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Measles

NOTIFIABLE

The disease

Measles is an acute viral illness caused by a morbillivirus of the paramyxovirus family. The prodromal stage is characterised by the onset of fever, malaise, coryza, conjunctivitis and cough. The rash is erythematous and maculopapular, starting at the head and spreading to the trunk and limbs over three to four days. Koplik spots (small red spots with blueish-white centres) may appear on the mucous membranes of the mouth one to two days before the rash appears and may be seen for a further one to two days afterwards.

Measles is spread by airborne or droplet transmission. Individuals are infectious from the beginning of the prodromal period (when the first symptom appears) to four days after the appearance of the rash. It is one of the most highly communicable infectious diseases. The incubation period is about ten days (ranging between seven and 18 days) with a further two to four days before the rash appears (Chin, 2000).

The following features are strongly suggestive of measles:

- rash for at least three days
- fever for at least one day, and
- at least one of the following – cough, coryza or conjunctivitis.

Laboratory confirmation of suspected cases is required (see section below on diagnosis).

The most common complications of measles infection are otitis media (7 to 9% of cases), pneumonia (1 to 6%), diarrhoea (8%) and convulsions (one in 200). Other, more rare complications include encephalitis (overall rate of one per 1000 cases of measles) and sub-acute sclerosing pan-encephalitis (SSPE) (see below) (Plotkin and Orenstein, 2004; Norrby and Oxman, 1990; Perry and Halsey, 2004; McLean and Carter, 1990; Miller, 1978). Death occurs in one in 5000 cases in the UK (Miller, 1985). The case–fatality ratio for measles is age-related and is high in children under one year of age, lower in children aged one to nine years and rises again in teenagers and adults (Plotkin and Orenstein, 2004, Chapter 19). Complications are more common and more

severe in poorly nourished and/or chronically ill children, including those who are immunosuppressed.

Measles encephalitis

There are different forms of measles encephalitis which occur at different times in relation to the onset of rash:

- post-infectious encephalomyelitis occurs at around one week after onset of the rash. Infectious virus is rarely found in the brain. The condition is associated with demyelination and is thought to have an auto-immune basis (Perry and Halsey, 2004).
- acute measles encephalitis of the delayed type (Barthez Carpentier *et al.*, 1992) occurs in immunocompromised patients. It may occur without a preceding measles-like illness (Kidd *et al.*, 2003) although there may be a history of exposure to measles several weeks or months previously (Alcardi *et al.*, 1997). It is characterised by acute neurological compromise and deterioration of consciousness, seizures and progressive neurological damage.
- SSPE is a rare, fatal, late complication of measles infection. One case of SSPE occurs in every 25,000 measles infections (Miller *et al.*, 2004). In children infected under the age of two, the rate is one in 8000 infections (Miller *et al.*, 2004; Miller *et al.*, 1992). Developing measles under one year of age carries a risk of SSPE 16 times greater than in those infected over five years of age (Miller *et al.*, 1992). The median interval from measles infection to onset of symptoms is around seven years but may be as long as two to three decades. SSPE may follow an unrecognised measles infection. Wild measles virus has been found in the brain of people with SSPE including those with no history of measles disease (Miller *et al.*, 2004).

History and epidemiology of the disease

Notification of measles began in England and Wales in 1940. Before the introduction of measles vaccine in 1968, annual notifications varied between 160,000 and 800,000, with peaks every two years (see Figure 21.1), and around 100 deaths from acute measles occurred each year.

From the introduction of measles vaccination in 1968 until the late 1980s coverage was low (Figure 21.1) and was insufficient to interrupt measles transmission. Therefore, annual notifications only fell to between 50,000 and 100,000 and measles remained a major cause of morbidity and mortality. Between 1970 and 1988, there continued to be an average of 13 acute measles

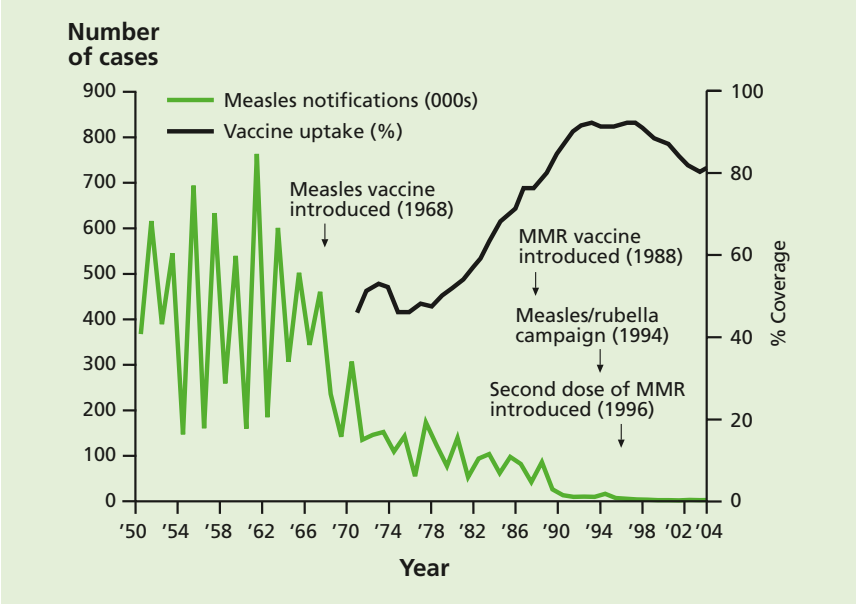

Figure 21.1 Coverage of measles vaccination and measles notifications from 1950 to 2004.

deaths each year. Measles remained a major cause of mortality in children who could not be immunised because they were receiving immunosuppressive treatment. Between 1974 and 1984, of 51 children who died when in first remission from acute lymphatic leukaemia, 15 of the deaths were due to measles or its complications (Gray *et al.*, 1987). Between 1970 and 1983, however, more than half the acute measles deaths that occurred were in previously healthy children who had not been immunised (Miller, 1985).

Following the introduction of measles, mumps and rubella (MMR) vaccine in October 1988 and the achievement of coverage levels in excess of 90%, measles transmission was substantially reduced and notifications of measles fell progressively to very low levels.

Because of the substantial reduction in measles transmission in the UK, children were no longer exposed to measles infection and, if they had not been immunised, they remained susceptible to an older age. Seroprevalence studies confirmed that a higher proportion of school-age children were susceptible to measles in 1991 than in 1986/7 (Gay *et al.*, 1995). A major resurgence of measles was predicted, mainly affecting the school-age population (Gay *et al.*, 1995; Babad *et al.*, 1995). Small outbreaks of measles occurred in England

and Wales in 1993, predominantly affecting secondary school children (Ramsay *et al.*, 1994). In 1993–94, a measles epidemic, affecting the west of Scotland, led to 138 teenagers being admitted to one hospital.

In order to prevent the predicted epidemic, a UK vaccination campaign was implemented in November 1994. Over 8 million children aged between 5 and 16 years were immunised with measles-rubella (MR) vaccine. At that time, insufficient stocks of MMR were available to vaccinate all of these children against mumps. Susceptibility to measles fell seven-fold in the target population and endemic transmission of measles was interrupted (Vyse *et al.*, 2002; Ramsay *et al*., 2003).

To maintain the control of measles established after the MR campaign, a two-dose MMR schedule was introduced in October 1996. A second dose of MMR helps to prevent an accumulation of susceptible individuals that could otherwise be sufficient to re-establish measles transmission. The efficacy of a single dose of measles-containing vaccine is around 90% (Morse *et al*., 1994; Medical Research Council, 1977). A second dose of measles-containing vaccine protects those who do not respond to the first dose. In order to eliminate measles, the World Health Organization (WHO) recommends two doses of a measles-containing vaccine (see www.who.int/mediacentre/factsheets/fs286/en/).

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 it announced that it had interrupted endemic transmission (Plotkin and Orenstein, 2004). MMR is now routinely given in over 100 countries, including those in the European Union, North America and Australasia.

Until 2006, the last confirmed death due to acute measles in the UK had been in 1992. In 2006, an unimmunised 13-year-old boy who was immunocompromised died from acute measles. Since the MR campaign, between 1995 and 2003 there have been 13 deaths recorded to measles in England and Wales. All except one of these were due to late effects of measles acquired before 1995 (www.hpa.org.uk/infections/topics_ az/measles/data_death_age.htm). In the remaining case, measles infection was subsequently excluded by laboratory testing.

The reduced incidence of measles, brought about by vaccination, has caused the almost total disappearance of SSPE in England and Wales. In the early

1970s, when the SSPE Register was put in place, around 20 cases were reported each year. By the early 1990s, the annual total had fallen to around six cases and this has fallen further to between one and two in recent years (Miller *et al*., 2004). In a UK study of 11 cases of SSPE, sequencing of the measles virus strains identified wild-type (and not vaccine-type) virus in all individuals, including five with a history of measles-containing vaccine (Jin *et al.*, 2002). The presence of wild and not vaccine strains of measles virus has been confirmed by studies of SSPE cases in other countries (Miki *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.

Normal immunoglobulin

Normal immunoglobulin is prepared from pooled plasma derived from blood donations and contains antibody to measles and other viruses prevalent in the population. There are two types of preparations available, those for intramuscular or sub-cutaneous use and those for intravenous use. There is

currently no accepted minimum level of measles antibody required in normal immunoglobulin but levels of measles neutralising antibodies have declined in recent years.

Because of a theoretical risk of transmission of vCJD from plasma products, normal immunoglobulin used in the UK is now prepared from plasma sourced from outside the UK, and supplies are scarce.* All donors are screened for HIV and hepatitis B and C, and all plasma pools are tested for the presence of RNA from these viruses. A solvent detergent inactivation step for envelope viruses is included in the intramuscular/sub-cutaneous products.

Storage

The unreconstituted MMR 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.

HNIG should be stored in the original packaging in a refrigerator at +2˚C to +8˚C. These products are tolerant to ambient temperatures for up to one week. They can be distributed in sturdy packaging outside the cold chain if needed.

Presentation

Measles 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.

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* Normal immunoglobulin for measles prophylaxis is in short supply and from time to time alternative products and doses may need to be used. For latest advice please check with the Health Protection Agency (www.hpa.org.uk) or Health Protection Scotland (www.hps.scot.nhs.uk).

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, PCV 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.

HNIG can be administered in the upper outer quadrant of the buttock or anterolateral thigh (see Chapter 4). If more than 3ml is to be given to young children and infants, or more than 5ml to older children and adults, the immunoglobulin should be divided into smaller amounts and given into different sites.

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, Chapter 20). 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 or vaccination. 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 (Anon., 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 with chronic conditions such as cystic fibrosis, congenital heart or kidney disease, failure to thrive or Down's syndrome are at particular risk from measles infection and should be immunised with MMR vaccine.

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.

The decision on when to vaccinate 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.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). Infants from six months of age travelling to measles endemic areas or to an area where there is a current outbreak should receive MMR. As the response to MMR in infants is sub-optimal where the vaccine has been given before one year of age, immunisation with two further doses of MMR should be given at the recommended ages. Children who are travelling who have received one dose of MMR at the routine age should have the second dose brought forward to at least one month after the first. If the child is under 18 months of age and the second dose is given within three months of the first dose, then the routine pre-school dose (a third dose) should be given in order to ensure full protection.

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 signs 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 congenital rubella syndrome (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).

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 21.1).

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).

Table 21.1 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%)

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. One case of ITP attributable to vaccine, occurs for every 32,000 doses administered (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 the vaccinations were administered (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 when 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 now 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 Vertergaard, 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 in Japan despite withdrawal of MMR (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, 1998; Fombonne, 2001; 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; D'Souza *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 or viral RNA in oral fluid (saliva) samples, ideally taken as soon as possible 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.

Protection of contacts with MMR

As vaccine-induced measles antibody develops more rapidly than that following natural infection, MMR vaccine should be used to protect susceptible contacts from suspected measles**.** To be effective against this exposure, vaccine must be administered very promptly, ideally within three days. 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 measles-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.

Immunoglobulin is available for post-exposure prophylaxis in individuals for whom vaccine is contraindicated (see above). Antibody responses to the rubella and mumps components of MMR vaccine do not develop soon enough to provide effective prophylaxis after exposure to these infections.

Where immediate protection against measles is required, for example following exposure, MMR may be given from six months of age. As response to MMR in infants is sub-optimal, where the vaccine has been given before 12 months of age, immunisation with two further doses of MMR should be given at the normal ages. Where children who have received the first dose of MMR require immediate protection against measles, the interval between the first and second doses may be reduced to one month. If the child is under 18 months of age when the second dose is given, then the routine pre-school dose (a third dose) should be given in order to ensure full protection.

Protection of contacts with immunoglobulin

Children and adults with compromised immune systems who come into contact with measles should be considered for normal immunoglobulin as soon as possible after exposure. A local risk assessment of the index case (based on knowledge of the current epidemiology) and the exposure should be undertaken. If the index case is confirmed, epidemiologically linked or considered likely to be measles by the local health protection team, then the need for post exposure prophylaxis should be urgently addressed.

Because of scarce supply and declining levels of measles neutralising antibodies in normal immunoglobulin, recommendations for post-exposure prophylaxis for infants, immunosuppressed and pregnant contacts have recently been changed. More detailed information is available at www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1238565307587.

Many adults and older children with immunosuppression will have immunity due to past infection or vaccination. Normal immunoglobulin is therefore unlikely to confer additional benefit in individuals with detectable measles antibody as their antibody levels are likely to be higher than that achieved with a prophylactic dose. Most immunosuppressed individuals should be able to develop and maintain adequate antibody levels from previous infection or vaccination (see www.hpa.org.uk/web/HPAwebFile HPAweb_C/1238565307587). The use of immunoglobulin is therefore limited to those known or likely to be antibody negative to measles. Urgent assessment is required, and admission to hospital for administration of intravenous immunoglobulin may follow.

Measles infection in infants is associated with high rates of complications (Manikkavasagan et al., 2009a). Although infants of naturally immune mothers are likely to have protective levels of antibody until at least six months of age, a proportion of infants born to vaccinated mothers may not have protective titres even from birth (Brugha et al., 1996). Intra-muscular normal immunoglobulin may be required for infants exposed to measles depending on maternal age, maternal history of measles infection or vaccination and the infant's gestational age (see www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1238565307587).

Measles infection in pregnancy can lead to intra-uterine death and pre-term delivery, but is not associated with congenital infection or damage (Manikkavasagan et al., 2009b). Pregnant women who are exposed to measles may also be considered for intramuscular normal immunoglobulin. A very high proportion of pregnant women will be immune and therefore normal immunoglobulin is only offered to women who are likely to be susceptible based upon a combination of age, history and/or measles IgG antibody screening. Where the diagnosis in the index case is uncertain, this assessment should be done as part of the investigation of exposure to rash in pregnancy. www.hpa.org.uk/infections/topics_az/rubella/rash.pdf)

Dosage of normal immunoglobulin

To prevent or attenuate an attack:

Immunosuppressed patients
0.15g/kg of intravenous normal immunoglobulin (IVIG) given by intravenous infusion or
0.6ml/kg of subcutaneous human normal immunoglobulin (HNIG) given by sub-cutaneous infusion

Immunocompetent infants and pregnant women
Infants under one year of age: 0.6 ml/kg of subcutaneous human normal immunoglobulin (HNIG) up to maximum of one vial (approximately 5ml) by intra-muscular injection.
Pregnant women: 2250 mg of subcutaneous human normal immunoglobulin (HNIG) up to maximum of three vials (approximately 15ml) by intra-muscular injection.
An interval of at least three months must be allowed before subsequent MMR immunisation.

* Normal immunoglobulin for measles prophylaxis is in short supply and from time to time alternative products and doses may need to be used. For latest advice please check with the Health Protection Agency (www.hpa.org.uk) or Health Protection Scotland (www.hps.scot.nhs.uk).

Supplies

MMR vaccine

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

These vaccines are supplied by Healthcare Logistics (Tel: 0870 8711890) 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 vaccineholding centres. Details of these are available from the regional pharmaceutical procurement service
(Tel: 02890 552368).

Human normal immunoglobulin

Subcutaneous human normal immunoglobulin (HNIG)

England and Wales
Health Protection Agency, Centre for Infections Tel. 0208 200 6868

Scotland
Blood Transfusion Service, (telephone numbers)

Northern Ireland
Public Health Laboratory, Belfast City Hospital Tel. 01232 329241

Intravenous normal immunoglobulin

These products are currently under formal demand management (see www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_085235). Applications for supply will need to go through the hospital pharmacist.

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