SHOULD I GIVE MY CHILD THE MEASLES-MUMPS-RUBELLA VACCINE?

SHOULD I GIVE MY CHILD THE MEASLES-MUMPS-RUBELLA VACCINE?

This is a question posed by many mothers in our practice, a generally well-educated population who are anxious to do what is best for their child. Currently the rate of uptake at our surgery is 82.9%; in Britain the uptake is 84.2%, but in London it is 75%.

As General Practitioners we are trusted by our patients and need to be aware of the up-to-date evidence-based facts in our role in health promotion to help our patients make informed decisions. The Department of Health claims that the Measles-Mumps-Rubella (MMR) vaccine is safe, but there are worries in other quarters about its safety.

The aim of this project is to review the currently available evidence regarding the controversies surrounding MMR vaccine in a historical manner in order to provide a reasoned argument that MMR vaccine is safe, advisable and preferable to single vaccines.

I chose this topic having completed a Paediatric SHO post where our clinics had been flooded by parents wishing to discuss the MMR vaccine as a consequence of media hype.

METHOD

Initially, I referred to the health promotion literature from the Chief Medical Officer and Department of Health.

I performed an internet search via Pubmed under 'measles-mumps-rubella vaccine' (MESH), which produced few references of limited relevance to recent controversies. The Cochrane Library had nothing under the same keyword and therefore I broadened the search under 'vaccine' and then the subset'measles vaccine'; there were no meta-analyses of current literature relating to the MMR vaccine or even to the single vaccines.

I went on to refer to various websites on immunisations (1), Department of Health, Public Health Laboratory Service (2) and Royal College of General Practitioners.

Via a media search, I reviewed relevant articles from the main newspapers that inform our patients.

To conclude, I interviewed Or Barry Walsh, a local Public Health Consultant.

MEASLES-MUMPS-RUBELLA VACCINE

WHAT IS MMR?

Measles-mumps-rubella vaccine is a live attenuated vaccine offered to children at 12-15 months and then a further pre-school booster is offered at 4-5 years. It contains 3 separate vaccines in one injection. Its use was first licensed in the United Kingdom in 1972 but was not introduced to the general public until 1988 as a single dose. In 1996, the MMR booster was introduced to increase herd immunity and eradicate disease.

MEASLES

Measles is a viral infection, which had epidemics every 2-4 years. It is highly contagious and in the 1990s, measles killed a million children every year, with 42 million people being affected worldwide. Complications may include diarrhoea (1 in 6), otitis media (1 in 20), pneumonia or pneumonitis (1 in 25), febrile convulsions (1 in 50), encephalitis (1 in 5000),15% of which can be fatal and 20-40% of which can cause permanent neurological damage. Rarely subacute sclerosing panencephalitis occurs, (1 in 100,000), which results in a deterioration in intellectual and motor abilities years after the original infection and is usually fatal. (1)

MUMPS

Mumps is also a viral infection, which has 3 yearly epidemics. Postpubertal boys may get an epididymo-orchitis (1 in 4) which can rarely result in sterility. There is also a signif icant rise in first trimester miscarriages (i in 4). Infection can result in deafness (1 in 25) or meningo-encephalitis (1 in 300-400), which was the commonest cause of viral meningitis prior to vaccination.(1)

RUBELLA

Rubella is a mild, highly contagious viral illness with epidemics only every 6-9 years. Complications per se are unusual but include thrombocytopaenia (7 in 3000) and encephalitis (1 in 6000). However, pregnant women in the first half of pregnancy are at significant risk of developing congenital rubella syndrome which may include cardiac septal defects, meningoencepholitis, microcephaly, deafness, cataract, limb abnormalities and learning disability. 90% of fetuses are affected if less than 10 weeks gestation and 10-20% fetuses if 10-16 weeks gestation. (1)

IMPACT ON PUBLIC HEALTH

Measles, mumps and rubella are all notifiable diseases. In order to eradicate measles, mumps and rubella, 95%, 80-90% and 97% of children should be immunised respectively (2). If one assumes 90% uptake from the f irst dose of MMR vaccine,

then 80-95% of these should form an adequate antibody response (assume to be 90%), which would predict that as many as 19% children would be unprotected. Therefore, the second booster dose was introduced to improve herd immunity and help maintain disease eradication. Figure 1 shows how MMR vaccine has had a dramatic effect on the incidence of the three diseases. (3)

	Incidence of diseases	
	1989 incidence	1998 incidence
Measles	26,222	3728
Mumps	20,713	1587
Rubella	24,370	3208

Figure 1: Impact of MMR

ARE THERE ANY SIDE-EFFECTS?

There is a small risk of side-effects which are mostly minor. There may be local redness and swelling at the injection site. Ten days after the MMR, 5% children develop a fever with a slight measles-like rash (4), three to four weeks after vaccination, some children develop a mild mumps-like parotid swelling and six weeks later, a thrombocytopaenic-type rash may develop; these are often signs that

the measles, mumps and rubella parts of the vaccine, respectively, are beginning to work. Anaphylaxis is 1 in 100,000 and there is a full recovery if it is managed quickly.

More severe reactions can develop but the risks of these are less frequent and milder than the effects of the disease itself, as shown in Figure 2. (4)

	Natural disease	1' dose MMR
Convulsion	1 in 200	1 in 1000
Meningitis/encephalitis	1 in 200-300	<1 in million
Thrombocytopaenia	1 in 3000 (rubella) 1 in 6000 (measles)	1 in 22,300
Subacute sclerosing panencephalitis	1 in 8000 (<2 years)	0
Death	i in 2500-5000 (dependent on age)	0

Figure 2: Complications following disease and vaccine

IS MMR SAFE? - THE CONTROVERSIES

A link between measles vaccine and inflammatory bowel disease was first suggested in 1993 when it was reported that there were abnormalities in the

mesenteric blood supply of people with Crohn's disease and that this could be potentially caused by persistent viral infection. (5)

In 1998, the Inf lammatory Bowel Disease Study Group, led by Wakefield, described a syndrome in 12 previously normal children who developed chronic enterocolitis and regressive developmental disorder. Eight out of the twelve children's parents believed that the behavioural problems developed shortly after MMR vaccination. All twelve children were also found to have intestinal abnormalities on ileal and colonic biopsies. These findings suggested a possible link with MMR vaccine. However, this was a small group of self-referred patients, which reflects a selection bias. There was no comparison made to children with similar problems who had not had the MMR or with normal children who had had the MMR. The discussion stated that they "did not prove an association between MMR vaccine and the syndrome described". It suggested that if there was a causal link, then one would expect a rise in the incidence of this "syndrome" after the introduction of the vaccine in 1988 and further studies needed to be conducted in order to support or reject this theory. (d)

Following the publication of this paper there was huge media coverage.'The Independent's front page headline was `Doctors link autism to MMR vaccination' (7,8). The following week they quoted Dr Wakefield as a humble clinician saying'IF I AM wrong, I will be a bad person'... 'But I have to address the questions my patients

put to me. My duty is to investigate their stories. Me made the decision to'put his patients f irst' ...'as patients were approaching him'. (9)

As a result of this adverse publicity the uptake of MMR fell from 92% in 1996-7's immunisation statistics to 84% in 2000-2001. (75% in London) (1,3)

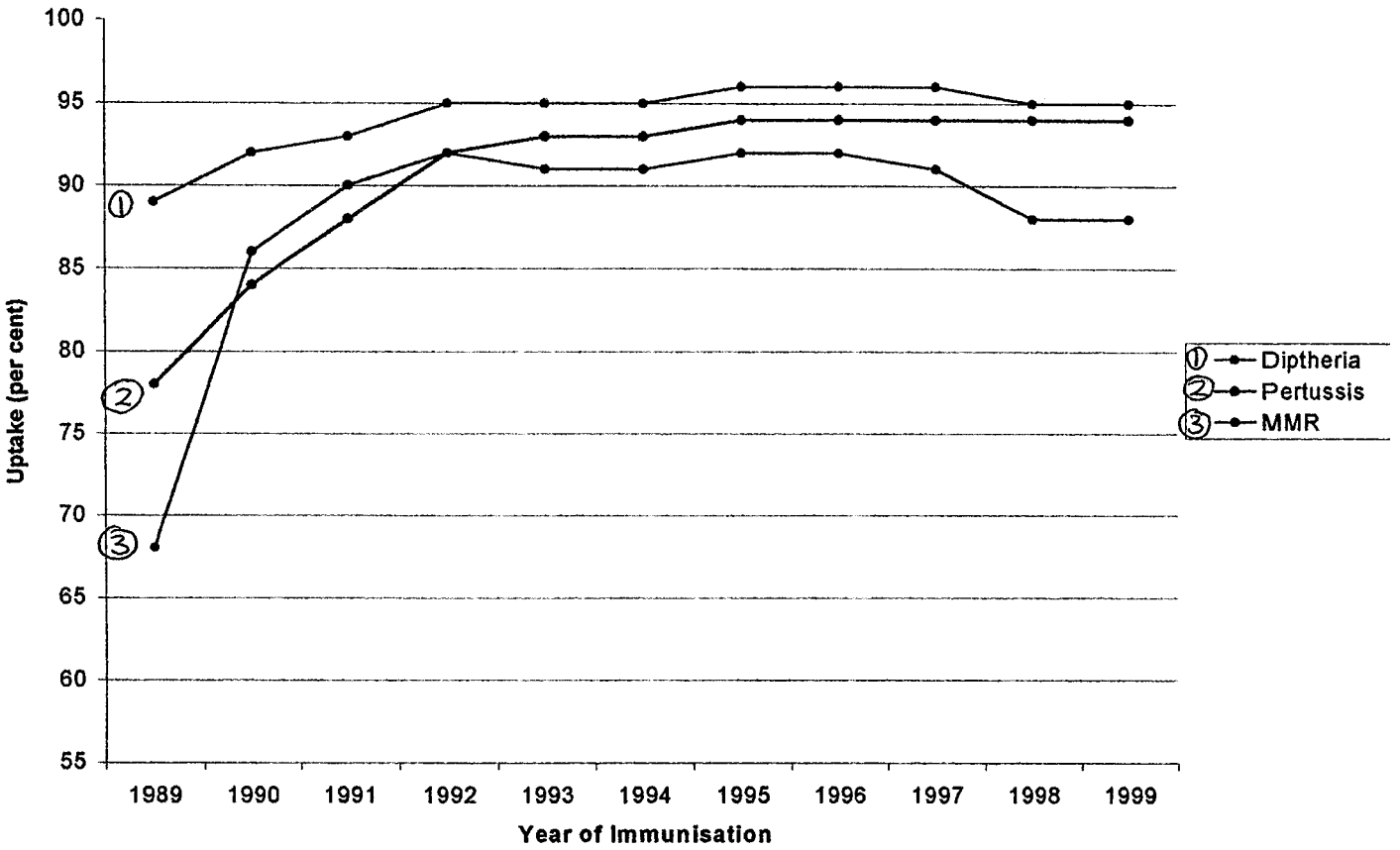

Figure 3: Immunisation Coverage 1989-2000

This level of uptake is insufficient for herd immunity and hence measles, a once common childhood illness, is now re-emerging amd we should expect an outbreak in

the near future. There was a serious outbreak of measles in Ireland, when uptake dropped to 74%, where 1376 cases were reported and there were 2 deaths. (10) There have also been 3 reported deaths in the Netherlands.

The response of the Committee on Safety of Medicines, to the adverse publicity and loss of public confidence in the vaccine, was to set up a Joint Committee of Vaccination and Immunisation to look into the safety of the MMR vaccine. The Report of the Working Party on MMR vaccine gave a detailed review of reports of suspected side-effects in children vaccinated with MMR or MR vaccines. The available information did not support a causal link between the vaccine and autism or Crohn's disease. (11,12) and was strongly supported by the Medical Research Council and World Health Organisation.

Wakefield's paper was criticised by the Department of Health for not commenting on evidence which contradicted his theory; the most sensitive and specific test available, reverse-transcriptase-polymerase chain reaction, was used to show that measles virus was not found in Crohn's disease tissue. (1,3) A well-conducted double-blind placebo-controlled trial of twins given MMR in Finland showed no association between MMR and autism or inflammatory bowel disease. (14)

At about the same time, researchers at the Royal Free Hospital and Public Health Laboratory Service published work that also showed no epidemiological evidence for a causal association. The first dose of MMR vaccine is given at 13-15

months. Autism is diagnosed in the second year of life. This demonstrates a temporal association between the timing of vaccination and diagnosis of autism. However, this population-based study of 498 children in the North Thames region demonstrated a steady increase in incidence of autism since 1979, ten years prior to the introduction of the MMR vaccine. The study failed to demonstrate a sharp change in trend coinciding with the introduction of the MMR vaccine and a clustering of autism diagnoses in the months following the vaccine. (15) One of the problems encountered by the group of researchers was that it was difficult to retrospectively confirm a diagnosis of autism by the ICD10 (International Classification of Diseases) criteria objectively; however, many of the children had been diagnosed by expert clinicians. Did this imply an improvement in autism diagnosis?

In 1999, another study suggested that children contracting measles and mumps within the same year were more likely to develop Crohn's disease. (16) It was therefore speculated that giving a combined vaccine would increase the likelihood of inflammatory bowel disease. However, at this stage there was still no evidence of an established link between inflammatory bowel disease and MMR vaccination.

A large prospective study followed up 1.8 million Finnish children following the MMR vaccine for 14 years since **1982.** All of them had received 2 doses of MMR (a similar vaccination programme to that in the UK). Of the 173 adverse drug reactions reported as being possibly caused by the vaccine, 45% were found to have another

cause and no case of inflammatory bowel disease or autism could be related to MMR vaccine. (17)

In the six-month period following MMR vaccine, one would expect there to be an increase in the general practitioner consultation frequency, if there was a causal link. In fact, this was found not to be the case by De Wilde et a/using the Doctor's Independent Network Database. (18) However, it is possible that the effect may be delayed by more than six months.

A more recent study looked at the United Kingdom General Practitioner Research Database to observe the changes in prevalence of autism 1998-99 and also the change in prevalence of autism in 2-5 year old boys as compared to the uptake of MMR vaccine 1988-93. It suggested no causal relationship. (19) But what then is the cause of the rising incidence of autism? It could be because of increased parental and general practitioners' awareness of the condition, changing diagnostic criteria or undiscovered environmental factors. As yet it still remains a mystery and as long as it does, people will still remain rather sceptical about the evidence presented against the link with MMR vaccine.

Wakefield and Montgomery suggested that the pre-licensing trials for combined MMR vaccine were short-term with a maximum 4-week follow up. (20) This is incorrect. In fact, the follow up was for 6-9 weeks, looking for adverse

events. The Committee on Safety of Medicine reports that at the time of licensing the MMR vaccines were licensed appropriately and were not issued prematurely. (21)

IS THE SECOND DOSE OF MMR IMPORTANT?

In order to increase the herd immunity and boost children with a low antibody response, the second dose of MMR vaccine is important. If herd immunity is high then there is unlikely to be an outbreak and those children that are unable to have the MMR due to contraindications or are non-responders to the vaccine will at least be partly protected from these diseases and their potentially serious complications.

Following the 1998 Wakefield paper a survey was conducted of health professionals in North Wales. It was found that almost half had reservations about the second dose and many felt unhappy to explain the rationale behind it to patients. The fact that only 20% of &Ps would unequivocally recommend it endorses the need for better informed health professionals competent to answer parents' questions.

Over 500 million doses have been given in over 90 countries including United States of America, Canada and Finland since 1970s and the vaccine has had a good safety profile. (2)

The alternative to the second dose of MMR would, in theory, be a blood test to look for a low antibody response. However, this is not recommended by the World

Health Organisation (WHO), blood tests are unpleasant for children and not 100% accurate.

WHAT ABOUT SINGLE ANTIGEN VACCINES?

Wakefield and Montgomery imply that the safety data on MMR was still insufficient and that separate vaccines could be given a year apart. (8,20) The single antigen vaccination programme is not a safer alternative. They may be less effective and have a lower safety profile. Japan is the only country that recommends single measles and rubella vaccines as it does not have a safe or suitable mumps vaccine. No country recommends single vaccines as part of their recommended immunisation programmes. (2)

The single antigen programme would involve six injections which would be more unpleasant, with a higher risk of adverse events or missing a dose and there would also be more time between vaccinations and hence, a greater risk of contracting the disease and for 'immunological interference'. (21)

Dr. Peter Mansfield, a general practitioner from Worcestershire, was recently referred to the General Medical Council for having prescribed single vaccines at a private clinic for children whose parents did not wish to have the MMR vaccine. (23,24) Colleagues across Britain openly supported his advocating of the single vaccines. (25) The case has, since, been dropped by the GMC.

The measles and mumps single vaccines are not licensed in the United Kingdom for use in this way. Even the drug companies who would profit most from this regime are not recommending them or making them more readily available. The monovalent vaccines are available in Britain for those children with a previous reaction to MMR vaccine or who have already started a single vaccine course.

One of the main problems in researching this project is the never-ending research and publicity that is still coming out. Even now, there is newer evidence coming to light supporting the safety of MMR and the media are acknowledging this; are we f inally making headway in the battle to convince the public that MMR is safe?

CONCLUSION

Our dilemma as general practitioners is to decide whether to strictly follow Department of Health recommendations without considering our patients as individuals. In fact, can we, as 6Ps, be truly objective if we have financial incentives for hitting MMR targets? If parents don't want the MMR, surely single vaccine immunisation would be better than no protection at all... and don't our patients have the right to make an informed choice? The worry is that we are encouraging patients to lose faith in a vaccine that we are recommending 1& providing an alternative. Where does are responsibility lie? - with the public as a whole or our patients as individuals?

Dr Barry Walsh acknowledges that there are still gaps in our knowledge but the scientific evidence is in favour of MMR; single vaccines would be 'colluding with bad medicine' and he advocates relying on herd immunity to cover those not wanting immunisation. However, this argument cannot be used to a mother whose only concern is the safety of her own child.

After researching this topic at length, my feeling is that we should be recommending the MMR vaccine and taking the time to explain this to our patients. We can also refer them to'Childhood Immunisation - The facts'. (26) However, despite all our efforts, if patients still remain sceptical we should empathise with them; offering single vaccines would probably be in the better interests of public health than allowing children to remain unimmunised. Our duty is to provide them with the facts.

WORD COUNT - 2835

REFERENCE LIST

1. www.immunisation.org.
2. www.doh.gov.uk
3. www.phis.co.uk
4. Kassianos G, Immunisation, Child and Travel Health, Oxford Blackwell Scientific, 1998.
5. Wakefield et al. Journal of Medical Virology 1993; 39: 345-353. Evidence of persistent measles virus infection in Crohn's disease
6. Wakefield et al. Lancet 1998; 351:637-41. Ileal-lymphoid nodular hyperplasia, non-specif is colitis and pervasive developmental disorder in children.
7. Laurance, The Independent 27/2/98 :pi. Doctors link autism to MMR vaccine.
8. Laurance, The Independent 27/2/98 :p5. Doctors warn of a new child vaccine danger.
9. Laurance, The Independent 3/3/98 :p14. Health: Not immune to how reearch can hurt.
10. Cronin, Epi-Insight Dublin 2000; 1(2): 2-3. Measles Outbreak.
11. Report from the Working Party on MMR vaccine. 1999 London, CSM.
12. Medicines Control Agency. Current Problems in Pharmacovigilance 1999; 25: 9-10. The safety of MMR

13. Chadwick et al. Journal of Medical Virology 1998; 55: 305-11. Measles virus RNA is not detected in Inflammatory Bowel Disease using hybrid capture and reverse transcription followed by polymerase chain reaction.

14. Peltola H. et al. Lancet1986; 1:939-42. Frequency of true adverse reactions to MMR vaccine; a double-blind, placebo controlled trial of MMR in twins.

15. Taylor B. et al. Lancet 1999; 353: 2026-9. Autism and Measles, Mumps and Rubella vaccine; no epidemiological evidence for a causal association.

16. Montgomery et al. Gastroenterology 1999; 116: 798-803. Paramyxovirus Infections in Childhood and Subsequent Inflammatory Bowel Disease.

17. Patja et al. Paediatric Infectious Diseases Journal 2000; 19: 1127-34. Serious adverse events during a 14 year prospective follow-up.

18. De Wilde et al. British Journal of general Practice 2001; 51 (464): 226-7. Do children who become autistic consult more often after MMR vaccination.

19. Kaye et al. British Medical Journal 2001; 322: 460-3. Measles, mumps and Rubella vaccine and incidence of autism reported by General Practitioners a time trend analysis.

20. Wakefield and Montgomery. Adverse Drug Reactions Toxicological Review 2000; 19(4): 265-83. Measles, Mumps Rubella vaccine : through a glass darkly.

21. Arlett p. et al. Adverse Drug Reactions Toxicological Review 2001; 20(1): 37-45. MMR vaccine not issued prematurely; a response to Measles, Mumps Rubella vaccine : through a glass darkly.

22. Petrovic et al. British Medical Journal 2001; 322: 82-5. 5econd dose Measles Mumps Rubella vaccine: questionnaire survey of health professionals.

23. Wilson C. Doctor 2001; Aug 9: 1

24. Majeed A. British Medical Journal 2001; 323: 356. Editorial on referral of Dr Peter Mansfield to the &MC.

25. Charter D. The Times 7/8/01: p6. Doctors defend MMR single doses.

26. Bedford and Elliman. Childhood Immunisation -The facts. 2001