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MMR Vaccination and Autism

What is the Evidence for a Causal Association?

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Abstract

It has been suggested that vaccination with the measles-mumps-rubella (MMR) vaccine causes autism. The wide-scale use of the MMR vaccine has been reported to coincide with the apparent increase in the incidence of autism. Case reports have described children who developed signs of both developmental regression and gastrointestinal symptoms shortly after MMR vaccination.

A review of the literature revealed no convincing scientific evidence to support a causal relationship between the use of MMR vaccines and autism. No primate models exist to support the hypothesis. The biological plausibility remains questionable and there is a sound body of epidemiological evidence to refute the hypothesis. The hypothesis has been subjected to critical evaluation in many different ways, using techniques from molecular biology to population-based epidemiology, and with a vast number of independent researchers involved, none of which has been able to corroborate the hypothesis.

The Danish physician and epidemiologist Peter Panum documented in 1846 that measles is a contagious disease and that the infection provides lifelong immunity.[1] More than a century later, Enders and Peebles isolated the measles virus and thus prepared the way for the development of a measles vaccine, which was licensed in 1963.[2,3] The combined measles-mumps-rubella (MMR) vaccine was licensed in 1971. Since then, MMR vaccine coverage rates have increased markedly and the WHO's ultimate goal of the vaccination programme is to eradicate measles.[4] A global vaccine coverage rate of approximately 94% is needed to achieve this goal.[5] So far, vaccine coverage is much lower than the target and in many developed countries the coverage is still not high enough to prevent outbreaks.[6-8] The suggestion of a causal link between MMR vaccines and autism has threatened to lower vaccine coverage still further.[9,10]

The proposed hypothesis suggests that MMR vaccination may cause a syndrome of mild inflammatory bowel disease associated with behavioural regression. This hypothesis will be referred to as the 'gut-mediated toxic encephalopathy hypothesis' in this article. It is also known as the 'Wakefield hypothesis'.[9,10] Moreover, the wide-scale use of the MMR vaccine has been reported to coincide with the apparent increase in the incidence of autism.[11] These observations have received much public attention and are perhaps the reason for falling MMR vaccination coverage rates in some countries.[12,13]

The aim of this review is to study the evidence on MMR vaccines and the occurrence of autism with particular focus on the epidemiological literature.

The gut-mediated toxic encephalopathy hypothesis was put forward by Wakefield et al. in 1998 when the group published case reports in the Lancet, including 12 children from a gastroenterology clinic

who showed signs of both developmental regression and gastrointestinal symptoms.[9] Eight of these children had experienced the onset of developmental symptoms in relation to their MMR vaccination. The study was followed by a larger survey from the same research group, which came to the conclusion that a new variant of inflammatory bowel disease was present in children with developmental disorders.[10] According to the hypothesis, the MMR vaccine is responsible for a novel lymphocytic colitis with infiltration of T cells and plasma cells in quantities disproportionate to inflammation seen on routine histological examination.[14,15] Wakefield et al. found that mucosal inflammation in combination with ileocolonic lymphoid nodular hyperplasia was seen in children with developmental disorders as opposed to developmentally normal children with similar gastrointestinal symptoms.[10] The nature of the interaction between the gut lesion and the cognitive impairment is unclear but autoimmunity and 'toxic gut-brain encephalopathy' have been suggested.[14]

These findings led the group to propose a new syndrome called the 'gut-mediated toxic encephalopathy hypothesis' characterised by the combination of ileocolonic lymphoid nodular hyperplasia and lymphocytic colitis, in association with developmental disorders.[10,14]

Measles infection is caused by an RNA virus that affects virtually all organs. Involvement of the CNS is relatively common and can lead to a variety of CNS syndromes including meningitis, encephalitis, post-infectious encephalomyelitis and subacute sclerosing panencephalitis (SSPE).[16,17]

The pathogenesis of the post-infectious encephalomyelitis is probably due to measles virus proliferation in lymphoid cells, that in turn leads to a distorted immune response to myelin proteins.[18] Singh et al. have shown a correlation between measles-IgG-positive sera and autoantibodies to basic protein antibodies.[19] Furthermore, persistent measles infection in the CNS is associated with SSPE, a rare chronic progressive demyelinating disorder that affects children and adolescents. After a latent period of 6–8 years, multiple parts of the brain are affected. The condition might be caused by a mutation of the measles virus.[20] Electroencephalographic changes have been noted not only in patients with measles infection, but also in children who have been vaccinated with live attenuated measles virus.[21] Studies have shown that wild-type and attenuated viruses have similarities in tissue tropism, and, in theory, persistent CNS infection with vaccine-strain virus could occur.[22] Two partly-related research groups have detected and sequenced measles virus from peripheral blood in patients with inflammatory bowel disease and autism.[14,23] However, rigourous attempts to reproduce these findings have not been successful.[24-28] Thus, the evidence to support the existence of persistent infection with attenuated measles virus in non-immunocompromised children is not available.

The mumps virus is known to cause encephalitis and some vaccine strains (especially Urabe) are renowned for the conveyance of an increased risk of viral meningitis in the weeks following vaccination,[29,30] but persistent infection with mumps in the CNS has not been documented.

Post-infectious rubella encephalitis is a recognised complication to acquired rubella infection, while a progressive rubella panencephalitis (similar to SSPE in measles) occurs very rarely.[31] Persistent infection with attenuated rubella virus has not been reported. Congenital rubella syndrome due to rubella infection during pregnancy is associated with CNS complications, such as encephalitis, mental retardation, deafness, blindness and autism.[32] Pregnancy remains a contraindication to MMR vaccination, although no evidence of damage to the fetus by rubella vaccine strains exists and rubella vaccination during pregnancy is not considered a valid medical indication for a provoked abortion.[33,34]

The fact that the MMR vaccine contains three different strains of live attenuated viruses, administered simultaneously, has never been shown to be associated with an increased risk of adverse events[35] and is not associated with demyelinating diseases.[36]

In short, it is doubtful whether any biologically plausible explanation for a causal association between MMR vaccination and the subsequent development of persistent complications to the CNS exists.

No well established animal model for the complex pathogenesis of autism exists.[37] The model with Borna disease virus-infected rats is at present the most suitable with regard to the neuroanatomical and behavioural aspects of autism.[37,38] The rats are infected perinatally with Borna disease virus and the persistent infection alters the rat brain in areas known to be associated with autism, especially the medial temporal lobes.[39] However, the Borna disease virus is not related to measles and therefore not suitable for the assessment of a potential link between attenuated viruses in the MMR vaccination and autism. New primate models for the evaluation of vaccine safety issues are under way, but at present they are not ready to be used in the MMR autism context.[40,41]

In summary, no adequate animal model exists for the evaluation of the hypothesised causal association between MMR vaccination and autism.

1. Epidemiological Evidence

In the following section, the epidemiological evidence including case reports, case series, ecological studies, cross-sectional studies and cohort studies is evaluated. We searched literature in Medline (1996 to December 2003), Embase (1966 to December 2003), Social Sciences Index (1986 to December 2003) and the Allied and Complementary Medicine Database (1985 to December 2003) using different keywords with relation to MMR vaccination and autism. Moreover, we manually went through the reference lists of prior reviews and related articles.[42] The epidemiological studies are summarised in table I. The studies with autism as the endpoint under study were selected for this review, and studies restricted to the relation between MMR vaccination and the occurrence of inflammatory bowel disorders were omitted.

Table I. Summary of the epidemiological studies examining the association between measles-mumps-rubella (MMR) vaccination and autism

Study	Year	Country	Study period	Design	Definition of autism	No. of autistic children	Support for MMR autism hypothesis
Peltola et al.[43]a	1998	Finland	1982–96	Case reports	Not stated	0	No
Gillberg and Heijbel[44]	1998	Sweden	1975–84	Ecological	DSM-III-R and ICD-10	74	No
Taylor et al.[45]b	1999	UK	1979–98	Case series method	ICD-10	498	No
Patja et al.[46]a	2000	Finland	1982–96	Case reports	Not stated	0	No
Farrington et al.[47]b	2001	UK	1979–98	Case series method	ICD-10	357	No
Kaye et al.[48]	2001	UK	1988–99	Ecological	Not stated	305	No
Dales et al.[49]	2001	USA	1980–94	Ecological	ICD-9	Not stated[c]	No
Fombonne and Chakrabarti[50]	2001	UK	1954–95	Cross-sectional	ICD-10	262	No
Madsen et al.[51]	2002	Denmark	1991–98	Retrospective cohort	ICD-10	738	No
Mäkelä et al.[52]a	2002	Finland	1982–96	Case reports	ICD-8 and ICD-9	309	No

a These studies used the same source population.

b These studies used the same source population.

c The number can be estimated to >5000 children from the figure in the published results.

DSM = Diagnostic and Statistical manual of Mental Disorders; **ICD** = International Classification of Diseases.

1.1 Case Report Studies

A Finnish case report study by Peltola and colleagues[43] made use of a population-based passive surveillance system for adverse events following the MMR vaccination. They followed up on all children reporting any gastrointestinal symptoms following MMR vaccination in the period 1982–96. Close to 3 million children had been vaccinated during the study period and 31 were reported to have gastrointestinal symptoms. No episodes of autism were reported during the follow-up period, nor did any children develop inflammatory bowel disease. The mean follow-up period was 9 years (range 1–15 years). The authors concluded that their data did not support the hypothesis that MMR vaccination causes autism, although the study was not specifically designed to address that issue.

In our opinion, the study had two limitations. Firstly, the relation between MMR vaccine and autism was examined only in the context of the gut-mediated toxic encephalopathy hypothesis. A stronger approach would have been to evaluate the risk of autism after vaccination regardless of whether or not the child had experienced gastrointestinal symptoms. Secondly, the study was based on a passive surveillance system, which is a method prone to under-reporting.[53] This is probably still the case despite an extensive public campaign encouraging doctors to report all suspected serious adverse effects.

The Finnish case report study by Patja et al.[46] is based on the same dataset as the study by Peltola et al.,[43] in which all routinely reported serious adverse events were reviewed. By considering all adverse effects following vaccination, whether or not the child had experienced gastrointestinal symptoms, the authors dealt with one of the points of criticism raised in regard to their first study.[43] Over a period of 14 years, 173 events were reported, of which 77 were reported as neurological disorders following MMR vaccination. None of the reported adverse effects were symptoms known to be associated with autism; in fact, more than two-thirds were febrile seizures. Again, it is likely that the passive surveillance system led to an under-reporting of adverse effects, especially of effects that occurred long after the vaccination.

Mäkelä et al.[52] published the third case report study based on the Finnish surveillance data provided by the National Public Health Institute. The aim of the study was to examine whether neurological adverse effects (including autism) could be detected after vaccination against MMR, but this time was not restricted to reports of adverse effects. The vaccinated group was linked to the Finnish Hospital Discharge Register and a total of 309 children were diagnosed with autism (classified using the International Classification of Diseases [ICD] 8th and 9th Edition) during the study period. They found no clustering in the interval from vaccination to hospitalisation. Furthermore, no children with autism were hospitalised because of inflammatory bowel disorder. However, outpatient visits were not included in the study and no formal time-trend analyses were presented. Also, no validation of the autism cases was performed even though the diagnostic classification changed from ICD-8 to ICD-9 during the study period. The study was designed primarily to look for neurological disorders that occur shortly after vaccination. Nonetheless, the study provides evidence against a causal relationship between MMR vaccination and autism.

1.2 Case Series Studies

A British study on MMR vaccination and autism by Taylor and colleagues was conducted using the self-controlled case series method.[45] This well-designed population-based study used computerised data from special needs registries and records from special schools to identify children with typical autism, atypical autism and Asperger's syndrome. The authors identified 498 cases from the sampling area, comprising of eight health districts in North London. In a Poisson regression model, the number of cases according to the year of birth was fitted for each of the autistic subgroups. A steady increase was observed throughout the period of observation, but no sudden 'step-up' or change of trend was identified after the introduction of the MMR vaccine in the UK in October 1998. Among the autistic

children, the age of diagnosis was similar, whether the child had been vaccinated before or after the age of 18 months or if they had not been vaccinated at all. Finally, there was no temporal association between changes in the incidence of autism and changes in vaccination coverage. The diagnosis could be verified with ICD-10 criteria, from information recorded in the clinical notes in 82% of the cases of autism.

Interpretation of the results was complicated by the fact that a 'catch-up' vaccination programme was launched along with the introduction of the MMR vaccine. It was targeted at children who were too old to be included in the routine MMR vaccination programme. In a subsequent analysis, Taylor et al. assessed this potential source of bias and found it unlikely that the 'catch-up' vaccination programme could have influenced the negative result.[54] Furthermore, it could be argued that a more gradual increase should be expected since autism is a disorder with insidious onset and a certain diagnostic delay. However, despite these points, the study provides solid evidence against a causal relationship between MMR vaccination and autism.

A British study by Farrington et al.[47] was performed as a follow-up to the Taylor et al. study.[45] In order to deal with the problems of onset of disease and diagnostic delay, the data were re-analysed under the same hypothesis as the original study but without pre-specifying any time interval after vaccination during which the risk of autism may be increased. Farrington et al. used a case-series method, derived from a Poisson cohort model by conditioning on the occurrence of an event and on vaccination histories.[55] The result showed no association between vaccination and autism in any time interval after vaccination.

1.3 Ecological Studies

The Swedish ecological study by Gillberg and Heijbel[44] was a re-analysis of a previously reported study.[56] Gillberg and Heijbel divided the population-based dataset into two birth cohorts: one consisting of children born between 1975 and 1980 before the introduction of the MMR vaccination (n = 47) and one consisting of children born between 1980 and 1984 after the introduction (n = 27). The authors argued that if a causal connection between MMR vaccination and autism exists they would expect the numbers of children with autism born in the latter period to be at least half the total number of autistic children, since the size of the birth cohorts were approximately equal. The fact that there were less than expected in the second period is interpreted as evidence against a causal connection. However, the study is confounded by a lack of consistency in the length of follow-up. The second group (post-MMR vaccine introduction) only had 4 years of follow-up for part of the group. Most children will be diagnosed by the age of 4 years, but even with a moderate diagnostic delay, some of the children in this group would not have been included. We believe that this may explain the unexpectedly low number of autistic children found in the post-introduction vaccination group.

An ecological study by Kaye et al. used the UK General Practice Research Database to conduct a time-trend analysis to assess a temporal association between the changes in vaccination coverage and the incidence of autism.[48] The researchers found that the risk of autism at 4 years of age increased from 8 per 10 000 in 1998 to 29 per 10 000 in 1993, while the vaccination coverage remained constant at 97% in the same time period. If there had been an increase in autism due to MMR vaccination, the authors argued, the incidence of autism would stop rising within a few years after the vaccine was extensively used. This was clearly not the case. The study provided evidence against the hypothesis but there were limitations. First, incidence may rise in the entire incubation and latent period of autism, which could be longer than the study period. Second, the authors did not validate the case status. Third, the observed prevalence of autism was very low – probably because a substantial number of children were not included in the General Practice Research Database. These problems are being addressed in an ongoing study using the same database for case ascertainment.[57]

The ecological study from California, USA, by Dales et al.[49] used basically the same approach and was published less than 1 month after the study of Kaye et al.[48] Cases were provided by the California Department of Developmental Services and comprised all children diagnosed with classic autism, using the ICD-9 classification system, from 1980 to 1994. Data on MMR vaccination status was obtained from the California Department of Health Services' annual surveys of the immunisation levels in Californian kindergartens (samples of 600–1900 children every year). No association was found between the secular trend of childhood vaccination rates in California and the secular trend in the incidence of children entering California's regional service centre system. As in the study by Kaye et al., a marked increase in the number of children with autism was observed. In the 14-year period, the number of cases of autism rose from 4 per 10 000 in 1980 to 21 per 10 000 in 1994 (373% relative increase), whereas the vaccination coverage by the age of 24 months only rose from 72% to 82% (14% relative increase). This study had the same limitations as the study by Kaye et al.,[48] but still provides some evidence against a causal association between MMR vaccination and autism.

1.4 Cross-Sectional Studies

A British cross-sectional study by Fombonne and Chakrabarti[50] studied the temporal association between MMR vaccination and autism, and the frequency of regression in children with autism. They used three existing samples of autistic children, one pre-MMR vaccination (n = 98) and two post-MMR vaccination (n = 96 and n = 68), and analysed the data using different strategies. The authors predicted that if a connection existed, the mean age of onset of autism would be closer to the mean immunisation date in the MMR vaccinated children compared with the unvaccinated children. However, they observed no shift towards a younger age of onset in the post-MMR vaccination samples. They found no evidence of more children experiencing regression in the later samples. Finally, they found no association between autism and gastrointestinal symptoms; in fact, no cases of inflammatory bowel disorder were reported in their study. In conclusion, the study did not support that a connection between vaccination and autism exists, nor did it support the gut-mediated toxic encephalopathy hypothesis.

1.5 Cohort Studies

The Danish study performed by Madsen et al. is the only population-based cohort study performed to date. It included all children born in Denmark between 1991 and 1998.[51] A total of 537 303 children were included in the cohort and approximately 82% had been vaccinated. Information on vaccination history and autism diagnoses was obtained from the Danish national registry systems. During the follow-up period, 738 children were diagnosed with autistic spectrum disorders according to the ICD-10 classification system. To estimate the validity of the diagnosis of autistic disorder, 40 patients were examined and 92.5% (n = 37) met the operational criteria for autistic disorder according to a systematic coding scheme developed by the US Centers for Disease Control and Prevention (CDC) for surveillance of autism and used in a prevalence study in Brick Township, New Jersey.[58] The study showed similar risks of autism in vaccinated and unvaccinated children (adjusted relative risk 0.92; 95% CI 0.68, 1.24) and no temporal clustering of autism in the time after immunisation. The lack of an association was seen for children diagnosed with an autistic disorder (n = 316), as well as children with other spectrum disorders (n = 422). The design of this study reduced the risk of selection and misclassification bias. However, the study had no information on the family history of autism or other mental disorders. If families with a history of autism avoid MMR vaccination, a bias towards no effect could be present. Also, the study had no information on whether or not regression had been present in the autism cases. Nonetheless, the Danish study provides arguments against any significant causal relation between MMR vaccination and autism.

1.6 Summary of Epidemiological Evidence

In summary, we identified ten epidemiological studies based on seven datasets that examined a possible link between MMR vaccination and autism. The studies used different designs and none corroborated the hypothesis that MMR vaccination is causally related to autism. Apart from the initial case reports from Wakefield et al.,[9,10] not one single piece of epidemiological evidence lends support to the hypothesis.

1.7 Ongoing Studies

We are aware of at least four ongoing studies dealing with the possible link between MMR vaccination and autism.

The US CDC are currently conducting a case-control study based on their ongoing monitoring of the occurrence of mental retardation, hearing loss, vision impairment, cerebral palsy and autism.[59] Since the unvaccinated group is expected to be small, the main outcome measure will be the distribution of ages at vaccination. Case ascertainment is expected to be very thorough and additional information on clinical characteristics and confounding factors will be included.

A British study will use the UK General Practice Research Database to set up a case-control study with ten controls per case selected from the database.[57] All diagnoses will be validated by a detailed review of hospital records and by using information derived from a parental questionnaire. In addition, case series analyses will be undertaken to estimate the relative incidence of onset of autism in defined time intervals after vaccination.

The outline of a study of 2400 autistic children was described in a US Institute of Medicine report.[42] The study will be very large and cover three distinct time periods: (i) a period before measles vaccination; (ii) a period of monovalent measles vaccination; and (iii) a period of MMR vaccination. Although ecological in design, it may produce some interesting time trends.

Finally, a Danish study evaluating the possible 'healthy vaccination effect' is in the planning stage. It has been shown that children of parents with a previous history of autism or other psychiatric disorders have an increased risk of autism.[60] Furthermore, it is conceivable that families with a history of autism or other psychiatric disorders will avoid MMR vaccination. If this is the case, confounding by family risk could mask an association between MMR vaccination and autism and explain the negative findings.

2. Discussion

We have found no convincing scientific evidence to support a causal relationship between the MMR vaccine and the development of autism. The biological plausibility remains questionable and there is a sound body of epidemiological evidence to refute the hypothesis. The alleged link rests largely on two observations.

First, the 'gut-mediated toxic encephalopathy hypothesis' based on findings by Wakefield et al. In our opinion, this hypothesis is weak. Even if the mucosa is damaged by MMR vaccination, it would require at least impaired function of the liver and the blood-brain barrier in order to lead to autism. The liver would have to allow the passage of foreign proteins, which would be filtered and degraded in a person with a normal liver function.[61] The blood-brain barrier, fully developed shortly after birth in term-born children, is impermeable to large molecules and thus would not allow the passage of toxins, as suggested in the gut-mediated toxic encephalopathy hypothesis.[62] Finally, if the toxins did reach the brain, they would have to be neurotoxic in a way that, to our knowledge, has not been demonstrated in humans or in animal models.

Second, some parents report that the first sign of autistic symptoms in previously normal children occurred shortly after MMR vaccination. Moreover, the wide-scale use of the MMR vaccine in some regions has been claimed to coincide with the apparent increase in the incidence of autism,[63] although this is not a uniform finding. Data on temporal trends in autism occurrence and MMR vaccination coverage show that the increase in autism both in California, USA[49] and the UK[48] occurred well

after the introduction of the MMR vaccine. The same pattern was found in Denmark where the MMR vaccination was introduced in 1987. The prevalence of autism in children 2–10 years of age was below 1.0 per 10 000 until 1993 and since then the rates have increased in all age groups. In 2000, the prevalence was >30 per 10 000 among children 2–10 years of age.[64]

Several *ad hoc* expert groups have reviewed the problem of MMR vaccination and autism. The US Institute of Medicine's Immunisation Safety Review Committee reviewed all available data and their main conclusion was that the evidence favours rejection of a causal relationship.[42] The same conclusion was reached after a major review of the literature conducted under the auspices of the American Academy of Pediatrics.[65] Finally, the British Medical Research Council also found no evidence for the hypothesis.[66] Several experts in vaccine adverse events likewise concluded, in independent reviews, that the hypothesis has little support.[67-70]

3. Conclusions

Does this mounting body of evidence prove that no causal connection between the MMR vaccination and autism exists? The hypothesis has been subjected to critical evaluation in many different ways using techniques from molecular biology to population-based epidemiology. A vast number of independent researchers have been involved, none of which have been able to establish corroboration for the hypothesis. Still there are no ways of proving the null hypothesis. We cannot rule out the possibility that at least one child would not have become autistic, if he or she had not been vaccinated, and that point alone may be sufficient for stating causality. Unfortunately, this assumption cannot be subjected to a critical test unless it is better specified. However, we can conclude that if this causal link exists, it is not frequent. The existence of a susceptible subgroup with an increased risk of autism if vaccinated cannot be ruled out, but such a subgroup must be small. We can say that MMR vaccination is not the explanation for an increasing incidence in autism, if such an increasing incidence exists. We can say that MMR vaccination is not one of the common causes of autism.[71]

The hypothesis that MMR vaccination causes autism has been subjected to critical evaluation by many researchers who found no support for the theory.

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