Does the MMR triple vaccine cause autism?

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Abstract

In recent years, there has been widespread public concern about the hypothesis that MMR triple vaccine may increase the risk of autism in children. In this review, we examine the background to, and implications of, this controversy. We then assess and explain, using a transparent and replicable method, all the scientific evidence for and against the hypothesis. We conclude that there are no grounds to suggest that MMR vaccine increases the risk of autism.

Measles, mumps and rubella are dangerous diseases, which were endemic in the pre-vaccine era

In the pre-vaccine era almost every child caught measles and about 7% suffered complications of the disease. In England and Wales between 1959 and 1968, when measles vaccine was introduced, an average of 87 children died from measles each year. Rubella, although a mild disease for most people who experience it, can have devastating effects (collectively called Congenital Rubella Syndrome [CRS]) on the unborn baby if caught by the mother in early pregnancy. Mumps used to be the commonest cause of viral meningitis in children and young people and was an important cause of unilateral deafness. Both mumps and measles are more severe if contracted by adults.

A live attenuated single measles vaccine was introduced to the UK in 1968 having already been in use in the USA for five years. It was offered to children over 12 months of age. In 1988 this was replaced by MMR (measles, mumps, rubella combined vaccine). This was based upon experience in the USA where the combined vaccine had been in use since 1972. Universal rubella vaccination of young children had proved to be a more effective approach than selective immunisation of schoolgirls and susceptible adult woman as practised in the UK. Although both policies resulted in a reduction in CRS, this was greater following the US practice as it resulted in the elimination of rubella disease in young children and thus broke the chain of transmission to pregnant women.
Mumps vaccine had never been routinely used in the UK but by the late 1980s the uptake of vaccinations was such that it was considered appropriate to introduce it. Previously there had been concerns that the poor uptake associated with the measles vaccine, whilst reducing the incidence of disease, would not be sufficiently high as to create herd immunity. This would result in a general upward shift in the average age of acquisition of infection resulting in a higher rate of complications. The same concerns applied to the introduction of rubella vaccination for young children.

**MMR vaccines virtually eliminate measles, mumps and rubella, provided uptake is high**

There has been a dramatic decrease in the incidence of measles, mumps and rubella throughout the world since the introduction of MMR vaccination. Before the advent of the MMR vaccine, the monovalent measles, mumps and rubella vaccines were all found to be highly effective in preventing the respective diseases (90% efficacy or greater) in trials conducted in the 1960s. MMR has been routinely used in the USA for over 30 years. One study in that setting showed that unvaccinated children were 35 times more likely to develop measles compared to those who had been immunised. In the UK, there was a 92% reduction in mumps related hospitalisation following the start of MMR vaccination. However, mumps vaccines differ widely in their effectiveness and in one study where different mumps vaccine strains were used as part of the MMR vaccine, the effectiveness of the Rubini mumps vaccine was much lower than the Jeryl-Lynn vaccine (−4% compared with 87%). MMR also prevents rubella transmission and this has resulted in an impressive decline in the incidence of CRS in countries with high vaccine coverage. In Britain the number of CRS cases decreased from 200-300 in non-epidemic years in the pre-vaccine era to a total of only 40 cases 1991-2003.

Prevention of these diseases is not solely dependent on efficacy of the vaccine in individuals. High population immunity, achieved through high vaccine coverage and repeated-dose schedules, is required to control measles, mumps and rubella in the long term. For instance, following a 12-year, two dose MMR vaccination programme with uptake rates above 90%, the three diseases were eliminated in Finland. In contrast, a study from Greece showed that when MMR vaccination for children was introduced, poor coverage plus a lack of a catch-up programme for adolescents and young women led to a greater number of women being infected with rubella and higher CRS rates.

Studies of disease outbreaks illustrate the consequences of low vaccine coverage. In Campania in Italy, where vaccine coverage was less than 70%, a measles outbreak of 1571 cases was reported in 2002. The outbreak led to 594 hospitalizations and 4 deaths. Only 7% of these people were vaccinated. In the Dublin area, Eire, an outbreak of 1115 notified cases of measles occurred in 2002, in an area with less than 70% coverage. The outbreak led to 111 admissions and 3 deaths. Another measles outbreak occurred in Coburg, Germany, involving 910 cases, 96% of whom were unvaccinated. In many parts of Europe, achieving high coverage is a continuing challenge. In the UK, falling coverage was fuelled by public concerns that MMR may cause autism. As the MMR uptake has fallen in the UK in the wake of this controversy, measles disease has become more frequent with a possibility of it becoming endemic again. In 2003, the incidence of mumps dramatically increased (to almost double the average annual rate) in England and Wales with 1529 confirmed cases compared with an annual average of 400 in the previous 7 years. More than half of these were related to people older than 15 years of age. This is not surprising since older children and young adults are more likely to have received only one dose of MMR or no vaccination at all.

**What generated concern that MMR vaccine may cause autism?**

In the early 1990s the Inflammatory Bowel Disease Study Group (IBDSG) at the Royal Free Hospital, London, published a paper suggesting a link between early measles infection (i.e. during pregnancy or early childhood) and onset of IBD in adulthood. Later they similarly suggested a link between measles vaccine and adult IBD. Both associations were subsequently disproved by other researchers as well as the IBDSG themselves. However, by this time the group had established a reputation for being interested in possible adverse effects of measles-containing vaccines. In 1998 they published an “early report” of 12 children with behavioural problems and bowel symptoms. In 8 children, the parents or physicians recalled that the behavioural symptoms followed soon after (24 hours-2 weeks) the receipt of MMR vaccine. The
authors described what they considered to be a new syndrome of autistic enterocolitis. They also suggested that there might be a link between this syndrome and MMR vaccine. There were, however, many limitations to the methods used in this study. It was a self selected group of children; there were no controls; there was the potential for recall bias, and the age at which the vaccine was given would normally coincide with the age at onset of the behaviour problems described even if there were no causal link.35 Bearing in mind these limitations, the authors were careful to point out that they had not proven a link between MMR vaccine and the syndrome they had described and that further research was needed. At the time of publication, one of the authors publicly said he had sufficient concern over the safety of MMR vaccine to recommend the use of single vaccines given at yearly intervals. This received a lot of publicity and caused anxiety to parents and professionals alike resulting in confusion and a fall in vaccine uptake.28

The hypothesis that MMR vaccine causes autism is, at best, tenuous. However, the implications of the public concern and of the consequent fall-off in vaccination rate demand that the evidence for and against this hypothesis be thoroughly investigated.

How did we examine the evidence?

We have taken two approaches to examining the evidence: first we examined whether MMR vaccine is associated with autism, and second, given the postulated new syndrome of autistic enterocolitis, we examined whether the MMR vaccine or measles virus was associated with autistic enterocolitis. However, we did not address the issue of whether there is a specific entity of autistic enterocolitis. In February 2004, the following databases were searched from their origin: Medline, Embase, Cochrane Library (2004 issue 1) for systematic reviews, randomised controlled trials (RCTs), and observational studies. As RCTs could be considered unethical in assessing the clinical efficacy of measles virus, observational studies such as cohort studies and national population surveillance data were included.

What does the evidence show?

Is MMR vaccine associated with autism?

Following publication of the Lancet paper, studies34,36–42 have been conducted to explore a link between the vaccine and autism (see Table 1). Using a variety of methods including cross-sectional series, a large retrospective cohort study (537,000 children of whom 18% had not received MMR) and other observational studies, no link was found between MMR vaccine and autism. The Institute of Medicine Committee on Immunisation Safety Reviews have recently published their second review of vaccines and autism.43 The committee identified the same studies that we have described, and concluded that "the evidence favors rejection of a causal relationship between MMR vaccine and autism".

Is measles virus associated with autistic enterocolitis?

There is a paucity of published data on this subject with only two studies claiming to have found an association between autistic enterocolitis and the measles virus. A group of authors from Dublin was involved with both studies. Similar selection criteria for cases and controls as well as similar virological detection tests were used in both studies.

The co-authors of the first paper included members of the Inflammatory Bowel Disease Study Group at the Royal Free Hospital, London. The study investigated the gut biopsies of 91 children with inflammatory bowel disease and developmental disorder from the Royal Free Hospital. These were then compared with biopsies from developmentally normal children [controls].44 Seventy-five of the 91 children (82%) with bowel problems were positive for measles virus compared with 5 out of the 70 (7%) controls. The second study looked at gut biopsies of 77 children with inflammatory bowel disease and developmental disorder and compared these with biopsies from 17 children without developmental disorder (but inclusive of appendicectomies and children who had biopsies for other reasons).45 It was found that 95% of "affected" children had measles virus detected in their gut compared with 11% in the "non affected" group. The authors of both studies concluded that there was sufficient evidence to demonstrate an association between measles virus and gut disease in children with developmental disorders.

However there were many limitations to these studies:

- Both studies failed to adequately define the selection of cases and controls.
- There was a lack of information regarding the subject’s vaccination history or previous exposure to measles disease.
- Although cases were described as having developmental disorders, the specific diagnoses of autism or autistic spectrum disorders were not mentioned.
### Table 1 Review of primary studies addressing a possible link between MMR vaccine and autism

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods: Type of study, size and what was done</th>
<th>Results</th>
<th>Authors’ Conclusion</th>
<th>Comments</th>
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<td>34 Wakefield et al (1998)</td>
<td>Case series of 12 consecutive children referred with diarrhoea and abdominal pain and normal development followed by loss of skills including language. Each child underwent a detailed investigation.</td>
<td>In 8 of the 12 children, parents or GPs said the developmental symptoms had come on soon after having MMR vaccine.</td>
<td>Suggested they had identified a chronic enterocolitis that may be related to the developmental problems. There may be a link with the MMR vaccine, which needed further investigation.</td>
<td>This study describes a highly selected group of children most of whom one would have expected to have had MMR vaccine. Any temporal link is likely to be coincidental rather than causal. At best this study could only ever be hypothesis generating. In early 2004, 10 of the 13 authors wrote to the Lancet formally retracting any suggestion of a link between MMR vaccine and autism.</td>
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<td>36 Peltola et al (1998)</td>
<td>Prospective cohort, 3 million vaccine doses, review of those who developed significant gastrointestinal symptoms.</td>
<td>31 children developed significant GI symptoms lasting 24 hours or longer following MMR vaccine. None of them lasted longer than 6 weeks and none went onto develop autism.</td>
<td>Children who have GI symptoms following MMR do not go on to develop autism or chronic bowel problems.</td>
<td>If autism is caused by MMR vaccine as a result of gastrointestinal disturbance, one might expect to see cases of autism in children who had such symptoms following MMR. While it does not prove conclusively that MMR does not cause autism it suggests that if it does this is not the mechanism.</td>
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<td>37 Taylor et al (1999)</td>
<td>The clinical and vaccination records of children with autistic disorders, born after 1979 and diagnosed by mid-1998 were linked. In 293 children the diagnosis of autistic spectrum disorder was confirmed.</td>
<td>Time trend analysis showed no effect of the introduction of MMR on the incidence of autism. The uptake of MMR in the children with autism did not differ significantly from that in the same birth cohorts in the same region.</td>
<td>If there was any link between MMR vaccine and autism it would be very rare.</td>
<td>In children with autism the authors found a clustering of parental concern 6 months after MMR vaccine was given. Further analysis suggested this was artefactual.</td>
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<td>Reference</td>
<td>Study Description</td>
<td>Findings</td>
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<td>Patja et al 2000</td>
<td>Enhanced passive reporting of adverse events following MMR vaccine. Over a 14 year period 1.8 million were given 3 million doses of vaccine. The researchers assessed which adverse events might be due to the vaccine.</td>
<td>No cases of autism were associated with MMR vaccination.</td>
<td>They concluded there was no evidence of onset of autism within a short period following vaccine.</td>
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<td>Kaye et al 2001</td>
<td>Time trend analysis of the relationship between MMR vaccine and autism using general practice research database. 114 boys born between 1988-1993 were diagnosed as autistic between the ages of 2 and 5 years.</td>
<td>While the estimated incidence of autism rose over the period in question, the uptake of MMR remained constant.</td>
<td>The results provide evidence against a causal relation between MMR vaccination and autism.</td>
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<td>Dales et al 2001</td>
<td>Similar study on a different population came to similar conclusions</td>
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<td>Farrington et al 2001</td>
<td>This was a similar study to Taylor et al 1999 but with a longer period of follow up i.e. 5 years post vaccination. The conclusions were identical to those of the earlier study.</td>
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<td>Madsen et al 2002</td>
<td>Retrospective cohort study of all 537,303 children born in Denmark 1991-1998. The risk of autism was compared between vaccinated (440,655) and unvaccinated children.</td>
<td>Relative risk of developing an autistic disorder after MMR vaccine was 0.92 (5% CI 0.68-1.24).</td>
<td>There was no association between MMR vaccination and autism.</td>
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<td>This is the largest epidemiological study that has been conducted. On the basis of this alone it is difficult to believe that MMR plays a significant role in the aetiology of autism.</td>
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The control groups included patients with other forms of inflammatory bowel disease or patients who had their appendices removed. Biopsies therefore, may have been taken from different parts of the bowel in controls when compared to cases.

Both studies used a genetic detection test to look for measles virus. This test can be prone to contamination. No information was provided regarding the storage and handling of samples.

The genetic material that was obtained was not sequenced to see if the virus found was vaccine strain or the wild type.

Neither of the studies actually isolated the virus and there was a lack of information regarding the validity of the virological detection methods used.

It is worth noting that even if the findings of these studies are genuine, there is still a lack of evidence showing that measles virus indeed causes the syndrome of "autistic enterocolitis". Even if virus were reliably detected, the studies could only demonstrate co-existence of measles virus and autistic enterocolitis, and not a causal relationship.

Conclusions

There is overwhelming evidence that MMR vaccine is not causally related to autism or bowel disease. However concerns raised by the publicity surrounding the paper in 1998 shook the confidence of some health professionals; and parents, such the uptake of MMR vaccine was significantly depressed. The subsequent research showing no link has only partially countered these concerns. This may be in part due to the nature of media coverage with less attention paid to findings which suggest no link, giving the impression that the evidence is almost equally balanced. Whereas the reality is overwhelmingly in favour of no link.

The concern about MMR, albeit unsubstantiated, has also led to parents suggesting that their children receive single antigen vaccines as an alternative. Parents often rationalise their decision by saying that they would prefer to "take no risk." The implication is that, while there have been doubts about the safety of MMR, the safety of the single antigen vaccines has never been questioned. However, the failure to ask similar questions about the safety of the single antigen vaccines is one of the reasons why this argument falls down: There has been a lot of research that clearly refutes the potential link between MMR vaccine and autism, but there has been no reliable research looking at the possible link between the single vaccines and autism.

On the other hand, it is clear that vaccination using single antigens given at intervals delays protection against all three diseases and is therefore unlikely to be as effective as MMR.

The lack of confidence in the MMR is in part fuelled by a lack of awareness of the scientific evidence and an ability to judge its validity. In the face of this challenge, it is important that health professionals, who are often in a position of trust and influence, are not only fully aware of all the information themselves, but also are in a position to explain this to parents and, when they wish for further information, can direct them to appropriate resources.

References

14. Vaccination against measles: clinical trial of live measles vaccine given alone and live vaccine preceded by killed


