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 diagnosis 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 observed 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 passive 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 communications 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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