

Relationship Between MMR Vaccine and Autism

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OBJECTIVE: To evaluate the proposed link between the administration of the measles, mumps, and rubella (MMR) vaccine and the development of autism.

DATA SOURCES: A literature search utilizing MEDLINE (1966–November 2003), with the key terms measles, mumps, rubella, and autism, was conducted. Review of the references listed in the articles identified was also performed.

DATA SYNTHESIS: Ten articles that specifically evaluated the possible relationship between the MMR vaccine and autism were identified. Review articles, commentaries, and evaluations of a link between gastrointestinal symptoms in autistic children and MMR immunization were excluded.

CONCLUSIONS: Based upon the current literature, it appears that there is no relationship between MMR vaccination and the development of autism.

KEY WORDS: autism, MMR vaccine.

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REQUEST

Is there a relationship between the administration of the measles, mumps, and rubella (MMR) vaccine and the development of autism?

RESPONSE

BACKGROUND

Autism is a serious and incurable developmental disorder characterized by abnormalities in social interactions and communication.¹ Autism's etiology is unknown; however, some hypotheses include genetic abnormalities, obstetric complications, neuronal damage, and prenatal or postnatal infections. In some children, autistic characteristics have been described within a few weeks of receiving the MMR vaccine. This is complicated by the fact that symptoms of autism typically begin during the second year of life, which is close to the time the first dose of MMR vaccine is administered. It is unclear whether the recent increase in the incidence of autism is due to an increase in vaccination rates, a result of better recognition and changes

in diagnostic criteria, or additional precipitating factors that have yet to be identified.

Recently, there has been a great deal of discussion in the medical literature regarding a possible association between the MMR vaccine and the development of autism. The controversy was brought to the forefront following a 1998 case series report in which the authors hypothesized a “unique disease process” of bowel abnormalities and autism in a small group of children who had received MMR immunization.² The authors hypothesized that the MMR vaccine causes inflammation of the gastrointestinal tract, producing a leaky bowel that allows for the circulation of neurotoxins that can cause central nervous system damage and developmental regression.³ Of note, 10 of the 13 authors from the original report retracted their findings in March 2004 after allegations of conflict of interest.⁴

Prior to the introduction of vaccines for measles, mumps, and rubella in the 1960s, between 50 000 and 500 000 cases of those diseases were reported annually.⁵⁻⁷ Encephalopathy, pneumonia, sterility, spontaneous abortions, congenital rubella syndrome, and death were the primary sequelae following infection from these viruses. Between 1989 and 1991, a measles outbreak occurred in the US.⁵ Nearly 100 000 cases were reported, resulting in >100 deaths. The

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outbreak was attributed to low immunization rates. After this outbreak, an effort to immunize all school-aged children resulted in a dramatic increase in immunization rates (70% in 1990 vs 91% in 1997) and a dramatic decrease in the number of cases of measles (<500/y).

Recent reports from the Public Health Laboratory Service in the UK showed the number of cases of mumps has increased following a 12% decline in the number of children being immunized.⁸ In Northern Ireland, the number of cases of mumps increased tenfold from 1999 to 2001 (95 vs 1000 cases) due to decreases in immunization rates. This decrease is being attributed to the increasing anxiety that the vaccine might trigger autism.

The MMR vaccine is usually administered during a time when autistic characteristics begin to present themselves (~15–18 mo of age). This fact, combined with the recent media publicity regarding the possible link of autism to MMR vaccine, has raised a great deal of concern for parents and practitioners. The purpose of this article is to discuss the primary literature evaluating an association between administration of MMR vaccine and the development of autism.

LITERATURE REVIEW

Data Sources

A MEDLINE search using the terms measles, mumps, rubella, and autism was performed. The results of the search were then combined and limited to human and English-language reports. The search yielded >200 references, which were further reduced to find articles that specifically assessed the link between MMR vaccine and autism. A reference review of the identified articles was performed to ensure that no primary literature was missed. Review articles and commentaries have been excluded from this discussion. Ten articles that met inclusion criteria were identified and are discussed here.

Studies Evaluating Cause and Effect

The studies reviewed here sought to evaluate whether a causal relationship can be determined between administration of MMR vaccine and the development of autism. In the first of these investigations, Wakefield et al.² submitted a case series report of 12 children between 3 and 11 years of age who were referred to a pediatric gastroenterology clinic with symptoms of enterocolitis and a history of normal development followed by a loss of acquired skills. All children underwent gastrointestinal, neurologic, and behavioral assessment. In 8 of the children, the onset of behavioral problems was linked in proximity by the parents or the child's physician to the administration of the MMR vaccine, with a mean onset of 6.3 days after immunization. All 12 children had some gastrointestinal dysfunction; however, it is unclear whether those symptoms were present prior to administration of the vaccine. The authors concluded that the similarity in gastrointestinal abnormalities could be the manifestation of a previously undescribed syndrome of gastroenteritis and autism. Although the au-

thors were unable to demonstrate an association between autism and MMR vaccine, the findings sparked suspicion regarding the safety of the vaccine in both the general public and the medical community.

Following the Wakefield et al.² report, another group conducted a cross-sectional epidemiologic study to evaluate whether the MMR vaccine could be causally associated with autism.⁹ Four hundred ninety-eight autistic children born between 1979 and 1998 were identified using the special needs and disability registers of North East Thames, UK. A time-trend analysis was performed to evaluate whether there was a change in the incidence of autism after the addition of the MMR vaccine to the immunization schedule. The number of cases of autism by year of birth showed a significant upward trend through the 1992 birth cohort, but no spike or change in the autism trend occurred after MMR vaccine was introduced in 1988.

The rate of MMR immunization leveled off as the prevalence of autism continued to increase. In addition, no differences were detected in age at diagnosis of autism between vaccinated patients with autism and unvaccinated patients with autism. The authors concluded that the increasing trend in the incidence of autism could not be temporally associated with the initiation of MMR vaccine, since autism rates continued to increase despite a plateau in the rates of vaccination. In addition, the age of diagnosis of autism was unrelated to the administration of MMR vaccine.⁹

A series of articles from Finland also concluded that no link between MMR immunization and the development of autism could be made.¹⁰⁻¹² The largest report, a retrospective study, examined >500 000 children aged 1–7 years.¹² The authors evaluated vaccine administration records between November 1982 and June 1986 and compared them with discharge records for children admitted to Finnish hospitals for encephalitis, aseptic meningitis, or an autistic disorder during the same time period. The time from immunization to hospital admission for children with autism (n = 309) ranged from 3 days to >12 years, and no clustering was seen at any time point following MMR immunization during the study period. No autistic children were admitted to the hospital for inflammatory bowel disease. The authors concluded that there was no link between MMR vaccine and autism with or without concomitant inflammatory bowel disease. Since symptoms of autism usually do not develop acutely, the major limitation of this study is the possibility of under-representation of autistic children who were never admitted to a hospital for evaluation.

The results of the mentioned studies suggest that there is no causal association between MMR immunization and the development of autism. The primary limitations of many of these studies were a lack of defined diagnostic criteria to validate the diagnosis of autism and database or medical record variability, especially related to age of onset of parental concern.

Population-Based Studies

The primary goal of most of the studies discussed here was to determine whether the incidence of autism paral-

leled immunization rates for the described populations. One study sought to determine the autism risk in immunized and unimmunized children, as well as whether clustering of autism diagnoses occurred at any time point after immunization.¹³

A time-trend analysis was conducted to determine whether a correlation existed between the increased prevalence of autism and routine MMR immunization.¹⁴ The authors examined population data on early childhood MMR immunization rates in California for children born between 1980 and 1994. The data were compared with the autism case load for the California Department of Health Services from annual surveys of kindergarteners born between 1980 and 1994. There was a relative increase in MMR immunization rates (72% in 1980 vs 82% in 1994). During the same time period, a relative increase in autism from 176 to 1182 cases was noted (an increase of 572%). One major limitation of this study was that the immunization records of the autistic children were not available for review to evaluate what portion of the autistic children received MMR immunization, and it was impossible to determine whether autistic children had similar immunization rates as non-autistic children. In addition, the incidence of autism might have been skewed by fluctuations of children moving to or from California.

Kaye et al.¹⁵ found similar results in their time-trend analysis of autistic children in the UK, where they observed a sevenfold increase in the incidence of autism in light of a plateau in MMR immunization rates from 1988 to 1999. They noted that, if MMR vaccine administration was associated with the increase in autism incidence, one would expect the prevalence of autism to level off as the immunization rates level off. Since the number of children with autism continued to increase, the investigators concluded that administration of MMR vaccine was not linked to the development of autism.

Taylor et al.¹⁶ conducted a follow-up population study to investigate whether administration of MMR vaccine was associated with bowel problems and developmental regression in children with autism, as was hypothesized by Wakefield et al.² Autistic children born from 1979 to 1998 were identified using the special needs and disability registers of North East Thames, UK. The children were evaluated for bowel disorders, age of onset of developmental concerns, and symptoms of developmental regression. At baseline, 17% of the children had bowel problems, while 25% had signs of regression. No trends were identified for bowel problems or regression based upon year of birth. In addition, there was no evidence of an association between bowel symptoms and MMR immunization. Children who had signs of regression had a higher incidence of bowel disorders, but no link was identified with exposure to MMR vaccination or year of birth. The authors concluded that no change occurred in the incidence of regression or bowel symptoms in autistic children over the 20-year study period, and children who experienced developmental regression were more likely to develop bowel symptoms.¹⁶ These findings suggest that there does not appear to be evi-

dence linking MMR vaccine to a new, variant form of autism associated with bowel dysfunction, a conclusion that was echoed in a cross-sectional evaluation of children born in the UK.¹⁷

The primary limitation of the Taylor et al. study was the variability in information recorded in the database. A few patients did not have information regarding developmental milestones or age of onset of parental concern; in addition, the parental history regarding onset of regressive symptoms changed in 13 patients following publicity of the link between MMR vaccination and autism.¹⁶

A retrospective follow-up study, the largest to date, evaluated all children born in Denmark between January 1991 and December 1998 using a number of national registries to evaluate whether a link between MMR vaccination and the development of autism could be made.¹³ Immunization records for >500 000 children were reviewed and compared with the immunization records of children diagnosed with autism using standardized criteria. No increase in the incidence of autism or autistic spectrum disorders was detected between vaccinated and unvaccinated children. The authors also found no association between the child's age at immunization and the development of autism. The authors concluded that there was no difference in the risk of autism between vaccinated and unvaccinated children. In addition, there was no clustering of cases of autism around the time of immunization, suggesting the lack of a temporal relationship between administration of MMR vaccine and the development of autism.

In general, the population studies demonstrated an increase in the prevalence of autism that was out of proportion to the immunization rates for the populations identified. In addition, some of the studies reported that the risk of developing autism was similar between immunized and unimmunized children.

SUMMARY

The current MMR vaccine has been in full use since 1979 in the US, 1982 in Finland, and 1988 in the UK and Denmark. Immunization rates since the late 1980s have been relatively constant in all 4 countries, while the rates of autism have continued to rise. While all of the studies discussed here showed an increase in the incidence of autism, none was able to demonstrate a causal association with MMR immunization. The question still remains, however, of whether there is a subset of the population at risk of developing autism precipitated by the administration of the MMR vaccine. Based upon the available data, the potentially devastating risks of withholding the vaccine are greater than the risks of vaccination. Until further data are available to establish a causal relationship, healthcare providers should continue to recommend MMR immunization to their patients.

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EXTRACTO

OBJETIVO: Evaluar el vínculo propuesto entre la administración de la vacuna contra el sarampión, la papera y la rubéola (MMR, por sus siglas en inglés) y el desarrollo de autismo.

FUENTES DE INFORMACIÓN: Se llevó a cabo una búsqueda de la literatura médica en MEDLINE (1966–noviembre 2003) y una revisión de referencias.

SÍNTESIS: Se identificaron 10 artículos que evaluaron, específicamente, la posible relación entre la MMR y el autismo. Se excluyeron los artículos de repaso, los comentarios, y las evaluaciones del vínculo entre los síntomas gastrointestinales de niños con autismo y la MMR.

CONCLUSIONES: Según la literatura actual, parece que no hay ninguna relación entre la vacuna contra la MMR y el desarrollo de autismo.

Rafaela Mena

RÉSUMÉ

OBJECTIF: Evaluer le lien supposé entre la vaccination contre la rougeole, les oreillons et la rubéole (ROR), et le développement de l'autisme.

REVUE DE LITTÉRATURE: Littérature primaire repérée par une recherche sur MEDLINE (1966 à novembre 2003) et une revue de bibliographie. Les revues, les commentaires, et les évaluations d'un lien entre les symptômes gastro-intestinaux des enfants autistes et le vaccin ROR ont été exclus.

RÉSUMÉ: Dix articles évaluant la possibilité d'une relation entre le vaccin ROR et l'autisme ont été identifiés. Les études épidémiologiques montrent une augmentation de la prévalence de l'autisme hors de proportion avec les taux de vaccination ROR pour les populations étudiées. Plusieurs études rapportent que le risque de développer l'autisme est similaire chez les enfants vaccinés ou non vaccinés par ROR.

CONCLUSIONS: D'après la littérature disponible, il apparaît qu'il n'y a pas de lien entre la vaccination ROR et le développement de l'autisme.

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