



## Autism

Recently, stories carried by the media have caused some parents to fear that the combination measles-mumps-rubella vaccine (MMR) causes autism. Below are summarized:

### The “Wakefield studies”

Two studies have been cited by those claiming that the MMR vaccine causes autism. Both studies are critically flawed.

#### First study

In 1998, Andrew Wakefield and colleagues published a paper in the journal, *Lancet*. Wakefield’s hypothesis was that the MMR vaccine caused a series of events that include intestinal inflammation, entrance into the bloodstream of proteins harmful to the brain, and consequent development of autism. In support of his hypothesis, Dr. Wakefield described 12 children with developmental delay — eight had autism. All of these children had intestinal complaints and developed autism within 1 month of receiving MMR.

The Wakefield paper published in 1998 was flawed for two reasons:

1. About 90 percent of children in England received MMR at the time this paper was written. Because MMR is administered at a time when many children are diagnosed with autism, it would be expected that most children with autism would have received an MMR vaccine, and that many would have received the vaccine recently. The observation that some children with autism recently received MMR is, therefore, expected. However, determination of whether MMR causes autism is best made by studying the incidence of autism in **both** vaccinated and unvaccinated children. This wasn't done.
2. Although the authors claim that autism is a consequence of intestinal inflammation, intestinal symptoms were observed **after**, not before, symptoms of autism in all eight cases.

#### Second study

In 2002, Wakefield and coworkers published a second paper examining the relationship between measles virus and autism. The authors tested intestinal biopsy samples for the presence of measles virus from children with and without autism. 75 of 91 children with autism were found to have measles virus in intestinal biopsy tissue as compared with only five of 70 patients who didn't have autism. On its surface, this was a concerning result. However, the second Wakefield paper was also critically flawed for the following reasons:

1. Measles vaccine virus is live and attenuated. After inoculation, the vaccine virus probably replicates (or reproduces itself) about 15-20 times. Measles vaccine virus is likely to be taken up by specific cells responsible for virus uptake and presentation to the immune system (termed antigen-presenting cells or APCs). Because all APCs are mobile, and can travel throughout the body (including the intestine), it is plausible that a child immunized with MMR would have measles virus detected in intestinal tissues using a very sensitive assay. To determine if MMR is associated with autism one must determine if the finding is **specific** for children with autism. Therefore, children with or without autism must be identical in two ways. First, children with or without autism must be matched for immunization status (i.e. receipt of the MMR vaccine). Second, children must be matched for the length of time between receipt of MMR vaccine and collection of biopsy specimens. Although this information was clearly available to the investigators and critical to their hypothesis, it was specifically omitted from the paper.

2. Because natural measles virus is still circulating in England, it would have been important to determine whether the measles virus detected in these samples was natural measles virus or vaccine virus. Although methods are available to distinguish these two types of virus, the authors chose not to use them.
3. The method used to detect measles virus in these studies was very sensitive. Laboratories that work with natural measles virus (such as the lab where these studies were performed) are at high risk of getting results that are incorrectly positive. No mention is made in the paper as to how this problem was avoided.
4. As is true for all laboratory studies, the person who is performing the test should not know whether the sample is obtained from a case with autism or without autism (blinding). No statements were made in the methods section to assure that blinding occurred.

### **Studies showing that MMR vaccine does not cause autism**

Studies have been performed that disprove the notion that MMR causes autism. In 1999, Brent Taylor and coworkers examined the relationship between receipt of MMR and development of autism in an excellent, well-controlled study. Taylor examined the records of 498 children with autism or autism-like disorder. Cases were identified by registers from the North Thames region of England before and after the MMR vaccine was introduced into the United Kingdom in 1988. Taylor then examined the incidence and age at diagnosis of autism in vaccinated and unvaccinated children. He found that:

1. The percentage of children vaccinated was the same in children with autism as in other children in the North Thames region.
2. No difference in the age of diagnosis of autism was found in vaccinated and unvaccinated children
3. The onset of symptoms of autism did not occur within 2, 4 or 6 months of receiving the MMR vaccine.

Subsequent studies by Nathalie Smith published in the *Journal of the American Medical Association* and by Hershel Jick in the *British Medical Journal* found that the increase in the number of children reported to have autism was not associated with an increase in the use of the MMR vaccine.

Perhaps the best study was that performed by Madsen and colleagues in Denmark between 1991 and 1998 and reported in the *New England Journal of Medicine*. The study included 537,303 children representing 2,129,864 person-years of study. Approximately 82 percent of children had received the MMR vaccine. The group of children was selected from the Danish Civil Registration System, vaccination status was obtained from the Danish National Board of Health, and children with autism were identified from the Danish Central Register. The risk of autism in the group of vaccinated children was the same as that in unvaccinated children. Furthermore, there was no association between the age at the time of vaccination, the time since vaccination, or the date of vaccination and the development of autism.

### **Studies on the causes of autism**

#### **Genetics**

One of the best ways to determine whether a particular disease or syndrome is genetic is to examine the incidence in identical and fraternal twins. Using a strict definition of autism, approximately 60 percent of identical and 0 percent of fraternal twins have autism. Using a broader definition of autism (i.e. autistic spectrum disorder), approximately 92 percent of identical and 10 percent of fraternal twins have autism. Therefore, autism clearly has a genetic basis.

#### **"Home-movie" studies**

Clues to the causes of autism can be found in studies examining when the symptoms of autism are first evident. Perhaps the best data examining when symptoms of autism are first evident are the "home-movie studies". These studies took advantage of the fact that many parents take movies of their children during their first birthday (before they have received the MMR vaccine). Home movies from children who were eventually diagnosed with autism and those who were not diagnosed with autism were coded and shown to developmental specialists. Investigators were, with a very high degree of accuracy, able to separate autistic from non-autistic children at one year of age. These studies found that subtle symptoms of autism were present earlier than some parents had suspected, and that receipt of the MMR vaccine did not precede the first symptoms of autism. Other investigators extended the home-movie studies of one-year-old children to include videotapes of children taken at 2-3 months of age.

### Timing of first symptoms

Using a sophisticated movement analysis, videos from children eventually diagnosed with autism or not diagnosed with autism were coded and evaluated for their capacity to predict autism. Children who were eventually diagnosed with autism were predicted from movies taken in early infancy. This study supported the hypothesis that very subtle symptoms of autism are present in early infancy and argues strongly against vaccines as a cause of autism.

### Structural abnormalities of the nervous system

Toxic or viral insults to the fetus that cause autism, as well as certain central nervous system disorders associated with autism, support the notion that autism is likely to occur in the womb. For example, children exposed to thalidomide during the first or early second trimester were found to have an increased incidence of autism. However, autism occurred in children with ear, but not arm or leg, abnormalities. Because ears develop before 24 days gestation, and arms and legs develop after 24 weeks gestation, the risk period for autism following receipt of thalidomide must have been before 24 weeks gestation. In support of this finding, Rodier and colleagues found evidence for structural abnormalities of the nervous system in children with autism. These abnormalities could only have occurred during development of the nervous system in the womb.

### Natural rubella infection

Similarly, children with congenital rubella syndrome are at increased risk for development of autism. Risk is associated with exposure to rubella before birth but not after birth.

### Conclusions

The following studies all support the fact that autism occurs during development of the nervous system early in the womb:

- The genetics of autism
- The timing of the first symptoms of autism (home-movie studies)
- The relationship between autism and the receipt of the MMR vaccine
- Structural abnormalities of the nervous system of children with autism
- Thalidomide and natural rubella infection

Unfortunately, for current and future parents of children with autism, the controversy surrounding vaccines has caused attention and resources to focus away from a number of promising leads.

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