

Executive Summary

Immunization to protect infants and children from vaccine-preventable diseases is one of the greatest achievements in public health. The use of vaccines is not without risks, however. It is well established, for example, that vaccines sometimes cause anaphylactic shock, and that the oral polio vaccine can on rare occasions cause paralytic polio. Given the widespread use of vaccines, state mandates requiring vaccination of children for entry into school or daycare, and the importance of ensuring that trust in immunization programs is justified, it is essential that immunization-safety concerns receive assiduous attention.

Thimerosal, an organic mercury compound that is metabolized to ethylmercury and thiosalicylate, has been used since the 1930s as a preservative in some vaccines and pharmaceutical products to prevent bacterial and fungal contamination. In 1999, the U.S. Food and Drug Administration (FDA) determined that under the recommended childhood immunization schedule, infants might be exposed to cumulative doses of ethylmercury that exceed some federal safety guidelines established for exposure to methylmercury, another form of organic mercury (Ball et al., 2001). The methylmercury exposure limits calculated by these agencies are not limits above which injury is certain to occur. Rather, they should be interpreted as general levels of exposure below which there is confidence that adverse effects will be absent. As a precautionary measure that was part of a public health effort to minimize exposure of infants and children to mercury, a joint statement was issued in July 1999 by the American Academy of Pediatrics (AAP) and the U.S. Public Health Service (PHS) recommending removal of thimerosal from vaccines as soon as possible (CDC, 1999a). The statement also recommended a temporary

suspension of the birth dose of hepatitis B vaccine for children born to low-risk mothers until a thimerosal-free alternative became available. With the licensure of a thimerosal-free hepatitis B vaccine in August 1999 (CDC, 1999b), at least one formulation of each vaccine on the recommended childhood immunization schedule for children age six years or younger was available without thimerosal. With the FDA approval of a thimerosal-free version of DTaP vaccine in March 2001, all formulations of vaccines on the recommended childhood immunization schedule that are given to children six years of age or younger are available thimerosal-free in the United States (CDC, 2001a).

Because evidence suggests that exposure to mercury and mercurial compounds can affect the nervous system, it remains important to resolve whether or not the past presence of thimerosal in some vaccines could have caused neurodevelopmental problems. Moreover, thimerosal remains in use in many countries, which continue to depend on multi-dose supplies of vaccine that currently are protected by thimerosal from microbial contamination.

In this report, the Immunization Safety Review committee examines the hypothesis of whether or not the use of vaccines containing the preservative thimerosal can cause neurodevelopmental disorders (NDDs), specifically autism, attention deficit/hyperactivity disorder (ADHD), and speech or language delay. Autism is a complex, severe developmental disorder characterized by impairments of social interaction, communication, and behavior. ADHD is a behavioral disorder characterized by persistent patterns of inattention and/or hyperactivity. Speech or language delay refers to several disorders characterized by significant impairments in vocabulary and difficulty in forming sentences, comprehending words or sentences, or forming age-appropriate speech sounds.

The Institute of Medicine's Immunization Safety Review Committee is responsible for examining a broad variety of vaccine-safety concerns. Committee members have expertise in pediatrics, neurology, immunology, internal medicine, infectious diseases, genetics, epidemiology, biostatistics, risk perception and communication, decision analysis, public health, nursing, and ethics. While all the committee members share the view that vaccination is beneficial, none of them has a vested interest in the vaccine-safety issues that come before the group.

For each immunization-safety hypothesis to be examined, the committee has been asked by the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) to assess both its scientific plausibility and the significance of the issue in a broader societal context. The *plausibility assessment* has two components: (1) an examination of any pathogenic mechanism(s) relevant to the hypothesis, often referred to as biological plausibility; and (2) an examination of the evidence regarding a possible causal relationship between the vaccine and any adverse events, often referred to as causality. The *significance assessment* addresses such considerations as the nature of the health risks associated with the vaccine-preventable disease(s) and with the adverse event(s) in question. The findings of the plausibility and significance assess-

ments provide the basis for the committee's recommendations on *public health response*, including immunization-policy review, current and future research, and effective communication strategies.

In its review, the committee considered both published and unpublished reports and data. The committee acknowledges that its approach differs from the state of the art for evidence-based reviews of clinical practices in medicine, which does not include consideration of unpublished or non-peer-reviewed information (U.S. Preventive Services Task Force, 1996). However, the Immunization Safety Review Committee was convened specifically to assess topics of immediate and usually intense concern. In some cases, the committee's review will take place when data are only beginning to emerge. Thus, given the unique nature of this project, the committee thought it was important to review and consider unpublished information. The committee did not perform primary or secondary analyses of unpublished data, however. In general, the committee cannot rely heavily on unpublished data in making its plausibility assessment because the studies have not been subjected to a rigorous peer review process and therefore must be interpreted with caution. (All unpublished data reviewed by the committee and cited in this report are available in the form reviewed by the committee through the public access files of the National Academy of Sciences, 202-334-3543, national-academies.org/publicaccess.)

PLAUSIBILITY ASSESSMENT

Biological Plausibility

Thimerosal contains 49.6% mercury by weight. Upon administration of thimerosal, its metabolite ethylmercury quickly dissociates from thiosalicylic acid and binds to blood or other tissue. The toxicological profile of ethylmercury from thimerosal is thought to be similar to that of ethylmercury from other sources (Magos, 2001; Suzuki et al., 1963, 1973). At high doses, mercury and mercuric compounds, including thimerosal, ethylmercury, and methylmercury, are well-established as nephro- and neuro-toxicants (ATSDR, 1999; EPA, 1997; NRC, 2000). The data regarding toxicity of low doses of thimerosal and ethylmercury are very limited, and only delayed-type hypersensitivity reactions have been demonstrated. Prenatal exposure to low doses of methylmercury, however, has been associated in some studies with subtle neurodevelopmental abnormalities (EPA 1997).

The hypothesis that thimerosal exposure through the recommended childhood immunization schedule has caused neurodevelopmental disorders is not supported by clinical or experimental evidence because:

- low-dose thimerosal exposure in humans has not been demonstrated to be associated with effects on the nervous system,

- neurodevelopmental effects have been demonstrated for prenatal but not postnatal exposures to low doses of methylmercury,
- the toxicological information regarding ethylmercury, particularly at low doses, is limited,
- thimerosal exposure from vaccines has not been proven to result in mercury levels associated with toxic responses,
- signs and symptoms of mercury poisonings are not identical to autism, ADHD, or speech or language delay,
- autism is thought primarily to originate from prenatal injury, and
- there is no evidence that ethylmercury causes any of the pathophysiological changes known to be associated with autism, such as genetic defects, and there are no well-developed pathological markers of ADHD or delay of speech or language that could be compared to effects of ethylmercury on the nervous system.

The information related to biological plausibility is indirect because:

- high-dose thimerosal exposures are associated with neurological damage,
- an extensive toxicological and epidemiological literature establishes methylmercury, a close chemical relative, as a toxicant to the developing nervous system,
- some children who received the maximum number of thimerosal-containing vaccines on the recommended childhood immunization schedule had exposures to ethylmercury that exceeded some estimated limits of exposure based on federal guidelines for methylmercury intake, and
- some children could be particularly vulnerable or susceptible to mercury exposures due to genetic or other differences.

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

Causality

There are no published, controlled epidemiological studies bearing directly on the question of whether or not thimerosal-containing vaccines could cause neurodevelopmental disorders. Two unpublished epidemiological studies were presented to the committee. The first study was a controlled epidemiological study that tested the hypothesis that certain neurodevelopmental disorders are related to exposure to thimerosal-containing vaccines. The study was based on data from the Vaccine Safety Datalink (VSD)—a large linked database that includes vaccination, clinic, hospital-discharge, and demographic data. The VSD, formed as a partnership between CDC and seven health maintenance organiza-

tions (HMOs), was initiated in 1991 and covers approximately 2.5 percent of the U.S. population.

The study was conducted in two phases. Phase I was designed to screen data for potential associations between thimerosal-containing vaccines and selected outcomes. Phase II was designed to test the hypotheses generated in the first phase. Both phases were designed as retrospective cohort studies, but the study populations differed.

Preliminary results of the Phase I analysis produced statistically significant but weak associations (relative risk ratios < 2.00 per 12.5 μg increment of mercury) between various cumulative exposures to thimerosal-containing vaccines and the following neurodevelopmental diagnoses: unspecified developmental delays; tics; attention deficit disorder; language and speech delay; and general neurodevelopmental delays. No association was found between exposures to thimerosal and other neurological disorders, including autism, or renal disorders (Stehr-Green, 2000, 2001). Re-analyses of the Phase I data were presented at the IOM committee's meeting in July 2001, showing positive but weak associations (relative risk ratios < 2.00) with several neurodevelopmental diagnoses (Verstraeten, 2001). Although the detailed results of the re-analysis differ slightly from the original analysis, the magnitude of the associations was generally consistent with those in preliminary analysis.

The Phase II study population provided a sufficient number of cases for analysis of only two of the outcomes, ADHD and speech delays. The Phase II analysis, however, identified no significant differences in risk with the receipt of thimerosal-containing vaccines and these two outcomes; however, the small sample size limited the power of the study to detect a small effect, if it exists (Stehr-Green, 2001; Verstraeten, 2001). The committee concludes that the Phase I and II VSD analyses are inconclusive with respect to causality.

The only other epidemiological analysis presented to the committee is an unpublished ecological analysis of rates of autism during the period of increased exposures to thimerosal through the recommended childhood immunization schedule (Blaxill, 2001). Absent other controlled epidemiological analyses, ecological data are usually noncontributory to causality assessments. The case reports found in the Vaccine Adverse Events Reporting System (VAERS) were uninformative with respect to causality.

Thus the committee concludes that the evidence is inadequate to accept or reject a causal relationship between exposure to thimerosal from vaccines and the neurodevelopmental disorders of autism, ADHD, and speech or language delay. The committee's conclusion is based on these factors:

- The available case reports are uninformative with respect to causality.
- There are no published epidemiological studies examining the potential association between thimerosal-containing vaccines and neurodevelopmental disorders.

- The unpublished and limited epidemiological studies provide only weak and inconclusive evidence regarding the hypothesis that exposure to thimerosal-containing vaccines may lead to certain neurodevelopmental disorders.

SIGNIFICANCE ASSESSMENT

Even though vaccines on the recommended childhood immunization schedule that are manufactured today and given to children six years of age or younger do not contain thimerosal as a preservative, the hypothesis that exposure to thimerosal-containing vaccines may be associated with neurodevelopmental disorders remains of public health significance.

First, the diseases against which thimerosal-containing vaccines were directed—diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b (Hib), and hepatitis B—are serious infectious diseases that can lead to significant morbidity and mortality. It is imperative that immunizations continue against these and other serious vaccine-preventable diseases. It is also important to understand whether or not past vaccine use has increased the risk of neurodevelopmental disorders, which affect a large number of children and impose a significant burden on those children, their families, and society.

Second, understanding the risks of thimerosal is important because of its continued use in other vaccines and biological and pharmaceutical products. Some vaccines that are not recommended for all children, but may be given to special populations (e.g., diphtheria-tetanus toxoid [DT], influenza), still contain thimerosal as a preservative. In addition, an unknown quantity of thimerosal-containing Hib vaccine, hepatitis B, and the acellular pertussis vaccine (DTaP), which are on the recommended childhood immunization schedule, are still on the shelf and being used by providers.

Third, while the World Health Organization (WHO) supports the U.S. decision to remove thimerosal, many countries still depend on it in their multi-dose supplies of vaccines. Reasons include the proven benefits of thimerosal as a preservative, the proven benefits of immunization, and the practical constraints related to the worldwide removal of thimerosal, such as the lack of alternative preservatives for multi-dose vials and increased costs and cold chain requirements associated with the introduction of single-dose vials (WHO, 2000).

In addition, lessons can be learned from the decisionmaking process surrounding the policy changes on hepatitis B immunization. Within two months of the AAP/PHS recommendation to suspend the birth dose of hepatitis B vaccination for children born to low-risk mothers, the CDC announced the availability of a new thimerosal-free hepatitis B vaccine and recommended resumption of routine hepatitis B vaccination of all newborns (CDC, 1999b). Several studies suggest that the two major policy changes within three months were misunderstood by some providers and may have had negative effects on hepatitis B newborn immunizations (CDC, 2001b; Hurie et al., 2001; Oram et al., 2001). The

EXECUTIVE SUMMARY

7

confusion that resulted among some providers suggests not that the policy decision was fundamentally flawed, but that improvements could be made in the formulation and communication of vaccine policies regarding uncertain risks.

Finally, concerns related to the potential adverse effects of thimerosal-containing vaccines and continued use of thimerosal in some vaccines have the potential to erode trust in immunization and can lead to declines in immunization rates. The presence of mercury in some vaccines can raise doubts about the entire system of ensuring vaccine safety, and late recognition of the potential risk of thimerosal in vaccines may contribute to a perception among some that careful attention to vaccine components has been lacking.

There are no data that elucidate how much, if any, mercury exposure from all sources contributes to the prevalence of autism, ADHD, or speech or language delay. Thus, it is not possible to predict whether or not removing thimerosal from vaccines will reduce the prevalence of these neurodevelopmental disorders. There is no reason to believe, however, that removing thimerosal exposure by switching to preservative-free single dose vials of vaccine will pose a risk to children's health. It is possible that replacing thimerosal with a less effective preservative in multi-dose vials could increase risk to children's health. It is also likely that decreased immunization rates due to fears about the risks of thimerosal could increase the risk of serious and even fatal vaccine-preventable diseases.

PUBLIC HEALTH RESPONSE

It is important to resolve whether or not children might have experienced neurodevelopmental disorders because of an unrecognized incremental mercury burden from thimerosal, given the responsibility for assuring the safest vaccines possible. Therefore, the committee sees significant reasons for continued public health attention to concerns about thimerosal exposure and neurodevelopmental disorders:

- The committee has found inadequate evidence to accept or reject a causal relationship between thimerosal-containing vaccines and neurodevelopmental disorders. Although the available evidence is indirect and incomplete, and the relationship is not established, it is biologically plausible. Because thimerosal was used in millions of vaccines doses over several decades, it is important that additional research be done to understand the nature of the risk, if any, from this exposure to thimerosal.
- There is a need for more evidence on the risks and benefits associated with thimerosal-containing vaccines and biological and pharmaceutical products in use in the United States and elsewhere.
- As concerns continue to emerge about other vaccines it is likely that policymakers will again be faced with the need to consider action regarding vaccine

safety in the face of great uncertainty, as they were with thimerosal. It is critical that policymakers be better prepared to handle these concerns.

- It is important to do everything possible to restore, maintain, and build trust in vaccines.

The committee provides recommendations in three areas of public health response: policy review and analysis, public health and biomedical research, and communications.

Policy Review and Analysis

The committee supports prior decisions by the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP) to call for the removal of thimerosal from vaccines. Fortunately, technology was available to the manufacturers in this country to do so in a timely manner. Vaccine manufacture is a complex process, and the committee understands that to remove a constituent, reformulate and repackage a vaccine, and receive FDA approval in a short time is no small feat.

The committee was unable to conclude, however, from the existing evidence whether thimerosal does or does not cause neurodevelopmental disorders. In the United States, thimerosal has been removed from most vaccines and some biological products to which infants, children, and pregnant women are exposed. Although mercury exposures from currently available thimerosal-containing products may not exceed estimated exposure limits for methylmercury derived from federal guidelines, further action to remove thimerosal from all vaccines and other biological and pharmaceutical products might be warranted to ensure that exposures to thimerosal do not contribute to combined mercury exposures that could exceed guidelines for safe exposure. This is consistent with the precautionary principle (Goldstein, 2001; Kriebel and Tickner, 2001), which states that “when an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically.” Finally, these actions could do a great deal to simplify decision-making by clinicians and parents regarding the use of vaccines, other biologicals, or pharmaceuticals without potentially compromising the health of the child. A decision not to remove thimerosal from other products in the United States should be based on an assessment of the risks and benefits which demonstrate that action is unwarranted. Risk-benefit assessments conducted on U.S. populations might not be valid for other populations and caution should be exercised when generalizing these recommendations to other countries.

An unknown number of thimerosal-containing DTaP, Hib, and hepatitis B vaccine doses are still on the shelves. Given that alternatives are now available, **the committee recommends the use of the thimerosal-free DTaP, Hib, and hepatitis B vaccines in the United States, despite the fact that there might be**

remaining supplies of thimerosal-containing vaccine available. The committee could not explore the mechanisms by which this could be accomplished. However, the committee is concerned that, because of meeting schedules and other requirements—for example, the development of official statements on this issue by advisory groups such as the Red Book Committee of the AAP or the ACIP—action might be delayed. Other mechanisms might be available: “Dear Doctor” letters could be sent for instance, or existing supplies could be bought back from providers by vaccine makers or the CDC (in the case of doses purchased for the Vaccines for Children program).

The removal of thimerosal as a preservative from vaccines on the recommended childhood immunization schedule does not eliminate exposure to thimerosal from the other vaccines, such as DT or influenza, that some infants, children, and pregnant women receive. **Therefore, the committee recommends that full consideration be given by appropriate professional societies and government agencies to removing thimerosal from vaccines administered to infants, children, or pregnant women in the United States.** However, the committee draws attention to the recent recommendation of the ACIP that high-risk children and women beyond their first trimester of pregnancy during the influenza season should be vaccinated. The ACIP states “because pregnant women are at increased risk for influenza-related complications and because a substantial safety margin has been incorporated into the health guidance values for organic mercury exposure, the benefit of influenza vaccine outweighs the potential risks for thimerosal” (CDC, 2001c).

Thimerosal is also present in some pharmaceuticals, such as nasal sprays, used by infants, children, and pregnant women. The committee is unaware of risk assessments of thimerosal in pharmaceutical products, nor is it aware of the status of research into alternative preservatives. However, it seems prudent that alternatives to thimerosal in these products be explored and, if risk analyses suggest a need to do so, be used. **Therefore, the committee recommends that appropriate professional societies and government agencies review their policies about the non-vaccine biological and pharmaceutical products that contain thimerosal and are used by infants, children, and pregnant women in the United States.** This recommendation is consonant with a recent statement by the Committee on Environmental Health of the American Academy of Pediatrics that advocated reducing mercury exposure in children (Goldman and Shannon, 2001).

As the immunization schedule becomes more complex, and as vaccine safety concerns continue to emerge, it is likely that the public health community, medical professionals, and vaccine manufacturers will again be faced with the need to consider action regarding vaccine safety in the face of great uncertainty and of theoretical—rather than demonstrated—risks. **The committee recommends that policy analyses be conducted that will inform these discussions in the future.**

- First, **the committee recommends a review and assessment of how public health policy decisions are made under uncertainty**, in order to develop suggestions to improve the decisionmaking process about vaccines in the future. These studies might consider factors such as who should bear the costs of added safety and the impact of decisions on trust in the vaccine or health care system.
- In addition, **the committee recommends a review of the strategies used to communicate rapid changes in vaccine policy, and it recommends research on how to improve those strategies.**

Public Health and Biomedical Research

The committee recommends a diverse public health and biomedical research portfolio. This will be most effective if it involves several different agencies (thus maximizing resources), provides some findings fairly quickly, and utilizes a variety of approaches. These recommendations for additional research, some of which are underway or in development by CDC, NIH, FDA, universities, and vaccine manufacturers could support evidence-based decisions in other countries regarding whether or not to continue using thimerosal-containing vaccines. While the United States chose to remove thimerosal as a precautionary measure and because it was feasible to do so, the committee understands that practical considerations and an assessment of the risks and benefits in other countries may lead those countries to reach different conclusions regarding continued use of thimerosal in vaccines. Research should be designed to accommodate the switch to non-thimerosal-containing products as soon as it is beneficial to change formulations. Specific recommendations on epidemiological, clinical, and basic science research are as follows:

Epidemiological Research

- **The committee recommends case-control studies examining the potential link between neurodevelopmental disorders and thimerosal-containing vaccines.** These studies should include multiple cognitive outcomes, including autism. In addition, because thimerosal poisonings were associated with adverse renal effects, renal outcomes should also be included in the epidemiological, clinical, and basic science studies of thimerosal exposure recommended in this report. Although there are many challenges that will arise in planning and conducting these studies (e.g., appropriate control group selection, conducting a retrospective assessment of mercury exposure from other sources), the committee believes that multiple case-control studies are an efficient approach for seeking answers to the causality questions.
- The committee is aware of several cohorts of children who did not receive thimerosal-containing doses as part of clinical trials conducted in other countries of the acellular pertussis vaccine, DTaP. **The committee recommends further**

analysis of neurodevelopmental outcomes in these populations. Although the exposure levels to thimerosal in these children are lower than exposure levels in the United States, these cohorts have the powerful analytic benefit of randomized assignment to the vaccine exposure of interest.

- The removal of thimerosal from vaccines on the recommended childhood immunization schedule in the United States presents a unique opportunity to study whether this change affected rates of neurodevelopmental disorders in children. **The committee recommends conducting epidemiological studies that compare the incidence and prevalence of neurodevelopmental disorders before and after the removal of thimerosal from vaccines.**
- **The committee recommends an increased effort to identify the primary sources and levels of prenatal and postnatal exposure to thimerosal (e.g., Rho (D) Immune Globulin, which is given to Rh-negative mothers during pregnancy) and other forms of mercury (e.g., maternal consumption of fish) in infants, children, and pregnant women.** Studies of background levels of exposure to mercury may identify populations or quantify the number of children at higher risk for mercury toxicity.

The committee is aware of the planning under way for a two-stage follow-up study (Phase III) to the findings from the Phase I and II VSD studies. Three issues loom large regarding the proposed Phase III study: feasibility, resources, and technical study design issues. The committee has reservations about such an ambitious and therefore resource-intensive study. It will be a few years until results and meaningful analyses are available. In addition, the power of the study to detect small relative risks is limited. The proposed Phase III study could be contributory for future causality assessments, but would best be undertaken as part of an overall package of research.

Clinical Research

- Better understanding of the pharmacokinetics of ethylmercury would have greatly facilitated the risk assessment of thimerosal in vaccines. **The committee recommends research on how children, including those diagnosed with neurodevelopmental disorders, metabolize and excrete metals—particularly mercury.** Studies of proteins known to be associated with metal metabolism, such as glutathione and metallothionein, could be undertaken.
- **The committee recommends continued research on theoretical modeling of ethylmercury exposures, including the incremental burden of thimerosal on background mercury exposure from other sources.**
- The committee is aware of several specialized pediatric practices that use chelation therapy (which mobilizes and removes heavy metals from bodily tissue) to treat autistic children; these practitioners report unusual metal profiles in their patients as well as clinical improvement following chelation therapy. Che-

lation therapy has not been established to improve renal or nervous system symptoms of chronic mercury toxicity (Sandborgh Englund et al., 1994). Moreover, chelation therapy is not without risks; for example some chelation therapies might cause the release of mercury from soft-tissue stores, thus leading to increased exposure of the nervous system to mercury (Wentz, 2000). Given that chelation therapy is not a benign treatment, **the committee recommends careful, rigorous, and scientific investigations of chelation when used in children with neurodevelopmental disorders, especially autism.** Although studies of chelation would not be able to link excreted metal specifically with vaccine exposure, and therefore would not contribute to causality assessments, it is important to pursue these uncontrolled clinical observations in order to establish an evidence base for appropriate therapeutic uses of chelation.

Basic Science Research

- Many countries continue to use thimerosal-containing vaccines given the proven benefits of thimerosal as a vaccine preservative for many years and the benefits of continued immunization. Complete risk assessments have not been done for other countries that would indicate the need to switch to thimerosal-free vaccines. However, **the committee recommends research to identify a safe, effective, and inexpensive alternative to thimerosal for countries that decide they need to switch.**
- Comparative animal studies of the toxicity of ethylmercury and methylmercury are limited, although teratological effects of methylmercury in rodents and primates is well established. **The committee recommends research in appropriate animal models on neurodevelopmental effects of ethylmercury.** These would help elucidate the comparability and validity for ethylmercury of the risk assessments based on methylmercury.

Communications

The committee identified three specific impediments to effectively communicating the risks and benefits of thimerosal-containing vaccines to parents and practitioners. First, the different exposure levels in the federal guidelines and the lack of evidence on ethylmercury, have made for complicated and possibly confusing messages about the risks of using thimerosal-containing vaccines. Second, finding information about thimerosal-containing vaccines on federal agency websites is difficult. Third, information about vaccine risks on government websites contains words, such as “should,” that may be perceived as judgmental by some. Using words that are less directive and prescriptive is important in effectively communicating vaccine risks (NRC, 1989).

As the committee noted in its previous report (IOM, 2001), there are broad and recurring communication concerns in various vaccine safety issues. The

committee has not attempted to address these issues here, but will examine them in a separate, more general context.

SUMMARY

Mercury is a known neurotoxicant. Little is known about ethylmercury (the active component in thimerosal) compared to methylmercury. However, the committee believes that the effort to remove thimerosal from vaccines was a prudent measure in support of the public health goal to reduce the mercury exposure of infants and children as much as possible. The committee urges, in fact, that full consideration be given to removing thimerosal from any biological or pharmaceutical product to which infants, children, and pregnant women are exposed.

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

The committee also concludes that the evidence is inadequate to accept or reject a causal relationship between thimerosal exposures from childhood vaccines and the neurodevelopmental disorders of autism, ADHD, and speech or language delay. The limited and unpublished epidemiological data constitute weak and inconclusive evidence regarding causality. However, because thimerosal remains in vaccines in other countries and in biological and pharmaceutical products in the United States, and because it is important to restore and maintain trust in vaccines, the committee believes that continued public health attention must be paid to this issue in the form of policy review and analysis, public health and biomedical research, and improved communication strategies. Box ES-1 summarizes the committee's conclusions and recommendations.

BOX ES-1 Committee Recommendations and Conclusions

CONCLUSIONS

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

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

PUBLIC HEALTH RESPONSE RECOMMENDATIONS

Policy Review and Analysis

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

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

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

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

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

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

Public Health and Biomedical Research

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

(continued)

Epidemiological Research

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

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

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

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

Clinical Research

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

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

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

Basic Science Research

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

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

REFERENCES

- ATSDR (Agency for Toxic Substances and Disease Registry). 1999. *Toxicological Profile for Mercury (Update)*.
- Ball LK, Ball R, Pratt RD. 2001. An assessment of thimerosal use in childhood vaccines. *Pediatrics* 107(5):1147–1154.
- Blaxill M. 2001. Presentation to Immunization Safety Review Committee. Rising Incidence of Autism: Association with Thimerosal: Cambridge, Massachusetts. July 16, 2001.
- CDC (Centers for Disease Control and Prevention). 1999a. Thimerosal in vaccines: A joint statement of the American Academy of Pediatrics and the Public Health Service. *MMWR Morb Mortal Wkly Rep* 48(26):563–565.
- CDC. 1999b. Availability of hepatitis B vaccine that does not contain thimerosal as a preservative. *MMWR Morb Mortal Wkly Rep* 48(35):780–782.
- CDC. 2001a. Notice to Readers: Update on the Supply of Tetanus and Diphtheria Toxoids and of Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine. *MMWR Morb Mortal Wkly Rep* 50(10): 189–190.
- CDC. 2001b. Impact of the 1999 AAP/USPHS joint statement on thimerosal in vaccines on infant hepatitis B vaccination practices. *MMWR Morb Mortal Wkly Rep* 50(6):94–97.
- CDC. 2001c. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep* 50(RR–4).
- EPA (Environmental Protection Agency). 1997. *Mercury Study Report to Congress: Volume I Executive Summary* EPA 452/R–97–003. Washington, D.C.: EPA.
- Goldman LR, Shannon MW, Committee on Environmental Health. 2001. Technical report: Mercury in the environment: Implications for pediatricians. *Pediatrics* 108(1):197–205.
- Goldstein BD. 2001. The precautionary principle also applies to public health actions. *Am J Public Health* 91:1358–1361.
- Hurie MB, Saari TN, Davis JP. 2001. Impact of the joint statement by the American Academy of Pediatrics/U.S. Public Health Service on thimerosal in vaccines on hospital infant hepatitis b vaccination practices. *Pediatrics* 107(4):755–758.
- IOM (Institute of Medicine). 2001. *Immunization Safety Review: Measles-Mumps-Rubella Vaccine and Autism*. Washington, DC: National Academy Press.
- Kriebel D, Tickner J. 2001. Reenergizing public health through precaution. *Am J Public Health* 91:1351–1355.
- Magos L. 2001. Review on the toxicity of ethylmercury, including its presence as a preservative in biological and pharmaceutical products. *J Appl Toxicol* 21(1):1–5.
- NRC (National Research Council). 1989. *Improving Risk Communication*. Washington DC: National Academy Press.
- NRC (National Research Council). 2000. *Toxicological Effects of Methylmercury*. Washington, DC: National Academy Press.
- Oram RJ, Daum RS, Seal JB, Lauderdale DS. 2001. Impact of recommendations to suspend the birth dose of hepatitis B virus vaccine. *JAMA* 285:1874–1879.
- Sandborgh Englund G, Dahlqvist R, Lindelof B, Soderman E, Jonzon B, Vesterberg O, Larsson KS. 1994. DMSA administration to patients with alleged mercury poisoning from dental amalgams: A placebo-controlled study. *J Dent Res* 73(3):620–628.
- Stehr-Green PA. 2000. Summary and Conclusions: Review of Vaccine Safety Datalink Information on Thimerosal-Containing Vaccines. *Rapporteur's Report of National Immunization Program, Centers for Disease Control and Prevention*.

EXECUTIVE SUMMARY

17

- Stehr-Green PA. 2001. Presentation to Immunization Safety Review Committee. Protocol for National Immunization Program Study on Thimerosal: Cambridge, Massachusetts. July 16, 2001.
- Suzuki T, Miyama T, Katsunuma H. 1963. Comparative study of bodily distribution of mercury in mice after subcutaneous administration of methyl, ethyl, and n-propyl mercury acetates. *Japan J Exp Med* 33(5):277–282.
- Suzuki T, Takemoto T, Kashiwazaki H, Miyama T. 1973. Metabolic fate of ethylmercury salts in man and animal. Miler MW, Clarkson TW, Editors. *Mercury, Mercurials and Mercaptans*. Springfield, IL: Charles C Thomas.
- U.S. Preventive Services Task Force. 1996. *Guide to Clinical Preventive Services*. 2nd ed. Baltimore: Williams and Wilkins.
- Verstraeten T. 2001. Presentation to Immunization Safety Review Committee. Vaccine Safety Datalink (VSD) Screening Study and Follow-Up Analysis with Harvard Pilgrim Data: Cambridge, Massachusetts. July 16, 2001.
- Wentz PW. 2000. Chelation therapy: Conventional treatments. Advance/Laboratory. Available on www.advanceforAL.com.
- WHO (World Health Organization). 2000. Thiomersal as a vaccine preservative. *Wkly Epidemiol Rec* 75(2):12–16.

