

Autism and Measles-Mumps-Rubella Vaccination

Controversy Laid to Rest?

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Abstract

It has been suggested that vaccination, particularly with measles-mumps-rubella (MMR) vaccine, may be related to the development of autism. The main evidence for a possible association is that the prevalence of autism has been increasing at the same time that infant vaccination coverage has increased, and that in some cases there is an apparent temporal association in which autistic characteristics are first noted shortly after vaccination. Although the prevalence of autism and similar disorders appears to have increased recently, it is not clear if this is an actual increase or the result of increased recognition and changes in diagnostic criteria. The apparent onset of autism in close proximity to vaccination may be a coincidental temporal association. The clinical evidence in support of an association derives from a series of 12 patients with inflammatory bowel conditions and regressive developmental disorders, mostly autism. The possibility that measles vaccine may cause autism through a persistent bowel infection has generated much interest, since it provides a possible biological mechanism. Epidemiological studies, however, have not found an association between MMR vaccination and autism. The epidemiological findings are consistent with current understanding of the pathogenesis of autism, which has a strong genetic component and in which the neurological defects probably occur early in embryonic development. It seems unlikely that a vaccination that is given after birth could cause autism. A minority of cases of autism may have onset after 1 year of age (regressive autism), but the single epidemiological study that included such cases did not find an association with MMR vaccination. Currently, the weight of the available epidemiological and related evidence does not support a causal association between MMR vaccine, or any other vaccine or vaccine constituent, and autism.

It has been suggested that vaccination, particularly with measles-mumps-rubella (MMR) vaccine, may be related to the development of autism. The two main arguments that are used in support of a possible association are: (i) the prevalence of autism has been increasing at the same time that

infant vaccination coverage has increased; and (ii) in some cases of autism, there is an apparent temporal association in which autistic characteristics become apparent within a few weeks to a few months after vaccination. Neither argument, however, is compelling. Although the prevalence of au-

tism and similar disorders appears to have increased recently, it is not clear if this is an actual increase or the result of increased recognition and changes in diagnostic criteria. The apparent onset in close proximity to vaccination may be a coincidental temporal association. Typically, autism is first diagnosed or suspected during the second year of life, which is also when MMR vaccine is given.

In this report, we will review the evidence for a possible causal association between MMR vaccine and autism, as well as suggestions that other vaccines or vaccine constituents may be related to autism. We identified relevant articles through a search of Medline and the reference lists of reviewed articles. The concerns about other vaccines have come to our attention primarily through conferences or public meetings, the lay media, public inquiries and the internet.

1. The Autistic Enterocolitis Hypothesis

The hypothesis that MMR vaccine may cause autism was given prominence with the publication of a report by Wakefield and colleagues^[1] describing 12 patients with inflammatory bowel conditions and regressive developmental disorders, mostly autism. In 8 of the 12 cases, the child's parents or paediatrician suspected that MMR vaccine had contributed to the onset of behavioural problems. Wakefield and colleagues^[1] hypothesised that MMR vaccine may have been responsible for the bowel dysfunction (enterocolitis) which subsequently resulted in neurodevelopmental disorders. The report generated great interest because it seemed to provide a biological mechanism by which MMR vaccine could cause autism. Others, however, including a special panel of the British Medical Research Council, found the evidence unconvincing for a number of reasons.^[2,3] First, the small number of cases referred to a gastroenterology clinic may not have been representative of the general population of children with autism and referral bias was possible. Secondly, no information on the source population was provided and there was no unaffected comparison group. Thirdly, the possibility of a coincidental, but not causal, tempo-

ral association with MMR vaccination was not addressed. Fourthly, the most commonly identified bowel abnormality, ileocolonic lymphonodular hyperplasia, may not necessarily represent a pathological condition. Fifthly, the postulated link between bowel disease and autism was tenuous, as there was no confirmatory laboratory evidence (i.e. measles virus was not detected in the bowel) and bowel disease did not precede onset of autism in any of the cases (as would be required for a causal association).

Subsequent studies by Wakefield and colleagues^[4,5] also were not supportive of the hypothesis. In particular, Wakefield's group, as well as other researchers, reported that in patients with inflammatory bowel disease, the postulated mechanism for autism after MMR vaccination, highly specific laboratory assays are in fact negative for measles virus.^[4,6,7] Wakefield's group also conducted an epidemiological follow-up study of a 1970 British birth cohort in which no overall association was found between measles disease or measles vaccination and the subsequent occurrence of inflammatory bowel disease (i.e. ulcerative colitis or Crohn's disease).^[5] A case-control study conducted within the Vaccine Safety Datalink project of the US Centers for Disease Control and Prevention (CDC) found no association between MMR vaccine (or other measles-containing vaccines) and inflammatory bowel disease.^[8]

Wakefield and collaborators have since proposed that they have identified a new syndrome consisting of milder gastrointestinal conditions, predominantly ileocolonic lymphonodular hyperplasia and mild intestinal inflammation, associated with behavioural regression.^[9] They have reported identifying laboratory evidence of measles virus genome in the peripheral white blood cells and bowel biopsy specimens of a few such patients.^[10,11] The relevance of these laboratory findings, however, is not clear given that no association has been established in epidemiological studies between MMR vaccine (or other measles-containing vaccines) and inflammatory bowel disease or autism.

2. Epidemiological Studies of Measles-Mumps-Rubella Vaccine and Autism

Since the initial publication of the Wakefield et al.^[1] paper, epidemiological studies have failed to find an association between MMR vaccination and autism. The most thorough epidemiological study to date was conducted by Taylor and colleagues.^[12] Those authors identified all 498 known patients with autism spectrum disorders (ASDs) in the North East Thames district of London who had been born in 1979 or later and linked them to an independent regional vaccination registry. The ASDs included classical autism, atypical autism and Asperger's syndrome, but the results were similar when cases of classical autism were analysed separately. The authors first showed that the known number of ASD cases has been increasing since 1979 and there was no sharp increase after the introduction of MMR vaccine in 1988. Secondly, they found that patients vaccinated before 18 months of age had similar ages at diagnosis as did patients who had been vaccinated after 18 months or not vaccinated, indicating that vaccination does not result in earlier expression of autistic characteristics. Thirdly, they showed that at age 2 years the MMR vaccination coverage among the patients with ASD was nearly identical to the coverage in children in the same birth cohorts in the whole district, providing evidence of an overall lack of association with vaccination. Taylor and colleagues^[12] then employed an innovative 'case series' methodology to assess the relative incidence of autism within predefined time periods after vaccination. These analyses involved three different measures of autism onset (date of diagnosis, date of first parental concern, and date of regression) and two vaccine categories (MMR and any measles-containing vaccine). No statistically significant associations were found in the 14 comparisons, except for a small increase in relative incidence (1.48) for the association of MMR vaccination and initial parental concern. Further follow-up of this cohort has continued to find no evidence

of an association between MMR vaccine and autistic regression.^[13]

Three other published studies^[14-16] also provide evidence against an association between MMR vaccination and autism. A study in Sweden found no increase in autism among children born after, compared with those born before, the introduction of MMR vaccination.^[14] An analysis of a large database of British general medical practices found that the incidence of autism increased seven-fold between 1988 and 1999, whereas the prevalence of MMR vaccination was over 95% throughout the time period.^[15] A similar analysis in California, US, also found increasing trends in the number of people receiving developmental services for autism during a time when coverage with MMR vaccine was fairly stable.^[16]

3. Other Evidence Related to Measles-Mumps-Rubella Vaccine and Autism

The epidemiological findings are consistent with current understanding of the pathogenesis of autism, a syndrome defined by certain behavioural and developmental characteristics that may have a variety of causes. In few cases, however, is a specific cause identified. Autism has a strong genetic component and the associated neurological defects probably occur early in embryonic development.^[17,18] Thus, in most cases, autism is present at birth, although it may not be diagnosed until later in life when communication delays and characteristic behaviours become apparent. It seems unlikely therefore that a vaccination that is given after birth could cause autism. In a minority of cases, however, a child can appear to be developing completely normally but then regresses and develops autistic characteristics. It is such cases of regressive disorders, as noted by Wakefield and colleagues,^[1] for which a biologically plausible link with vaccination could be made. Thus, the analyses of Taylor and colleagues^[12] that found no association between vaccination and onset of regression provides particularly persuasive evidence against

the hypothesis that MMR vaccination may cause autism or exacerbate its symptomatology.

The concern about MMR vaccine (or other measles-containing vaccines) and autism or inflammatory bowel disease was also addressed in a clinical review of cases by a Working Party on MMR Vaccine of the British Committee on Safety of Medicines.^[19] The Working Party was charged with the evaluation of several hundred reports of autism, Crohn's disease or similar disorders developing after receipt of MMR or measles-rubella (MR) vaccine that had been collected by a British law firm. The Working Party conducted a systematic review of parental and physician information. Although acknowledging that it is impossible to prove or refute the suggested associations (because of variable data quality, biased selection of cases and lack of a control group), the Working Party concluded that the information available 'did not support the suggested causal associations or give cause for concern about the safety of MMR or MR vaccines'. In the opinion of the reviewers, the cases did not represent any unique or unusual syndrome.

Some parents have reported that the onset of autism in their children occurred following an adverse reaction to vaccines, such as a convulsion or loss of consciousness. Such reactions were noted in 6 of the 12 cases reported by Wakefield et al.^[1] Adverse reactions to vaccines do occur, but for the most part these tend to be minor and resolve rather quickly. Severe vaccine reactions are rare. Probably of greatest concern regarding a potential relationship to autism would be reactions that affect the brain (for example encephalopathy). The largest study of encephalopathy following vaccination was the national childhood encephalopathy study conducted in Britain. The study identified all children in the country who had been hospitalised for encephalopathy or severe convulsions during 1976 to 1979. The study did not find an increased risk of acute encephalopathy or long-term neurological effects associated with measles vaccine.^[20] A total of 940 cases were identified, of which 16 were associated with prior measles vaccination, resulting in a nonsignificant relative risk of 1.85. Follow-up of

the study participants 10 years later revealed that many of the children who had an acute encephalopathy continued to have neurological problems at follow-up, but the long-term outcome was not different in vaccine-associated cases compared with cases that did not follow vaccination. At follow-up, three of the patients who had initially developed symptoms following measles vaccination had died or had educational, neurological or behavioural dysfunction, resulting in a nonsignificant relative risk of 0.84. Given that measles vaccine is not associated with acute encephalopathy or long-term neurological dysfunction, measles vaccination could not cause autism as a result of such a reaction.

Another follow-up study of a national MMR vaccination programme in Finland indicated that children who experience gastrointestinal symptoms shortly after vaccination also are not at increased risk of neurodevelopmental problems.^[21] Out of about 3 million vaccine doses administered, reports of gastrointestinal complaints were received from 31 recipients. These individuals were followed-up 1 to 15 years (median 10 years) later and none had developed autism. Although the small number of individuals with gastrointestinal problems preclude making firm conclusions about the risk of autism in people experiencing gastrointestinal reactions, the results indicate that any possible association following MMR vaccination would have to be extremely rare.

4. Other Vaccines

Although MMR vaccine has received the most attention, other concerns have been raised about vaccinations and autism. These have included suggestions that autism risk may be increased by pertussis vaccination, by the thimerosal in vaccines, by the receipt of multiple vaccine antigens, or by peripartum rubella vaccination of a child's mother.^[22] It has also been suggested that risk of autism after vaccination may be restricted to individuals with a genetic predisposition or those with immunological abnormalities. No published data are currently available to address any of these

hypotheses. It should be noted that monovalent measles vaccine has not been implicated as being related to autism. The hypothesis of Wakefield's group^[23] is specific to MMR vaccine and they have advocated administration of monovalent measles vaccine as a safer alternative.^[23]

Speculation about vaccines and autism has been further fuelled by an apparent increase in the number of people with autism enrolled in special education or public service programmes for people with disabilities. The situation in the US state of California, in particular, has received much attention following publication of a detailed report documenting such an increase in the state's Developmental Services system.^[24] There has been speculation about the possible role that vaccination (i.e. increasing vaccination coverage or increasing the number of vaccines) may have played in the apparent increase in people with autism. Trying to correlate changes in numbers of autism cases with changes in vaccination schedules and coverage, however, is very difficult on a state or national level because many other factors also changed over the same time period (e.g. eligibility and reporting requirements for disability services, migration into and out of the state, etc.). Interpretation of the California data is further complicated by changes in diagnostic criteria for autism and possible increased awareness and recognition of the condition, resulting in more frequent diagnosis. Epidemiological data on the prevalence of autism are not available for California, nor for the US as a whole. Reviews of population-based surveys that have been conducted primarily in Europe have reached conflicting conclusions as to whether or not the prevalence of autism has been increasing in recent years.^[25,26] Nonetheless, even if the Developmental Services data are accepted as providing an accurate reflection of autism trends in California, Dales et al.^[16] have shown that there is not a correlation with MMR vaccination coverage levels.

5. Causality Assessment

An adverse event can be said to be caused by a vaccine (i.e. a true reaction) if it is associated with

Table I. Summary of causality assessment for a possible association between measles-mumps-rubella (MMR) vaccination and autism

Criterion	Evidence
Strength of association	None
Consistency of findings	Inconsistent
Biological plausibility	Weak
Temporality	Not demonstrated
Bias	Possible

a specific laboratory finding,^[27] a specific clinical syndrome,^[28] or both. Alternatively, a clinical or epidemiological study is needed to find out whether the rate of a given syndrome in vaccinated persons exceeds that expected among unvaccinated persons. Such studies require acquisition of data in an unbiased way.^[29] The most persuasive evidence would be provided by a randomised controlled trial, but such data are not available regarding MMR vaccine and autism.

Because of the inherent methodological limitations of epidemiological studies, other factors, such as biological plausibility, consistency and strength of association, are often considered in inferring causation. Table I provides a summary of the causality assessment of the proposed association between MMR vaccination and autism. In the initial case reports published by Wakefield and colleagues,^[1] population rates or comparison groups were not available and no measures of association (e.g. relative risks) could be calculated. The study by Taylor et al.^[12] is the only population-based epidemiological study that has been able to calculate relative risks, and no association was found between MMR vaccine and the development of autism. There have been no consistent findings of an increased risk of autism following MMR vaccination; in fact, results of recent studies^[12-16] have consistently found lack of association. The only evidence suggesting a possible association comes from a series of cases referred to a university gastroenterology clinic.^[1] The source of the cases and the reasons for referral are not known. Thus, selection or referral bias is a possibility. The one necessary condition for a causal association is that the

putative causal factor must precede the onset of the disease. In the initial study by Wakefield et al.^[11] of the 12 patients with behavioural regression and enterocolitis, none of the cases developed bowel symptoms before the onset of regression.

Biological plausibility is probably the strongest argument against a causal association. In most cases of autism, neuroanatomical abnormalities probably develop *in utero*. It is thus unlikely that an exposure that occurs after birth, such as vaccination, could cause autism. An association with developmental regression may be biologically plausible, but evidence is beginning to suggest that biological abnormalities are present at birth even in cases of autistic regression.^[18] The suggestion that MMR vaccine causes mild inflammatory bowel conditions and through this mechanism causes neurotoxic effects has been cited as providing a biologically plausible mechanism of how MMR vaccine could cause autism.^[10,11] The positive laboratory findings thus far all emanate from one group and there has been no independent verification by other investigators in other populations. Moreover, the relevance of the laboratory findings is not clear since no associations have been established between vaccination and autism or inflammatory bowel disease.

6. Conclusion

The notion that MMR vaccine, or any other vaccine or vaccine constituent, may cause autism is a hypothesis with little supporting evidence. The weight of the currently available epidemiological and related evidence does not support a causal association. A similar conclusion was reached by an expert review panel of the American Academy of Paediatrics (AAP).^[22] A committee of the Institute of Medicine (IOM)^[30] rejected a causal association at the population level, with the caveat that it could 'not exclude the possibility that MMR vaccine could contribute to ASD in a small number of children'. The IOM committee recommended further targeted research, but both the IOM and AAP panels supported current vaccination policies, includ-

ing administering the combined MMR vaccine to immunise against measles, mumps and rubella.

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