HEALTH CONCERNS & THE MMR VACCINE

POST 131
Post Note December 1999

A number of recent scientific studies have investigated possible adverse health effects in infants receiving the MMR (Measles, Mumps and Rubella) vaccine. The studies focus on the question of whether measles-containing vaccines, including MMR, are associated with the onset of intestinal complaints and/or behavioural disorders.

This briefing summarises the evidence from such studies and examines the issues that arise.

BACKGROUND

Since 1988, the Department of Health (DH) has recommended MMR vaccine for all children without valid contraindications. The vaccine contains live measles, mumps and rubella viruses that have been weakened to prevent them from causing disease. Vaccinating children with MMR familiarises their immune systems with the 'tame' viruses, equipping them with the ability to mount effective immune responses if they ever encounter the 'real' versions[1]. MMR vaccine is first routinely given at the age of 12-15 months; since October 1996, a second MMR jab has been added to the schedule as a pre-school booster.

A mass measles/rubella (MR) campaign was conducted in 1994, targeted at all 8 million 5-16 yearolds in the UK; 92% of this target population were immunised. The Joint Committee on Vaccination and Immunmisation (CVI) judged this campaign necessary to avert a UK measles epidemic affecting a predicted 150,000 people in 1995.

BENEFITS

MMR vaccine has reduced cases of measles (**Figure 1**), mumps and rubella (**Figure 2**) notified to the Public Health Laboratory Service's (PHLS) Communicable Disease Surveillance Centre. For measles, the first effective vaccine was introduced in the 1960s. High rates of MMR coverage combined with the recent MR campaign have driven notifications even lower (Figure 1), in line with the World Health Organisation (WHO) European Region strategy for eliminating measles. MMR vaccine has also reduced notifications of both mumps and rubella (Figure 2) since the late 1980s. Rubella is included because of the risk of foetal damage if women contract it in the first 16 weeks of pregnancy. The rationale for giving the rubella component to both boys and girls is to reduce the circulation of this virus in the population at large.

1 See POST report 'Vaccines and their Future Role in Public Health', July 1995 for further details of how vaccines work.

FIGURE 1 MEASLES NOTIFICATIONS AND DEATHS

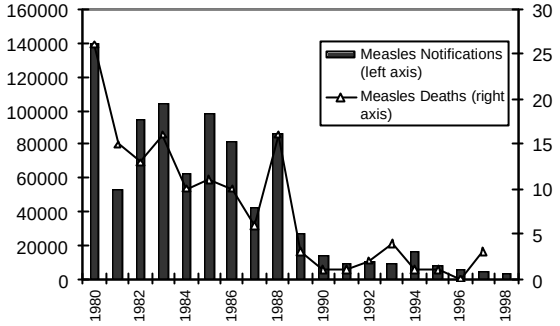
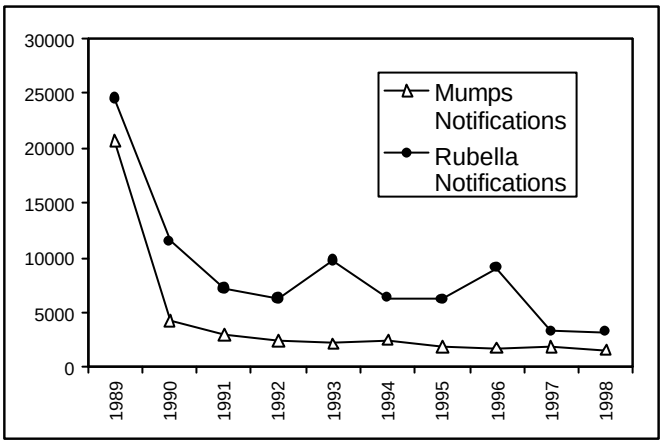


FIGURE 2 MUMPS AND RUBELLA NOTIFICATIONS



Note: Data for both Figures for England and Wales only (source PHLS)

TABLE 1 RISK OF CONDITIONS FROM MMR VACCINE COMPARED WITH NATURAL DISEASE

Condition	Rate after natural disease	Rate after first dose of MMR
Convulsions	1 in 200	1 in 1,000
Meningitis /encephalitis	1 in 200 to 1 in 5,000	1 in 1,000,000
Conditions affecting blood clotting	1 in 3,000	1 in 24,000
Severe allergic response		1 in 100,000
Death	1 in 8,000 to 1 in 10,000 (depends on age)	0

Source: HEA MMR Immunisation Factsheet, February 1997

RISKS

General

As with any other medical intervention, vaccination is not entirely free from risk (**Table 1**). The diseases that the MMR vaccine protects against are potentially fatal, causing conditions such as convulsions, meningitis/encephalitis and various disorders affecting blood clotting. As shown in Table 1, while the MMR vaccine may also be associated with such conditions, the risks are lower than for the diseases themselves, and the conditions are milder (e.g. are not fatal).

BOX 1 IBD AND AUTISM

Irritable Bowel Disease (IBD) – is an umbrella term that includes:

- Crohn's disease, an inflammation that can affect any part of the digestive tract, but is most commonly associated with the lower part of the small intestine.
- Ulcerative colitis, an inflammation of the colon (large intestine).

Autism - is a pervasive developmental disorder that affects the way a person communicates with and relates to those around them. **Core autism** is characterised by three diagnostic criteria:

- abnormal/impaired social interaction **and**;
- abnormal/impaired communication **and**;
- restricted, repetitive behaviour.

These abnormalities manifest themselves in childhood, before the age of three years (most cases are diagnosed in the second year of life). Usually there is no prior period of normal development, although some cases are **regressive** (i.e. where the child appears to be developing normally before starting to display autism). **Atypical autism** is diagnosed where not all three criteria above are fulfilled, and/or where onset is after the age of three years.

BOX 2 RESEARCH SUPPORTING A LINK

A 1995 study[3] compared rates of IBD among 3,500 people born in 1962/63 with those among a group of 11,000 people born in 1958. IBD rates in the first group (who all received measles vaccine in 1964) were higher (7 per 1,000 compared with 2 per 1,000) than those in the second group (who had **not** received measles vaccine, but had all suffered measles). Certain aspects of the study design were criticised at the time[4]; e.g. disparities (in age, geographical location, etc.) between the compared populations, and the fact that different methods were used to identify cases of IBD in each group.

A 1998 study[5] raised the possibility of a link between MMR vaccine and regressive behavioural disorders. The research described clinical features of 12 children referred to a gastroenterology unit:

- All appeared to develop normally before developing disorders.
- All were suffering from both intestinal abnormalities and developmental disorders (regressive autism in 9 of 12 cases).
- Onset of behavioural symptoms was associated with MMR vaccination by the childrens' parents in 8 of the 12 cases. In each case, symptoms appeared within days or weeks of vaccination.

The researchers noted that the study "*did not prove an association*" between MMR vaccine and the syndrome they described. This study was also criticised.

Irritable Bowel Disease (IBD)/Autism

Recent research has focused on possible links between:

- measles vaccine (M or MMR), the disease itself, and intestinal disorders (IBD, see **Box 1**);
- MMR vaccine and developmental disorders (autism, see Box 1).

Evidence Supporting Possible Links

The main studies claiming to show a possible link between measles, measles vaccine and IBD/autism were conducted by a group at the Royal Free Hospital in London (**Box 2**). They include:

- A 1995 study that found higher rates of IBD among people receiving the measles vaccine compared to those that had not been vaccinated;
- A 1998 study of 12 children, all of whom developed symptoms of regressive developmental disorders **and** intestinal abnormalities, 8 after receiving MMR vaccine and one after measles infection.

The researchers postulated that MMR vaccine might cause intestinal disease. They suggested this might affect absorption of chemicals across the gut; this in turn could allow molecules (possibly peptides) access to the brain, where they might trigger behavioural disorders. However, there is no published evidence to support this hypothesis.

Parents' Reports

In the wake of the publicity triggered by these studies, hundreds of parents contacted solicitors because they believed their children had been permanently damaged by MMR vaccine. One firm of solicitors has received more than 500 such reports[2]. Several hundred have now been evaluated for the Committee on Safety of Medicines (CSM) by an expert working party organised by the Medicines Control Agency (MCA; see **Box 3**). It found that the medical information they contained was variable in quality and completeness, and of limited overall use (cases were self-selecting and there was no control group available for comparison). Only 8 out of 92 autism cases and 4 of 15 Crohn's disease cases satisfied the working party's minimum criteria for vaccine damage to be a possibility. It concluded:

- It was impossible to prove or refute the suggested links between MMR and autism/IBD.
- The information did not support a causal link, or cause concern over the safety of MMR vaccine.

Evidence Not Supporting Possible Links

Other studies have failed to produce evidence of a causal link (**Box 4**). These include population studies that found no differences in rates of autism and/or IBD in immunised compared with unimmunised populations, as well as molecular studies that failed to detect measles virus in bowel tissue from patients with IBD. The most recent study (Box 4) provides evidence of an increase in cases of autism in one area of the UK since 1979 (**Figure 3**). However, this upward trend, which appears to be exponential, started in the late 1970s. It is thus unlikely to be linked with the introduction of MMR vaccine in 1988. As detailed in Box 4, the study yielded no other evidence of a link between MMR vaccine and autism (Box 4).

2 Hodge Jones & Allen Solicitors, London

3 Thompson et al, 1995, The Lancet, 345, 1071-74.
4 Patriarca and Beeler, 1995, The Lancet, 345, 1062-63.
5 Wakefield et al, 1998, The Lancet, 351, 637-41

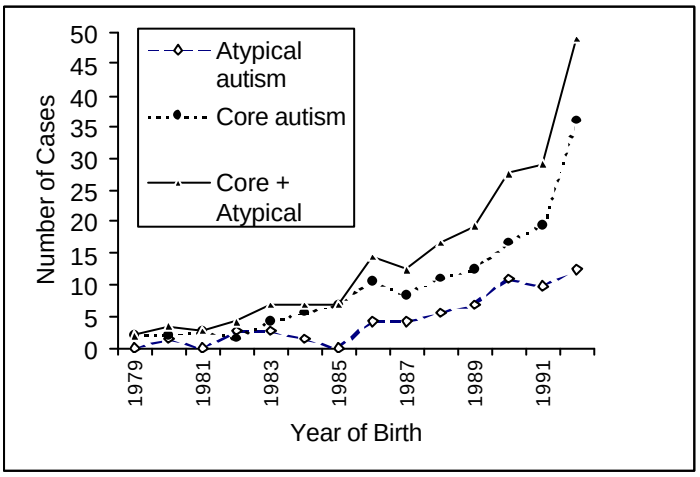
BOX 3 CSM REVIEW OF PARENTS' REPORTS

The Committee on Safety of Medicines (CSM) asked an independent expert working party to assess reports from parents who believed that their children had been damaged by measles vaccine. It obtained details from the children's GPs and other medical specialists[6], and evaluated 92 cases of autism and 15 of Crohn's disease. It focused on 4 main criteria:

- Medical confirmation of diagnosis (possible in 81 of the autism cases and 12 of the Crohn's).
- Close temporal link between vaccination and onset of symptoms. A cut-off period of 6 weeks was chosen (the time viral replication can be detected after vaccination). In 39 of the autism cases, the parents reported symptom onset within 6 weeks (and in 5 of the Crohn's cases).
- The absence of relevant previous medical history (e.g. of behavioural abnormality in the autism cases).
- The absence of an alternative cause (e.g. family history of the condition in question).

In all, 8 of the 92 autism cases and 4 of the 15 Crohn's cases fulfilled all four criteria. The working party noted that even in these cases, the evidence did not constitute proof that vaccination caused the symptoms. It pointed out that the apparent link might merely be temporal coincidence since the age at which children receive their first MMR jab coincides with that at which most autism cases are first diagnosed anyway. It also noted that in none of the autism cases was there any record of vaccination causing an unexpected/unexplained acute neurological event.

FIGURE 3 CHILDHOOD AUTISM IN NE THAMES, 1979-92



Source:Taylor et al 1999, The Lancet, 353, 2026-29

The researchers concluded that the results "*do not support the hypothesis that MMR vaccination is causally related to autism*", noting that "*if such an association occurs, it is so rare that it could not be identified in this large regional sample*".

ISSUES

Expert Review

Evidence of possible links between MMR and autism or IBD has been reviewed by various independent expert bodies. These include international (e.g. the WHO) and national bodies (the JCVI and CSM) and an *ad hoc* group of more than thirty experts convened by the Medical Research Council (MRC).

6 MCA/CSM, 1999, Curr. Prob. in Pharmacovigilance, 25, 9-10

BOX 4 RESEARCH NOT SUPPORTING A LINK

Research that has failed to yield evidence of a link between measles vaccine and IBD and/or autism includes:

- Two further population studies (a case control study[7] and a cohort study[8]) that failed to implicate the measles vaccine as a risk factor in IBD.
- Powerful new molecular studies[9] have also failed to find evidence of measles virus DNA in bowel tissue from IBD patients.
- Epidemiological studies from other countries that have failed to find evidence of a causal link between MMR vaccine and autism (Sweden) and/or Crohn's disease (Finland).

Further research[10] commissioned by the MCA has looked at trends in the incidence of autism before and after MMR vaccine was introduced (October 1988). It identified children with autism born since 1979 from special needs/disability registers in health districts in North East (NE) Thames, cross-linking this data with immunisation records. The main findings included:

- An exponential upward trend in the number of cases of autism diagnosed over the whole of the period 1979-92 (**Figure 3**) – i.e. from before the introduction of MMR.
- There was no sharp change in the trend line coinciding with the introduction of MMR vaccine in October 1988 (Figure 3).
- No difference in age of diagnosis between MMR immunised and unimmunised children. Nor was there evidence of 'clustering' of regressive cases of autism in the months following vaccination.
- One analysis did show an apparent 'cluster' – a disproportionate number of parents recalled the onset of symptoms occurring within 6 months of vaccination (when the child was ~18 months). The researchers suggested that this reflected difficulty in defining the precise age of onset of symptoms: '18 months' is a convenient label for 'somewhere between 1 and 2 years'.

The reviewers had to decide whether the apparent temporal relationship between vaccination and the onset of symptoms was evidence of cause and effect, or merely coincidence. This question arises because autism is most often first diagnosed at around the same age as children receive their first MMR jab. All of these expert bodies independently reached the same conclusions – that there is:

- no evidence that MMR causes IBD or autism;
- no need to change MMR vaccination policy.

Advice to Parents

Based on the research, the DH issued a press release[11] in June 1999 emphasising the public health benefits of MMR vaccination and stating that it "*does not cause autism or Crohn's disease*". A recent HEA leaflet[12] on MMR reiterates this advice, stating:

- "*the evidence is firmly against any link between measles and MMR vaccines and Crohn's disease*";
- "*there is no evidence, other than coincidence, to link MMR with autism*".

However, some have questioned this advice. For instance, a debate in the House of Lords in January 1999 on MMR vaccine raised a number of issues:

7 Thompson et al, 1995, Eur J Gastroenterol Hepatol, 7, 385-90
8 Morris et al, 1997, Gut, 41, 37.
9 Chadwick et al, 1998, J Med Virol, 55, 305-11
10 Taylor et al, 1999, The Lancet, 353, 2026-29
11 DH Press Release 1999/0342, 10/6/99
12 DH/HEA, 1999 MMR – The Facts

- Whether the DH/HEA advice to parents was justified by the available scientific evidence. Several speakers felt it overstated the benefits of MMR and downplayed the risks, while others contested those opinions.
- The role of the DH – whether it should actively encourage participation in immunisation programmes or merely dispense impartial advice on risks and benefits?

For its part, the DH has a responsibility to ensure that immunisation policy in this country is based on objective, scientific reasoning and that expert independent advice is obtained to interpret both research data and clinical experience. The DH view is based on all of the available information. All the expert reviews conducted to date judge the public health benefits of MMR to far outweigh any individual risks associated with the vaccine. In addition, the DH points to the long history of safe use of MMR in the UK and elsewhere (250 million doses of MMR in 40 countries over 26 years).

As for its wider role in vaccine programmes, the DH sees the main challenge as presenting parents with the facts to allow them to make an informed decision. One recent development here is that parents receiving an invitation to bring their child in for MMR vaccination now also receive a copy of a leaflet from the HEA (MMR-The Facts) outlining the recent research. The DH hopes that this approach will at least encourage parents to seek further advice on the pros and cons of MMR vaccination from health professionals.

Effect on Coverage

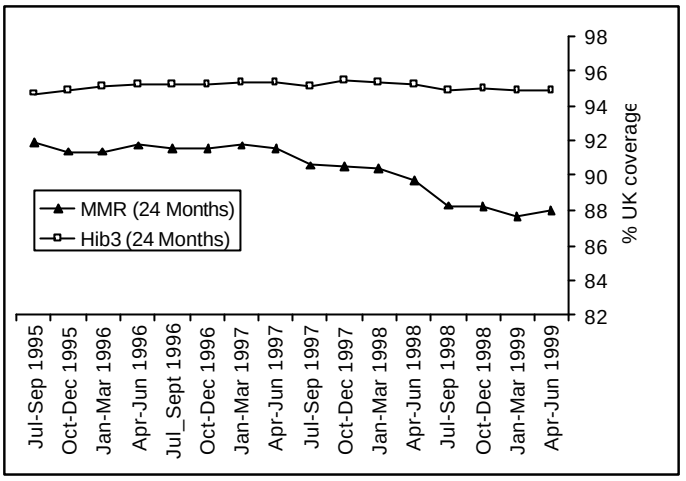
Overall, the proportion of UK children given MMR vaccine by age 24 months dropped from ~91% in 1995, bottoming out at 87.6% in January-March 1999 (**Figure 4**). However, the most recent figures (April-June 1999) show a slight recovery, to 88%. Over the same period, coverage of other vaccines such as Hib (*Haemophilus influenzae b*) has remained close to the DH's 95% target. Parental confidence in MMR vaccine may take some time to restore, particularly as studies finding no evidence of links between MMR and autism/IBD tend to attract less media coverage than those claiming to show links.

Single Antigen Vaccines

Media reports in recent years – without any scientific corroboration - have suggested that it might be safer to give the vaccines as three separate jabs at least a year apart (based on the notion that MMR 'overloads' a child's immune system). But the DH opposes any such move, on the grounds that:

- there is no evidence that combined vaccines cause the conditions postulated;
- there is no evidence that separate vaccines would prevent these postulated associations;
- take-up for three separate jabs would inevitably be lower than for a single MMR jab;
- children would remain unimmunised and thus at risk of disease for a longer time;
- there is evidence that some single antigen mumps and measles vaccines are much less effective than MMR.

FIGURE 4 COVERAGE OF MMR AND HIB VACCINES



Note: Figures are for the UK (Source PHLS)

A second suggestion - based on doubts over the seriousness of (and thus the need to immunise against) mumps and rubella - is to switch from MMR to measles-only vaccine. Again, any such move is opposed by the DH and expert advisory bodies on the grounds there is no evidence of specific risks associated with mumps or rubella vaccine, and both carry significant public health benefit.

Compensation

As noted previously, MMR vaccine is not completely free of risk, and doctors are obliged to report any adverse effects to the CSM through the 'yellow card' system. Such risks have to be weighed against public health benefits when vaccine policy is decided. Since 1979, those who suffer severe (80% or greater) mental/physical disablement following vaccination can apply for a one-off payment through the Vaccine Damage Payments scheme. The upper limit for such awards was recently raised to £40,000. Some see this figure as inadequate in view of the serious nature of the disabilities involved and are seeking compensation from vaccine manufacturers through the UK courts; no such cases have yet been successfully concluded.