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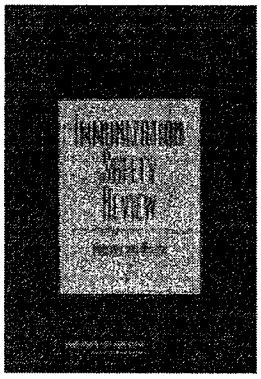

Immunization Safety Review: Vaccines and Autism

Immunization Safety Review Committee

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This eighth and final report of the Immunization Safety Review Committee examines the hypothesis that vaccines, specifically the measles-mumps-rubella (MMR) vaccineand thimerosal-containing vaccines, are causally associated with autism. The committeereviewed the extant published and unpublished epidemiological studiesregarding causality and studies of potential biologic mechanisms by which theseimmunizations might cause autism.Immunization Safety Review: Vaccines and Autism finds that the body of epidemiologicalevidence favors rejection of a causal relationship between thimerosal-containingvaccines and autism. The book further finds that potential biological mechanismsfor vaccine-induced autism that have been generated to date are only theoretical. Itrecommends a public health response that fully supports an array of vaccine safetyactivities and recommends that available funding for autism research be channeledto the most promising areas. The book makes additional recommendations regardingsurveillance and epidemiological research, clinical studies, and communicationrelated to these vaccine safety concerns.

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Executive Summary

ABSTRACT

This eighth and final report of the Immunization Safety Review Committee examines the hypothesis that vaccines, specifically the measles-mumps-rubella (MMR) vaccine and thimerosal-containing vaccines, are causally associated with autism. The committee reviewed the extant published and unpublished epidemiological studies regarding causality and studies of potential biologic mechanisms by which these immunizations might cause autism. The committee concludes that the body of epidemiological evidence favors rejection of a causal relationship between the MMR vaccine and autism. The committee also concludes that the body of epidemiological evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism. The committee further finds that potential biological mechanisms for vaccine-induced autism that have been generated to date are theoretical only.

The committee does not recommend a policy review of the current schedule and recommendations for the administration of either the MMR vaccine or thimerosal-containing vaccines. The committee recommends a public health response that fully supports an array of vaccine safety activities. In addition, the committee recommends that available funding for autism research be channeled to the most promising areas. The committee makes additional recommendations regarding surveillance and epidemiological research, clinical studies, and communication related to these vaccine safety concerns. Please see Box ES-1 for a summary of all conclusions and recommendations.

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Immunization to protect children and adults from infectious diseases is one of the greatest achievements of public health. Immunization is not without risks, however. It is well established, for example, that the oral polio vaccine on rare occasion has caused paralytic polio and that vaccines sometimes produce anaphylactic shock. Given the widespread use of vaccines, state mandates requiring vaccination of children for entry into school, college, or day care, and the importance of ensuring that trust in immunization programs is justified, it is essential that safety concerns receive assiduous attention.

At the request of the sponsoring agencies, the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH), the Institute of Medicine (IOM) established the Immunization Safety Review Committee to evaluate the evidence on possible causal associations between immunizations and certain adverse outcomes, and to then present conclusions and recommendations. The committee's mandate also includes assessing the broader significance for society of these immunization safety issues.

The specific vaccine safety hypotheses issues examined by the committee are determined by the Interagency Vaccine Group (IAVG), whose members represent several units of the Department of Health and Human Services: the CDC's National Vaccine Program Office, National Immunization Program, and National Center for Infectious Diseases; the NIH's National Institute of Allergy and Infectious Diseases; the Food and Drug Administration (FDA); the Health Resources and Services Administration's National Vaccine Injury Compensation Program; and the Centers for Medicare & Medicaid Services. The IAVG also includes representation from the Department of Defense and the Agency for International Development. The committee has issued seven previous reports on vaccine safety issues over the three-year study period (2001-2003). This eighth and final report from the committee examines the hypothesis that vaccines, specifically the measles-mumps-rubella (MMR) vaccine and vaccines containing the preservative thimerosal, cause autism. In its first two reports that were published in 2001, the committee examined the hypothesized causal association between the MMR vaccine and autism, and thimerosal-containing vaccines and neurodevelopmental disorders, respectively (IOM, 2001a,b). The IAVG asked the committee to revisit the hypothesized causal association between vaccines and autism in its final report in order to update its conclusions and recommendations based on the significant number of studies that have been undertaken in the last three years.

The committee begins from a position of neutrality regarding the specific immunization 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 clinical and epidemiologic evidence determines whether it is possible to shift from that neutral position to a finding for causality ("the evidence favors acceptance of a causal relationship") or against causality ("the evidence favors rejection of a causal relationship"). The committee does not conclude that the vaccine does not cause the adverse event

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merely because the evidence is inadequate to support causality. Instead, it maintains a neutral position, concluding that the "evidence is inadequate to accept or reject a causal relationship."

The committee's causality assessments must be guided by an understanding of relevant biological processes. Therefore the committee's scientific assessment includes consideration of biological mechanisms by which immunizations might cause an adverse event. The examination of experimental evidence for biological mechanisms has been referred to in previous reports of this committee (IOM, 2001a,b) and others (IOM, 1991, 1994) as an assessment of "biological plausibility." The committee has noted, however, that the term "biologic plausibility" is a source of confusion on at least two fronts. First, it is associated with a particular set of guidelines (sometimes referred to as the Bradford Hill criteria) for causal inference from epidemiological evidence (Hill, 1965); second, readers sometimes regard the term with a degree of certainty or precision the committee never intended. For example, a relationship between immunization and a particular adverse event may be found to be biologically plausible at the same time that the epidemiological evidence is found to be inadequate to accept or reject a causal relationship.

Given the resulting lack of clarity, the committee adopted a new terminology and a new approach to its discussions of experimental biological data in its third report (IOM, 2002). The committee now reviews evidence regarding "biological *mechanisms*" that might be consistent with the proposed relationship between immunization and a given adverse event.

The biological mechanism evidence reviewed in this report comes from human, animal, and *in vitro* studies of biological or pathophysiological processes. If the committee identifies evidence of biological mechanisms that could be operating, it offers a summary judgment of that body of evidence as weak, moderate, or strong. Although the committee tends to judge biological evidence in humans as "stronger" than biological evidence from highly contrived animal models or *in vitro* systems, the summary judgment of the strength of the evidence also depends on the quantity (e.g., number of studies or number of subjects in a study) and quality (e.g., the nature of the experimental system or study design) of the evidence. Obviously, the conclusions drawn from this review depend both on the specific data and scientific judgment. To ensure that its own summary judgment is defensible, the committee aims to be as explicit as possible regarding the strengths and limitations of the biological data.

In this report, the committee examines the hypothesis of whether the MMR vaccine and the use of vaccines containing the preservative thimerosal can cause autism. Autism is a complex and severe set of developmental disorders characterized by sustained impairments in social interaction, impairments in verbal and nonverbal communication, and stereotypically restricted or repetitive patterns of behaviors and interests (APA, 1994; Filipek et al., 1999; Volkmar and Pauls, 2003). Over time, research has identified subtle differences in the onset and

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progression of autistic symptoms. Autism is classified under the umbrella category of "pervasive developmental disorders" (PDDs) (APA, 2000). PDD refers to a continuum of related cognitive and neurobehavioral disorders that reflects the heterogeneity of symptoms and clinical presentations, and includes autistic disorder, childhood disintegrative disorder, Asperger's syndrome, Rett's syndrome, and pervasive developmental disorder not otherwise specified (PDD-NOS, or atypical autism). The term "autistic spectrum disorders" (ASD) has come into common use and is essentially synonymous with the term PDD (Volkmar et al., 2003). In this report, the terms "autism," "autistic," and "autistic spectrum disorders" are used interchangeably to refer to this broader group of pervasive developmental disorders.[1] Although Rett's syndrome is among the autistic spectrum disorders, it is considered by many to be a distinct neurologic disorder and thus its diagnosis is not included in most research that has evaluated the association of the vaccines and autism.

There is considerable uncertainty about the prevalence and incidence of autism and trends over time. Some studies have found an increase, but it is difficult to discern how much of the observed increase is real or possibly due to other factors, such as the adoption of a broader diagnostic concept of autism, improved recognition of autism, or variations in the precision of the studies (Fombonne, 1999, 2003; Gillberg and Wing, 1999).

In the committee's first report, which reviewed the hypothesized causal association between the MMR vaccine and autism (IOM, 2001a), the committee concluded that the evidence at the time favored rejection of a causal relationship at the population level between MMR vaccine and autism. The committee's conclusion did not exclude the possibility that MMR could contribute to autism in a small number of children because the epidemiological studies lacked sufficient precision to assess rare occurrences; it was possible, for example, that epidemiological studies would not detect a relationship between autism and MMR vaccination in a subset of the population with a genetic predisposition to autism. The biological models for an association between MMR and autism were not established but nevertheless not disproved.

In a subsequent report, the committee reviewed the hypothesized link between thimerosal-containing vaccines (TCVs) and a broad range of neurodevelopmental disorders (NDD), including autism (IOM, 2001b). Thimerosal, an organic mercury compound, 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 multidose vials of vaccines, except live virus vaccines, to prevent fungal and bacterial contamination (General Biologics Product Stan-

[1]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-TR) (APA, 2000).

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dards, 2000), which can lead to serious illness and death in recipients. In that report, the committee concluded that the evidence was inadequate to accept or reject a causal relationship between exposure to thimerosal from vaccines and the NDDs of autism, attention deficit hyperactivity disorder (ADHD), and speech or language delay. The committee's causality conclusion was based on the fact that there were no published epidemiological studies examining the potential association between TCVs and NDDs, and the two unpublished, epidemiological studies that were available (Blaxill, 2001; Verstraeten, 2001) provided only weak and inconclusive evidence of an association between TCVs and NDDs. The committee also concluded that the hypothesis linking TCVs with NDDs was not yet established and rested on incomplete evidence. However, because mercury is a known neurotoxin, and prenatal exposures to methylmercury (a compound closely related to the form of mercury in TCVs) have been documented to negatively affect early childhood development (see NRC, 2000),[2] a potential biological mechanism could be hypothesized based on analogies with this compound.

New epidemiological studies and biological mechanism theories on both issues have emerged since the publication of these IOM reports. In this report, the committee incorporates the new epidemiological evidence and studies of biologic mechanisms relating to vaccines and autism; it does not address the hypothesized link between vaccines and other NDDs.

Until 1999, thimerosal was contained 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. The controversy over thimerosal in vaccines erupted that year, when FDA researchers 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, 1999). With the licensure of a thimerosal-free hepatitis B vaccine in August 1999 and approval of a thimerosal-free preservative hepatitis B vaccine in March 2000, children had access to a hepatitis B vaccine that did not contain thimerosal as a preservative by March 2000. With the FDA approval of a second thimerosal-free version of DTaP vaccine in March 2001, all formulations of vaccines on the U.S. recommended childhood immunization schedule for children 6 years of age or younger became available free of thimerosal used as a preservative (FDA, 2002). Based on information from vaccine

[2]For example, there is evidence that fetal exposure to mercury might lead to detectable differences in neurodevelopmental testing that might be consistent with some neurodevelopmental disabilities (see NRC, 2000).

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manufacturers provided to the FDA, the lots of vaccine manufactured before this time that contained thimerosal as a preservative and had been released to the market had expiration dates in 2002 (FDA, 2004). Based on these changes, the maximum amount of mercury from vaccines on the recommended childhood immunization schedule that an infant (less than 6 months of age) can now be exposed to is <3 μg,[3] down from 187.5 μg in 1999 (FDA, 2001, 2004).

The controversy regarding the hypothesized link between the MMR vaccine and autism began in 1998 when Dr. Andrew Wakefield and colleagues published a case series describing 12 children with pervasive developmental disorder associated with gastrointestinal (GI) symptoms and developmental regression (Wakefield et al., 1998). For eight of these children, the onset of their behavioral problems was associated, through retrospective accounts by their parents or physicians, with MMR vaccination. This study put forth a hypothesis that a new phenotype of autism characterized by GI symptoms and developmental regression could be associated with the MMR vaccine. While the authors acknowledged that the study did not prove an association between MMR and the conditions seen in these children, the report generated considerable interest and concern about a possible link between MMR vaccination and ASD—regressive autism in particular. A recent statement from 10 of the original 13 authors states that the data were insufficient to establish a causal link between MMR vaccine and autism (Murch et al., 2004).

Causality Argument

Epidemiological studies examining TCVs and autism, including three controlled observational studies (Hviid et al., 2003; Miller, 2004; Verstraeten et al., 2003) and two uncontrolled observational studies (Madsen et al., 2003; Stehr-Green et al., 2003), consistently provided evidence of no association between TCVs and autism, despite the fact that these studies utilized different methods and examined different populations (in Sweden, Denmark, the United States, and the United Kingdom). Other studies reported findings of an association. These include two ecological studies[4] (Geier and Geier, 2003a, 2004a), three studies using passive reporting data (Geier and Geier, 2003a,b,d) one unpublished study using Vaccine Safety Datalink (VSD) data (Geier and Geier, 2004b,c), and one

[3]3μg is the maximum amount that could have been received by an infant in the first 6 months of life if they received trace-containing formulations (e.g., Engerix B hepatitis B vaccine, Tripedia DTaP vaccine) as opposed to those that contain no thimerosal (e.g., Recombivax HB hepatitis B vaccine pediatric formulation, Infanrix DTaP, Daptacel DTaP) (FDA, 2004d).

[4]These studies were classified as ecological because they rely on aggregate data rather than individual-level data to make inferences about causality. However, the authors appear to attempt an individual-level analysis, but it is unclear how this can be, given the data they used. Based on the available information, the study design is indeterminate. See text for more information.

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unpublished uncontrolled study (Blaxill, 2001). However, the studies by Geier and Geier cited above have serious methodological flaws and their analytic methods were nontransparent, making their results uninterpretable, and therefore noncontributory with respect to causality (see text for full discussion). The study by Blaxill is uninformative with respect to causality because of its methodological limitations. Thus, based on this body of evidence, **the committee concludes that the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism.** This conclusion differs from the committee's finding in its 2001 report on TCVs and NDDs which was that the evidence was "inadequate to accept or reject a causal relationship between exposure to thimerosal from childhood vaccines and the neurodevelopmental disorders of autism, ADHD, and speech and language delay." (IOM, 2001b, p. 66) The committee's conclusion in 2001 was based on the fact that there were no published epidemiological studies examining the potential association between TCVs and NDDs, and the two unpublished, epidemiological studies that were available (Blaxill, 2001; Verstraeten, 2001) provided only weak and inconclusive evidence of an association between TCVs and NDDs. Furthermore, the conclusion in the 2001 report pertained to a broader set of NDDs, while this report's conclusion applies *only* to autism.

Studies examining the association between MMR and autism, including nine controlled observational studies (DeStefano et al., 2004; DeWilde et al., 2001; Farrington et al., 2001; Fombonne and Chakrabarti, 2001; Madsen et al., 2002; Makela et al., 2002; Takahashi et al., 2003; Taylor et al., 1999, 2002), three ecological studies (Dales et al., 2001; Gillberg and Heijbel, 1998; Kaye et al., 2001), and two studies based on passive reporting system in Finland (Patja et al., 2000; Peltola et al., 1998), consistently showed evidence of no association between the MMR vaccine and autism. Two studies reported findings of a positive association between MMR and autism. The first was an ecological study (Geier and Geier, 2004a) that reported a potential positive correlation between the number of doses of measles-containing vaccine and the cases of autism reported to the special education system in the 1980s. The second was a study of passive reporting data by the same authors (Geier and Geier, 2003c) that reported a positive correlation between autism reports in the Vaccine Adverse Events Reporting System (VAERS) and estimated administered doses of MMR. However, these two studies are characterized by serious methodological flaws and their analytic methods were nontransparent, making their results uninterpretable, and therefore noncontributory with respect to causality (see text for full discussion). The case series study by Wakefield and colleagues (Wakefield et al., 1998), which originally raised the hypothesis linking MMR and autism, is uninformative with respect to causality. Based on this body of evidence, **the committee concludes that the evidence favors rejection of a causal relationship between MMR vaccine and autism.** This conclusion is consistent with the finding in the committee's previous report on MMR and autism (IOM, 2001a).

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Biological Mechanisms

Autism is a very complex disorder. A strong genetic component clearly exists, but there is a growing understanding that environmental factors might be important contributors to the expression of that genetic susceptibility. Animal models (primarily rat models), clinical observations, and pathological data point to an array of possible pathways by which autism develops, though none are proven. Many different pathways might lead to similar expressions, which could account for the multiple presentations of autism.

A link between vaccine components, such as the measles vaccine-strain virus or the ethylmercury preservative thimerosal, is difficult to establish because of the early stage of scientific understanding about the cause(s) of autism. The committee read, and heard presentations at their workshop, about several hypotheses. Data presented to support these hypotheses derive from rodent models of human autism, observations of abnormalities in children with autism or their families, and *in vitro* studies.

One hypothesis about the MMR vaccine involves the presence of measles virus lodging in the intestine of some children, which releases gut-brain mediators or toxins, leading to autism (Wakefield et al., 2002). Another hypothesis related to MMR vaccine is that children with autism have immune abnormalities that are indicative of vaccine-induced-central-nervous system, immune-mediated damage that leads to autism (Singh, 2004).

The thimerosal-related hypothesis is that some genetically susceptible population of children react to the thimerosal in vaccines with increased accumulation and decreased excretion of mercury from the brain, which alters several key biochemical pathways—for example, apoptosis and DNA metabolism—leading to autism (Bradstreet, 2004). A genetically susceptible subset of children who develop autism following vaccinations is offered as one theoretical explanation for the findings in epidemiological studies of no association between vaccination and autism.

Autism is a heterogeneous syndrome with a broad range of behavioral symptoms and severity. As yet, a biological marker specific for autism has not been defined. It is thus possible that autism encompasses a spectrum of disease subtypes that have different etiologies. This may explain the wide range of immunological abnormalities that have been found in the serum of patients with autism, with some studies reporting evidence of decreased cell-mediated immunity (CMI), and others reporting increased/overactive CMI. Other support for an association of autism with immune dysfunction includes the increased frequency of an extended major histocompatibility complex (MHC) haplotype in autism, increased autoantibodies to brain antigens, and the increased incidence of autoimmune diseases noted in a retrospective study of relatives of people with autism.

However, despite evidence of immune dysregulation in the serum of people with autism, there is as yet no evidence that the immune system plays a direct role

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in the neuropathogenesis of autism. Unlike neuroimmunological diseases such as multiple sclerosis, there is no evidence of immune activation or inflammatory lesions in the brains or cerebrospinal fluid of people with autism. This fact also makes it likely that a link with MMR vaccination is circumstantial rather than causal.

It is clear from twin and family studies that there is a strong genetic basis for autism. The recent discovery of the genetic basis of Rett's syndrome, a phenotypically similar NDD with similarly described immunological abnormalities, may shed some light on the pathogenesis of autism. Similar epigenetic mechanisms may be operating in autism that lead to simultaneously abnormal development in the immune and central nervous systems.

The hypothesis reviewed by the committee is that vaccine-induced autism represents the end result of a combination of susceptibility (possibly genetic) to immune dysfunction or to abnormal mercury metabolism. Posited intermediate steps include enzymatic abnormalities that might be related to the apoptosis and cellular signaling, leading to an array of behavioral, cognitive, sensory, and motor disturbances. Other environmental exposures have similar effects.

Rodent models suggest that reactions to some infectious agents (e.g., bornavirus and group A streptococcus) lead to somewhat specific neuronal cell death and evidence of autoimmune reactions in the developing and adult brains of rodents. The animals also exhibit abnormal behaviors. These immunological and behavioral findings are similar to those seen in some humans after infection: the behavior in children with PANDAS or in the animal models resembles the behavior constellations in children with autism. A similar set of comparisons can be made with mercury exposures (Bernard et al., 2001), although autism has never been documented as a consequence of high-dose mercury exposure, including acrodynia. While analogies are useful for hypothesis generation, they do not substitute for direct evidence.

Other evidence offered for the vaccine-autism hypothesis includes analogies between rodent behavior and human behavior as well as clinical observations of metabolic or immunologic differences between individuals with autism and normal subjects or subjects with other conditions. In the clinical studies, it is not clear to what extent the abnormalities are antecedents or are comorbid disease expressions, rather than causal factors. That is, it is possible that some people with autism, perhaps even a subgroup that could be identified at some time in the future by genetic markers, also have abnormal immune reactions and abnormal mercury metabolism but that vaccination does not cause these abnormalities, nor do they cause autism.

The committee notes several factors that limit acceptance at this time of the hypothesis that vaccines cause autism. The evidence offered for the hypothesis includes data from *in vitro* experimental systems, analogies between rodent behavior, and human behavior and clinical observations that are at least as well explained as being comorbid disease expressions than as causal factors. That is, it

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is possible that some people with autism, perhaps even a subgroup that could eventually be identified by genetic markers, have abnormal immune reactions and abnormal mercury metabolism, but that vaccination of these individuals does not cause these abnormalities or autism itself. However, the experiments showing effects of thimerosal on biochemical pathways in cell culture systems and showing abnormalities in the immune system or metal metabolism in people with autism are provocative; the autism research community should consider the appropriate composition of the autism research portfolio with some of these new findings in mind. However, these experiments do not provide evidence of a relationship between vaccines or thimerosal and autism.

In the absence of experimental or human evidence that vaccination (either the MMR vaccine or the preservative thimerosal) affects metabolic, developmental, immune, or other physiological or molecular mechanisms that are causally related to the development of autism, the committee concludes that the hypotheses generated to date are theoretical only.

SIGNIFICANCE ASSESSMENT

Autism leads to substantial challenges for the families of affected individuals because many people with autism remain dependent throughout their lives. Special education costs can exceed $30,000 per year. The annual cost of care in a residential school may be as much as $80,000-100,000 (CDC, 1999). In addition to the substantial financial strains, families of children with autism face other demands. During the committees' public session in March 2001 and in the material submitted for the February 2004 meeting, the committee heard about the difficulties of caring for children with autism. Parents described round-the-clock efforts to care for their child, the difficulty of finding knowledgeable and sympathetic health care providers, the challenges in finding high-quality information, and the frustrations of seeing their child change from being active and engaged to being aloof and nonresponsive. Many clinicians, including several committee members, have treated children with autism and witnessed the difficulties and pain experienced by the children and their families.

Although autism is recognized as a serious condition and strides have been made in understanding the disease in many areas, significant gaps remain, particularly regarding its etiology and risk factors. These gaps include uncertainty about prevalence and incidence trends; limited knowledge of the natural history of autism, including its early onset and regressive forms; the lack of a strong biological model for autism; limited understanding of potentially associated features (e.g., immune alterations, enterocolitis); and no current basis for identifying possible subtypes of autism with different pathogeneses related to genetic and environmental interactions. Research has been hindered by changing case definitions and the heterogeneity of study populations that may include cases linked to other known medical risk factors (e.g., Fragile X).

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The hypothesis that vaccines, specifically MMR vaccine and the preservative thimerosal, cause autism is among the most contentious of issues reviewed by vaccine safety committees of the IOM. One needs to read just one of the many websites and Internet-based discussion groups on the issue of autism[5] to get a picture of the complicated lives of families with children with autism and the anger of some families toward the federal government (particularly the CDC and FDA), vaccine manufacturers, the field of epidemiology, and traditional biomedical research. The volume of correspondence to the committee on this issue is impassioned and impressive. There are, however, little data to shed light on how many families believe that vaccination actually caused their child's autism,[6] so that the magnitude of concern in the general population is uncertain. **However, the committee concludes that because autism can be such a devastating disease, any speculation that links vaccines and autism means that this is a significant issue.**

There are many examples in medicine of disorders defined by a constellation of symptoms that have multiple etiologies, and autism is likely to be among them. Determining a specific cause in the individual is impossible unless the etiology is known and there is a biological marker. Determining causality with population-based methods such as epidemiological analyses requires either a well-defined at-risk population or a large effect in the general population. Absent biomarkers, well-defined risk factors, or large effect sizes, the committee cannot rule out, based on the epidemiological evidence, the possibility that vaccines contribute to autism in some small subset or very unusual circumstances. However, there is currently no evidence to support this hypothesis either.

The committee concludes that much more research must be conducted on autism. However, research should be directed towards those lines of inquiry most supported by the current state of knowledge. The vaccine hypotheses are not currently supported by the evidence. Much remains unknown about the etiology or etiologies of autism. Furthermore, there have not been many studies on treatments for autism. Research should be directed towards better understanding the etiology or etiologies of autism and on treatments for autism.

While the committee strongly supports targeted research that focuses on better understanding the disease of autism, from a public health perspective the committee does not consider a significant investment in studies of the theoretical vaccine-autism connection to be useful at this time. The nature of the debate about vaccine safety now includes the theory by some that genetic susceptibility makes vaccinations risky for some people, which calls into question the appropriateness of a public health, or universal, vaccination strategy. However, the benefits of vaccination are proven and the hypothesis of susceptible populations is

[5]See http://health.groups.yahoo.com/group/Autism-Mercury/messages.

[6]Over three thousand families have filed claims for compensation for autism with the Vaccine Injury Compensation Program (VICP).

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presently speculative. Using an unsubstantiated hypothesis to question the safety of vaccination and the ethical behavior of those governmental agencies and scientists who advocate for vaccination could lead to widespread rejection of vaccines and inevitable increases in incidences of serious infectious diseases like measles, whooping cough, and Hib bacterial meningitis.

The committee encourages that research on autism focus more broadly on the disorders' causes of and treatments for it. Thus, **the committee recommends a public health response that fully supports an array of vaccine safety activities. In addition the committee recommends that available funding for autism research be channeled to the most promising areas.**

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. Although the hypotheses related to vaccines and autism will remain highly salient to some individuals, (parents, physicians, and researchers), this concern must be balanced against the broader benefit of the current vaccine program for all children.

RECOMMENDATIONS FOR PUBLIC HEALTH RESPONSE

Specific recommendations regarding policy review, epidemiologic research and surveillance, and communication follow. The committee also revisits and discusses many of the recommendations of its two previous reports on vaccines and autism (IOM, 2001a,b).

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 the administration of the MMR vaccine.**
- **At this time, the committee does not recommend a policy review of the current schedule and recommendations for the administration of routine childhood vaccines based on hypotheses regarding thimerosal and autism.** Currently, thimerosal has been removed from all universally recommended childhood vaccines except influenza vaccine. A thimerosal-free version of the influenza vaccine exists, however, and is available for use in infants, children, and pregnant women. There are a few vaccines with thimerosal (e.g., Td) that infants and young children[7] could be exposed to, but only under very special circumstances.

[7]Td is recommended for children 12-18, but it is conceivable that some infants and young children could receive Td in lieu of DTaP.

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• The committee also recommended in its prior report that the appropriate professional societies and government agencies review their policies on the non-vaccine biological and pharmaceutical products that contain thimerosal and are used in infants, children, and pregnant women. The committee's recommendation reflected concern about total mercury burden and potential risk of certain NDDs. While the United States chose to eliminate thimerosal from routine childhood vaccines as a precautionary measure and because it was feasible, the committee recognizes that other countries have different constraints and other factors; their own assessments of the risks and benefits may lead those countries to reach different conclusions regarding the thimerosal content of their vaccines. **Given the lack of direct evidence for a biological mechanism and the fact that all well-designed epidemiological studies provide evidence of no association between thimerosal and autism, the committee recommends that cost-benefit assessments regarding the use of thimerosal-containing versus thimerosal-free vaccines and other biological or pharmaceutical products, whether in the United States or other countries, should not include autism as a potential risk.**

Surveillance and Epidemiologic Research

• The committee reaffirms its previous recommendation to use standard and accepted case definitions and assessment protocols for ASD to enhance the precision and comparability of results from surveillance, epidemiological studies, and biological investigations. Studies should also address the heterogeneity in the etiology of ASD and the spectrum of clinical presentation.

• The committee reaffirms its previous recommendation to conduct 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 of ASD.

• Surveillance of adverse events related to vaccines is important and should be strengthened in several ways:

— The committee recommends that standardized case definitions for adverse events be adopted.

— The committee recommends that formal guidelines or criteria be developed for using VAERS data to study adverse events.

— The committee recommends the continued use of large-linked databases, active surveillance, and other tools to evaluate potential vaccine-related adverse events.

— The committee supports the development of Clinical Immunization Safety Assessment (CISA) centers to improve understanding of adverse events at the individual level.

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• Many of the epidemiological research recommendations of the committee's 2001 report on thimerosal and NDDs are either under way or have been completed. **Insofar as monitoring of ASD occurs, one area of complementary research that the committee continues to recommend is surveillance of ASD as exposure to thimerosal declines.** Any research in this area should be conducted with critical attention to case definition, diagnostic criteria, and other factors (for example, data collection procedures and definitions of autism in the special education system) that could affect prevalence estimates of ASD.

• Little is known about the levels of background exposure to mercury in the population. **The committee recommends increased efforts to quantify the level of prenatal and postnatal exposure to thimerosal and other forms of mercury in infants, children, and pregnant women.**

Clinical Studies

• The committee heard from some parents of children with ASD who have chosen to rely on chelation therapy as a treatment. The committee saw no scientific evidence, however, that chelation is an effective therapy for ASD or is even indicated in these circumstances. Chelation therapy is currently indicated only for high-dose, acute mercury poisonings. **Because chelation therapy has potentially serious risks, the committee recommends that it be used only in carefully controlled research settings with appropriate oversight by Institutional Review Boards protecting the interests of the children who participate.**

Communication

Many parents described to the committee their concerns about the MMR vaccine and thimerosal use in vaccines. Many expressed their frustration and difficulties in making informed decisions about vaccination of their children as their level of trust in the government, media, and science in general has declined. Because of the importance and difficulty of maintaining mutual trust, a model that focuses on increasing public participation in risk decisionmaking is likely to make that process more democratic and improve the relevance and quality of the technical analysis (Slovic, 1999). Such participative processes may not necessarily lead to increased acceptability of risk policies, but may lead to higher quality decision-making processes (Arvai, 2003). However, better risk-benefit communication requires attention to the needs of both the scientific and public communities. Many scientists need to develop a more comprehensive understanding of what risk-benefit communication entails and the rich knowledge base that can be used to design strategic communication programs. Appreciating that risk-benefit communication requires two-way exchanges of information and opinions (NRC,

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1989) and working from a larger frame of communication methods, scientists will be able to work more effectively with the public to address vaccine-related issues. A mix of information, dissemination, education services, and community-based dialogues are probably needed (NRC, 1989).

To address these goals, **the committee recommends developing programs to increase public participation in vaccine safety research and policy decisions and to enhance the skills and willingness of scientists and government officials to engage in constructive dialogue with the public about research findings and their implications for policy development.** Programs such as Project LEAD®, COPUS Grant Schemes, or the IOM Vaccine Safety Forum may serve as useful models. Any proposed program should be easily accessible to the public and should involve a wide range of individuals. Additionally, ways to rebuild trust between the public, scientists, professionals, media, and government should be explored.

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BOX ES-1
Committee Conclusions and Recommendations

SCIENTIFIC ASSESSMENT

Causality Conclusions

The committee concludes that the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism.

The committee concludes that the evidence favors rejection of a causal relationship between MMR vaccine and autism.

Biological Mechanisms Conclusions

In the absence of experimental or human evidence that vaccination (either the MMR vaccine or the preservative thimerosal) affects metabolic, developmental, immune, or other physiological or molecular mechanisms that are causally related to the development of autism, the committee concludes that the hypotheses generated to date are theoretical only.

SIGNIFICANCE ASSESSMENT

The committee concludes that because autism can be such a devastating disease, any speculation that links vaccines and autism means that this is a significant issue.

PUBLIC HEALTH RESPONSE RECOMMENDATIONS

The committee recommends a public health response that fully supports an array of vaccine safety activities. In addition the committee recommends that available funding for autism research be channeled to the most promising areas.

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 the administration of the MMR vaccine.

At this time, the committee does not recommend a policy review of the current schedule and recommendations for the administration of routine childhood vaccines based on hypotheses regarding thimerosal and autism.

Given the lack of direct evidence for a biological mechanism and the fact that all well-designed epidemiological studies provide evidence of no association between thimerosal and autism, the committee recommends that cost-benefit assessments regarding the use of thimerosal-containing versus thimerosal-free vaccines and other biological or pharmaceutical products, whether in the United States or other countries, should not include autism as a potential risk.

Surveillance and Epidemiologic Research

The committee reaffirms its previous recommendation to use standard and accepted case definitions and assessment protocols for ASD to enhance the pre-

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