoimmune diseases.

The committee emphasizes the need for continuing surveillance of vaccine recipients and possible adverse events. Changes in the immunization schedule may present opportunities to study whether or not the incidence of adverse health outcomes also changes. Several vaccine-related data resources already exist, including the Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD), and state and local immunization registries. **The committee recommends exploring the feasibility of using existing vaccine surveillance systems, alone or in combination, to study safety questions related to asthma and other important allergic disorders, as well as to study type 1 diabetes and other important autoimmune diseases.** An important component of such research will be the use of uniform standards of observation and evaluation.

In addition, surveillance of autoimmune diseases and allergic disorders should be strengthened. Disease registries and long-term research programs that identify individuals with these diseases, or with known genetic risk factors, could be an efficient means of finding subjects for either retrospective or prospective studies of possible vaccine-related risks. **The committee recommends exploring the use of such cohorts for research on possible vaccine-related disease risks. Furthermore, the committee recommends that disease registries and research programs for autoimmune and allergic disorders routinely collect immunization histories as part of their study protocols.**

Research on the developing human immune system, especially in relation to vaccines, is limited. Studies of animal models are essential to advancing knowledge of the immune system, but those studies have limits because of important

differences between humans and animals. Thus, **the committee recommends continued research on the development of the human infant immune system.**

Genetic factors are known to be an important source of variability in the responses of the human immune system and in the risk of allergic or autoimmune disease. But understanding of the complex interactions among genetic variables, as well as of the interactions between those variables and environmental exposures (including vaccines and wild-type viral and bacterial agents), remains incomplete. **The committee endorses current research efforts aimed at identifying genetic variability in human immune system development and immune system responsiveness as a way to gain a better understanding of genetic susceptibility to vaccine-based adverse events.**

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For some autoimmune and allergic disorders, surrogate biological markers of disease or disease risk have been identified. In particular, in individuals at risk for type I diabetes, the development of multiple autoantibodies to GAD65 (glutamic acid decarboxylase), IA-2 (protein tyrosine phosphatase-like molecule), and insulin correlate strongly with later development of overt type I diabetes (Notkins and Lernmark, 2001). However, there are to date no other surrogate markers that have sufficient predictive power to be useful in monitoring risk for other autoimmune diseases in children receiving routine immunizations (Leslie et al., 2001). For allergic disorders, the clinical history of allergic diseases should be collected in follow-up evaluations, and the feasibility of specific tests for atopy considered. In theory, collecting data on known markers in the course of vaccine research and testing would present an opportunity to study the prevalence of such markers before and after vaccination. Similarly, it might also be possible to study whether the prior presence of a marker was associated with differences in the response to a vaccine. **The committee recommends exploring the feasibility of collecting data on surrogate markers for type I diabetes and clinical history of allergic diseases in the vaccine testing and licensing process.** Such might also be useful in vaccine-related studies in high-risk cohorts. **The committee recommends exploring surrogates for type I diabetes and clinical history of allergic diseases in existing cohort studies of variations in the immunization schedule.**

Communication

Along with the increasingly complicated immunization schedule has come a dramatic increase in the complexity of immunization safety issues, and it appears that some people have redefined their conceptions of the related risks and benefits. The focus seems to have shifted from whether children will get a disease if they are not vaccinated to whether children will experience temporary or potentially longer-term adverse events if they *are* vaccinated (McPhilips and Marcuse, 2001).

The committee is not convinced, however, that available reports on such attitudes provide an adequate scientific basis for understanding either these

changes in perception or the groups that are experiencing them. More information is needed in order to develop effective risk-benefit communication strategies on immunization and immunization safety.

A deeper understanding of why and how people make decisions as they do is needed, but relying on impressions, assumptions, or any single research method (e.g., survey, focus group, mental modeling, decision analysis) will be too limited. Therefore, **the committee recommends that an appropriate panel of multidisciplinary experts be convened by the Department of Health and Human Services. It would develop a comprehensive research strategy for knowledge leading to the optimal design and evaluation of vaccine risk-benefit communication approaches.**

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SUMMARY

A review of the possible biological mechanisms for any adverse effects of multiple immunization on immune function does not support the hypothesis that the infant immune system is inherently incapable of handling the numbers of antigens presented during routine immunization.

A review of the clinical and epidemiological literature suggests that multiple immunizations do not lead to risk of infection or type 1 diabetes, and that the possible role in the risk of allergy is indeterminate. Meanwhile, the biological evidence that immunization might lead to infection, autoimmune disease, or allergy is more than only theoretical. This literature base is somewhat limited, however, and the concern is great among a significant minority of parents.

Therefore the committee recommends limited but continued public health attention to this issue in terms of exploiting current research efforts. No recommendations for policy change are made, but the committee does recommend considering new frameworks for immunization policy, particularly as the number of licensed vaccines increases.

TABLE ES-1 Biological Mechanisms for the Possible Role of Immunizations in Increasing the Risk of Immune Dysfunction

Adverse Health Outcome	Mechanism	Committee Conclusion About the Weight of the Biological Evidence
Autoimmune disease	Molecular mimicry	Theoretical only
	Bystander effect	Weak
	Loss of protection induced by homologous infection	Theoretical only
	Via the hygiene hypothesis	Theoretical only
	Collective mechanistic possibilities	Weak
Allergic disease	Bystander effect	Weak
	Via the hygiene hypothesis	Theoretical only
	Collective mechanistic possibilities	Weak
Heterologous Infections	Carrier-induced epitope suppression	Strong
	Competition for antigen presentation	

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BOX ES-1 Committee Conclusions and Recommendations

SCIENTIFIC ASSESSMENT

Causality Conclusions

The committee concludes that the epidemiological and clinical evidence favors rejection of a causal relationship between multiple immunizations and an increased risk of heterologous infections.

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

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

Biological Mechanisms Conclusions

Autoimmune Disease

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

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

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

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

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

Allergic Disease

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

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

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

Heterologous Infection

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

SIGNIFICANCE ASSESSMENT

Conclusions

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

PUBLIC HEALTH RESPONSE RECOMMENDATIONS

Policy Review

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

The committee does not recommend a policy review—by the CDC's Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics' Committee on Infectious Diseases, and the American Academy of Family Physicians—of the current recommended childhood immunization schedule on the basis of concerns about immune system dysfunction.

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

Research

Epidemiological Research

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

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

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Basic Science and Clinical Research

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

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

The committee recommends exploring the feasibility of collecting data on surrogate markers for type I diabetes and clinical history of allergic diseases in the vaccine testing and licensing process.

The committee recommends exploring surrogates for type I diabetes and clinical history of allergic diseases in existing cohort studies of variations in the immunization schedule.

Communication

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

REFERENCES

Anderson HR, Poloniecki JD, Strachan DP, Beasley R, Bjorksten B, Asher MI. Immunization and symptoms of atopic disease in children: results from the International Study of Asthma and Allergies in Childhood. *Am J Public Health.* 2001;91:1126–1129.

Asher MI, Weiland SK. The International Study of Asthma and Allergies in Childhood (ISAAC). ISAAC Steeriing Committee. *Clin Exp Allergy.* 1998;28 Suppl 5:52–66; discussion 90–91.

Black SB, Cherry JD, Shinefield HR, Fireman B, Christenson P, Lampert D. Apparent decreased risk of invasive bacterial disease after heterologous childhood immunization. *Am J Dis Child.* 1991;145:746–769.

view: Multiple Immunizations and Immune Dysfunction
talog/10306.html

Blom L, Nystrom L, Dahlquist G. The Swedish childhood diabetes study. Vaccinations and infections as risk determinants for diabetes in childhood. *Diabetologia.* 1991;34:176–181.

Burstein JL, Fleisher GR. Does recent vaccination increase the risk of occult bacteremia? *Pediatr Emerg Care.* 1994;10:138–140.

Classen JB. The timing of immunization affects the development of diabetes in rodents. *Autoimmunity.* 1996;24:137–145.

Davidson M, Letson GW, Ward JI, Ball A, Bulkow L, Christenson P, Cherry JD. DTP immunization and susceptibility to infectious diseases. Is there a relationship? *Am J Dis Child.* 1991;145:750–754.

DeStefano F, Mullooly JP, Okoro CA, Chen RT, Marcy SM, Ward JI, Vadheim CM, Black SB, Shinefield HR, Davis RL, Bohlke K. Childhood vaccinations, vaccination timing, and risk of type 1 diabetes mellitus. *Pediatrics.* 2001;108:E112.

EURODIAB. Variation and trends in incidence of childhood diabetes in Europe. EURODIAB ACE Study Group. *Lancet.* 2000;355:873–876.

Farooqi IS, Hopkin JM. Early childhood infection and atopic disorder. *Thorax.* 1998;53:927–932.

Feudtner C, Marcuse EK. 2001. Ethics and immunization policy: Promoting dialogue to sustain consensus. *Pediatrics.* 107(5):1158–1164.

Fisher BL. On behalf of National Vaccine Information Center. Letter to Kathleen Stratton. November 5, 2001.

Gellin BG, Maibach EW, Marcuse EK. 2000. Do parents understand immunizations? A national telephone survey. *Pediatrics* 106(5):1097–1102.

Grant EN, Wagner R, Weiss KB. Observations on emerging patterns of asthma in our society. *J Allergy Clin Immunol.* 1999;104:S1–9.

Griffin MR, Taylor JA, Daugherty JR, Ray WA. No increased risk for invasive bacterial infection found following diphtheria-tetanus-pertussis immunization. *Pediatrics.* 1992;89:640–642.

Heijbel H, Chen RT, Dahlquist G. Cumulative incidence of childhood-onset IDDM is unaffected by pertussis immunization. *Diabetes Care.* 1997;20:173–175.

Hiltunen M, Lonnrot M, Hyoty H. Immunisation and type 1 diabetes mellitus: Is there a link? *Drug Saf.* 1999;20:207–212.

Hurwitz EL, Morgenstern H. Effects of diphtheria-tetanus-pertussis or tetanus vaccination on allergies and allergy-related respiratory symptoms among children and adolescents in the United States. *J Manipulative Physiol Ther.* 2000;23:81–90.

Hyoty H, Hiltunen M, Reunanen A, Leinikki P, Vesikari T, Lounamaa R, Tuomilehto J, Akerblom HK. Decline of mumps antibodies in type 1 (insulin-dependent) diabetic children and a plateau in the rising incidence of type 1 diabetes after introduction of the mumps-measles-rubella vaccine in Finland. Childhood Diabetes in Finland Study Group. *Diabetologia*. 1993;36:1303–1308.

IOM (Institute of Medicine). 1991. *Adverse Events Following Pertussis and Rubella Vaccines*. Washington, DC: National Academy Press.

IOM. 1994. *Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality*. Washington, DC: National Academy Press.

IOM. 2000. *Clearing the Air*. Washington, DC: National Academy Press.

IOM. 2001a. *Immunization Safety Review: Measles-Mumps-Rubella Vaccine and Autism.* Washington, DC: National Academy Press.

IOM. 2001b. *Immunization Safety Review: Thimerosal-Containing Vaccines and Neurodevelopmental Disorders*. Washington, DC: National Academy Press.

Jacobson DL, Gange SJ, Rose NR, Graham NM. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. *Clin Immunol Immunopathol*. 1997;84:223–243.

Karvonen M, Cepaitis Z, Tuomilehto J. Association between type 1 diabetes and Haemophilus influenzae type b vaccination: Birth cohort study. *BMJ.* 1999;318:1169–1172.

view: Multiple Immunizations and Immune Dysfunction
talog/10306.html

Karvonen M, Viik-Kajander M, Moltchanova E, Libman I, LaPorte R, Tuomilehto J. Incidence of childhood type 1 diabetes worldwide. Diabetes Mondiale (DiaMond) Project Group. *Diabetes Care.* 2000;23:1516–1526.

Kemp T, Pearce N, Fitzharris P, Crane J, Fergusson D, St. George I, Wickens K, Beasley R. Is infant immunization a risk factor for childhood asthma or allergy? *Epidemiology.* 1997;8:678–680.

Kollman T. T Cell Immunity in Infants and Immune System Overload Hypothesis. Presentation to Immunization Safety Review Committee: Seattle, WA. 2001.

Kristensen I, Aaby P, Jensen H. Routine vaccinations and child survival: Followup study in Guinea-Bissau, West Africa. *BMJ.* 2000;321:1435–1438.

Leslie D, Lipsky P, Notkins AL. 2001. Autoantibodies as predictors of disease. *J Clin Invest* 108(10):1417–1422.

Mannino DM, Homa DM, Pertowski CA, Ashizawa A, Nixon LL, Johnson CA, Ball LB, Jack E, Kang DS. Surveillance for asthma—United States, 1960–1995. *Mor Mortal Wkly Rep CDC Surveill Summ.* 1998;47:1–27.

Marrack P, Kappler J, Kotzin BL. Autoimmune disease: why and where it occurs. *Nat Med.* 2001;7:899–905.

McPhillips H, Marcuse EK. 2001. Vaccine safety. *Curr Probl Pediatr* 31(4):91–121.Nilsson L, Kjellman NI, Bjorksten B. A randomized controlled trial of the effect of pertussis vaccines on atopic disease. *Arch Pediatr Adolesc Med.* 1998;152:734–738.

Notkins AL, Lernmark A. 2001. Autoimmune type 1 diabetes: Resolved and unresolved issues. *J Clin Invest* 108(9):1247–1252.

Offit PA, Quarles J, Gerber MA, Hackett CJ, Marcuse EK, Kollman TR, Gellin BG, Landry, S. Addressing parents' concerns: Do multiple vaccines overwhelm or weaken the infant's immune system? *Pediatrics.* 2002;109:124–129.

Otto S, Mahner B, Kadow I, Beck JF, Wiersbitzky SK, Bruns R. General nonspecific morbidity is reduced after vaccination within the third month of life—the Greifswald study. *J Infect.* 2000;41:172–175.

Parham P. 2000. Overreactions of the immune system. Parham P. *The Immune System*. First ed. New York: Garland Publishing. Pp. 269–297.

Rook G. Hygiene Hypothesis. Immunization Safety Review Committee Meeting: Seattle, WA. 2001.

Rook GA. Clean living increases more than just atopic disease. *Immunol Today.* 2000;21:249–250.

Strachan DP. Family size, infection and atopy: The first decade of the "hygiene hypothesis." *Thorax.* 2000;55 Suppl 1:S2–10.

Wickens K, Crane J, Kemp T, Lewis S, D'Souza W, Sawyer G, Stone L, Tohill S, Kennedy J, Slater T, Rains N, Pearce N. A case-control study of risk factors for asthma in New Zealand children. *Aust N Z J Pub Health*. 2001;25:44–49.

Wills-Karp M, Santeliz J, Karp CL. The germless theory of allergic disease: Revisiting the hygiene hypothesis. *Nature Rev Immunol*. 2001;1:69–75.