28

Rubella

NOTIFIABLE

The disease

Rubella is a mild disease caused by a togavirus. There may be a mild prodromal illness involving a low-grade fever, malaise, coryza and mild conjunctivitis. Lymphadenopathy involving post-auricular and sub-occipital glands may precede the rash. The rash is usually transitory, erythematous and mostly seen behind the ears and on the face and neck. Clinical diagnosis is unreliable as the rash may be fleeting and is not specific to rubella.

Rubella is spread by droplet transmission. The incubation period is 14 to 21 days, with the majority of individuals developing a rash 14 to 17 days after exposure. Individuals with rubella are infectious from one week before symptoms appear to four days after the onset of the rash.

Complications include thrombocytopaenia (the rate may be as high as one in 3000 infections) and post-infectious encephalitis (one in 6000 cases) (Lokletz and Reynolds, 1965; Plotkin and Orenstein, 2004). In adults, arthritis and arthralgia may occasionally be seen after rubella infection; chronic arthritis has rarely been reported (Plotkin and Orenstein, 2004).

Maternal rubella infection in pregnancy may result in fetal loss or in congenital rubella syndrome (CRS). CRS presents with one or more of the following:

- cataracts and other eye defects
- deafness
- cardiac abnormalities
- microcephaly
- retardation of intra-uterine growth
- inflammatory lesions of brain, liver, lungs and bone marrow.

Infection in the first eight to ten weeks of pregnancy results in damage in up to 90% of surviving infants; multiple defects are common. The risk of damage declines to about 10 to 20% with infection occurring between 11 and 16 weeks gestation (Miller *et al*., 1982). Fetal damage is rare with infection after 16 weeks of pregnancy, with only deafness being reported following infections up to 20

weeks of pregnancy. Some infected infants may appear normal at birth but perceptive deafness may be detected later (Miller *et al*., 1982; Plotkin and Orenstein, 2004).

History and epidemiology of the disease

Before the introduction of rubella immunisation, rubella occurred commonly in children, and more than 80% of adults had evidence of previous rubella infection (Morgan Capner *et al*., 1988).

Rubella immunisation was introduced in the UK in 1970 for pre-pubertal girls and non-immune women of childbearing age to prevent rubella infection in pregnancy. Rather than interrupting the circulation of rubella, the aim of this strategy was to directly protect women of childbearing age by increasing the proportion with antibody to rubella; this increased from 85 to 90% before 1970 to 97 to 98% by 1987 (Vyse *et al.*, 2002). Surveillance for congenital rubella was established in 1971 to monitor the impact of the vaccination programme. During the period 1971–75 there were an average of 48 CRS births and 742 terminations annually in the UK (Tookey and Peckham, 1999) (see Figure 28.1).

Although the selective immunisation policy was effective in reducing the number of cases of CRS and terminations of pregnancy, cases of rubella in pregnancy continued to occur. This was mainly because the few women who remained susceptible to rubella could still acquire rubella infection from their own and/or their friends' children.

Universal immunisation against rubella, using the measles, mumps and rubella (MMR) vaccine, was introduced in October 1988. The aim of this policy was to interrupt circulation of rubella among young children, thereby protecting susceptible adult women from exposure. At the same time, rubella was made a notifiable disease. A considerable decline in rubella in young children followed the introduction of MMR, with a concomitant fall in rubella infections in pregnant women – from 167 in 1987 to one in 2003.

A seroprevalence study in 1989 showed a high rate of rubella susceptibility in school-age children, particularly in males (Miller *et al.*, 1991). In 1993, there was a large increase in both notifications and laboratory-confirmed cases of rubella. Many of the individuals affected would not have been eligible for MMR or for the rubella vaccine. For this reason, the combined measles-rubella (MR) vaccine was used for the schools campaign in November 1994 (see Chapter

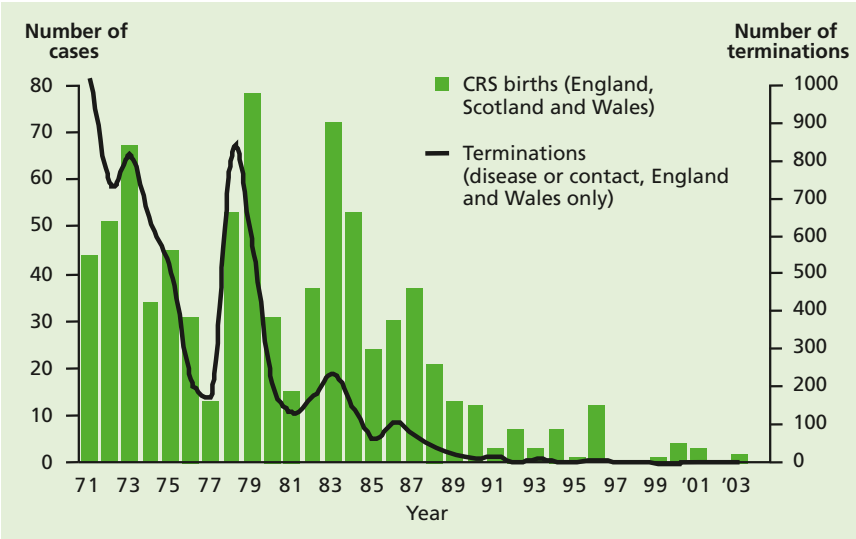

Figure 28.1 Congenital rubella syndrome births (source: National Congenital Rubella Surveillance Programme 1971–2004) and rubella-associated terminations (source: Office for National Statistics 1971–2003)

21). At that time, insufficient stocks of MMR were available to vaccinate all of these children against mumps. Over 8 million children aged between 5 and 16 years were immunised with the MR vaccine.

In October 1996, a two-dose MMR schedule was introduced and the selective vaccination policy of teenage girls ceased. A single dose of rubella-containing vaccine as used in the UK confers around 95 to 100% protection against rubella (Plotkin and Orenstein, 2004).

In Finland, a two-dose MMR schedule was introduced in 1982; high coverage of each dose has been achieved consistently. Indigenous measles, mumps and rubella have been eliminated since 1994 (Peltola *et al.*, 1994). The United States introduced its two-dose schedule in 1989 and, in 2000, announced that it had interrupted endemic transmission (Plotkin and Orenstein, 2004, Chapter 20). MMR is now routinely given in over 100 countries, including those in the European Union, North America and Australasia.

A further resurgence of rubella was observed in the UK in 1996. Many of these cases occurred in colleges and universities in males who had already left school before the 1994 MR campaign (Vyse *et al.*, 2002). Sporadic rubella

cases have been reported since then, mainly linked to imported cases (Health Protection Agency website).

Since 1991, only around one-third of CRS infants have been born to UK-born women who acquired infection in the UK. The remaining two-thirds of CRS infants were born to women who were themselves born overseas. Of these, around one-half acquired infection overseas, mostly during early pregnancy, in their country of origin. The remaining women acquired infection in the UK, usually within two years of arrival (Rahi *et al*., 2001; Tookey and Peckham, 1999; Tookey *et al*., 2002; Tookey, 2004). This latter observation is explained by higher susceptibility rates among some minority ethnic groups in the UK who had not been infected or immunised before coming to this country (Tookey *et al*., 2002).

The MMR vaccination

MMR vaccines are freeze-dried preparations containing live, attenuated strains of measles, mumps and rubella viruses. The three attenuated virus strains are cultured separately in appropriate media and mixed before being lyophilised. These vaccines contain the following:

Priorix®

Each 0.5ml dose of reconstituted vaccine contains:

not less than $10^{3.0}$ cell culture infective $dose_{50}$ ($CCID_{50}$) of the Schwarz measles virus
not less than $10^{3.7}$ $CCID_{50}$ of the RIT 4385 mumps virus
not less than $10^{3.0}$ $CCID_{50}$ of the Wistar RA 27/3 rubella virus strains.

MMRVaxPRO®

Each 0.5ml dose when reconstituted contains not less than the equivalent of:

1000 tissue culture infective $dose_{50}$ ($TCID_{50}$) of the more attenuated Enders line of the Edmonston strain of measles virus
20,000 $TCID_{50}$ of mumps virus (Jeryl Lynn® Level B strain)
1000 $TCID_{50}$ of rubella virus (Wistar RA 27/3 strain).

MMR vaccine does not contain thiomersal or any other preservatives. The vaccine contains live organisms that have been attenuated (modified). MMR is recommended when protection against measles, mumps and/or rubella is required.

Storage

The unreconstituted vaccine and its diluent should be stored in the original packaging at +2˚C to +8˚C and protected from light. All vaccines are sensitive to some extent to heat and cold. Heat speeds up the decline in potency of most vaccines, thus reducing their shelf life. Effectiveness cannot be guaranteed for vaccines unless they have been stored at the correct temperature. Freezing may cause increased reactogenicity and loss of potency for some vaccines. It can also cause hairline cracks in the container, leading to contamination of the contents.

The vaccines should be reconstituted with the diluent supplied by the manufacturer and either used within one hour or discarded.

Presentation

Rubella vaccine is only available as part of a combined product (MMR).

Priorix is supplied as a whitish to slightly pink pellet of lyophilised vaccine for reconstitution with the diluent supplied. The reconstituted vaccine must be shaken well until the pellet is completely dissolved in the diluent.

MMRVaxPRO is supplied as a lyophilised powder for reconstitution with the diluent supplied. The reconstituted vaccine must be shaken gently to ensure thorough mixing. The reconstituted vaccine is yellow in colour and should only be used if clear and free from particulate matter.

Dosage and schedule

Two doses of 0.5ml at the recommended interval (see below).

Administration

Vaccines are routinely given intramuscularly into the upper arm or anterolateral thigh. However, for individuals with a bleeding disorder, vaccines should be given by deep subcutaneous injection to reduce the risk of bleeding.

MMR vaccine can be given at the same time as other vaccines such as DTaP/IPV, Hib/MenC and hepatitis B. The vaccine should be given at a separate site, preferably in a different limb. If given in the same limb, they should be given at least 2.5cm apart (American Academy of Pediatrics, 2003). See chapter 11 for the routine childhood immunisation schedule. If MMR cannot be given at the same time as an inactivated vaccine, it can be given at any interval before

or after. The site at which each vaccine is given should be noted in the child's record.

MMR should ideally be given at the same time as other live vaccines, such as BCG. If live vaccines are given simultaneously, then each vaccine virus will begin to replicate and an appropriate immune response is made to each vaccine. After a live vaccine is given, natural interferon is produced in response to that vaccine. If a second live vaccine is given during this response, the interferon may prevent replication of the second vaccine virus. This may attenuate the response to the second vaccine. Based on evidence that MMR vaccine can lead to an attenuation of the varicella vaccine response (Mullooly and Black, 2001), the recommended interval between live vaccines is currently four weeks. For this reason, if live vaccines cannot be administered simultaneously, a four-week interval is recommended.

Four weeks should be left between giving MMR vaccine and carrying out tuberculin testing. The measles vaccine component of MMR can reduce the delayed-type hypersensitivity response. As this is the basis of a positive tuberculin test, this could give a false negative response.

When MMR is given within three months of receiving blood products, such as immunoglobulin, the response to the measles component may be reduced. This is because such blood products may contain significant levels of measles-specific antibody, which could then prevent vaccine virus replication. Where possible, MMR should be deferred until three months after receipt of such products. If immediate measles protection is required in someone who has recently received a blood product, MMR vaccine should still be given. To confer longer-term protection, MMR should be repeated after three months.

Where rubella protection is required for post-partum women who have received anti-D immunoglobulin, no deferral is necessary as the response to the rubella component is normally adequate (Edgar and Hambling, 1977; Black *et al*., 1983). Blood transfusion around the time of delivery may inhibit the rubella response and, therefore, a test for rubella antibody should be undertaken six to eight weeks after vaccination. The vaccination should be repeated if necessary.

Disposal

Equipment used for vaccination, including used vials or ampoules, should be disposed of at the end of a session by sealing in a proper, puncture-resistant 'sharps' box (UN-approved, BS 7320).

Recommendations for the use of the vaccine

The objective of the immunisation programme is to provide two doses of MMR vaccine at appropriate intervals for all eligible individuals.

Over 90% of individuals will seroconvert to measles, mumps and rubella antibodies after the first dose of the MMR vaccines currently used in the UK (Tischer and Gerike, 2000). Antibody responses from pre-licence studies may be higher, however, than clinical protection under routine use. Evidence shows that a single dose of measles-containing vaccine confers protection in around 90% of individuals for measles (Morse *et al*., 1994; Medical Research Council, 1977). A single dose of a rubella-containing vaccine confers around 95 to 100% protection (Plotkin and Orenstein, 2004). A single dose of a mumps-containing vaccine used in the UK confers between 61% and 91% protection against mumps (Plotkin and Orenstein, 2004). A more recent study in the UK suggested that a single dose of MMR is around 64% effective against mumps (Harling *et al.*, 2005).

Therefore, two doses of MMR are required to produce satisfactory protection against measles, mumps and rubella.

MMR is recommended when protection against measles, mumps and/or rubella is required. MMR vaccine can be given irrespective of a history of measles, mumps or rubella infection. There are no ill effects from immunising such individuals because they have pre-existing immunity that inhibits replication of the vaccine viruses.

Children under ten years of age

The first dose of MMR should be given between 12 and 13 months of age (i.e. within a month of the first birthday). Immunisation before one year of age provides earlier protection in localities where the risk of measles is higher, but residual maternal antibodies may reduce the response rate to the vaccine. The optimal age chosen for scheduling children is therefore a compromise between risk of disease and level of protection.

If a dose of MMR is given before the first birthday, either because of travel to an endemic country, or because of a local outbreak, then this dose should be ignored, and two further doses given at the recommended times between 12 and 13 months of age (i.e. within a month of the first birthday) and at three years four months to five years of age (see chapter 11).

A second dose is normally given before school entry but can be given routinely at any time from three months after the first dose. Allowing three months between doses is likely to maximise the response rate, particularly in young children under the age of 18 months where maternal antibodies may reduce the response to vaccination (Orenstein *et al.*, 1986; Redd *et al*., 2004; de Serres *et al*., 1995). Where protection against measles is urgently required, the second dose can be given one month after the first (ACIP, 1998). If the child is given the second dose less than three months after the first dose and at less than 18 months of age, then the routine pre-school dose (a third dose) should be given in order to ensure full protection.

Children aged ten years or over and adults

All children should have received two doses of MMR vaccine before they leave school. The teenage (school-leaving) booster session or appointment is an opportunity to ensure that unimmunised or partially immunised children are given MMR. If two doses of MMR are required, then the second dose should be given one month after the first.

MMR vaccine can be given to individuals of any age. Entry into college, university or other higher education institutions, prison or military service provides an opportunity to check an individual's immunisation history. Those who have not received MMR should be offered appropriate MMR immunisation.

All seronegative women of childbearing age who need to be protected against rubella should be offered MMR vaccine. Satisfactory evidence of protection would include documentation of having received two doses of rubella-containing vaccine or a positive antibody test for rubella.

The decision on when to vaccinate other adults needs to take into consideration the past vaccination history, the likelihood of an individual remaining susceptible and the future risk of exposure and disease:

- individuals who were born between 1980 and 1990 may not be protected against mumps but are likely to be vaccinated against measles and rubella. They may never have received a mumps-containing vaccine or had only one dose of MMR, and had limited opportunity for exposure to natural mumps. They should be recalled and given MMR vaccine. If this is their first dose, a further dose of MMR should be given from one month later.

- individuals born between 1970 and 1979 may have been vaccinated against measles and many will have been exposed to mumps and rubella during childhood. However, this age group should be offered MMR wherever feasible, particularly if they are considered to be at high risk of exposure. Where such adults are being vaccinated because they have been demonstrated to be susceptible to at least one of the vaccine components, then either two doses should be given, or there should be evidence of seroconversion to the relevant antigen.
- individuals born before 1970 are likely to have had all three natural infections and are less likely to be susceptible. MMR vaccine should be offered to such individuals on request or if they are considered to be at high risk of exposure. Where such adults are being vaccinated because they have been demonstrated to be susceptible to at least one of the vaccine components, then either two doses should be given or there should be evidence of seroconversion to the relevant antigen.

Individuals with unknown or incomplete vaccination histories

Children coming from developing countries will probably have received a measles-containing vaccine in their country of origin but may not have received mumps or rubella vaccines (www-nt.who.int/immunization_monitoring/en/globalsummary/countryprofileselect.cfm). Unless there is a reliable history of appropriate immunisation, individuals should be assumed to be unimmunised and the recommendations above should be followed. Individuals aged 18 months and over who have not received MMR should receive two doses at least one month apart. An individual who has already received one dose of MMR should receive a second dose to ensure that they are protected.

Healthcare workers

Protection of healthcare workers is especially important in the context of their ability to transmit measles or rubella infections to vulnerable groups. While they may need MMR vaccination for their own benefit, on the grounds outlined above, they also should be immune to measles and rubella for the protection of their patients.

Satisfactory evidence of protection would include documentation of:

- having received two doses of MMR, or
- positive antibody tests for measles and rubella.

Individuals who are travelling or going to reside abroad

All travellers to epidemic or endemic areas should ensure that they are fully immunised according to the UK schedule (see above).

Contraindications

There are very few individuals who cannot receive MMR vaccine. When there is doubt, appropriate advice should be sought from a consultant paediatrician, immunisation co-ordinator or consultant in communicable disease control rather than withholding the vaccine.
The vaccine should not be given to:

- those who are immunosuppressed (see chapter 6 for more detail)
- those who have had a confirmed anaphylactic reaction to a previous dose of a measles-, mumps- or rubella-containing vaccine
- those who have had a confirmed anaphylactic reaction to neomycin or gelatin
- pregnant women.

Anaphylaxis after MMR is extremely rare (3.5 to 14.4 per million doses) (Bohlke *et al.*, 2003; Patja *et al*., 2000; Pool *et al*., 2002; D'Souza *et al*., 2000). Minor allergic conditions may occur and are not contraindications to further immunisation with MMR or other vaccines. A careful history of that event will often distinguish between anaphylaxis and other events that are either not due to the vaccine or are not life-threatening. In the latter circumstances, it may be possible to continue the immunisation course. Specialist advice must be sought on the vaccines and circumstances in which they could be given. The lifelong risk to the individual of not being immunised must be taken into account.

Precautions

Minor illnesses without fever or systemic upset are not valid reasons to postpone immunisation. If an individual is acutely unwell, immunisation should be postponed until they have fully recovered. This is to avoid confusing the differential diagnosis of any acute illness by wrongly attributing any sign or symptoms to the adverse effects of the vaccine.

Idiopathic thrombocytopaenic purpura

Idiopathic thrombocytopaenic purpura (ITP) has occurred rarely following MMR vaccination, usually within six weeks of the first dose. The risk of

developing ITP after MMR vaccine is much less than the risk of developing it after infection with wild measles or rubella virus.

If ITP has occurred within six weeks of the first dose of MMR, then blood should be taken and tested for measles, mumps and rubella antibodies before a second dose is given. Serum should be sent to the Health Protection Agency (HPA) Virus Reference Laboratory (Colindale), which offers free, specialised serological testing for such children. If the results suggest incomplete immunity against measles, mumps or rubella, then a second dose of MMR is recommended.

Allergy to egg

All children with egg allergy should receive the MMR vaccination as a routine procedure in primary care (Clark *et al.,* 2010). Recent data suggest that anaphylactic reactions to MMR vaccine are not associated with hypersensitivity to egg antigens but to other components of the vaccine (such as gelatin) (Fox and Lack, 2003). In three large studies with a combined total of over 1000 patients with egg allergy, no severe cardiorespiratory reactions were reported after MMR vaccination (Fasano *et al.,* 1992; Freigang *et al.,* 1994; Aickin *et al.,* 1994; Khakoo and Lack, 2000). Children who have had documented anaphylaxis to the vaccine itself should be assessed by an allergist (Clark *et al.,* 2010).

Pregnancy and breast-feeding

There is no evidence that rubella-containing vaccines are teratogenic. In the USA, UK and Germany, 661 women were followed through active surveillance, including 293 who were vaccinated (mainly with single rubella vaccine) in the high-risk period (i.e. the six weeks after the last menstrual period). Only 16 infants had evidence of infection and none had permanent abnormalities compatible with CRS (Best *et al.*, 2004). However, as a precaution, MMR vaccine should not be given to women known to be pregnant. If MMR vaccine is given to adult women, they should be advised to guard against pregnancy for one month.

Termination of pregnancy following inadvertent immunisation should not be recommended (Tookey *et al*., 1991). The potential parents should be given information on the evidence of lack of risk from vaccination in pregnancy. Surveillance of inadvertent MMR administration in pregnancy is being conducted by the HPA Immunisation Department, to whom such cases should be reported (Tel: 020 8200 4400).

Pregnant women who are found to be susceptible to rubella should be immunised with MMR after delivery.

Breast-feeding is not a contraindication to MMR immunisation, and MMR vaccine can be given to breast-feeding mothers without any risk to their baby. Very occasionally, rubella vaccine virus has been found in breast milk, but this has not caused any symptoms in the baby (Buimovici-Klein *et al.,* 1997; Landes *et al*., 1980; Losonsky *et al*., 1982). The vaccine does not work when taken orally. There is no evidence of mumps and measles vaccine viruses being found in breast milk.

Premature infants

It is important that premature infants have their immunisations at the appropriate chronological age, according to the schedule (see chapter 11).

Immunosuppression and HIV

MMR vaccine is not recommended for patients with severe immunosuppression (see Chapter 6) (Angel *et al*., 1996). MMR vaccine can be given to HIV-positive patients without or with moderate immunosuppression (as defined in Table 28.1).

Table 28.1 CD4 count/µl (% of total lymphocytes)

Age	<12 months	1–5 years	6–12 years	>12 years
No suppression	⩾1500 (⩾25%)	⩾1000 (15–24%)	⩾500 (⩾25%)	⩾500 (⩾25%)
Moderate suppression	750–1499 (15–24%)	500–999 (15–24%)	200–499 (15–24%)	200–499 (15–24%)
Severe suppression	<750 (<15%)	<500 (<15%)	<200 (<15%)	<200 (<15%)

Further guidance is provided by the Royal College of Paediatrics and Child Health (www.rcpch.ac.uk), the British HIV Association (BHIVA) *Immunisation guidelines for HIV-infected adults* (BHIVA, 2006) and the Children's HIV Association of UK and Ireland (CHIVA) immunisation guidelines (www.bhiva.org/chiva).

Neurological conditions

The presence of a neurological condition is not a contraindication to immunisation. If there is evidence of current neurological deterioration, including poorly controlled epilepsy, immunisation should be deferred until the condition has stabilised. Children with a personal or close family history

of seizures should be given MMR vaccine. Advice about likely timing of any fever and management of a fever should be given. Doctors and nurses should seek specialist paediatric advice rather than refuse immunisation.

Adverse reactions

Adverse reactions following the MMR vaccine (except allergic reactions) are due to effective replication of the vaccine viruses with subsequent mild illness. Such events are to be expected in some individuals. Events due to the measles component occur six to 11 days after vaccination. Events due to the mumps and rubella components usually occur two to three weeks after vaccination but may occur up to six weeks after vaccination. These events only occur in individuals who are susceptible to that component, and are therefore less common after second and subsequent doses. Individuals with vaccine-associated symptoms are not infectious to others.

Common events

Following the first dose of MMR vaccine, malaise, fever and/or a rash may occur, most commonly about a week after immunisation, and last about two to three days. In a study of over 6000 children aged one to two years, the symptoms reported were similar in nature, frequency, time of onset and duration to those commonly reported after measles vaccine alone (Miller *et al*., 1989). Parotid swelling occurred in about 1% of children of all ages up to four years, usually in the third week.

Adverse reactions are considerably less common after a second dose of MMR vaccine than after the first dose. One study showed no increase in fever or rash after re-immunisation of college students compared with unimmunised controls (Chen *et al*., 1991). An analysis of allergic reactions reported through the US Vaccine Adverse Events Reporting System in 1991–93 showed fewer reactions among children aged six to 19 years, considered to be second-dose recipients, than among those aged one to four years, considered to be first-dose recipients (Chen *et al*., 1991). In a study of over 8000 children there was no increased risk of convulsions, rash or joint pain in the months after the second dose of the MMR vaccination given between four and six years of age (Davis *et al*., 1997).

Rare and more serious events

Febrile seizures are the most commonly reported neurological event following measles immunisation. Seizures occur during the sixth to eleventh day in one in 1000 children vaccinated with MMR – a rate similar to that reported in the same period after measles vaccine. The rate of febrile seizures following MMR is lower than that following infection with measles disease (Plotkin and

Orenstein, 2004). There is good evidence that febrile seizures following MMR immunisation do not increase the risk of subsequent epilepsy compared with febrile seizures due to other causes (Vestergaard *et al*., 2004).

One strain of mumps virus (Urabe) in an MMR vaccine previously used in the UK was associated with an increased risk of aseptic meningitis (Miller *et al*., 1993). This vaccine was replaced in 1992 (Department of Health, 1992) and is no longer licensed in the UK. A study in Finland using MMR containing a different mumps strain (Jeryl Lynn), similar to those used currently in MMR in the UK, did not identify any association between MMR and aseptic meningitis (Makela *et al.*, 2002).

Because MMR vaccine contains live, attenuated viruses, it is biologically plausible that it may cause encephalitis. A recent large record linkage study in Finland looking at over half a million children aged between one and seven years did not identify any association between MMR and encephalitis (Makela *et al*., 2002).

ITP is a condition that may occur following MMR and is most likely due to the rubella component. This usually occurs within six weeks and resolves spontaneously. ITP occurs in about one in 22,300 children given a first dose of MMR in the second year of life (Miller *et al.,* 2001). If ITP has occurred within six weeks of the first dose of MMR, then blood should be taken and tested for measles, mumps and rubella antibodies before a second dose is given (see above).

Arthropathy (arthralgia or arthritis) has also been reported to occur rarely after MMR immunisation, probably due to the rubella component. If it is caused by the vaccine, it should occur between 14 and 21 days after immunisation. Where it occurs at other times, it is highly unlikely to have been caused by vaccination. Several controlled epidemiological studies have shown no excess risk of chronic arthritis in women (Slater, 1997).

All suspected adverse reactions to vaccines occurring in children, or in individuals of any age after vaccines labelled with a black triangle (▼), should be reported to the Commission on Human Medicines using the Yellow Card scheme. Serious, suspected adverse reactions to vaccines in adults should be reported through the Yellow Card scheme.

Other conditions reported after vaccines containing measles, mumps and rubella

Following the November 1994 MR immunisation campaign, only three cases of Guillain-Barré syndrome (GBS) were reported. From the background rate, between one and eight cases would have been expected in this population over this period. Therefore, it is likely that these three cases were coincidental and not caused by the vaccine. Analysis of reporting rates of GBS from acute flaccid paralysis surveillance undertaken in the WHO Region of the Americas has shown no increase in rates of GBS following measles immunisation campaigns when 80 million children were immunised (da Silveira *et al*., 1997). In a population that received 900,000 doses of MMR, there was no increased risk of GBS at any time after vaccinations (Patja *et al*., 2001). This evidence refutes the suggestion that MMR causes GBS.

Although gait disturbance has been reported after MMR, a recent epidemiological study showed no evidence of a causal association between MMR and gait disturbance (Miller *et al*., 2005).

In recent years, the postulated link between measles vaccine and bowel disease has been investigated. There was no increase in the incidence of inflammatory bowel disorders in those vaccinated with measles-containing vaccines compared with controls (Gilat *et al*., 1987; Feeney *et al*., 1997). No increase in the incidence of inflammatory bowel disease has been observed since the introduction of MMR vaccination in Finland (Pebody *et al*., 1998) or in the UK (Seagroatt, 2005).

There is overwhelming evidence that MMR does not cause autism (www.iom.edu/report.asp?id=20155). Over the past seven years, a large number of studies have been published looking at this issue. Such studies have shown:

- no increased risk of autism in children vaccinated with MMR compared with unvaccinated children (Farrington *et al*., 2001; Madsen and Vestergaard, 2004)
- no clustering of the onset of symptoms of autism in the period following MMR vaccination (Taylor *et al*., 1999; De Wilde *et al*., 2001; Makela *et al*., 2002)
- that the increase in the reported incidence of autism preceded the use of MMR in the UK (Taylor *et al*., 1999)

- that the incidence of autism continued to rise after 1993, despite the withdrawal of MMR in Japan (Honda *et al*., 2005)
- that there is no correlation between the rate of autism and MMR vaccine coverage in either the UK or the USA (Kaye *et al*., 2001; Dales *et al*., 2001)
- no difference between the proportion of children developing autism after MMR who have a regressive form compared with those who develop autism without vaccination (Fombonne, 2001; Taylor *et al*., 2002; Gillberg and Heijbel, 1998)
- no difference between the proportion of children developing autism after MMR who have associated bowel symptoms compared with those who develop autism without vaccination (Fombonne, 2001; Fombonne, 1998; Taylor *et al*., 2002)
- that no vaccine virus can be detected in children with autism using the most sensitive methods available (Afzal *et al.*, 2006).

For the latest evidence, see the Department of Health's website: www.dh.gov.uk/en/Publichealth/Healthprotection/Immunisation/Keyvaccineinformation/DH_103952

It has been suggested that combined MMR vaccine could potentially overload the immune system. From the moment of birth, humans are exposed to countless numbers of foreign antigens and infectious agents in their everyday environment. Responding to the three viruses in MMR would use only a tiny proportion of the total capacity of an infant's immune system (Offit *et al*., 2002). The three viruses in MMR replicate at different rates from each other and would be expected to reach high levels at different times.

A study examining the issue of immunological overload found a lower rate of admission for serious bacterial infection in the period shortly after MMR vaccination compared with other time periods. This suggests that MMR does not cause any general suppression of the immune system (Miller *et al*., 2003).

Management of cases, contacts and outbreaks

Diagnosis

Prompt notification of measles, mumps and rubella to the local health protection unit (HPU) is required to ensure public health action can be taken promptly. Notification should be based on clinical suspicion and should not await laboratory confirmation. Since 1994, few clinically diagnosed cases are

subsequently confirmed to be true measles, mumps or rubella. Confirmation rates do increase, however, during outbreaks and epidemics.

The diagnosis of measles, mumps and rubella can be confirmed through non-invasive means. Detection of specific IgM in oral fluid (saliva) samples, ideally between one and six weeks after the onset of rash or parotid swelling, has been shown to be highly sensitive and specific for confirmation of these infections (Brown *et al*., 1994; Ramsay *et al*., 1991; Ramsay *et al*., 1998). It is recommended that oral fluid samples should be obtained from all notified cases, other than during a large epidemic. Advice on this procedure can be obtained from the local HPU.

Infants with suspected congenital rubella infection should be reported to the National Congenital Rubella Surveillance Programme, either directly to the Institute of Child Health (Tel: 020 7905 2604) or via the British Paediatric Surveillance Unit (Tel: 020 7323 7911).

Protection of contacts with MMR

Antibody response to the rubella component of MMR vaccine does not develop soon enough to provide effective prophylaxis after exposure to suspected rubella. Even where it is too late to provide effective post-exposure prophylaxis with MMR, the vaccine can provide protection against future exposure to all three infections. Therefore, contact with suspected measles, mumps or rubella provides a good opportunity to offer MMR vaccine to previously unvaccinated individuals. If the individual is already incubating measles, mumps or rubella, MMR vaccination will not exacerbate the symptoms. In these circumstances, individuals should be advised that a rubella-like illness occurring shortly after vaccination is likely to be due to natural infection. If there is doubt about an individual's vaccination status, MMR should still be given as there are no ill effects from vaccinating those who are already immune.

Protection of contacts with immunoglobulin

Human normal immunoglobulin is not routinely used for post-exposure protection from rubella since there is no evidence that it is effective. It is **not** recommended for the protection of pregnant women exposed to rubella. It should only be considered when termination of pregnancy is unacceptable. Serological follow-up of recipients is essential.

To prevent or attenuate an attack:
Dose: 750mg

Supplies

- MMRVaxPRO® – manufactured by Sanofi Pasteur MSD.
- Priorix® – manufactured by GlaxoSmithKline.

These vaccines are supplied by Healthcare Logistics (Tel: 0870 871 1890) as part of the national childhood immunisation programme.

In Scotland, supplies should be obtained from local childhood vaccine holding centres. Details of these are available from Scottish Healthcare Supplies (Tel: 0131 275 6154).

In Northern Ireland, supplies should be obtained from local childhood vaccine holding centres. Details of these are available from the regional pharmaceutical procurement service (Tel: 02890 552368).

Human normal immunoglobulin

England and Wales:
Health Protection Agency, Centre for Infections
(Tel: 020 8200 6868).

Scotland:
Blood Transfusion Service
(Tel: 0141 3577700).

Northern Ireland:
Public Health Laboratory, Belfast City Hospital
(Tel: 01232 329241).0

References

ACIP (1998) Measles, mumps, and rubella – vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* **47**(RR-8): 1–57. www.cdc.gov/mmwr/preview/mmwrhtml/00053391.htm.

Afzal MA, Ozoemena LC, O'Hare A *et al*. (2006) Absence of detectable measles virus genome sequence in blood of autistic children who have had their MMR vaccination during the routine childhood immunisation schedule of the UK. *J Med Virol* **78**: 623–30.

Aickin R, Hill D and Kemp A (1994) Measles immunisation in children with allergy to egg. *BMJ* **308**: 223–5.

American Academy of Pediatrics (2003) Active immunization. In: Pickering LK (ed.) *Red Book: 2003 Report of the Committee on Infectious Diseases*, 26th edition. Elk Grove Village, IL: American Academy of Pediatrics.

Angel JB, Udem SA, Snydman DR *et al.* (1996) Measles pneumonitis following measles-mumps-rubella vaccination of patients with HIV infection, 1993. *MMWR* **45**: 603–6.

Best JM, Cooray S and Banatvala JE (2004) Rubella. In: Mahy BMJ and ter Meulen V (eds) *Topley and Wilson's Virology*, 10th edition. London: Hodder Arnold.

Black NA, Parsons A, Kurtz JB *et al*. (1983) Post-partum rubella immunisation: a controlled trial of two vaccines. *Lancet* **2**(8357): 990–2.

Bohlke K, Davis RL, Moray SH *et al.* (2003) Risk of anaphylaxis after vaccination of children and adolescents. *Pediatrics* **112**: 815–20.

British HIV Association (2006) *Immunisation guidelines for HIV-infected adults*. BHIVA. www.bhiva.org/pdf/2006/Immunisation506.pdf

Brown DW, Ramsay ME, Richards AF and Miller E (1994) Salivary diagnosis of measles: a study of notified cases in the United Kingdom, 1991–3. *BMJ* **308**(6935): 1015–17.

Buimovici-Klein E, Hite RL, Byrne T and Cooper LR (1997) Isolation of rubella virus in milk after postpartum immunization. *J Pediatr* **91**: 939–43.

Chen RT, Moses JM, Markowitz LE and Orenstein WA (1991) Adverse events following measles-mumps-rubella and measles vaccinations in college students. *Vaccine* **9**: 297–9.

Clark AT, Skypala I, Leech SC, *et al.* (2010). British Society for Allergy and Clinical Immunology guidelines for the management of egg allergy. *Clin Exp Allergy* **40**(8):1116-29.

Dales L, Hammer SJ and Smith NJ (2001) Time trends in autism and in MMR immunization coverage in California. *JAMA* **285**(22): 2852–3.

da Silveira CM, Salisbury DM and de Quadros CA (1997) Measles vaccination and Guillain-Barré syndrome. *Lancet* **349**(9044): 14–16.

Davis RL, Marcuse E, Black S *et al*. (1997) MMR2 immunization at 4 to 5 years and 10 to 12 years of age: a comparison of adverse clinical events after immunization in the Vaccine Safety Datalink project. *Pediatrics* **100**: 767–71.

Department of Health (1992) *Changes in supply of vaccine*. Circular (PL/CMO(92)11).

de Serres G, Boulianne N, Meyer F and Ward BJ (1995) Measles vaccine efficacy during an outbreak in a highly vaccinated population: incremental increase in protection with age at vaccination up to 18 months. *Epidemiol Infect* **115**: 315–23.

De Wilde S, Carey IM, Richards N *et al.* (2001) Do children who become autistic consult more often after MMR vaccination? *Br J General Practice* **51**: 226–7.

D'Souza RM, Campbell-Lloyd S, Isaacs D *et al*. (2000) Adverse events following immunisation associated with the 1998 Australian Measles Control Campaign. *Commun Dis Intell* **24**: 27–33.

Edgar WM and Hambling MH (1977) Rubella vaccination and anti-D immunoglobulin administration in the puerperium. *Br J Obstet Gynaecol* **84**(10): 754–7.

Farrington CP, Miller E and Taylor B (2001) MMR and autism: further evidence against a causal association. *Vaccine* **19**: 3632–5.

Fasano MB, Wood RA, Cooke SK and Sampson HA (1992) Egg hypersensitivity and adverse reactions to measles, mumps and rubella vaccine. *J Pediatr* **120**: 878–81.

Feeney M, Gregg A, Winwood P and Snook J (1997) A case-control study of measles vaccination and inflammatory bowel disease. The East Dorset Gastroenterology Group. *Lancet* **350**: 764–6.

Fombonne E (1998) Inflammatory bowel disease and autism. *Lancet* **351**: 955.

Fombonne E (2001) Is there an epidemic of autism? *Pediatrics* **107**: 411–12.

Fox A and Lack G (2003) Egg allergy and MMR vaccination. *Br J Gen Pract* **53**(495): 801–2.

Freigang B, Jadavji TP and Freigang DW (1994) Lack of adverse reactions to measles, mumps and rubella vaccine in egg-allergic children. *Ann Allergy* **73**: 486–8.

Gilat T, Hacohen D, Lilos P and Langman MJ (1987) Childhood factors in ulcerative colitis and Crohn's disease. An international co-opreative study. *Scan J Gastroenterology* **22**: 1009–24.

Gillberg C and Heijbel H (1998) MMR and autism. *Autism* **2**: 423–4.

Harling R, White JM, Ramsay ME *et al.* (2005) The effectiveness of the mumps component of the MMR vaccine: a case control study. *Vaccine* **23**(31): 4070–4.

Health Protection Agency (2006) Measles deaths, England and Wales, by age group, 1980-2004. www.hpa.org.uk/infections/topics_az/measles/data_death_age.htm

Honda H, Shimizu J and Rutter M (2005) No effect of MMR withdrawal on the incidence of autism: a total population study. *J Child Psychol Psychiatry* **46**(6): 572–9.

Kaye JA, del Mar Melero-Montes M and Jick H (2001) Mumps, measles and rubella vaccine and the incidence of autism recorded by general practitioners: a time trend analysis. *BMJ* **322**(7284): 460–3.

Khakoo GA and Lack G (2000) Recommendations for using MMR vaccine in children allergic to eggs. *BMJ* **320**: 929–32.

Landes RD, Bass JW, Millunchick EW and Oetgen WJ (1980) Neonatal rubella following postpartum maternal immunisation. *J Pediatr* **97**: 465–7.

Lokletz H and Reynolds FA (1965) Post-rubella thrombocytopaenic purpura. Report of nine new cases and review of published cases. *Lancet* **85**: 226–30.

Losonsky GA, Fishaut JM, Strussenberg J and Ogra PL (1982) Effect of immunization against rubella on lactation products. Development and characterization of specific immunologic reactivity in breast milk. *J Infect Dis* **145**: 654–60.

Madsen KM and Vestergaard M (2004) MMR vaccination and autism: what is the evidence for a causal association? *Drug Saf* **27**: 831–40.

Makela A, Nuorti JP and Peltola H (2002) Neurologic disorders after measles-mumps-rubella vaccination. *Pediatrics* **110**: 957–63.

Medical Research Council (1977) Clinical trial of live measles vaccine given alone and live vaccine preceded by killed vaccine. Fourth report of the Medical Research Council by the measles sub-committee on development of vaccines and immunisation procedures. *Lancet* **ii**: 571–5.

Miller C, Miller E, Rowe K *et al*. (1989) Surveillance of symptoms following MMR vaccine in children. *Practitioner* **233**(1461): 69–73.

Miller E, Cradock-Watson JE and Pollock TM (1982) Consequences of confirmed maternal rubella at successive stages of pregnancy. *Lancet* **2**: 781–4.

Miller EM, Waight P, Vurdein JE *et al.* (1991) Rubella surveillance to December 1990: a joint report from the PHLS and National Congenital Rubella Surveillance Programme. *CDR Review* **1**(4): R33–37.

Miller E, Goldacre M, Pugh S *et al*. (1993) Risk of aseptic meningitis after measles, mumps, and rubella vaccine in UK children. *Lancet* **341**(8851): 979–82.

Miller E, Waight P, Farrington P *et al*. (2001) Idiopathic thrombocytopaenic purpura and MMR vaccine. *Arch Dis Child* **84**: 227–9.

Miller E, Andrews N, Waight P and Taylor B (2003) Bacterial infections, immune overload, and MMR vaccine. Measles, mumps, and rubella. *Arch Dis Child* **88**(3): 222–3.

Miller E, Andrews N, Grant A *et al.* (2005) No evidence of an association between MMR vaccine and gait disturbance. *Arch Dis Child* **90**(3): 292–6.

Morgan Capner P, Wright J, Miller CL and Miller E (1988) Surveillance of antibody to measles, mumps and rubella by age. *BMJ* **297**: 770–2.

Morse D, O'Shea M, Hamilton G *et al.* (1994) Outbreak of measles in a teenage school population: the need to immunize susceptible adolescents. *Epidemiol Infect* **113**: 355–65.

Mullooly J and Black S (2001) Simultaneous administration of varicella vaccine and other recommended childhood vaccines – United States, 1995–1999. *MMWR* **50**(47): 1058–61.

Offit PA, Quarles J, Gerber MA *et al*. (2002) Addressing parents' concerns: do multiple vaccines overwhelm or weaken the infant's immune system? *Pediatrics* **109**(1): 124–9.

Orenstein WA, Markowitz L, Preblud SR *et al.* (1986) Appropriate age for measles vaccination in the United States *Dev Biol Stand* **65**: 13–21.

Patja A, Davidkin I, Kurki T *et al*. (2000) Serious adverse events after measles-mumps-rubella vaccination during a fourteen-year prospective follow-up. *Pediatr Infect Dis J* **19**: 1127–34.

Patja A, Paunio M, Kinnunen E *et al*. (2001) Risk of Guillain-Barré syndrome after measles-mumps-rubella vaccination. *J Pediatr* **138**: 250–4.

Pebody RG, Paunio M and Ruutu P (1998) Measles, measles vaccination, and Crohn's disease has not increased in Finland. *BMJ* **316**(7146): 1745–6.

Peltola H, Heinonen OP and Valle M (1994) The elimination of indigenous measles, mumps and rubella from Finland by a 12-year two-dose vaccination program. *NEJM* **331**(21): 1397–402.

Plotkin SA and Orenstein (eds) (2004) *Vaccines,* 4th edition. Philadelphia: WB Saunders Company, Chapters 19, 20 and 26.

Pool V, Braun MM, Kelso JM *et al*. (2002) Prevalence of anti-gelatin IgE antibodies in people with anaphylaxis after measles-mumps-rubella vaccine in the United States. *Pediatrics* **110**(6):e71. www.pediatrics.org/cgi/content/full/110/6/e71

Rahi K, Adams G, Russell-Eggitt I and Tookey P (2001) Epidemiological surveillance of rubella must continue (letter). *BMJ* **323**: 112.

Ramsay ME, Brown DW, Eastcott HR and Begg NT (1991) Saliva antibody testing and vaccination in a mumps outbreak. *CDR (Lond Engl Rev)* **1**(9): R96–8).

Ramsay ME, Brugha R, Brown DW *et al*. (1998) Salivary diagnosis of rubella: a study of notified cases in the United Kingdom, 1991–4. *Epidemiol Infect* **120**(3): 315–19.

Redd SC, King GE, Heath JL *et al*. (2004) Comparison of vaccination with measles-mumps-rubella at 9, 12 and 15 months of age. *J Infect Dis* **189**: S116–22.

Seagroatt V (2005) MMR vaccine and Crohn's disease: ecological study of hospital admissions in England, 1991 to 2002. *BMJ* **330**: 1120–1.

Slater PE (1997) Chronic arthropathy after rubella vaccination in women. False alarm? J*AMA* **278**: 594–5.

Taylor B, Miller E, Farrington CP *et al.* (1999) Autism and measles, mumps and rubella: no epidemiological evidence for a causal association. *Lancet* **353**(9169): 2026–9.

Taylor B, Miller E, Langman R *et al*. (2002) Measles, mumps and rubella vaccination and bowel problems or developmental regression in children with autism; population study. *BMJ* **324**(7334): 393–6.

Tischer A and Gerike E (2000) Immune response after primary and re-vaccination with different combined vaccines against measles, mumps, rubella. *Vaccine* **18**(14): 1382–92.

Tookey PA, Jones G, Miller BH and Peckham CS (1991) Rubella vaccination in pregnancy. *CDR London Engl Rev* **1**(8): R86–8.

Tookey PA and Peckham CS (1999) Surveillance of congenital rubella in Great Britain, 1971–96. *BMJ* **318**: 769–70.

Tookey PA, Cortina-Borja M and Peckham CS (2002) Rubella susceptibility among pregnant women in North London, 1996–1999. *J Public Health Med* **24**(3): 211–16.

Tookey PA (2004) Rubella in England, Scotland and Wales. *Euro Surveill* **9**: 21–2.

Vestergaard M, Hviid A, Madsen KH *et al.* (2004) MMR vaccination and febrile seizures. Evaluation of susceptible subgroups and long-term prognosis. *JAMA* **292**: 351–7.

Vyse AJ, Gay NJ, White JM *et al*. (2002) Evolution of surveillance of measles, mumps, and rubella in England and Wales: Providing the platform for evidence based vaccination policy. *Epidemiologic Reviews* **24**(2): 125–36.

WHO (2005) Vaccine Preventable Diseases Monitoring System. Global summary. www-nt.who.int/immunization_monitoring/en/globalsummary/countryprofileselect.cfm