

# 21

## 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 (0.5%). Other, rarer complications include encephalitis (overall rate of one to four per 1000-2000 cases of measles) and sub-acute sclerosing pan-encephalitis (SSPE) (see below) (Plotkin *et al*, 2018 Chapter 37; Norrby and Oxman, 1990; Perry and Halsey, 2004; McLean and Carter, 1990; Miller, 1978). Historically death occurred in one in 5000 cases in the UK (Miller, 1985). Prior to 2006, the last death from acute measles in England and Wales was in 1992. Between 2006 and 2016 there were 4 reported deaths (PHE, 2017). 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 *et al*, Chapter 37). 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)
- measles inclusion body encephalitis (also known as acute 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. Measles RNA can normally be detected from clinical specimens for several days or weeks
- 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 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).

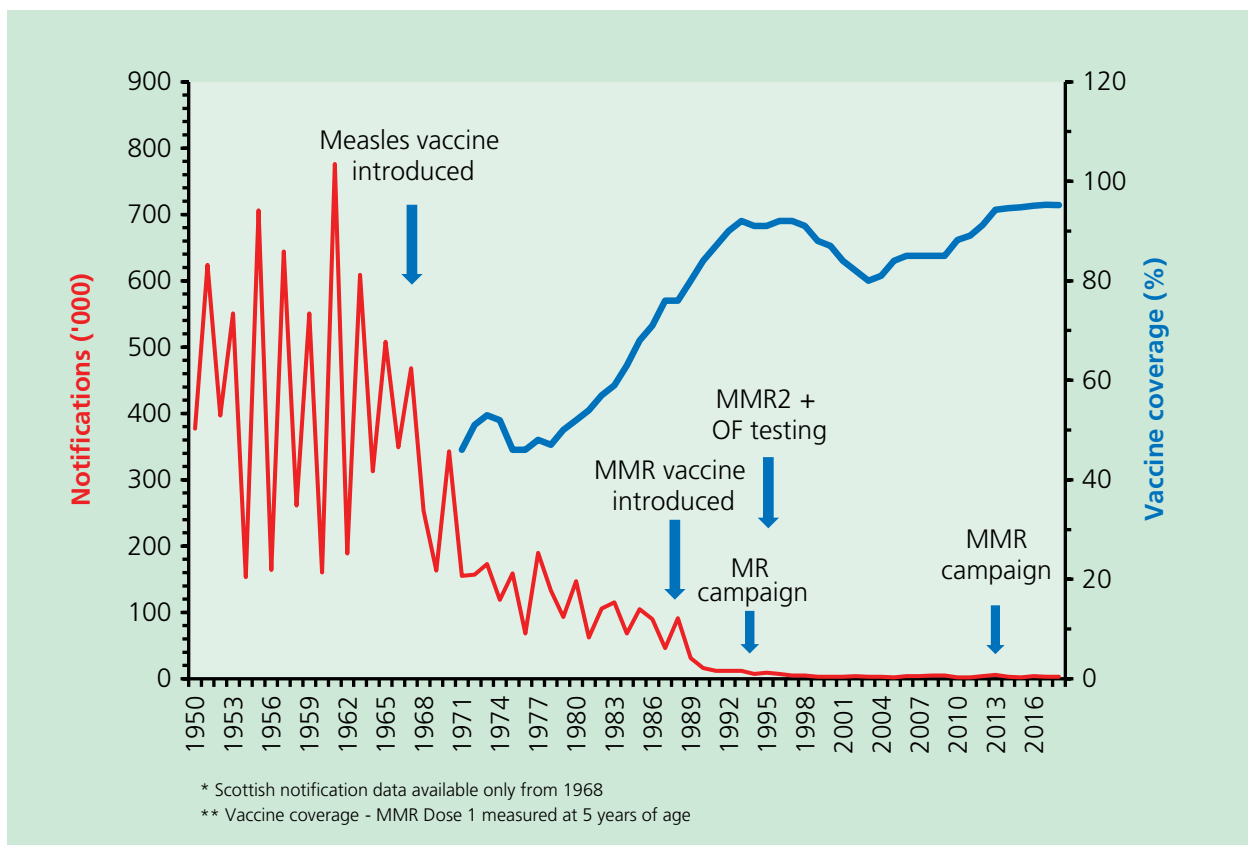


Figure 21.1 Coverage of measles vaccination and measles notifications from 1950 to 2018

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.

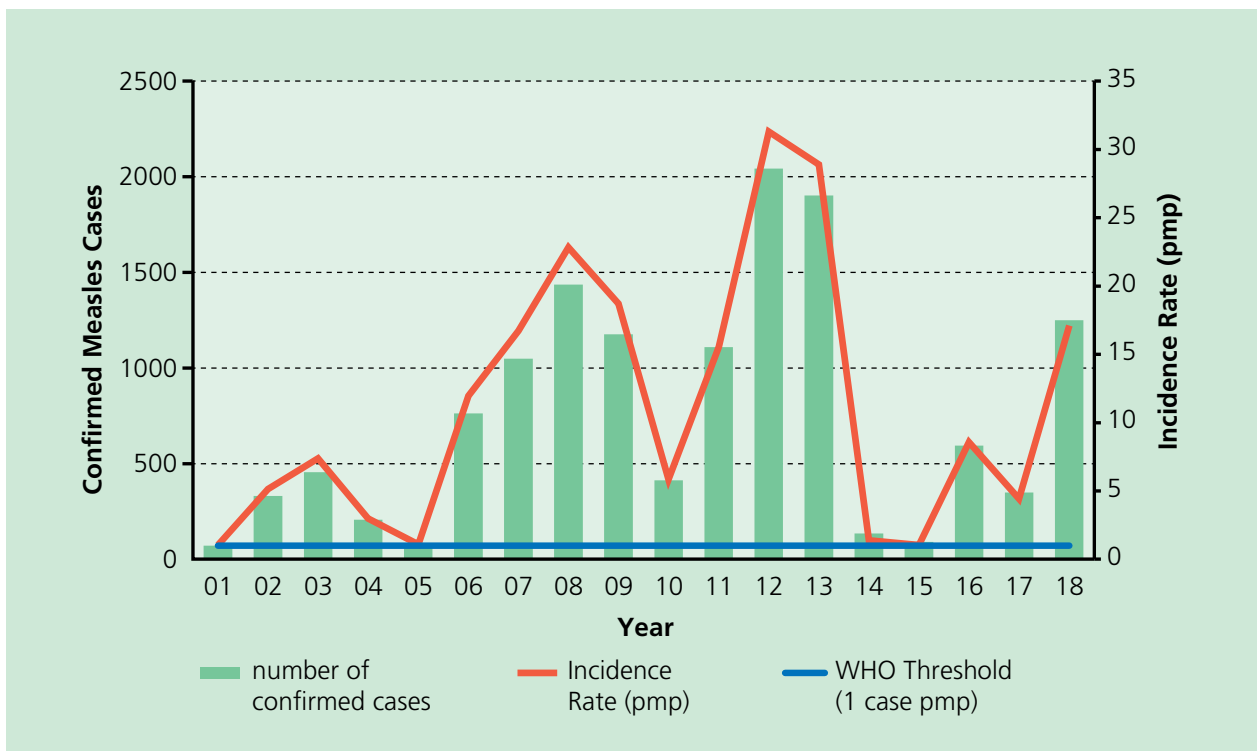
Because of the substantial reduction in measles transmission in the UK, children were no longer exposed to measles infection and, if they had not been immunised, they remained susceptible to an older age. Seroprevalence studies confirmed that a higher proportion of school-age children were susceptible 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. A single dose of measles-containing vaccine is at least 95% effective in preventing clinical measles (Demicheli V, *et al*, 2012). A second dose of measles-containing vaccine protects those who do not respond to the first dose (Wichmann O *et al* 2006). In order to eliminate measles, the World Health Organization (WHO) recommends two doses of a measles-containing vaccine (see: <http://www.who.int/immunization/diseases/measles/en/>).

In the late 1990s and early 2000s national vaccine coverage at two years of age dropped to below 80% for one dose of MMR due to widespread concern around the discredited link between the vaccine and autism. During this period, endemic transmission of measles remained interrupted, although the fall in coverage led to an increase in the number of susceptible children, with the potential for a large outbreak particularly in cities. A catch-up campaign targeting primary school-age children in London was launched in 2004/05. Measles cases continued to rise and in 2006 endemic transmission was re-established. In 2008, a nationwide catch-up programme for MMR vaccination for children of all ages from 13 months to 18 years (and those aged over 18 going on to further education) was implemented in England which led to a decrease in incidence, although there remained a significant proportion of susceptible children in teenage cohorts.



Measles

Figure 21.2. Annual number of laboratory confirmed measles cases and incidence\* from 2001 to 2018 (n=13,451), UK.

\* Incidence rate = confirmed measles cases / mid-year UK population. This excludes imported cases. Pmp = per million population.

In 2012 and early 2013 there was again an increasing number of reported cases, despite the highest ever national MMR vaccination level being achieved in two year olds in England. This was thought to be mostly attributable to the proportion of unprotected 10-16 year olds who missed out on vaccination in the late 1990s and early 2000s. In May 2013 a further national catch-up programme to increase MMR uptake in teenagers was commenced in England. Following on from the catch-up campaign in 2013 low case numbers were reported in 2014 and 2015.

By 2014, the UK had again interrupted endemic transmission of measles and in 2016 the WHO Regional Verification Committee (RVC) declared the UK had eliminated endemic measles. In England, vaccine coverage of the first MMR dose evaluated in 5 year olds reached the WHO 95% target for the first time in 2016/17. Annual vaccine coverage estimates for MMR1 at age two have been decreasing slowly since 2013/14, and the RVC declared that measles transmission had been re-established in the UK in 2018.

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 then, up until 2017 there have been another three deaths due to acute measles infection.

The reduced incidence of measles, brought about by immunisation, has also resulted in a major reduction in SSPE in England and Wales. In the early 1970s, when an SSPE Register was set up, 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 the late 1990s and early 2000s (Campbell *et al.*, 2007). There have been fewer than five cases of SSPE in individuals with presumed UK measles acquisition diagnosed in the last 10 years. 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 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<sub>50</sub> (CCID<sub>50</sub>) of live attenuated measles virus (Schwarz strain)
- not less than  $10^{3.7}$  CCID<sub>50</sub> of live attenuated mumps virus (RIT 4385 strain, derived from Jeryl Lynn strain)
- not less than  $10^{3.0}$  CCID<sub>50</sub> of live attenuated of rubella virus (Wistar RA 27/3 strain)

**M-M-RVaxPRO®**

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

- $1 \times 10^3$  CCID<sub>50</sub> of the live attenuated measles virus (Enders' Edmonston strain)
- $12.5 \times 10^3$  CCID<sub>50</sub> of live attenuated mumps virus (Jeryl Lynn™ [Level B] strain)
- $1 \times 10^3$  CCID<sub>50</sub> of live attenuated 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.

MMRVaxPRO contains gelatine of porcine origin as a stabiliser. Priorix may therefore be offered to individuals of Muslim origin (Jewish law accepts the use of porcine products in injections). Further information is available in the PHE publication [Vaccines and porcine gelatine](#).

**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 (human normal immunoglobulin, HNIG) and those for intravenous use (intravenous immunoglobulin, IVIG). There is currently no accepted minimum level of measles antibody required in normal immunoglobulin and levels of measles neutralising antibodies have declined in recent years. Details of the use of normal immunoglobulin in post-exposure prophylaxis can be found in the [PHE Guidelines on Post-Exposure Prophylaxis for measles](#).

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 can occasionally be scarce.<sup>1</sup> 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 enveloped 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.

1 Normal immunoglobulin for measles prophylaxis can be in short supply from time to time and alternative products and doses may need to be used. For latest advice please check with [Public Health England](#) (PHE) or Health Protection Scotland ([www.hps.scot.nhs.uk](http://www.hps.scot.nhs.uk)).

## Presentation

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

**Priorix** is supplied as a white to slightly pink powder in a glass vial for reconstitution with the solvent supplied in a pre-filled syringe. The reconstituted vaccine must be shaken well until the powder is completely dissolved in the diluent. The reconstituted vaccine may vary in colour from clear peach to fuchsia pink without deterioration of the vaccine potency.

**M-M-RVaxPRO** is supplied as a lyophilised powder in a glass vial for reconstitution with the solvent supplied in a prefilled syringe. The reconstituted vaccine must be shaken gently to ensure thorough mixing. Before mixing with the solvent, the powder is a light yellow compact crystalline cake. When completely reconstituted, the vaccine is a clear yellow liquid 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

### Administration site

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.

### Administration with other vaccines

MMR vaccine can be given at the same time as other vaccines such as DTaP/ IPV, Hib/ MenC, PCV, hepatitis B and Men B. If MMR cannot be given at the same time as an inactivated vaccine, it can be given at any interval before or after. Vaccines administered at the same time should preferably be given in a separate limb, but if this is not possible they should be given at least 2.5cm apart (American Academy of Pediatrics, 2003). The site at which each vaccine is given should be noted in the child's record.

Advice on intervals between live vaccines is based upon specific evidence of interference between vaccines.

The current advice for MMR is detailed in Table 21.1 on page 8.

Table 21.1 Recommended intervals between MMR and other live vaccines

Vaccine combinations	Recommendations
Yellow Fever and MMR	A four-week minimum interval period should be observed between the administration of these two vaccines. Yellow Fever and MMR should not be administered on the same day. <sup>1</sup>
Varicella (and zoster) vaccine and MMR	If these vaccines are not administered on the same day, then a four-week minimum interval should be observed between vaccines. <sup>2</sup>
Tuberculin skin testing (Mantoux) and MMR	If a tuberculin skin test has already been initiated, then MMR should be delayed until the skin test has been read unless protection against measles is required urgently. If a child has had a recent MMR, and requires a tuberculin test, then a four-week interval should be observed. <sup>3</sup>

1. Co-administration of these two vaccines can lead to sub-optimal antibody responses to yellow fever, mumps and rubella antigens (Nascimento *et al*, 2011). Where protection is required rapidly then the vaccines should be given at any interval; an additional dose of MMR should be considered.
2. A Study in the US (Mullooley & Black, 2001) showed a significant increase in breakthrough infections when varicella vaccine was administered within 30 days of MMR vaccine; suggesting that MMR vaccine caused an attenuation of the response to varicella vaccine. When the vaccines are given on the same day, however, the responses have been shown to be adequate (Plotkin *et al*, 2018, Chapter 37) As the zoster (shingles) vaccine contains the same virus as varicella (chicken pox) vaccine, this recommendation has been extrapolated to MMR and zoster. Where protection from either vaccine is required rapidly then the vaccines can be given at any interval and an additional dose of the vaccine given second should be considered.
3. Administering tuberculin (Mantoux) within 28 days of MMR vaccine may result in decreased reactivity of the tuberculin and the false negative reporting of results (Statens Serum Institute, 2011) If tuberculin testing has already been initiated, MMR should be delayed until the skin test has been read. If protection against measles is urgently required, then the benefit of protection from the vaccine outweighs the potential interference with the tuberculin test. In this circumstance, the individual interpreting the negative tuberculin test should be aware of the recent MMR vaccination when consider how to manage that individual.

### Administration with blood products

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.



## Disposal

For disposal of equipment used for vaccination, including used vials, ampoules, syringes or partially discharged vaccines please see [Chapter 3](#).

## 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). A single dose of measles-containing vaccine is at least 95% effective in preventing clinical measles (Demicheli V, *et al*, 2012). After a second dose of measles-containing vaccine protection increases to well above 95% (Wichmann O *et al* 2006). A single dose of a rubella-containing vaccine confers close to 100% protection against laboratory confirmed rubella (Plotkin *et al*, 2018, Chapter 53). A single dose of a mumps-containing vaccine used in the UK confers between 61 and 91% protection against mumps (Plotkin *et al*, 2018, Chapter 40). More recent studies in the UK suggested that a single dose of MMR has lower effectiveness against mumps and that protection declines with age (Harling *et al.*, 2005, Cohen *et al* 2007). A second dose of MMR increases the protection against mumps (Cohen *et al*, 2007) and fully vaccinated cases have a much lower likelihood of suffering complications of disease (Yung *et al*, 2011).

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 from eighteen months. Maternal antibodies may reduce the response to the first dose of vaccination up to the age of 18 months (Orenstein *et al.*, 1986; Redd *et al.*, 2004; De Serres *et al.*, 1995). To provide additional protection to those who fail to respond to the first dose, therefore, the second dose should not routinely be given below 18 months.

Where protection against measles is urgently required, a second dose can be given from one month after the first (ACIP., 1998). If the child is given the second dose at less than 15 months of age, then another routine dose (a third dose) should be given after 18 months in order to ensure full protection, if the child is given the second dose from 15 months of age, no further routine doses are required.

### Children aged ten years or over and adults

All children should have received two doses of MMR vaccine before they enter secondary school to reduce the risk of outbreaks in that setting. The teenage (school-leaving) booster session or appointment is also an opportunity to ensure that unimmunised or partially immunised children are given MMR.

Since the cessation of antibody screening for rubella in pregnancy, it remains important to encourage MMR vaccination of women of child-bearing age – for example at opportunities such as family planning consultations. In addition, unvaccinated or partially vaccinated women who become pregnant should be offered missing doses post-partum, for example at the post-natal check or if they accompany their infant to their routine immunisations. 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, and should be offered opportunistically and promoted to unvaccinated or partially vaccinated younger adults – particularly those born before 1990. New GP registration, and entry into college, university or other higher education institutions, prison or military service also 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 older 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 in the UK 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 measles or rubella, 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

Unless there is a reliable history of appropriate immunisation, individuals should be assumed to be unimmunised. See [chapter 11](#) for more information. 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 (including protection against mumps), they should also 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<sup>2</sup>, or
- positive antibody tests for measles and rubella.

All staff should be up to date with their routine immunisations. See [chapter 12](#) for more information.

### 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 with a high incidence of measles or to an area where there is a current outbreak, who are likely to be mixing with the local population, 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 15 months of age, 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 gelatine
- pregnant women

<sup>2</sup> Or two doses of measles-containing AND two doses of rubella-containing vaccines

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.

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. MMR vaccine should not be delayed or deferred in these groups.

### Idiopathic thrombocytopenic purpura

Idiopathic thrombocytopenic 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 Public Health England (PHE) 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 gelatine) (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. However, as a precaution, MMR vaccine should not be given to women known to be pregnant. When MMR vaccine is given to adult women, they should be advised to guard against pregnancy for one month.

There are no safety concerns, either for the mother or the baby, when rubella-containing vaccine is given in pregnancy or shortly prior to pregnancy. Women who have been

immunised with MMR or single rubella vaccine in pregnancy can be immediately reassured (see “[MMR vaccine: advice for pregnant women](#)”). Such an incident would not be a reason to recommend termination of pregnancy (Tookey *et al.*, 1991). Surveillance of inadvertent MMR administration in pregnancy is being conducted by the PHE 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 who are not immunosuppressed or those with moderate immunosuppression (as defined in Table 21.2).

Further guidance for the immunisation of HIV-infected individuals is provided by the British HIV Association (BHIVA; <http://www.bhiva.org/vaccination-guidelines.aspx>) and the Children’s HIV Association (CHIVA; <http://www.chiva.org.uk/guidelines/immunisation/>).

Table 21.2 CD4 count/ $\mu$ l (% of total lymphocytes)

Age	<12 months	1–5 years	6–12 years	>12 years
No suppression	$\geq 1500$	$\geq 1000$	$\geq 500$	$\geq 500$
	( $\geq 25\%$ )	(15–24%)	( $\geq 25\%$ )	( $\geq 25\%$ )
Moderate suppression	750–1499	500–999	200–499	200–499
	(15–24%)	(15–24%)	(15–24%)	(15–24%)
Severe suppression	<750	<500	<200	<200
	(<15%)	(<15%)	(<15%)	(<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 may be deferred for a short time until the condition has stabilised or diagnosed. If there is a risk of exposure, however, it may be more appropriate to counsel the patient about the benefits of protection rather than deferring. 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 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 *et al.*, 2018, Chapter 37). 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, and isolated cases have been reported in children with underlying immunosuppressive disorders. A 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). There have not been recent studies, but isolated cases of encephalitis associated with measles immunisation have been observed in children who were found to have underlying primary immunodeficiency, but none in otherwise healthy children.

Immune Thrombocytopaenia (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).

Anyone can report a suspected adverse reaction to the Medical and Healthcare products Regulatory Agency (MHRA) using the Yellow Card reporting scheme (<https://yellowcard.mhra.gov.uk/>). All suspected adverse reactions to vaccines occurring in children, or in individuals of any age after vaccination with vaccines labelled with a black triangle (▼), should be reported to the MHRA 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**

Evidence refutes the suggestion that measles-containing vaccines (including MMR) can cause Guillain-Barré syndrome (GBS). 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).

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 the past, a link between measles vaccine and bowel disease has been postulated and dismissed by the evidence. 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 was observed after 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 (<http://www.ncbi.nlm.nih.gov/books/NBK25344/>). 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)
- that no evidence of a link between vaccines and autism was detected in a recent meta-analysis of case-control and cohort studies (Taylor *et al.*, 2014)

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 (Andrews N, *et al.*, 2019).

## Management of cases, contacts and outbreaks

### Diagnosis

Prompt notification of measles, mumps and rubella to the local health protection team 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, the minority of 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 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). Oral fluid samples should be obtained from all notified cases. Advice on this procedure can be obtained from the local health protection team.



Pregnant women with rash illnesses, or contact with rash illnesses should be managed as per PHE guidance here:

<https://www.gov.uk/government/publications/viral-rash-in-pregnancy>

### **Protection of contacts with MMR**

As vaccine-induced measles antibody develops more rapidly than that following natural infection, MMR should be offered to any exposed healthy individual who is unvaccinated or incompletely vaccinated, and has not had measles in the past. 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 most 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.

Where immediate protection against measles is required, for example following exposure, MMR may be given from six months of age. (<https://www.gov.uk/government/publications/measles-post-exposure-prophylaxis>). 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 15 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. Details of the use immunoglobulin for post-exposure prophylaxis are found in the PHE Guidelines on Post-Exposure Prophylaxis for measles (<https://www.gov.uk/government/publications/measles-post-exposure-prophylaxis>)

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 <https://www.gov.uk/government/publications/measles-post-exposure-prophylaxis>). 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 <https://www.gov.uk/government/publications/measles-post-exposure-prophylaxis>)

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 (see <https://www.gov.uk/government/publications/measles-post-exposure-prophylaxis>). 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. (<https://www.gov.uk/government/publications/viral-rash-in-pregnancy>)

### Dosage of normal immunoglobulin

Details are to be found in the PHE Guidelines on Post-Exposure Prophylaxis for measles (<https://www.gov.uk/government/publications/measles-post-exposure-prophylaxis>)

## Supplies

### MMR vaccine

- M-M-RVaxPRO – manufactured by Merck Sharp and Dohme Ltd
- Priorix – manufactured by GlaxoSmithKline UK

Centrally purchased vaccines for the NHS as part of the national immunisation programme can only be ordered via ImmForm ([immform.dh.gov.uk](http://immform.dh.gov.uk)). Vaccines for use as part the national immunisation programme are provided free of charge.

Vaccines for private prescriptions, occupational health use or travel are NOT provided free of charge and should be ordered from the manufacturers. Further information about ImmForm is available at <https://www.gov.uk/government/collections/immform>, from the ImmForm helpdesk at [helpdesk@immform.org.uk](mailto:helpdesk@immform.org.uk) or Tel: 0844 376 0040.

In Scotland, supplies should be obtained from local childhood vaccine-holding centres. Details of these are available from Scottish Healthcare Supplies

(Tel: 0131 275 6725).

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: 028 9442 4089).

## Human normal immunoglobulin

### Subcutaneous human normal immunoglobulin (HNIG)

England and Wales

Subgam HNIG can be issued by the Rabies and Immunoglobulin Service (RIGS) at PHE Colindale and other PHE stockholders., Tel. 020 8327 6204 (<https://www.gov.uk/government/publications/immunoglobulin-when-to-use/rabies-and-immunoglobulin-rigs-changes-to-the-current-service>). Other HNIG products are available from local hospital pharmacies.

Scotland

Health Protection Scotland, Glasgow (0141 300 1100)

Northern Ireland

Belfast Health and Social Care Trust, Royal Victoria Hospital Pharmacy Department Tel. (028)9032 9241 (via switchboard and ask for Royal Pharmacy)

### Intravenous normal immunoglobulin

Applications for supply will need to go through the hospital pharmacist.

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