# Autistic spectrum disorder: No causal relationship with vaccines

Canadian Paediatric Society

Although immunization is known to provide effective life-saving benefits for children, it has sometimes been blamed for an array of diseases that have unknown causes (eg, autistic spectrum disorder [ASD], multiple sclerosis and sudden infant death syndrome). This is not surprising, given that immunizations are common and that humans are primed to attribute causality to events that precede an incident. We all use the 'after it, because of it' logic. This is how we learned not to touch a hot stove as young children. Unfortunately, this logic can be faulty. Causality assessment requires careful consideration of a wide range of factors. Beyond the temporal relationship, the consistency of the finding, the strength of the association, the specificity of the association and the biological plausibility, all need to be evaluated before attributing causality (1,2). This article reviews recent controversies surrounding immunizations and ASD, and concludes that there are no data to support any association between immunization and ASD. It replaces the Canadian Paediatric Society's 2001 position statement on this topic (3).

## MEASLES, MUMPS AND RUBELLA IMMUNIZATION

In 1998, a report was published (4) purporting to show that the administration of the measles, mumps and rubella (MMR) vaccine to young children leads to a new form of ASD characterized by the presence of chronic inflammatory colonic disease and a loss of acquired cognitive function, possibly due to an impaired absorption of vitamins or micronutrients and/or an increase in intestinal absorption of intact proteins which then stimulate formation of autoantibodies that damage the brain, causing autism. The causality interpretation in the report rested on claims by parents of the eight children studied, who said that their children's problems occurred within days of the MMR vaccination. Many studies have since been performed to examine this purported relationship.

Large population-based epidemiology studies (5-9) in Finland, Denmark, the United States and England have shown no association between MMR and autism. The evidence in these studies does not meet the consistency of the finding, the strength of the association or the specificity of the association causality assessment criteria. Both the Institute of Medicine (IOM) review and the Cochrane systematic review failed to show any association between MMR and autism. (10,11).

With respect to the biological plausibility criteria, several laboratories have used polymerase chain reaction (PCR) primer-based assays, and have reported detection of the measles virus or its genome in intestinal biopsies and in peripheral blood mononuclear cells of autistic children (12-14). However, PCR techniques are vulnerable to contamination errors (procedures and controls are critical) and overinterpretation errors if only copy number data are used, and further verification and validation of the amplification products are not performed. Real-time PCR is regarded by many as the gold standard for detection of microorganisms in human disease. A subsequent, carefully detailed laboratory study (15) has refuted previous claims and has provided documented explanations for the earlier reported erroneous results by using a more specific real-time fusion gene assay PCR for measles virus detection. This study also showed that there is no evidence of measles virus persistence in the peripheral blood mononuclear cells of children with ASD. Similarly, the report of elevated levels of antibodies in children with autism (16) has also been negated by more recent work (15).

Thus, the purported association between the MMR vaccine and autism fails to meet the causality assessment criteria. In addition, 10 of the 13 authors of the original paper have now retracted their interpretation of a connection between the MMR vaccine and ASD (17).

## THIMEROSAL-CONTAINING VACCINES

Thimerosal, a compound that contains ethyl mercury, has been used as an additive to biological therapies and vaccines because of its effect in preventing bacterial contamination, particularly in opened, multidose vials. In

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1997, the United States Food and Drug Administration (FDA) Modernization Act called for a review and assessment of the risk of all mercury-containing foods and drugs. This action stimulated the United States Public Health Service and the American Academy of Pediatrics to issue a joint statement in 1999 (18) calling for the removal of thimerosal from vaccines. This action was undertaken as a precautionary measure; there was no evidence that ethyl mercury was harmful at the doses being administered to infants.

Of note, at that time in Canada, in contrast to the United States, the regularly used infant immunization product (pentavalent DTaPIPVHib vaccine) did not contain thimerosal. Only two infant thimerosal-containing vaccines were used – hepatitis B vaccine and influenza vaccine; the latter was not administered to infants younger than six months of age, the age/size of infant of concern. Hence, any concerns about excessive ethyl mercury exposure in young Canadian infants were without foundation. Since 1999, several studies (19-23) have been conducted to evaluate the safety of thimerosal in vaccines. These studies were reviewed in detail by the IOM (10) in 2001 and 2004 with a focus on autism. The IOM Committee concluded that the evidence favoured rejection of a causal relationship between thimerosal-containing vaccines and autism, as well as MMR vaccine and autism (10). In the absence of experimental or human evidence that vaccination affects metabolic, developmental, immune, or other physiological or molecular mechanisms that are related causally to development of autism, the IOM concluded that the hypotheses generated to date are theoretical. In a separate critical review (24) of published original data, a link between thimerosal-containing vaccines and ASD was not shown. Epidemiological studies that supported a link demonstrated significant design flaws that invalidated conclusions of these studies (10,24). Additional data from Canada published since 2004 also showed no association between thimerosal-containing vaccines and autism (25).

An important factor to consider is what has happened to autism rates since the removal of thimerosal from vaccines. In studies from Canada (25), Denmark (20) and the United States (26) the rates of autism have continued to increase despite removal of thimerosal from vaccines.

Thus, the evidence is in, and the assessment of purported causality is clear. The MMR vaccine and immunization with thimerosal-containing vaccines are not causally associated with, nor are they a cause of, autism or ASD. There is mounting evidence (27) that ASD has a strong genetic component – a very plausible cause for the disorder.

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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. This article also appears in the May/June 2007 issue of *Paediatrics & Child Health*.