Measles-Mumps-Rubella Vaccine and Autistic Spectrum Disorder: Report From the New Challenges in Childhood Immunizations Conference Convened in Oak Brook, Illinois, June 12–13, 2000

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ABSTRACT. *Background.* **Parents and physicians are understandably concerned about the causes and treatment of autism, a devastating disease that affects the entire family. Although much has been learned about autism, there are many gaps in our knowledge about what causes the disorder and how it can be prevented. Autistic symptoms occur along a spectrum, often referred to as autistic spectrum disorder (ASD). Concern has been raised about a possible association between measles-mumps-rubella (MMR) vaccine and inflammatory bowel disease (IBD) and ASD, especially autism with regression. Also, increased requests for educational services related to ASD have raised concerns about possible increases in the incidence of ASD.**

Methods. **On June 12–13, 2000, the American Academy of Pediatrics (AAP) convened a conference titled "New Challenges in Childhood Immunizations" in Oak Brook, Illinois. At this conference, parents, practitioners, and scientists presented information and research on MMR vaccine and ASD. Attendees included representatives from select AAP committees and sections as well as federal and other organizations that address related issues. The multidisciplinary panel of experts reviewed data on what is known about the pathogenesis, epidemiology, and genetics of ASD and the available data on hypothesized associations with IBD, measles, and MMR vaccine. Supplemental information was requested from authors who have proposed the hypotheses and other experts in relevant areas.**

Results. **Autism is a complex disorder of uncertain and probably multiple etiologies. Genetic predisposition to ASD may involve as many as 10 genes. Many experts believe that the abnormal brain development in autism occurs before 30 weeks' gestation in most instances. In utero rubella is a known cause of autism. Animal model data support the biologic plausibility that exposure to yet unrecognized infectious or other environmental agents could cause ASD.**

Several factors may contribute to apparent increases in incidence of ASD in recent years. Most data indicate increased recognition and reporting as primary factors, but the epidemiologic data are insufficient to determine if there has been a true increase in the incidence of ASD. Increased reporting of ASD in recent years has occurred long after the introduction of MMR vaccine in the United States in 1971 and widespread use of this vaccine in the 1970s for routine immunization of children at 12 to 15 months of age. Appropriate detailed studies are needed to define the true incidence and prevalence of ASD. Epidemiologic studies in Europe indicate no association between MMR vaccine and ASD.

Some children with ASD have gastrointestinal symptoms, but an increased rate of any specific gastrointestinal disorder in children with ASD has not been established. Studies to detect evidence of measles virus in intestinal tissue specimens from patients with IBD or autism with gastrointestinal symptoms have not used uniform techniques. Several laboratories have found no evidence of measles viruses in tissue specimens from patients with IBD, but 2 groups have found evidence of measles virus using different techniques. A group that found evidence of measles virus in affected tissue specimens from patients with IBD has also reported detecting portions of measles virus in peripheral blood lymphocytes and intestinal tissue specimens from patients with autism and gastrointestinal disorders. Finding a portion of a virus using molecular techniques does not constitute evidence for a causal relationship, because some viruses persist in unaffected hosts. Additional controlled studies in several laboratories are needed to determine if portions of measles virus persist in intestinal and other tissues of people with and without gastrointestinal disease and/or ASD.

Conclusions. **Although the possible association with MMR vaccine has received much public and political attention and there are many who have derived their own conclusions based on personal experiences, the available evidence does not support the hypothesis that MMR vaccine causes autism or associated disorders or IBD. Separate administration of measles, mumps, and rubella vaccines to children provides no benefit over administration of the combination MMR vaccine and would result in delayed or missed immunizations. Pediatricians need to work with families to ensure that children are protected early in the second year of life from these preventable diseases. Continued scientific efforts need to be directed to the identification of the causes of ASD.**
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ABBREVIATIONS. ASD, autistic spectrum disorder; AAP, American Academy of Pediatrics; MMR, measles-mumps-rubella vaccine; PDD, pervasive developmental disorder; *DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition;* IBD, inflammatory bowel disease; CDC, Centers for Disease Control and Prevention; *DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revision;* MHC, major histocompatibility complex; CNS, central nervous system; SSPE, subacute sclerosing panencephalitis; HIV, human immunodeficiency virus; CSF, cerebrospinal fluid; PCR, polymerase chain reaction; PBMC, peripheral blood mononuclear cell; RT-PCR, reverse-transcriptase PCR.

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PURPOSE

Parents and physicians are understandably concerned about the causes and treatment of autism, a devastating disease that affects the entire family. Although much has been learned about autism, there are many gaps in our knowledge about what causes the disorder and how it can be prevented. Autistic symptoms occur along a spectrum, often referred to as autistic spectrum disorder (ASD).

The American Academy of Pediatrics (AAP) convened a multidisciplinary panel of experts to review evidence regarding possible associations between measles-mumps-rubella (MMR) vaccine and ASD. The questions raised by families of affected children, other concerned parents, and health care professionals indicated the need for a detailed scientific review of the evidence. The primary goal for this technical review panel was to address the question: Does the available evidence support a causal relationship between MMR vaccine and the pathogenesis of ASD?

Although hypotheses have been generated relating ASD to other vaccines, this report will concentrate solely on MMR vaccine. The term ASD is used throughout this document as a synonym for pervasive developmental disorders (PDDs), which are a continuum of disorders with symptoms related to social reciprocity, communication, and restricted interests, according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*.[1]

PROCESS

A panel was recruited to include experts in the areas of general pediatrics, developmental pediatrics, child neurology, pediatric infectious diseases, virology, pathology, public health, epidemiology, and psychiatry. A meeting was held June 12–13, 2000 in Oak Brook, Illinois, to review background information and recent studies to provide a common body of information to the panel. Information was presented on the genetics, epidemiology, and neurobiology of ASD; the known neurologic effects of measles, mumps, and rubella infections and vaccines; and the efforts to identify measles virus in intestinal tissue specimens from patients with autism (see agenda and list of speakers). Related information regarding a possible relationship of measles virus and/or vaccine and inflammatory bowel disease (IBD) was also examined. The standard scientific methods used to establish causality were reviewed. Authors whose work had bearing on a potential association between MMR vaccine and ASD were invited to present their data and opinions. Invited speakers who declined the invitation were asked to submit materials that formed the basis for their opinions. The panel reviewed the videotaped testimony of Andrew J. Wakefield, MD, and John O'Leary, MD, before the House Government Reform Committee on April 6, 2000, and written materials provided by Wakefield.

After the meeting, further information was requested from the speakers and other experts in specific areas relating to MMR vaccine and ASD. The panel reviewed and analyzed the available literature over the subsequent 6 months. The writing panel reviewed more than 1000 references in the medical literature. Because space limitations do not permit inclusion of all references, we have attempted to include key references to findings from different groups of investigators, especially when conflicting or inconsistent findings were obtained. During the past few years, there has been a proliferation of letters, editorials, and other expressions of opinion on the subjects covered here. There has been no attempt to include all such opinions. Many organizations, including The British Medical Research Council, the World Health Organization, and the American Medical Association, have concluded that there is no evidence of causal associations between measles or MMR vaccines and IBD or autism.[2–4] These reviews referenced primarily epidemiologic and a limited number of laboratory studies. The AAP technical panel elected to undertake a more comprehensive review of the biology of ASD and possible associations with IBD, measles, and measles virus-containing vaccines.

The hypothesis relating MMR immunization and the onset of symptoms of ASD is largely based on the work of Wakefield et al[5,6] Wakefield provided the following summary of his hypotheses in response to a request for clarification (A. J. Wakefield, MD, personal communication, September 20, 2000):

1. "Atypical patterns of exposure to measles virus, including a close temporal association with another infection, are a risk factor for chronic intestinal inflammation."
2. "There are factors, such as age, sex, and nature of concurrent exposure(s), that influence the phenotype of the intestinal pathology that develops (ie, Crohn's disease, ulcerative colitis, or autistic enterocolitis)."
3. "In children with autistic enterocolitis, persistent measles virus infection of the ileal lymphoid tissue causes chronic immune mediated pathology in the intestines."
4. "Associated changes in intestinal permeability and altered peptidase activity allow neurotoxic intestinal products (eg, exorphins) to reach the brain, which is particularly susceptible to permanent damage during times of rapid cerebral development such as infancy."
5. "In susceptible children (possibly for reasons of age, immune status, or genetic background) MMR vaccine is an atypical pattern of measles exposure that represents a significantly increased risk for intestinal infection and associated developmental regression compared with the monovalent vaccine, or natural infection."
6. "Accordingly, the widespread use of MMR immunization is a major determinant of the apparent (now substantiated) increase in rates of autism."

Wakefield and Montgomery[7] have advocated for the administration of monovalent measles, mumps, and rubella vaccines instead of the combination MMR vaccine, because they believe that simultaneous administration might lead to persistent infec-

tion or alteration of the clinical and immune response to the antigens. Additional hypotheses were offered by participants in the conference regarding other mechanisms by which MMR immunization might be related to ASD.

Yazbak[8] has hypothesized that maternal immunization with MMR before, during, or after pregnancy predisposes the child to autism. Megson[9] proposed the following:

1. Genetically at-risk children may be predisposed to autism by a G-alpha protein defect.
2. Live measles vaccine depletes body stores of vitamin A, resulting in metabolic and immunologic changes and precipitating behavior changes in children with ASD.
3. Supplementation with natural forms of vitamin A improves symptoms of ASD.

The AAP technical review panel examined the literature relevant to the above hypotheses, including the neurobiology of autism and the clinical effects and pathophysiology of measles, mumps, and rubella and vaccines.

ASSESSING CAUSALITY: REVIEW OF CRITERIA

The review of scientific literature was structured to address the question: Could MMR immunization be a cause of ASD? Identification of causal relationships often starts with personal observations. The criteria used to determine if the relationship between events are coincidental, causal, or have an interaction of another nature were initially defined in the 1960s.[10] These criteria have been revised several times, and most experts now agree on the use of the following 9 criteria to assess causality[11]:

1. **Strength of Association**. In general, the stronger the association, the lower the likelihood that the results are attributable to chance. Care must be taken to avoid selection and other biases when studying associations. Where there is a strong association and the suspect factor frequently results in the disease, small studies usually can reveal a causal association. When there is a weak association, there may be contributing factors other than the exposure in question that account for the association. In addition, with weaker associations, there is a greater likelihood that the relationship occurs by chance, so larger studies are needed to differentiate chance from causal associations.
2. **Consistency**. Finding the same results in studies conducted in different populations by different investigators provides strong evidence for or against causal association.
3. **Specificity**. Finding a single adverse event associated with the factor in question provides more suggestive evidence of a causal association than if multiple unrelated events are found. However, some factors can cause multiple adverse events.
4. **Temporality**. A causal association is more strongly suggested if the adverse events are clustered in time after the exposure than if the events are distributed over a longer and more varied time interval.
5. **Biologic gradient**. The presence of a dose-response effect of a drug or toxin provides increased evidence of a causal association.
6. **Plausibility**. If the adverse event is consistent with known biologic effects of the factor in question (or related factors), the evidence of a causal association is strengthened. The absence of a biologically plausible explanation does not rule out the possibility that the factor has caused a new disorder for which biologic mechanisms have not yet been determined.
7. **Coherence**. The evidence should fit together into a reasonable explanation for the observed association between the factor and the event.
8. **Experimental evidence**. Intervention studies that test a hypothesis can provide evidence for or against a causal association. For example, if removing exposure to the factor is followed by a reduction in disease, this provides supportive evidence that the factor may have caused the disease.
9. **Analogy**. It is often easy to draw on experience in other biologic systems to speculate regarding possible associations with human disease. Analogy is a weak criterion because of differences among species, differential responses to external stimuli, and confounding factors.

AUTISM: REVIEW OF CURRENT UNDERSTANDING

The behavioral characteristics and neurobiology of ASD were reviewed to provide a context for the hypotheses that have been generated associating MMR vaccine and autism. Issues related to diagnostic reliability, the nature of reported regression, and what is known about underlying brain abnormalities in autism are relevant to the process of assessing the quality of ASD studies.

What is ASD?

Defining autism and ASD is critical to the interpretation of epidemiologic and biologic data. In this report, the term ASD includes autism, Asperger syndrome, childhood disintegrative disorder, and related PDDs *(DSM-IV)*.[1] ASD is used synonymously with the term PDD as described in the *DSM-IV*. Specific studies that refer to one particular subset of the spectrum of diagnoses will be described as such. Because the symptoms of Rett syndrome are discrete and constitute a homogeneous neurologic disorder currently classified as a PDD, patients with this diagnosis are not typically included in research examining the heterogeneous group described as having ASD. Some studies reviewed for this document did not apply current diagnostic methods and may have inadvertently included some patients with Rett syndrome in their analyses.

ASD is a complex developmental disorder that is behaviorally defined. Guidelines for the assessment of children with ASD have been developed by a consortium of professional organizations including the Academy.[12] Behaviors that characterize the disorder include *qualitative* deficits in social interaction, communication, and restricted, repetitive, and stereotyped patterns of behaviors, activities, and interests.

- *Impairment in social interaction* may range from social isolation to inappropriate social behavior. Symptoms may include gaze avoidance, inattention when called, failure to participate in peer group activities, indifference to others, and diminished empathy.
- *Impairment in communication* may include the verbal and nonverbal ability to share information with others. Language deficits may range from a seeming absence of receptive or expressive language to fluent speech with or without characteristic echoing, pronoun reversals, or abnormal melody (singsong prosody, monotonous tone, or abnormal modulation of volume). The ability to initiate and maintain a conversation may be affected.
- *Repetitive and stereotyped patterns of behavior* may be attributable to the inability to predict what will happen in the environment by social or linguistic cues. Insistence on nonfunctional routines, attachments to unusual objects, fascination with parts of objects, repetitive movements, and preoccupations are common characteristics.

The range of symptoms described reflects a *behavioral phenotype* that exists as a spectrum of symptoms modified by language and cognitive ability, among other factors.

Are there subtypes of ASD?

Although the clinical presentation is heterogeneous, ASD is divided into subtypes in an attempt to identify homogenous groups for research purposes and to allow for appropriate service development (Table 1).[13] Subgroups could be defined by clustering of behavioral or biologic characteristics to test specific hypotheses. The heterogeneity of ASD may be attributable to different etiologies or to a combination of factors, including genetic predisposition, teratogenic and environmental exposures, and cognitive ability, among others. At present, there is no biologic marker to diagnose autism. Appropriate diagnosis of ASD is made on the basis of history and observation of behavior.[14]

How is the diagnosis of ASD made?

Clinical research requires objective and reliable diagnoses. In clinical practice, history and observation can be augmented by several screening tools (eg, Childhood Autism Rating Scale, Pervasive Developmental Disorder Screening Test, Checklist for Autism in Toddlers).[12] The Autism Diagnostic Interview-Revised and Autism Diagnostic Observation Schedule are reliable and valid instruments that are used to characterize patients for research studies.[15] Most epidemiologic and clinical studies investigating an association of MMR vaccine and autism did not confirm the diagnoses of autism or ASD using these measures, which are now standard for research in the field.

TABLE 1. Subgroups for PDDs[1]

Autism	At least 6 symptoms from the areas of communication, social reciprocity, and a restricted repertoire of activities
Asperger syndrome	Early language intact, IQ in typical range
Rett syndrome	Loss of skills, hand wringing, female sex
Childhood disintegrative disorder	Typical early development, loss of skills after 2 years of age
PDD—not otherwise specified	Does not meet diagnostic criteria for another PDD but has clinically significant symptomatology in the areas of communication and social reciprocity and a restricted repertoire of activities

What is the meaning of "regression" in ASD?

Assessing the hypothesis that MMR immunization leads to regression in children with ASD requires careful consideration of the phenomenon of regression in autism. There is no standard definition of what is meant by regression. When regression is reported, parents recall the loss of a few words or phrases acutely or over a period of time. Sometimes, the loss of language is accompanied by decreased social play or increased irritability. When milestones are examined closely, it may be difficult to determine if development was typical before the reported regression.[16] Studies of family videotapes made before the report of symptoms of regression or autism often reveal evidence of preexisting atypical development.[17,18] The age of recognition and age of onset of symptoms may not be the same, making the specific dating of events by parental recall more difficult.[19]

Approximately one third (29%–39%) of children with autism are reported to lose language or social skills during the second year of life.[16,20–22] In studies that reported a history of regression in children referred for assessments, the proportion has remained stable (37.2% in 1985; 39% in 1991; 30% in 1997; 29.6% in 1998).[16,20–22] Atypical development is identified in three quarters of children with autism before 2 years of age and in almost all children with autism by 3 years of age.[23] Tuchman and Rapin[16] found that parents of children seen by developmental specialists for the first time before 3 years of age reported regression more often than parents of children seen for the first time in later childhood (40% vs 28%). Sixty-four percent of parents who reported regression said that it occurred during the second year of life. Early concerns about regression in some children might have been dismissed as developmental variation or may not be recalled by parents of older children.

Various terms have been used to describe language and behavioral regression in children with autism, including autistic regression, setback-type autism, and acquired autistic syndrome. Childhood disintegrative disorder is described in *DSM-IV* as ASD characterized by typical development followed by language and cognitive regression after 2 years of age. Whether childhood disintegrative disorder is distinct from autistic regression is not known.[18] Significant cognitive limitation is more likely to occur in cases where there has been regression than in those without regression,[19,24,25] although this may not be true if regression occurs before 2 years of age.[16]

Summary

The loss of milestones during the second year of life is a terrifying realization for families of young

children with ASD and should not be dismissed as developmental variation. Observations of apparent regression in milestones indicate the need to carefully and thoroughly obtain a developmental history that examines social, language, and other behaviors and to corroborate with other health care providers and obtain previous records, if available. Evidence from multiple centers indicates that regression does occur in approximately one third of children with autism. Understanding the pathogenesis of this phenomenon is an important part of understanding the neurobiology of autism and warrants additional research (see "**RESEARCH NEEDED**").

What factors could contribute to changes in the incidence or prevalence of ASD?

Epidemiologic studies conducted to date have usually measured the prevalence of autism and ASD (ie, the extent of a problem across a population at a particular point in time). Knowledge of incidence is desirable for assessing etiology,[26] but incidence studies would require identification of a definite time of onset in a defined population at risk. Prevalence data can be used to estimate incidence in some circumstances. Changes in measurements of prevalence can occur as a result of many factors, including:

1. Substantial migration of affected children into or out of a community (eg, if families moved to certain areas because of improved treatment options);
2. Change in age of onset or recognition (diagnosis) over time (eg, an apparent increase in incidence and prevalence would be noted if new techniques resulted in diagnosis at younger ages);
3. Large changes in the denominator population (eg, influx of large numbers of unaffected children would appear to decrease prevalence in a population study);
4. Increased ascertainment of children with diagnoses of autism or ASD;
5. A change in the diagnostic criteria to include individuals with milder symptoms or different combinations of symptoms; and
6. A true increase in the incidence of the disorder, which could be attributable to new environmental exposures (eg, environmental chemicals or infectious agents).

What is known about the incidence and prevalence of ASD?

There are very few good population studies of prevalence or incidence of ASD. In a review of 23 epidemiologic studies of ASD using varied methods, Fombonne[27] noted that the median prevalence rate of autism in studies conducted from 1989 to 1998 was 7.2 per 10 000, compared with 4.3 per 10 000 for studies between 1966 and 1988. Fombonne attributed the apparent increase to changes in definitions and improved recognition of autism. When ASD is included, the minimum estimate of prevalence was 18.7 per 10 000. Wing and Gould[28] reported a prevalence rate of 20 per 10 000 in 1979 when ASD, rather than autism, was considered.

Studies to determine prevalence of autism and ASD are very susceptible to bias from differing methods of case ascertainment. More thorough studies use a tiered program in which all children in the defined population are screened for possible autism using standard and sensitive screening methods. If results of the screening are positive, children are referred for an in-depth psychodevelopmental evaluation.[29] Recent studies in Japan and Sweden that used this approach showed a rate for autism and ASD combined of 21 to 31 per 10 000 children.[30,31] Honda et al[30] attributed the increased prevalence to better ascertainment of children with typical cognitive abilities. A recent Swedish study was based on complete ascertainment in a small, regionally defined population.[32] The population prevalence of autism was 60 per 10 000 (95% confidence interval: 19–141 per 10 000); inclusion of Asperger syndrome and autistic-like condition (PDD-not otherwise specified) increased the prevalence to 121 per 10 000 (95% confidence interval: 58–225 per 10 000). A study from the United Kingdom using a tiered approach revealed a provisional rate of 31 per 10 000 children for autistic disorder and 58 per 10 000 children for ASD.[33] The only North American population-based study examined the prevalence of autism in Nova Scotia. All 20 800 children 6 to 14 years of age enrolled in school were screened using a 19-item questionnaire, and the 46 children reported to have symptoms were diagnostically assessed.[34] Twenty-one children met criteria for autism, for a prevalence of at least 10 per 10 000. Seventy-five percent of affected children had cognitive limitation. The Centers for Disease Control and Prevention (CDC) is currently examining prevalence in metropolitan Atlanta using a method of case ascertainment by school record abstraction and multiple source sampling. Because this does not include additional assessments after screening existing records for the school-aged population, it will not represent total community ascertainment. Higher-achieving students and students with comorbid handicapping conditions may not be identified using this method. Preliminary data released from an ongoing surveillance study suggests a prevalence of 20 to 30 per 10 000 for ASD.[35]

Recently, the CDC conducted an epidemiologic study of autism in Brick Township, New Jersey. The study was initiated in response to a request from the community about suspected higher rates of autism related to environmental exposures.[36] Cases were identified from multiple sources, including medical, educational, social, and psychologic services, and then carefully reviewed for specific clinical diagnoses based on *DSM-IV* criteria. In this small community of 9000 children 3 to 10 years of age, 75 were children identified as possibly having autism. Of these, 60 met *DSM-IV* criteria for autistic disorders. Of the 60 who met criteria, 36 were classified as having autism, for a prevalence 40 per 10 000 (95% confidence interval: 28–56 per 10 000). With inclusion of ASD, a prevalence of 67 per 10 000 was identified. Prevalence was similar for age groups 3 to 5 and 6 to 10 years. Seventy-three percent of the children with autism were boys. Ten of the 43 children with autism were reported to have had loss of ac-

quired skills before the diagnosis of autism. The use of clinical services in Brick Township for treatment of children with autism and related disorders was similar to the use in surrounding communities in New Jersey, suggesting the prevalence is not an aberration. This study did not include evaluation of children who were considered to have typical development or who were not referred; thus, it is likely that children with ASD who had less severe symptoms and average cognitive abilities and children who may have had other developmental disorders in addition to ASD were not included. The prevalence of ASD is probably higher than detected. The prevalence reported in Brick Township is higher than that in other studies noted previously that started with population screening. This study was not designed to assess a change in rate of the diagnosis of ASD over time. The preliminary report did not discuss the stability of the population or whether some of the high prevalence rates might be attributable to families moving to the region to access educational services for children with special needs.

The Brick Township investigation, like other recent studies finding higher rates of ASD, used intensive case ascertainment methods. In Brick Township, the relatively small size of the target population; the heightened awareness of parents, teachers, and clinicians; and the full cooperation of service providers allowed for thorough case ascertainment. Because a population screening method was not used, the prevalence may be an underestimate.

What are some possible reasons for increased rates of diagnosis of autism?

Several factors may contribute to the increased rate of diagnosing autism. Because publication of the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revision* (*DSM-III-R)* in 1983,[37] there has been an increased appreciation of the broad range of severity of autism-like disorders, allowing for a diagnosis of autism as well as ASD. With the introduction of *DSM-IV* in 1994, the diagnosis became more developmentally defined, and lower and higher functioning individuals could fulfill diagnostic criteria. Information on autism and ASD has increased greatly in the professional and lay literature, potentially increasing parental concerns and community demand for diagnostic services. Moreover, the availability of diagnostic services, treatment facilities, and professionals trained in child developmental disorders has greatly increased, resulting in an increased capacity of the health care system to evaluate children and make a diagnosis of autism or ASD. Increased capacity has occurred in the United States with the evolution of the Early Intervention Programs over the past 2 decades to provide educational and therapeutic services to children younger than 3 years of age at risk for developmental disabilities. Increased availability of effective educational programs for young children with autism is in large part attributable to advocacy by families. Reports that symptoms of autism may be greatly ameliorated by educational intervention have led to controversy,[38] including a push for earlier identification and treatment of affected children.[39] Also, greater public understanding that autism is not caused by inappropriate parenting has resulted in destigmatization and greater acceptance of applying the diagnosis of autism or ASD to affected children. The guidelines for assessment of children with autism prepared by a consortium of professional organizations concluded that increased awareness of the disorder and available treatments and the liberalization of diagnostic criteria are major factors contributing to an increased rate of diagnosis.[12,14]

A study by the California Department of Developmental Services revealed a marked increase in the number of patients with ASD receiving services in recent years.[40,41] The report clearly states that it is not a prevalence study of ASDs but a count by birth year of patients receiving services. With increasing recognition of ASD by health care professionals, use of a broader definition that includes milder cases, and identification of children with ASD at younger ages, a substantial increase in identified cases of autism by year of birth is expected. More children born recently are more likely to be receiving services than earlier born children or adults. Consistent with this reasoning, the California State Health Department notes that more children with recently diagnosed autism do not have mental retardation, compared with children in their program during previous years. Moreover, the California State Health Department also notes that ASD is being diagnosed in children at an earlier age. Additional data are required to interpret the California report, including the number of older children and adults with ASD who do not currently receive services, information about the migration of families of persons with ASD in California, and documentation of general population growth in the state.

Summary

Epidemiologic studies that use current diagnostic criteria and case ascertainment methods have reported higher prevalence rates than rates reported between 1966 and 1988. Several factors could have contributed to an apparent increased prevalence of autism in recent years. Existing data are insufficient to determine if there has been a true increase in incidence or whether some cases of autism might be related to environmental exposure. Much of the reported increase in prevalence of autism and related disorders is probably attributable to increased detection and changes in diagnostic criteria. Additional well-controlled studies are needed to evaluate the incidence and prevalence of the disorder and possible effects of environmental factors predisposing to ASD, including environmental interactions in genetically predisposed individuals.

Is the onset of autism temporally related to receipt of measles or MMR vaccines?

If measles or MMR vaccines were associated with an increased risk of ASD in the weeks or months after immunization, a temporal clustering in the time of onset after immunization should be identifiable. If such a temporal relationship was identified, there could be several possible explanations. First, the vaccine could unmask latent ASD in children who are predestined to develop autism. Second, vaccine

could cause ASD. Third, immunization could be an epiphenomenon, an event that occurs during the same time period as some other event that affects the outcome. Critical issues in evaluating possible temporal associations include determining whether or not there is clustering in time of onset after immunization and determining the "incubation period" between immunization and clinical onset of ASD.[42]

When regression occurs in ASD, recent events, such as immunization, physical injury, or an environmental exposure, are often assumed to be the cause of the observed behavioral changes. Because regression is often noted during the second year of life, which is around the time MMR vaccine is administered, parents and medical professionals may first recognize symptoms of autism at varying time periods after immunization, even if there was no causal association.

In 8 of 12 children with ASD evaluated for gastrointestinal symptoms by Wakefield et al,[5] parents or physicians linked MMR with the onset of behavioral symptoms. One patient had delays noted before MMR immunization, although subsequent regression was also reported. The developmental history was corroborated with medical records. The means of determining previous typical development was not reported. The authors noted that the first symptom was recalled from 1 to 14 days after MMR immunization in the 8 children. The authors further noted that the study did not prove a causal link between MMR immunization and behavioral and gastrointestinal symptoms.

A detailed study in the United Kingdom using the case-series method revealed no temporal relationship between MMR immunization and development of autism.[42] This study found no clustering of cases of developmental regression in the 2- to 4-month period after MMR immunization, no temporal association between ASD and MMR vaccine (over a 6-month interval), and no increase in the rate of reported ASD associated with the introduction of MMR vaccine. The appropriateness of using the case series method for detecting associations between vaccines and chronic diseases, which often have variable times of onset after exposure, was questioned by Roger.[43] However, Roger agreed that the data from the study by Taylor et al[42] indicate that if MMR vaccine were to trigger the onset of autism, it would be a rare event. Taylor et al based the time interval of study on the historical information in the original report of an association that suggested an interval of 24 hours to 2 months between MMR immunization and onset of behavioral symptoms.[5,44] Additional analyses using longer intervals after MMR immunization revealed no temporal associations. The increased rate of reporting of ASD was not affected by the introduction of MMR vaccine in the United Kingdom. A report using data from the United Kingdom general practice research database found a nearly fourfold increase in the incidence of autism among 2- to 5-year-old boys born between 1988 and 1993. The prevalence of MMR immunization rates during the same time period remained constant (95%).[45]

The California Department of Health has shown that the increase in reports of children receiving services for ASD occurred in the late 1980s and 1990s, long after the MMR vaccine was introduced.[46] From 1980 to 1987, there were only small increases in the percentage of children who had received MMR by 24 months of age. However, there was an almost sixfold increase in the number of children for whom services were requested for autism or PDD. Thus, the evidence from Europe and the United States do not support an association between introduction of MMR vaccine and increased reporting of autism. The lack of population-based data regarding a change in the incidence or prevalence of ASD with regression does not permit evaluation of whether children with ASD are more likely to have regression than in the past.

Summary

The current epidemiologic data do not support the hypothesis that MMR vaccine is associated with an increased risk of autism.

Is there a genetic predisposition to ASD?

The scientific literature supports a genetic predisposition to ASD. As many as 10 genes may interact to cause the disorder.[47] Once a family has 1 child with autism, the risk of autism in subsequent siblings is 3% to 7%, which is 50 times greater than the risk in families without an affected child.[10] When a dizygotic (fraternal) twin has autism, the risk of the twin to also have autism is no greater than the risk of another sibling.[48] For monozygotic (identical) twins, the risk that the other twin will be affected is at least 60%.[47] If symptoms of autism that do not meet criteria for formal diagnosis are included, the risk that the second twin will be affected is more than 90%. The inheritance pattern for autism and ASD is complex, but it definitely indicates that genetic mechanisms play a causal role. Specific polymorphisms of an early developmental gene, *HOXA*1, have been associated with ASD,[49] suggesting that genetic regulation of early brain development is involved in at least some cases. Another important genetic discovery is the association of a mutation of the MeCP2 gene with Rett syndrome, a disorder with many features of ASD in which almost all patients have a period of regression during the second year of life. This gene regulates the function of other genes that may affect prenatal and postnatal development.[50] Linkage studies in families with more than 1 member with an ASD have also identified possible genetic loci on chromosomes 15q11–15q13 and 7q.[12,47]

Symptoms of ASD occur in children affected by other disorders that have known genetic etiologies,[49] including tuberous sclerosis[52] and fragile X syndrome.[53] Some genetic disorders, like Down syndrome, are less commonly associated with ASD. Studying known genetic disorders that also manifest symptoms of ASD may aid in understanding the genetic mechanisms that cause ASD.

In addition, ASD may be associated with the interaction between environmental factors or insults and a genetic predisposition. Many factors have been proposed, including infection, aberrant immune response, and exposure to teratogens at critical periods of neurologic development.[54] Maternal ingestion of

thalidomide resulted in a dramatic increase in risk of ASD if exposure occurred in a discrete time period during the first month of gestation.[55] Knowledge of this timing led to the identification of the relationship between autism and the *HOXA1* gene, which participates in the regulation of brainstem development at this stage of gestation. Heritable metabolic disorders, such as untreated phenylketonuria, can result in symptoms of ASD.[56] Genetic differences in the major histocompatibility complex (MHC) genes might be responsible for immunologic differences that have been reported to be associated with ASD.[57,58] The reported increased frequency of the null allele of the locus for complement 4B, which is located in the MHC gene, might be associated with an aberrant immune response in people with ASD.[57] The original report of linkage in this region was not found in a study of another population.[29] The linkage related to the MHC gene may be different in families with multiple affected members and deserves further study.

Summary

ASD and its symptoms are probably caused by several factors, including complex genetic mechanisms and interaction with environmental factors or insults. The effects of environmental factors may be dependent on the timing of the exposure relative to neurologic development and gene expression.[59]

Do structural changes in localized areas of the brain in individuals with ASD suggest timing of the insult?

Brain development begins during the first month of gestation and continues through postnatal life. Examining brains from people with ASD should be helpful in identifying when etiologic events might have occurred in the context of current understanding of brain development. This is a complex proposition, however, because fewer than 36 brains have been examined. Most of the brains examined were from young adults; none were from children younger than 5 years. Implying etiology from structural findings is complicated by the dependence of later developing areas of the nervous system on the integrity of regions that formed earlier. Although there is much heterogeneity in reports to date, the most frequently identified findings were increased brain size[60–62] and decreased numbers of Purkinje cells in the cerebellum.[60,61,63–66] Other findings of prenatal origin found in some cases included disruption of the cells of the inferior olive,[60] small and tightly packed cells in the amygdala and hippocampus,[61] disruption of the cingulate gyrus,[64] abnormalities in migration of cells in the cortex,[60] and hypoplasia of cranial nerve nuclei.[67] The following anatomic findings have been corroborated in a larger number of patients in neuroimaging studies but are not uniform findings in individuals with ASD: increased head size,[66,68] hypoplasia of the cerebellar vermis,[69] and decreased volume of the amygdala.[70] Nonspecific findings have included ventricular and temporal lobe asymmetry.[12,14] As with anatomic findings, imaging results reflect the heterogeneity of the disorder. Advances in imaging technology should permit greater understanding of the underlying anatomic structure.

On the basis of anatomic findings, many experts believe that the abnormal brain development seen in these cases of ASD occurred before 30 weeks' gestation. On the basis of relatively well-preserved cerebellar architecture found in some cases, Bailey et al[60] raised the possibility that postnatal events may result in cell loss; however, this remains an area of controversy. Bailey et al[60] also proposed that seizures and head injuries were potential causes of glial response in the young adults they studied. No report of inflammation or conventional histologic evidence of response to infection or autoimmune phenomenon or demyelination is reported.

Summary

Anatomic differences in size and structure of several areas of the brain have been observed in persons with ASD, compared with those without ASD, but no single pattern is common to all individuals with ASD. Most findings suggest that atypical brain development occurs prenatally.

Are there underlying immunologic differences in children with ASD compared with unaffected children?

The presence of underlying immunologic abnormalities could contribute to increased rates of complications from viral infections or live-virus vaccines. Chronic ear infections, congestion, loose stools, and cutaneous candidal rash have been suggested as evidence of immunologic compromise in children with ASD. However, clinically significant immune compromise with increased frequency or severity of infections in children with ASD, compared with unaffected children, has not been documented.

Studies of immunologic function in children with autism reveal a wide array of findings, including decreased cellular immune function,[71–73] decreased plasma complement component C4b,[74] and increased antibody and autoantibody responses.[75] Compared with unaffected children, a relative decrease in Th1 (cell-mediated) and an increase in Th2 (humoral) immune responses have been reported in children with ASD.[76–78] These findings were not confirmed in all reports.[79] Decreased natural killer cell activity and increased levels of serum immunoglobulin E have been observed.[80,81] The finding of increased autoantibody production in children with ASD in several studies and increased rates of family histories of autoimmune disorders suggests the possibility that ASD may be a result of an autoimmune process, but conclusive data have not been demonstrated.[82–86]

Differences in mean values of immunologic parameters for children with ASD compared with other children have often been small and have not been consistently outside the range of normal values for the entire population.[86] Limited conclusions may be drawn from studies based on small, heterogeneous populations. Factors that could affect the measurement of immune function, such as time of blood collection, serum or plasma versus intracellular sources of cytokines, medications, age, recent or concurrent infections, immunizations, infectious disease

history, or family history of immune disorders, have not been addressed in the analyses.

Summary

Small differences in mean values for a variety of immunologic parameters in children with ASD have been documented, but the values are generally within normal range. The clinical relevance of these findings is unclear but could reflect genetic differences or an altered immune response to certain infections. Better definition of the clinical and laboratory nature of the immune function in well-described populations of individuals with ASD, compared with appropriate controls, is needed.

Are gastrointestinal symptoms associated with ASD?

Although comments have appeared in the medical and lay literature indicating that children with ASD commonly have symptoms related to the gastrointestinal tract,[87] no studies to date have investigated gastrointestinal symptoms in children with ASD on a population basis. Food refusal, cravings, and selectivity have long been recognized as common challenging behaviors in people with ASD.[88] Certain gastrointestinal disorders, such as gastroesophageal reflux, occur more frequently in children with developmental delays than in children with typical cognitive and motor development. A selected group of children with ASD referred to a gastroenterologist for assessment were found to have a rate of reflux higher than the expected rate in the general population.[89] Results of this study do not allow generalization to all children with ASD, and no conclusions regarding a general association between reflux and ASD can be made.

The enteric nervous system, the innervation and signaling mechanism for gut function, involves a complex system of peripheral and central components.[90] Neurotransmitters thought to be involved in ASD in the central nervous system (CNS), such as serotonin, are critical neurotransmitters for peristaltic and secretory functions in the intestine, although different receptor subtypes are responsible.[91] Increased plasma serotonin levels have been identified in people with ASD. Because the serotonin found in platelets is obtained from the gut, it is possible that the finding of increased serotonin levels reflects intestinal involvement in people with ASD.[92,93] Serotonin is a neurotransmitter with known CNS actions. Peptides involved with intestinal function have receptors in the CNS as well, although the functions are less well-established. Secretin is one such peptide with receptors identified in the gut and CNS that colocalizes in serotonin-containing cells in the duodenum.[94] A series of uncontrolled observations suggested that secretin administered to children during the course of endoscopy ameliorated symptoms of ASD.[95] Subsequent controlled studies have not documented a clinical effect.[96–99] Additional studies are in progress. Intestinal peptides could exert an action on the CNS through vagal stimulation[90,100] or attain vascular entry across the blood-brain barrier through the median eminence of the hypothalamus. Bidirectional interaction is possible between the CNS and the enteric nervous system. An example is the control of seizure activity in the brain by vagal stimulation. The converse is possible as well; CNS actions exert control of the most proximal (esophagus and stomach) and distal (rectosigmoid) sections of the gastrointestinal tract most prominently.[100] The enteric nervous system is derived from pluripotent cells of neural crest origin,[90] so it is possible for a genetic or teratologic event to affect both systems.

Enterocolitis was diagnosed in children with loose stools and ASD by Wakefield et al.[5,101] Children with ASD had been referred for gastrointestinal evaluation because of parental concerns about loose stools and behavioral regression. The authors found that a significantly greater proportion of children with developmental disorders (including ASD with regression) had ileal-nodular-lymphoid hyperplasia than did children with gastrointestinal symptoms who did not have a diagnosis of developmental disability (54 of 58 subjects vs 5 of 35 controls).[5,101] The authors describe this phenomenon as a new type of colitis. Focal lymphoid hyperplasia in the terminal ileum in childhood has been described and associated with intussusception. Most instances are thought to be preceded by gastrointestinal infections (eg, adenovirus).[102]

There are few studies of the incidence or prevalence of IBD in very young children in the United States. The prevalence of IBD is very low in infants and young children. Therefore, even if children with autism did have an increased risk of having IBD, children with both disorders would be uncommon, and identifying the association could be difficult. For example, if there was a 10-fold increase in the prevalence of IBD among children younger than 3 years with ASD, it would make the prevalence 5 per 10 000 compared with 5 per 100 000 children in the general population. Specialized centers that evaluate children with gastrointestinal disease are much more likely to see all of the children in the community with significant gastrointestinal symptoms, including those with ASD. Children with ASD and gastrointestinal problems studied to date have been those referred for gastrointestinal examinations. To determine the prevalence of gastrointestinal symptoms in children with ASD, a sample of all children with ASD in a defined community is necessary. Diarrhea can be aggravated by many factors, including infection, diet, supplements, medications, pica, anxiety, activity, and other factors, in children with and without developmental disabilities. The identification of colitis in children with ASD is an important observation that requires further scrutiny.

The onset of IBD in children without ASD is typically after entry into school with median age of onset between 10 and 12 years of age. Very few children demonstrate symptoms before 5 years of age, when diagnosis of ASD is usually made.[103,104] For children with ASD and gastrointestinal symptoms evaluated by a gastroenterologist, the onset of loose stools was variable and, when remembered by parents, it was usually during the second year of life.[105,106] In a French population of 325 000 school-aged children, no children with autism (n = 174; prevalence: 5.3 per 10 000) were diagnosed with

IBD.[107] Also, no concordance of IBD and ASD was documented in a data set of 8889 children and adolescents seen for psychiatric care at a tertiary center in London.[108] Gastrointestinal problems in children with ASD could be underdiagnosed because of challenging behaviors, developmental delays in toilet training, attribution of gastrointestinal symptoms to diet, or other factors.

Wakefield et al[105,106] have proposed that changes in the small intestine of children with ASD and chronic loose stools are associated with increased permeability in the gut for exogenous peptides. Excess absorption of exogenous opiate-like peptides has been hypothesized to contribute to development of ASD.[109,110] Peptides from gluten found in wheat and grain products and casein found in milk protein have been linked with symptoms of autism, including repetitive behavior, irritability, and social withdrawal.[109,110] Pharmacologic trials with the opiate antagonist naltrexone and direct measurement of blood or spinal fluid levels of endorphins have not demonstrated strong evidence of opiate excess being responsible for the core symptoms of ASD.[111,112] Measurement of urine peptide concentration has been reported to support the observation that exogenous opiates are excreted in greater concentrations in the urine of people with ASD who ingest milk and wheat products.[109,110] Increased intestinal permeability was observed in 9 of 21 children with ASD without known evidence of gastrointestinal or allergic disorders versus none of 40 controls.[113] The authors suggested that this indicated damage to the tight junctions at the villous tips where peptide might be absorbed. There are individual case reports of children who have demonstrated behavioral improvement with elimination of milk in the presence of antibodies to milk protein (milk allergy),[114] and there are many personal reports of behavioral improvement.[115] The improvement reported by some parents who feed their children a gluten- and casein-free diet could be attributable to hypothetically decreased absorption of exogenous opioids, a nutritional effect on the production or degradation of other neurotransmitters, improved comfort secondary to elimination of foods to which the child is intolerant, some other biologic factor, or a placebo effect.[116]

Megson has proposed that disruption of gastrointestinal integrity in ASD could be attributable to an inherited defect in G-alpha subunit proteins, leading to an increase in intestinal permeability, and that this defect is worsened by immunization.[9] The hypothesis is based on anecdotal reports of night blindness in family members of children with ASD and visual perceptual differences in probands that is improved with supplementation of natural forms of vitamin A. Megson further hypothesized that an association between measles infection or immunization and ASD might be related to decreases in vitamin A levels known to be associated with natural infection-exacerbating symptoms of ASD.[9] Although cell signaling defects are important areas to study in neurologic disorders, there are no clinical or experimental data to support these hypotheses at this time.

Summary

Gastrointestinal symptoms have been described in some children with ASD, but an increased rate of any specific gastrointestinal disorder, including IBD, has not been established. Studies are needed to evaluate the prevalence of abnormalities of the gastrointestinal tract in larger numbers of children with ASD with concurrent assessment of appropriate controls and consideration of other psychologic and biologic factors that could affect study results. The current understanding of the enteric nervous system suggests the possibility of behavioral symptoms linked with intestinal symptoms on the basis of common genetic or environmental insults affecting both systems. The available evidence does not demonstrate that gut disorders cause ASD.

How are vaccines evaluated for adverse events?

To understand the hypothesized association between MMR vaccine and autism, the panel reviewed how adverse events have been assessed for causal relationships with vaccines. Individual case reports or collections of case reports of adverse events after immunization do not constitute evidence of a causal association unless the vaccine involves use of a live infectious agent that is identified in the affected tissue. For example, measles vaccine virus has been isolated in lung tissue from immunocompromised children with pneumonia.[117,118]

Randomized, placebo-controlled trials provide the strongest evidence for assessing causal relationships with adverse events, and such studies were conducted with individual measles, mumps, and rubella vaccines before licensure. Increased rates of fever and rash were observed in children 6 to 14 days after they received measles vaccine, compared with unvaccinated children or children who had already had measles at the time of immunization.[119] In children who received rubella vaccine, age-related arthralgia and acute arthritis occurred at higher rates than in unvaccinated children, and in those who received mumps vaccine, an increased rate of parotitis was noted.[120]

Before the combination MMR vaccine was licensed, several studies revealed that the frequency of adverse events was similar to that when component vaccines were administered separately.[121,122] The limited size and duration of prelicensure studies precludes the ability to detect rare adverse events or events occurring long after immunization unless long-term follow-up studies are conducted.

After licensure, individual reports of adverse events are submitted to the Vaccine Adverse Events Reporting System, a program managed by the CDC and the Food and Drug Administration to monitor reports of adverse events that might signal the need for further study. This collection of passive reports can be used to provide clues to indicate the need for additional studies, but the reports of observed temporal associations do not constitute evidence for causal associations, and the underreporting of adverse events precludes accurate assessment of rates of disorders occurring after immunization.[123]

The CDC also maintains the Vaccine Safety Datalink[123] project, which collects information on immu-

nizations and adverse events in large health maintenance organizations, simplifying the task of conducting some of the following types of studies (if questions arise after licensure, these study designs can be used to test for associations between vaccine administration and adverse events):

1. **Case-control study**. Rates of previous immunizations of individuals with the disease or adverse effect under study are compared with rates in appropriately matched nonaffected controls. Case-control studies have found no evidence of an association between IBD and measles immunization.[124,125]
2. **Case-series method**. All persons who develop the adverse event in a defined population are evaluated to determine if there is significant clustering of the event in time after administration of a vaccine. This method can be particularly useful when the vaccine is administered to almost all persons. Farrington used this method to demonstrate an increased relative incidence of convulsions in the 6 to 11 days after MMR immunization, most likely attributable to increased rates of fever occurring in this time interval.[126,127]
3. **Retrospective (nonconcurrent) cohort studies**. All instances of the adverse event are identified in a defined population, and immunization records are examined. Rates of the adverse event in immunized persons are compared with rates in unimmunized persons. Use of this method demonstrated no increased risk of Gullain-Barre syndrome after large-scale measles immunization campaigns.[128]

What are the CNS and gastrointestinal complications of measles, mumps, and rubella infections and vaccines?

Understanding the known adverse effects of measles, mumps, and rubella infections and vaccines is important for assessment of causal criteria related to biologic gradient (dose effect) and plausibility.

Measles

Measles is caused by an RNA virus. Complications affecting nearly all organ systems have been reported.[129]

Seizures

Almost all infants and children who develop measles have moderate to high fever, which can precipitate febrile seizures, the most common neurologic complication of measles.[130] Seizures without fever or other neurologic signs also occur rarely. Fever, usually mild, occurs in 5% to 15% of children who receive measles vaccine; febrile seizures do occur, but at a much lower rate than with measles infection.[80]

Encephalitis

Changes in electroencephalograms have been noted in most studied children with uncomplicated measles.[131] These changes could have been attributable to fever and other metabolic changes. No changes were noted on electroencephalograms for children who received measles vaccine.[132] Encephalitis occurs in 1 to 3 per 1000 children with measles, usually 3 to 10 days after onset of the rash.[133] Measles virus has been demonstrated in cerebrovascular endothelial cells during the rash phase of disease, but measles virus rarely has been found anywhere in the CNS with postinfectious encephalitis.[134] The late onset and demyelinating pathology of encephalitis suggest an autoimmune mechanism. Abnormal immune responses to myelin proteins have been found in patients with encephalitis. The hypothesized pathogenesis is proliferation of measles virus in lymphoid cells resulting in altered immune responses to myelin proteins. Approximately 20% to 40% of survivors of measles encephalitis have lifelong neurologic sequelae, which are often severe.

Encephalitis has been reported after measles immunization at a rate of approximately 1 per 1 million vaccine recipients, a rate similar to the background rate of encephalitis of unknown etiology in unvaccinated children in the general population.[121] There is temporal clustering of reports in the 5 to 15 days after immunization when other adverse effects from the vaccine occur. Some experts believe that the vaccine can cause encephalitis; if this is true, the rate is at least 1000 times less than the rate after natural infection. There have been no cases of vaccine strain virus causing encephalitis in persons with intact immune systems confirmed by neuropathologic studies. The Institute of Medicine concluded that there was inadequate evidence to accept or reject a causal relation between measles (or mumps) vaccine and encephalitis or encephalopathy.[135]

Subacute sclerosing panencephalitis (SSPE)

Approximately 8.5 per 1 million children who have measles will develop SSPE, a slowly progressive infection and demyelinating disorder affecting multiple areas of the brain.[136] The onset of this disorder usually occurs an average of 7 to 9 years after measles. SSPE is caused by reactivation of latent measles virus infection, but the location of measles virus before the onset of symptoms in these children is unknown. Factors that allow for persistent infection are only partially understood, and whether or not measles virus persists in persons who do not develop SSPE is not known. Epidemiologic evidence, including geographic clustering, increased incidence in rural areas, and exposure to birds, suggested the possibility of a coinfection with another infectious agent.[137,138] However, no such agent has been identified, and no differences in the prevalence of serum antibody to several other infectious agents have been observed.[139] One early case-control study suggested that children with SSPE were more likely to have had varicella within 6 months of measles than were controls.[140] A subsequent larger study found no differences between cases and controls in histories of chickenpox, mumps, or rubella occurring within 6 months of measles.[139]

Measles vaccine prevents SSPE by preventing measles; SSPE has almost completely disappeared from the United States and other developed countries in recent years.[136,139] No cases of SSPE have been shown to be caused by measles vaccine. Genetic

sequencing of viruses obtained from the brains of patients with SSPE to date has revealed only viruses of wild-type origin (W. Bellini, PhD, personal communication, November 21, 2000). Although cases of SSPE have occurred in children without a history of measles who have received measles vaccine, careful investigation has usually revealed histories of measles-like illnesses and/or known exposures to measles followed by administration of passive immune globulin.[136,139] Passively acquired maternal antibody can mask signs of measles in children who were exposed during the first 10 months of life.

Measles encephalitis in immunocompromised patients

Measles encephalitis in immunosuppressed children, including children with human immunodeficiency virus (HIV) infection or leukemia, is sometimes referred to as subacute or inclusion body measles encephalitis and is caused by progressive measles virus infection.[141–143] Onset is usually 5 weeks to 6 months after acute measles, and virus has been identified in brain tissue and cerebrospinal fluid (CSF) specimens. Virus isolated from brain tissue specimens from several patients have been shown to be wild-type measles virus.[141,144] One patient with an undefined immune disorder who developed this disorder at 21 months of age was found to have measles vaccine virus in brain tissue.[145] One HIV-infected child who had received MMR vaccine at 15 months of age was found to have characteristic inclusion bodies on brain biopsy at 18 months of age, but no specific testing was performed to determine the source or identity of the virus.[146] Also, a 19-year-old HIV-infected man with hemophilia had paramyxovirus nucleocapsids in intranuclear inclusion bodies, and there was evidence of measles antigen on immunohistochemical staining, but the virus was not sequenced.[147] He had received measles vaccine at 10 years of age. There was no history of measles exposure in the year preceding the biopsy. The age he acquired HIV infection and possible subsequent exposures to measles were not reported.

One unresolved issue is whether or not measles virus persists in persons who do not develop SSPE or who are not immunocompromised at the time of measles infection or immunization. An HIV-infected intravenous drug user developed progressive measles retinitis and subsequent progressive CNS disease diagnosed as SSPE at 30 years of age.[148] His illness resembled measles encephalitis in immunocompromised individuals. He had a history of measles at 2 years of age, and HIV infection most likely occurred in later life secondary to intravenous drug abuse or sexual contact. One group of investigators[149] found measles nucleocapsid genomic RNA in brain and other specimens from persons without CNS disease, but there are no reports of persistence of replicating measles virus in immunocompetent persons who do not develop SSPE.

Gastrointestinal tract complications

Measles is associated with increased rates of diarrhea in infants and young children, but diarrhea is uncommon in older children and adults with measles.[133,150,151] In developing countries, measles has been associated with a protein-losing enteropathy that can persist for several weeks or months, contributing to the development of malnutrition.[150] Measles virus has been detected in the intestinal epithelium of immunologically healthy children who died within 5 days after onset of rash, but not in children who died later.[152] Measles vaccines administered at 6 months of age were associated with increased rates of diarrhea in 1 study[153] but not in other studies.[154–156] Rates of diarrhea among children who received standard-titer attenuated or further attenuated measles vaccines were similar to rates in unvaccinated children in large, well-designed, controlled trials in developed countries.[157–161] Vomiting is a nonspecific sign and was noted in some studies[157] to be associated with fever 7 to 11 days after measles immunization. Some other studies did not differentiate between vomiting and diarrhea.

Summary

Measles is associated with acute gastrointestinal symptoms, and measles virus causes encephalitis and SSPE. Measles vaccine may rarely cause encephalitis in immunologically healthy hosts and can cause a persistent CNS infection in immunodeficient individuals. Further attenuated measles vaccines used in the United States in standard titers are not associated with increased rates of gastroenteritis.

Mumps

Before 1970, mumps was the most common cause of encephalitis and meningoencephalitis in the United States. Approximately 50% of individuals with mumps have pleocytosis of the CSF, and about 10% of children have clinical manifestations of CNS infection.[130] The most common complication from mumps encephalitis is deafness, but in most instances, the disease is self-limited. Mumps virus has been isolated from the CSF early in the disease course. Transverse myelitis and hydrocephalus have been reported after mumps, but causal relationships have not been established for these disorders. Persistent mumps in the CNS has not been documented.

The major manufacturers of mumps vaccines have used different strains of mumps viruses. The Urabe strain has been widely used in Europe (but not in the United States) and has been associated with a risk of viral meningitis of between 1 per 20 000 and 1 per 1000. There have been many isolations of this virus in CSF.[120] An epidemiologic study in the United Kingdom has demonstrated an association between MMR vaccine containing the Urabe strain and increased risk of viral meningitis during the 17 to 26 days after immunization.[126,127] Although the vaccine strain used in the United States (Jeryl Lynn) has been isolated in a CSF sample from 1 child, no increased risk of fever, seizures, meningitis, or meningoencephalitis has been demonstrated after the use of this vaccine in the United States.[120] Although there have been individual case reports of Bell's palsy and/or deafness after immunization with the Jeryl Lynn strain of mumps virus, there are no reports of isolation of this strain of virus in CSF samples from these children. There are many other potential causes of

these disorders, so the temporal association does not establish a causal association. There is no evidence of an increased risk associated with monovalent mumps or MMR vaccines for the aforementioned disorders, including meningoencephalitis or meningitis.[162]

Gastrointestinal tract complications

Mumps is associated with infection of salivary glands and the pancreas.[130] Elevation in serum amylase is almost universal in children with symptomatic disease. In most instances, the only symptoms are swelling and tenderness of the salivary glands (parotitis). Vomiting can be a nonspecific response to infection or a sign of mild pancreatitis. Some cases of mumps in infants or young children have been associated with severe pancreatitis, including symptomatic hypoglycemia. Mumps vaccine has been associated with mild parotitis in 1% to 2% of children, but there has been no increased risk of pancreatitis or other gastrointestinal tract disorders associated with the mumps vaccine used in the United States.[120]

Summary

Mumps is a known cause of encephalitis, but mumps virus does not cause a chronic infection. The mumps strain used in vaccines in the United States is not associated with diarrhea.

Rubella

Rubella is a usually a mild illness; the low-grade fever associated with this illness has not been demonstrated to be a significant risk factor for febrile seizures. Postinfectious rubella encephalitis occurs in approximately 1 per 6000 cases, but in a Japanese outbreak, the incidence was estimated to be 1 per 1600 cases.[163] Very rarely, a progressive rubella panencephalitis has occurred that simulates SSPE. Rubella viruses have been detected in brain tissue specimens from such patients.[142] The incidence is undoubtedly much lower than that after measles, but the true rate of this complication has not been defined. Rubella during pregnancy is associated with congenital rubella syndrome. Complications of congenital rubella syndrome involving the CNS include encephalitis, microcephaly, mental retardation, ASD, central auditory deafness, and blindness.[164] Many children with congenital rubella syndrome were diagnosed with autism in the late 1960s and early 1970s. In some cases, autistic features accompany diffuse brain damage during gestation, and in many, there were also sensory deficits.[165,166]

Gastrointestinal tract complications

Children with congenital rubella syndrome have a high risk of developing type 1 diabetes, an autoimmune disorder involving the pancreas. No other gastrointestinal tract complications have been shown to be caused by wild-type or vaccine-strain rubella viruses.

Summary

Congenital rubella syndrome from natural rubella infection can result in an insult to the developing brain. ASD is one of many sequelae possible. Rubella may cause encephalitis. Adverse gastrointestinal and CNS effects have not been associated with rubella immunization.

Does postpartum administration of MMR vaccine predispose children to ASD?

Because postpartum immunization of rubella-susceptible women is recommended,[167] immunization of women of childbearing years is a common practice. Rubella vaccine alone or in combination MMR vaccine, when administered after pregnancy to susceptible women, has been associated with detection of rubella vaccine virus in breast milk, and some breastfed infants have had serologic evidence of infection.[168] No clinical manifestations of rubella were seen in those infants, and there has been no report of any harmful effect.[169,170]

Yazbak has hypothesized that maternal immunization before, during, or after pregnancy predisposes that child or subsequent children to ASD.[8] On the basis of the clinical observation that some mothers of children with ASD were vaccinated with MMR as adults, a request was posted on the Internet and in publications of vaccine-related and parent support groups to identify women who have been vaccinated as adults to provide information regarding their own health and the health and development of their children. Four hundred responses were received, and data on 54 of these were presented to the panel. Twenty mothers of children with ASD responded who reported having been vaccinated during the postpartum period. Four other mothers had children with chronic health problems. Seven mothers who reported having been vaccinated during early pregnancy or just before pregnancy had children with probable ASD. All health and developmental information was provided by history. This study is not yet published in the medical literature. An ascertainment bias is likely in this method of identifying cases, because people who recognized this association were most likely to respond.

Summary

Given the prevalence of ASD in the population and the common practice of vaccinating susceptible women with MMR vaccine after pregnancy, some women who received vaccine after pregnancy would be expected to have children with ASD. Case-control studies of children with ASD could be conducted to determine if there was any association with maternal immunization.

What are the effects of measles, mumps, and rubella occurring simultaneously or in close succession?

Before the availability of vaccines, measles, mumps, and rubella occurred in almost all children, and all 3 infections occurred during the same seasons—late winter and spring. No increased rates of complications were recognized in children who had more than one of these infections at the same time or during the same season.

Simultaneous administration of measles, mumps, and rubella vaccines is associated with similar rates of fever, rash, arthralgia, and other adverse events to those that occur when the vaccines are administered separately, and MMR vaccine is the preferred vac-

cine for routine immunization of children.[121,133,171] Although early studies showed the potential for some interference between these vaccine viruses as indicated by reduction in the mean antibody response to 1 or more of the components in the combined vaccines, adjusting the titers of the vaccine viruses resulted in similar responses for the combined and separate administration of these vaccines.[121,122,171–177] Wakefield and Montgomery[7] recently speculated that interference between viruses in combined vaccines could be associated with delayed clearance of the virus and an increased rate of adverse events. A careful review of multiple large studies revealed no increased rate of adverse events with the combined vaccine, including gastroenteritis, compared with vaccines administered separately.[121,177] Using an innovative double-blind trial design, Virtanen et al[178] compared the daily rate of adverse events after MMR immunization in 1162 twins, 1 in each set receiving vaccine and the other receiving placebo. No differences in the rates of diarrhea, nausea, or vomiting were observed between the vaccinated and unvaccinated twins on any day from 1 to 21 days after immunization.

Summary

The simultaneous administration of measles, mumps, and rubella vaccines in the MMR combination vaccine is not associated with an increased rate of adverse events, compared with the rate for administering the vaccines separately.

Is measles virus present in the intestinal wall in patients with IBD or ASD?

Wakefield et al[105,106] have proposed that measles causes IBD and that this infection contributes to intestinal disorders in patients with ASD. This theory is based on several lines of evidence generated by this group, including the following:

1. Measles nucleocapsid antigen was found in the intestinal wall of patients with IBD by immunohistochemical staining[179] and polymerase chain reaction (PCR) assay for measles genomic RNA.[180]
2. Wild-type measles virus genomic RNA was found in peripheral blood mononuclear cells (PBMCs) in 1 of 8 patients with Crohn's disease. Measles vaccine virus genomic RNA was found in the PBMCs from 1 of 3 patients with ulcerative colitis and in 3 of 9 children with autism and gastrointestinal disease but was not detected in PBMCs from 8 persons with other illnesses or healthy children.[181]
3. Higher concentrations of serum measles immunoglobulin M antibodies were detected in patients with IBD, compared with patients with hepatitis.[182]
4. A higher number of IBD cases than expected were identified after in utero exposure to measles virus.[183,184]

O'Leary et al reported in testimony before the House Government Reform Committee on April 6, 2000, that evidence of measles virus genomic RNA encoding for F and H proteins was found in intestinal wall tissue specimens provided by Wakefield from 24 of 25 children with autism and 1 of 15 children without autism.[185] No mention was made as to the genetic sequences of the viruses identified. Further methodologic details necessary for the scientific review of this report have not been published, and the information was not provided in response to a request.

Several laboratories have investigated the possible persistence of measles virus in intestinal tissue in IBD.[186,187] Iizuka et al[188] identified the antigen reacting with the monoclonal antibody used by Wakefield et al[179] and demonstrated that the antibody reacts to measles nucleocapsid antigen and to intestinal tissue in patients with Crohn's disease. Iizuka et al identified, isolated, and sequenced the protein in intestinal tissue specimens reacting with this monoclonal antibody and showed that the protein was of human, not measles virus, origin. Iizuka et al also identified the protein in increased amounts in patients with ulcerative colitis or noninflammatory colitis, compared with controls, and they found small numbers of cells containing this protein in esophagus, stomach, duodenum, and lung tissue specimens but not in liver, spleen, kidney, or heart tissue specimens. This group hypothesized that the "measles related antigen" could be the target of an autoantibody generated by measles through molecular mimicry. In a subsequent report, they were unable to detect cross-reacting antibodies to the measles related antigen detected in serum samples from 15 patients with Crohn's disease, 15 with ulcerative colitis, and 15 controls, which does not support the autoimmunity hypothesis.[189] Other laboratories were also unable to identify measles antigens in intestinal wall tissue specimens from patients with IBD using sensitive immunohistochemical staining and PCR and reverse-transcriptase PCR (RT-PCR) assays.[187,190–194] Chadwick et al,[195] working with Wakefield et al, were unable to detect measles virus in intestinal tissue specimens from patients with IBD using PCR assay. Afzal et al[186] recently reviewed published studies and concluded that the available data indicate the absence of measles virus in tissue specimens from patients with IBD. However, the studies by Iizuka et al do not resolve the findings of Katamaya et al,[149] who found measles nucleoprotein mRNA in 8% to 20% of brain, lung, liver, spleen, and kidney tissue specimens obtained at autopsy using RT-PCR assay. These individuals had no known gastrointestinal or neurologic disorders reported, indicating that measles virus may persist in unaffected tissue. If so, detection of portions of the virus in tissue may be unrelated to local disease. The panel learned of additional unpublished studies by Ward et al (B. Ward, MD, personal communication, June 12 and December 18, 2000) which are purported to reveal the presence of specific transcripts for the nucleocapsid gene of measles as well as another incompletely characterized paramyxovirus in a small number of patients with IBD and a control using degenerate primers and RT-PCR assay. No evidence was found for any other measles gene transcripts. The findings of measles nucleocapsid genomic RNA in affected tissue specimens from patients with otosclerosis[196] or Paget's disease[197,198] suggests the possibility that nucleocapsid genomic

RNA may persist after paramyxovirus infections in some tissues. Because lymphocytes are targets of the measles virus, disorders associated with inflammatory responses and lymphocyte infiltration could be associated with an increased likelihood of finding measles genomic RNA in affected tissues. As with several other viruses that persist after infection, finding evidence of a portion of the virus in affected tissue is insufficient evidence to establish a causal association with the disease.

Variations in methodology could explain some of the discrepancies in reported results from the different laboratories studying intestinal biopsy specimens.[199] False-positive results in highly capable laboratories have led to incorrect conclusions about infectious agents causing many chronic diseases, including multiple sclerosis and schizophrenia.[142,200,201]

Guidelines for establishing causation on the basis of molecular detection techniques are evolving.[202] The findings to date regarding detection of measles virus from studies of intestinal tissue specimens do not meet several of these guidelines. Nucleic acid sequences have not been found in most affected persons but have been found in hosts and tissues without disease. The nature of the disease is not consistent with what is known about the biologic characteristics of the organism, and the evidence has not been consistently reproducible.

Summary

Measles virus nucleocapsid RNA has been detected in peripheral blood cells and intestinal tissue specimens from individuals with ASD and gastrointestinal disease by one group of investigators. Several other groups studying IBD have not been able to confirm the presence of measles virus in the gut. Human tissue cross-reacting with measles antigen, possible nonpathologic persistence of measles nucleocapsid genomic RNA in multiple body tissues, or technical problems with PCR assays may affect results. Conflicting data regarding the detection of portions of measles virus in tissue specimens from patients with IBD in several laboratories indicate the need for collaborative studies involving multiple laboratories testing coded specimens to further address these issues. Intestinal tissue specimens from patients with IBD and children with ASD who have gastrointestinal symptoms should be collected by gastroenterologists and processed in laboratories (where no measles viruses have been studied to avoid possible contamination), and coded samples should be distributed to other laboratories for detection of measles virus by several different methods. Studies should include control tissue specimens, and all diagnoses should be masked.

Do epidemiologic studies support an association between measles, measles vaccine, or MMR vaccine and IBD?

Montgomery et al[6] prospectively studied a cohort of persons born during 1970 in the United Kingdom. History of childhood illnesses, including measles, mumps, pertussis, chickenpox, meningitis, and other febrile illnesses, was obtained from parents when the children were 10 years of age. A postal survey was conducted of 13 099 traceable members when the cohort was 25 to 26 years of age, and a representative return of 7019 subjects was attained. None of the individual childhood infections were significantly associated with IBD in adulthood. A significant association with IBD was found for having had measles and another infection in the same year during the first 6 years of life. If measles was not 1 of multiple infections in a year or if mumps was not included as a second infection, the association disappeared. The authors noted that mumps before 2 years of age seemed to be associated with ulcerative colitis and suggested that atypical patterns of exposure might be a risk factor for IBD. In this sample, only 4% of the entire population experienced this pattern of exposure.

There are several limitations to conclusions that one can draw from this study. First, the association between measles and mumps in the same year and IBD was one of many associations examined, and a finding of significance attributable to chance cannot be ruled out. Second, parental histories were obtained 4 to 10 years after reported infections occurred, and estimation of approximate ages at the time of infections could have resulted in artificial clustering by age. Third, the number of studied persons with IBD was small. Fourth, the IBD disorders studied (ulcerative colitis and Crohn's disease) have not been shown to occur at increased rates in persons with ASD. The findings have not yet been confirmed in other populations. A history of 2 wild-type paramyxovirus infections during the same year is not comparable immunologically to simultaneous immunization with attenuated virus vaccines.

No associations between measles or mumps and IBD were found in a carefully conducted, nested case-control study of 55 patients with IBD who were compared with 8 controls each.[203] The cases were identified as part of a long-term longitudinal cohort study, reducing or eliminating potential selection bias. No association with IBD was found in the offspring of 6 women who had measles between the second trimester of pregnancy and 6 months after pregnancy in Minnesota.[204] These investigators did find a greater-than-expected number of cases of IBD in a questionnaire follow-up of children who had developed measles before 5 years of age.[205]

No differences in measles immunization rates were observed between patients with IBD and controls in the United Kingdom.[123] In the United States, the CDC conducted a case-control study using the Vaccine Safety Datalink, including studies looking at age at immunization, and found no association between MMR immunization and IBD.[206] A study in Finland[206] found no instances of IBD or autism in a computerized review of medical records among 1.8 million children followed for 1 to 15 years after receiving MMR vaccine. In a population this size, some children would be expected to develop IBD and/or ASD. The study did identify other developmental and behavioral conditions. Further investigation is needed to explain this discrepancy. A detailed review of other serious adverse events after MMR immunization identified during a 14-year prospective

follow-up showed that these events are rare.[208] Epidemiologic studies in Scotland[209] have shown no association between MMR vaccine and Crohn's disease.

Summary

Laboratory and epidemiologic studies conducted to date do not provide convincing evidence implicating measles, measles vaccine, or MMR vaccine as predisposing or causative factors in the development of IBD.

Could ASD be of infectious origin?

The wide phenotypic expression of ASD might be related to differential effects of multiple etiologic factors acting at different stages of nervous and immune system development. Multiple genes are associated with ASD (see "**Is there a genetic predisposition to ASD?"**). Viral infections, such as prenatal rubella[165,210] and postnatal herpes simplex encephalitis, have resulted in brain damage and features consistent with autism in children.[211–213] Establishing a causal relationship between an infection with a microbe and a specific brain disease can be difficult, especially if there is no direct evidence of more generalized brain damage, as usually occurs with rubella and herpesvirus infections. Other mechanisms of damage, such as infections outside of the CNS stimulating cross-reactions with brain elements, as proposed for the Sydenham chorea, can occur.[214] Tics and obsessions seen with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection might be models for other neurobehavioral syndromes associated with infectious etiology.[215] Another mechanism that must be considered in neurologic disorders is persistent, noncytopathic viral infections. Such atypical agents have varying effects at different developmental states and may interact with other genetic or environmental risk factors to influence neurodevelopmental outcomes.

Borna virus infection in rats provides an example of the biologic plausibility of viruses causing structural and functional damage in specific brain regions with only transient and minimal inflammation when the infection occurs at a key stage of development.[216–218] Immunocompetent rats infected as adults have marked CNS inflammation, loss of brain mass, and gliosis accompanied by dramatic neurologic manifestations. Rats infected neonatally do not demonstrate persistent or severe inflammation[216,218] but they do have anatomic changes in the hippocampus and cerebellum and behavioral differences in spatial and aversive learning, play behavior, circadian rhythms, taste preference for salt, response to novel environments, social communication, stereotypic behaviors, and locomotor activity.[217,219] Because of the similarities of this behavioral profile with ASD, rats infected with Borna virus are being investigated as a potential animal model for autism.[219,220] Human studies have provided no evidence to date linking Borna virus with ASD.[219]

Summary

Viruses can affect the CNS, with minimal inflammation or conventional histologic evidence of infection, and cause long-term alteration in the development of localized areas of the brain and behaviors. Viral agents have not yet been associated with similar phenomena in humans.

APPLICATION OF CAUSALITY CRITERIA

The panel addressed the primary question: "Does the available evidence support a causal relationship between MMR vaccine and the pathogenesis of ASD?" by applying the formal causality criteria reviewed earlier.

1. **Strength of Association**. Some parents of children with ASD have noted a temporal association between onset of the first symptoms of ASD and the receipt of MMR vaccine. The broad age range for recognized onset of symptoms of ASD overlaps with the age when MMR vaccine is routinely administered. Thus, some temporal associations are expected by chance alone. Finding a temporal association in a selected population for a disorder with wide individual variation in timing of onset provides weak evidence for an association. Selection bias is likely for patients referred for study of gastrointestinal symptoms to a clinic where studies of associations between MMR immunization and IBD are being conducted.

   Increased reporting of ASD in recent years does not correlate with the introduction and widespread use of MMR vaccine, and no temporal clustering of reported onset of ASD symptoms has been noted in 1 study in the United Kingdom.
2. **Consistency**. There is no consistent pattern in the observed timing of onset of ASD symptoms after MMR immunization, and there is not uniform comorbidity with bowel disease. Available data from epidemiologic studies using scientifically sound methodology show no evidence of an association between MMR vaccine and ASD.
3. **Specificity.** Published evidence regarding the possible presence of residual measles virus in the intestinal wall of children with IBD or ASD suggests that this finding may not be specific. Measles nucleocapsid genomic RNA has been found in multiple tissue specimens obtained from people without apparent disease in the sampled organs. An association of the identification of autism with events that occur frequently in the second year of life, such as receipt of the MMR vaccine, may represent a chance, nonspecific occurrence.
4. **Temporality**. Changes in behavior and gastrointestinal function have been reported to occur as early as 1 day and as long as several months after MMR vaccine administration. Thus, there is temporal ambiguity in the timing of reports of behavioral and gastrointestinal symptoms after immunization. The inherent heterogeneity in the timing of onset of ASD manifestations, probable variability in expression of genetic predisposition, and known variability in the ultimate manifestations could contribute to this temporal ambiguity.
5. **Biologic Gradient**. Measles vaccines were introduced in the United States in 1963. In 1989, a second dose was recommended at 4 to 6 years of age or 11 to 12 years of age, which is well after the

usual age of onset for ASD.[123] During outbreaks, extra doses of measles vaccine have been administered to infants between 6 and 12 months of age, but only a small proportion of the population has received this extra dose. There have been no reports of late-onset ASD associated with the receipt of extra doses of measles or MMR vaccines. There are no data suggesting a dose-response effect between MMR vaccine and the development of ASD.

6. **Plausibility**. In utero rubella is associated with an increased risk of developing ASD and other neurologic impairments. There is no evidence that postnatal rubella or rubella vaccine viruses predispose to ASD. The ability of several infectious agents to cause disease in utero that does not occur with postnatal infection is well established.

   Some investigators have found evidence of persistent measles nucleocapsid antigen, genomic RNA, or transcripts in various body tissues, including intestinal tissue, long after measles or immunization in individuals with IBD, ASD with gastrointestinal symptoms, and in control specimens. However, other investigators have found no evidence of the presence of persistent measles virus in intestinal tissue specimens from individuals with IBD.

   It is biologically plausible for a viral infection occurring at a critical time of development to result in neurodevelopmental disability with no overt signs of encephalitis at the time of infection. In children who have not had congenital rubella syndrome or clinical signs of encephalitis attributable to other viruses, there is no evidence to implicate any specific virus as a cause of ASD. Investigations are ongoing into the possibility of previously unrecognized viruses causing neurobehavioral symptoms.

   At the present time, there is no reasonable biologic plausibility to support the hypothesis that administering measles, mumps, and rubella viruses together in the combination MMR vaccine is associated with an increased risk of ASD. There is scientific evidence against such an association.

   There is biologic plausibility for an association between abnormalities of the gastrointestinal tract and CNS, including ASD. Symptoms relating to the gastrointestinal tract and CNS function could be related to common gene action or common physiologic mechanisms and not a result of abnormalities in 1 organ system causing an abnormality in the other.

7. **Coherence**. Available data do not provide a coherent explanation for how MMR vaccine administration could predispose to autism. The literature does not support the hypothesis that a subgroup of patients with particular genetic, gastrointestinal, or other predisposing factors develops autism after MMR immunization.
8. **Experimental Evidence**. There is no experimental evidence supporting the hypothesis that MMR vaccine causes autism or that there is any benefit from administering the 3 vaccines separately. Some parents of children with ASD have withheld MMR vaccine from subsequent children. A controlled study of children at increased risk of ASD (eg, siblings of children with ASD) is conceivable, but such a study would have multiple confounding factors and could result in harm if there were delays in immunization.
9. **Analogy**. Neonatal Borna virus infection of rats and congenital rubella syndrome indicate that viral infections at key times in early stages of neurologic development might predispose an individual to autism. Analogy provides a weak form of evidence for a causal argument, however, and there is no analogous situation indicating that simultaneous administration of live viral vaccines or simultaneous infections with different viruses predisposes to ASD or other neurologic disorders.

RESEARCH NEEDED

Physicians and families of individuals with ASD have called for more and better research to understand and prevent ASD. The panel has identified several areas that need further study, including:

1. Factors associated with ASD, including genetics and environmental exposures in utero and during the first months after birth, or temporally associated with the onset of symptoms;
2. The nature and incidence of regression in persons with ASD;
3. Epidemiologic studies in representative populations in North America to determine if there are changes in the incidence or prevalence of autism and to evaluate risk factors that could contribute to an increased incidence of ASD with regression;
4. Whether measles and related viruses persist after infection or immunization in normal tissues and those affected by inflammatory processes;
5. Factors responsible for observed differences in measurements of immunologic parameters in persons with ASD, compared with unaffected individuals; and
6. Whether there is evidence for previously unrecognized infectious agents affecting the CNS of persons with ASD.

CONCLUSIONS

Although the possible association with MMR vaccine has received much public and political attention and there are many who have derived their own conclusions based on personal experiences, the available evidence does not support the hypothesis that MMR vaccine causes autism or associated disorders or IBD. Separate administration of measles, mumps, and rubella vaccines to children provides no benefit over administration of the combination MMR vaccine and could result in delays in immunization. Pediatricians need to work with families to ensure that children are protected early in the second year of life from these preventable diseases. Continued scientific efforts need to be directed to the identification of the causes of ASD.

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Agenda for New Challenges in Childhood Immunizations Conference, June 12-13, 2000

Day	Time	Topic	Presentation Title	Speaker
Monday	8:00 AM	Opening Remarks (continental breakfast)		Jon Abramson, MD, FAAP
	8:05 AM			Renee Feldman
	8:10 AM			Paul Melinkovich, MD, FAAP
	8:15 AM	Ground Rules		Paul Melinkovich, MD, FAAP
	8:20 AM	Background on Autism	Introduction of Speakers	Paul Melinkovich, MD, FAAP
	8:30 AM		Autism: Phenotypic Variability and Genetics	Edwin H. Cook, Jr, MD
	8:55 AM		Immunology and Autism	Andrew W. Zimmerman, MD, FAAP
	9:15 AM		The Epidemiology of Autism Spectrum Disorders	Eric Fombonne, MD, FRCPsych
	9:35 AM		The Brain in Autism	Eric Courchesne, PhD
	9:55 AM		The Gastrointestinal Tract in Autism	Barry Wershil, MD
	10:15 AM	Review of Methods	Assessing Causality	Neal A. Halsey, MD, FAAP
	10:35 AM	Biologic Plausibility	Viruses, Virus Vaccines, and the Central Nervous System	Samuel L. Katz, MD, FAAP
	10:55 AM		Development and Characterization of a Model of Virus-Induced Neurobehavioral Disease	Kathryn M. Carbone, MD
	11:15 AM	Open Questions		Moderator: Paul Melinkovich, MD, FAAP
	11:35 AM	Break		
	11:50 AM	MMR Vaccine and Autism Technical Reports	Introduction of Speakers	Jon Abramson, MD, FAAP
	12:00 PM		Maternal Vaccination Before, During or After Pregnancy Predisposes to Autism	F. Edward Yazbak, MD, FAAP
	12:20 PM		Is Autism a G Alpha Defect Treatable with Natural Vitamin A ?	Mary Megson, MD, FAAP
	12:40 PM	Lunch		
	1:45 PM	MMR Vaccine and Autism Technical Reports	Congressional Testimony to the Government Reform Committee U.S. House of Representatives, April 6, 2000	Andrew Wakefield, MB, BS, FRCS, and John O'Leary, MD, PhD, MSc, MRCPath
	2:15 PM		Paramyxovirus Gene Transcripts in Healthy and Diseased Bowel	Brian Ward, PhD
	2:35 PM		MMR, Autism, and Bowel Disease	Michael Langman, BSc, MD, FRCP
	2:55 PM		MMR and Autism: No Evidence for a Causal Association in North London	Brent Taylor, PhD, FRCP, FRACP
	3:15 PM		Critique of Laboratory Methodology	Ian Lipkin, MD
	3:35 PM		Open Questions	Moderator: Jon Abramson, MD, FAAP
	5:30 PM	Adjourn		
Tuesday	8:00 AM	Introduction of Speakers		Paul Melinkovich, MD, FAAP
	8:10 AM	Critique of Study Methods		Alexander Walker, MD, DrPh
	8:40 AM	Parent/Scientist Commentary	National Alliance for Autism Research	Eric London, MD
	8:55 AM		Autism Society of America	Ching Wang, MD, PhD
	9:10 AM	Speaker Responses to Panel Questions/ Panel Discussion		Moderator: Paul Melinkovich, MD, FAAP
	10:15 AM	Break		
	10:30 AM	Studies in Progress	Centers for Disease Control and Prevention	Catherine Murphy, MPH
	10:45 AM		National Institutes of Health	Marie Bristol-Power, PhD
	11:00 AM	Open Questions		Moderator: Jon Abramson, MD, FAAP
	11:25 AM	Closing Remarks		Paul Melinkovich, MD, FAAP
	11:30 AM	Adjourn		

Measles-Mumps-Rubella Vaccine and Autistic Spectrum Disorder: Report From the New Challenges in Childhood Immunizations Conference Convened in Oak Brook, Illinois, June 12–13, 2000

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