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The independent review from Consumers' Association

MMR vaccine – how effective and how safe?

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The introduction of combined measles, mumps and rubella (MMR) vaccine into the UK childhood immunisation schedule in 1988 has markedly reduced the incidence of these diseases and their complications, with, for example, no deaths from acute measles occurring since 1992.^{1,2} However, uptake of MMR vaccine has fallen since the publication, in 1998, of a study that suggested a link between exposure to the vaccine and the development of intestinal inflammation and autism.³ The study, and the subsequent debate, have attracted considerable media coverage and left many parents and some healthcare professionals uncertain about what to do.⁴ While in 1996, 92% of children in England and Wales had received their first dose of the vaccine by the age of 2 years, by 2001–2 this figure had fallen to 84%, with much lower uptake in some regions, threatening a resurgence of all three diseases.² Here, we review the evidence for the effectiveness and safety of MMR vaccine.

Background

Measles, mumps and rubella are highly contagious acute viral infections, notifiable by law. Common complications of measles include otitis media, pneumonia, bronchiolitis, diarrhoea and febrile seizures. Less commonly, measles results in acute encephalitis. Subacute sclerosing panencephalitis is a rare, late, fatal complication. Children aged less than 1 year, or who are poorly nourished, immunocompromised, or have a chronic disease, are especially vulnerable to measles. However, half of all children in the UK who died from the disease before the introduction of MMR vaccine were previously healthy.¹ Potential complications of mumps include orchitis, oophoritis, pancreatitis, meningitis, encephalitis and deafness. The main risk from rubella is damage to the unborn baby (stillbirth and congenital rubella syndrome) if the mother is infected during pregnancy, particularly during the first 16 weeks.

Single-antigen live attenuated measles vaccine, administered in the second year of life, was introduced into the UK in 1968, but uptake never achieved levels needed to eliminate the disease.² From the early 1970s, immunisation with live attenuated rubella vaccine was offered routinely to girls aged 11–14 years and to non-pregnant women of childbearing age who lacked rubella antibodies. As a result, around 97–98% of UK women of childbearing age are now protected against rubella,¹ but infection during pregnancy remains a risk for unprotected women exposed to young children or men with rubella. Prior to 1988, the routine immunisation schedule did not include a mumps vaccine. Childhood immunisation with MMR vaccine was introduced with the aim of eliminating

measles, rubella and mumps.¹ It replaced single-antigen measles vaccine, and rubella vaccination for schoolgirls was discontinued in 1995.

MMR vaccines

MMR vaccines contain live attenuated strains of measles, mumps and rubella viruses. Two licensed MMR vaccines are currently used in the UK.

MMR II (Aventis Pasteur MSD) contains the Enders' attenuated Edmonston strain of measles virus, the Jeryl Lynn strain of mumps virus, and the Wistar RA 27/3 strain of rubella virus. Vials of the vaccine also contain small quantities of neomycin, sorbitol, human albumin and gelatin.

Priorix (GlaxoSmithKline) contains the attenuated Schwarz strain of measles virus, the RIT 4385 mumps virus (derived from the Jeryl Lynn strain), and the Wistar RA 27/3 strain of rubella virus. Vials also contain neomycin, sorbitol, human albumin, lactose, mannitol and various amino acids.

The Department of Health recommends that the first dose of MMR vaccine be offered to all children without a contraindication as soon as possible after their first birthday.¹ A second dose should be given at, or around, the time of the preschool booster doses of other routine childhood immunisations. Routine administration of the second dose of MMR vaccine was introduced in 1996 because it had become clear that, even with high vaccine coverage, the protective efficacy of single doses was insufficient to ensure disease elimination.¹

Contraindications and precautions

In general, MMR vaccine is contraindicated in children with untreated malignant disease or altered immunity due to disease or treatment.¹ MMR immunisation is, however, recommended for children with HIV infection unless they have evidence of severe immunosuppression (as assessed by CD4 lymphocyte counts).^{5,6} The Department of Health recommends that, as a precaution, immunisation with MMR vaccine should be temporarily deferred if a child has an acute febrile illness, or has received another live vaccine within 3 weeks or immunoglobulin within 3 months.¹ Allergy to egg rarely causes adverse reactions to the vaccine and is not a contraindication.⁷ However, hospital assessment is indicated for any child suspected of previously having had a cardiorespiratory reaction to egg or to gelatin, neomycin or other constituents of MMR vaccines, and if vaccination of such children takes place, it should be closely supervised in hospital.⁷

Efficacy

Seroconversion rates after the first dose of MMR vaccine are around 88–100% for measles, mumps and rubella, similar to rates with single-antigen vaccines against these viruses.^{8–10} After the second dose, virtually all recipients of MMR vaccine have protective levels of antibodies.¹¹ At the population level, the high protective efficacy of MMR vaccine has been demonstrated by the marked fall in disease rates in countries where the vaccine has been introduced. This is particularly clear in countries that have long used a two-dose policy, such as Finland, where the diseases have been practically eliminated.¹¹ Since MMR vaccine was introduced in the UK, notifications of measles have fallen to the lowest recorded levels.² For mumps, which previously caused 1,200 hospital admissions per year in England and Wales, the number of confirmed cases was less than 400 annually for the years 1995–1999.²

Studies conducted during outbreaks of measles and mumps show that both single-antigen and MMR vaccines provide high levels of protection, especially in individuals who have received two doses.^{12–14} However, even with high levels of vaccine uptake, outbreaks can still arise in unimmunised groups, and can spread to people who are incompletely protected despite vaccination (e.g. who have had an inadequate response to a single dose).^{11,13,14}

Unwanted effects

After receiving MMR vaccine, some children develop symptoms compatible with mild measles, mumps or rubella infection, particularly if it is the first dose. These symptoms are not associated with contagious disease. In a randomised double-blind trial in 581 pairs of twins, of 460 children aged 14–18 months, 32% developed moderate or severe fever after MMR vaccine (vs. 9% with placebo; $p < 0.002$), with a peak incidence at 9–10 days.^{15,16} Irritability (7.3% vs. 4.0% with placebo), drowsiness (3.5% vs. 1.4%) and rash (4.3% vs. 3.0%) were also more common with MMR vaccine than with placebo at around 9–10 days. Around 15% in each group experienced mild respiratory symptoms (e.g. cough, coryza). The incidence of gastrointestinal symptoms

(e.g. diarrhoea, vomiting) was said to be low in the 3 weeks after MMR vaccine or placebo, and similar in each group.¹⁵ In other studies, which lacked a placebo arm, gastrointestinal symptoms were reported in 18–42% of children after MMR or single-antigen measles vaccine.^{9,10} Around 1.0–2.5% of children develop mild parotid swelling 3–6 weeks after MMR vaccination.^{9,10} Overall, none of these systemic effects were more frequent or severe with MMR than with single-antigen vaccines.^{8–10}

Randomised trials have been generally too small and too brief (3–6 weeks) to detect rare or delayed effects of vaccines. Detection of such effects depends on post-marketing surveillance and notification of suspected reactions, for instance through the Yellow Card system, which requires vigilance for unusual events possibly related to vaccination. However, under-reporting is common. For well-defined rare events that lead to hospitalisation, linkage of hospital admission and immunisation records can greatly enhance detection.¹⁷

A record-linkage study in the UK found that among children under 2 years old the incidence of hospital admission for febrile seizure within 6–11 days of MMR vaccination is 1 in 3,000.¹⁷ This is around three times the background rate,^{17,18} but many times lower than with measles in the second year of life. A large retrospective cohort study in the USA found no increase in the risk for subsequent seizures, learning disability or developmental delay, in children who had a febrile seizure after MMR vaccine when compared with children with a febrile seizure unrelated to vaccination.¹⁸

A record-linkage study in Finland found no increase in the risk of developing encephalitis or aseptic meningitis within 3 months of MMR vaccination, compared with background rates.¹⁹ By contrast, encephalitis can complicate both natural measles (in around 0.35 in 1,000 patients) and mumps (around 1.5 in 1,000 patients), and the risk of meningitis in patients with clinically apparent mumps is around 1 in 1,000.²⁰ Earlier MMR vaccines, containing the Urabe mumps strain, were withdrawn in the UK in 1992 when the strain was shown to be capable of causing aseptic meningitis.²¹ Subacute sclerosing panencephalitis has become even more rare since the introduction of MMR vaccine, and when it has occurred it has been caused by wild measles virus, not the vaccine.²²

Idiopathic thrombocytopenic purpura (ITP) attributable to MMR vaccine develops in around 1 in 25,000 children (vs. 1 in 3,000 with natural rubella) up to 6 weeks after vaccination (relative risk 6.3 vs. unvaccinated controls, 95% CI 1.3–30.1).²³ It is usually milder than ITP unrelated to vaccination and generally has no long-term sequelae.

Joint pains following MMR vaccination appear relatively uncommon, but in the randomised study in twins such symptoms were more common with MMR vaccine than with placebo (odds ratio 3.66, 95% CI 1.74–7.70).¹⁶ In a UK study, based on recall of symptoms after MMR vaccination, transient arthralgia or arthritis was reported in 1.5% of children within 6 weeks of vaccination (vs. 0.3% of non-immunised children; relative risk 4.5, 95% CI 1.6–13.0).²⁴

The 'autistic enterocolitis' controversy

Autism is a severe disorder characterised by delay in the development of language, communication and social interaction, with restricted, repetitive patterns of play, interests and behaviour.²⁵ Autism, 'atypical autism' and Asperger syndrome (also referred to as 'autism spectrum disorders') are part of a larger group known as pervasive developmental disorders. Genetic factors are believed to have a major role in causation.²⁶ In autism, problems with the child's development are usually noticed by the parent(s) at around 18 months to 2 years of age. In 15–40%, seemingly normal development for 15–19 months is followed by developmental regression.²⁶ Diagnosis of autism requires detailed assessments by specialists, using stringent criteria, and is often not made with certainty until 2–3 years after symptom onset.²⁵ In many parts of the world, the reported prevalence of autism has increased greatly in the last 20 years, but it is not clear whether this represents a true increase or is due to other factors, such as better diagnosis.²⁶ The apparent steady rise has led to speculation that some new form of environmental exposure(s) early in life might be partly responsible.

First signals of a possible link with MMR

The first signal of any suspected association between MMR vaccination and autism came in the mid-1990s from parents who linked the time of onset of their concerns with administration of the vaccine. Then, in 1998, the Inflammatory Bowel Disease Study Group at the Royal Free Hospital described a series of 12 consecutively referred children (aged 3–10 years) who had a history of pervasive developmental disorder, with loss of acquired skills, and gastrointestinal symptoms (diarrhoea, abdominal pain, bloating and food intolerance).³ The parents and/or physicians of 8 children reported that the behavioural problems had begun soon after MMR vaccination (average interval 6.3 days; range 1–14 days). Some children deteriorated precipitously. Parents were less clear about the timing of onset of the gastrointestinal symptoms. On ileocolonoscopy, all 12 children had intestinal abnormalities, and all but one had histological changes of chronic non-specific colitis and reactive ileal lymphoid nodular hyperplasia.

The authors proposed that this pattern of intestinal abnormalities and regressive developmental disorder might represent a syndrome.³ Although they stated that the study did not prove an association between MMR vaccination and such a syndrome, the findings were widely reported in the media as suggesting that the vaccine might cause autism.

The 'autistic enterocolitis' hypothesis

Two years later, the same research team reported on 60 consecutively referred children (including the original 12) with a range of developmental disorders (55 with autism spectrum disorders) and current intestinal symptoms.²⁷ All but 3 children were stated to have a clear history of developmental regression, with loss of acquired skills after normal development until at least the age of 1 year (as documented by GPs and health visitors). No precise data were given for the age of onset of the behavioural or gastrointestinal symptoms, or the rate of deterioration, and no mention was made of childhood immunisations. The

previously described pattern of colitis with reactive ileal lymphoid nodular hyperplasia was present in nearly all the children, but in none of a control group of developmentally normal children with similar intestinal symptoms.

The researchers postulated that the findings represented a new variant of inflammatory bowel disease with developmental disorder (which they later called 'autistic enterocolitis') that was likely to be antigen-driven.²⁷ Measles virus was discussed as a potential cause.²⁷ Later, following immunohistochemistry studies of the gut lesions,²⁸ they postulated that autoimmune damage to the gut epithelium might lead, through unknown mechanisms, to neurological damage, manifesting in regressive development and behavioural problems.^{29,30} They suggested that the unusual pattern of exposure to measles, mumps and rubella viruses, administered simultaneously in MMR vaccine at a crucial stage in immune and neurological development, might act as a trigger, possibly through immunological interference of the component viruses with one another (especially mumps with measles), leading to impaired clearance of vaccine virus.^{29–31}

In a recent study, measles virus RNA was identified in ileal node lymphoid tissue from 75 of 91 children with 'autistic enterocolitis' syndrome, but in only 5 of 70 developmentally normal controls (both with and without gastrointestinal disorders) ($p < 0.0001$).³² Whether the investigation was conducted blind was not stated. The source of the viral material, and its clinical relevance,¹⁵ remains unknown, and the findings (which require independent confirmation) cannot be taken as evidence that either wild measles or the measles component of MMR vaccine causes the gut pathology or autism. The data could equally be interpreted, for instance, as indicating that these disorders facilitate persistence of measles virus.

Comments on the studies

The original case series of 12 children is the only published peer-reviewed study to offer a clear statement on the temporal relationship between MMR vaccine and the (rapid) onset of these particular symptoms.³ The study was very small, uncontrolled, and involved a highly selected group of children referred to a specialist unit already researching possible links between measles virus and inflammatory bowel disease. Moreover, some temporal association with autism is unsurprising given the usual onset of symptoms in the second year of life, and would certainly be expected by chance in some children.

The later published studies have provided no fresh clinical data on the apparent association. Accompanying commentaries have emphasised developmental regression as a key feature of the postulated syndrome, possibly with a more variable or insidious onset after MMR vaccination than originally reported, and a number of possible co-factors have also been suggested.^{29,30} However, detailed, replicable developmental data on affected children (e.g. on intellectual functioning, language level, and severity of symptoms) have not been published, and it is unclear whether regression was ascertained by adequate methodology.³³ The gastrointestinal symptoms reported have been very heterogenous. It is impossible from this information

to derive a precise clinical picture of how and when affected children might present, and this makes independent clinical investigation of the putative syndrome very difficult. To date, therefore, investigation of a possible link between MMR vaccine, autism and bowel disease has had to rely almost entirely on epidemiological studies.

Epidemiological evidence

A population-based study in North East Thames region investigated trends in the incidence of autistic disorders among children born between 1979 and 1992.³⁴ There was a steady increase in recorded cases of autism by year of birth, antedating the introduction of MMR vaccine in 1988, with no evidence of a 'step up' in frequency, or a change in the exponential trend, after its introduction. Recorded cases continued to rise, while uptake of the vaccine remained stable, with no difference in rates of vaccine coverage between children with or without autism, or in the age at diagnosis between children vaccinated before 18 months of age, after 18 months, or not vaccinated. No significant clustering of the interval to diagnosis of autism, or to developmental regression, was found within defined short time periods after immunisation. An apparent clustering of parental concern in the first 6 months after immunisation seems to have been an artefact, as the effect ceased to be discernible when the data were reanalysed without specifying intervals for possible risk for autism following immunisation.³⁵ The reanalysis found no evidence for an association between MMR vaccine and autism at any time after vaccination.³⁵

A further study on the same population revealed no association between vaccination with MMR and the diagnosis of regression or the development of bowel symptoms.³⁶ There was also no difference in the proportions of parents who had become concerned about their child's development after receiving MMR vaccine, before receiving MMR vaccine, or when no vaccine was given. Another study included both population-based epidemiological data and clinical data on children referred to specialist clinics for evaluation of autism.³³ It found no evidence of any change in the age of the child when parents first expressed concern, or in the frequency of developmental regression in autism, between children born before or after MMR vaccine was introduced, and no association between regressive autism and gastrointestinal symptoms.³³

Other studies have used records from large primary care databases.^{37–39} One showed that, while MMR vaccination coverage remained virtually constant at 97%, the incidence of newly diagnosed autism in boys, for example, rose nearly fourfold, from 8 in 10,000 born in 1988 to 29 in 10,000 born in 1993 ($p < 0.0001$).³⁷ A case-control study suggested that children with autism were no more likely than those without autism to have had inflammatory bowel disease, chronic gastroenteritis, food intolerance or recurrent gastrointestinal symptoms at any time before autism was diagnosed, and found no temporal association between MMR vaccination and the onset of gastrointestinal symptoms.³⁸ A further study found no evidence that consultations for any cause (as an indicator of parental concern) increased in frequency in the 6 months before and after MMR immunisation in 71 children subsequently diagnosed

with autism, when compared with consultation rates for the equivalent periods for 284 matched controls (vaccinated, but without autism).³⁹ By contrast, consultation rates were significantly higher in cases than in controls in the 6 months before the diagnosis of autism.

As in the UK, epidemiological data from Sweden and the USA have revealed no correlation between time trends in the incidence of autism and the introduction and uptake of MMR vaccine.^{40,41} Data from Danish national registers found no increase in the risk of autism among MMR-vaccinated as compared with unvaccinated children, and no association between the age at vaccination, or the time since vaccination, and the date of diagnosis of autism.⁴²

Comments on the studies

Interpretation of these epidemiological studies is difficult, not least because the methodology is highly specialised and, in some instances, novel. In the absence of representative controls (children not given MMR vaccine but otherwise similar to those who were vaccinated), the studies have had to rely, for example, on comparing time trends for the reported incidences of autism and rates of MMR vaccine coverage, and on comparative data on the age at onset of parental concern (which is difficult to ascertain) or at diagnosis. Nonetheless, all of the studies, conducted in several different populations, are consistent and emphatic in finding no evidence for an association between MMR vaccine, inflammatory bowel disease and autism.

MMR or single-antigen vaccines?

Although UK licences for single-antigen measles and mumps vaccines exist, vaccines meeting the specifications of these licences are no longer manufactured or marketed in the UK. A clinician may prescribe an unlicensed single-antigen vaccine to meet the special needs of an individual patient on his or her personal responsibility. Unlicensed vaccines can only be obtained from a wholesale dealer licensed to import such medicines. Before importation, importers have to notify the licensing authority which will object if it has concerns over the safety or quality of the products.

Many have argued that parents who are concerned about MMR vaccine should instead be able to choose single-antigen measles, mumps and rubella vaccines, administered separately and at intervals.^{31,43,44} However, no sound scientific evidence exists to justify staged, sequential vaccination with single-antigen vaccines in pre-school children. Such an immunisation programme has not been tested, and would be experimental. No scientific rationale exists for determining the order and the interval between injections; an interval of 1 year would mean that children would not be fully protected against measles, mumps and rubella until at least 6 years old. Even with a shorter interval, many children would remain unprotected against these diseases for much longer than with MMR vaccination. Because it would entail six injections (rather than two with MMR vaccine), a single-antigen vaccination programme would be more complicated to implement and would increase discomfort for the child and the number of exposures to potential systemic effects. Such a programme would inevitably result in

lower overall uptake of the vaccines, lower levels of protection against measles, mumps and rubella throughout the population, and renewed outbreaks of these infections. This would present a particularly dangerous risk to the most vulnerable groups, such as infants too young to be immunised, children with immunosuppression or other contraindications to vaccination, and women who are pregnant.

Most parents with concerns about MMR vaccine seek advice from primary care professionals, and there is evidence that soundly based advice will allay many parents' fears.⁴

Conclusion

Immunisation with the combined measles, mumps and rubella (MMR) vaccine gives highly effective protec-

tion against all three diseases, and has the potential to eliminate these infections, including congenital rubella syndrome, saving many lives and preventing serious illness. In our view, there is no convincing evidence that MMR vaccine causes, or facilitates development of, either inflammatory bowel disease or autism. Similarly, we believe that there is no good reason to adopt an alternative immunisation policy that allows substitution of single-antigen vaccines for the combined vaccine. Such an arrangement has no sound scientific basis and is likely to result in increased rates of disease and an attendant increase in morbidity, mortality and risk to others. The weight of published evidence argues overwhelmingly in favour of MMR vaccine as the most effective and safest way of protecting children from measles, mumps and rubella.

[M=meta-analysis; R=randomised controlled trial]

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