# Overview: MMR vaccine and autism: Is there a link?


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Immunization programs are among the most effective strategies in healthcare. It has succeeded in eliminating or significantly decreasing the incidence of many once common diseases. However, regarding immunization, safety appears to be an increasing concern and this constitutes a real threat to the success of immunization programs [1].

New or long standing safety allegations may become threats to vaccination programs as they may erode public confidence on vaccines and lead to a consequent fall in vaccination coverage [2]. Such concerns may be fueled by the dissemination of anecdotal reports of alleged vaccine reactions by the media that cause parents and even some healthcare providers to question the justification for immunization.

One of the widely publicized allegations against vaccines was the claim of existence of a link between measles, mumps and rubella (MMR) vaccine and autism. This allegation has not been without cost, as there has been a drop in MMR vaccine uptake associated with significant measles outbreaks in the United Kingdom after this concern was first publicized [3]. The aim of this article is to provide healthcare professionals with information about the basis of this allegation and an overview of the accumulated scientific data addressing this issue. This should help healthcare providers with means to respond to the inquiries raised by parents regarding this matter.

## Studies suggesting a link between MMR Vaccine and Autism

In 1998, Wakefield and his colleagues published a report in the Lancet, titled “Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children” [4]. The paper reported on 12 children with pervasive developmental disorders (PDDs), 9 with autism who had gastrointestinal complaints and whose onset of behavioral symptoms was associated (parents’ report) with MMR vaccination. The paper hypothesized that MMR vaccine causes a series of events that include intestinal inflammation, loss of intestinal barrier function, entrance into the blood stream of encephalopathic proteins and consequent development of autism.

Although the authors stated that “we did not prove an association between MMR vaccine and the syndrome described ……”, however, they suggested that “further investigations are needed to examine this syndrome and its possible relation to the vaccine,” they did raise the possibility of a link. This interpretation of the data and the recommendations given by the principal author (Dr. Wakefield), in a press conference following publication of the paper, to the effect of avoiding the combined MMR vaccine, triggered a collapse in confidence in the UK’s MMR vaccination program [5]. Interestingly, in 2004, the Lancet published a retraction of the interpretation of the findings in the 1998 Lancet paper by 10 of the 13 authors [6].

Furthermore, the story unfolded to reveal that, in addition to the potential selection bias since the patients were referred to a gastroenterology unit involved in the study of the relations of measles vaccine to inflammatory bowel diseases [7], some patients were referred by a lawyer who worked for a group of parents who believed that MMR vaccine has damaged their children [8]. Dr. Wakefield was also involved at the time of submission of the report in another study funded by the UK Legal Aid Board to investigate the grounds for pursuing a multiparty legal action on behalf of the parents of allegedly vaccinedamaged children [8]. This potential conflict of interest was not disclosed to the reviewers or editors. Richard Horton, Editor of The Lancet, stated that “such a disclosure would have provided important information to editors and peer reviewers about the context in which this work was taking place – a context that would have been vital in making a final decision about publication.”[8].

In a second study published by Uhlmann and colleagues, intestinal biopsies of children with PDD and ileal lymphoid nodular hyperplasia were assessed [9]. RT-PCR was used to look for evidence for measles virus in the intestinal tissues. They reported identification of fragments of measles virus nucelocapside fusion protein and hemaglutinin DNA in 75 of the 91 study subjects while this was positive in only 5 of the 70 heterogeneous control groups [9]. However, it is worth knowing that hybridization of PCR products with probes to fusion protein and hemaglutinin DNA was done for only 4 of the 75 patients. Furthermore, a critical issued for interpretation of the above findings was the status of MMR vaccination for the subjects and the controls as well as the length of time between MMR vaccination and intestinal biopsies. These information, however, were not mentioned in the paper in spite of their critical importance to the interpretation of the findings in light of the hypothesis presented. MMR vaccine contains a live attenuated measles virus which replicates in the body after injection and circulate through various body sites where it could be detected by RT-PCR in urine [10]. It is plausible that those children biopsied shortly after vaccination would have measles virus antigen in the intestinal tissue. Furthermore, nonpathogenic persistence of measles nucleocapside genomic RNA in multiple body tissues has been identified by other investigators in individuals with no known diseases [11]. This would indicate that detection of portions of the virus in tissues may be unrelated to local diseases. The possibility that the identified fragments of measles virus might be of the wiled strain has, also, been raised by some reviewers [12].

## Studies refuting a link

Following emergence of the concern of existence of a link of PDD and MMR vaccine, several studies have been published to examine the association between PDD and the MMR vaccine [13-22]. Following is a summary of the main studies according to the scientific research question addressed:

1. Is there a change in the incidence rates of PDD with the introduction of MMR vaccine or the increase in vaccine coverage?

Several studies [13-18] have been conducted to answer this question in several countries including the United States [13], and the United Kingdom [14-18]. None of these studies showed an obvious association between an increase in PDD and an equivalent increase in the MMR vaccine coverage [13-17]. Some of the studies examined the rate of PDD before and after MMR vaccine introduction in the United Kingdom in 1988 [14,16,17]. One of these reported no change in trend in PDD or atypical forms of autism before and after that year [14]. The other study found no trend in increasing percentage of children with PDD who have bowel symptoms or had regression over the period 1979-1998 [17]. Another study examined the rates of developmental regression in samples of autistic children before and after introduction of the MMR vaccine and found no significant differences [18].

It should be pointed out that although the evidence provided by above studies is useful, it is limited by the potential of confounding related to secular trends in the mechanisms of diagnosis of PDD.

2. Is the rate of PDD higher in children vaccinated with MMR compared with those not vaccinated?

To answer this question, a comparison of PDD rate in vaccinated and nonvaccinated children at the same period utilizing a case control or a controlled cohort design is needed. The high vaccine coverage rates make such design challenging. Two well conducted population-based studies from two different countries, Denmark and the United Kingdom, addressed this question [19,20]. The Danish study utilized a retrospective controlled cohort design and included the children born in Denmark between 1991 and 1998 [19]. Of the 440,655 vaccinated individuals in the cohort, autism was diagnosed in 316 and other PDD were diagnosed in 422 giving a relative risk (RR) of autism in vaccinated children of 0.92 (95% confidence interval; 0.68 to 1.24) and RR of other PDD of 0.83 (95% CI, 0.65 to 1.07). Potential confounders were considered and were adjusted for [19].

The other population-based study utilized a matched case control design using the U.K. General Practice Research Database [20]. It included all individuals who had first recorded diagnosis of PDD between 1987 and 2001. For the 1294 cases with autism or other PDD, 4469 controls matched for age, sex and general practice were included. The odds ratio for the association between MMR vaccination and diagnosis of PDD was 0.86 (95% CI, 0.68 – 1.09, P=0.21) after adjustment for potential confounders [20]. The results for those with a diagnosis of autism only was 0.88 (95% CI, 0.67 – 1.15, P = 0.35) and for those with other PDDs was 0.75 (0.46 – 1.23, P = 0.25) [20].

These two studies provide strong evidence against presence of a link between the MMR vaccination and PDD.

3. Is there a temporal relation between MMR vaccination and the development of PDD in individuals?

Several studies addressed this question by examining for various aspects that could indicate presence of a temporal association between development of PDD and receiving the MMR vaccine [14,16,19,21]. Some studies compared the age at which PDD was diagnosed or parental concern developed in vaccinated and nonvaccinated patients [14,18,19]. No difference was found in the mean age at the time of diagnosis between the vaccinated and nonvaccinated patients. Other studies examined a cohort of children with PDD and found that these children were not more likely to be diagnosed as having PDD in specified periods after having been vaccinated with the MMR vaccine [14,16].

One study compared the rate of bowel symptoms or regression among autistic children who had received MMR vaccine before their parents become concerned about their development, autistic children vaccinated after parental concern, and autistic children who never been vaccinated with MMR. There were no significant differences between the 3 groups [17].

The Danish study found no association between development of PDD and interval since vaccination in their cohort [19].

A Finish study identified no post MMR vaccination cases of PDD in 1.8 million vaccine [21]. Another study from Finland found no clustering of hospitalization for autism after children had received the MMR vaccine [22].

## Other Relevant Studies

One study assessed the possibility that MMR vaccine leads to sub clinical intestinal inflammation in vaccinated infants during the immediate vaccination period [23]. It found no evidence that the vaccine induced an inflammatory reaction in healthy children during the four weeks postvaccination periods, which argues against the autistic enterocolitis hypothesis [23].

Another study reported on followup of a group of vaccinated children who have GI tract syndromes and found no cases of PDD in these children after the mean followup of 9 years [24].

A metaanalysis and three systemic reviews of studies addressing this issue have been published [20,25,26]. All concluded that no evidence is available for existence of an association between MMR vaccine and autism or other related disorders. Furthermore, several expert committees issued reports indicating the absence of evidence for a causal relationship between MMR vaccine and autism [27,28].

## Conclusion

The available evidence does not support the hypothesis that MMR vaccine causes developmental disorders including autism. Public health officials and other health care workers should reassure parents and the public of the safety of MMR vaccine. Research efforts should be directed towards identifying the real cause of autism and other related disorders.

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