

MMR and Autism – can a controversy be more one-sided?

Every time the MMR vaccine receives mention on UK press or television, it is referred to as the *controversial MMR vaccine*. The essence of controversy is the fair presentation of two or more opposing opinions, but media approaches usually depict families struggling with afflicted children and a heroic, patient loving David (Dr A J Wakefield) doing battle with those dogmatic and secretive authorities that gave you BSE and Foot and Mouth. The message: who would you rather trust? is clear; the facts rarely presented. Like many others, I am predisposed towards little David and I well-remember how the medical establishment rubbished Barry Marshall when first he proposed the hypothesis that *Helicobacter pylori* caused GI ulcer disease, a causal relationship now universally accepted. Following a disappointingly one-sided Panorama programme, this seemed a good time to review recent peer-reviewed evidence and see if a simple message could be given to the public; as so often, detailed information had to be analysed before simplicity can be achieved, but a straightforward message can be drawn:

Simple message

The possible role of MMR vaccine in causing autism is deeply worrying; proponents of this theory are clearly honourable and dedicated doctors and scientists; the personal tragedy for families with a child afflicted with autism is great.

The causal association seems highly unlikely because:

1. If MMR causes autism there would be a clear association between the date the MMR vaccine was introduced and the rise in autism. Autism is more common now than in the past, but the increase does not show a time relationship to the introduction of MMR vaccine.
2. The theory suggests a complicated mechanism whereby measles virus infects and damages the gut causing release of toxic materials which in turn attack the brain and cause autism; recent studies confirm the presence of measles virus in the gut of affected children. A new variant disease in which autism is associated with inflammatory bowel disease (IBD) is proposed. However, specific studies in the UK have shown that a new variant disease did not emerge after introduction of MMR; some children with autism do show IBD, but the proportion in whom this is found has not changed since the introduction of MMR vaccine.
3. The theory suggests MMR would cause more autism than individually administered measles, mumps and rubella, but there is no evidence for this. Use of single vaccines would replace a widely tested vaccine system by a relatively less tried system, with possible unknown risks.

It is not possible to prove a negative association nor can it be proved that no individual case of autism has ever been caused by MMR vaccination, but each proposition of the theory that there is a causative relationship has been shown to be invalid to date.

Baseline Review in year 2000

A major expert review was written following a conference convened in June 2000 by the American Academy of Pediatrics (AAP)¹. Characteristic of American openness, the meeting was not restricted to scientists and clinicians, but open to concerned

parents and their organisations. The views of Dr Wakefield were invited before the meeting, which he attended. His complex hypothesis linking MMR to autism is¹:

1. Atypical patterns of exposure to measles virus, including a close temporal association with another infection, are a risk factor for chronic intestinal inflammation.
2. There are factors, such as age, sex, and nature of concurrent exposure(s), that influence the phenotype of the intestinal pathology that develops (i.e. Crohn's disease, ulcerative colitis, or autistic enterocolitis).
3. In children with autistic enterocolitis, persistent measles virus infection of the ileal lymphoid tissue causes chronic immune mediated pathology in the intestines.
4. Associated changes in intestinal permeability and altered peptidase activity allow neurotoxic intestinal products (e.g. exorphins) to reach the brain, which is particularly susceptible to permanent damage during times of rapid cerebral development such as infancy.
5. In susceptible children (possibly for reasons of age, immune status, or genetic background) MMR vaccine is an atypical pattern of measles exposure that represents a significantly increased risk for intestinal infection and associated developmental regression compared with the monovalent vaccine, or natural infection.
6. Accordingly, the widespread use of MMR immunization is a major determinant of the apparent (now substantiated) increase in rates of autism.

The AAP review addressed relevant questions on the basis of current understanding:

Questions addressed at AAP Conference

<p>What is autistic spectrum disorder (ASD)? Are there subtypes of ASD? What is the meaning of "regression" in ASD? What factors could contribute to changes in the incidence or prevalence of ASD? What are some possible reasons for increasing rates of diagnosis of autism? Is the onset of autism temporally related to receipt of measles or MMR vaccines? Is there a genetic predisposition to ASD? Do structural changes in localised areas of the brain in individuals with ASD suggest timing of the insult?</p>	<p>Are there underlying immunologic differences in children with ASD compared with unaffected children? Are gastrointestinal symptoms associated with ASD? Does postpartum administration of MMR vaccine predispose children to ASD? What are the effects of measles, mumps and rubella occurring simultaneously or in close succession? Is measles virus present in the intestinal wall in patients with inflammatory bowel disease (IBD) or ASD? Do epidemiological studies support an association between measles, measles vaccine or MMR vaccine and IBD? Could ASD be of infectious origin?</p>
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(for conclusions from review of these questions, see the AAP review; full text can be obtained on the internet)

After review, nine criteria generally accepted as providing the best evidence of causality were applied. To précis some points from the review of these criteria:

- the recent increase in reporting of ASD does not correlate with the introduction and wide-spread use of MMR;
- there was no consistent pattern in the timing of onset of ASD symptoms after MMR vaccination;
- the finding of residual measles virus in the intestinal wall of children with IBD or ASD was inconsistent and did not seem to be specific to affected children;

a dose-response effect between MMR vaccine and the development of ASD was not shown;
there was no experimental evidence to support the hypothesis that MMR vaccine causes autism nor to show any benefit from administering the three vaccines separately.

Conclusions from this thorough and open review in June 2000 include:
available evidence does not support the hypothesis that MMR vaccine causes autism or associated disorders, nor does it cause IBD;
separate administration of components of the vaccine would provide no benefit and would result in delayed or missed immunisation.

Recent evidence

The extent to which media interest has influenced matters is shown by publication of some evidence in February 2002 in electronic versions of the journals, to the clear distress of some doctors who received information from the media rather than in the print versions of the publications. Evidence for and against the theory has emerged since the AAP review discussed above.

A large prospective study in Finland reporting on 1.8 million individuals receiving 3 million doses of MMR vaccine through 14 years found few severe reactions². Since this study did not pick up the cases of autism which should be present in the population at any time, it contributes little to this specific debate, but its large scale means that it has been widely quoted as good general evidence for the safety of the MMR vaccine.

The AAP review found no temporal relationship between the introduction of MMR vaccine and autism. This has been confirmed by a more recent time-trend analysis in the UK³ which showed a steadily rising increasing incidence of autism against a background of steady (95%) MMR vaccination, providing more evidence against the association. This analysis was based upon the UK general practice research database, a spin-off from a GP computer recording system. This is a system which may provide incomplete records, but which has been demonstrated to maintain a complete record of vaccinations given and would pick up major illnesses such as autism. A similar conclusion was reached when time-trends in autism and MMR immunisation coverage were studied in California⁴.

The AAP review in June 2000 found inconsistent results for the presence of measles virus in the intestinal wall of patients with autism associated with IBD. A recent publication⁵ describes a rigorous study into this issue from a group including Dr Wakefield. This showed that 75 of 91 children with a histologically confirmed diagnosis of ileal lymphonodular hyperplasia and enterocolitis were positive for measles virus in their intestinal tissue compared with 5 of 70 controls (most of whom had other GI diseases). Measles virus was found within the follicular dendritic cells and some lymphocytes in foci of reactive follicular hyperplasia. These findings were taken to confirm an association between the presence of measles virus and gut pathology in children with developmental disorder.

It should be noted that these authors start from the premise that the new variant inflammatory bowel disease associated with autism exists. This premise was not accepted at the June 2000 AAP review; more evidence against it has just been published⁶.

In this population study in 5 health districts in NE London, case notes were reviewed and linked to independently recorded vaccine administration data. 278 Children with core autism and 195 with atypical autism, born between 1979 and 1998 were studied. The proportion of children with developmental regression (25% overall) or bowel symptoms (17%) did not change significantly during the 20 years from 1979, a period which included the introduction of MMR vaccination in 1988. A possible association between non-specific bowel problems and regression in children with autism was seen, but this was unrelated to MMR vaccination. It was firmly concluded that there is no evidence to support the emergence of an MMR vaccination associated “new variant” form of autism with developmental regression and bowel problems.

A worrying feature of this study, revealed by detailed review of the case records, was that in 13 children the history given by parents had changed after publicity about MMR vaccine and autism. Before the publicity the parents often reported concerns early in their children’s life, usually before the first birthday; the current history for the same children recorded symptoms as developing only after MMR vaccination, in some cases shortly after.

This potential bias has considerable implications for future studies which will be conducted against the background of media interest and litigation. Plans have been published⁷ for a case-control study of autism and MMR vaccine, using the GP research database to identify patients and match controls. One of the information sources proposed is to be a parental questionnaire, the value of which may be distorted by similar bias.

The great expense involved in studying the possible role of MMR as a causative factor for autism is diverting resources away from research into other possible causes for the disease and its increased prevalence. The AAP review¹ suggest many that may be involved, including:

1. Substantial migration of affected children into or out of a community (e.g. if families moved to certain areas because of improved treatment options);
2. Change in age of onset or recognition (diagnosis) over time (e.g. an apparent increase in incidence and prevalence would be noted if new techniques resulted in diagnosis at younger ages);
3. Large changes in the denominator population (e.g. influx of large numbers of unaffected children would appear to decrease prevalence in a population study);
4. Increased ascertainment of children with diagnoses of autism or ASD;
5. A change in the diagnostic criteria to include individuals with milder symptoms or different combinations of symptoms; and
6. A true increase in the incidence of the disorder, which could be attributable to new environmental exposures (eg, environmental chemicals or infectious agents).

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