Vaccines and Autism: Evidence Does Not Support a Causal Association

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A suggested association between certain childhood vaccines and autism has been one of the most contentious vaccine safety controversies in recent years. Despite compelling scientific evidence against a causal association, many parents and parent advocacy groups continue to suspect that vaccines, particularly measles–mumps–rubella (MMR) vaccine and thimerosal-containing vaccines (TCVs), can cause autism.

MMR AND AUTISM

Autism is a serious, life-long developmental disorder characterized by marked impairments in social interactions; communication skills; and repetitive, restrictive, or stereotyped behaviors, interests, and activities. Autism encompasses the more severe end of autism spectrum disorders. Autism may have a variety of causes, but in only a few cases has a specific cause been identified. It has a strong genetic component and associated neurological defects probably occur early in embryonic development.[1] Although a diagnosis of autism may not be made until later in life, when communication delays and characteristic behaviors become apparent, in most cases the underlying neuropathology of autism is present at birth. In a minority of cases, a child can appear to be developing completely normally but then regress and develop autistic characteristics. It is for these cases of regressive autism that, at least theoretically, a biologically plausible link with vaccination could be made.

Concern about a possible link between vaccines and autism was initially ignited by a publication in *The Lancet* in February 1998.[2] The report described 12 children with inflammatory bowel conditions and regressive developmental disorders, mostly autism. In 8 of the 12 cases, the children's parents or pediatricians believed that MMR vaccine might have contributed to the onset of behavioral problems because onset followed shortly after vaccination. The study's authors hypothesized that MMR vaccine may have been responsible for the bowel dysfunction, which subsequently resulted in neurodevelopmental disorders. Some of the same investigators subsequently proposed a new syndrome consisting of gastrointestinal disorders, primarily ileocolonic lymphonodular hyperplasia and mild intestinal inflammation, associated with behavioral regression. One of the key pieces of evidence in support of the MMR and autism hypothesis was the reported identification of measles virus nucleic acid sequences in the blood cells and intestines of some of the affected children.[3,4] It was not determined, however, if the genetic material was from wild or vaccine strain virus. Other researchers have not been able to detect measles virus genome sequences in leukocytes of autistic children vaccinated with MMR.[5] Independent investigators have also been unable to find evidence of a unique syndrome of gastrointestinal disorders and regression in autistic children vaccinated with MMR,[6] and no correlation has been found with the onset of regression.[7]

One of the first population-based studies of the MMR and autism hypothesis identified all 498 known cases of autism spectrum disorders in a district of London who were born in 1979 or later and linked them to a regional vaccination registry.[8] The study found no sharp increase in autism after the introduction of the MMR vaccine in 1988 and no clustering of onset was identified within predefined intervals after vaccination. The study did not find a temporal relationship between vaccination and onset of regression. Another study of UK data from 1959 to 1993 also failed to find a step-up in the rates of autism following the 1998 introduction of MMR.[9]

Indirect evidence of a lack of association between MMR vaccine and autism was also provided by early ecological studies conducted in the United Kingdom[10] and California.[11] Each of these studies compared temporal trends in MMR vaccination coverage with corresponding trends in autism prevalence. Neither found a positive correlation. The California data, in particular, received much attention following the publication of a report documenting a large increase in the number of people with autism enrolled in the state's Developmental Services System. Correlating changes in the number of autism cases with changes in vaccination

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coverage, however, is complicated by changes in diagnostic criteria and possible increased awareness and recognition of autism. Even if the service data are accepted as valid, the study by Dales found that the increase in autism cases could not be explained by MMR coverage, which was relatively stable in California.[11] Recent studies from Japan and Canada have not found correlations between MMR use and autism prevalence. Studies in Japan found that even though MMR vaccination was completely discontinued in 1993, the prevalence of autism diagnoses increased among cohorts of children born between 1988 and 1996,[12] and there was no difference in the rates of regressive autism.[13] Similarly, a study conducted in Montreal found that the birth cohort prevalence of pervasive developmental disorders, which include autism, increased from 1987 to 1998, whereas during the same time MMR vaccination coverage showed a statistically significant decrease.[14]

Controlled epidemiologic studies have not found an association between MMR vaccination and autism. A retrospective cohort study from Denmark is particularly persuasive.[15] The study contained data on over half a million Danish children, including nearly 100,000 who had not been vaccinated with MMR. The relative risk associated with MMR was 0.92 (95% confidence interval (CI): 0.68–1.24) for autistic disorder and 0.83 (95% CI: 0.65–1.07) for other autism spectrum disorders. A large, population-based case-control study conducted by the Centers for Disease Control and Prevention (CDC) also did not find evidence to support an association between MMR and autism.[16] The study included 624 case children in metropolitan Atlanta and 1,824 matched controls. Vaccination data were abstracted from immunization forms required for school entry. The overall distribution of ages at MMR vaccination among children with autism was similar to that of matched control children. Another large case–control study of 1,294 cases of pervasive developmental disorder and 4,469 controls from the UK General Practice Research Database (GPRD) found a relative risk of 0.86 (95% CI: 0.68–1.09) for MMR vaccine.[17]

The results of independent studies conducted after the publication of the original report of a possible association between MMR and autism provide compelling evidence against the hypothesis. More recently, concerns have been raised about possible biases in enrollment of participants in the study by Wakefield *et al.*[18] and 10 of the original 13 authors published a formal retraction of the conclusions of the 1998 article.[19] An Immunization Safety Review Committee of the Institute of Medicine (IOM) reviewed the epidemiologic and other evidence on MMR vaccine and risk for autism spectrum disorders and concluded that the evidence favors rejection of a causal relationship.[20]

THIMEROSAL

Concerns that TCVs may cause autism stem from a Food and Drug Administration (FDA) review of the mercury content of vaccines. Thimerosal has been used as a preservative in vaccines since the 1930s. It is 49.6% mercury by weight and is metabolized into ethylmercury and thiosalicylate. In the late 1990s, prompted in part by increased awareness of the risks of exposure even to low doses of organic mercury, the FDA conducted a risk assessment of the use of thimerosal in vaccines. Between 1989 and 1998, as more vaccines (*e.g.*, hepatitis B and hemophilus influenzae type b (Hib)) were added to the recommended infant immunization schedule, exposure to ethylmercury from vaccines rose. Estimates of maximum potential exposure suggested that infants vaccinated according to the recommended schedule could have received total doses of ethylmercury in excess of the Environmental Protection Agency's exposure limit for methylmercury.[21] Although the review found no evidence of harm, the Public Health Service and the American Academy of Pediatrics called for the removal of thimerosal from infant vaccines as a precautionary measure and also because vaccines represent a source of mercury exposure that can be controlled.[22]

Concerns were quickly raised about the possibility that exposure to thimerosal in vaccines may cause autism. The evidence for a possible association was indirect and rested on analogy with neurotoxic effects of mercury compounds, ecological comparisons between vaccination and autism trends, and extrapolation from laboratory and animal studies. Studies of the neurodevelopmental effects of low dose exposure to organic mercury compounds in humans have mostly involved infants and children exposed *in utero* to methylmercury, primarily through maternal fish consumption. Subtle effects have been found on speech and verbal abilities, dexterity, attention, and visuospatial abilities.[23] The findings, however, have been inconsistent[24] and no studies have found an association with autism. Moreover, the half-life of ethylmercury, the form in thimerosal, is much shorter than methylmercury,[25,26] indicating that methylmercury is not necessarily a suitable reference for risk assessment of exposure to ethylmercury from thimerosal.[26]

A few studies have reported the effects of thimerosal exposure on neuronal cells, biochemical pathways, or animal behavior.[26–28] A study in monkeys found persistent low levels of inorganic mercury in the brains of monkeys exposed to ethylmercury, but the meaning of this finding is not known.[26] The laboratory data and animal models may provide theoretical evidence of possible biological mechanisms, but are of unproven relevance to effects in humans.

The increasing number of children with autism diagnoses enrolled in school special education programs and developmental disabilities services programs is cited as another indication of a possible link to exposure to thimerosal in vaccines. As noted previously, correlating changes in program services data with changes in vaccination coverage can be misleading because many other factors also changed over the same time period. The only studies purporting to show an association between TCVs and autism have been conducted by the same pair of researchers,[29] and all have been judged to have serious flaws and to be uninterpretable by a review committee of the IOM.[20]

Ecological studies from countries with population data on autism diagnoses have not found an association with use of TCVs. Although incidence and prevalence rates of autism in Sweden and Denmark grew rapidly in the 1990s, the average thimerosal exposures had begun to decrease in the late 1980s and were virtually eliminated by the early 1990s.[30] A recent study in Montreal also found that the prevalence of pervasive developmental disorders in birth cohorts not exposed to thimerosal in vaccines was significantly higher than the prevalence in thimerosal-exposed cohorts in which the exposure levels were as high as those in the United States.[14]

The three controlled observational studies[31–33] that have been reported to date have not found an association between TCVs and autism. An individual-level cohort study in Denmark failed to find an increased risk of autism associated with TCVs.[31] A GPRD study of 103,043 British children covering the years 1988–1999 included data on patient consultations, referrals, and vaccine information.[32] One hundred and four cases of autism were identified, and no increased risk was found in association with receipt of TCVs. Because the only TCVs in Denmark and the United Kingdom were diphtheric-tetanus-pertussis (DTP) or diphtheric-tetanus (DT), the studies from those two countries do not provide data on the higher levels of exposure to thimerosal that occurred in the United States.

To date, the only published controlled study from the United States was an analysis from the Vaccine Safety Datalink (VSD)—a collaborative project between the CDC and several health maintenance organizations (HMOs). For the autism analyses, a retrospective cohort study was conducted involving 110,833 children born in one of the VSD HMOs between 1992 and 1998.[33] Computerized medical encounter and vaccination databases were reviewed and 202 children with autism diagnoses were identified. The relative risk of autism associated with increasing cumulative exposure to thimerosal by 7 months of age was 1.00 (95% CI: 0.90–1.09) for each 12.5 μg increment of mercury exposure. Although the VSD analysis did not find an association between TCVs and autism, the CDC is conducting an additional study that includes in-person evaluation of potential cases and more in-depth information on vaccinations and other exposures.

The IOM Immunization Safety Review Committee concluded that the evidence is sufficient to reject a causal association between TCVs and autism.[20]

CONCLUSION

The current scientific evidence does not support a causal association between MMR vaccine or TCVs and autism.

CONFLICT OF INTEREST

The author declared no conflict of interest.

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