
**Immunization Safety Review: Thimerosal - Containing Vaccines and Neurodevelopmental Disorders**

Kathleen Stratton, Alicia Gable, and Marie C. McCormick, Editors, Immunization Safety Review Committee, Board on Health Promotion and Disease Prevention

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# IMMUNIZATION SAFETY REVIEW

## THIMEROSAL-CONTAINING VACCINES AND NEURODEVELOPMENTAL DISORDERS

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Immunization Safety Review Committee
Board on Health Promotion and Disease Prevention
INSTITUTE OF MEDICINE

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*Willing is not enough; we must do.*
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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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

# Foreword

Vaccines are among the greatest public health accomplishments of the past century. In recent years, however, a number of concerns have been raised about the safety of, and need for, certain immunizations. Indeed, immunization safety is a contentious area of public health policy, with discourse around it having become increasingly polarized and exceedingly difficult. The numerous controversies and allegations surrounding immunization safety signify an erosion of public trust in those responsible for vaccine research, development, licensure, schedules, and policymaking. Because vaccines are so widely used—and because state laws require that children be vaccinated to enter daycare and school, in part to protect others—immunization safety concerns should be vigorously pursued in order to restore this trust.

It is in this context that the Institute of Medicine (IOM) was approached more than a year ago by the Centers for Disease Control and Prevention and the National Institutes of Health to convene an independent committee that could provide timely and objective assistance to the Department of Health and Human Services in reviewing emerging immunization-safety concerns.

The IOM was chartered by the National Academy of Sciences in 1970 to serve as an adviser to the federal government on issues affecting the public's health, as well as to act independently in identifying important issues of medical care, research, and education. The IOM thus brings to this mission three decades of experience in conducting independent analyses of significant public health policy issues. In particular, as described in more detail in this report, the IOM has a long history of involvement in vaccine safety. The IOM published its first

major vaccine-safety report in 1977, followed by a subsequent report in 1988; both focused on the safety of polio vaccines. Two subsequent major reports, published in 1991 and 1994, examined the adverse events of childhood vaccines. Since then, the IOM has conducted several smaller studies and workshops focused on various vaccine-safety topics. These studies were all well received by both the public and policy makers, and previous IOM committees on vaccine safety issues have been viewed as objective and credible.

Given the sensitive nature of the present immunization safety review study, the IOM felt it was especially critical to establish strict criteria for committee membership. These criteria prevented participation by anyone with financial ties to vaccine manufacturers or their parent companies, previous service on major vaccine-advisory committees, or prior expert testimony or publications on issues of vaccine safety.

The rationale for imposing these stringent criteria was twofold. First, given growing public concern about vaccine safety and the public scrutiny surrounding this committee's work, it was important to establish standards that would preclude any real or perceived conflict of interest or bias on the part of the committee members. While the committee members all share a belief in the benefits of vaccines to the public health, none of them has any vested interest in any of the vaccine safety issues that will come before them. Second, the IOM wanted to ensure consistency in the committee membership and avoid having members recuse themselves from the deliberations because they had participated in the development or evaluation of a vaccine under study.

Thus, the IOM has convened a distinguished panel of 15 members who possess significant breadth and depth of expertise in a number of fields, including pediatrics, neurology, immunology, internal medicine, infectious diseases, genetics, epidemiology, biostatistics, risk perception and communication, decision analysis, public health, nursing, and ethics. The committee members were chosen because they are leading authorities in their respective fields, are well respected by their colleagues, and have no conflicts of interest. This committee brought a fresh perspective to these critically important issues and approached its charge with impartiality and scientific rigor.

The IOM does not propose the use of the criteria it has laid out above in selecting members for federal vaccine advisory committees. The IOM committee was convened for a very different purpose from the usual federal vaccine advisory committees and, as such, required different standards.

As with all reports from the IOM, the committee's work was reviewed by an independent panel of experts. The purpose of the review process is to enhance the clarity, cogency, and accuracy of the final report and to ensure that the authors and the IOM are creditably represented by the report published in their names. The report review process is overseen by the National Research Council's (NRC) Report Review Committee (RRC), comprised of approximately 30 members of the National Academy of Sciences, National Academy of Engi

neering, and IOM. The IOM, in conjunction with the RRC, appoints a panel of reviewers with a diverse set of perspectives on key issues considered in the report. Unlike the selection criteria for committee membership (discussed above), many reviewers will have strong opinions and biases about the report topic. The composition of the review panel is not disclosed to the committee until after the report is approved for release. While the committee must consider and evaluate all comments from reviewers, it is not obligated to change its report in response to the reviewers' comments. The committee must, however, justify its responses to the reviewers' comments to the satisfaction of the RRC's review monitor and the IOM's review coordinator. A report may not be released to the sponsors or the public, nor may its findings be disclosed, until after the review process has been satisfactorily completed and all authors have approved the revised draft.

This report represents the unanimous conclusions and recommendations of that dedicated committee whose members deliberated a critical health issue. The report's conclusions and recommendations should be of value to all concerned about these important matters.

Kenneth I.Shine

President, Institute of Medicine

# Acknowledgments

The committee would like to acknowledge the many speakers and attendees at its open meeting held on July 16 in Boston. The discussions were informative and helpful. The committee would also like to thank those people who have submitted information to the committee through the mail or e-mail. Finally, the committee would like to thank the IOM staff for their dedication to this project. Without their commitment, attention to detail, creativity, sensitivity, and hard work, this project would be unworkable.

# Contents

# 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

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.

*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.

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# Immunization Safety Review:

# Thimerosal-Containing Vaccines and Neurodevelopmental Disorders

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 the oral polio vaccine can on rare occasion cause paralytic polio, that some influenza vaccines have been associated with a risk of Guillain-Barré syndrome, and that vaccines sometimes cause anaphylactic shock. In recent years, the number of concerns regarding the safety of immunizations seems to have increased. 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 these safety concerns receive assiduous attention.

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 in order to present conclusions and recommendations regarding possible causal associations between vaccines and certain adverse outcomes. The committee's task also includes assessing the broader significance for society of these immunization safety issues.

In this report, the 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. Thimerosal, an organic mercury compound that is metabolized to ethylmercury and thiosalicylate, has been used since the 1930s as a preservative in some vaccines. Food and Drug Administra

tion (FDA) regulations require that preservatives be used in multidose vials of vaccines, except live viral vaccines, to prevent bacterial and fungal contamination (General Biologics Product Standards, 2000), which can lead to serious illness and death in recipients (Wilson, 1967). In addition to its use as a preservative, thimerosal is used as an inactivating or bacteriostatic agent in the manufacturing process for some vaccines. Uses other than as a preservative contribute little to the final concentration of thimerosal in vaccines (Ball et al., 2001). In this report, when the committee refers to thimerosal-free vaccines, it includes vaccines that contain only traces of thimerosal (<0.5 μg Hg per dose) left over from the manufacturing process.

In 1999, 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 ingestion of methylmercury, another form of organic mercury (Ball et al., 2001). In July 1999, the American Academy of Pediatrics (AAP) and the U.S. Public Health Service (PHS) issued a joint statement recommending the 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, 1999c), 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).

These actions do not, however, reduce the importance of trying to resolve whether the past presence of thimerosal in some vaccines could have caused neurodevelopmental problems in some children. Moreover, thimerosal remains in use in many other countries, which continue to depend on multi-dose supplies of vaccine that must be protected from microbial contamination.

## ORIGINS OF THE IMMUNIZATION SAFETY REVIEW PROJECT

The federal government has responded to concerns about the safety of vaccines through several mechanisms. In 1986, Congress passed the National Childhood Vaccine Injury Act (Public Law 99–660), followed by the Vaccine Compensation Amendments of 1987 (Public Law 100–203). This legislation mandated the establishment of the National Vaccine Injury Compensation Program and the Vaccine Adverse Event Reporting System (VAERS), a national passive surveillance system. The legislation also provided for the development of vaccine-information statements for parents of children receiving immuniza

tions. These activities are managed by three agencies of the U.S. Department of Health and Human Services (DHHS): the Centers for Disease Control and Prevention (CDC), the FDA, and the Health Resources and Services Administration (HRSA). The compensation program is jointly administered by HRSA and the Department of Justice.

The legislation also called for IOM to review evidence regarding possible adverse consequences of childhood immunizations. Three expert committees convened by IOM produced the reports *Adverse Effects Following Pertussis and Rubella Vaccines* (IOM, 1991a), *Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality* (IOM, 1994a), and *DPT Vaccine and Chronic Nervous System Dysfunction: A New Analysis* (IOM, 1994b). Following the completion of the third study, IOM was asked to organize the Vaccine Safety Forum to provide a framework for continued discussion of vaccine safety issues. Forum participants included representatives of government agencies, advocacy groups, and pharmaceutical companies, as well as parents, health care providers, academic researchers, and IOM staff. Forum discussions, on topics such as research strategies and risk communication, were documented in brief reports (IOM, 1996, 1997a,b) but were not intended to produce conclusions or recommendations.

In 1995 and 1997, in response to the findings and recommendations *of Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality* (IOM, 1994a), the Secretary of HHS updated the Vaccine Injury Table, a list of post-vaccination events that must be reported to DHHS and that are covered by the National Vaccine Injury Compensation Program. Also in 1995, the National Vaccine Advisory Committee (NVAC) of the National Vaccine Program Office of DHHS added a Vaccine Safety Subcommittee to its efforts. In 1999, this subcommittee expanded its scope and was renamed the Vaccine Safety and Communication Subcommittee. Concern over cases of vaccine-associated paralytic poliomyelitis prompted another CDC committee—the Advisory Committee on Immunization Practices—to recommend in 1997 that the immunization schedule be changed to replace oral poliovirus vaccine with inactivated poliovirus vaccine (CDC, 2000a).

Since the mid-1990s, additional challenges to the safety of vaccinations have gained attention in various settings. From 1999 through mid-2001, the Committee on Government Reform of the U.S. House of Representatives held eight hearings on vaccine safety issues. The media have covered these issues on news programs such as *60 Minutes, 20/20,* and *Nightline,* and the Internet is an increasingly important communication channel. Also, many consumer and professional organizations have sponsored conferences and scientific symposia to address vaccine safety concerns.

Given these growing concerns, CDC and the National Institutes of Health (NIH) recognized the need for an independent, expert group to address vaccine safety in a timely and objective manner. In 1999, as a result of IOM's previous work and its access to independent scientific experts, CDC and NIH began a

year of discussions with IOM to develop the Immunization Safety Review project to address vaccine safety issues both existing and emerging.

## THE CHARGE TO THE COMMITTEE

The 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 will come before the group. Additional discussion of the committee composition can be found in the Foreword, written by Dr. Kenneth Shine, President of the IOM.

The committee is charged with examining three vaccine safety hypotheses each year during the three-year study period (2001–2003). The Interagency Vaccine Group—made up of officials from the National Vaccine Program Office at DHHS, the National Immunization Program and the National Center for Infectious Diseases at the CDC, the National Institute for Allergy and Infectious Diseases at the NIH, the Department of Defense, the FDA, the National Vaccine Injury Compensation Program at HRSA, the Health Care Financing Administration, and the Agency for International Development—selects the hypotheses to be examined by the committee. For each of these, the committee reviews relevant literature and submissions by interested parties, and it holds an open scientific meeting followed directly by a one- to two-day closed meeting to formulate its conclusions and recommendations. The committee's findings are released to the public in a brief consensus report 60–90 days after its meeting.

For each hypothesis to be examined, the committee has been asked to assess both the scientific plausibility of the issue and its significance in a broader societal context. The *plausibility assessment* has two components: an examination of any pathogenic mechanism(s) relevant to the hypothesis (also known as biologic plausibility), and an examination of the evidence regarding a possible causal relationship between the vaccine and the adverse event. The *significance assessment* addresses such considerations as the nature of the health risks associated with the vaccine-preventable disease and with the adverse event in question. Other considerations may include the perceived intensity of public or professional concern, or the feasibility of additional research to help resolve scientific uncertainty regarding causal associations.

The findings of the plausibility and significance assessments provide the basis for the committee's recommendations on *public health response,* which includes immunization policy review, current and future research, and effective communication strategies for the specific immunization safety questions. Although the committee has been asked to make recommendations related to immunization

policy, there are clear limits on this element of the charge. For example, it would exceed the committee's authority to recommend a change in the licensure, scheduling, or administration of a vaccine. If the committee concluded that the scientific evidence or other important factors justified such action, it could recommend convening the appropriate advisory group(s) to examine the question.

## THE STUDY PROCESS

The committee held an initial organizational meeting in January 2001. CDC and NIH presented the committee's charge at the meeting, and the committee conducted a general review of immunization safety concerns and determined its methodology for assessing causality. This approach would be used for the hypotheses to be considered at subsequent meetings. A website (www.iom.edu/imsafety ) and a listserv were created to facilitate communication with the committee and provide the public access to information about its work. The committee's first report, *Immunization Safety Review: Measles-Mumps-Rubella Vaccine and Autism* (IOM, 2001), is summarized in Appendix A.

To evaluate the hypothesis on thimerosal-containing vaccines and neurodevelopmental disorders, the committee collected information from several sources. An extensive review was performed of the published, peer-reviewed scientific and medical literature pertinent to the hypothesis. A request was also sent through the project's listserv for information regarding specific adverse outcomes that may be related to thimerosal exposure and the biological mechanisms that may explain their hypothesized relationship; the committee reviewed the resulting submissions. In addition, a scientist was commissioned to prepare written answers to questions from the committee regarding the toxicity of ethylmercury (Magos, 2001a). This document was made available on the project's website for public review, and critiques of the answers were reviewed during the committee's deliberations. (The committee emphasizes that the commissioned material does not represent the views of the committee, only those of the author.)

At an open scientific meeting in July 2001 (see Appendix B), academic and independent researchers, scientists from federal agencies, and representatives of child-health and vaccine-safety advocacy groups gave presentations and offered comments. The formal presentations reviewed the knowledge regarding thimerosal-containing vaccines and the toxicology of ethyl- and methylmercury. Unpublished data shared with the committee through presentations and personal communications helped inform the committee's conclusions and recommendations.

## THE FRAMEWORK FOR ASSESSING CAUSALITY

The Immunization Safety Review Committee has adopted the framework for assessing causality developed by the committees previously convened by the IOM (1991a, 1994a) to address questions of vaccine safety. Assessments begin

from a position of neutrality regarding the specific vaccine safety hypothesis under review. That is, there is no presumption that a specific vaccine (or vaccine component) does or does not cause the adverse event in question. The weight of the available evidence determines whether it is possible to shift that neutral position *toward* causality ("the evidence favors acceptance of a causal relationship") or *away* from causality ("the evidence favors rejection of a causal relationship"). The committee does not conclude that the evidence favors rejecting causality merely if the evidence toward causality is inadequate. Table 1 describes the five categories that summarize the direction and strength of the evidence for causality. The table shows the differences in the wording of the causality categories in the 1991 and 1994 IOM vaccine safety reports. The wording was revised in the 1994 report because the IOM had found that some people misinterpreted the 1991 language. The types and strength of evidence required to determine a specific level of causal association were the same for the two reports. The Immunization Safety Review Committee is using the wording adopted in 1994.

The sources of evidence considered by the committee in its plausibility assessment include epidemiological studies, reports of individual cases or series of cases, and studies related to biological plausibility. Epidemiological studies carry the most weight in a causality assessment; these studies measure health-related exposures or outcomes in a defined sample of subjects and make inferences about the values of those exposures or outcomes, or the associations among them, in the population from which the study sample was drawn. Epidemiological studies can be categorized as observational (survey) or experimental (clinical trial), and as uncontrolled (descriptive) or controlled (analytic). Among these various study designs, experimental studies generally have the advantage of random assignment to exposures and therefore carry the most weight in assessing causality. Uncontrolled observational studies are important but are generally considered less definitive than controlled studies.

Case reports and case series are reviewed, although they are generally inadequate by themselves to establish causality. Despite the limitations of case reports, the causality argument for at least one adverse event (the relationship between vaccines containing tetanus toxoid and Guillain-Barré syndrome) was strengthened most by a single, well-documented case report on recurrence of the adverse event following re-administration of the vaccine, a situation referred to as a "rechallenge" (IOM, 1994a).

Evidence regarding biological plausibility is also reviewed. Biological plausibility exists on a spectrum, ranging from not plausible to established. The committee has not developed a formal rating system for biological plausibility, because an agreed upon hierarchy of evidence required for assessments of biological plausibility does not exist, nor does an associated terminology (Weed and Hursting, 1998). Individual researchers and organizations discuss this concept differently. It is generally agreed, however, that biological plausibility is a

domain of intellectual and research inquiry, requires less stringent standards than proof-of-principle for exploring ideas and possible connections, is usually in itself insufficient to warrant huge investments in research and development, and is clearly insufficient to describe inferences of causality. While evidence regarding biological plausibility can never prove causality, it can be used to support other kinds of evidence and is useful for generating hypotheses, which might be addressed by additional research. Proof-of-principle in biomedical research is a more stringent standard by which a biological relationship is judged sufficiently strong to conclude with certainty that agent A (protein, cell, drug, or the like) can lead to result B (biochemical reaction, cell function, symptom relief, or the like). Such conclusions may serve as the foundation upon which subsequent research seeking to test causality is based. Conclusions about causality have been discussed in other sections of the report and require evidence from human studies. This evidence is, with only rare exceptions, a body of consistent and well-controlled epidemiological research.

Published reports that have been subjected to a rigorous peer review process carry the most weight in the committee's assessment. Unpublished data and other reports that have not undergone peer review have value, and they are often considered by the committee; they could be used, for example, in support of a body of published literature with similar findings. If the committee concluded that the unpublished data were well described, had been obtained using sound methodology, and presented very clear results, the committee could report, with sufficient caveats in the discussion, how those data fit with the entire body of published literature. But only in extraordinary circumstances could an unpublished study refute a body of published literature. In general, the committee cannot rely heavily on unpublished data in making its plausibility assessment because they have not been subjected to a rigorous peer review process, and therefore must be interpreted with caution.

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 that are usually of immediate and 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 reviewing unpublished material, the committee applied generally accepted standards for assessing the quality of scientific evidence, as described above. (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 Academies, 202–334–3543, www.national-academies.org/publicaccess.)

TABLE 1 Summary Categories and Levels of Evidence Regarding Causality

| Category | IOM, 1991a | IOM, 1994a | Level of Evidence |
|---|---|---|---|
| 1 | No evidence bearing on a causal relation | No evidence bearing on a causal relation | No case reports or epidemiological studies identified. |
| 2 | Evidence insufficient to indicate a causal relation | The evidence is inadequate to accept or reject a causal relation | One or more case reports or epidemiological studies were located, but the evidence for the causal relation neither outweighs nor is outweighed by the evidence against a causal relation. |
| 3 | Evidence does not indicate a causal relation | The evidence favors rejection of a causal relation | Only evidence from epidemiological studies can be used as a basis for possible rejection of a causal relation. Requires a rigorously performed epidemiological study (or meta-analysis) of adequate size that did not detect a significant association between the vaccine and the adverse event. |
| 4 | Evidence is consistent with a causal relation | The evidence favors acceptance of a causal relation | The balance of evidence from one or more case reports or epidemiological studies provides evidence for a causal relation that outweighs the evidence against such a relation. |
| 5 | Evidence indicates a causal relation | The evidence establishes a causal relation | Epidemiological studies and/or case reports provide unequivocal evidence for a causal relation. |

## UNDER REVIEW: THIMEROSAL-CONTAINING VACCINES AND NEURODEVELOPMENTAL DISORDERS

The Immunization Safety Review committee examined the hypothesized causal relationship between exposure to thimerosal-containing vaccines and neurodevelopmental disorders (NDDs), specifically autism, ADHD, and speech or language delay. Thimerosal contains 49.6% mercury by weight. At high doses, mercury and mercuric compounds—including thimerosal, its metabolite ethylmercury, and methylmercury—are well- established nephro- and neurotoxicants (ATSDR; 1999; EPA, 1997; NRC, 2000). The data regarding the toxicity of low doses of thimerosal and ethylmercury are very limited, and only delayed hypersensitivity reactions have been demonstrated. Prenatal exposure to low doses of methylmercury, however, has been associated with subtle neurodevelopmental abnormalities (EPA, 1997).

### Thimerosal in Vaccines

Thimerosal, also known as thiomersal, has been used as a preservative in some vaccines and other biological and pharmaceutical products since the 1930s. FDA regulations require the use of preservatives in multi-dose vials of vaccines to prevent fungal and bacterial contamination (General Biologics Products Standards, 2000). Until 1999, thimerosal was present in over 30 vaccines licensed and marketed in the United States, including some of the vaccines administered to infants for protection against diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b (Hib), and hepatitis B (see Table 2, Figure 1, and Appendix C). Prior to 1991, the only thimerosal-containing vaccine that was recommended for all infants was the whole-cell pertussis vaccine (DTP).[1] In 1991, Hib and hepatitis B vaccines were also recommended for all infants (CDC, 1991a; CDC, 1991b).[2] Inactivated polio vaccine (IPV) and live viral vaccines, such as measles-mumps-rubella (MMR), varicella, and oral polio vaccine (OPV) do not contain, and have never contained, thimerosal (AAP, 1999; FDA, 2001).

The potential significance of the thimerosal content of these vaccines was identified through a FDA risk assessment that was called for by the FDA Modernization Act of 1997 (FDAMA) (Ball et al., 2001). Specifically, FDAMA required that FDA compile a list of drugs and foods that contain intentionally introduced mercury compounds, and provide a quantitative and qualitative analysis of the mercury compounds in the list (Section 413(a) Pub L. 105–115).

[1] Acellular pertussis vaccines (DTaP) replaced whole-cell pertussis (DTP) vaccines on the recommended schedule in the 1990s. Infanrix, the first thimerosal-free DTaP vaccine (produced by Glaxo-Smith Kline) was licensed in 1997 (CDC, 1997).

[2] Only one Hib vaccine that was given to children 6 months or younger contained thimerosal (Appendix C; AAP, 1999).

In December 1998 and April 1999, FDA requested information from U.S. vaccine manufacturers about the thimerosal content of their vaccines.

TABLE 2 Estimated Exposure to Mercury from Vaccines in U.S. Infants in 1999 and in 2001. (` 6 Months)

| **Vaccines** | **1999 Maximum Mercury Dose (µg)** | **2001 Maximum Mercury Dose (µg)** |
|---|---|---|
| 3 doses of DTaP | 75.0 | 0 |
| 3 doses of Hep B | 37.5 | 0 |
| 3 doses of HIB | 75.0 | 0 |
| 3 doses of IPV | 0 | 0 |
| [1 dose of influenza] * (selected populations) | [12.5] | [12.5] |
| **TOTAL** | **187.5 [200]** | **[12.5]** |

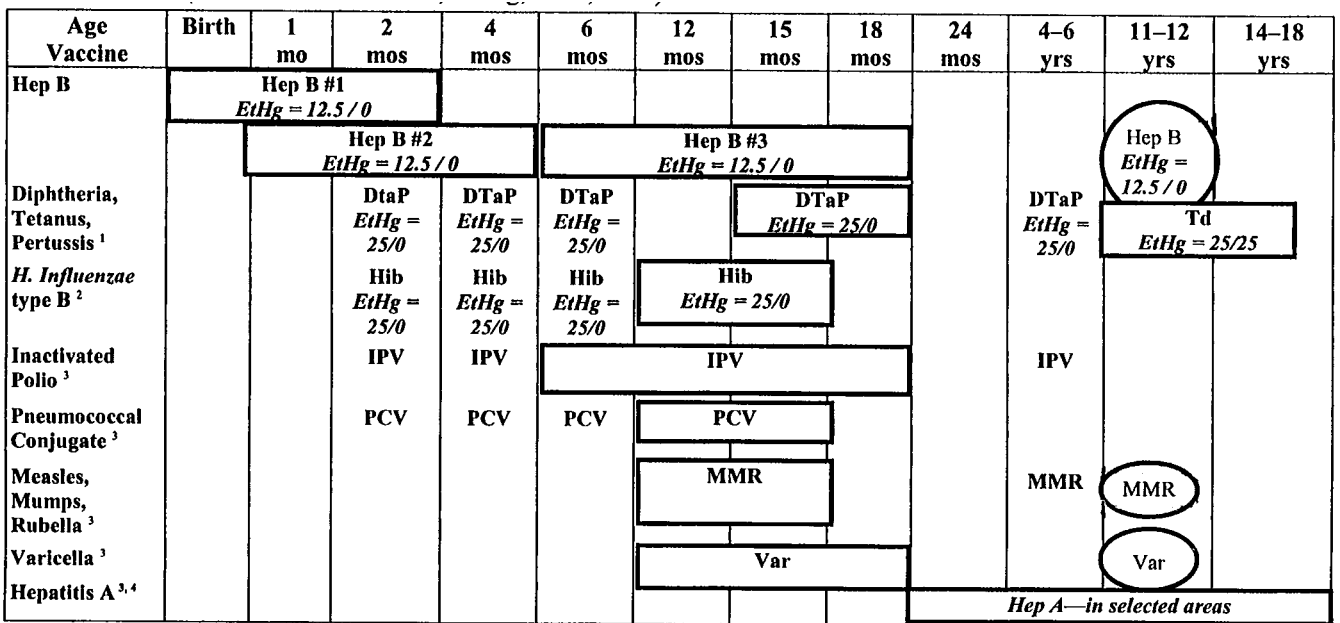
Estimated Exposure to Mercury from Vaccines in U.S. Infants in 1999 and in 2001. (< 2 Years)

| **Vaccines** | **1999 Maximum Mercury Dose (µg)** | **2001 Maximum Mercury Dose (µg)** |
|---|---|---|
| 4 doses of DTaP | 100 | 0 |
| 3 doses of Hep B | 37.5 | 0 |
| 4 doses of HIB | 100 | 0 |
| 3 doses of IPV | 0 | 0 |
| [3 doses of influenza] * (selected populations) | [37.5] | [37.5] |
| **TOTAL** | **237.5 [275]** | **[37.5]** |

SOURCE: AAP, 1999, FDA 2001.

As a result of their review, FDA scientists determined that under the recommended childhood immunization schedule (see Figure 1), infants could receive a cumulative dose of mercury from vaccines as high as 187.5 µg during the first 6 months of life, depending on the specific vaccines and administration schedule used. A 2-year-old could receive as much as 237.5 µg of mercury. Some high-risk children may also receive the influenza vaccine, increasing the maximum cumulative dose to approximately 200 µg in the first 6 months and 275 µg in the first 2 years of life (see Table 2).

The maximum cumulative doses of mercury from vaccines in the first six months and two years of life were then compared to estimated cumulative limits for mercury exposure based on guidelines of the Environmental Protection




Vaccines are listed under routinely recommended ages. Bars indicate range of recommended ages for immunization. Any dose not given at the recommended age should be given as a "catch-up" immunization at any subsequent visit when indicated and feasible. Ovals indicate vaccines to be given if previously recommended doses were missed or given earlier than recommended minimum age. This schedule indicates the recommended ages for routine administration of currently licensed childhood vaccines as of November 1, 2000 for children through 18 years. Additional vaccines may be licensed and recommended during the year.

Information in italics is the estimated maximum EtHg amount in 1999 versus the estimated maximum EtHg amount in 2001(μg/0.5mL).

[1] Some DTP vaccines did not contain thimerosal in 1999.

[2] Some Hib vaccines did not contain thimerosal in 1999.

[3] Never had thimerosal.

[4] Recommended only in selected states/regions, and for certain high-risk groups.

**FIGURE 1** Thimerosal content in vaccines recommended in childhood immunization schedule United States, January-December 2001 (ADAPTED from CDC, 2001g; FDA, 2001).

Agency (EPA), the Agency for Toxic Substance and Disease Registry (ATSDR), the FDA, and the World Health Organization (WHO). This comparison found that six-month-olds could have received cumulative doses of mercury that exceeded the EPA limits calculated for each body-weight category, and the ATSDR limits for the lowest-weight infants who also received the influenza vaccine (see Table 3). These estimated exposure levels were a source of concern, but they did not constitute direct evidence of harm, and no other evidence of harm other than delayed-type hypersensitivity reactions was found at the time of the FDA review. FDA then sent a letter to vaccine manufacturers on July 1, 1999, requesting their plans to remove thimerosal from U.S.-licensed vaccines, or an explanation for its continued use. Also in July 1999, a joint statement was issued by the American Academy of Pediatrics (AAP) and the U.S. Public Health Service (PHS), and consented to by the American Academy of Family Physicians (AAFP), recommending the removal of thimerosal from vaccines as soon as possible (CDC, 1999a).

The AAP-PHS statement also recommended one temporary change in the immunization schedule: deferring the first hepatitis B vaccination from birth until two to six months of age for children born to low-risk mothers (i.e., hepatitis B-surface-antigen-negative). However, with the rapid development of single-antigen, thimerosal-free hepatitis B vaccine, which was approved in August 1999, the Advisory Committee on Immunization Practices (ACIP) recommended in September 1999 that the birth dose of hepatitis B vaccine be resumed (CDC, 1999c).

Substantial progress has been made in removing thimerosal from childhood vaccines in the United States. At this time, vaccines currently manufactured or marketed that are on the recommended immunization schedule and given to children six years of age or younger contain no thimerosal as a preservative or contain only trace amounts (<0.5 µg Hg per dose) of thimerosal left over from the manufacturing process (CDC, 2000b). Some amounts of previously produced lots of vaccines that still contain thimerosal as a preservative, however, also remain available at present, although the amounts are unknown because it is considered proprietary information by the manufacturers. In addition, thimerosal is used as a preservative in other vaccines, such as influenza, that are given to adults and certain high-risk children. For these children, the typical cumulative dose of mercury from the influenza vaccine is 12.5µg at six months and 37.5µg by two years old. Some children are administered the diphtheria-tetanus toxoids vaccine without a pertussis component (DT), which contains 25 µg mercury.

TABLE 3 Calculated Exposure Limits for Mercury, Using Various Agency Guidelines for Exposure to Methylmercury, in Infants `6 Months of Age by Percentile Body Weight

| | Percentile Body Weight | | |
|---|---|---|---|
| **Agency** | **5th** | **50th** | **95th** |
| EPA | 65 µg | 89 µg | 106 µg |
| ATSDR | 194 µg | 266 µg | 319 µg |
| FDA | 259 µg | 354 µg | 425 µg |
| WHO | 305 µg | 7 µg | |

• Calculate Exposure Limit=dose/kg body weight/week×average weight×26 weeks×0.932 (mercury molecular weight/methylmercury molecular weight); e.g., EPA calculated exposure limit=0.7 ug/kg body weight/week×26 weeks×(2.36kg+5.25 kg) /2×0.93=65 µg.

• Assumes average of 5th, 50th, and 95 th % weight for females at birth (2.36 kg, 3.23 kg, 3.81 kg) and 6 months (5.25 kg, 7.21 kg, 8.73 kg)=3.81 kg, 5.22 kg, 6.27 kg. Females were selected because their smaller body weight makes them more susceptible than males.

• Recommended limits on methylmercury exposure: EPA: 0.1 µg/kg body weight/day; ATSDR: 0.3 µg/kg/ body weight/day; FDA: 0.4 µg/kg body weight/day; WHO 3.3 µg/kg body weight/week. For calculations, daily limits multiplied by 7 to obtain weekly limits.

NOTE: Areas were shaded by the IOM, not by the original authors of the table.

SOURCE: Ball et al., 2001. Reprinted with permission from *Pediatrics* 107:1150, Table 1, Copyright 2001.

## Neurodevelopmental Disorders

In its assessment of possible neurodevelopmental effects from exposure to thimerosal in vaccines, the committee decided to focus on a few clinically defined diagnoses of NDDs rather than on markers of subclinical differences, such as psychometric test scores, that may or may not correlate well with differences in diagnosis. The specific NDDs considered by the committee were autism, attention deficit/hyperactivity disorder (ADHD), and speech or language delay. The committee selected these outcomes based on two factors. First, published reports (Grandjean et al., 1997; NRC, 2000) have associated deficits in language, attention, and memory with prenatal exposure to methylmercury. Also, unpublished epidemiological data (Verstraeten, 2001) show weak associations between diagnoses of ADHD and speech or language delay and exposure to thimerosal-containing vaccines. Second, some parents and members of the medical and scientific communities have expressed concern that exposure to thimerosal in vaccines may cause autism. Complicating these hypotheses, however, is the fact that NDDs often are recognized and diagnosed only when children are old enough to have already received most of the recommended vaccinations.

**Autism**

Autism is a complex and severe developmental disorder characterized by impairments of social interaction, impairments in verbal and nonverbal communication, and restricted or repetitive and stereotyped patterns of behaviors and interests (APA, 1994; Filipek et al., 1999). Over time, research has identified subtle differences in the onset and progression of autistic symptoms. The term "autistic spectrum disorders" (ASD), synonymous with "pervasive developmental disorders" (PDD), refers to a continuum of related cognitive and neurobehavioral disorders that reflects the heterogeneity of these symptoms. ASD encompasses the more narrowly defined "autistic disorder" as well as childhood disintegrative disorder, Asperger's syndrome, Rett's syndrome, and pervasive developmental disorder not otherwise specified (PDD-NOS, or atypical autism). Box 1 lists diagnostic criteria for autistic disorder.

Research has established a strong genetic component in the etiology of autism, but other factors, including infectious, neurological, metabolic, immunological, and environmental insults, may play important roles. Although the consensus of most scientific experts is that most cases of autism are caused by early prenatal exposures such as valproic acid (Moore et al., 2000) or thalidomide (Stromland et al., 1994), or are linked to early developmental genes (Ingram et al., 2000; Persico et al., 2001; Wassink et al., 2001), significant gaps still remain in our understanding of the risk factors and etiological mechanisms of ASD.

There is considerable uncertainty about the prevalence of autistic disorder and other ASDs. Two large reviews of epidemiological studies conducted outside the United States conclude that the best conservative estimate of prevalence of autistic disorder is approximately 10 per 10,000 (Fombonne, 2001b; Gillberg and Wing, 1999). This estimate does not include other categories of ASD. A recent study conducted in Britain suggests that the prevalence of autistic disorder may be higher than previously thought; this study estimated the prevalence of autistic disorder to be 16.8 per 10,000, and the prevalence of ASD to be 62.6 per 10,000 (Chakrabarti and Fombonne, 2001). Information about the prevalence of autism in the United States is limited, reflecting a lack of epidemiological research on autism in this country.

**Attention Deficit/Hyperactivity Disorder (ADHD)**

Attention deficit/hyperactivity disorder (ADHD) is a behavioral disorder characterized by persistent patterns of inattention and/or hyperactivity. (In this report, the terms ADHD and Attention Deficit Disorder (ADD) are used interchangeably. ADHD is the term used in the *Diagnostic and Statistical Manual* (DSM-IV), while ADD refers to a specific ICD-9 code (314.0) that can include hyperactivity symptoms. Such patterns must be present before a child is seven

**BOX 1 DSM-IV CRITERIA FOR AUTISTIC DISORDER (299.0)**

A. A total of at least six items from (1), (2) and (3), with at least two from (1), and one each from (2) and (3):

1. Qualitative impairment in social interaction, as manifested by at least two of the following:

a. marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction;
b. failure to develop peer relationships appropriate to developmental level;
c. markedly impaired expression of pleasure in other people's happiness,
d. lack of social or emotional reciprocity.

2. Qualitative impairments in communication as manifested by at least one of the following:

a. delay in or total lack of the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gestures and mime);
b. in individuals with adequate speech, marked impairment in the ability to initiate or sustain conversation with others;
c. stereotyped and repetitive use of language or idiosyncratic language;
d. lack of varied spontaneous make-believe play or social imitative play appropriate to developmental level.

3. Restricted repetitive stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:

a. encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus;
b. apparently compulsive adherence to specific, nonfunctional routines or rituals;
c. stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole body movements);
d. persistent preoccupation with parts of objects.

B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age three: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play.

C. Not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder.

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years old, and must cause significant interference and impairment in at least two areas of life—such as home and school, or home and work (APA, 1994). Standard diagnostic criteria for ADHD are listed in Box 2. There is currently no clinical test for diagnosing ADHD. Rather, diagnosis depends on careful observation and evaluation of the child in multiple settings. Psychometric tests, such as the Continuous Performance Test (CPT), a standard measure of attention, are often used, however, there is no relation between CPT scores alone and a diagnosis of ADHD.

The most commonly cited prevalence rate suggests that 3–5% of school-age children are affected by ADHD, making it the most commonly diagnosed behavioral childhood disorder (NIH, 1998). Boys are diagnosed with ADHD more often than girls, although the exact ratio is unclear. Three- to nine-fold differences between the sexes are reported (Eme and Kavanaugh, 1995), and sex differences are also seen in the prevalence of subtypes of ADHD (Wolraich et al., 1996b). However, prevalence of the disorder is still debated. Wolraich and colleagues (1996a) reported an increase in prevalence to 12.4% as a result of a change in diagnostic criteria in 1995. A recent review also found that prevalence varied, depending on which DSM criteria were used in evaluation (Brown et al., 2001).

### Speech or Language Delay

Medical diagnostic codes (ICD-9) for speech or language delay correspond with three communication disorders described in DSM-IV, namely expressive language disorder, mixed receptive-expressive language disorder, and phonological disorder (see Box 3). Expressive language disorder is characterized by a significant impairment in vocabulary, difficulty forming sentences of developmentally appropriate length, and misuse of verb tense (APA, 1994). Mixed receptive-expressive language disorder has similar features, with additional difficulties comprehending words and sentences. Phonological disorder is characterized by difficulties in forming age-appropriate speech sounds.

Close clinical observation and standardized tests of language and intelligence are used to diagnose speech or language delay. For expressive language disorders, a child's scores are lower on tests of expressive language than they are for receptive language and intelligence. For mixed receptive-expressive language disorder, a child will score lower on tests of receptive and expressive language than on tests of nonverbal intellectual capacity (APA, 1994). These communication disorders can also be diagnosed when a child's speech development and language skills are significantly behind those of other children of the same age (Leung and Kao, 1999).

Estimates of the prevalence of speech or language delay vary, largely because of differences in terminology and diagnostic criteria used by practitioners, the subjective nature of parent and practitioner observations (Leung and Kao, 1999), and the age at which the child was evaluated. For example, 9–17% of two-year olds were reported to have a language delay, but prevalence was 1–3%

by age 5 (Whitehurst and Fischel, 1994). A recent review (Leung and Kao, 1999) reported speech delay for 3–10% of all children, which is consistent with additional rates reported in the literature (Boyle et al., 1994; Shriberg et al., 1999; Silva et al., 1983). The researchers also noted that speech delay affects boys three to four times more often than girls (Leung and Kao, 1999). Other researchers reported a median prevalence of speech or language delay of 6% for children aged 0–7 years, and that this prevalence had remained constant over the past 30 years (Law et al., 2000).

**BOX 2 DSM-IV CRITERIA FOR ATTENTION-DEFICIT/ HYPERACTIVITY DISORDER (ADHD) (314.00, 314.01)**

A. Either (1) or (2)

1. Six (or more) of the following symptoms of **inattention** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

***Inattention***

a. often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
b. often has difficulty sustaining attention in tasks or play activities
c. often does not seem to listen when spoken to directly
d. often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
e. often has difficulty organizing tasks and activities
f. often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
g. often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
h. is often easily distracted by extraneous stimuli
i. is often forgetful in daily activities

2. Six (or more) of the following symptoms of **hyperactivity-impulsivity** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

***Hyperactivity***

a. often fidgets with hands or feet or squirms in seat
b. often leaves seat in classroom or in other situations in which remaining seated is expected

c. often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
d. often has difficulty playing or engaging in leisure activities quietly
e. is often "on the go" or often acts as if "driven by a motor"
f. often talks excessively

***Impulsivity***

g. often blurts out answers before questions have been completed
h. often has difficulty awaiting turn
i. often interrupts or intrudes on others (e.g., butts into conversations or games)

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.

C. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).

D. There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.

E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g. Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

Code based on type:

314.01 Attention-Deficit/Hyperactivity Disorder, Combined Type: if both Criteria A1 and A2 are met for the past 6 months

314.00 Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive Type: if Criterion A1 is met but Criterion A2 is not met for the past 6 months

314.01 Attention-Deficit/Hyperactivity Disorder, Predominantly Hyperactive-Impulsive Type: if Criterion A2 is met but Criterion A1 is not met for the past 6 months

**BOX 3 DSM-IV CRITERIA FOR SPEECH OR LANGUAGE DELAY (315.31 AND 315.39)**

315.31 *Expressive Language Disorder*

A. The scores obtained from standardized individually administered measures of expressive language development are substantially below those obtained from standardized measures of both nonverbal intellectual capacity and receptive language development. The disturbance may be manifest clinically by symptoms that include having a markedly limited vocabulary, making errors in tense, or having difficulty recalling words or producing sentences with developmentally appropriate length or complexity.

B. The difficulties with expressive language interfere with academic or occupational achievement or with social communication.

C. Criteria are not met for Mixed Receptive-Expressive Language Disorder or a Pervasive Developmental Disorder.

D. If Mental Retardation, a speech-motor or sensory deficit, or environmental deprivation is present, the language difficulties are in excess of those usually associated with these problems.

315.31 *Mixed Receptive-Expressive Language Disorder*

A. The scores obtained from a battery of standardized individually administered measures of both receptive and expressive language development are substantially below those obtained from standardized measures of nonverbal intellectual capacity. Symptoms include those for Expressive Language Disorder as well as difficulty understanding words, sentences, or specific types of words, such as spatial terms.

B. The difficulties with receptive and expressive language significantly interfere with academic or occupational achievement or with social communication.

C. Criteria are not met for a Pervasive Developmental Disorder.

D. If Mental Retardation, a speech-motor or sensory deficit, or environmental deprivation is present, the language difficulties are in excess of those usually associated with these problems.

315.39 *Phonological Disorder*

A. Failure to use developmentally expected speech sounds that are appropriate for age and dialect (e.g., errors in sound production, use, representation, or organization such as, but not limited to, substitutions of one sound for another [use of /t/ for target /k/ sound] or omissions of sounds such as final consonants).

B. The difficulties in speech sound production interfere with academic or occupational achievement or with social communication.

C. If Mental Retardation, a speech-motor or sensory deficit, or environmental deprivation is present, the speech difficulties are in excess of those usually associated with these problems.

## PLAUSIBILITY ASSESSMENT

The Immunization Safety Review Committee undertook its review to answer the following question: What is the causal relationship between thimerosal-containing vaccines and the neurodevelopmental disorders of autism, attention deficit/hyperactivity disorder, and speech or language delay? The sources of evidence considered by the committee in its plausibility assessment include studies of biological mechanisms, reports of individual cases or series of cases, and epidemiological studies.

### Evidence Regarding Association: Biological Plausibility

Biological plausibility rests on the existence of scientifically viable mechanisms by which exposure to thimerosal-containing vaccines from the recommended childhood immunization schedule could be associated with autism, ADHD, or speech or language delay. Evidence for such an association can come from demonstration of the mechanism through clinical, animal, or *in vitro* studies. The evidence regarding thimerosal is indirect and incomplete, however. There are no direct studies, in either humans or animals, of thimerosal exposures of a magnitude similar to those resulting from vaccines that would firmly establish a biological model connecting it to NDD. Only indirect evidence, from decades of study of methylmercury and from high-dose thimerosal exposures, informs biological plausibility for neurodevelopmental effects from thimerosal exposure in vaccines.

The FDA risk assessment (Ball et al., 2001) included an extensive review of the available toxicity data on thimerosal and related data on ethyl- and methylmercury. The committee also reviewed much of these data, as well as published and unpublished reports that have become available since the FDA's review in 1999. Presented here is a brief summary of data on mercury toxicity, the toxicokinetic comparability of ethylmercury and methylmercury, and the documented effects of high-dose exposures to thimerosal, ethylmercury, and methylmercury. Also examined are models of mercury accumulation and investigations related to concentrations of mercury and heavy metals in children with autism. The application of methylmercury-exposure guidelines to ethylmercury exposures resulting from the use of thimerosal-containing vaccines is discussed as well.

### Mercury Toxicokinetics

Mercury occurs in inorganic and organic forms. Inorganic mercury includes elemental, or metallic mercury ($Hg^0$), and the mercurous ($Hg^+$) and mercuric ($Hg^{2+}$) salts. Organic mercury, defined as mercury compounds containing carbon bonds, includes ethylmercury ($CH_3CH_2Hg^+$) and methylmercury ($CH_3Hg^+$), as well as other compounds. Mercury exposure can occur through inhalation of metallic mercury vapor, ingestion (with almost complete absorption of methyl

mercury), and absorption through the skin, as well as through intravenous, intramuscular, and subcutaneous injections (ATSDR, 1999; NRC, 2000). The toxicokinetic profile of mercury exposure can differ depending on the form of mercury, the route of exposure, the size of the dose, and age at exposure, but the toxicity of all mercury compounds is due to the mercury itself.

Thimerosal is a thiosalicylate salt of ethylmercury. Upon administration, 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, 2001b; Suzuki et al., 1963, 1973).

Mercury is clearly neurotoxic and nephrotoxic. Organic mercury forms of interest, ethyl- and methylmercury, are metabolized to mercuric mercury. The effects of mercuric mercury are greatest in the kidneys, whereas the effects of organic mercury are greatest in the central and peripheral nervous systems (Aschner and Aschner, 1990). Generally, mercury is thought to induce cytotoxicity through inhibition of protein synthesis and cellular enzyme-mediated reactions, resulting in structural changes of cells, interference with cellular metabolism, and inhibition of cell migration (Clarkson, 1972). More specifically, mercuric mercury exposure can cause acute renal failure and toxicity, characterized by proteinuria, oliguria, and hematuria. Case studies have also reported congested medulla, pale and swollen cortex, extensive necrosis, and degeneration of tubular epithelium (ATSDR, 1999). Similar measures of toxicity such as necrosis of proximal tubules, proteinuria, and general renal nephropathy have been demonstrated in animal studies (ATSDR, 1999).

**Comparisons of Ethylmercury and Methylmercury**

The limited data on the toxicology and pharmacokinetics of thimerosal and ethylmercury are summarized here, along with information about methylmercury, which has been studied extensively (see ATSDR, 1999; EPA, 1997; NRC, 2000; for detailed reviews). Many features of the toxicity of ethylmercury are thought likely to be qualitatively similar to those of methylmercury (Ball et al., 2001).

Methylmercury has a whole-body half-life in the range of 70 to 80 days. The half-life of ethylmercury is not known, but may be shorter given its more rapid conversion to inorganic mercury. Methylmercury in blood appears to have a half-life of 50 days (WHO, 1990). Methylmercury is excreted primarily in feces and bile, mostly in the form of inorganic mercury (NRC, 2000). Organic and inorganic mercury complexed with glutathione are excreted in bile (Ballatori and Clarkson, 1984). Methylmercury secreted in bile undergoes subsequent re-absorption in the intestinal tract. Urinary excretion plays a minor role in the elimination of methylmercury from the body. Urinary excretion may be higher after ethylmercury due to its more rapid conversion to inorganic mercury. In general, based on studies of methylmercury in rodents (Ballatori and Clarkson,

1984), suckling infants do not excrete methylmercury. At weaning, the process of biliary excretion is suddenly activated.

After ethylmercury administration in mice, more total mercury has been found in the blood and kidney—compared with methylmercury—and less in the brain (Suzuki et al., 1963). Methylmercury can pass through the blood-brain barrier and into nerve cells as part of a methylmercury-cysteine complex (Kerper et al., 1992). It is unclear whether ethylmercury passes readily through the blood-brain barrier at the concentrations that result from exposure through vaccines. This may result from lack of an amino acid transport system like that available to methylmercury. Glutathione, present in high concentrations inside cells, readily binds to methylmercury and may play a protective role. Methylmercury is transported out of cells probably as a complex with glutathione, as will be discussed later. Little is known about the transport mechanisms for ethylmercury out of cells, but it probably follows those of methylmercury. Ethylmercury also is converted more rapidly than methylmercury to mercuric mercury, which does not cross the blood-brain barrier as readily as the organic compounds (Magos, 2001b). It has also been postulated that mercury has a direct toxic effect on the blood-brain barrier at high doses, making it more permeable (Aschner and Aschner, 1990).

Once present in brain tissue, organic mercury is converted into inorganic mercury. Studies have shown that ethylmercury has a significant and fast conversion to inorganic mercury and that the rate of conversion is slower for methylmercury. Suzuki and colleagues (1973) reviewed several studies and compared inorganic mercury levels in the brain after methylmercury or ethylmercury exposure. One study found that up to 75% of the total mercury in the brain was inorganic mercury three days after injection of ethylmercury or thimerosal. Other studies suggest that the percentage of inorganic mercury resulting from ethylmercury exposure is lower (11–46%). In comparison, the total mercury in the brain at one to ten days after injection of methylmercury was 2.8% (reviewed in Suzuki et al., 1973). Furthermore, the amounts of inorganic mercury in the brain increased over time following exposure to ethylmercury (Suzuki et al., 1973). The characteristics of exposure also influence the conversion rate. Studies have found a higher fraction of inorganic mercury after chronic low dosing of methylmercury than after acute exposure (Aschner and Aschner, 1990).

Upon conversion from organic mercury, mercuric mercury does not as readily cross the blood-brain barrier to move into the blood stream for elimination. Thus it is retained in the neural tissue for a longer period of time (ATSDR, 1999). However, the relative contributions of inorganic and organic mercury to neural cytotoxicity are not known at this time. It is known that methylmercury can inhibit neuronal protein synthesis and several enzymatic processes that control cell metabolism and respiration (Chang et al., 1980). Unpublished data from *in vitro* studies presented to the committee suggest that ethylmercury from thimerosal in vaccines binds to various neuronal cellular proteins (Haley, 2001).

However, because many metals bind to cellular proteins, the significance of this finding with respect to biological plausibility is unclear. Following organic mercury injection in the mature brain, distribution of mercury (reviewed in Clarkson, 1972 and Chang et al., 1980) indicates greatest retention in the calcarine cortex, frontal, temporal, and occipital cortex, cerebellum, and the spinal dorsal root ganglions. In the developing brain, methylmercury exposure leads to widespread damage, affecting virtually all areas of the brain (Clarkson, 1997).

Mercuric mercury accumulated in the kidney is bound to the protein metallothionein, which may play a protective role in renal toxicity. In the blood, ethyl- and methylmercury are bound to cysteine residues of hemoglobin and to plasma proteins (Clarkson, 1972; NRC, 2000; Takeda et al., 1968). Methylmercury exposure results in a greater ratio of mercury in the red blood cells to plasma compared with ethylmercury (reviewed in Suzuki et al., 1973). The blood-distribution ratio of organic mercury is species-dependent.

Methylmercury is avidly accumulated from the blood stream into scalp hair (for review, see WHO, 1990). The average hair to blood concentration ratio is 250:1. Once incorporated into the formed elements of the hair strand, the concentration remains unchanged. Thus, longitudinal analysis along the length of the hair strand will recapitulate previous blood levels (Amin-Zaki et al., 1976). Hair grows at an approximate rate of 1 cm per month. Thus depending on the length of the hair strand, recapitulation can take place over many months or even years. Hair is especially useful as a biological monitor for prenatal exposure as a hair sample that covers the entire period of pregnancy can be collected from the mother at or soon after delivery. Thus hair has been used as the primary biological monitor in all epidemiological studies of prenatal exposure or in one case to complement the use of cord blood (NRC, 2000). Especially important, it has recently been shown that levels in the mother's hair at delivery predict levels in autopsy brain samples from newborn infants that died of various causes (Cernichiari et al., 1995).

Organic mercury is also known to cross the placenta easily, allowing for prenatal mercury exposure. In addition, methylmercury is excreted in breast milk (Sundberg and Oskarsson, 1992; Yoshida et al., 1992).

## Health Effects of High-Dose Exposures to Thimerosal, Ethylmercury, and Methylmercury

High-doses of thimerosal, ethylmercury, and methylmercury have been found to produce severe health problems. High-dose thimerosal exposures have been iatrogenic or, in one case, resulting from a deliberate use in a suicide attempt. High-dose ethylmercury poisonings have resulted from environmental and occupational exposures, with poisoning from ethylmercury-containing fungicides being frequently fatal. Methylmercury poisoning has resulted from consumption of contaminated fish and grain. Neurological effects were prominent

in all of these poisonings, and prenatal exposures to methylmercury resulted in birth defects and serious neurodevelopmental deficits. Although these exposures are at levels far higher than those resulting from vaccination, the evidence of neurotoxicity offers some support for, but does not establish, the biologic plausibility of neurotoxic effects at lower doses.

**Thimerosal Exposure.** Several cases of high-dose exposure to thimerosal have been reported in the literature. Six patients (age 6 weeks to 39 years), who were given intramuscular injections of improperly formulated chloramphenicol, each received 71–330 mg/kg of thimerosal—1,000 times the correct level (Axton, 1972). Symptoms were mainly neurological, including restlessness, slurred speech, hemiparesis, confusion, unsteady gait, hallucinations, and coma; five of the six patients died. An 18-month-old girl, who ingested 127 mg/kg of thimerosal (in a merthiolate solution) over a one-month period, developed ataxia, hand tremors, vomiting, staring spells, and renal and hepatic failure before dying (Rohyans et al., 1984). (Chelation therapy did not appear to be associated with clinical improvement in neurological function.) Ten of 13 infants treated with topical applications of a 0.1% tincture of thimerosal for omphaloceles (herniations of the bowel through the umbilicus) died (Fagan et al., 1977). Autopsy studies of three infants found high levels of mercury in the liver (11.8–26.6 μg/g), the kidney (2.36–4.6 μg/g), and the brain (0.65–5.1 μg/g). A neurological follow-up at 10 years on a surviving patient found no abnormal focal neurological findings but included third-person reports of restlessness and easy distractibility in school.

Ingestion of 5g of thimerosal in a suicide attempt resulted in delirium, sensorimotor polyneuropathy culminating in mechanical ventilation, and coma, along with acute renal failure (which resolved after 40 days), fever, oral exanthema, and gingivitis (Pfab et al., 1996). The patient recovered completely at 148 days post-ingestion, except for sensory defects in two toes.

Toxicity was also reported in a 44-year-old male who had received approximately 20 mg of thimerosal from HBV immunoglobulin, administered intramuscularly or intravenously, after a liver transplant for end-stage liver failure due to hepatitis B, C, and D infection (Lowell et al., 1996). Beginning on the third postoperative day, the patient began developing symptoms that included paranoid thoughts, slurred speech, slowed movements, decreased muscle strength, inability to ambulate, and tremor in both hands. The patient's symptoms completely resolved in five weeks following chelation therapy with DMSA (dimercaptsuccinic acid). The diagnosis of mercury toxicity in this case has been questioned because of the brief exposure period, the absence of visual field constriction, and a blood-mercury level (104 μg/L on day nine) considered too low for the development of the symptoms described when compared with other cases (Magos, 2001b).

In contrast to these reports of high-dose thimerosal toxicity, early studies in animals and humans failed to show neurotoxic effects (Jamieson and Powell, 1931). Rabbits tolerated intravenous thimerosal doses of 25 mg/kg of body

weight; at higher doses, fatalities resulted from kidney and intestinal disease. In rats, the tolerated dose was 45 mg/kg body weight. A report on 22 human subjects who received total doses of up 180 ml of a 1% solution of merthiolate (10 mg/kg) noted only local skin irritation (Powell and Jamieson, 1931). However, the study was not designed to test toxicity (Ball et al., 2001).

**Other Ethylmercury Exposures.** Mercury poisonings occurred in Iraq from consumption of bread made from grain treated with a fungicide containing 7.7% ethylmercury p-toluene sulphonanilide (Damluji, 1962; Jalili and Abbasi, 1961). Symptoms generally occurred one to two months after consumption of the treated wheat, and patients differed in the mix and severity of their symptoms. Among the neurological symptoms seen were ataxia, difficulty in walking, speech disturbances, constriction of visual fields, and blindness. Effects were also seen on the renal system, the skin, the cardiac system, and the gastrointestinal system.

In China, similar effects were seen from consumption of rice treated with ethylmercury chloride (2–2.5%) (Zhang, 1984). Symptoms began one to two weeks following consumption of the rice and continued for several months. Common neurological symptoms included weakness, dizziness, numbness of extremities, paresthesia, ataxia, and unsteady gait. Fewer people experienced symptoms of impaired vision, coma, speech disturbance, or hand tremor. The mildest cases resulted from doses of 0.5–1 mg/kg body weight, moderate cases from 1–2 mg/kg, severe cases from 2–3 mg/kg, and lethal cases above 4.0 mg/kg body weight.

Four cases of mercury poisoning occurred in Romania from consumption of pork from animals fed seed treated with ethylmercury chloride fungicides (Cinca et al., 1980). Symptoms were similar to those seen in Iraq and China, including ataxia, dysarthria, dysphagia, increased tendon reflexes, inability to stand or walk, coma, and constricted visual fields. Autopsy results from two boys aged 10 and 15 showed the greatest nerve-cell loss and proliferation of neuroglia in the cerebral cortex, especially in the calcarine cortex, the midbrain, and the bulbar reticular formation. Demyelination was apparent in the ninth and tenth cranial-nerve roots, and moderate cell loss and other lesions were found in the granular and Purkinje cells of the cerebellum. Motorneuron loss was evident in the ventral horns of the spinal cord.

Fatal ethylmercury poisoning has also resulted from a seven-week occupational exposure to ethylmercury in an insecticide factory (Hay et al., 1963). The presenting symptoms included dysarthria, ataxia, leg weakness, bilateral nerve deafness, increased reflexes, and poor coordination. At autopsy, the brain showed loss of neurons from areas of the cerebral cortex (especially calcarine cortex) and some degeneration of Purkinje and granule cells of the cerebellum. In contrast to typical findings, a greater amount of mercury was found in the brain, especially in the corpus callosum, than in the liver.

**Methylmercury Exposures.** Methylmercury at high doses is a well-documented neurotoxicant (NRC, 2000). The most severe neurological effects

reported in humans occurred after accidental methylmercury-poisoning episodes in Japan and Iraq. Major epidemics of methylmercury poisoning occurred in Minamata and Niigata, Japan, during the 1950s and 1960s following consumption of contaminated fish and seafood, and first raised awareness of the neurological sequelae of high-dose exposures to methylmercury (Harada, 1995; Tsubaki and Irukayama, 1977). Poisoning episodes in Iraq in the 1960s and 1970s resulted from consumption of homemade bread made from grain treated with a methylmercury-containing fungicide (Bakir et al., 1973).

In adults, these high-dose exposures to methylmercury resulted in symptoms that included paresthesia, ataxia, and impairments of speech, hearing, and vision. In children exposed during fetal development, there were severe neurological dysfunctions and developmental abnormalities, including mental retardation, cerebral palsy, deafness, blindness, and dysarthria (Harada, 1995; Marsh et al., 1987; NRC, 2000). In both Japan and Iraq, the neurological effects observed in children exposed to methylmercury *in utero* were more serious than those observed in adults, and sometimes occurred at lower doses than in adults, indicating the increased susceptibility of the fetus to methylmercury exposure (NRC, 2000). The exposures that produced these effects were very high, and precise dose-response relationships at low doses were not established (NRC, 2000).

### Health Effects of Low-Dose Exposures to Thimerosal and Methylmercury

Studies of low-dose exposures to thimerosal and methylmercury would be potentially more informative regarding the biological plausibility of neurodevelopmental effects from thimerosal exposures from vaccination. The data on thimerosal are limited, however, and the studies of the effect of ingested methylmercury are not directly applicable.

**Hypersensitivity Reactions to Thimerosal.** Immune-mediated reactions to mercury-containing compounds are well documented in humans and in experimental animals (for reviews see Enestron and Hultman, 1995; Griem and Gleichman, 1995; Pollard and Hultman, 1997). The most common manifestation is contact allergy (i.e., delayed-type hypersensitivity), although immune-complex-mediated disorders, such as glomerulonephritis, and immediate-type hypersensitivity (i.e. allergy) reactions have also been reported. Thimerosal can induce contact hypersensitivity responses in humans. Positive patch tests have been seen in 1–16% of individuals tested (reviewed in Cox and Forsyth, 1988). However, the frequency of clinically important contact hypersensitivity is much lower, and its significance is a matter of controversy (Ball et al., 2001).

Ethylmercury in vaccines and other pharmaceutical products may rarely cause immediate-type hypersensitivity reactions, including anaphylaxis, although conclusive proof that mercury in thimerosal is the causative component is lacking. In one case in which anaphylaxis occurred in association with hepatitis B

vaccine administration, a repeat challenge suggested that thimerosal was not responsible (Ball et al., 2001). Similarly, one report of laryngeal obstruction after a patient used a throat spray containing thimerosal (Maibach, 1975) might reflect the corrosive effect of mercury rather than a hypersensitivity reaction.

Acrodynia has been reported in a patient receiving gammaglobulin injections containing .01% thimerosal (Matheson et al., 1980). Acrodynia, or pink disease, occurs in a small fraction of exposed individuals, primarily children, and may represent a hypersensitivity response to mercury. It presents with a pink, pruritic skin rash, especially on the soles and palms. Other symptoms can include photophobia, irritability, and lethargy. Acrodynia is most closely associated with infants exposed to inorganic mercury in products like teething powders, which are no longer marketed. The 20-year-old patient receiving gammaglobulin had congenital agammaglobulinemia and a history of allergic reactions and sensitivity to sulphonamide drugs. He had been receiving gammaglobulin shots over the course of 15 years. It was estimated that the patient was exposed to 40–50 mg of mercury during the year in which he presented with symptoms.

**Methylmercury Exposure.** The lack of data on the effects of low-dose ethylmercury exposure has led those concerned about thimerosal-containing vaccines to examine studies of chronic low-dose exposures to methylmercury, occurring primarily through consumption of fish and marine mammals. The neurodevelopmental effects in children resulting from moderate to low-level prenatal and postnatal exposures to methylmercury are less clear than the serious effects seen in high-dose poisonings (see NRC, 2000 for a review of epidemiological studies).

Two large prospective cohort studies are currently under way to evaluate the more subtle endpoints of neurotoxicity resulting from low-dose prenatal exposure to methylmercury. The first study is being conducted in the Faroe Islands, in the North Sea, and the second in the Republic of the Seychelles, a nation of islands in the Indian Ocean off the coast of East Africa. In the Faroe Islands, the predominant source of mercury exposure is from consumption of pilot whale meat. In the Seychelles, mercury exposure comes from consumption of ocean fish. To date, the two studies have reached different conclusions.

The Faroe Islands study is following a cohort of approximately 1,000 children born in 1986–1987. Developmental outcomes were assessed for 917 of the children at age 7 using a battery of domain-specific neuropsychological and neurophysiological tests. Prenatal methylmercury exposure, as measured by umbilical cord blood levels, was associated with subtle neuropsychological deficits most notable in the areas of attention, memory, and language, and to a lesser extent in visuospatial and motor functions. Postnatal exposures, measured by the child's hair mercury concentration at ages 1 year and 7 years, were less useful risk predictors (Grandjean et al., 1997).

The Seychelles study is following two cohorts of children, a Pilot Study cohort (N=789) and a Main Study cohort (N=779), enrolled in 1987 and 1989,

respectively. The cohorts have been followed longitudinally and outcomes have been assessed at multiple ages. Prenatal and postnatal mercury exposures were measured in maternal hair and child hair cut at each testing, respectively. Evaluations conducted through 5.5 years of age, using global assessments, found no adverse associations between prenatal or postnatal exposure to methylmercury and childhood developmental outcomes (Davidson et al., 1995, 1998, 2000). Preliminary analyses from evaluations of pilot cohort members at age nine using domain-specific tests also show no adverse associations (Davidson et al., 2000; Myers, 2001).

The discrepant findings in these two studies may reflect differences in study design or in the characteristics of the populations examined. There were differences in exposure measures (cord blood versus maternal hair), types of neurological and psychological tests administered (domain-specific versus global developmental outcomes), the age of testing (7 years versus 5.5 years of age), possible confounders (PCB exposure or genetic differences in the populations studied), and biostatistical issues related to data analysis (NRC, 2000). Additional analyses of the Seychelle Islands data are under way and will address some of these differences (Myers, 2001).

The committee carefully considered the significance of the evidence of subtle neurological deficits from the Faroe Islands study for its assessment of the biological plausibility of a causal association between exposure to thimerosal-containing vaccines and the neurodevelopmental disorders of autism, ADHD, and speech or language delay. The conclusion was that those findings add indirect support to the biological plausibility of such an association but do not demonstrate a direct biological mechanism or provide evidence of causality. As was stated in the recent FDA risk assessment of thimerosal in vaccines (Ball et al., 2001), extrapolating the toxicity of methylmercury exposure to ethylmercury exposure in thimerosal-containing vaccines is problematic. Data on the comparative toxicology of ethyl- and methylmercury are limited. In addition, data on the metabolism and excretion of ethylmercury compared with methylmercury have not been well established. The comparability of the effects of chronic low-dose exposure to methylmercury via ingestion versus those of intermittent exposure to ethylmercury via intramuscular injection is unknown. The relative susceptibility of the fetus compared with the infant is also unknown. Furthermore, the neuropsychological deficits detected in the Faroe Island studies are not reliable predictors for the specific neurodevelopmental diagnoses of autism, ADHD, and speech or language delay.

### Investigations Related to Mercury and Heavy Metals in Children with Autism

Similarities between autism and mercury intoxication have been offered as evidence that thimerosal in childhood vaccines could cause autism (Bernard et

al., 2001; El-Dahr, 2001). The identified similarities include psychiatric disturbances, speech or language deficits, sensory abnormalities, motor disorders, cognitive impairments, unusual behaviors (such as head banging and sleep difficulties), physical disturbances (such as rashes, diarrhea, abnormal feeding behaviors), and biological indices (such as metal metabolism, immune system effects, CNS structure, neurochemistry, and neurophysiology). However, the analogy is weakened by differences in mechanistic understanding of some of the symptoms of mercury intoxication and of autism. For example, impaired visual fixation associated with mercury toxicity is due to problems with motor control of eye muscles. This is unrelated mechanistically to problems in joint attention associated with autism, which are most likely a problem of social reciprocity, not motor control (Tanguay, 2000). In addition, there are manifestations from ethylmercury toxicity not seen in autism, for example, polyuria, ataxia, and tremor. Analogies like these are important for hypothesis generation, but they have limited value in causality assessments.

Others have argued that thimerosal may cause autism based on the observation that some autistic children have abnormal blood-metal profiles. One method being used to indicate levels of mercury in autistic children is chelation therapy. Three unpublished reports of chelation-based estimates of mercury in autistic children were presented to the committee (Bradstreet, 2001). In one study, higher urinary mercury levels were found in autistic children than in neurologically normal children after provocation with the chelator DMSA. In a case report that also used DMSA provocation, mercury levels in an autistic boy were much more elevated than those of his mother, father, or brother. Finally, in a study of 27 autistic children in Indonesia, 70% had detectable mercury levels, with the levels in 30% of the children exceeding adult mercury levels. Some have reported improvements in functioning of autistic children after chelation therapy (Cave, 2000; Sykes, 2001).

Chelation therapy has not been established to improve renal or nervous system symptoms of chronic mercury toxicity (Sandborgh Englund et al., 1994) and has had no effect on cognitive function when used for excretion of another heavy metal, lead (Rogan et al., 2001). Because it is unlikely to remove mercury from the brain, it is useful only immediately after exposure, before damage has occurred (Evans, 1998). 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). In addition, chelation therapies are not specific to one metal.

The presence of abnormal metal profiles in autistic children does not mean that the metal burden is the cause of autism. It could indicate a comorbidity between autism and an inability to handle heavy metals. Further, a favorable response to chelation therapy is not proof that the mercury levels caused the neurological dysfunction. Chelation therapy is non-specific, and the observed effects could be caused by other metals or other factors.

## Application of Methylmercury Exposure Guidelines to Thimerosal Exposure from Vaccines

Concern over the use of thimerosal in childhood vaccines was originally triggered by calculations showing that vaccines on the recommended childhood immunization schedule might result in cumulative ethylmercury exposures that exceed estimated limits of safe exposure based on some federal guidelines for methylmercury intake. Three U.S. federal agencies—EPA, ATSDR, and FDA—have developed guidelines for assessing exposure to methylmercury. The EPA is responsible for monitoring mercury concentrations in the environment and regulating industrial releases of mercury to air and surface water. The FDA is responsible for regulating commercially sold fish and seafood based on mercury concentrations. Although ATSDR does not have regulatory authority, it monitors the potential for human exposure to methylmercury and investigates reported health effects (NRC, 2000). Currently, each of the agencies has a different guideline for assessing safe exposure to mercury, and different limits of methylmercury intake, ranging from 0.1 µg/kg/day for EPA (EPA, 2001), to 0.3 µg/kg/day for ATSDR (ATSDR, 1999), to approximately 0.4 µg/kg/day for FDA (FDA, 1979).[3] The differences in the agencies' recommended limits can be attributed to the use of different risk-assessment methods and uncertainty factors, variation in primary data sources, and the different mandates of each agency (NRC, 2000). Although a consensus for safe mercury exposure does not exist, all of the recommended limits are within the same order of magnitude.

The methylmercury exposure limits calculated by these agencies are not limits above which injury is sure to occur. Rather, they should be interpreted as general levels of exposure below which there is confidence that adverse effects will be absent, although the margin of safety reflected in those limits is uncertain (EPA, 1997). Definitions of the exposure measures used in the three federal guidelines are provided in Box 4.

It is important to understand the specific data and assumptions on which these guidelines are based, however, when considering the possible implications of thimerosal exposures that exceed the guidelines on methylmercury intakes. As a result, the computation of the federal guidelines is briefly reviewed here, although an in-depth discussion of the development of the guidelines is beyond the scope of this report. (The interested reader is referred to a recent review in NRC, 2000.) The estimates of the maximum mercury exposures associated with recommended childhood immunization are then compared against the recommended exposure

[3] FDA's acceptable daily intake (ADI) of methylmercury is 30 µg/day (FDA, 1979). FDA has never officially expressed its standard on a body weight basis. For general comparison purposes with the EPA's and ATSDR's guidelines, FDA's ADI of 30 µg/day has been converted to a µg/kg/day basis, assuming a 70 kg average body weight, which is roughly equivalent to 0.4 µg/kg/day. Varying the assumptions about average body weight will affect the conversion.

limits based on the federal guidelines. Also discussed are sources of additional uncertainty that arise from the application of these methylmercury-based guidelines to ethylmercury exposures resulting from the use of thimerosal-containing vaccines.

**BOX 4 DEFINITION OF MEASURES USED IN FEDERAL EXPOSURE GUIDELINES**

***Environmental Protection Agency Reference Dose (RfD):***

An estimate (with uncertainty spanning perhaps an order of magnitude) of daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime (EPA, 1997, pp. 3–27).

***Agency for Toxic Substances and Disease Registry (ATSDR) Minimal Risk Level (MRL):***

An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure (ATSDR, 1999, p. 613).

***Food and Drug Administration (FDA) Acceptable Daily Intake (ADI):***

An estimate of the daily intake of a chemical which, if ingested over a lifetime, appears without appreciable risk (IOM, 1991b).

**Computation of Federal Guidelines for Methylmercury Exposure.** Although the details differ, the basic approaches used to compute EPA's Reference Dose (RfD), ATSDR's Minimal Risk Level (MRL), and FDA's Acceptable Daily Intake (ADI) are similar. Each calculation begins with a "point of departure" exposure that can be loosely interpreted as the lowest dose that has been empirically associated with a specific type of illness or injury in typical members of the population. The point of departure dose may then be divided by one or more factors that account for uncertainty or variability in the risk estimate. These factors, which are often referred to as uncertainty, adjustment, safety, or modifying factors, typically range in value from one to ten. These factors serve the same two general purposes. First, they are used to protect against the possibility that the true minimum exposure at which injury or disease occurs in typical members of the population is lower than the identified level (i.e., the point of departure dose). Second, they are used to protect the health of "sensitive" members of the population, who could for either pharmacokinetic reasons (more of the active agent is delivered to the target tissue per unit exposure) or pharmacodynamic reasons (the tissue reacts to a greater extent per unit of the active agent delivered), be adversely affected at a lower level than the level at which typical members of the population are adversely affected. Dividing by factors that exceed one makes the resulting standard more stringent or protective. Thus, for example, if it is suspected that another uninvestigated

health effect might occur at exposure levels ten times lower than the effect used to compute the point of departure, the point of departure can be divided by a factor of ten. Similarly, if it is suspected that sensitive members of the population are adversely affected at an exposure level one-third as great as the level of exposure at which typical members of the population are adversely affected, the point of departure can be divided by a factor of three.

To set its RfD of 0.1 µg/kg/day for methylmercury intake, EPA originally used findings from a study of 81 children in Iraq exposed *in utero* to high levels of methylmercury from maternal consumption of seed grain (Marsh et al., 1987). Developmental effects, quantified in terms of a composite score reflecting "late walking, late talking, mental symptoms, seizures" (NRC, 2000) or adversely affected neurological function, were observed at lower levels of exposure than any other health effects, making them the most sensitive indicator of health risk. EPA estimated that with 95% confidence, the maternal mercury exposure that increased developmental risk for an unborn child by 10% corresponded to hair mercury concentrations of no less than 11 ppm (parts per million), estimated as equivalent to daily consumption of 1.1 µg of mercury per kg of bodyweight (1.1 µg/kg/day). The EPA applied uncertainty factors—with a total value of 10—to produce the exposure limit value of 0.1 µg/kg/day (EPA, 2001).

A National Research Council (2000) review of EPA's methylmercury RfD recommended maintaining the exposure limit of 0.1 µg/kg/day but suggested basing the value on data from the Faroe Islands study of the effects of chronic dietary exposure to mercury rather than on the acute high-exposure data from Iraq. As described above, the Faroe Islands study used a variety of performance tests to measure neurological and cognitive function among children with prenatal exposures to methylmercury.

Several sources of uncertainty and variability were included in the EPA's composite uncertainty factor of 10. First, a factor of 3 accounted for pharmacokinetic differences among members of the population. Another factor, also 3, addressed pharmacodynamic variability and uncertainty. EPA rounded the product of the uncertainty factors—in this case, 9—to one significant digit, thus yielding 10 (EPA, 2001).

In contrast, the ATSDR exposure limit of 0.3 µg/kg/day, established in 1999 (ATSDR, 1999), is based on data from the Seychelle Islands study (described above) (Davidson et al., 1998), which did not find an association between prenatal methylmercury exposure and deficits in neurological function. ATSDR used these data to identify the *maximum* level of mercury exposure *not* associated with adverse health effects. The highest exposure group in that study had hair mercury concentrations of 15.3 ppm, which ATSDR estimated to be associated with consumption of 1.3 µg/kg/day of methylmercury. To obtain the MRL, the ATSDR applied a composite factor of 4.5, which reflects (1) an uncertainty factor of 1.5 for pharmacokinetic differences in the population, (2) plus an uncertainty factor of 1.5 for inter-individual variability (pharmacodynamic)

differences, (3) multiplied by an additional modifying factor of 1.5 to address the possibility that domain-specific tests, as employed in the Faroe Islands study, might be able to detect subtle neurological deficits not tested for in the Seychelles cohort (ATSDR, 1999).

The FDA set its action level of 1 ppm of methylmercury in the edible portion of fish in 1979, based on an ADI of 30 µg/day (equivalent to approximately 0.4 µg/kg/day assuming a 70 kg average body weight). The ADI estimates were based primarily on Swedish studies of methylmercury poisonings from consumption of highly contaminated fish in Niigata, Japan (FDA, 1979). Unlike the EPA and ATSDR exposure limits, which are based on effects of prenatal exposure to methylmercury, the FDA limit is based on exposure effects in adults. In deriving its ADI, FDA estimated the lowest daily intake at which adverse effects could appear in adults (300 µg/day). The FDA then applied a ten-fold margin of safety that it uses when human data are available, to obtain the 30 µg/day ADI (FDA, 1979).

In summary, exceeding federal exposure guidelines for mercury does not mean that adverse health effects should necessarily be expected to result. All the guidelines discussed here have additional factors built in to protect members of the population who might be more sensitive for either pharmacokinetic or pharmacodynamic reasons and address the possibility that (perhaps different) effects will occur at lower levels than those that have been empirically observed.

**Comparing Childhood Vaccine Exposures with Federal Guidelines.** As part of the FDA risk assessment of thimerosal, Ball and colleagues (2001) sought to compare the maximum mercury exposures resulting from the recommended childhood immunization schedule with the estimated cumulative limits for mercury exposure based on the three federal guidelines, as well as those of the World Health Organization (WHO).[4] Table 3 shows the calculated exposure limits based on application of these guidelines to a female infant at the 5$^{th}$, 50$^{th}$, and 95$^{th}$ percentile body weight between birth and 26 weeks, the time when most vaccines are given. The maximum vaccine-related cumulative mercury dose at age 6 months (based on the mercury content of the recommended vaccines in 1999; see Table 2) was 187.5 µg (and 200 µg for children who also received the influenza vaccine), which exceeded the EPA limits calculated for each bodyweight category and the ATSDR limits for the lowest-weight infants who also received the influenza vaccine (see shaded portions of the table).

There is, however, no scientific or clinical basis for knowing that this is the appropriate way to compare vaccine-related mercury exposure with the federal guidelines. Ball and colleagues essentially averaged exposures over the first six months of life, but because mercury exposures associated with vaccines are episodic, one can argue for an even shorter averaging period. Changing the averag

[4] The WHO guideline is less conservative than the mercury exposure guidelines in the United States. It is expressed as 3.3 µg/kg/week, which corresponds to 0.47 µg/kg/day for purposes of comparison.

ing period can have a substantial impact on comparisons with federal guidelines. Halsey (1999a) made alternative comparisons in which exposures were averaged over periods of one month, one week, and one day. For example, using an averaging period of one month, a single dose of hepatitis B vaccine with 12.5 µg mercury given to a child with an average weight of 4 kg yields an average daily dose of 0.1 µg/kg/day, which is equal to EPA's RfD. Alternatively, if the exposure is averaged over a single day, it amounts to approximately 3.1 µg/kg/day, which exceeds EPA's standard by more than a factor of 30. Figure 2 shows Halsey's estimates of maximum single-day mercury exposure from recommended vaccines given at birth and ages 2, 4, and 6 months, for a range of body weights at each age. He assumed mercury doses of 12.5 µg at birth, 62.5 µg at age 2 months, 50 µg at age 4 months, and 62.5 µg at age 6 months.

An alternative approach produces a substantially lower estimate of exposure. Because the federal guidelines are defined in terms of exposures over a "long period of time" or even over a lifetime, the daily doses assumed by Halsey could conceivably be averaged over a typical lifetime duration of approximately 25,000 days. Doing so yields doses of at least a factor of 400 below the EPA's RfD.

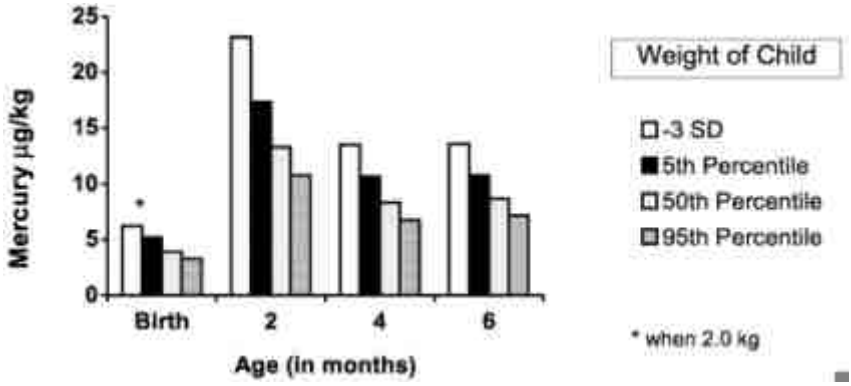


**FIGURE 2** Mercury (µg/kg) administered by age and weight if thimerosal-containing vaccines are given for Hepatitis B, Hib, and DTaP. *Amount of Hg received (in micrograms)=12.5 at birth, 62.5 at 2 and 6 months, 50 at 4 months.*

SOURCE: Halsey, 1999a. Reprinted with permission from the author.

In order to resolve the apparently arbitrary selection of an averaging duration, the committee compared the maximum blood mercury concentration associated with vaccine exposures to the blood mercury concentrations that would be associated with long-term exposures equal to EPA's RfD, the most stringent of the mercury intake standards reviewed. NRC (2000) estimated the cord blood concentration associated with its point of departure dose to be 58 µg/L. Based on that estimate, it follows that EPA's RfD corresponds to a blood mercury concentration of 5 µg/L.[5] This assumes that the blood mercury concentration is an appropriate indicator of the biologically relevant dose of mercury.[6]

To estimate blood mercury levels resulting from environmental exposures, the committee used data from the National Health and Nutrition Examination Survey (NHANES) (CDC, 2001d). The NHANES measurements in children one to five years old (N=248) show median blood mercury concentrations of 0.2 µg/L (95% CI 0.2–0.3 µg/L) and 90$^{th}$ percentile values of 1.4 µg/L (95% CI 0.7–4.8 µg/L).

Estimates of blood mercury levels resulting from children's vaccine exposures were taken from unpublished theoretical estimates and both published and unpublished observational data reported to the committee at its July 2001 meeting.

Brown (2001) presented unpublished results to the commmitte based on a biokinetic model for methylmercury exposures from fish (Ginsberg and Toal, 2000) to produce a range of estimates based on assumptions about body weight and patterns of mercury elimination. Assuming an average body weight during the first 18 months of life and adult patterns of mercury excretion, vaccine doses produced peak blood mercury levels of 14 µg/L; peak levels corresponded with recommended vaccine doses at ages two, four, and six months. With assumptions of low body weight and no elimination of mercury, blood mercury levels rose over time with each recommended vaccine dose and reached an outer bound estimate of 40 µg/L at age six months. This model is useful only as a starting point for estimating maximum possible blood mercury levels following vaccine exposures. Furthermore, the model is based on methylmercury and must

[5] NRC (2000, p. 287) estimated that the lower confidence limit on its benchmark dose corresponded to a cord blood mercury concentration of 58 µg/L and a hair mercury concentration of 12 ppm. The ratio of those two measures is approximately 5 µg/L per ppm hair. Because EPA's RfD corresponds to a hair mercury concentration of 1 ppm (i.e., a lower confidence limit benchmark dose of 11 ppm divided by 10 and rounded), the EPA RfD corresponds to a blood mercury concentration of 5µg/L.

[6] Several biomarkers (e.g., in hair or urine) may be used to estimate mercury exposure. Recent exposure to methylmercury is better indicated by the concentration of mercury in whole blood than urine. Blood and urine are less informative with respect to past exposures (Evans, 1998). Mercury in hair is approximately 90% methylmercury. Hair measurements provide a historical record of methylmercury exposure but do not accurately reflect exposure to inorganic mercury (NRC, 2000). Since ethylmercury accumulates in the kidneys and decomposes to inorganic mercury much more quickly than methylmercury, blood may or may not be the most appropriate biomarker for ethylmercury. A review of the various biomarkers is beyond the scope of this report. The interested reader is referred to a recent review in NRC, 2000.

be more fully developed to be useful in risk assessments of thimerosal-containing vaccines.

In a recent published observational study (Stajich et al., 2000), total blood mercury levels were measured before and after the administration of the birth dose of hepatitis B (containing 12.5 µg of ethylmercury) in a group of 15 preterm infants and a control group of 5 term infants. Measurements of mercury levels were taken within 48 to 72 hours after vaccination. Comparisons of pre-and post-vaccination mercury levels demonstrated elevated blood mercury levels after a single dose of hepatitis B vaccine in both preterm and term infants. Preterm infants (mean=.54 µg/L; +/–.79 SD) had a tenfold higher mean blood mercury level at baseline compared with term infants (mean=.04 µg/L; +/–.09 SD), although the difference was not significant. Post-vaccination mean blood mercury levels in preterm infants (mean=7.36 µg/L•;+/– 4.99 SD) were 3 times higher than those in term infants (mean=2.24 µg/L;+/–.58 SD), and differences were significant.

Unpublished observational data funded by NIAID (Pichichero et al., 2001; Sager, 2001) show lower blood mercury levels than Brown's model-based estimates or the observational study by Stajich et al. (2000). Among two-month-olds (N=16) receiving an average of 45.6 µg of mercury (range 37.5–62.5 µg), blood mercury concentrations at 3 to 20 days after vaccination (average 11.25 days) averaged 1.5 µg/L (range < 0.75–4.11 µg/L). Among six-month-olds (N= 20) receiving an average cumulative dose of 111.3 µg mercury (range 87.5–175 µg), blood mercury concentrations 4 to 27 days post vaccination (average 13.3 days) averaged 0.98 µg/L (range < 0.05–1.5µg/L).

Two differences among the three studies should be noted. The delay between vaccination and blood mercury sampling in the NIAID data means that these measurements are not directly equivalent to the peak levels estimated by Brown or the measures by Stajich et al. (2000) taken within 48 to 72 hours. The delay was not substantial, given mercury's relatively long half-life, but the half-life of ethylmercury is probably shorter than the half-life of methylmercury (Brown, 2001), implying that earlier observation would have shown higher blood mercury levels. The findings of the NIAID study are consistent with excretion of ethylmercury. The children in the NIAID study also received lower cumulative mercury doses from their vaccines than the theoretical maximums modeled by Brown. Once again, however, this difference in dose (roughly a factor of 2) does not explain the differences between the modeled and measured blood mercury levels reported by Brown and NIAID, respectively. However, Brown's model is preliminary and is based on assumptions about methylmercury, which may explain why the results differ substantially from the empirical findings by Stajich et al. (2000) and NIAID. Furthermore, given the small size of the study populations in the two observational studies, the significance of the findings cannot be assessed.

**Sources of Uncertainty.** As the previous discussion shows, comparing mercury exposures from vaccines with federal mercury-exposure guidelines does not provide proof of either excess risk or adequate safety. In addition to considerations like the choice of an appropriate averaging duration, there are several other key factors that make comparisons between vaccine doses of ethylmercury and federal exposure guidelines uncertain. Many of these points are also raised elsewhere in this report.

The EPA and ATSDR exposure guidelines were set based on adverse effects of prenatal exposures to methylmercury resulting from maternal consumption of contaminated food. This means that vaccine exposures differ in terms of the age of exposure, the route of exposure, and the type of mercury. The developing fetal brain is known to be highly susceptible to toxic exposures, but data on the effects of early postnatal exposures are limited, for both methylmercury and ethylmercury. There is also little basis for determining whether the effects of exposures through injection are comparable to those from ingestion.

Furthermore, because the pharmacokinetics of ethylmercury are not well documented, it is difficult to know whether the biomarkers used in establishing the methylmercury guidelines can be applied to ethylmercury exposures. Magos (2001b) points out that blood mercury levels following exposure to ethylmercury appear to correspond to lower concentrations of mercury in the brain, and therefore perhaps less risk of neurotoxicity, than are found with similar blood levels resulting from methylmercury exposure. A key uncertainty is the rate of excretion of ethylmercury in infants. Although data from animal tests and data on methylmercury excretion in infants suggest little excretion in infants, the preliminary data from the NIAID study suggest significant mercury elimination in children given thimerosal-containing vaccines.

However, abnormalities or genetic variations in mercury metabolism might lead to an underestimate of mercury levels from thimerosal-containing vaccines. The preliminary report that autistic children have a higher risk than non-autistic children for metallothionein metabolic disturbances (Walsh and Usman, 2001), together with case reports from some pediatric practices that some autistic children have high mercury and other heavy-metal profiles, might contribute to the concern of some that a subgroup of children with NDDs might be at risk for mercury toxicity at levels of exposure that are safe for other children. This does not, however, imply that mercury exposures have caused the NDDs.

Due to differences in drug distribution or clearance, concentrations of mercury reached in specific tissues may vary between individuals receiving the same amount of mercury (or whose intake of mercury is similar). Other individuals may have genetic differences that make them more susceptible to mercury-induced injury at a given concentration of mercury in a particular tissue. It might be prudent to reduce mercury exposure as much as possible in these children. The role of the mercury metabolism (or other metabolic defects) in the genesis of concomitant NDDs is unclear, however, and cause and effect should not be inferred.

## Biological Plausibility Argument

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.**

## Evidence Regarding Association: Case Reports, Case Series, and Uncontrolled and Controlled Epidemiological Studies

Considered in this section are the case reports and epidemiological studies related to thimerosal-containing vaccines and neurodevelopmental disorders.

### Case Reports and Case Series

**VAERS.** A search of the Vaccine Adverse Event Reporting System (VAERS), for the period from its inception in November 1990 through May 2001, identified 176 unique reports based on the following search strategy. During this 11-year period, about 120,000 reports were submitted to VAERS, including approximately 5,000 foreign reports (CDC, 2001b). Reports of interest were identified by searching all text fields using the terms "thimerosal," "thiomersal," "mercury," or "merthiolate," or a portion thereof (e.g., for "mercury," the text string "merc" was used).

The reports referred to the following thimerosal-containing vaccines: hepatitis B (79), influenza (48), diphtheria-tetanus (DT) (3), diphtheria-tetanus-pertussis (DTP) (4), *Haemophilus influenzae* type b (Hib) (1), tetanus-diphtheria (Td)(9), DTP-Hib (5), pneumococcal (3), tetanus (4), rabies (1) and concurrent but separate administration of influenza and pneumococcal (3), influenza and TD (1), DTwP and hepatitis B (1), DTP and Hib (5), and DTaP, Hib, and hepatitis B (1). Eight reports listed an adverse event in response to the cumulative childhood vaccine schedule. Reports involving *only* non-thimerosal-containing vaccines (e.g., MMR or OPV) were excluded from the reporting.

Thirty-three reports were for children ages 15 years and younger and were distributed as follows: 6 months and younger (6 reports), 7 months to 2 years (11 reports), 3 to 5 years (9 reports), and 6 to 15 years (7 reports).

The reported adverse reactions were categorized into three groups: the neurodevelopmental outcomes addressed in this report (autism, ADHD, speech or language problems); other neurological outcomes; and non-neurological outcomes. Table 4 details the type and number of outcomes reported in these three categories.

In the first category, there were nine reports of autism and nine reports of speech or language problems. There were no reports of ADHD, although there was one report of attention problems (not otherwise specified) for a child with autism.

In the second category, the types of neurological outcomes reported include: headache (15), paresthesia (11), dizziness (9), asthenia (6), non-febrile seizure (4), developmental delay (3), cognitive abnormality (2), and hypertonia (2). Five reports describe mercury poisoning in the patient, but not did not identify a specific outcome. See Table 4 for less frequently reported neurological outcomes.

TABLE 4 Summary of Outcomes Attributed on VAERS Reports to Thimerosal

| Outcome | Number of Cases Reported |
|---|---|
| Autism | 9 |
| Speech or Language Problems | 9 |
| ADHD | 0 |
| Other Neurological Outcome | |
| Headache | 15 |
| Paresthesia | 11 |
| Dizziness | 9 |
| Asthenia | 6 |
| Myasthenia | 4 |
| Seizure (not febrile) | 4 |
| Behavior changes | 3 |
| Developmental delay | 3 (1 of which with autism and mercury toxicity) |
| Hypokinesia | 3 |
| Loss of eye focus | 3 |
| Amnesia | 2 |
| Cognitive abnormality | 2 |
| Confusion | 2 |
| Guillain-Barré syndrome | 2 |
| Hypertonia | 2 |
| Neuropathy | 2 |
| Tremor | 2 |
| Twitch | 2 |
| Atrophy muscle | 1 |
| Auditory processing disorder | 1 |
| Buzzing in head | 1 |
| Catatonia | 1 |
| CSF abnormality | 1 |
| Coordination abnormality | 1 |
| Encephalopathy | 1 |
| Febrile seizure | 1 |
| Learning impairment | 1 (also reported autism) |
| Mitochondrial disorder | 1 |
| Neuralgia | 1 |
| Neuralgic amyotrophy | 1 |
| Sound and light sensitive | 1 |
| Strabismus | 1 |
| Unspecified neurological sequelae | 1 (also reported mercury toxicity) |
| Vertigo | 1 |
| Mercury poisoning (no specific outcome identified) | 5 |
| Non-Neurological Outcome | 155 |

In the third category, 155 people reported non-neurological outcomes. The most commonly reported event was delayed hypersensitivity reactions. Because the focus of this report is on neurodevelopmental outcomes, non-neurological outcomes are not reported in detail here.

There were 12 rechallenge cases identified involving 11 non-neurological outcomes, and one neurological outcome (headache). The one neurological-related rechallenge case reported a headache after receiving the first and second doses of the hepatitis B vaccine.

The committee concluded that these reports were uninformative with respect to causality. VAERS and other case reports submitted to the committee are useful for hypothesis generation, but they are generally inadequate to establish causality. The analytical value of data from passive surveillance systems is limited by such problems as underreporting, lack of detail, inconsistent diagnostic criteria, and inadequate denominator data (Ellenberg and Chen, 1997; Singleton et al., 1999).

## Epidemiological Studies

**Published Studies.** None.

**Unpublished Studies.** *Controlled Observational Studies.* One unpublished controlled epidemiological study, funded by CDC, has tested whether or not certain neurodevelopmental and renal 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 organizations (HMOs), was initiated in 1991 and covers approximately 2.5 percent of the U.S. population (Verstraeten, 2001).

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

In Phase I, the original study population included children born between 1992 and 1997 who were enrolled continuously during their first year of life in one of two large West Coast HMOs and who received at least two polio vaccinations by one year of age. Excluded from the study were infants with diagnoses of congenital or severe perinatal disorders or who were receiving hepatitis B immunoglobulins, and premature infants with gestational ages less than 38 completed weeks. Of the approximately 213,000 infants born into these HMOs between 1992 and 1997, approximately 110,000 met the eligibility criteria for inclusion in the analyses. (The eligible children from both HMOs were combined

into a single cohort in the original Phase I analysis.) Separate analyses were conducted for the premature infants (Stehr-Green, 2000).

For each child, cumulative vaccine-related mercury exposure was calculated at the end of the first, second, third, and sixth months of life from individual automated vaccination records. Each vaccine a child received was assumed to contain the mean amount of thimerosal reported by manufacturers to the FDA, meaning that the ethylmercury content per dose of each childhood vaccine was assumed to be as follows: diphtheria-tetanus-pertussis (whole-cell or acellular), 25.0 µg; hepatitis B, 12.5 µg; *Haemophilus influenzae* type b, 25.0 µg; measles-mumps-rubella, polio, pneumococcal, and varicella, 0.0 µg. The level of mercury exposure was categorized in increments of 12.5 µg. The outcomes studied included a range of plausible neurological and renal disorders identified in the mercury toxicity literature, and defined by specific ICD-9 diagnostic codes.

Cox proportional hazard models were used to compare the risk of adverse developmental outcomes. The endpoint of the observation period for each child was defined as the date of the first of the following events: first diagnosis, first disenrollment, or the close of the study period (December 31, 1998). The analysis was stratified by HMO, year, and month of birth; adjustments were made for sex. To obtain sufficient power to detect any association, the study examined only outcomes with more than 50 identified cases.

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 and the following neurodevelopmental diagnoses: unspecified developmental delays; tics; attention deficit disorder (ADD); language and speech delay; and general neurodevelopmental delays. No association was found for renal disorders or other neurological disorders with more than 50 cases, including autism (Stehr-Green, 2000, 2001). The researchers interpreted the analysis as showing a possible association between certain neurological developmental disorders and exposure to mercury from thimerosal-containing vaccines prior to six months of age (Stehr-Green, 2000).

An outside review panel (known as the Simpsonwood Panel), convened in June 2000, concluded that the Phase I VSD screening analyses did not provide adequate evidence to support or refute a causal relationship between exposure to thimerosal-containing vaccines and specific neurodevelopmental disorders, but recommended that these issues be vigorously investigated. The Simpsonwood panel also noted several concerns about factors that could affect the interpretability of the Phase I study results (Stehr-Green, 2000, 2001):

- An ascertainment or health-care-seeking bias could exist. Children whose parents make greater use of health care services may be more likely to have received all recommended vaccinations—and therefore the highest doses of thimerosal-containing vaccines—and to have had a greater opportunity to receive a diagnosis for a neurodevelopmental disorder.

- The inexactness in the diagnosis of neurodevelopmental disorders, especially for young children, and inconsistencies in diagnoses across clinicians, clinics, and HMOs could result in misclassifications or biases that affect the clinical significance of the findings.
- The lack of data on known familial and genetic predispositions to the neurobehavioral outcomes could mask factors that confound the relationship between thimerosal exposure and the outcomes being studied.
- The data and analyses are limited in their ability to distinguish any effects of thimerosal exposure from excess risks attributable to other vaccine components or other vaccine-related associations.

The Simpsonwood panel also expressed reservations about the applicability of findings from the studies of methylmercury exposures to possible effects of thimerosal exposures from vaccines (Stehr-Green, 2000, 2001).

Re-analyses of the Phase I data, reflecting modifications to address some of the concerns of the Simpsonwood panel and others, were reported at the IOM committee's scientific meeting in July 2001 (Verstraeten, 2001). Among the modifications made in the re-analysis were: conducting separate analyses for each HMO (referred to as HMO A and HMO B); adjusting for additional variables in the models; making additional controls and adjustments to avoid a health-care-utilization bias; and checking for outcome misclassification through chart review of select diagnoses.

Of the 22,647 children born from 1992 through 1997 into HMO A, 15,309 children were eligible and retained in the final cohort for analysis. Of the 184,723 children born from 1992 through 1998 into HMO B, 114,966 children were eligible and were retained in the final cohort. Table 5 shows the neurological and renal outcomes with more than 50 identified cases that were examined in the analysis. Two control diagnoses, flat feet/toe deformities and injury at unspecified site, were also included in the analysis to check for a potential health-care-seeking bias. These diagnoses were thought to be associated with the worry of parents and increased health-seeking behavior, but *a priori* were not expected to be associated with thimerosal exposure. Because the final cohort at HMO B is about eight times as large as the cohort at HMO A, there are relatively more children included in the outcome categories at HMO B. Not all of the outcomes that were examined at HMO B could be examined at HMO A due to insufficient numbers of cases in some outcome categories at HMO A.

As in the original Phase I analysis, the re-analysis identified positive but weak associations (relative risk ratios < 2.00) with several neurodevelopmental diagnoses (see Table 6). Results from unadjusted and adjusted models were presented to the committee. The adjusted models, which are used in epidemiology to control for potential confounders, included the following additional variables: birthweight, gestational age, mother's age at delivery, race and ethnicity, and

Apgar score at 5 minutes (the last at HMO A only). The adjusted models included only approximately 80 percent of the eligible children because variables were missing for some children. For HMO A, positive but weak associations were found between exposures to thimerosal and stammering, sleep disorders, and emotional disturbances. The association with sleep disorders did not persist in the adjusted models, and the association with emotional disturbances appeared only in the adjusted models. For HMO B, positive but weak associations were found for: any neurodevelopmental disorder, stammering, language delay, speech delay, attention deficit disorder, and tics. The association with attention deficit disorder and tics did not persist in the adjusted models. In both rounds of analysis of Phase I data, the results failed to show a consistent dose-response pattern.

TABLE 5 Neurodevelopmental, renal outcomes, and control diagnoses > 50 children

| Neurodevelopmental outcomes > 50 children | | | |
|---|---|---|---|
| ICD 9 | Disorders | HMO A | HMO B |
| | Any neurodevelopment disorder | 869 | 2989 |
| 299.0 | Autism | (19) | 150 |
| 299.8 | Childhood psychosis | (11) | 76 |
| 307.0 | Stammering | 54 | 75 |
| 307.2 | Tics | (32) | 121 |
| 307.4 | Sleep disorders | 56 | 123 |
| 307.5 | Eating disorders | (5) | 74 |
| 313 | Emotional disturbances | 79 | 203 |
| 314.0 | Attention deficit disorder | 69 | 517 |
| 315.31 | Language delay | (15) | 494 |
| 315.39 | Speech delay | 604 | 1448 |
| 315.4 | Coordination disorder | 76 | (31) |
| Renal outcomes and control diagnoses > 50 children | | | |
| ICD 9 | Disorders | HMO A | HMO B |
| | Any renal disorder | 24 | 197 |
| 5939 | Unspecified kidney or ureter disease | 14 | 80 |
| 734, 735 | Flat feet or toe deformities | 86 | 848 |
| 959.9 | Injury at unspecified site | 112 | 2428 |

Numbers in brackets indicate outcomes for which there were insufficient numbers of children at HMO A or B.
Provisional Results—may be subject to change. Verstraeten, 2001.

The inconsistent findings between HMO A and B in the re-analysis could be due to several factors. At HMO B, a positive association was found in both unadjusted and adjusted models between thimerosal exposure and the control diagnosis of flat feet/toe deformities, indicating a potential health-care-seeking bias at HMO B. In addition, the sample size was considerably larger at HMO B, providing more power to detect small differences in risk, if they exist. It should also be noted that the chances of finding an association between thimerosal exposure and these outcomes, if it exists, depends on the range of thimerosal exposures in the population; an HMO that is particularly successful in vaccinating its children would have less range of exposure and ability to detect positive findings.

The Phase II study was conducted in mid-2000 to examine more closely the significant associations identified in the original Phase I analysis by replicating the Phase I study design with data from an East Coast HMO. However, the study population had only approximately 17,500 eligible children, providing a sufficient number of cases for analysis of only two of the outcomes, ADD and speech delays. The Phase II analysis identified no significant differences in risk with the receipt of thimerosal-containing vaccines and these two outcomes;

TABLE 6 Relative risks by increase of 12.5 µg ethylmercury—Summary of positive associations *: $p < 0.05$ **: $p < 0.01$.

| | HMO A | | HMO B | |
|---|---|---|---|---|
| Outcome | Unadjusted | Adjusted† | Unadjusted | Adjusted† |
| Any neurodevelopmental disorder | | | ** | ** |
| Stammering | * | * | ** | ** |
| Tics | | | * | |
| Sleep disorders | * | | | |
| Emotional disturbances | | * | | |
| Attention deficit disorder | | | ** | |
| Language delay | | | ** | ** |
| Speech delay | | | ** | ** |
| Flat feet or toe deformities | | | * | * |

†Adjusted for birthweight, gestational age, mother's age at delivery, race and ethnicity, and Apgar score at 5 minutes [the last in HMO A only].

Notes: Final cohort size—HMO A: 15,309 and HMO B: 114,966.

The diagnosis of flat feet or toe deformities was included as control for health-care-seeking behavior. Because the analyses in this study are not yet complete and are as yet unpublished, the committee has chosen to show only summary information about the significant findings, not detailed quantitative results.

Provisional results—may be subject to change. Verstraeten, 2001.

however, the small sample size limited the power of the study to detect a small effect, if it exists (Verstraeten, 2001).

As a result of the inconsistent findings from the first two phases, a protocol for a Phase III follow-up study has been developed, although funding for the study is not confirmed. As described to the committee at its scientific meeting in July 2001 (Stehr-Green, 2001), the study will use a retrospective cohort design and will focus on primary diagnoses from the Phase I analysis, including ADD, language and speech deficits, and tics. Autism is not included because a substantially larger study population (and therefore a substantially more expensive study) would be needed to identify a sufficient number of cases for a retrospective cohort study. A separate case-control study of thimerosal exposure and autism has been proposed, but no study protocol has been developed. The Phase III protocol is discussed further in the research recommendations section of this report.

The committee notes several limitations of the Phases I and II of the VSD study. First, the consistency and accuracy of the diagnoses have not been established. Second, the variation between HMOs in the results of the updated Phase I analysis indicates an ascertainment or health-care-seeking bias could exist at HMO B among parents of study subjects who received the highest doses of thimerosal-containing vaccines. The exclusion of children who disenrolled from the HMOs is another potential source of bias. In addition, the effect sizes are small and thus difficult to interpret. Furthermore, with an observation period of only one year for some children, diagnoses usually made at older ages may be under-represented. With its restriction to diagnoses with at least 50 cases, the study is uninformative about other important but less common diagnoses. In addition, there is not a consistent dose-response relationship. Also, information on prenatal exposure to mercury is sparse. Finally, the findings from Phase I and Phase II of the study are inconsistent. Given these caveats, the committee believes that the Phase I and II VSD analyses are inconclusive with respect to causality.

*Uncontrolled Observational Studies.* An unpublished ecological analysis comparing aggregate trends in autism rates in California with the trends in mercury exposure from thimerosal-containing vaccines was presented to the committee (Blaxill, 2001). To estimate the average level of mercury exposure for children 19–35 months of age in a given year, the mercury content of all recommended vaccine doses (assumed to be 37.5 µg for 3 doses of hepatitis B, 75 µg for 3 doses of Hib, and 75–100 µg for 3 or 4 doses of DTP) was weighted by estimates from the National Health Interview Survey of coverage rates for the specific vaccines for the specified year. Estimates of the number of children with autism were obtained from annual caseload data from the California Department of Developmental Services database. These data were retabulated by year of birth, and birth-cohort prevalence rates were calculated using census data on births by year in California. The presenter concluded that the increasing trends seen in these data, in both the prevalence of autism and the levels of mercury exposure from thimerosal-containing vaccines, are consistent with the hy

pothesis that mercury exposure had a direct role in an increasing incidence of autism in the 1990s.

As noted in previous IOM reports (IOM, 1994 a,b, 2001), a positive ecological correlation constitutes only weak evidence of causality, and additional research would be needed to establish a causal association. In addition, the appropriateness of the transformation of the cross-sectional autism-caseload data into birth-cohort prevalence data, as was done in this analysis, is questionable. The data used in this analysis are cross-sectional and reflect the number of children with a diagnosis of autism who are registered in the California Developmental Services system. Transforming the cross-sectional data by dividing by birth cohort, creates the artificial impression of a cohort effect when the data are cross-sectional in nature (Fombonne, 2001a). Furthermore, the authors of a report on the California autism caseload data stress that their study was not designed to measure trends in autism and that the data should therefore be interpreted with caution (California Department of Developmental Services, 1999). The analytical value of the data is limited by the inability to account for any changes over time in diagnostic concepts, case definitions, or age of diagnosis (Fombonne, 2001a). As a result, the committee cannot assess trends in the prevalence of autism from these data. The committee concludes that this unpublished ecological analysis is uninformative with respect to causality.

## CAUSALITY ARGUMENT

A number of case reports have been submitted through VAERS and directly to the committee asserting an association between exposure to thimerosal-containing vaccines and neurological outcomes, autism in particular. Case reports are very useful in hypothesis generation and identifying areas for investigation, but are rarely useful in establishing causality. The case reports reviewed by the committee are uninformative with respect to causality.

There are no published epidemiological studies that examine the potential association between exposure to thimerosal-containing vaccines and neurodevelopmental disorders. Unpublished studies reviewed by the committee provide inconclusive evidence of a potential association between exposure to thimerosal-containing vaccines and certain neurological developmental disorders. Among the unpublished reports, only one—an examination of the hypothesis using data from the VSD (Verstraeten, 2001)—is from a controlled epidemiological study. The committee, like other experts convened by the CDC, has several concerns about this study. These include: the inexactness of the diagnoses and inconsistencies across clinicians, clinics, and study sites; variation in results between study sites, indicative of potential ascertainment or health-care-seeking bias; potential bias due to disenrollment; the small effect sizes; the inconsistent duration of observation; insufficient power to detect less common diagnoses; lack of information on prenatal exposures to mercury; and lack of a consistent dose-

response relationship. Furthermore, the findings between the two phases of this study are inconsistent.

The committee therefore believes that the VSD study is inconclusive with respect to causality. The committee also found that an unpublished ecological analysis of trends in the prevalence of autism and in exposure to mercury from vaccines is uninformative with respect to causality. See Table 7 for a summary of the evidence reviewed by the committee.

As stated above, the committee concludes that the hypothesized relationship is biologically plausible. **However, the committee concludes that the evidence is inadequate to accept or reject a causal relationship between exposure to thimerosal from childhood vaccines and the NDDs of autism, ADHD, and speech or language delay.** The committee's conclusion on causality 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 weak and inconclusive evidence regarding the hypothesis that exposure to thimerosal-containing vaccines may lead to certain neurodevelopmental disorders.

## SIGNIFICANCE ASSESSMENT

In contrast to the majority of previous IOM vaccine safety studies, which limited conclusions to causality assessments and recommendations for future research, the Immunization Safety Review Committee has been asked to recommend a public health response to immunization safety concerns. Such a response potentially encompasses a broad range of activities, including policy reviews, new research directions, and changes in communication to the public and to health care providers about issues of vaccine safety. In formulating the breadth and direction of the recommended public health response, the committee considers not only its conclusions regarding causality, but also the significance of the vaccine safety issues in a broader social context—the context in which policy decisions must be made. These considerations can include, but are not limited to, the burden (the seriousness, risk, and treatability) of the adverse health events in question and of the diseases that the vaccines are intended to prevent, as well as the potential consequences of public concerns about the safety of vaccine use.

**TABLE 7** Summary of Evidence for Assessments of Causality and of Biological Plausibility

| Evidence | Type of Study | Direct/ Indirect | Published/ Unpublished | Potential Role in Causality Assessment | Potential Role in Biological Plausibility Assessment |
|---|---|---|---|---|---|
| **VSD Phase I, II**[1] | Controlled observational study | Direct | Unpublished | Evidence of this type could be used to determine nature of causal relationship | N/A |
| **Ecological Analyses of ASD rates**[2] | Uncontrolled observational analysis | Indirect | Unpublished | Evidence of this type could support causality | N/A |
| **Thimerosal and ethylmercury poisonings**[3] | Case reports, case series | Indirect | Published | Evidence of this type could support causality | Supports |
| **Hg levels after vaccination**[4] | Clinical studies; theoretical modeling | Indirect | Published; unpublished | Evidence of this type could inform causality assessments | Supports |
| **Hg exposure guidelines**[5] | Modeling, theoretical calculations | Indirect | Published | Evidence of this type could inform causality assessments | Supports |
| **Methylmercury poisonings**[6] | Epidemiological, clinical studies | Indirect | Published | Hypothesis generation only | Supports |
| **"Island Studies"**[7] | Epidemiological studies | Indirect | Published | Hypothesis generation only | Supports |
| **Clinical studies of children with ASD**[8] | Case reports, clinical studies | Indirect | Published; unpublished | Hypothesis generation only | Supports |
| **TMS, EtHg, MeHg toxicology and kinetics**[9] | *In vitro,* laboratory animal | Indirect | Published; unpublished | None | Supports |

**Direct evidence** refers to evidence that specifically addresses a relationship between thimerosal in vaccines and neurodevelopmental disorders. All other evidence is therefore **indirect.**

References are representative and are not a complete guide to the literature.

1. Verstraeten, 2001
2. Blaxill, 2001
3. Axton, 1972; Cinca et al., 1980; Fagan et al., 1977; Hay, 1963; Jalili and Abbasi, 1961; Lowell et al., 1996; Pfab et al., 1996; Royhans et al., 1984; Zhang, 1984.
4. Brown, 2001; Pichichiero et al, 2001; Sager, 2001; Stajich et al., 2000
5. Ball et al., 2001; Halsey, 1999; Halsey and Goldman, 2001; NRC, 2000
6. Bakir et al., 1973; Harada, 1995; Mahaffey, 1999; NRC, 2000; Tsubaki, 1977
7. Davidson et al., 2000; Grandjean et al., 1997; Grandjean, 2001; Myers, 2001; NRC, 2000
8. Bradstreet, 2001; Cave, 2000; Sykes, 2001; Walsh and Usman, 2001
9. Ball et al., 2001; Jamieson and Powell, 1931; Magos, 2001b; Suzuki et al., 1963

Public concerns about immunization safety are particularly important to understand and to weigh, because most vaccines are given to healthy children not only for their direct protection but also to help protect others in the population. In fact, to achieve this broader level of protection, vaccinations are mandatory in all 50 states for school and daycare entry. Exemptions on medical grounds (contraindications) are allowed, although they are considered too limited by some (Fisher, 2001). Exemptions are also allowed on religious grounds in 48 states and on philosophical grounds in 15 states (Evans, 1999). However, such exemptions are rare, and it is argued that these public health mandates, particularly because they are imposed on healthy children, place a particular responsibility on the government for rigorous attention to safety issues, even for rare adverse outcomes.

In the present case, the hypothesis that exposure to thimerosal-containing vaccines may be associated with neurodevelopmental disorders remains of public health significance, even though thimerosal has been removed from all vaccines on the recommended childhood immunization schedule that are given to children six years of age or younger. First, neurodevelopmental disorders impose substantial burdens on the affected individuals, their families, and society, and because it is important to understand whether or not past vaccine use has increased the risks of such disorders. In addition, thimerosal continues to be used in other biological and pharmaceutical products. A better understanding of the potential risks may be useful to those countries that still use thimerosal-containing vaccines because they cannot easily or immediately switch to alternatives. Furthermore, examination of the 1999 series of rapid changes in hepatitis B immunization policy in response to concerns about thimerosal may provide lessons for improving future vaccine safety policymaking. Finally, the use of thimerosal in vaccines may have eroded trust in the safety of vaccines.

## Concern Regarding Neurodevelopmental Disorders

The neurodevelopmental disorders that are addressed in this report—autism, ADHD, and speech or language delay—are of considerable concern. In the aggregate, these conditions affect a large number of children.

Autism is a serious developmental disorder characterized by deficits in communication and behavioral, emotional, and social functioning. There are no agreed upon estimates of the prevalence or incidence of autism in the United States. Autism cannot be cured, but behavioral therapies are used to manage symptoms (Wing, 1997) and medication may help alleviate symptoms such as hyperactivity, anxiety, and repetitive behavior (Lainhart and Piven, 1995). Furthermore, early educational and social interventions may improve functioning and integration into society for some autistic children (Harris and Handelman, 1997; Howlin and Goode, 1998).

Autism leads to substantial challenges for the families of affected individuals, many of whom remain dependent throughout their lives. In addition to the substantial financial strains, families of children with autism must meet other demands, such as arranging for around-the-clock efforts to care for their child. They face the difficult tasks of finding knowledgeable and sympathetic health-care providers and of finding high-quality information, and they must endure the frustrations of seeing their children develop abnormally or regress from being active and engaged to being aloof and nonresponsive.

ADHD, one of the most common of the psychiatric disorders that appears in childhood, usually becomes evident in preschool or early elementary years (NIH, 2001). Children may have problems functioning in school and other social settings. There are often impairments in memory, cognitive processing, motor skills, social skills, and response to discipline (NIH, 2001). People with ADHD often have other disorders as well, such as learning disabilities, language disorders, conduct disorder, oppositional-defiant disorder, and mood and anxiety disorders (NIH, 2001). ADHD is incurable, but medications and behavioral interventions may improve functioning for 80% of the people with the disorder (CDC, 1999b). Treatment for ADHD may not be covered by health insurance, however, and two recent studies found that the cost and use of medical care for children with ADHD is significantly higher than for other children (Guevara et al., 2001; Leibson et al., 2001). Special educational services are often needed. The national public school system's additional costs for students with ADHD was more than $3 billion in 1995 (NIH, 1998).

The prevalence of speech or language delay is difficult to estimate. Speech and language delay refers to a group of symptoms resulting from many different causes. Some causes are known, such as mental retardation, genetic deformities, deafness, and structural abnormalities like cleft palate (Shriberg et al., 1999). In other cases, no specific cause can be identified. Children with speech and language delay often experience additional problems, including poor school performance, psychological and behavioral disturbances, and, later, speech and language problems (Whitehurst and Fischel, 1994).

## Continued Exposure to Thimerosal

In the United States, currently manufactured or marketed vaccines on the recommended childhood immunization schedule and given to children six years of age or younger contain no thimerosal, or only trace amounts (<0.5 µg Hg per dose) of thimerosal left over from the manufacturing process (CDC, 2000c). However, given the public health goal of reducing children's exposure to mercury as much as possible, concerns have been raised about the continued presence of thimerosal in other vaccines and biological and pharmaceutical products.

Some vaccines that are not part of the recommended childhood immunization schedule still contain thimerosal as a preservative and may be given to some

children. These include diphtheria-tetanus toxoid (DT), tetanus toxoid (TT), influenza, and Pnu-Immune 23 pneumococcal (recommended only for children 2 years or older) vaccines. Other thimerosal-containing vaccines, given only to older children and adults, are tetanus-diphtheria (Td), meningococcal vaccine, and the adult formulation for one hepatitis B vaccine (Recombivax-B).

There is also a lingering concern that there remains "on the shelf" an unknown quantity of thimerosal-containing Hib, hepatitis B, and DTaP vaccines. However, because of turnover and of the expiration date of current vaccines, it is estimated by CDC that few, if any, of those containing thimerosal as a preservative are still being administered (CDC, 2001f).

Other biological products that have traditionally contained thimerosal may be used in infants, children, and pregnant women. (A list of all drug and food products containing mercury identified during the 1997 FDAMA review can be accessed at the following website: http://www.fda.gov/cber/genadmin/merclst.htm. An updated list is not available, but some of the products on this list may no longer contain thimerosal.) For example, some preparations of Rho (D) Immune Globulin, which are given to Rh-negative mothers during pregnancy, contain thimerosal. Approximately 15% of the population is Rh-negative, and use of these thimerosal-containing products exposes the fetus to ethylmercury. The amount of thimerosal in these products ranged from 0.003 to 0.01% thimerosal (PDR, 2001; Physicians' GenRx, 1993). Rho(D) Immune Globulin is currently being manufactured without thimerosal in the United States. Other such products that contain thimerosal and are available over-the-counter include some nasal sprays, contact lens solutions, and antibacterial/anti-itch creams (FDA, 1999). The committee is not aware, however, of any risk assessments of the use of these products in infants, children, and pregnant women. Nevertheless, the NHANES survey indicates that 10% of women have mercury levels within one-tenth of the potentially hazardous levels estimated in the NRC toxicological review of methylmercury, indicating a potential benefit for some women from efforts to reduce mercury exposure (CDC, 2001d; NRC, 2000).

### Use of Thimerosal-Containing Vaccines in Other Countries

In contrast to the rapid removal of thimerosal from vaccines in the United States, many other countries have taken a less urgent approach to removing thimerosal from vaccines. In a July 1999 statement, the European Agency for the Evaluation of Medicinal Products (EMEA) recommended as a precautionary measure, that the use of thimerosal-free products should be promoted and efforts should be made to eliminate mercury preservative in vaccines in the shortest possible time frame (EMEA, 1999). However, the EMEA recommended that vaccination proceed in accordance with normal schedules while vaccine

reformulation proceeded. Overall, reducing or eliminating thimerosal in Europe was considered to be a "middle and long term effort" (EMEA, 2001).

Several factors may have contributed to the difference in the risk assessments conducted by the United States and European countries. First, the potential exposure to thimerosal through vaccines was less in European countries than in the United States, given the differences in recommended childhood immunization schedules. Second, the EMEA compared cumulative ethylmercury exposures from vaccines to the WHO's recommended level of intake for methylmercury (3.3 µg/kg/week or 0.47 µg/kg/day), which is less stringent than the U.S. federal standards for methylmercury intake (e.g., EPA's is 0.1 µg/kg/day). Third, other vaccine safety concerns (e.g., the hypothesized link between measles-mumps-rubella vaccine and autism) may have figured more prominently in these countries (Freed and Andreae, 2001).

Many other nations, particularly developing countries, continue to rely on multi-dose vaccine vials which contain thimerosal as a preservative. Although the World Health Organization (WHO) supports the July 1999 statement by the AAP and U.S. PHS to phase out use of thimerosal in vaccines, the WHO recommends the continued use of thimerosal-containing vaccines because of the benefits of thimerosal as a preservative and the benefits of continued immunization (WHO, 2000). The WHO notes that removing thimerosal from vaccines worldwide is a complex process. Removing thimerosal from multidose vials is not a viable option given the lack of alternative preservatives; thus, removal of thimerosal could increase the risk of bacterial contamination which could lead to toxic shock syndrome or other illnesses. In addition, switching from multi-dose to single-dose vials imposes practical constraints. Most notably, switching to single-dose vials could impose a significant burden on the cold chain making this strategy prohibitive for developing countries. Furthermore, even if a mercury-free preservative were developed in the future, many local vaccine producers may not have easy access to it. This is important since, for example, 60% of the whole-cell DTP vaccine used in developing countries is produced locally (WHO, 2000). In the interim, the WHO believes that the known risks of morbidity and mortality from vaccine-preventable diseases and contaminated multi-dose vaccine vials outweigh the potential risk of thimerosal (Clements et al., 2000).

The committee concluded that it was important to more fully research the possible effects of thimerosal in vaccines in order to provide evidence that could be useful to countries facing a decision of 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. Analyses of the costs associated with reducing the potential risk from thimerosal, and comparisons of

the risks and benefits of current vaccines with more expensive thimerosal-free alternatives, could help inform decisions in other countries.

### Confusion from Changes in Hepatitis B Immunization Policy

Public health agencies, the medical community, and vaccine manufacturers acted swiftly to reduce the potential risk from thimerosal exposure when the FDA risk assessment revealed that vaccines could expose some children to cumulative levels of ethylmercury that exceeded one of the three federal guidelines on methylmercury exposure. Although no evidence showed that thimerosal in vaccines had caused harm, AAP and PHS in July 1999 recommended as a precautionary step the removal of thimerosal from vaccines as soon as possible (CDC, 1999a).

To reduce exposure to thimerosal in the smallest infants, the joint statement also recommended postponing the first dose of hepatitis B vaccine from birth until two to six months of age for infants born to low-risk mothers who were hepatitis B-surface antigen negative. (The birth dose of hepatitis B was still recommended for infants whose mothers had a positive or unknown hepatitis B surface antigen status, thereby continuing to reduce the risk of vertical transmission of hepatitis B [CDC, 1999a].). Within two months, however, the CDC announced the availability of a new thimerosal-free hepatitis B vaccine and also recommended resumption of routine hepatitis B vaccination of all newborns, reversing the initial recommendation (CDC, 1999c).

Concerns have been raised by some about the sudden shifts in hepatitis B vaccination policy and the general decision-making process that led to the change (Freed and Andreae, 2001; Offit, 2000; Plotkin, 2000; Seal and Daum, 2001). One criticism centered on the rapidity of the process, which caught some members of the medical and scientific community by surprise and led to a perception that decisions to issue policy guidelines were made in haste (Freed and Andreae, 2001; Plotkin, 2000; Seal and Daum, 2001). Another controversial aspect of the process was the lack of agreement among members of the key organizations issuing the policy statement (AAP, AAFP, PHS) regarding the nature and level of the risk from thimerosal. Some believed it posed only a theoretical risk, while others perceived it to be an actual risk (Freed and Andreae, 2001; Halsey, 1999b; Offit, 2000; Seal and Daum, 2001). In addition, the existence of three different federal standards on methylmercury exposure (EPA, FDA, ATSDR) resulted in confusion about the potential risks of thimerosal and questions about the relevance of the guidelines in assessing the risk from thimerosal in vaccines (Freed and Andreae, 2001).

There are debates on whether or not policymakers adequately gauged the potentially negative effects on the hepatitis B newborn-immunization program when implementing the policy changes (Halsey and Goldman, 2001; Seal and

Daum, 2001). Recent surveys indicate that as a result of the initial recommendation, some hospitals did not have appropriate policies in place for vaccinating infants whose mothers' hepatitis B surface antigen status was positive or unknown (Hurie et al., 2001); and that many hospitals had failed to resume hepatitis B vaccination after the CDC recommendation to do so (CDC, 2001c; Hurie et al., 2001; Oram et al., 2001).

The committee believes that the AAP, AAFP and PHS had clearly acted with the best interest of children in mind—both in issuing the guidelines to suspend the hepatitis B birth dose, and reversing them shortly thereafter once a thimerosal-free alternative was approved. The experience may offer lessons for improving future vaccine safety policymaking, however.

## Trust in the Safety of Vaccines

Concerns related to the potential adverse effects of thimerosal-containing vaccines and continued use of thimerosal in some vaccines have the potential to erode public trust. The presence of thimerosal in some vaccines can raise doubts about the entire system for ensuring vaccine safety. Although vaccine packaging included information about thimerosal content, the amount of mercury in individual vaccine doses and the cumulative exposure were not calculated until the FDAMA-required risk assessment. This late recognition of the amount of mercury in vaccines may contribute to a perception among some that careful attention to vaccine components has been lacking.

The issue of thimerosal in vaccines has been the focus of media stories (Atkins, 2001; Manning, 2000), Congressional hearings (U.S. House of Representatives, Committee on Government Reform, 2000, 2001), lawsuits (*Joseph Counter, et al.* v. *Abbott Laboratories, Inc., et al.* Cause No. GN100866), and Internet sites, all which indicate some level of public concern and distrust about vaccine safety. However, with few exceptions (Gellin et al., 2000), there is a paucity of studies that have objectively and routinely assessed public and physician opinions about vaccine safety. Unpublished findings from one recent CDC-sponsored survey of pediatricians and family physicians suggest that thimerosal in vaccines is a concern for physicians and parents (Freed and Andreae, 2001). This cross-sectional survey administered by mail during spring 2000 to a national random sample of 750 pediatricians and 750 family physicians (response rate of 70%), asked physicians about their perceptions of parents' views and their self-perceptions regarding vaccine safety. The findings show that 27% of pediatricians and 18% of family physicians surveyed perceived that parents were more concerned about vaccine safety as a result of the thimerosal issue. In addition, the practitioners themselves had some doubts—13% of pediatricians and 24% of family physicians—and reported that they were more concerned about vaccine safety as a result of thimerosal issues.

The committee emphasizes that confidence in the safety of vaccines is essential to an effective immunization program—one that provides maximum protection against vaccine-preventable diseases with the safest vaccines possible. Questions about vaccine safety must be addressed responsibly by public health officials, health professionals, and vaccine manufacturers.

## Conclusion

The committee sees significant reasons for continued public health attention to concerns about thimerosal exposure and neurodevelopmental disorders. The committee considered the burden of the potential adverse neurodevelopmental outcomes and of vaccine-preventable disorders, and it considered the extent of continued use of thimerosal-containing products. Diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b, 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. Historically, several concerns about the safety of vaccines have led to declines in immunization coverage rates and outbreaks of disease, as observed during the pertussis outbreaks in the United Kingdom during the 1970s. Similar disease outbreaks could easily occur, with devastating effects, were immunization rates to decline as a result of fears that our childhood vaccines are not as safe as absolutely possible.

Neurodevelopmental disorders are pervasive and impose a significant burden on affected children, their families, and society. Mercury is a well-known neurotoxicant and efforts are being made to reduce the exposure of vulnerable populations to this environmental contaminant.

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 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 multidose 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.

Therefore, the committee considers the presence of thimerosal in pediatric vaccines to be a significant issue, and it supports precautionary public health efforts to reduce mercury exposure. 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.

## RECOMMENDATIONS REGARDING THE PUBLIC HEALTH RESPONSE

Prompt action by federal agencies, medical professionals, and vaccine manufacturers to remove thimerosal from vaccines has ensured that any risk thimerosal exposure may pose has been substantially reduced for the future. However, 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 vaccine 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 ACIP, AAP, and AAFP to call for the removal of thimerosal from vaccines as a precautionary step in the effort to minimize children's exposure to mercury. Fortunately, technology was available to 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 demonstrates 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.

However, 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.** Remaining thimerosal-containing vaccines should be reserved for use *only* in response to serious shortages or emergencies, when failure to vaccinate would increase the risk of vaccine-preventable disease. The committee understands that this could result in a financial loss. However, it is confusing to the public to continue to use thimerosal-containing vaccines when alternatives are available. The committee did not explore the mechanisms by which this could be accomplished. But, 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 or the ACIP—might delay action. 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 influ

enza 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, 2001e).

Thimerosal is also present in some pharmaceuticals, such as nasal sprays, used by infants, children, and pregnant women. The committee is unaware of risk-benefit analyses or risk assessments of thimerosal in pharmaceutical products, nor is it aware of the status of research into alternative preservatives. It seems prudent, however, 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 et al., 2001).

The confusion that resulted among some providers following the rapid changes in recommendations regarding the birth dose of hepatitis B vaccine suggests not that the policy decision was fundamentally flawed, but that improvements could be made in the formulation, communication, and implementation of vaccine policies. 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, for example, how costs should be weighed against uncertain risks, who should bear the cost 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

Although the risk of exposure to thimerosal through recommended childhood vaccinations has been mostly eliminated, questions remain as to whether or not thimerosal-containing vaccines may have previously contributed to neurodevelopmental disorders in some children. **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 the vaccine manufacturers, could support evidence-based decisions in other countries regarding whether or not to continue using thimerosal-containing 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 Studies

- **The committee recommends case-control studies examining the potential link between neurodevelopmental disorders and thimerosal-containing vaccines.** The studies should use clearly defined outcomes, specifically diagnoses (e.g., identified in terms of ICD-9 coding) that correspond to current practice. Gradients of performance on neurodevelopmental tests should be used as outcome measures only if they can be linked to specific diagnoses. Furthermore, the committee recommends examining 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 outside the United States who did not receive thimerosal-containing doses as part of a clinical trial of DTaP vaccine. **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 thimerosal-free or thimerosal-containing vaccines. Studies using these already-defined cohorts could probably be completed more quickly than a study that

would have to define and recruit some other population in the United States or elsewhere.

- 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 the 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.** These studies should focus on multiple renal and cognitive outcomes, including autism. Collaborations with existing research studies, such as NIMH's Epidemiological Catchment Area studies or the Collaborating Program of Excellence in Autism, might be efficient and should be explored. Ecological studies are not well-suited to making individual-level causal inferences and comparisons before and after the removal of the thimerosal are problematic when the criteria for diagnosis, or the manner in which the criteria are applied, change over time, as they have with autism. However, the committee believes that well-designed ecological studies can provide support to other epidemiological studies.
- **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.** Data on background exposures to mercury are sparse; additional studies may identify populations or quantify the number of children at higher risk for mercury toxicity. A feasibility assessment should be done to see if a meaningful study could be conducted regarding the risk of neurodevelopmental disorders due to thimerosal exposures through Rh immunoglobulin during pregnancy.

Where possible, studies of the rates of specific neurodevelopmental diagnoses in cohorts of children exposed to varying levels of thimerosal would be of interest. Such studies have to be large enough to have sufficient variation in exposure and in incidence rates of the diagnoses of interest to detect an association. They also should include uniform data on thimerosal exposure, clear definitions of neurodevelopmental disorders using current diagnostic rubrics, the use of standard clinical protocols for diagnosing neurodevelopmental disorders, and assessment of neurodevelopmental diagnoses by professionals who do not know the patients' exposure status.

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. The plans for Phase III have been presented to several groups, including the committee at its July 2001 meeting (Stehr-Green, 2001). The Phase III study is conceived as a two-part retrospective cohort study in which participants, seven- to nine-year-old children, would be enrolled into one of three groups, based on exposure to thimerosal-containing vaccines at specified points in the past. The

three groups would be defined according to two exposure factors: level of mercury exposure at birth, based on whether the birth dose of hepatitis B vaccine was received; and cumulative level of exposure to all thimerosal-containing vaccines during the first three months of life. The decision to group participants on the basis of levels of exposure during the earliest ages of life reflects the advice of expert consultants and a review of the methylmercury literature. The study will collect data on all vaccine exposures so as to permit analyses based on cumulative exposure at any age.

The study would focus on specific primary diagnostic outcomes identified from the Phase I screening analysis, including ADD, language and speech deficits, and tics. Autism is not included as an outcome in this study because of the high cost of the large sample size that would be needed to identify a sufficient number of cases of autism for a retrospective cohort design. A separate case-control study of autism has been proposed, although no study protocol has been developed.

The proposed follow-up study uses a two-part approach to assessing outcomes. In the first stage, a standardized set of neuropsychological tests would be administered to all study participants to identify children whose performance suggests the presence of selected neurodevelopmental disorders (NDD). In the second stage, confirmatory neuropsychological tests would be administered for ADD and speech or language delay specifically. The study would also develop measures of potential confounders (e.g., exposures to mercury, lead, PCBs, alcohol and other drugs, genetic predisposition, family medical history) and would attempt to evaluate the independent contribution of other vaccine antigens and components.

The committee recognizes that this study is still in the planning phase. Three issues loom large regarding the proposed Phase III study: feasibility, resources, and several technical 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 thus be contributory, but would best be undertaken as part of an overall package of research and only if it accurately identifies neurodevelopmental conditions of concern.

### Clinical Studies

- Very little is known about the pharmacokinetics of ethylmercury exposure in humans. Better understanding of these mechanisms 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. Some of this re

search could be done expeditiously through autism research centers, which have great expertise in identifying and working with autistic children.

- **The committee recommends continued research on theoretical modeling of ethylmercury exposures, including the incremental burden of thimerosal with background mercury exposure from other sources.** It would be particularly helpful to have such theoretical modeling done in conjunction with empiricists, so that the models could be better constructed.
- The committee is aware of several specialized pediatric practices that use chelation therapy to treat autistic children. These practitioners report unusual metal profiles in their patients as well as clinical improvement following chelation. However, chelation therapy is currently indicated only for acute, high-dose mercury poisonings. 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 Studies

- 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, though the teratological effects of methylmercury in rodents and primates is well established. Several important questions regarding the potential risk of thimerosal exposure could have been informed by a wider and deeper literature from studies in laboratory animals. **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. The first is the challenge of communicating policy changes given

the differing guidelines for mercury exposure. The differences in the exposure levels calculated by EPA, FDA, and ATSDR arise from use of different key studies and different uncertainty factors. In addition, concerns about risks related to thimerosal are difficult to convey, given the lack of direct evidence on the toxic effects of low-level exposure to ethylmercury. Partly because of the different exposure levels in the federal guidelines and the lack of evidence on ethylmercury, the messages about the risks of using thimerosal-containing vaccines have been complicated and not well understood by some professionals (Halsey and Goldman, 2001).

Second, finding information about thimerosal-containing vaccines on the websites of federal agencies is difficult. Federal agencies with responsibilities related to vaccines do not necessarily have pages on their websites devoted to concerns about thimerosal-containing vaccines. In order to design websites that respond more effectively to vaccine safety concerns, additional information is needed about how parents access such information. Similarly, additional information is needed about how clinicians (physicians, nurses, and others) access vaccine safety information and the most successful communication strategies for reaching them.

Third, information about vaccine risks on government websites contains words that may be perceived as judgmental, such as "should." Using words that are less directive and prescriptive is important in effectively communicating vaccine risks (NRC, 1989). For example, the message may be more effective if it is stated as "CDC is confident that…." rather than, "parents should feel confident that…." Establishing trust is an important factor in communicating risk effectively, but the message loses its effectiveness when the source of the information is not considered credible and when the language is not understandable (Carpenter, 1995; NRC, 1989). Communication strategies need to be specific to the intended audience and should ensure that language levels are appropriate for that audience.

As the committee noted in its previous report (IOM, 2001), there are numerous 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 ex

posed. **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 imperative 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 5 summarizes the committee's conclusions and recommendations.

**BOX 5 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, and 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.

*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.

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# Appendix A

# Immunization Safety Review: Measles-Mumps-Rubella Vaccine and Autism Executive Summary

Immunization is widely regarded as one of the most effective and beneficial tools for protecting the public's health. In the United States, immunization programs have resulted in the eradication of smallpox, the elimination of polio, and the control and near elimination of once-common, often debilitating and potentially life-threatening diseases, including measles, mumps, rubella, diphtheria, pertussis, tetanus, and *Haemophilus influenzae* type b.

Along with the benefits of widespread immunization, however, have come concerns about the safety of vaccines. No vaccine is perfectly safe or effective, and vaccines may lead to serious adverse effects in some instances. Furthermore, if a serious illness is observed after vaccination, it is often unclear whether that sequence is coincidental or causal, and it can be difficult to determine the true nature of the relationship, if any, between the vaccination and the illness.

Ironically, the successes of vaccine coverage in the United States have made it more difficult for the public to weigh the benefits and complications of vaccines because the now-controlled diseases and their often-serious risks are no longer familiar. However, because vaccines are so widely used—and because state laws require that children be vaccinated before entering daycare and school, in part to protect others—it is essential that safety concerns be fully and carefully studied.

This report, the first of a series from the Institute of Medicine (IOM) Immunization Safety Review Committee, presents an assessment of the evidence regarding a hypothesized causal association between the measles-mumps-rubella (MMR) vaccine and autism, an assessment of the broader significance for soci

ety of the issues surrounding the MMR-autism hypothesis, and the committee's conclusions and recommendations based on those assessments.

## OVERVIEW OF THE IMMUNIZATION SAFETY REVIEW PROJECT

Since the mid-1990s, an increasing number of challenges to the safety of vaccinations have gained attention in various settings. The Committee on Government Reform of the U.S. House of Representatives held seven hearings on vaccine-safety issues during 1999–2000, and the media—including news programs such as *60 Minutes, 20/20,* and *Nightline*—have covered these issues as well. Also, many consumer and professional organizations have sponsored related conferences and scientific symposia, and the Internet is playing an increasingly important communications role.

With these growing concerns about vaccine safety, the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) recognized the need for an independent group to address safety concerns in a timely and objective manner. In 1999, as a result of previous IOM work on vaccine safety and the Institute's access to independent scientific experts, CDC and NIH began a year of discussions with IOM to develop the Immunization Safety Review project to address existing and emerging vaccine-safety concerns.

The Immunization Safety Review Committee, convened in the fall of 2000, comprises 15 members with expertise in pediatrics, neurology, immunology, internal medicine, infectious diseases, genetics, epidemiology, biostatistics, risk perception and communication, decision analysis, public health, nursing, and ethics. To preclude any real or perceived conflicts of interest, committee members were subject to strict selection criteria that excluded anyone who had financial ties to vaccine manufacturers or their parent companies, previous service on vaccine advisory committees, or prior expert testimony or publications on issues of vaccine safety.

The committee is charged with examining three vaccine-safety hypotheses each year during the 3-year study period (2001–2003). The Interagency Vaccine Group (IAG) comprising officials from the National Vaccine Program Office at the U.S. Department of Health and Human Services (DHHS), the National Immunization Program and the National Center for Infectious Diseases at the CDC, the National Institute for Allergy and Infectious Diseases at the NIH, the Department of Defense, the Food and Drug Administration, the National Vaccine Injury Compensation Program at the Health Resources and Services Administration, the Health Care Financing Administration, and the Agency for International Development, will select the hypotheses to be examined by the committee. The committee's findings will be released to the public in a series of brief consensus reports.

In contrast to previous IOM vaccine-safety studies (e.g. IOM, 1991, 1994a,b), which limited their conclusions to causality assessments and recommendations on future research directions, the Immunization Safety Review Committee has been asked to assess not only the scientific plausibility of the hypothesized association but also the significance of the issue in a broader societal context. The plausibility assessment has two components: (1) an examination of the causal relationship between the vaccine and the adverse event, and (2) an examination of any pathogenic mechanisms that support the hypothesis. The significance assessment addresses such considerations as the burden of the adverse health event in question, the burden of disease that the vaccine prevents, and the level and potential consequences of public concern about the safety of vaccine use.

The findings of the plausibility and significance assessments provide the basis for the committee's recommendations regarding public health response, immunization policy review, current and future research, and effective communication strategies for the specific immunization-safety questions.

The committee adopted the framework for assessing causality developed by the committees previously convened by the IOM (IOM, 1991, 1994a) to address questions of vaccine safety. To evaluate the hypothesis on MMR vaccine and autism, the committee collected information from several sources, including a review of the published, peer-reviewed scientific and medical literature, and commissioned a background paper reviewing the epidemiological studies of MMR vaccine and autism. The committee also held an open scientific meeting in March 2001 (see Appendix B) to review the current understanding of the etiology and epidemiology of autism and on-going investigations regarding the MMR vaccine and autism hypothesis.

## THE HYPOTHESIZED RELATIONSHIP BETWEEN MMR AND AUTISM

Autism is a complex and severe developmental disorder characterized by impairments of social interaction, impairments in verbal and nonverbal communication, and restricted or repetitive and stereotyped patterns of behaviors and interests (APA, 1994; Filipek et al., 1999). Over time, research has identified subtle differences in the onset and progression of autistic symptoms. The term "autistic spectrum disorders" (ASD), synonymous with "pervasive developmental disorders" (PDD), refers to a continuum of related cognitive and neurobehavioral disorders that reflects the heterogeneity of these symptoms. ASD includes autistic disorder, childhood disintegrative disorder, Asperger's syndrome, Rett's syndrome, and pervasive developmental disorder not otherwise specified (PDD-NOS or atypical autism). While the primary deficits are similar for all of these disorders, patients vary in the severity of their symptoms and level of cognitive impairment. Although Rett's syndrome is included in the diagnostic category of ASD, it is considered by many to be a distinct neurologic disorder and this diag

nosis is not included in most research which has evaluated the association of the MMR vaccine with autism. In this report, the terms "autism," "autistic," and "autistic spectrum disorders" are used interchangeably to refer to this broader group of pervasive developmental disorders. The term "autistic disorder" refers to a more narrow diagnosis defined by criteria in the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV) (APA, 1994).

Research has established a very strong genetic component in the etiology of autism, but other factors, including infectious, neurologic, metabolic, immunologic, and environmental insults, may play important roles. However, significant gaps still remain in our understanding of the risk factors and etiologic mechanisms of ASD.

Clinical descriptions of autism suggest two different types of presentation, including early onset and regression, distinguished by the reported time-course of the developmental abnormalities. Most cases of autism appear to be early onset, resulting from prenatal or early postnatal insults (Bristol et al., 1996); however, the diagnosis of early-onset cases is characteristically not made until the second year of life, when symptoms become more pronounced. In a second course, suggested in a minority of cases, apparently normal development is followed by regression (or the sudden loss of previously established developmental milestones), usually in the second year, which leaves open the possibility that MMR vaccination precedes the onset of the disorder. However, there is no scientifically established definition of regression.

Current attention to the possible relationship between MMR and ASD stems primarily from a case series reported in 1998 (Wakefield et al., 1998). Twelve children with a history of normal development followed by loss of acquired skills and gastrointestinal symptoms were referred to a London gastroenterology clinic that was interested in the connection between measles virus and bowel disease. For eight of these children, the onset of their behavioral problems was associated, through retrospective accounts by their parents or physicians, with MMR vaccination. The resulting report, and numerous other cases reported by parents, have generated considerable interest and concern about a possible link between MMR vaccination and ASD, and regressive autism in particular.

There are also more general concerns in the United States and the United Kingdom that the introduction and wide-scale use of the MMR vaccine coincide with an apparent increase in the occurrence of ASD. Information about the rates of ASD in the United States and changes in incidence or prevalence is limited, reflecting a lack of epidemiological research on ASD in this country. However, a recent report by the California Department of Developmental Services (1999), which shows a significant increase between 1987 and 1998 in its caseload of children with ASD, is often cited as evidence of this increasing trend, although the reported increases occurred well after the licensure and introduction of MMR in the United States in 1971. Published studies of trends in ASD prevalence and incidence, in fact, have been unable to resolve how much of the ob

served increase is real or due to other factors such as reporting bias, changes in diagnostic criteria, or better case ascertainment over time (Fombonne, 1999, 2001a; Gillberg and Wing, 1999).

## PLAUSIBILITY ASSESSMENT

The committee proceeded in order to answer the following question: What is the causal relationship between MMR vaccine and ASD? The committee's primary finding is that a number of epidemiological studies (both uncontrolled and controlled) provide no support for an association on a population level between MMR immunization and ASD (Dales et al., 2001; Gillberg and Heijbel, 1998; Kaye et al., 2001; Patja et al., 2000; Peltola et al., 1998; Taylor et al., 1999). Findings from unpublished studies, which were shared with the committee publicly and through personal communications and which are in the process of being submitted for publication (Fombonne, 2001b; Miller et al., 2001), seemed to provide additional evidence of no association between MMR and ASD, although the findings still need to be peer-reviewed, published, and subjected to scrutiny by the broader scientific community.

Although these epidemiological studies do not support an association at a population level, it is important to recognize the inherent methodological limitations of such studies in establishing causality. Studies may not have sufficient precision to detect very rare occurrences on a population level. A poor understanding of the risk factors and failure to use a standard case definition may also hamper the ability of epidemiological studies to detect rare adverse events. In addition, since MMR exposure is virtually universal in developed countries, elucidating any association with adverse outcomes requires the creative use of administrative and other data sets and complex research designs. Furthermore, the rarity of the individual autistic spectrum disorders and the difficulty in determining their exact onset, and therefore the temporal relationship between onset and vaccination, make certain epidemiological study designs (e.g., cohort studies) impractical.

Second, the committee concludes that the case series of children with ASD and bowel symptoms (Wakefield et al., 1998) is uninformative with respect to causality between MMR and ASD. The small number of cases, the potential selection bias, the difficulty in diagnosing children with ASD, multiple diagnoses in the patients, and the lack of detail regarding the criteria for the behavioral diagnoses of the children in the series limit the utility of this study in establishing causality. Although parents or doctors made a temporal link between the onset of their children's behavioral disorders and the MMR vaccine, the authors of the resulting paper acknowledge that their findings do not prove an association between MMR and the condition they describe. Furthermore, it is not possible to describe from this study the nature of any relationship among vaccine-strain measles virus infection, ASD, and bowel symptoms. In addition, case reports submitted to the Vaccine Adverse Event Reporting System, a national pas

sive surveillance system in the United States, sometimes note a temporal association between MMR vaccination and the onset of symptoms, but these reports vary substantially in their level of detail and supporting medical documentation. The committee found them uninformative in assessing causality.

Third, the biologic model linking MMR and ASD is incomplete and fragmentary. Possible immunologic and metabolic mechanisms have been described but have not been supported by validated and replicated controlled studies. While some believe that disrupted viral immunity following administration of polyvalent vaccines could lead to atypical or persistent measles infection, possibly resulting in ASD or bowel disease, there is no biological precedent or sufficient evidence from existing research to support this scenario. Furthermore, with the exception of the results from two groups (Kawashima 1996, 2000; Wakefield, 2001), there is no evidence to support persistent infection with vaccine-strain measles virus except for individuals with compromised immunity. The groups' findings, however, have not been adequately replicated and validated by controlled studies. In the absence of such studies, the existence of persistent vaccine-strain measles virus infection in ASD with bowel inflammation is uncertain.

Finally, there is no relevant animal model. The model based on Borna disease virus infection in rats may be useful for studying the induction of symptoms of ASD by insults, especially infectious, to brain development during the prenatal and perinatal periods, but this model is not adequate for studying the association between the MMR vaccine and the subsequent onset of ASD. Also, primate models which are effective for the study of vaccine safety and immunogenicity or the neurobehavioral aspects of ASD do not adequately represent any relationship between the MMR vaccine and ASD.

**Thus, the committee concludes that the evidence favors rejection of a causal relationship at the population level between MMR vaccine and autistic spectrum disorders (ASD). The committee bases this conclusion on the following evidence:**

- A consistent body of epidemiological evidence shows no association at a population level between MMR vaccine and ASD.
- The original case series of children with ASD and bowel symptoms and other available case reports are uninformative with respect to causality.
- Biologic models linking MMR vaccine and ASD are fragmentary.
- There is no relevant animal model linking MMR vaccine and ASD.

**However, the committee notes that its conclusion does not exclude the possibility that MMR vaccine could contribute to ASD in a small number of children, because the epidemiological evidence lacks the precision to assess rare occurrences of a response to MMR vaccine leading to ASD and the proposed biological models linking MMR vaccine to ASD, although far from established, are nevertheless not disproved.**

It is important to note that the committee evaluated the hypothetical association between MMR vaccine and ASD from a starting position of neutrality. A shift from that position is possible only if sufficient evidence is available to convince the committee that a causal association is either likely or unlikely.

## SIGNIFICANCE ASSESSMENT

In its significance assessment, the committee considered the burden (i.e., the seriousness, risk, and treatability) of the vaccine-preventable diseases (measles, mumps, and rubella) and the potential adverse event (ASD), and the level of public concern surrounding this issue. Measles, mumps, and rubella can lead to significant morbidity and mortality, and treatment of these infectious diseases and their associated complications is limited to symptomatic relief and physiologic support until the condition resolves.

Historically, concerns about the safety of vaccines have led to declines in immunization coverage rates followed by outbreaks of disease, as observed with pertussis in the United Kingdom during the 1970s. Similar outbreaks could easily occur were immunization rates to decline as a result of fears regarding MMR. Yet, because MMR vaccine is a mandatory vaccine that is administered to healthy children—in part, as a public health measure to protect the health of others—the responsibility of the government to ensure the safety of this vaccine is high, even if the adverse outcome is rare.

Thus, the significance of the hypothesized adverse event—ASD, a group of incurable and serious behavioral disorder—requires consideration of all possible etiologies. In addition, the level of public concern about MMR vaccine safety is high.

## RECOMMENDATIONS

### Public Health Response

Although the committee has concluded that the evidence favors rejection of the causal relationship at the population level between MMR vaccine and autistic spectrum disorders, **the committee nevertheless recommends that this issue receive continued attention.** It does so in recognition that its conclusion does not exclude the possibility that MMR vaccine could contribute to ASD in a small number of children, as well as the following factors: the identified limitations of the evidence, the burden of ASD, the burden of the diseases prevented by the vaccine, the immense concern of parents, and the prominence of the issue in public debate.

Specific recommendations regarding policy review, research and surveillance, and communication follow.

### Policy Review

- At this time, the committee does not recommend a policy review of the licensure of MMR vaccine or of the current schedule and recommendations for administration of MMR vaccine.

### Research Regarding MMR and ASD

The committee concludes that further research on the possible occurrence of ASD in a small number of children subsequent to MMR vaccination is warranted and has identified targeted research opportunities that could lead to a clearer understanding of the relationship. The committee makes the following research recommendations, recognizing that it has no basis for judging whether the results of such research will alter the balance of evidence that led to the committee's original conclusion:

- Use accepted case definitions and assessment protocols for ASD to enhance the precision and comparability of results from surveillance, epidemiological studies, and biologic investigations.
- Explore whether exposure to MMR vaccine is a risk factor for ASD in a small number of children.
- Develop targeted investigation of whether or not measles vaccine-strain virus is present in the intestines of some children with ASD.
- Encourage all who submit reports to the Vaccine Adverse Event Reporting System to provide as much detail and as much documentation as possible when any diagnosis of ASD is thought to be related to MMR vaccine.
- Study the possible effects of different immunization exposures—for example, studying children whose families have chosen not to have them receive the MMR vaccine.
- Conduct further clinical and epidemiological studies of sufficient rigor to identify risk factors and biological markers of ASD in order to better understand genetic or environmental causes.

### Communications

The committee heard repeatedly in its open sessions and discussions with parents and advocacy groups that obtaining unbiased and accurate information on the possible relationship between MMR vaccine and ASD has been difficult. The committee will address this issue more fully in the future. **In the meantime, it specifically recommends that government agencies and professional organizations, CDC and the Food and Drug Administration (FDA) in particular, review some of the most prominent forms of communication regarding the hypothesized relationship between MMR vaccine and ASD, including information they provide via the Internet and the ease with which Internet information can be accessed.** They should especially be attentive to how commu

nications are perceived and used by parents of children about to be immunized or those who believe their child has been adversely affected by a vaccine. Direct input from parents and other stakeholders would be invaluable in conducting a systematic and effective evaluation of current communication tools.

### General and Crosscutting Issues

In its discussion of recommendations related specifically to the MMR-ASD question, the committee identified more general concerns that it could not adequately or appropriately address in this report. These include deficiencies in the available information on the risks and benefits of vaccines, inadequate discussion on the ethics of providing information regarding the risks and benefits of vaccinations, the role of public input into vaccine advisory committees, and inadequate clinical-provider information on vaccine safety or the Vaccine Adverse Event Reporting System. The committee sees a need for a dialogue between vaccine safety advocates of every kind, in order to come to common understanding of how to align the appropriate public health attention with a possibly small vaccine safety risk. Finally, the committee did not have time to address responsibly the appropriateness of alternative immunization schedules or practices, which might be requested in a clinical setting. These concerns will be more completely considered in future reports. In the meantime, the committee urges the CDC, FDA, NIH, American Academy of Pediatrics (AAP), and similar organizations to take to heart the serious concerns and earnest offers of help on information exchange and communication from the members of the public concerned about the safety of vaccines.

## SUMMARY

The Immunization Safety Review Committee concludes that the evidence favors rejection of a causal relationship at the population level between MMR vaccine and ASD. However, this conclusion does not exclude the possibility that MMR vaccine could contribute to ASD in a small number of children, because the epidemiological evidence lacks the precision to assess rare occurrences of a response to MMR vaccine leading to ASD and the proposed biological models linking MMR vaccine to ASD, although far from established, are nevertheless not disproved.

Because of the limitations of the evidence, the significant public concern surrounding the issue, the risk of disease outbreaks if immunization rates fall, and the seriousness of ASD, the committee recommends that continued attention be given to this issue. Thus, the committee has provided targeted research and communication recommendations. However, at this time, the committee does not recommend a policy review of the licensure of MMR vaccine or of the current schedule and recommendations regarding administration of MMR vaccine.

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# Appendix B

# Monday, July 16, 2001 Meeting Agenda

**IMMUNIZATION SAFETY REVIEW COMMITTEE Thimerosal-Containing Vaccines and Neurodevelopmental Outcomes Public Meeting**

**The Charles Hotel Conant Wadsworth B Conference Room One Bennett Street Cambridge, MA**

PUBLIC SESSION

| | |
|---|---|
| 8:00–8:10 a.m. | **Welcome and Introductions**<br>*Marie McCormick, M.D., Sc.D.*<br>*Chair, Immunization Safety Review Committee* |
| 8:10–8:30 a.m. | **Risk Assessment of Thimerosal in Childhood Vaccines**<br>*Leslie K.Ball, M.D.*<br>*Division of Vaccines and Related Product Applications*<br>*Office of Vaccines Research and Review*<br>*Center for Biologics Evaluation and Research*<br>*Food and Drug Administration* |
| 8:30–9:00 a.m. | **History of Thimerosal Concern and Comparative Policy Actions**<br>*Gary L.Freed, M.D.*<br>*The Percy and Mary Murphy Professor of Pediatrics and Child Health Delivery*<br>*Director, Division of General Pediatrics*<br>*Professor of Health Management and Policy*<br>*University of Michigan* |

| | |
|---|---|
| | *Margie Andreae, M.D.*<br>*Associate Director for Clinical Services*<br>*Division of General Pediatrics*<br>*University of Michigan* |
| 9:00–9:35 a.m. | **Biologic Plausibility and Planned Research**<br>*Jane M.El-Dahr, M.D.*<br>*Head, Section of Pediatric Allergy, Immunology, Rheumatology*<br>*Tulane University Health Sciences Center*<br>*David S.Baskin, M.D.*<br>*Professor of Neurosurgery*<br>*Baylor College of Medicine* |
| 9:35–10:00 a.m. | **The Role of Heavy Metals in Autism**<br>*Jeffrey Bradstreet, M.D.*<br>*Director of Research*<br>*The International Autism Research Center* |
| 10:15–10:45 a.m. | **Pharmacokinetic Modeling of Hair Mercury Levels from Thimerosal**<br>*David Brown, Sc.D.*<br>*Toxicologist and Independent Consultant*<br>*Connecticut* |
| 10:45–11:30 a.m. | **Vaccine Safety Datalink (VSD) Screening Study and Follow-Up Analysis with Harvard Pilgrim Data**<br>*Thomas Verstraeten, M.D., M.Sc.*<br>*EIS Officer, National Immunization Program-*<br>*Centers for Disease Control and Prevention* |
| 11:30–12:00 noon | **Protocol for National Immunization Program Study on Thimerosal**<br>*Paul Stehr-Green, Dr.P.H., M.P.H.*<br>*Associate Professor of Epidemiology*<br>*University of Washington School of Community Medicine and Public Health*<br>*William Thompson, Ph.D. (for Q&A period only)*<br>*Epidemiologist, National Immunization Program-*<br>*Centers for Disease Control and Prevention* |

| | |
|---|---|
| 1:00–1:30 p.m. | **Seychelles Islands Study**<br>*Gary Myers, M.D.*<br>*Professor of Neurology and Pediatrics*<br>*University of Rochester School of Medicine and Dentistry* |
| 1:30–2:00 p.m. | **Faroe Islands Study**<br>*Philippe Grandjean, M.D., D.M.Sc.*<br>*Institute of Community Health*<br>*Odense University, Denmark* |
| 2:00–2:30 p.m. | ***In Vitro* Studies of Thimerosal Toxicity**<br>*Boyd E.Haley, Ph.D.*<br>*Chairman and Professor, Department of Chemistry*<br>*University of Kentucky* |
| 2:30–3:00 p.m. | **Comparative Toxicology of Ethyl and Methyl Mercury**<br>*George Lucier, Ph.D.*<br>*Former Director, Environmental Toxicology Program*<br>*National Institute for Environmental Health Sciences* |
| 3:15–3:30 p.m. | **Rising Incidence of Autism: Association with Thimerosal**<br>*Mark F.Blaxill, M.B.A.*<br>*Autism Society of America, Massachusetts Chapter* |
| 3:30–3:45 p.m. | **NIH Studies on Thimerosal**<br>*Polly Sager, Ph.D.*<br>*National Institute of Allergy and Infectious Diseases*<br>*National Institutes of Health* |
| 3:45–4:10 p.m. | **Wrap-Up Commentary on Thimerosal Risk**<br>**From the Perspective of a Developmental Toxicologist**<br>*George Lambert, M.D.*<br>*Environmental and Occupational Health Sciences Institute*<br>*Robert Wood Johnson Medical School* |
| 4:10–4:35 p.m. | **Wrap-up Commentary on Thimerosal Risk**<br>**From the Perspective of a Pediatric Vaccinologist**<br>*Neal Halsey, M.D.*<br>*Professor and Director*<br>*Division of Disease Control*<br>*Department of International Health*<br>*The Johns Hopkins University* |
| 4:35–5:00 p.m. | **Public comment period** |

# Appendix C

# Thimerosal Content in Licensed Vaccines

(Adapted from FDA, 2001; AAP, 1999)

**TABLE C-1** Vaccines on the Recommended Childhood Immunization Schedule in the United States

**Currently Licensed Childhood Vaccines That Contained Thimerosal**

| | | | Previous Thimerosal Content (August/September 1999) | | Current Thimerosal Content (June 2001) | |
|---|---|---|---|---|---|---|
| **Vaccine** | **Brand Name** | **Manufacturer** | **% Thim Conc** | **Hg µg/0.5mL** | **% Thim Conc** | **Hg µg/0.5mL** |
| **DTaP** (Diphtheria and tetanus toxoids and acellular pertussis) | Tripedia | Pasteur Merieux Connaught | 0.01 | 25 | <0.0002 | <0.5 |
| | Infanrix | Glaxo-SmithKline | 0 | 0 | 0 | 0 |
| | *Acel-Immune | Wyeth-Ayerst | 0.01 | 25 | N/A | N/A |
| | *Certiva | North Amer. Vaccine | 0.01 | 25 | N/A | N/A |
| **Td** (Tetanus and diphtheria toxoids) | All Products | Aventis Pasteur Lederle | 0.01 | 25 | 0.01 | 25 |
| **DTaP-Hib** (Diphtheria and tetanus toxoids with acellular pertussis combined with *Haemophilus influenzae* type b) | TriHIBit | Aventis Pasteur | 0.01 | 25 | 0 | 0 |
| **Hib** (*Haemophilus influenzae* type b) | ActHIB | Aventis Pasteur | 0 | 0 | 0 | 0 |
| | HibTITER Single dose | Wyeth-Ayerst | 0 | 0 | 0 | 0 |
| | Omni HB | Aventis Pasteur | 0 | 0 | 0 | 0 |
| | PedvaxHIB liquid | Merck | 0 | 0 | 0 | 0 |
| | *HibTITER (multi-dose) | Wyeth-Ayerst | 0.01 | 25 | N/A | N/A |
| | *ProHIBit[1] | Aventis Pasteur | 0.01 | 25 | N/A | N/A |
| **Hib/HepB** (*Haemophilus influenzae* type b combined with Hepatitis B) | COMVAX | Merck | 0 | 0 | 0 | 0 |

[1] Not given to children less than 15 months of age.

| | | | | | | |
|---|---|---|---|---|---|---|
| **Hep B** (Hepatitis B) | Engerix B[2] *(pediatric formulation)* | Glaxo-SmithKline | 0.005 | 12.5 | <0.0002 | <0.5 |
| | Recombivax HB *(pediatric formulation)* | Merck | 0.005 | 12.5 | 0 | 0 |
| **Pneumococcal**[3,4] | Prevnar (pneumoconjugate) | Wyeth-Ayerst | N/A | N/A | 0 | 0 |
| | Pneumovax 23 | Merck | N/A | N/A | 0 | 0 |
| **Currently Licensed Childhood Vaccines That Never Contained Thimerosal** | | | | | | |
| **IPV** (Poliovirus vaccine, inactivated) | IPOL | Aventis Pasteur | 0 | 0 | 0 | 0 |
| | Poliovax | Aventis Pasteur | N/A | N/A | 0 | 0 |
| **MMR** (Measles, mumps, rubella) | MMR-II | Merck | 0 | 0 | 0 | 0 |
| **Varicella** | Varivax | Merck | 0 | 0 | 0 | 0 |
| **Vaccines No Longer Part of the Current Recommended Childhood Immunization Schedule** | | | | | | |
| **DTwP** (Diphtheria and tetanus toxoids with whole-cell pertussis) | *All products | No longer produced in the United States | 0.01 | 25 | N/A | N/A |
| **DTwP-Hib** (Diphtheria and tetanus toxoids with whole-cell pertussis combined with *Haemophilus influenzae* type b) | *Tetramune | Lederle Laboratories | 0.01 | 25 | N/A | N/A |
| **OPV**[5] (Poliovirus, live oral) | *Orimune | Wyeth-Ayerst | 0 | 0 | N/A | N/A |

[2] Adult formulation contains thimerosal.

[3] Added to immunization schedule in 2000.

[4] Pnu-Immune 23, a pneumococcal vaccine manufactured by Wyeth-Ayerst, contains 0.01% thimerosal (25 µg Hg/0.5mL). This vaccine is adminstered only to children two years or older.

[5] Part of routine schedule (sequential schedule for 3rd & 4th doses of polio vaccine) until Jan.

*No longer available in the United States.

N/A means that the product was not available in 1999 or is no longer currently produced or distributed in the United States.

TABLE C-2 Currently Licensed Vaccines That Are Recommended for Some Children

| | | | Current Thimerosal Content (June 2001) | |
|---|---|---|---|---|
| **Vaccine** | **Brand Name** | **Manufacturer** | **% Thim Conc** | **Hg µg/0.5mL** |
| **DT** (Diphtheria and tetanus toxoids) | All Products | Lederle | 0.01 | 25 |
| **TT** (Tetanus Toxoid) | All Products | Lederle | 0.01 | 25 |
| **Hepatitis A** | Havrix A | SmithKline Beecham | 0 | 0 |
| | Vaqta | Merck | 0 | 0 |
| **Influenza** | All | Aventis Pasteur, Medeva, and Lederle-Wyeth | 0.01 | 25 |

NOTE: The formulation of vaccines listed in C-2 and C-3 have not changed since August/September 1999.

TABLE C-3 Other Licensed Vaccines in the United States

| | | | Current Thimerosal Content (June 2001) | |
|---|---|---|---|---|
| **Vaccine** | **Brand Name** | **Manufacturer** | **% Thim Conc** | **Hg µg/0.5mL** |
| **Anthrax** | Anthrax Vaccine | BioPort Corporation | 0 | 0 |
| **BCG** | | | N/A | N/A |
| **Hepatitis A-Hepatitis B** | Twinrix | Glaxo-SmithKline | 0 | 0 |
| **Hepatitis B** | Engerix B *(adult formulation)* | Glaxo-SmithKline | 0.005 | 12.5 |
| | Recombivax HB *(adult formulation)* | Merck | 0.005 | 12.5 |
| **Lyme** | LYMErix | Glaxo-SmithKline | 0 | 0 |
| **Meningococcal**[6] | Menomune A, C, AC and A/C/Y/W-135 | Aventis Pasteur | 0.01 | 25 |
| **Rabies** | IMOVAX | Aventis Pasteur | 0 | 0 |
| | Rabavert | Chiron | 0 | 0 |
| | Rabies Vaccine Adsorbed[7] | Bioport Corporation | N/A | N/A |
| **Typhoid Fever** | Typhim Vi | Aventis Pasteur | 0 | 0 |
| | Typhoid Ty21a | Vivotef Berna | 0 | 0 |
| | Typhoid Vaccine | Wyeth-Ayerst | 0 | 0 |
| **Yellow Fever** | Y-F-Vax | Aventis Pasteur | 0 | 0 |

[6] Menomune A/C/Y/W-135, a thimerosal-containing vaccine, is not indicated for infants and children younger than 2 years of age except as short-term protection of infants 3 months and older against Group A.(*Physician's Desk Reference,* 2001).

[7] This vaccine is no longer available but did contain 0.01% thimerosal (25 µg Hg/0.5mL).

N/A means that the product is no longer currently produced or distributed in the United States.

# APPENDIX D

# Immunization Safety Review Committee Biosketches

**Marie C.McCormick, M.D., Sc.D., (Chair),** is Summer and Esther Feldberg Professor and Chair of the Department of Maternal and Child Health at the Harvard School of Public Health. She received her M.D. degree from Johns Hopkins Medical School, and her Sc.D. degree from Johns Hopkins School of Hygiene and Public Health. Dr. McCormick is a member of the Institute of Medicine and has served as chair of the Committee on Preventing Perinatal Transmission of HIV and the Committee on Prenatal and Newborn Screening for HIV Infection, and as a member of the Committee on Unintended Pregnancy. Her research involves epidemiological and health services research in areas related to infant mortality and outcomes of high-risk neonates. Her expertise is in pediatrics, maternal and child health policy, and program evaluation.

**Ronald Bayer, Ph.D.,** is Professor in the Division of Sociomedical Sciences at the Joseph L.Mailman School of Public Health at Columbia University. Dr. Bayer received his Ph.D. in political science from the University of Chicago. Since 1982, he has been involved in the study of the ethical and policy dimensions of the AIDS epidemic. He served on the National Research Council's Committee on the Social Impact of AIDS and, more recently, the Committee on the Elimination of Tuberculosis in the United States. He is author of numerous articles on ethical issues posed by AIDS and tuberculosis, including *Private Acts, Social Consequences: AIDS and the Politics of Public Health,* and *Blood Feuds: AIDS, Blood, and the Politics of Medical Disaster.* His most recent co-authored book is *AIDS Doctors: Voices from the Epidemic.*

**Alfred Berg, M.D., M.P.H.,** is Professor and Chair of the Department of Family Medicine at the University of Washington School of Medicine. Dr. Berg received his M.D. from Washington University and his M.P.H. from the University of Washington. He is a member of the Institute of Medicine. Dr. Berg presently serves as chair of the third U.S. Preventive Services Task Force and is a member of the American Academy of Family Physicians and the Society of Teachers of Family Medicine. He is also an Associate Editor for the *Journal of the American Board of Family Practice.* Dr. Berg's research interests include clinical epidemiology, evidence-based medical practice, preventive medicine, and clinical practice guidelines.

**Rosemary Casey, M.D.,** is an Associate Professor of Pediatrics at Jefferson Medical College, and the Director and practicing physician of Lankenau Faculty Pediatrics. Dr. Casey is board-certified in Pediatrics, and a member of the American Academy of Pediatrics and the Ambulatory Pediatric Association. She also serves as editorial consultant on several journals, including *Pediatrics, Pediatric Emergency Care, Clinical Pediatrics,* and *Journal of the Ambulatory Pediatric Association.* Her interests include diagnostic problems and behavioral pediatrics. Dr. Casey received her M.D. from Harvard Medical School and completed her residency in pediatrics at the Children's Hospital of Philadelphia. She was a Robert Wood Johnson Clinical Scholar at the University of Pennsylvania.

**Joshua Cohen, Ph.D.,** is a Senior Research Associate with the Harvard Center for Risk Analysis. Dr. Cohen received his Ph.D. in Decision Sciences from Harvard University. His research includes assessing population risk related to styrene production and use, and developing a computer model to quantify the risk of bovine spongiform encephalopathy being introduced into the United States and contaminating the food supply. In addition, he is the project director for a comparative evaluation of alternative propulsion systems for heavy-duty urban vehicles. He is the author of a case study conducted for U.S. EPA demonstrating the application of decision analytical techniques to the evaluation of alternative drinking water treatment technologies. His research focuses on the application of decision analytical techniques to environmental risk management problems, with a special emphasis on the proper characterization and analysis of uncertainty.

**Vernice Davis-Anthony, M.P.H., R.N.,** is Senior Vice President of Corporate Affairs and Community Health at St. John Health System in Detroit, Michigan, where she oversees system-wide management and development of community health policies and programs, strategic planning, marketing and public relations, and government relations. Ms. Davis-Anthony was the former Director of the Michigan Department of Public Health, where she achieved the lowest infant mortality rate in Michigan's history and reduced the teen pregnancy rate in that state. In addition, Ms. Davis-Anthony established the Michigan Task Force of

Violence Reduction and Prevention and the Michigan Abstinence Partnership. She was also appointed to serve as a Governor of Wayne State University. She received her M.P.H. from the University of Michigan School of Public Health and Bachelor of Science in Nursing from Wayne State University.

**Betsy Foxman, Ph.D.,** is Professor in the Department of Epidemiology at the University of Michigan School of Public Health, and Director of the Center for Molecular and Clinical Epidemiology of Infectious Diseases. Her research focuses on the combination of epidemiological field methods and modern molecular techniques to examine the individual and joints effects of host behaviors, host characteristics, and agent characteristics on disease risk, especially on urinary tract infection, vulvovaginal candidiasis, lactation mastitis, and otitis media. She serves on various professional organizations, including Chair of the Epidemiology Division of the American Public Health Association, is a member of the program committee for the first North American Congress of Epidemiologists, and is a fellow of the Infectious Diseases Society of America. She received her Ph.D. in epidemiology from the University of California, Los Angeles.

**Constantine Gatsonis, Ph.D.,** is Professor of Medical Science and Applied Mathematics, and Director of the Center for Statistical Sciences at Brown University. He has served on numerous review and advisory panels, including as a consultant/ad hoc panel member on the FDA Center for Devices and Radiological Health, the Data Safety and Monitoring Board of the VA Cooperative Studies in Health Services, the Commission of Technology Assessment of the American College of Radiology, the NINDS Data Safety and Monitoring Board, and the HCFA Technical Experts Panel. Dr. Gatsonis is the founding editor-in-chief of *Health Services and Outcomes Research Methodology* and is on the editorial board of *Academic Radiology, Statistics in Medicine,* and *Medical Decision Making.* His research interests include Bayesian inference and its applications to problems in biostatistics, methodological aspects of health services and outcomes research, and medical technology evaluation with emphasis on diagnostic radiology. Dr. Gatsonis received his Ph.D. in mathematical statistics from Cornell University.

**Steven Goodman, M.D., M.H.S., Ph.D.,** is Associate Professor of Oncology, Pediatrics, Epidemiology and Biostatistics at the Johns Hopkins Schools of Medicine and Public Health. Dr. Goodman received his M.D. from New York University, his M.H.S. and Ph.D. degrees from Johns Hopkins University, and trained in pediatrics at Washington University in St. Louis. He has been a member of two IOM committees: the Committee for a Review of Evidence Regarding the Link Between Exposure to Agent Orange and Diabetes, and the Committee to Review the Health Effects in Vietnam Veterans of Exposure to

Herbicides: Second Biennial Update. As a statistician for the Johns Hopkins Oncology Center, General Clinical Research Center, and Pediatric Clinical Research Unit, he has participated in the design and analysis of a wide range of clinical and epidemiological studies. He is co-director of the Johns Hopkins Evidence-Based Practice Center, and has served as Statistical Editor for the *Annals of Internal Medicine* since 1987. His research interests include metaanalysis, statistical inference, the ethics of clinical trials, and the use of likelihood and Bayesian methodology in clinical research.

**Ellen Horak, M.S.N.,** is Chief of Local Health Services in the office of Local and Rural Health at the Kansas Department of Health and Environment. Ms. Horak is the Past President of the Association of State and Territorial Directors of Nursing, as well as Past District President of the Kansas State Nurses Association. She is also a member of the American Public Health Association and Kansas Public Health Association. Ms. Horak received her M.S.N. from the University of Kansas.

**Michael Kaback, M.D.,** Michael Kaback is Professor of Pediatrics and Reproductive Medicine at the University of California in San Diego. He is an Institute of Medicine member and has served on previous IOM committees, including the Committee on Assessing Genetic Risks: Issues and Implications for Health. His expertise is in medical genetics and pediatrics, and his research interests include the applications of human genetic technology to treatment and prevention of hereditary disease and congenital defects; technical, social, psychological, legal, and ethical implications of new genetic technologies; and public health and medical practice implications. Dr. Kaback received his M.D. from the University of Pennsylvania School of Medicine.

**Gerald Medoff, M.D.,** is Professor of Medicine and Microbiology and Immunology, and Senior Advisor to the Chairman of the Internal Medicine Department at Washington University School of Medicine. He was formerly Head of the Infectious Disease Division at Washington University School of Medicine. He has served on various committees, including the Committee on Infectious Diseases of the American Board of Internal Medicine, the Executive Board of the AIDS Clinical Trials Unit, and the Pharmacy and Therapeutics Committee of Blue Cross and Blue Shield. In addition, he was Chairman of the AIDS Research Advisory Committee of the National Institute of Allergy and Infectious Diseases. Dr. Medoff's research interests include AIDS, fungal diseases, other infectious diseases, and antimicrobial agents. He received his M.D. from Washington University School of Medicine.

**Rebecca Parkin, Ph.D., M.P.H.,** is Associate Research Professor at The George Washington University Medical Center. Dr. Parkin received her Ph.D.

and M.P.H. from Yale University. She is a former director of scientific, professional, and section affairs at the American Public Health Association as well as assistant commissioner for the Division of Occupational and Environmental Health of the New Jersey Department of Health. She is a member of the National Research Council Water Science and Technology Board, and has served on several NRC committees. She is a liaison member of the DHHS's National Advisory Committee on Childhood Lead Poisoning Prevention, and a peer reviewer for the New Jersey Cancer Research Commission. She continues to serve on subcommittees of EPA's Science Advisory Board, and has been a member of study panels of the Agency for Toxic Substance Disease Registry. She is currently conducting research in the areas of environmental epidemiology, risk assessment, risk perception and communication, and immunization programs.

**Bennett A.Shaywitz, M.D.,** is Professor of Pediatrics and Neurology and Chief of Pediatric Neurology at the Yale University School of Medicine where he is also Co-Director of the Yale Center for the Study of Learning and Attention. He has served on previous IOM committees, including the Committee to Study Fetal Alcohol Syndrome, the Committee on New Research on Vaccines, the Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines, Committee for a Review of an Epidemiology Study of Neurologic Illness and Vaccination in Children, and the Committee on Reye's Syndrome and Medication. Currently, he leads a research group that is using functional magnetic resonance imaging (fMRI) to investigate the neural basis of reading and reading disability (dyslexia). Recently, he and his colleagues have used this technology to discover differences in brain organization and function in children and adults with dyslexia, and he has now begun to use fMRI to study how the brain changes as children with dyslexia are taught to read.

**Christopher Wilson, M.D.,** is Professor and Chair of the Department of Immunology at the University of Washington. He is a fellow of the American Association for the Advancement of Science, the Infectious Diseases Society of America, and the American Academy of Pediatrics. He was also a member of the Maternal and Child Health Research Committee of the National Institute of Child Health and Human Development. His research includes laboratory work on the elucidation of the molecular mechanisms by which functional differences between naïve and memory/effector T-cells are imposed, thereby allowing them to exhibit fixed and heritable patterns of effector functions. In addition, his work includes addressing mechanisms governing the development of immunity following primary function, in particular with the intracellular pathogens *M. tuberculosis, Listeria monocytogenes,* and herpes simplex virus. Dr. Wilson received his M.D. from the University of California, Los Angeles.

**Board on Health Promotion Disease Prevention Liaison**

**Richard Johnston Jr., M.D.,** is currently Professor of Pediatrics at the National Jewish Medical and Research Center at the University of Colorado School of Medicine. He was formerly the Medical Director of the March of Dimes Birth Defects Foundation, and Chief of the Section of Immunology in the Department of Pediatrics at Yale University School of Medicine. Among his previous appointments is the position of Chairman of Pediatrics, University of Pennsylvania. He is a member of the Association of American Physicians and the Institute of Medicine and a Fellow of the American Association for the Advancement of Science. His publications include work on immune diseases in children and mechanisms of host defense and inflammation. Dr. Johnston is a past president of the society for Pediatric Research and the American Pediatric Society. He is a member of the Board on Health Promotion Disease Prevention of the Institute of Medicine and has chaired four IOM committees, including Multiple Sclerosis: Current Status and Strategies for the Future, the Assessment of Asthma and Indoor Quality, and the Vaccine Safety Committee. He has served on several other IOM committees, including the Committee to Review Adverse Consequences of Pertussis and Rubella Vaccines and the Immunology Benchmarking Guidance Group.