

12

Measles

Measles vaccine introduced in 1985/ MMR introduced in 1988

NOTIFIABLE

In some circumstances, advice in these guidelines may differ from that in the Summary of Product Characteristics of the vaccines. When this occurs, the recommendations in these guidelines, which are based on current expert advice from NIAC, should be followed.

Introduction

Measles is an acute viral illness caused by a morbillivirus of the paramyxovirus family. There is only one antigenic type, with a number of genotypes. Humans are the only known host. Both infection and appropriate immunisation confer long-lasting immunity.

One case of measles can infect 15-20 unvaccinated people. A vaccine uptake rate of at least 95% with 2 doses is therefore required to halt endemic transmission of the virus and thus eliminate measles.

Measles vaccination resulted in a 79% drop in measles deaths between 2000 and 2010 worldwide. In spite of this drop, measles remains an important cause of vaccine-preventable death worldwide. In 2014, there were 114 900 measles deaths globally – about 314 deaths every day or 13 deaths every hour.

In 2014, about 85% of the world's children received one dose of measles vaccine by their first birthday through routine health services – up from 73% in 2000. During 2000-2014, measles vaccination prevented an estimated 17.1 million deaths making measles vaccine one of the best buys in public health.

The World Health Organization (WHO) target date for the interruption of endemic measles and rubella virus transmission for >12 months was 2015 and 2018 is the target data for the elimination of measles and rubella in Europe.

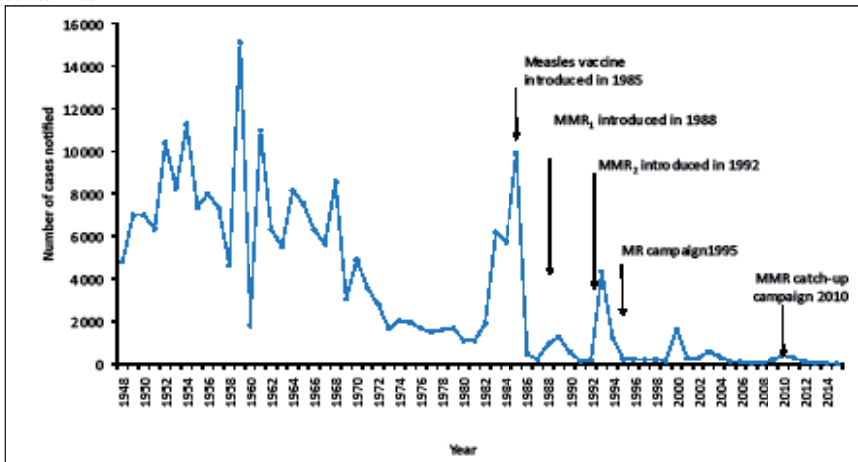
Epidemiology

Measles is a notifiable disease and information on its incidence in Ireland is available since 1948. Between 1948-1984 an average of more than 5,000 cases were reported annually. The incidence in Ireland declined dramatically after the introduction of monocomponent measles vaccine in 1985, from 10,000 cases in that year to 201 cases in 1987. In 1988 a combined measles, mumps and rubella vaccine (MMR) was introduced for children aged 12-15 months. In 1992 a second dose of MMR was recommended to be given at 10-14 years of age. In 1995 a measles and rubella (MR) vaccination catch-up campaign was carried out. In 1999 the age for the second dose of MMR was reduced to 4-5 years. In 2010 a MMR vaccination catch-up campaign for children in the senior cycle (last three years) of second level schools was undertaken in response to a national mumps outbreak.

An outbreak of measles in 1993 affected more than 4,000 people and in 2000 over 1,600 cases of measles were reported, with 3 associated deaths. Additional local and national outbreaks have occurred since then, predominantly affecting sub groups of the population with low vaccination coverage (Figure 12.1).

Figure 12.1 Number of measles notifications in Ireland, 1948-2015.

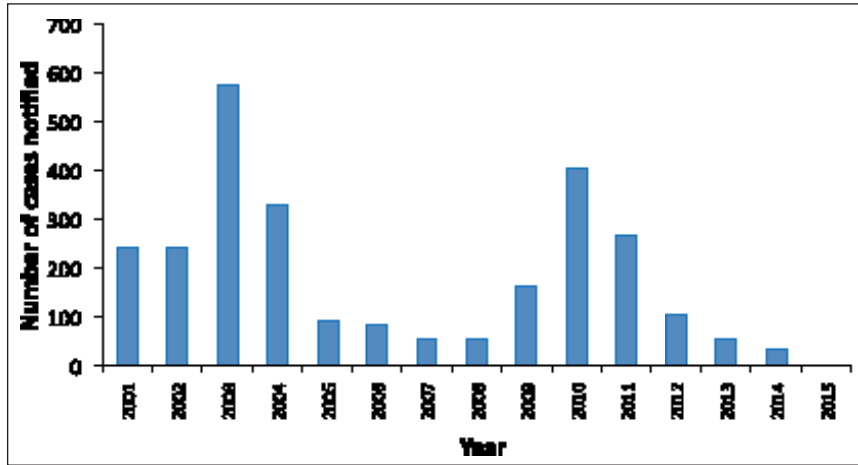
Source: HPSC



From 2001-2015 there were 2,693 cases of measles notified in Ireland. Incomplete vaccine coverage together with a pool of susceptible unvaccinated older children resulted in rapid spread of the infection during these outbreaks (Figure 12.2).

Figure 12.2 Number of measles notifications in Ireland, 2000 - 2015.

Source: HPSC



Transmission of measles is by airborne or droplet infection. The virus can remain viable on infected surfaces for up to 2 hours.

The incubation period from exposure to prodrome averages 10-12 days, and from exposure to rash onset averages 14 days (range 7-21 days). The prodrome (before rash onset) usually lasts 2-4 days (range 1-7 days). Patients are infectious from 4-5 days before to 4 days after the onset of rash.

Effects of measles

The prodromal phase is characterised by fever, malaise, rhinitis (coryza), conjunctivitis and cough. The erythematous and maculopapular rash first appears behind the ears and spreads to the face, trunk and limbs over 3-4 days. The rash may become confluent in places. It begins to fade after 3-4 days, leaving a temporary brownish discolouration. Koplik's spots, which are small red spots with blueish-white centres, may appear on the buccal mucosa near the exit of the parotid duct, opposite the maxillary 2nd molar, from 1-2 days before to 1-2 days after the rash appears.

Approximately 30% of measles cases have one or more complications, which are more common in children under 5 years of age and in adults over 20 years of age. These complications include pneumonia (1-6%), otitis media

Chapter 12 Measles

(7-9%), diarrhoea (8%), convulsions (0.5%) and encephalitis (0.1%). Transient immune deficiency can occur, with decreased numbers of CD4 T cells in lymphoid tissue for weeks and leucopenia for about a week.

There are three types of measles encephalitis:

1. Acute demyelinating encephalomyelitis occurs about one week after the onset of the rash in approximately 1/1,000 cases, has a mortality of about 15% and results in residual neurological sequelae in 20-40% of survivors.
2. Measles inclusion body encephalitis, a delayed type of encephalitis, occurs in immunocompromised persons. It can occur without a preceding measles-like illness, and is characterised by acute neurological compromise, loss of consciousness, seizures and progressive neurological damage.
3. Sub-acute sclerosing panencephalitis (SSPE), a degenerative CNS disease progressing to death. If measles infection occurs in children under 2 years of age the rate of SSPE is 1 in 8,000. If infection occurs in children under 1 year of age, the risk of SSPE is 16 times greater than with infection occurring over 5 years of age.

Death occurred in 1 in 500 notified cases in Ireland in the outbreak of 2000. The case fatality rate is highest in children under 1 year of age, lowest in those aged 1-9 and rises again in teenagers and adults. Pneumonia accounts for 56-86% of measles-associated deaths.

Complications and mortality rates are high in the immunocompromised, the malnourished and in those with vitamin A deficiency. Severe complications may occur in up to 80% of these persons, with case-fatality rates of 70% in persons with cancer. Measles is the most important cause of blindness in children with borderline vitamin A levels, by precipitating xerophthalmia.

Modified measles occurs primarily in those who receive immunoglobulin as post-exposure prophylaxis or in infants with residual maternal antibodies. It is characterised by a prolonged incubation period, mild prodrome and a sparse, discrete rash of short duration. A similar illness has been reported in previously vaccinated persons.

Measles vaccine

Measles vaccine is only available as MMR (Measles, Mumps and Rubella vaccine). The vaccine contains live attenuated measles, mumps and rubella viruses which are cultured separately and mixed before lyophilisation.

Approximately 95% of individuals develop immunity to measles after 1 dose of a measles containing vaccine. Two doses give protection in about 99% of

people. Serological and epidemiological evidence indicates that vaccine-induced immunity is possibly lifelong.

Lower rates of seroconversion occur in those under 12 months of age, because of maternal antibodies.

Laboratory investigation to determine vaccine response is not routinely recommended.

An up-to-date list of licensed vaccines can be accessed on the HPRA website www.hpra.ie

A list of the vaccines currently available from the National Cold Chain Service can be found at www.immunisation.ie

MMR does not contain thiomersal or any other preservatives. It must be kept refrigerated at +2 to +8°C, and protected from light. It should be used within 1 hour of reconstitution. Failure to adhere to these recommendations can result in loss of vaccine potency and diminished effectiveness.

If a vaccine has been frozen it should not be used.

There is no evidence to recommend or support the use of single vaccines against measles, mumps and rubella instead of the combination MMR vaccine.

Dose and route of administration

The dose is 0.5 ml by intramuscular injection into the deltoid or the anterolateral thigh.

Alcohol swabbing of the injection site should be avoided as alcohol can inactivate the MMR vaccine. If an alcohol swab is used injection should be delayed for 30 seconds to ensure the alcohol will have evaporated.

MMR vaccine may be given at the same time as any other vaccine (except yellow fever vaccine).

There must be an interval of 4 weeks between the administration of MMR and varicella or zoster vaccines if they are not given at the same time.

Indications

1. All children at 12 months of age, with a second dose at 4-5 years of age. Where protection against measles is urgently required the second dose can be given 1 month after the first. If children aged under 18 months are given the second dose less than 3 months after the first dose, they need a third dose at 4-5 years to maximise the response and to ensure full protection.

MMR vaccine can be given to those who have a history of measles, mumps or rubella infection.

Children receiving their first dose of MMR vaccine at 4-5 years should be given a second dose one month later.

Older unvaccinated children should be given MMR vaccine as soon as possible and a second dose one month later.

Children aged 6-11 months of age, travelling to other countries and regions where measles outbreaks are reported, are recommended MMR vaccine (see below). A dose given before 12 months of age does not replace the dose that would normally be given at 12 months of age.

2. Measles outbreaks

Outbreaks of measles should be controlled by immunising all susceptible individuals within 72 hours of contact, as vaccine - induced immunity develops more rapidly than that following infection.

- If these persons have had no previous measles vaccine, a second dose is given one month later.
 - During an outbreak, particularly if there are high attack rates in younger infants, MMR vaccine may be given to infants as young as 6 months of age. However, maternal antibodies may compromise the response to the vaccine. Therefore infants vaccinated before their first birthday should have a repeat vaccination at 12 months of age, at least 1 month after the first vaccine, with a further dose at 4-5 years of age.
 - Some persons may require HNIG (see below).
3. Children and adults of migrant or ethnic minority groups or coming from low resource countries are less likely to have been vaccinated with MMR. Without documented evidence of measles vaccination they should be offered two doses of MMR vaccine one month apart.

- All health care workers, both clinical and non-clinical, who have direct patient contact should be immune to measles (See Chapter 4).

This applies to roles in which:

- work requires face to face contact with patients, or
- normal work location is in a clinical area such as a ward, emergency department or outpatient clinic, or
- work frequently requires them to attend clinical areas.

Presumptive evidence of immunity to measles is:

- written documentation of vaccination with 2 doses of MMR vaccine at least 1 month apart

or

- serological evidence of prior measles exposure (i.e. detectable measles specific IgG in blood) from an Irish National Accreditation Board (INAB) accredited laboratory.
- Most individuals born before 1978 are likely to have had measles infection. MMR vaccine should be offered to such individuals on request if they are considered at high risk of exposure.

Serological testing after routine vaccination is not recommended.

When measles outbreaks occur, susceptible persons should be given MMR within 72 hours of contact with a case.

Antibody response to the mumps and rubella components of the MMR vaccine *does not* develop quickly enough to provide effective prophylaxis after exposure to suspected mumps or rubella.

Contraindications

- Anaphylaxis to any of the vaccine constituents.
- Significantly immunocompromised persons, such as those with untreated malignant disease and immunodeficiency states other than HIV infection, and those receiving immunosuppressive therapy, high-dose x-ray therapy and current high-dose systemic corticosteroids (see Chapter 3).
- Pregnancy. Furthermore, pregnancy should be avoided for 1 month after MMR.
- MMR should not be administered on the same day as yellow fever vaccine as co-administration of these two vaccines can lead to suboptimal

antibody responses to mumps, rubella and yellow fever antigens. If rapid protection is required then the vaccines should be given on the same day or at any interval and an additional dose of MMR should be given.

The following are NOT contraindications to MMR vaccine

1. Allergy to egg, including anaphylaxis following egg. Currently-used measles, mumps and rubella vaccines do not contain significant amounts of egg cross-reacting proteins and recent data suggest that anaphylaxis following MMR is not associated with hypersensitivity to egg antigens but to other vaccine components (Gelatin or Neomycin).
2. Breast-feeding.
3. HIV-positive patients who are not severely immunocompromised (see Chapter 3).
4. Personal or family history of convulsions.
5. Immunodeficiency in a family member or household contact.
6. Uncertainty as to whether a person has had 2 previous MMR vaccines.
7. If women have received anti-RhD immunoglobulin it is not necessary to defer MMR vaccination as the response to the vaccine is not affected.
8. Hereditary fructose intolerance.

Precautions

1. Acute severe febrile illness, defer until recovery.
2. Injection with another live vaccine within the previous 4 weeks.
3. Recent administration of blood or blood products.

Blood and blood products may contain significant levels of virus-specific antibodies, which could prevent vaccine virus replication. MMR should be deferred for at least 5 months after receipt of low-dose HNIG, 6 months after packed red-cell or whole-blood transfusion and 11 months after high-dose HNIG (as used for e.g. Kawasaki Disease) see Chapter 2 Table 2.4. If the MMR vaccine is administered within these timeframes, a further 1 or 2 doses as required, should be given outside these times.

4. Tuberculin skin testing should be deferred for at least 4 weeks after MMR vaccine as the measles vaccine can reduce the tuberculin response and could give a false negative result.
5. Patients who developed thrombocytopenia within 6 weeks of their first dose of MMR should undergo serological testing to decide whether a second dose is necessary. The second dose is recommended if the patient is not fully immune to the 3 component viruses.

6. Topical tacrolimus and other topical immunomodulators should be discontinued for 28 days before and not restarted until 28 days after the administration of MMR vaccine.

Adverse reactions

Local: Soreness and erythema may occur at the injection site (3-8%).

General: Fever (6%), rash (7%), headache, vomiting and salivary gland swelling may occur. A febrile convulsion occurs in 1 in 1,000 children.

'Mini-measles' may occur 6-10 days after immunisation and consists of mild pyrexia and an erythematous rash. 'Mini-mumps' with salivary gland swelling may rarely occur during the third week after immunisation. Very rarely, anaphylaxis, erythema multiforme, thrombocytopenia and nerve deafness have been reported.

The rubella component may occasionally produce a rash, mild arthralgia, and lymph-node swelling 2-4 weeks post-vaccination, particularly in post-pubertal females (up to 25% of recipients). The incidence is lower than after natural disease.

There is no evidence of congenital rubella syndrome or increase in other teratogenic effects in women inadvertently given rubella vaccine during pregnancy, but pregnancy remains a contraindication.

Significant adverse reactions are considerably less common (under 1%) after a subsequent dose of MMR.

Scientific evidence confirms no association between the MMR vaccine and autism or inflammatory bowel disease.

Post Exposure Prophylaxis of Measles

This advice is based on the following premises:

1. An exposure to measles is considered significant if:
 - a susceptible individual is exposed to a confirmed or probable case of measles who is infectious at the time of exposure (i.e. four days before to four days after rash onset) in any of the following ways:
 - there is face-to-face contact of any duration
 - an immunocompetent individual is in a room with the case for more than 15 minutes
 - an immunocompromised person is in the room with an case for any

duration or enters a room vacated by a case within two hours of the case leaving the room

Note: *Within this section the term 'exposure' refers to a 'significant' exposure as defined above.*

2. Certain groups are at increased risk for severe illness and complications including:
 - infants younger than 12 months of age
 - pregnant women without measles immunity
 - people with severe immunocompromise
3. Household contacts of a case have a higher intensity exposure and an increased risk of more severe disease than non-household contacts.
4. Most Irish-born mothers born after 1985 (when routine measles vaccination was introduced) are unlikely to have had measles infection. The levels of transplacentally acquired antibodies in infants born to vaccinated mothers tend to be lower than in infants of mothers who had natural infection and to wane more rapidly, usually declining within weeks of birth. If mothers have had measles infection, maternal antibodies may protect the infant for a few months after birth.
5. Immunity from MMR vaccine develops more rapidly than immunity from infection and thus MMR vaccine can be successfully used to prevent infection following exposure. When used for prophylaxis, MMR vaccine should be given within 72 hours of exposure.
6. Because maternal antibodies can interfere with an infant's response to MMR vaccine for up to 9 and possibly 11 months of age, infants who received MMR vaccine when under 12 months of age need two **additional** doses of MMR vaccine, at 12 months and 4-5 years of age, in accordance with the national schedule.
7. Human Normal Immunoglobulin (HNIG) contains sufficient anti-measles antibodies to be able to prevent or ameliorate infection in susceptible persons. It is available for subcutaneous, intramuscular or intravenous (IVIG) use. Ideally it should be given within 72 hours of exposure, but may provide some protection if given within 6 days of exposure.

Post exposure prophylaxis of vulnerable measles contacts with significant exposure:

1. Infants (see Table 12.1)

- aged <6 months should receive HNIG, ideally within 72 hours of exposure. HNIG can be given with potential benefit up to 6 days following exposure.

- aged 6 to <9 months
 - who are exposed in household or household type settings should receive HNIG.
 - who are exposed in non-household settings are less likely to have the intensity of exposure to develop severe disease. They should receive MMR vaccine within 72 hours of exposure. If MMR vaccine cannot be given within 72 hours of exposure, HNIG should be considered.
- aged 9 months or older (household or non-household exposure) should receive MMR vaccine as the response to MMR vaccine is improved at this age.

Table 12.1. Assessment and management of infants with significant exposure to measles

Age	Management	
< 6 months	Assume susceptible regardless of maternal status Give HNIG ideally within 72 hours (can be given up to six days after exposure)	
6 – <9 months	Household or household type exposure Give HNIG ideally within 72 hours (can be given up to six days after exposure) ¹	Non-household exposure Give MMR vaccine, ideally within 72 hours. If not possible to give MMR vaccine in a timely fashion, consider HNIG up to 6 days post exposure ²
≥ 9 months	Administer MMR vaccine, ideally within 72 hours of exposure ²	

¹ Children who have received HNIG should wait 6 months before subsequent MMR vaccination.

² If MMR vaccine is given <12 months of age, two further doses are required, at 12 months (at least 4 weeks after 1st dose) and 4-5 years of age.

Where post-exposure vaccination is indicated (Table 12. 1) MMR vaccine should ideally be given within three days of exposure. Where exposure is likely to be ongoing (for example following a single case in a nursery or during a community outbreak), MMR vaccine offered beyond three days may provide protection from subsequent exposures.

2. Pregnant mothers

HNIG should be administered (ideally within 72 hours of exposure) to pregnant women without evidence of measles immunity who have had significant exposure to measles. Women with measles IgG titres reported as 'positive' or 'weak positive' can be considered protected and do not need HNIG.

3. Immunocompromised persons

Most immune suppressed individuals can maintain protective antibodies from prior vaccination or natural infection and can be managed based on history of natural infection or prior measles antibody test results.

Immunosuppression is likely in the following: individuals on high dose steroid therapy or who received high dose steroids in the preceding 3 months, adults on methotrexate >25mg/week, azathioprine >3.0mg/kg/day, cyclosporine, cyclophosphamide or leflunomide or children who have received any of these drugs.

If prior documentation of measles immunity is available, post exposure prophylaxis is not required. If no such documentation is available, urgently assess serologic status and give post exposure HNIG prophylaxis to exposed individuals who are antibody negative.

People with leukaemia, lymphoproliferative disorder, or post solid organ transplant, who are more than 12 months post haematopoietic stem cell transplant (HSCT) or 6 months following completion of biologic therapies, or who have AIDS may lose protective antibodies over time. They should be urgently assessed for measles immunity at the time of exposure regardless of past vaccination history or serologic test result. If measles IgG is detected, post exposure prophylaxis is not required. If seronegative offer post exposure prophylaxis with IVIG.

Exposed individuals with **severely** compromised immune systems, i.e. those who have received a HSCT within the preceding 12 months and those with severe primary immunodeficiency, should receive **IVIG, not IM or SC HNIG**, regardless of immunologic or vaccination status.

Immunocompromised patients who are regular recipients of immunoglobulin therapy do not require additional prophylaxis if they have received a dose of HNIG within 3 weeks prior to exposure.

NB: Post-exposure prophylaxis with HNIG or MMR vaccine is not always fully effective in preventing measles infection. Therefore, exposed persons who receive post-exposure prophylaxis remain an infection control risk within the health care system. They should be managed in accordance with usual infection control procedures following a measles exposure.

HNIG

Although HNIG products are not licensed for post exposure prophylaxis, use of HNIG has proven effective in preventing or attenuating measles if given early following exposure.

HNIG products available for measles case contacts include:

1. **Subgam** (BPL), 160g/L.

This is available from the HSE National Cold Chain Service.

Subgam can be administered subcutaneously or intramuscularly.

Subcutaneous administration is preferable because large volumes may be required. This product should **never** be given intravenously.

Always consult the product literature for information about administration before usage.

2. **Subcuvia** (Baxalta), 160g/L. (available from manufacturer).

Subcuvia can be administered subcutaneously or intramuscularly.

Subcutaneous administration is preferable because large volumes may be required. This product should **never** be given intravenously.

Always consult the product literature for information about administration before usage.

A number of other HNIG preparations are available, including **Gammanorm** and **Cuvitru** and are likely to contain similar levels of measles antibodies.

Dosage of HNIG (160g/L):

Infants under 1 year of age: 0.6 ml/kg up to maximum of 1 vial (5 ml)

Pregnant women: 15ml (generally 3 vials)

IVIG

If SC or IM HNIG is not available, in certain high-risk situations IVIG can be substituted.

IVIG is the preferred immunoglobulin product for use in the immunocompromised patient.

A number of different IVIG products (e.g. **Kiovig**, **Flebogamma**, **Intratect**) are licensed for use in Ireland and are generally available through hospital pharmacies.

Dosage of IVIG:

A minimum of 0.15g/kg (can round up to use all of the vial).

Higher doses (0.4 – 0.5g/kg) are generally used for replacement therapy.

Always consult the product literature for information about product usage and administration.

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