

MMR

MMR: where are we now?

David Elliman, Helen Bedford

There is no scientific evidence of a link between bowel disease and/or autism and MMR vaccine. Attainment of a high uptake of the vaccine should be encouraged.

The combined measles, mumps and rubella (MMR) vaccine was introduced to the UK in 1988 and uptake of the vaccine rose rapidly to a high of 92%. In 1992, brands containing the Urabe strain of the mumps vaccine virus were withdrawn after it was noted to be associated with an increased risk of aseptic meningitis.¹ This did not appear to have a deleterious effect on uptake. In 1995, a paper was published suggesting a link between measles vaccines and the development of bowel disorders in adulthood.² This was associated with a small decline in the uptake of MMR vaccine. In 1998, the same group of researchers published observations of 12 children with pervasive developmental disorders and bowel disease and suggested that the latter may have led to the former.³ In eight children, the history of the onset of symptoms coincided with receipt of MMR vaccine. Although the researchers stated in the paper that "we did not prove an association between measles, mumps, and rubella vaccine and the syndrome described", and an accompanying commentary was heavily critical of any suggestion of such a link,⁴ the story attracted much attention in the media. This was largely fuelled by a paragraph in the press release accompanying a press conference: "The majority opinion among the researchers involved in this study supports the continuation of MMR vaccination. Dr Wakefield feels that vaccination against the measles, mumps, and rubella infections should undoubtedly continue but until this issue is resolved by further research there is a case for separating the three vaccines into separate measles, mumps, and rubella components and giving them individually spaced by at least 1 year".⁵ Subsequently, public confidence in the vaccine was dented and uptake of the vaccine in England fell to 79%, with some parents seeking the single antigen components. In this article we consider the evidence in relation to the proposed link, the effect the scare has had on the control of measles, mumps and rubella, and the current situation.

EPIDEMIOLOGICAL STUDIES

While there are known adverse reactions following receipt of the vaccine, as with any live vaccine, these are predictable in that they are also complications of the diseases, for example febrile convulsions and idiopathic thrombocytopenic purpura.⁶ On the other hand, features of autism do not follow postnatal measles, mumps or rubella, unless accompanied by severe encephalitis. For this reason, prior to its release, no studies had been carried out specifically looking for autism after administration of the vaccine and no significant concerns had been raised in this respect after 16 years of use in the USA. However, once the question was posed, it had to be addressed. Because the vaccine was already used in most children in the countries where it was available, it would have been unethical to conduct randomised controlled trials with administration of the vaccine being delayed or withheld entirely. Thus, the studies that have been carried out have been observational, although in many cases they included controls.

Numerous studies have been conducted in different countries. It is not within the remit of this article to review these in full and we will thus only consider some of the key papers using sound methods. A few months after the *Lancet* article appeared, Gilberg and Heijbel reported no rise in referrals of children with autism to their clinic in Sweden following the introduction of MMR.⁷ Studies conducted in London by Taylor and colleagues have shown no link between MMR and autism, either in general or, specifically, with disintegrative autism.^{8,9} Using record linkage in Denmark, Madsen and colleagues¹⁰ compared the incidence of autism in children who had had MMR vaccine with those who had not and found no significant difference. While all of these studies have some limitations, it is most unlikely that between them they would have failed to detect a significant link between MMR and autism and even in a review which adopted the most restrictive inclusion criteria for the studies reviewed, the

authors concluded "no credible evidence of an involvement of MMR with either autism or Crohn's disease was found".¹¹

VIROLOGICAL STUDIES

As well as carrying out epidemiological studies, some researchers have tried to ascertain whether there is any evidence of abnormal persistence of measles virus in children with autism, in particular those with bowel disease. This is a very difficult area of research, requiring obsessive attention to detail, particularly in avoiding cross-contamination with measles virus, rigorous testing and selection of controls. Early studies had suggested the presence of measles virus antigen in the bowel wall of patients with Crohn's disease.^{12,13} However, subsequent studies,^{14,15} including one from the original research group,¹⁶ have cast doubt on these findings. A number of groups aligned with the original protagonists of a link have suggested that measles virus can be found in the peripheral blood,¹⁷ bowel mucosa¹⁸ and cerebrospinal fluid (CSF)¹⁹ of a high proportion of children with autism and bowel problems. Independent researchers have not been able to study the presence of measles virus in the bowel and CSF of such children as, in the absence of any therapeutic benefit to the children, most practitioners have considered it unethical to obtain bowel biopsies or CSF. They have attempted to replicate the findings on peripheral blood but have been unable to do so. Afzal *et al.*,²⁰ using similar methodology to Uhlmann *et al.*,¹⁸ sought measles antigen in peripheral leucocytes of children with autism and known to have received MMR vaccine. They were unable to isolate it, in spite of finding it in known positive samples, such as brain tissue from subacute sclerosing panencephalitis (SSPE). Another independent study examined peripheral white cells and found that it was easy to obtain false positive results using the methodology of Uhlmann *et al.* However, when carefully modified, positive results were only obtained from known positive samples and not from children with autism.²¹ This does not explain why some groups obtained positive results in children with autism and not in "control" children, but does emphasise the importance of correct technique. In a further study (Baird *et al.* Measles vaccination and antibody response in autism spectrum disorders, unpublished), using highly sensitive techniques, evidence of measles viral genome was found in the blood of 1/98 children with autism spectrum disorders (ASD), 2/70 children with learning disorders without ASD and 0/90 controls. These positive findings could not be reproduced.

Even if measles virus were found to persist in children with autism, it is worth remembering the cautionary words of Morris and Aldulaimi,²² who in commenting on the paper by Uhlmann *et al*, pointed out that the presence of measles virus does not imply causation. Indeed in this case it may be that rather than the measles virus "causing" the bowel problems, the colitis or the developmental disorder "causes" the persistence of the measles virus. This could be a reflection of the inability of patients with a developmental disorder or enterocolitis to clear the virus: the enterocolitis may cause failure of viral clearance. They concluded "...in no way can the data presented here be used to support the generalisation that MMR causes all autism and/or inflammatory diseases of the bowel".

PARENTS' ATTITUDES

Parents' perceptions of the safety of vaccines are an important determinant of vaccine uptake.²³ Studies conducted since 1998, focussing on attitudes to MMR vaccine, have reported fears over the safety of the vaccine among parents who accept the vaccine as well as those who decline it.^{24–25} Of greater concern, perhaps, is that some studies report parents' mistrust of government sources of information about MMR vaccine and consider the information provided by official sources is biased and one sided. This is partly as a consequence of GPs' target payments for immunisation as well as the effects of the controversy over new variant CJD.^{24–27} However, both improving coverage rates and attitudinal work suggest that parents' confidence in the safety of the vaccine is being restored.²⁸

HEALTH PROFESSIONALS

Parents most frequently cite healthcare professionals, particularly health visitors, as their source of advice on immunisation.^{24–29–30} However, healthcare professionals have been found to be poorly informed about vaccines.^{31–33} Shortly after publication of the 1998 case series,³ some healthcare professionals reported having lost confidence in the safety of MMR vaccine.³⁴ A more recent investigation of over 100 primary healthcare professionals' knowledge and attitudes to MMR vaccine, conducted at the end of 2005 in one inner London primary care trust (PCT), found that, although the vast majority had positive attitudes to the safety of MMR vaccine, they demonstrated significant gaps in knowledge about both contraindications to the vaccine and adverse side effects. This could have the effect of denying the vaccine to children on the basis of a non-existent contraindication and could also result in

parents being given inconsistent advice by different professionals leading to confusion or mistrust.

VACCINE UPTAKE

Coverage of MMR vaccine has improved gradually in England from a low of 79% in 2003³⁵ and is now 85%,³⁶ with uptake in Scotland, Wales and Northern Ireland even higher.³⁶ However, there is a wide range in particular between London districts. For 2005/6, the average uptake of MMR in London at 2 years old was 72%, with a range of 52–91%.³⁷ The decline in uptake of MMR since 1998 was greater in more affluent areas^{38–39} and lower in areas with less highly educated residents.⁴⁰ Single antigen vaccines are only obtainable on a private basis, and since there is no transfer of information regarding their use into NHS information systems, routine data on uptake are not available. One recent study attempted to assess the use of single vaccines in England and Wales based on requests for importation and figures from some providers.⁴¹ It was estimated that, of the cohorts of children born in 2001 and 2002, a minimum of 1.7% and 2%, respectively, received the single measles vaccine by 2 years old, with a maximum of 5.6%. However, these estimates involved many assumptions and another study based on interviews with over 14 500 parents, found that approximately 6% of 3-year-old children in the UK have had one or more single antigen vaccines (Anna Pearce, David Elliman, Catherine Law, Helen Bedford, unpublished data, 2007).

OUTBREAKS OF DISEASE

In 2006, there were more confirmed cases of measles (736) reported than at any other time since the current system of reporting was instituted in 1995.⁴² There have been sizeable outbreaks, mainly among travelling communities, and a 13-year-old boy on immunosuppressive treatment died,⁴³ the first death due to acute measles since 1992. While there have been no major outbreaks of mumps due to the fall in uptake, there have been many cases among young adults too old to have received the MMR vaccine. Fortunately, to date, there has been no increase in rubella, or more importantly, congenital rubella. However, there are significant pockets of susceptibility to rubella among pregnant women who depend on current levels of herd immunity for protection.⁴⁴

CONCLUSION

In 1998, it was suggested that there might be a link between receiving MMR vaccine and the subsequent development of autism and bowel disease. In spite of no

substantial evidence to support this hypothesis, concerns were such that the uptake of the vaccine fell. Over the following period, overwhelming evidence of no link between MMR vaccine, autism and bowel disease, has emerged. The fall in confidence has been reversed and this has been reflected in recent increases in uptake of the vaccine. However, in 2006, the greatest number of cases of confirmed measles were reported in any one year since confirmation of notifications started in 1995. It is important, therefore, that health professionals continue to strive to ensure that all children are offered two doses of MMR. Until a consistently high uptake of the vaccine has been achieved, the goal of elimination will not be attained. All contacts with children and young people should be seen as an opportunity to check that they are fully immunised. This applies as much in secondary care as in primary care.⁴⁵ When measles deaths are falling dramatically in most of the world,⁴⁶ it would be tragic if the disease were to return to the UK and there were further unnecessary deaths.

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