Post-measles exposure Immunoglobulin Pathway

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Introduction

Measles is an acute, highly contagious viral infectious disease. Infectivity is close to 100% in susceptible individuals and in the pre-vaccine era measles would affect nearly every individual during childhood[1]. Immunisation has dramatically reduced the incidence of measles in Europe but despite overall high immunisation coverage, measles continues to cause frequent outbreaks.

Globally in 2023, large numbers of measles cases were reported in Yemen, Azerbaijan, Kyrgyzstan Kazakhstan, Liberia and Gabon[2]. In Europe, there have been increasing numbers of measles cases notified since the beginning of 2023. Outbreaks were reported in France, Romania, Austria and the UK[3].

The clinical course of measles infection is characterised by a prodromal phase with fever, significant malaise, anorexia, rhinitis, conjunctivitis and cough. The prodromal symptoms typically intensify a few days before the rash appears. The erythematous, maculopapular rash first appears behind the ears and spreads to the face, trunk and limbs over 3-4 days. Koplik spots (small red spots with white centres) may appear on the buccal mucosa near the exit of the parotid duct, 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 those aged <5 and >20 years of age[4].

Measles is extremely communicable, and it is estimated that almost 100% of non-immune people exposed to an infective individual will contract the disease. The virus is transmitted from person to person via respiratory droplets produced when infected sick people cough and sneeze. Virus-containing droplets can remain in the air for several hours and the virus remains infectious on contaminated surfaces for up to two hours [4].

Immunisation is the only effective preventive measure against acquiring measles. Measles vaccine is at least 95% effective and seroconversion rates are close 100%. Experience and modelling shows that two doses of measles vaccine is required to interrupt indigenous transmission and achieve herd immunity.[1] Measles vaccine in Ireland is given as part of the combines Measles, Mumps and Rubella (MMR) vaccine. Two doses of MMR vaccine are included in the childhood immunisation schedule in Ireland:[4]

- Dose 1, given at 12 months of age in general practice
- Dose 2, given at 4-5 years of age in junior infants in Primary Schools, by HSE school immunisation teams.[1]

[1] In Sligo, Leitrim and Donegal, the second MMR dose is given in general practice

Current situation in Ireland

Measles is a notifiable infectious disease in Ireland[5]. Clinicians and clinical directors of laboratories are required to immediately notify the local Medical Officer of Health once they suspect a case of measles. For the most up to date information on measles epidemiology in Ireland, visit https://www.hpsc.ie/a-z/vaccinepreventable/measles/surveillancereports/ . Public Health continue to investigate a number of possible cases.

Post exposure prophylaxis of measles

Following the notification of a laboratory confirmed or clinically suspect case of measles, Public Health will undertake a risk assessment. Part of this risk assessment will be to identify contacts of the case who are non-immune, and have had significant exposure to measles and therefore, should be offered post-exposure prophylaxis. Exposure to measles is considered significant if a susceptible individual is exposed to a confirmed or probable case of measles during the infectious period (four days before to four days after rash onset) in any of the following ways:[4]

- Face-to-face contact of any duration.
- An immunocompetent individual is in a room with the case for more than 15 minutes. This includes those who, within the preceding six days, may have been exposed to measles in the setting of an emergency department or an outpatient clinic where the intensity of such exposure cannot accurately be judged.
- An immunocompromised person is in a room with the case for any duration or enters a room vacated by a case within two hours of the case leaving the room.

Cohorts at increased risk for severe illness and complications include:

- Infants younger than 12 months of age
- Pregnant women without measles immunity
- Those who are severely immunocompromised
- Household contacts of a case have higher intensity exposure and an increased risk of more severe disease than non-household contacts.

There are two types of post-exposure prophylaxis (PEP) available depending on the individuals at risk, MMR vaccine and Human normal immunoglobulin (HNIG). PEP MMR vaccine should be given within three days of measles exposure. Further information on the use of PEP MMR is available in the Measles Chapter of NIAC Guidelines.[4] Immunoglobulin should be administered, where possible, within three days of measles exposure but can be given up to six days post exposure.

Following the Public Health risk assessment, Public Health may advise that contacts from the following cohorts of contacts should be offered post exposure immunoglobulin (PEP IG)[4]:

- Infants aged < 6 months of age
- Non-immune pregnant women
- Immunocompromised individuals

Infants aged < 6 months of age*

Give HNIG SC preferably within 72 hours of exposure but can be given up to 6 days post exposure.

*Immunoglobulin may also be recommended to infants aged 6 to <9 months depending on timing of measles exposure.

Non-immune pregnant women[4]

HNIG SC should be administered to pregnant women without evidence of measles immunity who have had significant exposure to measles. Ideally it should be given within 72 hours of exposure but can be given up to six days. Women with measles IgG titres reported as 'positive' or 'weak positive' are likely to have measles infection induced immunity and do not need HNIG SC.

Additional information on measles exposure in pregnancy is available at https://www.hpsc.ie/a-z/vaccinepreventable/measles/guidance/

Note: If SC or IM HNIG is not available, Intravenous immunoglobulin (IVIG) can be substituted

Immunocompromised individuals**

IVIG is recommended for use in immunocompromised contacts. When providing PEP IG to immunocompromised individuals, consultation with the individual's treating consultant is advised.

**See Appendix A for more information regarding immunocompromised individuals

Referral pathway for post-exposure immunoglobulin

A local pathway for hospital referral for PEP IG should be agreed by Public Health and the treating hospital.

An example is via the Hospital Operational ADON on duty who would identify key clinical team members on duty that day.

List of designated acute hospitals available at https://www.hpsc.ie/a-z/vaccinepreventable/measles/guidance/

Post-exposure Immunoglobulin Pathway

This pathway is intended for use in the provision of PEP IG to sporadic contacts of measles cases. A second pathway will be delivered for use should a large number of contacts require PEP IG simultaneously.

To ensure that the hospital can provide the appropriate service for administration of PEP IG, preparation in advance is required. Each hospital will need to have:

1. Identified suitable location(s) for administration of immunoglobulin.
2. Sufficient SC HNIG/IVIG stock available.
3. Assigned the appropriate medical and nursing team to undertake this task with appropriate training.
4. Cleaning plan for decontamination of the treatment room.
5. Both discharge and escalation plans in place.

This service is required 7 days a week. It is preferable to avoid giving SC HNIG or IVIG for post exposure prophylaxis (PEP) at night. In the event that there is a concern with regard to time frame for administration post exposure, guidance will be provided by the Consultant Microbiologist/Infectious Disease Consultant/Medical Consultant on duty.

1. Location within the hospital

- Depending on the hospital type, each hospital group will need to identify up to three suitable locations for administration of immunoglobulin to the three vulnerable cohorts (see above) as appropriate.
- The identified rooms should ideally be single occupancy cubicle with closed door and preference for en-suite/toileting facility.
- Asymptomatic Immunocompromised individuals will require protective isolation and therefore should be treated in a positive pressure ventilation lobby (PPVL) room where possible. Otherwise, they should be treated in a single room as described above. Vulnerable asymptomatic immunocompetent individuals such as pregnant women and infants aged less than 6 months of age* should be treated in a single cubicle as described above.
- Individuals who present with symptoms of measles should be isolated appropriately immediately and should not receive immunoglobulin.

2. Pharmacy Support

- The hospital pharmacy department should ensure that sufficient stock of IVIG and SC HNIG are available, including outside of usual working hours. There should be clear pathway in place within the hospital on how to access these medications. See Product information for storage requirements. It is important that sub-cutaneous (s/c) giving sets are available to administer HNIG SC. IVIG is administered using a standard IV giving set.

3. Medical and Nursing Team

- Staff immunity to measles will need to be identified and should be available through Occupational Health Department. Where possible staff with immunity to measles should be part of the PEP IG administration team.
- Sufficient appropriate PPE should be available to the medical and nursing team. Refer to NCEC IPC Guidelines for PPE advice linked here.
- A medical doctor should be available to medically review patients attending for administration of PEP IG and to prescribe these medicines.

- Patients will be consented by the medical/nursing team in the usual manner.
- Guidelines should be available on the medical review of these patients as well as on the prescribing of these medications^. For patients who are immunocompromised due to illness or medications, their treating consultant should be contacted to discuss their treatment plan.
- In some instances, two nurses will be required to administer PEP IG. The two-nurse requirement applies particularly to administration of immunoglobulin to infants and children and administration of IVIG.
- The nursing team time requirement will vary depending on the HNIG product used and the individual patient.
- Education and Training will be required for the team administering PEP IG, including mode of administration, possible side effects etc. For administration of PEP IG in children please see the CHI Formulary (Search Clinibee in App store or Play store and follow instructions). If necessary, training on how to administer SC HNIG may be available via the manufacturer. Contact hospital pharmacy for details of manufacturer.
- Guidelines for pre-, during and post-administration monitoring of these patients will be required.

4. *Decontamination of treatment room*

- There should be a plan in place for immediate cleaning of the room post-administration of PEP IG.
- Cleaning staff immunity to measles should be identified and should be available to Department managers. All staff should be aware of their immune status. Where possible cleaning staff with immunity to measles should be deployed for decontamination of a treatment room and be provided with appropriate PPE. Refer to NCEC IPC Guidelines for cleaning and decontamination advice linked here

5. *Discharge planning and escalation plan*

- Each patient should have a discharge plan in place. Patients should be provided with information on measles and on what to do if they develop signs and symptoms of measles.
- All patients should be provided with a GP letter providing information on their treatment.
- A letter should also be provided to the patient's treating consultant.
- Any individual who presents with symptoms of measles should be isolated appropriately immediately, medically assessed and should not receive immunoglobulin. Please notify local MOH at the regional Public Health Department https://www.hpsc.ie/notifiablediseases/whotonotify/
- Patients receiving PEP IG should receive a Patient Information Leaflet – see Appendix B
- An escalation protocol should be available, in the event that:
    - the patient becomes unwell while receiving PEP IG
    - or is unwell on arrival to the hospital.

For additional information on measles guidance, visit https://www.hpsc.ie/a-z/vaccinepreventable/measles/guidance/

List of designated acute hospitals available at https://www.hpsc.ie/a-z/vaccinepreventable/measles/guidance/

References

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4. National Immunisation Advisory Committee. NIAC Immunisation Guidelines. Chapter 12. Measles. Available at https://rcpi.access.preservica.com/uncategorized/IO_3a9e3acb-949b-48e5-a2b5-d353f88bde37/ , accessed 22/03/2024
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6. United Kingdom Health Security Agency. National measles guidelines. February 2024. https://assets.publishing.service.gov.uk/media/65ddd0e9f1cab3001afc4774/national-measles-guidelines-Feb-2024.pdf

Appendix A – Immunocompromised individuals[4,6]

Immunocompromised individuals should receive IVIG.
Immunocompromised individuals may be categorised into three groups:

Group A[4,6]
Most immunosuppressed individuals can maintain protective antibodies from prior vaccination or natural infection and can be managed based on a history of natural infection or prior measles antibody test results. This includes patients with:

- Patients receiving or within 6 months of completing immunosuppressive chemotherapy or radiotherapy for malignant disease (other than those with leukaemia, a lymphoproliferative disorder or who have had haematopoietic stem cell transplantation (HSCT)).
- Patients with human immunodeficiency virus (HIV) infection:
    - i) over 5 years of age and with a CD4 count less than 200 cells/µl (but without a diagnosis of AIDS) or
    - ii) aged 5 years or less, with a CD4 count less than 500 cells/µl
- Patients with chronic immune mediated inflammatory disease who are receiving or have received immunosuppressive therapy:
    - moderate to high dose corticosteroids (equivalent ≥20mg prednisolone per day; children one mg/kg/day) for more than 10 days in the previous month
    - long term moderate dose corticosteroids (equivalent to ≥10mg prednisolone per day or children 0.5 mg/kg/day for more than 4 weeks) in the previous 3 months
    - adults on non-biological oral immune modulating drugs, for example, methotrexate >20mg per week (oral and subcutaneous), azathioprine >3.0mg/kg/day; 6-mercaptopurine >1.5mg/kg/day, mycophenolate >1g/day, in the previous 3 months
    - children on any dose of non-biological oral immune modulating drugs
    - certain combination therapies at individual doses lower than stated above, including those on ≥7.5mg prednisolone per day in combination with other immunosuppressants (other than hydroxychloroquine or sulfasalazine) and those receiving methotrexate (any dose) with leflunomide in the previous 3 months Individuals who have received a short course of high dose steroids (equivalent >40mg prednisolone per day or children 2 mg/kg/day for more than a week) for any reason in the previous month. National measles guidelines January 2024 50
- Individuals who had received brief immunosuppression (≤40mg prednisolone per day) for an acute episode (for example, asthma, COPD or COVID-19) and individuals on replacement corticosteroids for adrenal insufficiency are not considered severely immunosuppressed and can be treated with the standard post exposure treatment.

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 PEP IG to exposed individuals who are antibody negative. Immunoglobulin should ideally be given within three days of exposure but can be given up to six days post exposure.

Group B1[4,6]
There is a cohort of patients who are severely immunocompromised and may not maintain adequate antibody levels following past exposure or vaccination. This includes patients:

- with leukaemia
- with lymphoproliferative disorder
- post solid organ transplant
- patients who are ≥12 months post haematopoietic stem cell transplant (HSCT)

- receiving or within six months of completion of biologic therapies
- with a diagnosis of AIDs.

These patients should be urgently assessed for measles immunity at the time of exposure regardless of past vaccination history or previous serologic test result. If measles IgG is detected, post exposure prophylaxis is not required. If seronegative, offer PEP IG.

Group B2[4,6]

Severely immunocompromised patients including:

- those who have received a HSCT within the preceding 12 months
- those with severe primary immunodeficiency
- patients with persistent agammglobulinaemia (IgG less than 3g/L) due to primary immunodeficiency (for example, common variable immunodeficiency) or secondary to disease or therapy

Group B2 should receive IVIG, 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 immunoglobulin within three weeks prior to exposure.

Additional information available at

- https://assets.publishing.service.gov.uk/media/65ddd0e9f1cab3001afc4774/national-measles-guidelines-Feb-2024.pdf
  Sections 2.2 and Annex 2
- https://rcpi.access.preservica.com/uncategorized/IO_3a9e3acb-949b-48e5-a2b5-d353f88bde37/

Appendix B Patient Information Leaflet

Information for Close Contacts of Measles Cases Who Require Human Normal Immunoglobulin (HNIG)

More information on measles can be found on HSE.ie: https://www2.hse.ie/conditions/measles/

This leaflet is designed for people who have been identified by Public Health as being a contact of someone with measles and may benefit from a treatment called Human Normal Immunoglobulin.

What is Human Normal Immunoglobulin (HNIG)?

A treatment called human normal immunoglobulin (HNIG) can be used if you've come in contact with someone with measles, to prevent measles or to lessen the severity of the symptoms. ***Most people do not need HNIG.*** Public Health can tell you if this treatment is recommended for you.

HNIG is like a short-term boost for the immune system made from healthy people's blood. It contains ***antibodies*** that help fight infections, including measles. If someone is at risk of getting very sick from measles, they can be given HNIG to help their body fight off the virus. It needs to be given within 6 days of exposure.

Who should get HNIG?

Public Health will let you know if you (or your family member) needs HNIG. HNIG is only recommended for people who have a higher risk of complications if they get measles. This includes people in the following groups:

- babies under 6 months of age
- pregnant women who have not been fully vaccinated or have not had measles before
- people with weak immune systems - for example, those with HIV or people receiving treatment that weakens their immune system

How is HNIG given?

HNIG is given as a once-off dose in a healthcare facility. Most people who need HNIG can get it as an injection, either intramuscularly (meaning into the muscle) or subcutaneously (meaning under the skin). Some people may need it given intravenously (directly into the blood stream) via a drip. Public Health or your doctor will tell you which route is right for you (or your family member).

How effective is HNIG in preventing measles?

The effectiveness of HNIG in preventing measles depends on factors such as the timing of administration (it should be given within 72 hours if possible but can be given up to 6 days after exposure) and the individual's immune response. HNIG will not prevent measles infection in everyone, so you should still look out for measles symptoms (see below). If you (or your family member) develop any measles symptoms, stay at home and call your GP for advice.

Vaccination with the MMR vaccine is still the most effective way to prevent measles in those who can get the vaccine. However, babies under 6 months, pregnant women, and people with weakened immune systems will not be able to get the MMR vaccine. People who have been given HNIG should still get the MMR vaccine at a later date once they are eligible (see below).

What are the symptoms of measles to look out for?

The first symptoms of measles are:

- cold-like symptoms such as aches and pains, runny nose, sneezing and cough
- sore, red eyes that may be sensitive to light
- a temperature of 38°C or above (fever), which may reach around 40°C
- small greyish-white spots in your mouth
- loss of appetite
- tiredness, irritability and a general lack of energy

The rash appears around 2 to 4 days after the first symptoms. The rash:

- is made up of small red-brown, flat or slightly raised spots - these may join together into larger blotchy patches
- usually first appears on the head or neck and then spreads outwards to the rest of your body
- is slightly itchy for some people

What are the risks/side effects of HNIG?

As with all medical treatments, there are some potential side effects. However, serious side effects are rare, and public health would not recommend HNIG unless the benefits outweighed the risks.

If you (or your family member) experience any of these side effects after getting HNIG, you should report these to your doctor, or in an emergency call an ambulance.

Common side effects (may occur in 1 in 10 people)	***Uncommon side effects*** (may occur in 1 in 100 people)	***Serious side effects*** (these are very rare)
• headache • diarrhoea, and nausea, abdominal pain • redness, and pain at the site of infusion • tiredness • dizziness, migraine, and drowsiness • decreased blood pressure • itching, and rash • muscular pain • swelling, itching, rash, and bruising at the site of infusion • mild fever	• burning sensation • swelling at the site of infusion • positive blood tests for antibodies • haemolysis (mildly increased breakdown of red blood cells in the blood vessels - rarely this may require a blood transfusion)	• anaphylaxis (an extreme allergic reaction that can cause difficulty breathing, swelling, and low blood pressure) • thrombosis (formation of blood clots) • renal dysfunction (impaired kidney function) • aseptic meningitis (inflammation of the protective membranes covering the brain and spinal cord – this is reversible)

When can I get MMR vaccine if I decide to get post exposure immunoglobulin (HNIG)?

If you are a non-immune pregnant woman or an infant aged < 9 months and have received post exposure immunoglobulin following exposure to measles, you should not get an MMR vaccine for at least 6 months post immunoglobulin.

If you are immunocompromised and have received post exposure immunoglobulin following exposure to measles, you should not get an MMR vaccine for at least 8 months post immunoglobulin.

What will happen if I decide to get HNIG?

Public health will work with doctors in a healthcare facility to arrange for you to receive HNIG. Arrangements will be made for you to be seen in the healthcare facility, without being in a waiting area with other people. You may be asked to wait in your car and ring the clinical team to let them know you have arrived.

The clinical team will see you, and after being assessed you will receive the injection with the HNIG. You will be watched for a short while (approx. 2 hours) after receiving the HNIG. After the monitoring time is over and you are feeling well you will be discharged from hospital.

As you are a contact of a measles case you will still have to follow any Public Health advice you are given. You will be advised to remain at home where possible and stay away from vulnerable people (pregnant women, young babies, and those with weak immune systems) from the time you have been informed to 21 days from last exposure. Children should be kept home from crèche/childcare/school and other non-essential group activities (e.g. parties, play-dates etc.). If you need to be admitted to hospital during this time, you will be isolated.

After receiving the HNIG your risk of getting measles is lower, but you could still get it, so you need to continue to follow public health advice.

You will be asked to keep an eye out for symptoms of measles for 28 days from the last time you were exposed to the measles case. If you think you are getting symptoms seek medical advice (from your GP usually) – ring them first and let them know that you are a contact of a measles case and tell them that you have developed symptoms. They may wish to assess you over the phone or may arrange for you to be seen separately to avoid exposing others.

If you become very unwell or need urgent medical care, do not delay seeking medical attention but ring ahead and let the healthcare setting or emergency services know that you are a contact of measles. If attending antenatal appointments, let your midwife or obstetrician know ahead of time that you are a contact of a measles case.

What will happen if I decide not to get immunoglobulin?

As you are a contact of a measles case you will still have to follow any Public Health advice you are given. You will be advised to remain at home where possible and stay away from vulnerable people (pregnant women, young babies, and those with weak immune systems) from the time you have been informed to 21 days from last exposure. Children should be kept home from crèche/childcare/school and other non-essential group activities (e.g. parties, play-dates etc.). If you need to be admitted to hospital during this time, you will be isolated.

You will be advised to keep an eye out for symptoms of measles for 21 days from the last time you were exposed to the measles case. If you think you are getting symptoms seek medical advice (from your GP usually) – ring them first and let them know that you are a contact of a measles case and tell them that you have developed symptoms. They may wish to assess you over the phone or may arrange for you to be seen separately to avoid exposing others.

If you become very unwell or need urgent medical care, do not delay seeking medical attention but ring ahead and let the healthcare setting or emergency services know that you are a contact of measles. If attending antenatal appointments, let your midwife or obstetrician know ahead of time that you are a contact of a measles case.