



Measles-mumps-rubella vaccine and autistic spectrum disorder: A hypothesis only

In 1998, Andrew Wakefield and colleagues (1) published a report in which the administration of measles-mumps-rubella (MMR) vaccine to young children was hypothesized to precipitate chronic inflammatory bowel disease that could lead to autism. The proposed mechanism through which this disease process was thought to occur is as follows: MMR vaccine may produce ileal-lymphoid-nodular hyperplasia, a nonspecific colitis; and the colitis may induce either malabsorption of vitamins or micronutrients, or an increase in intestinal permeability to protein, eventually giving rise to the formation of autoantibodies that are deleterious to brain tissue or other organs. The authors proposed that these events would then lead to the development of autism. The hypothesis generated was based on a case series involving nine children with inflammatory bowel disease and autism who had previously been immunized with MMR vaccine. Three other children without autism, but with behavioural difficulties, were also included. Since the Wakefield et al report (1) was published, it has resulted in significant controversy in the medical community, the lay press, the general public and the United States Congress.

The association among MMR immunization, inflammatory bowel disease and autism described by Wakefield and colleagues (1) could be coincidental, causal or an interaction related to another unknown event. To determine whether a relationship is likely to be causal, the following criteria are generally assessed: the strength of the association; consistency in studies conducted in different populations and by different investigators; specificity; whether events are temporarily clustered in time after an exposure; biological gradient; plausibility (although its absence does not rule out a causal association); coherence; supportive experimental evidence; and, finally, analogies with other illnesses (2).

Causality could not be shown in the Wakefield et al report (1) because of the small numbers of children studied, selection bias from a highly specialized gastroenterology clinic, recall bias of the timing of symptom onset by parents and the lack of a control group. A subsequent report by Wakefield and colleagues (2), involving additional numbers of affected children along with a control group, also had a number of methodological flaws that precluded its ability to support a causal association (3).

Since the initial report by Wakefield et al (1) was released, a number of studies that addressed whether the hypothesized association between MMR and autism has scientific merit have been published.

- The National Board of Health and National Public Health Institute of Finland (4) reviewed 14 years of data collected on adverse events related to MMR vaccination of 1.8 million children (involving approximately three million vaccine doses) and did not find a single case similar to those described by Wakefield and colleagues (1).
- Taylor et al (5) reviewed 498 cases of autism among children born since 1979 and did not find an epidemiological link with MMR vaccine administration. Specifically, there was no 'step-up' increase in the diagnosis of autism or significant change in the

autism diagnosis trend lines associated with the introduction and uptake of MMR vaccine in the universal vaccine schedule. As well, there was no difference in the age of diagnosis among children who were never vaccinated, those vaccinated before 18 months of age and those vaccinated after 18 months of age. No temporal association between the onset of autism and the receipt of the vaccine was seen. There was no clustering of developmental regression in the months following MMR vaccination among children with diagnosed autism.

- Two studies, one in England (6) and one in California (7), looked at trends in increases of reported cases of autism in association with changes in MMR vaccine coverage and found no difference in vaccine coverage associated with the rapid rises in autism diagnoses. In the English study, reported rates of autism increased from 0.3/10,000 person-years in 1988 to 2.1/10,000 person-years in 1999, while the MMR vaccine rate was steady at 95% throughout the observed interval (6). In the California study, reporting of autism increased from 44 cases/100,000 live births in 1980 to 208 cases/100,000 live births in 1994 (7). This represented a 373% relative increase in the reporting rates of autism. In contrast, changes in the rates of MMR immunization by the age of 24 months increased from 72% to 82% during the same period. This represented a relative increase of only 14%. In summary, an examination of available data from Britain and California does not demonstrate a correlation between secular trends in early childhood MMR immunization coverage and the prevalence of autism. A similar lack of correlation has also been noted in Sweden where prevalence rates of autism did not change following the introduction of MMR immunization (8).

There has been a significant apparent increase in the incidence of children diagnosed with autism or autistic spectrum disorder during the past decade (6,7,9). Proponents of the theory that MMR vaccination causes autism regard this apparent increase as providing supportive evidence for the theory's validity. The reasons for the apparent increase in the diagnosis of autism are not entirely clear. Experts in child development believe that the two most important factors related to the increases in diagnoses of autism are an increased awareness of the disorder and liberalization of the diagnostic criteria for the condition during the early 1990s (9,10). The use of the diagnosis of autism spectrum disorder rather than autism results in the inclusion of many more children, which significantly increases the reported rates of the

disorder. However, there is insufficient evidence to exclude the possibility of a true increase in this disorder or whether some cases may be related to environmental changes. One difficulty is that there is no biological marker for making a diagnosis. A diagnosis of autism is made on the basis of history and physical examination in combination with one or more screening tools and diagnostic criteria (11). Also, approximately one-third of autistic children present with a regression in milestones or abilities. Unfortunately, there is no standardized definition of this variant, which is the one with the theorized association with MMR vaccine.

The association between MMR vaccination and autism has been reviewed by a number of other organizations. In 1998, the Medical Research Council of the United Kingdom reviewed the existing evidence and found that there was insufficient evidence to support an association between MMR vaccination and autism (12). In April 2001, a review that included more recent information was published in the *Canada Communicable Disease Report* (13), and the authors reached the same conclusion as the Medical Research Council of the United Kingdom. Finally, the report from the New Challenges in Childhood Immunizations Conference, which convened in Oak Brook, Illinois from June 12 to 13, 2000 and dealt with this issue in detail, was published in May 2001 (14). The conclusions from the conference, which reviewed all the available published and unpublished data concerning this subject, were also that: "the available evidence does not support the hypothesis that MMR vaccine causes autism or associated disorders or IBD [inflammatory bowel disease]."

RECOMMENDATIONS

- The Canadian Paediatric Society (CPS) supports the conclusions reached by other groups that the evidence available internationally to date does not support an association between MMR vaccination and the development of autism.
- The CPS supports the continued universal use of MMR combination vaccine for Canadian children. There is no evidence that the separate administration of measles, mumps and rubella vaccines is of benefit, and, thus, would result in an unnecessary increase in the number of injections received by children and increase the likelihood of missed or delayed immunizations.
- The CPS actively promotes and supports properly designed scientific studies related to ensuring the safety of MMR and other vaccines.
- The CPS encourages targeted basic scientific and epidemiological studies with rigorous data analysis to determine the causes of autism, devise improvements in its management and design prevention strategies.

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The recommendations in this statement do not indicate an exclusive course of treatment or procedure to be followed. Variations, taking into account individual circumstances, may be appropriate.

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