REVIEW ARTICLE

Measles-Mumps-Rubella Vaccine and the Development of Autism or Inflammatory Bowel Disease: The Controversy Should End

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Vaccines have been administered to millions of individuals, usually infants and children, with few serious adverse effects. In 1998 a report suggested that there may be a link between the measles-mumps-rubella vaccine and the development of behavioral abnormalities (i.e., autism) and inflammatory bowel disease in children. This report generated considerable media and political attention, which many feared would result in a decreased willingness of parents to immunize their children against these contagious diseases. Over the past decade, an increasing number of healthcare practitioners have been credentialed to administer vaccinations. Therefore, it is imperative for all medical professionals to understand the controversy surrounding this issue and to be able to appropriately educate and advise parents accordingly. This review article evaluated the primary and secondary literature pertaining to this topic and concluded that the available epidemiological and scientific evidence does not support a causal association between the MMR vaccine and autism or inflammatory bowel disease.

Key words: Measles-Mumps-Rubella, MMR, vaccine, autism, inflammatory bowel disease

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INTRODUCTION

Recent media reports have raised parental concerns regarding the safety of immunizations that are commonly given to infants and children. Parents are now questioning the risk versus benefit of administering scheduled immunizations to their infants and children in order to prevent the occurrence of infectious diseases. Unfortunately, failure to adequately immunize may have detrimental consequences not only to the individual child, but to the overall wellness of society. For the past five years, there has been widespread debate over a possible relationship between the measles-mumps-rubella vaccine (MMR) and developmental regression (e.g., autism). A decrease in MMR vaccination may lead to a recurrence of these three infections, which

have been highly controlled over the past decades. In order to appropriately educate parents, medical professionals should be aware of medically based evidence concerning the controversy surrounding MMR and the development of autism or inflammatory bowel disease.

BACKGROUND-AUTISM

Autism is a subtype of a pervasive disorder that is associated with life-long, developmental disability. It is characterized by difficulties with social interactions, communication, and behavior. It is estimated that about 1 in every 1000 children has autism and that as many as 5–20 per 10,000 children exhibits some form of the disorder.¹ While males are more likely to develop autism (i.e., 2:1 in severely handicapped, 4:1 in moderately handicapped), the disorder has no predilection for race, ethnicity, or socioeconomic status.¹

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Although an autistic disorder can be present at birth, the infant may appear normal for the first few months of life. Those with the disorder become more and more unresponsive to stimuli and begin to develop clinical signs and symptoms consistent with a diagnosis of autism by early childhood. Parents may begin to suspect developmental issues in their child by 2 years of age, but a formal diagnosis of autism may be deferred for several years until the practitioner is certain of the diagnosis.¹ Signs and symptoms may vary widely among patients but typically include underdeveloped or non-developed verbal and non-verbal communication skills, and atypical speech patterns.^{2,3} These children also have poor social skills, such as difficulty maintaining a conversation and building friendships.^{2,3} Classically, autistic children are withdrawn, tend to play alone, and adhere strictly to a daily routine.^{2,3} When this routine is disturbed, the child will often display tantrums. A few children have normal to high intelligence, but most are classified as functionally retarded.¹⁻³ Specific criteria are outlined in the Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition (DSM-IV) and must be met before a child can be diagnosed with autism (Table 1).⁴

Several etiologies have been suggested; however, the cause of autism remains illusive.⁵ One

of the leading theories has focused on a genetic link to autism.^{5,6} While an exact mechanism of inheritance has not been identified, data from twin studies provide the strongest support for a possible genetic predisposition. Bailey et al. reported that 60% of monozygotic (identical) twins were concordant for autism compared to no dizygotic (non-identical) pairs.⁷ Herault and colleagues noted a positive association between autism and two HRAS markers.⁸ Current research suggests that between 3–10 genes are likely to be involved.⁶ Overlapping findings from genome screens suggest that genes will be identified on at least chromosomes 2, 7, 15, 16, and 17.⁵ It is likely that brain imaging techniques and advances in molecular biology will help to identify the genetic pedigree of autism.

No curative treatment for autism has been identified, and management has focused on the control of symptoms that involves educational, behavioral and pharmacological therapies. The most effective model appears to be the program for the Treatment and Education of Autistic and Related Communication Handicapped Children (TEACCH).⁹ Education therapies concentrate on speech and language development, while behavioral therapies include reward and punishment for desirable/undesirable actions. In an attempt to improve behaviors that may cause self-injury

Table 1. DSM-IV TR Criteria for Autistic Disorder

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- A. A total of six (or more) items from I, II, or III with at least two from I, and one each from II and III
- I. Qualitative impairment in social interaction, as manifested by at least two of the following:
 - a. Marked impairment in the use of multiple nonverbal behaviors (e.g., eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction)
 - b. Failure to develop peer relationships appropriate to developmental level
 - c. A lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by lack of showing, bringing, or pointing out objects of interest)
 - d. Lack of social or emotional reciprocity
 - II. Qualitative impairments in communication as manifested by at least one of the following:
 - a. Delay in or total lack of the development of spoken language (not accompanied by an attempt to compensate through alternative methods of communication such as gesture or mime)
 - b. In individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
 - c. Stereotyped and repetitive use of language or idiosyncratic language
 - d. Lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level
 - III. Restricted, repetitive, and stereotyped patterns of behavior, interests, and activities as manifested by at least one of the following:
 - a. Encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
 - b. Apparently inflexible adherence to specific, nonfunctional routines and rituals
 - c. Stereotyped and repetitive motor mannerisms
 - d. Persistent preoccupation with parts of objects
- B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play
- C. Disturbance is not better accounted for by Rhett's Disorder or Childhood Disintegrative Disorder
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Table 2. Impact of the MMR vaccine on the natural history of each disease in the United States¹³

	Measles		Mumps		Rubella	
Comparison Years	1941	1995	1968	1995	1969	1995
Number of Cases	894,134	288	152,209	840	57,686	200
% decrease	99.97		99.45		99.65	

or interfere with social abilities, mood or behavior altering medications are used in addition to educational and behavioral therapies. Medications may also prove beneficial in managing comorbid target symptoms.^{10,11}

BACKGROUND – MMR VACCINE

Measles, mumps, and rubella are three common childhood diseases that are caused by RNA viruses. For 1998, the World Health Organization reported 30 million case of measles worldwide that resulted in 888,000 deaths.¹² In developing countries, approximately 10% of all deaths in children <5 years of age were related to the measles virus.¹²

The measles vaccine was introduced in 1968, and 20 years later it was combined with the Mump and Rubella vaccines (M-M-R II; Merck & Co., Inc., West Point, PA). MMR is a live virus vaccine for immunization against measles (rubeola), mumps and rubella (German measles).¹³ The impact of MMR administration in the United States can be assessed by comparing the maximum number of measles, mumps, and rubella cases reported in a given year prior to vaccine use to the number of cases of each disease reported in 1995 (Table 2).¹³ The current immunization schedule represents a consensus of The Advisory Committee on Immunization Practices, the American Academy of Pediatrics, and the American Academy of Family Physicians. These groups currently recommend administration of the first dose of MMR at 12–15 months of age and administration of the second dose at 4–6 years of age.¹⁴

Common adverse effects associated with the vaccine are primarily limited to reactions at the site of injection. Moderate (38.3–39.4) to high (>39.4) fever is the most common systemic reaction and generally begins 7–12 days after vaccination and persists for 1–2 days.¹³ A transient rash occurs in 5% of those given the vaccine. Serious side effects have been reported (e.g., encephalitis, encephalopathy, measles inclusion

body, death), but are extremely rare.¹³ Importantly, no permanent sequelae or deaths were reported in a post-marketing surveillance study that was conducted over a 12-year period in Finland.¹⁵ This study involved 1.5 million children and young adults who were vaccinated with M-M-R II during 1982–1993.

SCIENTIFIC EVIDENCE-MMR and AUTISM

The study reported by Wakefield and colleagues was the first that alluded to an association between the MMR vaccine and autism.¹⁶ The report is a consecutive case series that described 12 children (11 males) 3–10 years of age who were referred to a pediatric gastroenterology clinic with chronic enterocoliti. Gastrointestinal symptoms included abdominal pain, diarrhea, and bloating. Some children also had food intolerance. Each child also had a history of normal development that was followed by a loss of acquired skills, including language.

The children were hospitalized for one week while they underwent extensive testing. Gastroenterological assessment included ileocolonoscopy with biopsy and when possible barium follow-through. Urinary methylmalonic acid, an indicator of vitamin B-12 status, has been reported to be elevated in those with inflammatory bowel diseases; hence, urine was randomly collected from eight children for analysis of methylmalonic acid. The urinary values of this substance were significantly elevated in eight children when compared to age-matched controls.

Biopsy samples were taken from the terminal ileum, colon, and rectum. The results of the procedure were compared with data from colonoscopies that were deemed normal. Histology revealed patchy chronic inflammation in the colons of 11 children. Nine had lymphoid nodular hyperplasia of the terminal ileum, but no granulomas were noted. All children were antiendomysial-antibody negative. Stool cultures for common pathogens (e.g., *Campylobacter*

sp., *Salmonella* sp., *Shigella* sp.) were negative. Sera was also negative for *Yersinia enterocolitica*. None of the children had neurological abnormalities on clinical examination, MRI, EEG, or CSF profiles. To exclude known causes of childhood neurodegenerative diseases, thyroid function, serum long-chain fatty acids, and cerebrospinal fluid (CSF) lactate were measured, all of which were normal.

Medical histories and developmental records including details of immunizations and exposure to infectious diseases were obtained from parents, health visitors, and general practitioners. Developmental records noted that all children satisfactorily achieved early developmental milestones. In 8 of the 12 children the onset of behavioral difficulties were linked by the parents or the child's physician to MMR vaccination. The average interval from vaccination to the appearance of the first symptom was 6.3 days with a range of 1–14 days. The parents were not consistently able to recall the time of onset of abdominal symptoms. Although one child had received the monovalent measles vaccine at 15 months of age, no association was made to the vaccine. However, when he received the MMR at 4.5 years, his mother noted behavioral decline the following day. Another child who received the MMR at 16 months of age began to display behavioral symptoms within two months. The authors concluded that they had identified a chronic enterocolitis that might be related to neuropsychiatric dysfunction. They also reported that in most cases the onset of symptoms occurred after administration of MMR and that MMR (specifically measles) might be involved in induction of bowel abnormalities. They fell short of concluding that a relationship existed but did suggest that an association between MMR and an autism-bowel syndrome should be further investigated.

There have been many criticisms of the above. Of the 12 children reported, only eight with autism-bowel syndrome received MMR, and the time between onset of the disorder and administration of MMR was only reported in 5 children. Although the authors claimed that autism is a consequence of gastrointestinal inflammation, gastrointestinal symptoms were observed after, not before, symptoms of autism in all 8 cases. The cases were consecutively seen in clinic; however, the authors did not report the

time period over which the cases were identified. Because all of the children were referred to a pediatric gastroenterology clinic, there may have been selection bias.

The authors made no mention of overall immunization rates and whether the rates were similar in children with autism and those who were considered "healthy". The authors did note that the concurrent development of intestinal and behavioral disorders may have occurred by chance. To the investigators' credit, they did use normal age-matched cohorts for urinary methylmalonic acid concentration comparisons; however, they failed to use age-related normal values for many of their laboratory test.¹⁷ While the five ileocolonic biopsy series were age-matched and site-matched to histologically normal mucosa, the report fails to note if the three pathologist investigators who assessed the tissue histology were blinded to patient information or to one another's assessment. Finally, the authors failed to address the influence of time on the ability of parents to recall specific events.

For example, child number 4 was reported to have received the monovalent measles vaccine at 15 months of age and subsequently was given the MMR at 4.5 years of age. The day after receiving the MMR, his mother described "a striking deterioration in his behavior that she did link with the immunization." At the time this patient was evaluated in the gastroenterology clinic, he was 10 years of age. While their report offered interesting findings, it is hampered by multiple limitations that have been highlighted by a plethora of letters to the editor.¹⁷⁻²⁷ Perhaps the most poignant criticism of the Wakefield paper was offered by Chen and DeStefano, who addressed the difference in casual and coincidental reactions and suggested that the findings were simply temporal coincidence.²⁸

In response to the first study by the Wakefield group,¹⁶ Taylor and colleagues performed an epidemiological population-based, retrospective study to determine whether there may be a causal association between the MMR vaccine and autism.²⁹ They included children 0–59 months of age who were born with autism since 1979. Children were identified from registers and were linked to clinical records of immunization in eight North Thames health districts in the United Kingdom. The study identified 498 cases of autism, of which only 293 cases could be

confirmed by the criteria of the International Classification of Diseases, tenth revision (ICD10). Using these criteria, the diagnosis of autism was confirmed from information in the child's record. Using the same records, the child's present condition was compared to his/her condition between the ages of 18 months and 3 years.

For children who were diagnosed with autism after 18 months of age, the investigators compared the ages of vaccinated and unvaccinated children at the time of diagnosis. Children were classified into three categories: those who received the MMR vaccine before 18 months, those administered MMR at ≥ 18 months, and those who were never vaccinated with MMR. The analysis was done on logarithms of age, with linear regression for comparison. They found no difference in age at diagnosis of autism in cases vaccinated before or after 18 months of age. Likewise, there was no difference between those who were or were not vaccinated.

Finally, the researchers conducted a case-series to determine if there was a temporal association relating vaccination and the age that autism was diagnosed, the recorded child age when parental concern was expressed, and the age when developmental regression was confirmed. This study found no correlation between the MMR vaccine and risk of developing autism. They found that the age of onset within 1–2 years of diagnosis was independent of vaccination with MMR. Developmental regression did not cluster within 2 or 4 months after administration of MMR. Likewise, there was no temporal clustering for age at onset of parental concern, with the exception of a single interval within 6 months of MMR. The authors concluded that there was not a causal relationship between MMR and autism. Following a letter to the editor by Altmann, the Taylor group provided further analysis of their data.³⁰

Although there are several criticisms of the above study, there seems to be an overall reliability in the way the study was conducted.^{31,32} Unfortunately, the diagnosis of autism could not be verified according to ICD10 criteria in all cases; hence, the discovery of the diagnosis may have been incomplete. However, because there was close similarity between the ICD10-confirmed and non-confirmed cases, the authors were confident in the overall diagnosis of autism. The investigators noted that there was variability in the

quality of clinical notes and that the information may not have contained regularly updated data. Taylor et al. conducted another study to further assess whether the MMR vaccine was associated with bowel problems and a "new variant" form of autism.³³ The investigation was a population study that employed a review of case notes that were independently linked to vaccine data. The data were obtained from five health districts in North East London and included 278 children with core autism and 195 with atypical autism. These children were born between 1979 and 1998 and were primarily identified from computerized disability registers. The investigators noted bowel problems lasting ≥ 3 months and the age of the child when developmental regression was reported.

In order to assess whether MMR caused or triggered autism or bowel problem, the investigators evaluated the relationship of both bowel disorders and developmental regression to vaccination with MMR. No significant differences were found in rates of bowel problems or regression in children who received MMR before their parents became concerned about their development, those who received MMR after such concern was noted, and those who did not receive the MMR vaccine. Although the authors noted a possible association between non-specific bowel problems and developmental regression in children with autism, this was unrelated to MMR. The investigators concluded that this study offered additional evidence against any involvement of the MMR vaccine with the development of a "new variant" form of autism.

Another report emanated from Finland.³⁴ Makela and colleagues performed a retrospective study to evaluate if a relationship exists between MMR and encephalitis, aseptic meningitis, and autism. The study linked individual MMR vaccination information with data from a nationwide hospital discharge register that contained information on 535,544 children (1–7 years old). The data included those who were vaccinated between November 1982 and June 1986 and those hospitalized for autism between November 1982 and December 1995. The investigator identified children hospitalized for autism after vaccination. The researchers also assessed hospitalizations because of inflammatory bowel diseases for children with a diagnosis of autism. Of those who received the MMR vaccine, 309

children (0.057%) were admitted for autism following immunization. The time between vaccination and hospitalization in this group was 3 days to 12.4 years. There was no clustering of autism when the time between vaccination and hospitalization was assessed, and none of the autistic children were hospitalized for inflammatory bowel diseases. The authors concluded that there was no association between MMR and autism.

SCIENTIFIC-ASSOCIATION WITH INFLAMMATORY BOWEL DISEASE (IBD)

The virus responsible for causing measles infects the respiratory system and subsequently spreads to lymphatic tissue. Lymph cells in the gastrointestinal tract are infected during the acute phase of the infection, but whether this consequently causes chronic inflammation is highly questionable. Although it has not been validated, one hypothesis speculates that the measles virus persists in the intestine of some individuals and later elicits a chronic inflammatory infection. MMR contains a very weak live measles virus; therefore, some have theorized that vaccination with MMR could cause an inflammatory process in the intestine that is subsequently linked to the development of a developmentally regressive disorder.

The first paper by Wakefield suggested such a link between MMR and inflammatory bowel disease.¹⁶ In the discussion section of that paper, the authors suggested that ongoing virology studies might help to clarify the matter. These studies were extremely germane since the authors have speculated that a measles virus-induced bowel abnormality was somehow linked to the development of autism. In a less publicized subsequent paper they used a highly sensitive assay for the detection of measles virus RNA.³⁵ The investigators used peripheral blood mononuclear cells and tissue resected from the intestines of individuals with inflammatory bowel disease and compared them to control clinical samples. The positive control samples confirmed the sensitivity of the assays employed. Interestingly, none of the samples were positive for measles N- or H-gene RNA using RT-PCR. In another study, the Wakefield group tested intestinal biopsy samples for the presence of the measles virus genome in children with and with-

out autism.³⁶ The measles virus was detected by reverse-transcriptase polymerase chain reaction (RT-PCR) and *in situ* hybridization. Seventy-five of 90 children with autism were found to have measles virus genome in their intestinal biopsy tissue as compared with only 5 of 70 control patients. The paper has been criticized in three areas.³¹ The first concern focuses on whether the presence of the measles virus in intestinal tissue is unique to children with autism. □ For this to be true, children with or without autism must be matched for immunization status (i.e., received MMR), and they must be matched for the length of time between administration of MMR and collection of the intestinal specimen. Although this information was essential to the investigators' hypothesis and should have been available for analysis, it was not reported.³¹

The second criticism involves the authors' failure to determine if the intestinal measles virus genome contained natural measles (i.e., measles was still prevalent in England at the time of this study) or the vaccine measles virus. It would have been easy to determine which measles virus was present since primers were available to distinguish these two types of virus. The third criticism involved the RT-PCR test used to identify the measles virus. This is a very sensitive assay that may be subject to a high risk of false positive results. Lizuka et al. noted that a possibility exists that a host-derived antigen or gene might be misinterpreted as the measles virus.³⁷ Finally, the authors did not state if the individual performing RT-PCR analysis was blinded whether the tissue was from a case or a control.

The final study by the Wakefield group came in 2002.³⁸ Again the group examined the association between measles vaccination and age of child at measles immunization with the later development of inflammatory bowel disease. The study design involved a prospective population-based national birth cohort of individuals born in Great Britain during one week in April 1970. Included in the data set were 7616 individuals who had complete vaccination histories and who could be located as adults. A diagnosis of Crohn's disease, ulcerative colitis, and diabetes mellitus (a control disease) was obtained using a survey when these individuals were 26 years of age. The diagnoses were then confirmed by their physicians. Vaccination and measles and

mumps infection data were obtained from the survey at age 5 years and 10 years, respectively. Adjustment was made for gender, the number of individuals living in the household during the individual's childhood, and the father's social class at the individual's birth. There was no statistically significant association between measles vaccination status at 5 years of age and Crohn's disease, ulcerative colitis, or diabetes. The authors did note a trend with increasing age of measles vaccination and a risk for the development of Crohn's disease; however, this conclusion was based on very few cases who were vaccinated after the age of 2 years. The investigators concluded that the monovalent measles vaccination is not associated with inflammatory bowel disease by 26 years of age.

A large number of papers have been published on the correlation between the MMR vaccination and inflammatory bowel disease. Although the list of studies is not inclusive, some investigators have shown an association,³⁹⁻⁴⁵ while others reported no link between the measles vaccination and the development of inflammatory bowel disease.⁴⁶⁻⁵² It is important to note that 4 of the seven studies cited above as supporting an association have emanated from the Wakefield group.^{39,41,42,44} At this time, epidemiological and pathological studies by different investigators have provided conflicting results. For this reason, many organization have concluded that a link cannot be established.^{5, 53} For a more extensive review, the reader is referred to several publications on the controversy.⁵⁴⁻⁵⁶

SCIENTIFIC-INCREASE IN THE RATE OF AUTISM

No one would refute that there has been an increase in the diagnoses of autism over the past two decades. Following a review of 23 epidemiologic studies, Fomborne reported a median prevalence rate for studies performed between 1966-1988 (prevaccine) of 4.3 per 10,000 compared to studies conducted between 1989-1998 of 7.2 per 10,000.⁵⁷ If the MMR vaccine is causally related to the development of an autistic disorder, it is logical to assume that the rate of MMR vaccination should have increased simultaneously and proportionally to the increased rate of diagnosis of autism. However, the rate of MMR vaccination has not changed.⁵⁸

Dales and colleagues conducted a retrospective analysis to examine trends in the occurrence of autism in relation to the MMR vaccine.⁵⁹ The objective of the study was to determine if there was a correlation between trends in MMR immunization and the onset of behavioral symptoms (i.e., autism). The study examined children born between 1980 and 1994 (600-1900 children/year) who were enrolled in California kindergartens. The study retrospectively determined MMR immunization rate as of ages 17 months and 24 months of age and the numbers of Department of Developmental Services system enrollees diagnosed with autism, grouped by year of birth. School immunization records of kindergarten children sampled were assessed to identify when they received their immunizations. The authors reported that an increase in diagnosis of autism over the time period was 373% while MMR immunizations increased only by 10%. The authors also noted that the increasing trend of autism cases persisted after the numbers of MMR immunization coverage had leveled off. This trend in increasing cases of autism is many times greater in relative magnitude than the modest increase in MMR coverage; hence, this paper does not support a cause-effect relationship between MMR and autism.

Although retrospective analysis is an appropriate method to use when studying trends over time, there were some weaknesses of the above study that the investigators address. Examination of immunization and autism records on the individual children would have proven valuable to this research effort; however, these data could not be linked. The study could not determine with certainty how many children with autism were not enrolled in the system. Likewise, they were unable to assess the changing numbers of children and the distribution of California children over time as the system expanded and matured. Further, the immunization data provided vague measurement of the percentages of children who received the combined MMR vaccine versus immunization with the individual components (i.e., measles, mumps, and/or rubella components). Historical information regarding the use of the MMR vaccine in the United States in the 1984-1994 birth cohorts would suggest that administration of the combined MMR vaccine was standard of practice.

Kaye et al. performed a time trend analysis

to investigate the relationship between the MMR vaccine and the diagnosis of autism.⁶⁰ They examined data from 305 children, ages 12 years or younger, who were diagnosed with autism during 1988–1999. The researchers evaluated computer-recorded information from the United Kingdom general practice research database for each of these children and estimated the annual incidence and age-specific incidence of autism. The four-year cumulative risk of diagnosed autism was calculated from data evaluated in 1988 and 1993. Data were further analyzed from 114 boys whose first diagnosis of autism occurred between ages 2–5 years. Annual birth cohorts were evaluated separately. The researchers found that the estimated yearly incidence of autism among children ≤ 12 years of age increased sevenfold, from 0.3 to 2.1 per 10,000 patients. The median age at first diagnosis remained stable over time. The four-year cumulative risk of diagnosed autism quadrupled from 1988–1993 with an increase from 8 to 29 cases per 10,000 patients. In contrast, the prevalence of MMR vaccination among those children remained constant at 97%. The researchers further assessed the possible temporal relationship between the MMR vaccination and the risk of autism to determine if altered time of first vaccination increased the risk of developing autism. Data were analyzed from children with an autistic disorder and from the general population. It was found that both groups of children were vaccinated at nearly identical ages, indicating that a temporal relationship between MMR and autism is unlikely.

Using population-based data from the general practice database, this study found that the overall incidence of newly diagnosed autism increased dramatically from 1988 to 1993 and that the risk of autism increased between males ages 2–5 years. However, the prevalence of MMR vaccination remained nearly constant. These data confirm that there is no connection between the MMR vaccine and the risk of autistic disorder. While this information is beneficial, as the authors conclude, full clinical information from the diagnosing practitioners is needed to further assess whether there are other explanations for the remarkable increase in the incidence of autism. Taylor and colleagues assessed trends in the time series of cases.²⁹ Because there was some lack of availability of cases in the later years, only chil-

dren between the ages of 0–59 months at diagnosis and those born between 1979 and 1992 were included. The investigators reported that there was no significant sudden increase or change in the trend for the diagnosis of autism after the introduction of the MMR vaccine. Although the study did recognize some increase in the incidence of autism in recent times, they concluded that the increase may be a reflection of several factors including better recording of data.

Taylor et al. also reported that the percentage of children with developmental regression (25% overall) or bowel symptoms (17%) did not change significantly ($P=0.50$ and 0.47 , respectively) during the 20-year study period. This window of time included the period in which MMR was introduced.³³ Several reports have shown a significant increase in the diagnosis of autism from between 1987 and 1998. Many individuals and medical organizations have proposed that a variety of factors may account for the rise in the number of children with this disorder. An increase in the number of cases is often cited as evidence of an increasing trend; however, these increases occurred well after the licensure and introduction of MMR. Most investigators and practitioners have concluded that the increase may be attributed to reporting bias, changes in the diagnosis of autism, and/or better case ascertainment over time.

Hasley et al. contribute the increasing rate to improved recognition of the disorder and refinement of the DMS-IV criteria.⁶¹ Prior to the DSM-III-R, autism was classified as part of pervasive developmental disease, not a separate condition. Revision to the 3rd edition of the DSM-III recognized the broad spectrum of severity of autism and allowed for the diagnosis of autistic spectrum disorder.⁶¹ The DSM-IV, which was released in 1994, considered autism as a disorder in and of itself and not as part of the larger classification of pervasive developmental disorder. The criteria were expanded to stress developmental aspects; hence, both higher and lower functioning children could now fit the criteria.⁶¹

POLITICAL HEARINGS

In April of 2001, Congressman Dan Burton (R-IN), chair of the House Committee on Government Reform, called a series of congressional hearings to investigate the role of the MMR vac-

cine in the development of autism.⁶² Congressman Burton's passion for this issue emanated from his belief that his grandson's regressive autism was linked to administration of a variety of vaccines in one day. Dr. McCormick, professor at the Harvard School of Public Health was there to respond to questions about the Institute of Medicine committee's report on the MMR vaccine and autism.⁶³ Dr. McCormick steadfastly supported the report of the IOM committee, which concluded that there was no evidence that vaccination with MMR is associated with the development of autism. In response to the congressman's inference that the report was unduly influenced by member ties to the pharmaceutical industry, the IOM appointed a panel of experts that had no financial ties to the vaccine industry.⁶⁴ Despite this approach, the congressman continued to emphasize potential financial associations of committee members and peer reviewers with the pharmaceutical industry. Although he was told that "None of our (IOM) recommendations or conclusions were changed after peer review", he threatened to subpoena financial records of the reviewers and questioned whether their employers (i.e., universities) had ever received monies from pharmaceutical companies.⁶²

During these hearings, Dr. Wakefield proposed that more clinical investigations are needed before epidemiological research is to conclusively answer the question. He also testified that his studies have been misinterpreted by the IOM. He stated, "We're not saying it [the MMR vaccine] is the cause [of autism], but what we are saying is 'What's going on?'" He then commented on a recent study showing measles virus in the intestines of children with autism and proposed pursuing new investigations to further evaluate this matter.³⁶

Dr. Gershon from Columbia University explained the scientific improbability of a connection between the MMR vaccine and autism. He stated that in order for the MMR vaccine to cause an autistic disorder, "three miracles" would have to occur: 1) the virus would have to enter the gut, 2) the virus would have to create a toxin that would leak from the intestines, 3) the toxin would have to bypass the liver, and 4) the toxin would have to penetrate the blood-brain barrier. Dr. Bradstreet, of the International Autism Research Center and father of a child with autism, sug-

gested that researchers explore an interaction between the vaccines and autoimmune response.

POSITION OF MAJOR MEDICAL ORGANIZATIONS

A number of expert review panels have reviewed the available literature to determine if there is an association between MMR and autism. The British Medical Research Council,⁵ the World Health Organization,⁶⁵ the American Academy of Pediatrics,⁶¹ the Institute of Medicine,^{63,64,66} the American Medical Association,³¹ and the Population and Public Health Branch of Canada⁶⁷ have all concluded that there is no association between MMR and autism. The three most extensive reviews were conducted by the British Medical Research Council, the Institute of Medicine, and the American Academy of Pediatrics.

The first extensive review of this controversy was conducted by the American Academy of Pediatrics (AAP).⁶¹ In 2000, the AAP assembled a panel of experts in the following areas to review information related to a possible relationship between MMR and autism or inflammatory disease: general pediatrics, developmental pediatrics, child neurology, pediatric infectious diseases, virology, pathology, public health, epidemiology and psychiatry. The panel heard presentations on the genetics, epidemiology, and neurobiology of autism; known neurologic effects of measles, mumps and rubella and vaccine; and evidence related to identification of the measles virus in the gastrointestinal tract of those with autism.

The authors who had published work on MMR and autism were invited to either present their work or to provide material that formed the basis of their conclusions. The group also reviewed videotaped testimony of Drs. Wakefield and O'Leary that was given before the House Government Reform Committee. The panel concluded that the available evidence does not support the hypothesis that MMR vaccine causes autism, associated disorders, or IBD. The expert panel also concluded in its report that "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."

In early 2001 the British Medical Research

Council (MRC) was commissioned by the Department of Health to review the scientific literature concerning the epidemiology of autism.⁵ The MRC established an *ad hoc* meeting of experts that convened in March of that year. The group was charged with examining the available evidence relating MMR vaccination to chronic gastrointestinal inflammation and autism. Three groups of scientists assessed the research evidence. Additionally, a lay group was established and two members of that group attended each meeting of a scientific group. Four meetings of the subgroups were held between July and November of 2001. In order to ensure the integrity of the report, the draft report was subjected to external review by non-group members who were recognized as experts in the field. The British Medical Research Council endorsed the Group's final recommendations, which are presented in the "Review of Autism Research; epidemiology and causes".⁵ The expert panel concluded that current evidence does not support the proposed link of the combined measles, mumps and rubella (MMR) vaccine to Autism Spectrum Disorders.

The final group to extensively assess this controversy was the Institute of Medicine (IOM) of the National Academy of Sciences (NAS).^{63,64} The Centers for Disease Control and Prevention and the National Institutes of Health (NIH) petitioned the IOM to evaluate the available body of scientific evidence concerning MMR and autism. The Immunization Safety Review committee consisted of 14 individuals with expertise in medicine (e.g., pediatrics, nursing, infectious disease, internal medicine), public health (epidemiology, biostatistics, health communication), medical and scientific research (immunology, genetics, neurology), risk perception, decision analysis, and ethics. In March of 2001 the committee held a public information-gathering scientific meeting on MMR and autism. Handouts and audio recordings of the presentations are available on the Institute of Medicine's website.⁶⁵ After review of the available scientific evidence, the committee concluded that the measles-mumps-rubella vaccine does not cause autism and that there are no proven biological mechanisms that would explain a relationship between the two.

CONCLUSION

While the Wakefield group of investigators has persisted in raising concerns about a possible link between the measles-mumps-rubella vaccine and autism or inflammatory bowel disease, other investigators have found no association between the vaccine and autism. Clearly, the benefits of immunization with MMR outweigh the possible risks associated with the vaccine. Three of the senior investigators on the first Wakefield et al. paper¹⁶ that implicated MMR in developmental regression could not have emphasized the benefits of vaccination more when they subsequently endorsed the current MMR vaccination recommendations.⁶⁸

After consideration of all available information and presentations, leading pediatricians, developmental pediatricians, child neurologists, pediatric infectious disease specialists, virologists, pathologists, epidemiologists, psychiatrists and researchers in the field, The British Medical Research Council, the World Health Organization, the American Medical Association, the Institute of Medicine, and the American Academy of Pediatrics all reached the same conclusion - the available evidence *does not* support an association between the MMR vaccine and autism or inflammatory bowel disease.

As healthcare practitioners, we should take comfort in the fact that the weight of available epidemiological and scientific evidence does not support a causal association between MMR vaccine and autism or inflammatory bowel disease. Hence, we should continue to encourage parents to have their children immunized with the recommended two doses of the M-M-R II vaccine.

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