UK Health Security Agency

National measles guidelines

April 2024

Contents

Document history

Date	Reason for change	Issue number
October 2023	New document created from merging of the ‘PHE National Measles Guidelines (November 2019) and ‘PHE Guidelines on post-exposure prophylaxis for measles, June 2019’. Reformatted in UKHSA style and branding. Updates and text clarification: case definitions and risk assessment. Update to HNIG and IVIG product guidance.	1.0
17 January 2024	Added new section, 2.2.6 ‘Defining the time window for receiving post-exposure prophylaxis’.	2.0
1 February 2024	Updated information relating to immunosuppressed patients in Group B and updated differential diagnoses.	3.0
23 February 2024	Clarification of responsibilities for risk assessment in healthcare settings page 37. Further product information added on immunoglobulin product, Cuvitru, page 35.	4.0
9 April 2024	Highlighted relevant NHS information on pages 17 and 37. Removed reference to withdrawn pages on gov.uk, page 38. Updated reference to guidance for health protection teams working on international travel or air travel, pages 38, 40, 41.	5.0

1. Background

1.1 Introduction

Measles is highly infectious, the most infectious of all diseases transmitted through the respiratory route. Measles can be severe, particularly in immunosuppressed individuals and young infants. It is also more severe in pregnancy, and increases the risk of miscarriage, stillbirth, or preterm delivery (1).

The most effective way to control measles is by achieving high uptake of 2 doses of measles, mumps, and rubella (MMR) vaccine. High sustained coverage is key to achieving elimination of endemic measles, defined by the World Health Organization (WHO) as the absence of endemic measles circulation for at least 12 months in a country with a high-quality surveillance system (2). Recent uptake of MMR in England (2021 to 2022) is below 90% for the first dose at 2 years of age and at 86% for 2 doses at 5 years of age, well below the ≥95% WHO target. Analyses conducted by the UK Health Security Agency (UKHSA) (formerly Public Health England (PHE)) highlight that population immunity levels in the UK are well below those required to interrupt measles transmission in many birth cohorts (3). Young people born between 1998 and 2004 (aged 19 to 25 years in 2023) are the most susceptible. London remains the most vulnerable region with immunity targets not achieved for many birth cohorts, including younger children of primary and secondary school age (3). There are also inequalities in vaccine uptake by ethnicity, deprivation and geography and the burden of measles falls disproportionately on under vaccinated communities such as the Charedi Orthodox Jewish community, the Traveller community, Steiner (Anthroposophic) community and recent migrants (4 to 6).

After briefly achieving endemic measles elimination in 2016 and 2017, by 2018 measles virus transmission had re-established in the UK, at a time when the whole of Europe was experiencing large epidemics. Measles activity reduced dramatically during the COVID-19 pandemic due to the implementation of wide ranging societal and travel restrictions. This interrupted transmission and has resulted in measles elimination status technically being re-gained, in the UK in 2023 (reflecting 2022 surveillance data). However, the incidence has increased again in England during 2023, as it has globally, with large outbreaks currently underway in multiple countries in South Asia and Africa and so this is unlikely to be sustained.

To maintain measles elimination status measles surveillance needs to remain highly sensitive to detect sporadic cases and to classify cases as endemic or imported/import-related on the basis of complete epidemiology and the viral sequence information. Discarding a sufficient proportion of suspected cases is an important indicator of the sensitivity of the surveillance system and is a WHO requirement for measles elimination (2). Determining epidemiological and virological links between confirmed cases is also vital for detecting outbreaks. Outbreaks pinpoint susceptible communities where vaccination coverage is low, and thus inform targeted vaccination activity. In recent years, several such outbreaks have occurred, particularly amongst Charedi Orthodox

Jewish communities, Traveller communities, Anthroposophic (Steiner) communities and migrants, where vaccine uptake is suboptimal (4 to 6).

This document provides detailed public health guidance on the risk assessment of suspected measles cases, the management of their contacts and a description of the laboratory testing services available to support this. This is set in the context of a national surveillance system which is required to support and monitor progress towards WHO elimination targets, as outlined in the UK Measles and Rubella Elimination Strategy.

1.2 Rationale for public health action

During periods of low measles incidence, the reliability of a clinical diagnosis declines and it is therefore important that every suspected case is investigated and excluded using appropriate laboratory methods. Good epidemiological and virological surveillance is an important element of measles control by establishing the source of sporadic cases. Laboratory testing to confirm or discard suspected cases and identify chains of transmission early is critical to ensure effective interventions can be targeted appropriately and initiated promptly to limit further spread. Given the limited effectiveness of most post-exposure interventions, accurate surveillance to inform this pro-active strategy is a high priority.

Clinicians are required to notify all suspected measles cases as soon as possible to their local health protection team (HPT), both as part of surveillance and so that timely public health management can be undertaken. Vulnerable contacts (such as immunosuppressed individuals, young infants and pregnant women) should be considered for post-exposure prophylaxis (PEP) to reduce the risk of complications where possible. Where there are large numbers of cases and contacts, the priority for public health action is to identify and assess the risk to immunosuppressed individuals (7), even after limited exposure or when exposed to cases of breakthrough measles (previously referred to as ‘reinfection’, see section 1.3.2).

For immunocompetent vulnerable individuals, local health protection teams (HPTs) should prioritise contact tracing efforts to those most likely to have had close prolonged exposure. Individuals in this group (immunocompetent, vulnerable individuals, for example, pregnant women) do not need to be identified and risk assessed if the index case is a presumed breakthrough measles (see later section for definition).

Susceptible healthy contacts, including unimmunised children and adults, are unlikely to benefit from post-exposure vaccination, unless offered rapidly following exposure.

Healthy contacts who work with vulnerable individuals, in particular health care workers, can be a source of transmission and need urgent assessment and possible exclusion from work. Vaccination of unimmunised contacts should confer benefit against future exposures and will also provide protection against mumps and rubella infections. In outbreak settings, such as

schools, mass vaccination of susceptible individuals should be considered to prevent tertiary transmission.

1.3 Clinical and epidemiological features of measles, and definitions

Robust measles surveillance and timely public health management rely on clinicians and public health professionals recognising measles based on a combination of clinical and epidemiological features. With increasing progress towards measles elimination, physicians are less likely to have experience of clinically diagnosing measles cases, and therefore adequate testing of all suspected cases is essential. Before test results are available, however, management of suspected cases and contacts should proceed on the basis of risk assessment. This requires consideration of a range of factors including the age of the case, vaccination history, clinical presentation and epidemiological features such as local outbreaks or an epidemiological link to a confirmed case. Collecting information on possible epidemiological links is essential to making a reliable risk assessment and will contribute towards a better understanding of measles transmission in the population.

1.3.1 Epidemiological parameters

A good understanding of the transmission parameters of measles is important to undertake an appropriate risk assessment. Information about the incubation period, period of infectiousness, transmission route and infectivity are summarised here:

The incubation period is typically around 10 to 12 days from exposure to onset of symptoms but can vary from 7 to 21 days (9).

The period of infectiousness generally starts from 4 days before the rash and lasts up to 4 full days after the onset of rash (9).

The transmission route of measles is mostly airborne by droplet spread or direct contact with nasal or throat secretions of infected persons; much less commonly, measles may be transmitted by articles freshly soiled with nose and throat secretions, or through airborne transmission with no known face-to-face contact (16, 17).

Measles is extremely infectious, with a basic reproduction number (R0) estimated around 15 to 20 (that is, on average, there will be 15 to 20 individuals infected from a single case in a totally susceptible population); the secondary attack rate is highest among close unimmunised contacts, particularly household contacts (13, 14).

Vaccine effectiveness: based on available evidence, vaccination with one dose of MMR vaccine is at least 95% effective in preventing clinical measles and 92% effective in preventing secondary cases among household contacts (13).

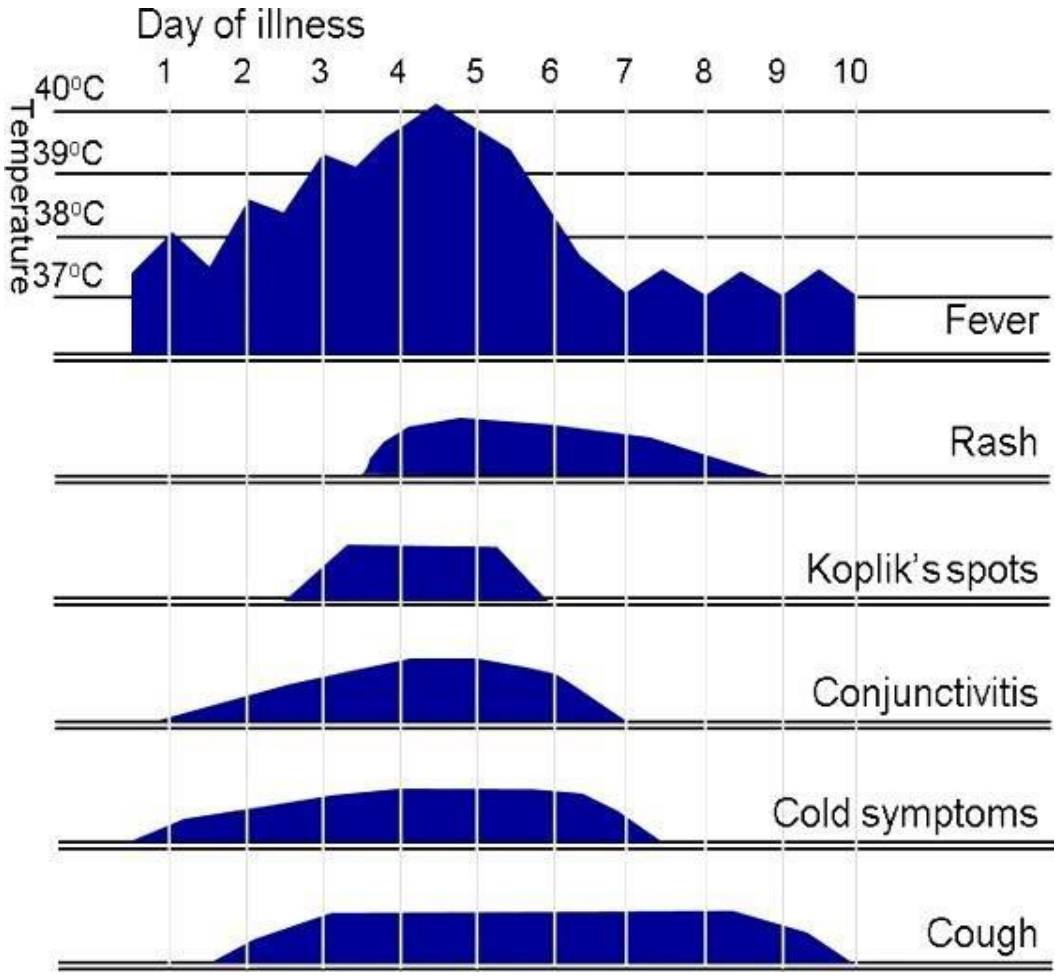
As no vaccine offers 100% protection a very small proportion of individuals may get infected despite vaccination.

There are 2 main types of vaccine failure: primary failure occurs when an individual fails to make an initial immunological response to the vaccine. Secondary failure occurs when an individual responds initially but then protection wanes over time. Although primary vaccine failure is rare, it can occur (particularly after a single dose). In settings with high levels of close interpersonal contact, such as large households or school settings, controlling measles outbreaks requires a high coverage of 2 doses of MMR (12).

1.3.2 Clinical presentation of primary measles infection

Figure 1 below shows the clinical course of primary measles infection and its main symptoms.

Figure 1. Clinical course of primary measles infection



Source: WHO Manual for the laboratory diagnosis of measles and rubella infection (8).

Measles starts with a 2 to 4 day illness ('prodromal phase') before the rash appears, which typically includes high fever, coryzal symptoms, cough and conjunctivitis. The latter is a more

specific symptom that differentiates measles from many other causes of influenza-like illness. Symptoms typically peak on the first day of the rash (7).

Fever typically increases during the prodromal phase, peaks (generally over 39°C) around the rash onset, as shown in Figure 1, and will gradually decrease after that.

The maculopapular rash generally starts on the face and behind the ears. The number of lesions/spots generally increase in the first 2 to 3 days, and their distribution expands further to the face, trunk, and can sometimes be generalised. Lesions can become confluent, particularly on the face and the trunk. The rash is red, blotchy, maculopapular (that is non-vesicular), not itchy, and generally lasts for 3 to 7 days, fading gradually (6).

Koplik spots may appear around the time of the rash, usually one day before, and last for 2 to 3 days after the rash appears. These are small spots with white or bluish-white lesions, of about 2 to 3mm in diameter, on an erythematous base on the buccal mucosa.

These can be confused with other lesions in the mouth and therefore their suspected presence is an unreliable marker for measles.

Several other common rash illnesses have a similar clinical presentation, although the combination of rash, fever, coryzal symptoms with conjunctivitis is almost unique to primary measles infection. Rash illnesses including roseola (HHV6 infection), fifth disease (parvovirus B19 infection) and scarlet fever can be indistinguishable based on clinical features alone, particularly in children, and clinical diagnosis is often unreliable. The timing and nature of symptoms is often helpful in the differential diagnosis. For example, while symptoms, including fever, peak with the onset of rash in measles; in roseola, the onset of rash generally coincides with clinical improvement.

A summary of the clinical features of each of these conditions is provided in Annexe 1.

1.3.3 Complications of primary measles infection

The most frequent complications include viral pneumonitis and otitis media, as well as diarrhoea (7, 9). Measles infection often leads to a temporary reduction in immune responses in the few weeks following infection, which may increase the risk of severe secondary bacterial and viral infections (1). Tracheobronchitis (‘measles croup’) and pneumonia due to secondary bacterial infection are frequent complications of measles (7).

Encephalitis occurs more rarely, in about 0.05% to 0.1% of measles cases (10).

Subacute sclerosing panencephalitis (SSPE) is a very rare but very severe complication, occurring in about 0.01% of cases (10). Cases of SSPE present a few years after measles infection with progressive neuro-cognitive symptoms which in most cases lead to coma and

death. The risk of SSPE is increased in children who acquire measles before the age of one year.

Immunosuppressed individuals are at higher risk than immunocompetent individuals of developing prolonged and severe measles, and of suffering complications. Viral pneumonitis is the most frequent severe complication, which generally develops within 2 weeks of symptom onset. It is also the most common cause of death in immunosuppressed individuals (7). Patients at highest risk include those who have severely impaired cell-mediated immunity, such as patients who have recently undergone bone marrow transplantation, patients with primary T-cell dysfunction, AIDS patients and patients with acute lymphoblastic leukaemia (ALL). The risk of severe disease also remains high for patients with other forms of immunosuppression, such as those with other forms of malignancy, and those receiving high doses of steroids or other types of immunosuppressive drugs. Further information about the classification of immunosuppressed individuals is provided in Annexe 2 and section 2.2.3.

Measles can be particularly debilitating in very young infants and adults, who are more likely to develop complications and require hospitalisation.

Measles can be severe in pregnant women and leads to an increased risk of prematurity and foetal loss, although there is no evidence that it leads to congenital defects (11). Young infants are at high risk of complications such as pneumonia, otitis media, and SSPE and of a fatal outcome (12).

1.3.4 Transmission of primary measles

A patient with suspected measles should be advised to isolate and in particular to avoid contact with immunosuppressed individuals and other vulnerable people (such as pregnant women and infants) while potentially infectious. Although most suspected cases will turn out not to be measles it is important to also avoid exposing contacts to other infectious causes of rash illness. Individuals with primary measles infection are infectious from about 4 days before rash onset until 4 full days after the rash appears. Generally, secondary transmission is higher among close contacts, such as household members and non-household members with whom prolonged contact has occurred – such as students in the same classroom (13, 14).

Close prolonged interpersonal contact, such as in household settings, may also lead to a higher infectious dose of virus, which increases both the risk of transmission and the risk of developing more severe disease (7).

Appropriate measures for triage and isolation in health care settings are essential to avoid prolonged exposure to suspected measles cases in waiting areas. In a recent series of cases associated with transmission in health care settings, 5 of the 7 secondary cases were in the same room as the index case for between 2.5 and 4 hours (15).

However, whilst most transmission events require face-to-face and/or prolonged contact, transmission through more casual contact has also been documented (16, 17). For this reason, where a large group of people have been exposed, but the level of contact cannot be defined at an individual basis, it may be appropriate to initiate a mass communication, for example using approaches such as e-mail, text messaging or posters to 'warn and inform' those who may have been exposed. This approach aims to encourage rapid self-identification of those who may be vulnerable, to ensure that any linked cases are identified and diagnosed promptly and to provide reassurance to those who are likely to already be protected.

1.3.5 Breakthrough measles (reinfection)

The term 'breakthrough measles' (previously referred to as 'reinfection', or secondary vaccine failure) is used to describe a confirmed case of measles in someone who developed immunity to measles, either from natural measles or from prior receipt of measles containing vaccine, typically between 6 and 30 years after infection or immunisation (see section 1.5.3).

Breakthrough infection is usually associated with intense and/or prolonged exposure to an infected individual, for example, directly caring for an acutely ill person, and so is generally only seen in healthcare workers or in household settings.

Cases of breakthrough measles are generally mild; conjunctivitis is generally absent and the rash may not follow typical progression. The illness tends to be of shorter duration, and the infectivity of these cases is much lower and transient, unlike primary measles infection. Although polymerase chain reaction (PCR) positive, the presence of neutralising antibodies in respiratory secretions greatly reduces the infectiveness of the virus.

In measles endemic areas breakthrough cases represent fewer than 10% of total infections, but this will increase as vaccination coverage in the general population rises. In a highly vaccinated population and with the increasing availability of PCR testing it is inevitable that more breakthrough measles infections will be identified. For example, it is not unusual to pick up breakthrough infections in outbreaks linked to healthcare or other settings through active case finding. It is important to note that breakthrough measles is not thought to pose a significant public health threat in the context of global measles elimination efforts.

1.3.6 Rash illness 10 to 12 days post-MMR

MMR is an attenuated vaccine, and in some individuals, they develop a rash 10 to 12 days post vaccination. Individuals may have a mild fever but are otherwise well. Measles virus can be detected in oral fluid samples and mouth and throat swabs. Standard PCR cannot distinguish between vaccine and wild-type measles and so sample should be sent to Virus Reference Department for either their measles vaccine-specific PCR assay or formal genotyping.

1.4 Surveillance of measles

Measles is a notifiable disease under the Health Protection (Notification) Regulations (England) 2010. Health protection teams should work with local partners to raise awareness of measles among health professionals in order to facilitate early recognition, diagnosis and reporting (see section 3.1). Notification to the local health protection team fulfils the physician's responsibility to notify the Local Authority Proper Officer. Physicians managing the case should inform the HPT by phone as soon as is reasonably practical.

1.4.1 Laboratory surveillance

Since November 1994, enhanced surveillance including oral fluid (OF) testing of all notified and suspected cases has been provided through the Virus Reference Department (VRD) at Colindale.

When a suspected case of measles is reported and/or notified to the local Health Protection Team (HPT), the HPT should arrange for an OF kit to be sent directly to the case (or their parent/guardian), or via their general practitioner (GP). Samples should be taken as soon as possible after measles is suspected, and posted or couriered back to the Virus Reference Department, UKHSA Colindale, where it is tested for anti-measles IgM, measles IgG and/or measles RNA. Results are reported back to the patient's GP and to the local HPT. All relevant oral fluid kit documents can be found online.

Staff from the national Immunisation and Vaccine Preventable Diseases (VPD) division at UKHSA Colindale will follow up both cases confirmed by the VRD and cases which have tested positive at local diagnostic laboratories to obtain further epidemiological and clinical information and to document vaccination history. This will be collated from information already collected by the HPT where possible.

Accurate national data is essential to understanding chains of transmission and identifying susceptible populations where the vaccination strategy may require modification.

1.4.2 International surveillance standards

To monitor progress towards endemic measles elimination in England, the surveillance system should be able to identify and test all suspected cases of measles, reliably exclude cases based on appropriate laboratory testing in a WHO accredited laboratory and define chains of transmission (2). To support the national surveillance system, laboratory testing of suspected measles cases is undertaken at VRD Colindale. This enables systematic testing, using reference methods which are both highly sensitive and specific. Adequate testing to discard a high proportion of suspected cases, using WHO approved methods, is an important indicator of the sensitivity of the UK surveillance system and is a requirement in the WHO process of certifying measles elimination.

Confirmatory testing, genotyping and further characterization are undertaken at the WHO Global Specialised Reference Laboratory based in VRD, Colindale. Measles virus sequences are entered on the WHO global Measles Nucleotide Sequence (MeaNS) database hosted by UKHSA. VRD also report monthly data on the number of samples tested for measles to the WHO laboratory network.

The UKHSA Immunisation and VPD Division holds the central repository of all confirmed cases in England and conducts systematic follow up of all confirmed cases. Epidemiological data including travel history, visits to healthcare settings and attendance at mass gathering events should be collated by the local HPT (see the epidemiological surveillance form).

When combined with genotyping, this enables classification of imported cases and the identification and disentangling of local clusters. This process is critical to assessing progress towards elimination, to identify pockets of susceptibility and inform appropriate public health interventions.

The UKHSA Immunisation and VPD Division is also responsible for reporting case-based information on confirmed cases monthly to the WHO via their data collection system, WIISE. A new epidemiological surveillance form has been developed to help HPTs collect all the information necessary for identifying exposures, chains of transmission and clusters of measles. The intelligence collected supports our elimination efforts and allows the national team to fulfil international surveillance obligations. HPTs are asked to note the form and check that any locally developed forms capture the same information.

The form can be uploaded directly onto HPZone/CIMS or submitted by email to phe.MMRsurveillance@nhs.net

1.5 Laboratory investigation

1.5.1 Types of samples

Measles is a single-stranded RNA virus (genus Morbillivirus, family Paramyxoviridae). There are 24 described genotypes, many of which have been eliminated as part of the global control of measles. As of 2021 fewer than 3 genotypes are currently found globally, the distribution of which varies across geographic areas. For WHO purposes, a measles antibody test is required to exclude measles. Genotyping on confirmed samples is also an integral part of laboratory surveillance for measles, to identify imported cases and monitor progress towards elimination. In the UK oral fluid (OF) is the optimal sample for measles surveillance. These samples are minimally invasive and are more acceptable than serum for confirming cases in infants and children.

Importantly, OF can be tested for IgM, IgG and measles RNA, and can therefore:

1. Reliably exclude measles diagnosis, as well as confirm it.
2. Indicate whether the case is primary or breakthrough measles (reinfection).
3. Genotype confirmed cases.

In the absence of an oral fluid sample, serum and a mouth swab should be sent to VRD instead.

Figure 2 provides an overview of the timing of laboratory tests and biological parameters for measles diagnosis.

It is important to note that oral fluid samples cannot be used to assess the immune status of vulnerable contacts and serum should be used instead.

Oral fluid

Oral fluid (OF), also known as gingival crevicular fluid, is the optimal sample for measles surveillance and should be taken from all suspected cases regardless of any other samples that may have already been taken, including when other laboratory methods have not confirmed measles.

OF can be tested for both measles IgM/IgG (as required by WHO) using specific enzyme immunoassays (EIA), and viral RNA using specifically designed assays.

Testing for IgM on OF is more sensitive and more specific than serum, particularly in the first few days after the rash, as IgM antibodies are positive in over 50% of samples on day one of the rash, and in over 90% by day 3 of the rash (Figure 2). For oral fluid samples taken within 7 days of onset of disease, the VRD also performs PCR analysis for RNA detection.

Oral fluid can be tested for measles IgG, and although measles IgG avidity is not done on OF samples, the relative level of measles IgG can be used to predict whether the case is a primary or breakthrough infection with measles.

Measles viral RNA can be detected from before the onset of the rash and for at least 2 weeks after the onset of symptoms.

Genotyping for molecular epidemiology can be performed on PCR positive samples, which allows the characterisation of the virus into one of the 24 known genotypes and helps identify clusters and imported cases.

Measles genotyping also allows the distinction between wild-type virus and vaccine in those developing a measles-like rash following vaccination.

OF is not appropriate to assess the immune status of contacts, for which serum should be tested instead (see below).

Serum

Serum samples can be used for IgM/IgG detection through enzyme immunoassays (EIA), preferably using a mu-capture assay for detecting IgM.

Serum is the most appropriate sample to assess the immune status of contacts.

Serum samples may still be IgM negative within 3 days of onset of rash (Figure 2). This may be longer for non-mu-capture IgM assays used in laboratories other than VRD, the timing of the sample in relation to rash onset is therefore essential to properly interpret results.

Serum can be used to confirm breakthrough measles (reinfection) by detection of high avidity measles IgG.

Serum is generally not suitable for PCR detection and viral typing.

Serum cannot be used to distinguish wild-type measles from vaccine-derived measles following recent vaccination.

Mouth swabs

Mouth swabs can be used for PCR if collected within 6 days of the onset of rash. These should be taken by a healthcare professional except in rare circumstances where clinical need necessitates an urgent test and alternatives are not available. A negative PCR result does not exclude a diagnosis of measles, especially in the absence of a test for cellular RNA to check the sample is suitable.

Mouth swabs can be used to distinguish between wild-type virus and vaccine in someone who has recently been vaccinated.

Mouth swabs cannot be used for measles IgM/G testing and cannot be used to distinguish between a primary infection and a breakthrough measles (reinfection).

Throat swabs or nasopharyngeal aspirate

Such samples can be used for PCR if collected within 6 days of the onset of rash (see Figure 2) but these should be collected by a health care professional. As with mouth swabs, a negative PCR result does not negate a diagnosis of measles, especially in the absence of a test for cellular RNA.

Nose swabs and eye swabs are not suitable for measles testing.

Urine

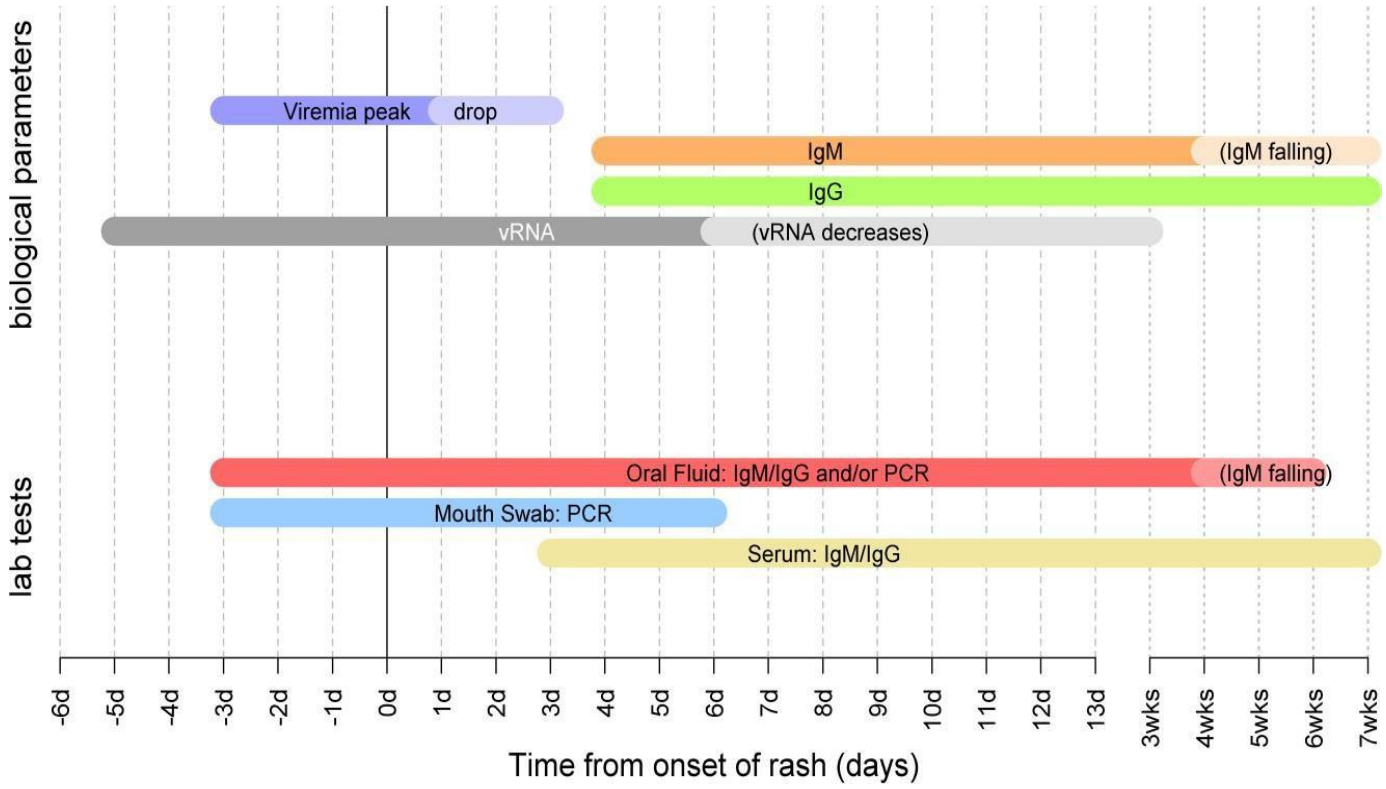
Urine samples can be highly variable and are therefore not advised for measles testing in the UK.

EDTA blood

Samples can be used for testing for measles IgM and IgG, although serum samples are generally preferable. EDTA samples can also be used for molecular characterisation if no other

suitable sample has been collected, although tends to be less sensitive than oral fluid/mouth swabs or nasopharyngeal aspirates.

Figure 2. Dynamics of biological or viral indicators and timings of laboratory tests during primary measles infection



Collection of samples

Kits for collecting routine surveillance oral fluid samples are available through the local HPT. It is important that the sample is collected according to the instructions.

The swab needs to be rubbed along the gum line for 2 minutes.

If young children chew on the swab whilst the sample is being collected it should not compromise the sample collection. Sputum samples are not suitable for testing.

Oral fluid samples sent for measles IgM testing are also tested for total IgG as an indication of whether the sample is suitable for testing. If the total IgG is less than 1mg/L then this indicates a poor quality sample and the test may need to be repeated. If oral fluid collection kits are not available, then a serum sample plus mouth swab can be taken instead (and sent to VRD).

A mouth swab should be collected by rubbing the swab along the gum line and then over the tongue.

A serum or oral fluid sample is required for distinguishing a primary infection from breakthrough measles (reinfection).

Note: any viral swab may be used for measles PCR testing, including a dry swab. A bacterial swab cannot be used as these contain PCR inhibitors.

1.5.2 Laboratory definitions

Laboratory confirmed case of measles

A suspected case with evidence of laboratory confirmation of acute measles infection (that is measles IgM in blood or oral fluid (OF) in the absence of recent vaccination or confirmed wild-type measles RNA in any clinical specimen).

Presumed primary infection

A laboratory confirmed case with no evidence of 2 doses of measles containing vaccine.

Presumed breakthrough measles (reinfection)

Detection of measles virus RNA in a suspected case of measles with mild or atypical symptoms and a reliable history of having received 2 doses of measles containing vaccine. Breakthrough measles can be confirmed by detection of high avidity measles IgG in serum or high levels of measles specific IgG in oral fluid. Measles IgM in serum may be negative.

1.5.3 Measles IgG testing of contacts

Assays can be either qualitative, where results are reported as positive, negative, or equivocal, or quantitative, where a defined measure of antibody level is provided. Enzyme immunoassays (EIA) are commonly used to test for measles IgG antibody, and various assays are available. A positive test is useful to avoid unnecessary use of human normal immunoglobulin (HNIG) or intravenous immunoglobulin (IVIG). However, although the specificity of most qualitative EIAs is high, their sensitivity remains low, and recommendations about post-exposure prophylaxis for equivocal results will differ by age and type of vulnerability (see PEP guidelines below).

2. Public health management

Guidance on the clinical management of measles may be found at: Measles guidance for primary, community care, emergency departments and hospital.

The public health management of the index case and their contacts, based on the initial assessment, is summarised in Figure 3. For accurate exclusion of measles an oral fluid (OF) sample should always be requested, an OF kit sent to the patient or their GP, and the OF sample sent back to VRD regardless of any local test results. The specimen should be taken as soon as possible and up to 6 weeks after the onset of rash (see section 1.5). All samples from cases testing positive at a local laboratory should be forwarded to VRD for confirmation and further characterisation.

2.1 Assessment of the index case

When measles is not endemic, the positive predictive value of a clinical diagnosis is generally poor. In the absence of laboratory results, the likelihood of measles will therefore depend upon an assessment of the epidemiological features.

Case management should commence based on this assessment, without waiting for the results of laboratory testing (even when requested urgently). Public health professionals should advise, as needed, on the use of appropriate laboratory samples for testing, at the right time, to reduce the likelihood of false negative results (see section 1.5).

2.1.1 Case management definitions

The HPT should conduct a public health risk assessment for every suspected case of measles reported by a clinician in order to decide on management. For cases that are reported from sources other than a clinician, if the source is considered reliable and the history of the illness is compatible, the case should be managed as a suspected case whilst seeking further information. ‘Patient information…’ below summarises the information to collect. All suspected cases should be entered onto HPZone/CIMS by the HPT.

Each case should be promptly investigated and classified according to laboratory results, clinical features, and epidemiological features. For each reported case the classification may change as more information (for example on the epidemiology or laboratory results) becomes available. The distinction between likely and unlikely is a qualitative judgement based on the overall picture, rather than presence or absence of a specific number of criteria.

Patient information required for assessment of suspected measles cases

Demographic details

- name
- gender
- date of birth
- date, address, NHS number
- contact details

Clinical and laboratory features

- signs and symptoms: collect information on signs and symptoms, and importantly the onset dates of rash
- laboratory results: document the type of tests conducted and results

Individual epidemiological features

- travel: any travel within and outside the UK during the incubation period, with an assessment of whether travel was in an area where measles is known to be circulating
- ethnic and cultural or religious background: obtain details on the patient's ethnicity, and importantly, assess whether the patient is a member of an under-vaccinated population group (for example, Charedi Orthodox Jewish community, Steiner community)
- immunisation history: any known vaccination history or history of measles; if not known, ask where the patient was born and grew up to help assess the likelihood of vaccination and/or natural exposure
- epidemiological link: assess if there has been a known epidemiological link with another laboratory or epidemiologically confirmed case

Table 1. Case definitions for measles

Case definition categories	Definition
Laboratory confirmed	A suspected case with laboratory confirmation of acute infection.
Epidemiologically confirmed (a term used for surveillance purposes to define confirmed cases in the absence of a laboratory test to confirm measles)	A clinically classical case of measles with a direct epidemiological link to a confirmed case (where onset of symptoms occurred within 7 to 21 days of exposure),or related to another epidemiologically confirmed case (for example in an outbreak setting).
Likely (probable)	A clinically classical case of measles with epidemiological features that either increase the likelihood of the patient having been exposed and/or favour the diagnosis of measles relative to other causes of rash illness. Clinical features are outlined in Table 2 and epidemiological risk factors are summarised in 'Factors to consider…' below.
Likely breakthrough	A suspected case of measles in a patient who has had 2 doses of measles containing vaccine (usually at least 6 years after vaccination) or has confirmation of previous measles infection (IgG positive). The case will usually have mild symptoms (Table 2) and epidemiological information that suggest exposure to measles (see 'Factors to consider…' below). Please note these cases are rare.
Unlikely (possible)	A suspected case of measles which does not meet the definition of a likely case, either because it is not clinically classical (Table 2) or because the epidemiological context is not suggestive of measles.

Table 2. Clinical features of measles

Clinical features	Symptoms

Classical primary measles: generally very unwell and considered measles until proven otherwise	• fever equal to or over 39°C in the absence of antipyretics, and
	• generalised maculopapular rash, and
	• one or more of:
	  ○ conjunctivitis
	  ○ cough
	  ○ coryza

Mild: generally a milder illness	• fever typically 37.5°C to 39°C • rash may be more localised • may not have conjunctivitis, coryza or cough
Rash or fever following vaccination	Rash and mild fever on day 10 or 11 post-MMR vaccination is likely to be vaccine related

Generally, epidemiological information is a better predictor of measles than the clinical features. Given the implications of an incorrect classification, it is recommended that classification for public health management should be undertaken by or in discussion with an experienced member of the health protection team.

Local transmission

If there have been no confirmed recent cases, despite adequate surveillance, in the area and the index case has not visited an area where cases are occurring, (either in the UK or internationally) during the incubation period, most cases can be assumed to be unlikely. To ensure that true cases are not missed however, there should be a very low threshold for OF testing and all suspected measles cases should be tested irrespective of whether they meet the clinically compatible criteria (see algorithm Figure 3) (18).

Factors to consider in the risk assessment

Factors increasing the risk of exposure

- membership of a community known to be more susceptible, for example, Traveller community, Charedi Orthodox Jewish community, anthroposophical (Steiner) communities, local community with low MMR vaccination coverage (2, 3)
- visited an area (local or international) where measles is known to be circulating, during the incubation period
- attendance at large international mass gathering events, where substantial mixing occurs between individuals potentially travelling from areas where measles is circulating; this would include, for example, events such as music festivals (19)

Factors favouring the diagnosis of primary measles infection

- age: the likelihood of a suspected case being confirmed as measles is higher among adolescent and young adults. In infants and toddlers, measles-like clinical

presentations due to other illnesses, such as roseola or scarlet fever, are common (see Annexe 1)
- a lack of immunity or incomplete vaccination: the diagnosis is more likely if cases are unvaccinated or partially vaccinated, and have no prior history of measles infection

Testing of the index case

Regardless of any other testing performed, all cases should have OF samples taken and sent to VRD for exclusion or confirmation of the diagnosis.

Oral fluid testing

All suspected cases (including cases confirmed by local laboratory testing) require an oral fluid sample to be sent for testing at the VRD in Colindale (see section 1.5.1 and section 1.5.2). Contacts of epidemiologically or laboratory confirmed cases (by other methods) should be risk assessed and managed without awaiting the result of the oral fluid test in the index case. Immunosuppressed contacts of likely cases (including breakthrough measles (reinfection)) should be risk assessed and managed without awaiting the result of the oral fluid test in the index case.

Where the case is considered unlikely, there have been no recent cases locally and there has been no indication on notification that the case has clinically classical features, awaiting the results of a posted oral fluid kit without further investigation, is appropriate. This approach is underpinned by a sensitive surveillance system which relies on high uptake of oral fluid kit return rates. Where OFK return rates are low, measures to improve use should be implemented.

Urgent testing

Measles is a clinical diagnosis and whilst all cases should be confirmed for surveillance purposes, urgent testing will only be necessary in certain circumstances and where results will be available in time to inform action, for example:

- to confirm diagnosis in a likely case where significant public health intervention may be avoided if the diagnosis is excluded, for example, administration of MMR or HNIG to exposed infants under one year of age in a nursery setting
- to inform use of HNIG/IVIG for vulnerable contacts of a likely case, during periods of low level transmission
- to inform the risk assessment of an immunocompromised contact of an unlikely case, where presentation is not classical but there are epidemiological features that increase the risk of exposure, or uncertainty in the extent of epidemiological features

PCR and/or IgM testing are available through the public health laboratories and should be discussed with the local health protection team. The date of onset of symptoms including date of onset of rash and history or dates of MMR should be documented on the request form, which must be included with the sample. A negative local result does not necessarily exclude measles, as it will depend upon the timing and adequacy of the sample and the tests undertaken.

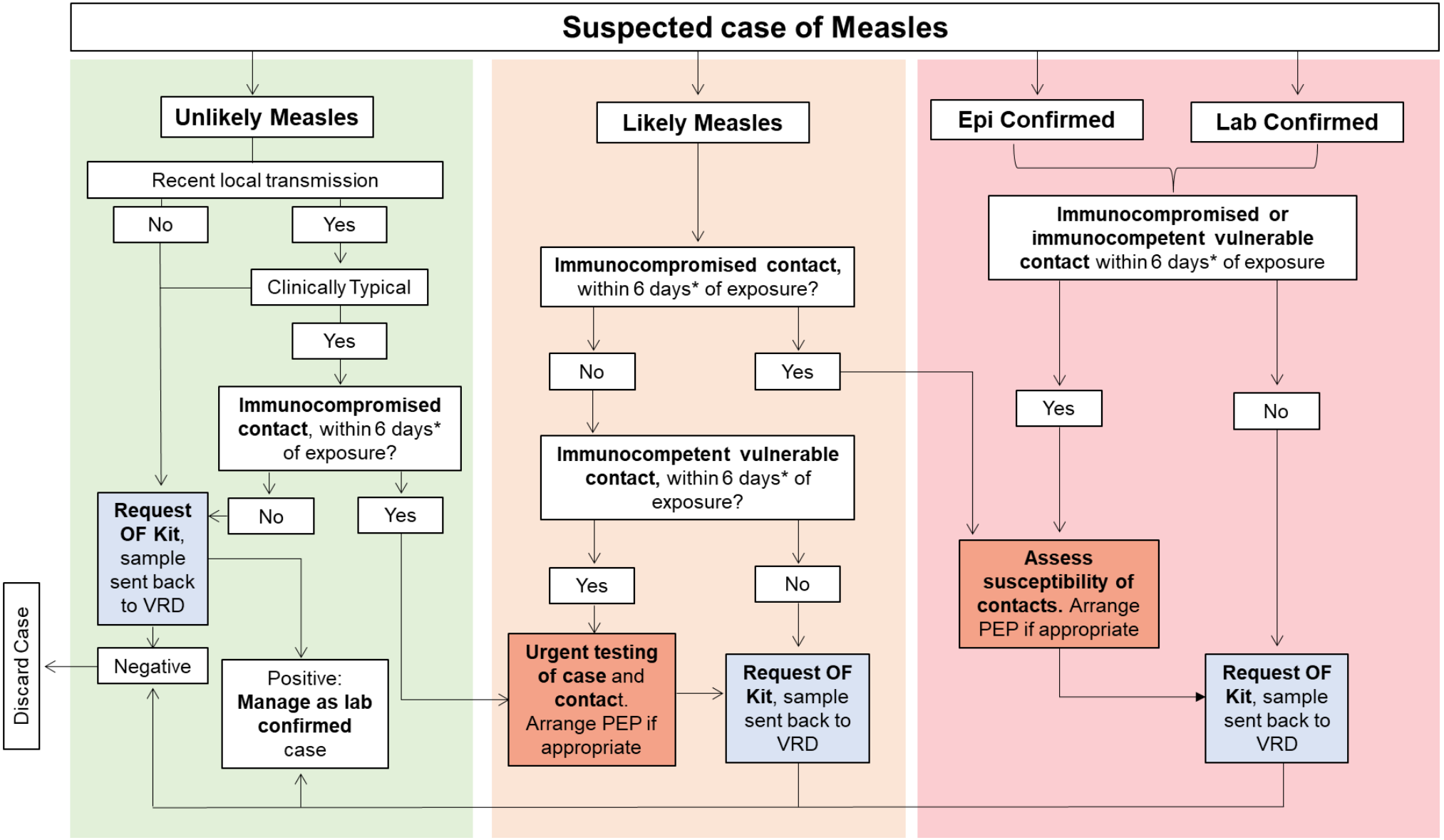
As WHO has specific requirements for suspected cases to be discarded, local laboratory testing does not preclude the requirement for obtaining an oral fluid surveillance sample for testing at the reference laboratory.

All locally tested measles IgM and/or measles PCR positive samples should also be forwarded on to Colindale/VRD for further testing and characterisation.

2.1.2 Risk assessment

The risk assessment should take into account the clinical features, epidemiological features, vaccination history and laboratory results to decide on the need for further testing and post-exposure prophylaxis of vulnerable contacts. Figure 3 illustrates the principles of risk assessment and public health management.

Figure 3. Principles of risk assessment and public health management



Note: In Figure 3 an asterisk (*) indicates that for immunosuppressed patients where exposure or susceptibility is recognised late (more than 6 days post exposure), risk assessment is required with the specialist caring for the individual and consideration of immunoglobulin to attenuate infection.

Text version of Figure 3. Principles of risk assessment and public health management

The diagram is divided into 3 sections:

1. Unlikely measles case

Step 1. Identify any recent local transmission, if none continue to step 5.
Step 2. Identify if the symptoms are clinically typical of measles, if not continue to step 5.
Step 3. Identify if any close contact is immunocompromised, if not continue to step 5.
Step 4. Assess susceptibility of immunocompromised contacts (including urgent testing as appropriate), arrange urgent testing of case, and then PEP for contacts if necessary.
Step 5. Request oral fluid kit for the patient.
Step 6. If positive manage as a laboratory confirmed case, if negative discard case.

2. Likely measles

Step 1. Identify if there are any immunocompromised contacts, if not continue to step 3.
Step 2. Assess the susceptibility of immunocompromised contacts (including urgent testing as appropriate), and then arrange for PEP if necessary.
Step 3. Identify if there are any immunocompetent vulnerable contacts, if not continue to step 5.
Step 4. Assess susceptibility of immunocompetent vulnerable contacts (including urgent testing as appropriate), arrange urgent testing of the case, and then PEP for contacts if necessary.
Step 5. Request the oral fluid kit to be sent to the case.
Step 6. If positive manage as a laboratory confirmed case, if negative discard case.

3. Epi or lab confirmed cases

Step 1. Identify if there are any immunocompromised or immunocompetent vulnerable contacts, if not continue to step 3.
Step 2. Assess the susceptibility of immunocompromised or immunocompetent vulnerable contacts; arrange for PEP if necessary.
Step 3. Request the oral fluid kit to be sent to the case if not undertaken already.
Step 4. Manage as a laboratory confirmed case. If negative in reference laboratory discard case.

End of text version of Figure 3

2.1.3 Exclusion of the index case

Confirmed and likely cases should stay at home and avoid contact with vulnerable people and are therefore excluded from school, nursery or work for the entire period of infectiousness (from 4 days before onset of rash and for 4 days after rash onset where the date of rash onset is day 0). Given the high risk of secondary infection following measles, it is advisable to return only after full recovery.

Immunosuppressed individuals may be infectious for longer and may not display typical symptoms, and so timings should be adjusted as appropriate in consultation with clinicians managing the case's immunosuppression.

Details on exclusion of healthcare worker contacts and close contacts from educational settings are provided in section 3.2.3 and section 3.3, respectively.

2.2 Management of contacts and post-exposure prophylaxis

2.2.1 Identification of contacts

The best way to protect individuals and to achieve measles elimination is with high vaccination coverage with 2 doses of MMR vaccine (95% and over). There is a duty of care to follow up each reported case of measles with the aim of identifying others who may have been exposed, both to a common source of infection and to the reported case. This will help to ensure early identification of chains of transmission and inform the need for pro-active interventions to prevent tertiary and subsequent waves. Where practicable, all contacts should be provided with information on symptoms of measles and advised to exclude themselves from schools or other settings if they develop symptoms.

Although post exposure prophylaxis is of limited effectiveness, there may be an opportunity to offer some protection to exposed vulnerable contacts. This requires identification of contacts in the following order of priority:

1. Immunosuppressed contacts.
2. Pregnant women and infants less than 12 months.
3. Health care workers.
4. Healthy contacts.

The management of each identified contact will depend on their exposure risk (including whether the index case is presumed to be primary or breakthrough measles (reinfection)) and their vaccination status or susceptibility to measles. For immunosuppressed contacts, an appropriate assessment of the nature and level of immune suppression is essential to assess the requirement for post-exposure prophylaxis.

2.2.2 Defining exposure risk

2.2.2.1 Defined contacts

Contact tracing should identify close contacts within the infectious period, from 4 full days before and until completion of 4 full days after rash onset. Generally, secondary transmission is higher among close contacts, such as members of a household or individuals who have close contact with each other over a long period of time, or students in the same classroom (13, 14).

Immunosuppressed individuals
Whilst most transmission events require face-to-face contact, transmission through more casual contact does occur (16, 17). For immunosuppressed individuals, who are more likely to develop severe measles disease (7), it is particularly important to consider even limited exposure. Any level of contact should trigger an assessment of an immunosuppressed individual, even if the index case is presumed to be breakthrough measles (reinfection). If immunosuppressed contacts are identified, assessment of their susceptibility and post-exposure prophylaxis should be considered without waiting for, or in parallel with, laboratory testing of the index case.

Due to the potential for live attenuated vaccines to replicate and cause disease in immunosuppressed individuals, inadvertent administration of MMR to an immunosuppressed individual should be risk assessed as a potential exposure to measles (further details are in the next section).

Vulnerable immunocompetent individuals (infants, pregnant women)
For immunocompetent vulnerable individuals (infants, pregnant women), local HPTs should prioritise contact tracing efforts to those most likely to have had close or prolonged exposure to a primary measles infection. If the index case is presumed breakthrough measles (reinfection), individuals in this group do not need to be identified and assessed.

Contact tracing should focus primarily on:

- close contacts including household contact
- face to face contact of any length
- more than 15 minutes in a small, confined area, for example room in a house, classroom, 4-bed hospital bay (including healthcare workers)

2.2.2.2 Poorly defined contacts

There will often be situations where a number of individuals may have been exposed in a shared setting, for example hospital A&E or GP waiting area, where the level of contact is unclear.

When the information provided cannot clearly define the level of contact but there are known immunosuppressed individuals involved, these should be managed as close contacts and rapidly assessed for post-exposure prophylaxis.

Where there is a defined list of contacts, but it is not clear if the group contains immunosuppressed individuals, an individual risk assessment is not practicable. In this situation, warn and inform letters or messaging should be issued to all potential contacts.

If there is no identifiable list of contacts at all, then other means of case finding should be considered, such as writing to local healthcare providers, information leaflets or posters in public areas and other communication activities as relevant to the setting.

2.2.3 Immunosuppressed patients

2.2.3.1 Assess risk and susceptibility

All immunosuppressed patients, as defined in chapter 6 of Immunisation against Infectious Disease, are at risk of severe measles and should be considered for intravenous immunoglobulin (IVIG) following any exposure to measles, which would need to be sourced from NHS hospital pharmacies.

Prophylaxis will depend on the level of immunosuppression and the likelihood that the individual would have retained any pre-existing measles immunity. Many adults and older children with immunosuppression will have immunity due to past infection or vaccination. A prophylactic dose of immunoglobulin is unlikely to offer additional benefit to those who have detectable measles antibody using standard assays, as their antibody levels are probably significantly higher than those achieved after a prophylactic dose of immunoglobulin.

This guidance is based largely on the assessment of individuals born and raised in the UK. In many other countries, a higher proportion of older adults are likely to be immune, and therefore following the UK algorithm would be a safe approach. Individuals who have come from a small number of countries where measles control has been achieved for a longer period than in the UK but who are not known to be fully vaccinated, however, may remain susceptible to an older age, and therefore testing is recommended. For example, individuals from the USA can generally only be assumed to be immune if fully vaccinated or born before 1957 (26). Similar considerations may apply for individuals from Canada and some Scandinavian countries. People with severe defects of cell mediated immunity who are on regular IVIG replacement therapy do not require additional IVIG if the most recent dose was administered 3 weeks or less before exposure. Such individuals should be under the management of specialists in immunology and their need for replacement immunoglobulin therapy will have already been assessed by their immunologist (in line with advice disseminated through the UK Primary Immunodeficiency Network – UK PIN).

All other individuals with immunosuppression who are not already on IVIG replacement therapy will require assessment at the time of an exposure. These individuals can be divided into 2 main groups (Groups A and B, see below), depending on their ability to maintain adequate antibody from past exposure or vaccination.

Group A

Group A includes most patients with immunosuppression.

These individuals should be able to develop and maintain adequate antibody from any prior successful vaccination or infection and can therefore be managed on the basis of evidence of protection at any time (prior to or since the diagnosis or treatment end).

Patients in this group are likely to have developed an adequate response to vaccination or measles during childhood, and so it is recommended that their measles status is established

prior to exposure (for example at the next out-patient appointment) so that post-exposure prophylaxis can be informed.

For individuals born and raised abroad, where the history of measles may be less reliable, an individual risk assessment, ideally with rapid IgG antibody testing, is recommended.

Group B
Group B includes individuals who are unlikely to have developed or maintained adequate antibody levels from past exposure or vaccination.

This group can be further subdivided into:

- B (i) individuals who can be managed based on a measles IgG test at the time of exposure or at any point since the end of treatment or diagnosis
- B (ii) individuals who require IVIG following an exposure without the need for testing

In principle, individuals should have been re-vaccinated (when they have recovered sufficiently to receive live vaccines) or have had their immunity against measles tested, after completing their treatment. Any measles exposed patient who has recovered but has not been revaccinated may need their measles IgG checked and be considered for IVIG. The supervising clinician will be able to advise if the patient is fully recovered or if they remain immunosuppressed.

Other individuals
Other individuals who do not meet the criteria for either Group A or B (for example, HIV positive individuals with CD4 cell count greater than 200/mm^3, individuals receiving non-biological immune modulating drugs more than 3 months ago), should be considered as immunocompetent for the purposes of measles PEP. However, the decision on the use of IVIG in these groups may be taken on an individual basis by their specialist clinician.

2.2.3.2 Management of immunosuppressed patients

Group A
Patients in group A should be urgently assessed for the need for IVIG. In the absence of a positive measles IgG test at any time (either prior to or since diagnosis or treatment or at the time of exposure), an assessment of susceptibility needs to be urgently undertaken based on the individual's age, history of measles infection and vaccine status (see Table 3).

For those requiring IgG testing, this should be done as soon as possible following exposure, given that the effectiveness of IVIG is likely to be higher when administered as early as possible following exposure (ideally within 72 hours) although it can be given up to 6 days following exposure. Urgent IgG testing is available in all regional public health laboratories, as well as many NHS laboratories. Most testing can be done the same day or out of hours.

Group B

For patients in group B (i) who have a documented positive measles IgG since diagnosis or treatment end, no IVIG is required. For all others in group B (i), urgent IgG testing should be conducted at the time of exposure. If it is not possible to test within 72 hours of exposure, IVIG should be administered.

For patients in group B (ii), IVIG should be provided regardless of previous measles IgG results and without the need for testing.

For patients in group B, IVIG, if required, needs to be provided as soon as possible after exposure, ideally within 72 hours.

For immunosuppressed patients where exposure is recognised late or who are found to be antibody negative or equivocal between 6 and 18 days after exposure, discussion with the specialist caring for the individual should take place, and IVIG may be considered in order to attenuate infection. Where a second exposure occurs more than 3 weeks after a first dose of immunoglobulin, a further dose of immunoglobulin will need to be considered.

Table 3. Assessing evidence of protection in immunosuppressed contacts of measles

Table 3a. Group A: individuals who should develop and maintain adequate antibody from past exposure or vaccination

Age and history of measles exposure or vaccination		Recommendation
All ages	Previous measles IgG positive	Assume immune – do not give IVIG
Born before 1970	Positive history of measles infection	Assume immune – do not give IVIG
	No history of measles infection	Rapid IgG test and issue if negative or equivocal If not possible to test within 6 days of exposure, assume immune – do not give IVIG
Born between 1970 and 1990	Positive history of measles infection or vaccination	Rapid IgG test and give IVIG if negative or equivocal If not possible to test within 6 days of exposure, assume immune – do not give IVIG
	No history of measles infection or vaccination	Rapid IgG test and give if negative or equivocal If not possible to test within 6 days of exposure, give IVIG
Born after 1990	History of 2 measles containing vaccines	Rapid IgG test and give if negative or equivocal If not possible to test within 6 days of exposure, assume immune – do not give IVIG
	History of one measles containing vaccine	Rapid IgG test and give if negative or equivocal If not possible to test within 6 days of exposure, give IVIG
	Unvaccinated	Give IVIG

Table 3b. Group B: individuals who lose or may not maintain adequate antibody levels from past exposure or vaccination

Age and history of measles exposure or vaccination		Recommendation
Group B (i)	Measles IgG positive since diagnosis or treatment completed	Assume immune – do not issue
	No documentation or negative IgG since treatment or diagnosis	Rapid IgG test and give IVIG if negative or equivocal If not possible to test within 3 days of exposure, give IVIG
Group B (ii)	Offer IVIG regardless of status	

2.2.4 Immunocompetent vulnerable contacts: pregnant women

2.2.4.1 Assessing susceptibility

Seroprevalence studies have shown that less than 1% of individuals born before 1970 and less than 10% born between 1970 and 1989 are antibody negative to measles. The low susceptibility is confirmed by few cases being confirmed in these age groups (data collated by UKHSA Immunisation and VPD Division at Colindale). Younger adults may have been naturally infected or vaccinated as children, with those born after 1978 being eligible for a second dose of measles-containing vaccine during the 1994 schools campaign. Routine measles IgG tests are likely to be specific and therefore have a high positive predictive value in adult populations (27).

Individuals who tested IgG positive or equivocal for measles antibody on standard assays were all shown to have detectable measles antibody by neutralisation assays performed at the Virus Reference Department, Colindale (VRD). Therefore, HNIG is unlikely to offer additional benefit to individuals who are measles IgG positive or equivocal. As routine antibody tests lack sensitivity, however, a high proportion of those found to be measles IgG equivocal or negative are likely to be truly immune. Therefore, in older women (born before 1990) with a reliable history of measles infection, antibody testing is unnecessary and should be avoided.

Individuals born after 1990 are unlikely to have been exposed to natural measles and will mainly have acquired immunity through vaccination. Around 90% of individuals respond to a single dose of measles-containing vaccine and around 95% will be protected following 2 doses.

2.2.4.2 Management of pregnant contacts

Recommendations for pregnant women are therefore based upon a combination of age, history and/or antibody testing. The current recommendations are summarised in Table 4.

Table 4. Assessment and treatment of pregnant women

Born before 1990	History of measles infection	Assume immune
	No history of measles infection	Test and administer HNIG within 6 days only if measles antibody negative
	History of 2 measles containing vaccines	Assume immune
Born 1990 or later	History of 2 measles vaccines	Assume immune
	History of one measles vaccine	Test and administer HNIG within 6 days only if measles antibody negative
	Unvaccinated	Test and administer HNIG if measles antibody negative. If not possible to test within 6 days of exposure, offer HNIG.

The main aim of measles PEP for pregnant women is attenuation of disease and therefore human normal immunoglobulin (HNIG) can be used. This will be issued up to 6 days after exposure, allowing time for assessment of immunity status in most instances. Where a second exposure occurs more than 3 weeks after a first dose of immunoglobulin, a further dose may need to be considered. Pregnant women who remain susceptible should be reminded to have MMR vaccination following delivery to protect them in subsequent pregnancies.

2.2.5 Immunocompetent vulnerable contacts: infants

Most UK born mothers were born after routine measles vaccination was introduced and are unlikely to have had exposure to natural measles. Among vaccinated mothers, the levels of trans-placentally acquired antibodies tend to be low and to wane rapidly, generally in a few weeks after birth (28, 29). If mothers have had a history of measles, maternal antibodies may protect for longer, but recent evidence shows that passive maternal immunity is unlikely to confer effective protection later than a few months after birth (28, 29). All infants under 6 months old who have a significant exposure to measles should get HNIG due to the high likelihood of maternal antibodies interfering with the response to MMR vaccine (see Table 5).

Infants aged 6 to 8 months who are household contacts of a case and therefore have a higher intensity exposure should be given HNIG due to the increased risk of more severe disease. Infants aged 6 to 8 months who have exposures in non-household settings are less likely to have the intensity of exposure to develop severe disease and so should receive MMR vaccine. Infants aged 9 months or older should receive MMR vaccine as response to MMR is improved

at this age. Vaccine is also preferred in non-household settings as it may protect against a tertiary wave of cases in that setting.

Where post-exposure vaccination is indicated (Table 5) MMR should ideally be given within 3 days of exposure. Offering HNIG between 3 and 6 days after exposure is unlikely to offer substantial additional benefit in immunocompetent infants. Where exposure is likely to be on-going (for example following a single case in a nursery or during a community outbreak), MMR offered beyond 3 days may provide protection from subsequent exposures.

Table 5. Assessment and treatment of infants

Infants under 6 months	Assume susceptible and administer HNIG, ideally within 72 hours but up to 6 days, regardless of maternal status.	
Infants aged 6 to 8 months	For household exposure, administer HNIG, ideally within 72 hours but up to 6 days if necessary.	For exposures outside of the household, administer MMR, ideally within 72 hours.
Infants 9 months and older	Administer MMR vaccine, ideally within 72 hours of exposure.	

Due to interference from maternal antibody, the efficacy of a dose of vaccine provided between 6 to 11 months of age is lower than that provided at 12 to 13 months (30), and therefore doses offered before one year of age should be discounted and children should be offered 2 doses of MMR vaccine according to the national schedule. All additional immunisations should be recorded in the red book and should be notified to the local Child Health Information System (CHIS).

2.2.6 Defining the time window for receiving post-exposure prophylaxis

Cases are considered infectious from 4 days before to 4 days after the onset of rash with peak infectiousness occurring during the prodromal phase.

Household contacts

For household contacts or any contact with ongoing exposure during the episode of illness, the time window for receiving post exposure prophylaxis should be calculated from the date of onset of rash in the index case.

Other contacts

For other contacts, the time window for receiving post exposure prophylaxis should be calculated from the last day of exposure. In most instances, susceptible contacts will have been exposed on a single day. However, if exposure has occurred over several days (for example, a child attending nursery in the early prodromal phase) the time for receiving post exposure prophylaxis should be calculated from the last day of exposure to the infectious source.

2.2.7 Post-exposure prophylaxis following inadvertent vaccination with measles containing vaccine

Due to the potential for live attenuated vaccines to replicate and cause disease in immunosuppressed individuals, administration of MMR to an immunosuppressed individual should be risk assessed as a potential exposure to measles and managed as per these guidelines (section 2.2). The risk assessment should be undertaken in consultation with the clinician caring for the immunosuppressed patient; if the clinical assessment is that the patient is not sufficiently immunosuppressed and can tolerate the attenuated vaccine virus, IVIG is not required.

Pregnant women do not require post-exposure prophylaxis if they are inadvertently given MMR.

UKHSA and its predecessor organisations has undertaken surveillance of vaccination in pregnancy since 1981 and the data to date are reassuring with regards to maternal and infant outcomes, when MMR is given in pregnancy or shortly prior to pregnancy. However, these cases should be reported and followed up. Further information about MMR vaccine for pregnant women is available online.

2.3 Dosage and administration of immunoglobulins

Public Health England (PHE) performed plaque neutralisation testing many of the currently available immunoglobulin products manufactured by BPL and Baxalta and has received similar data from CSL Behring. Based on these results and applying the protective per/kg dose established by Endo and others (31), the doses of intramuscular HNIG recommended in the past are not fully protective (9), and therefore a fully protective dose cannot be realistically achieved using an intra-muscular injection (see Annexe 3 for more information). The following recommendations are therefore made allowing for the lowest levels of neutralising measles antibody observed in products available in the UK.

2.3.1 Immunosuppressed patients

For immunosuppressed individuals, the protective dose should be provided using intravenous immunoglobulin (IVIG). This is available through NHS hospital pharmacies and not from UKHSA stockholders. This would constitute a grey indication in the current National Demand Management plan.

Based on testing results of products from 3 manufacturers the mean content of measles antibody by plaque neutralisation varies from 4 to 34 IU/ml (80 to 330 IU/g) for IVIG. A minimum protective dose of approximately 11 IU/kg measles antibody should therefore be achievable using a dose of 0.15 g/kg of IVIG. Products available are listed in Annexe 3.

2.3.2 Immunocompetent infants and pregnant women

For immunocompetent infants and pregnant women, who are normally managed in the community where IVIG is not practical, intramuscular HNIG is recommended. Given the lower dose of measles antibody recommended, the aim of providing HNIG is to attenuate, rather than prevent, disease. The following intra-muscular doses are recommended:

- pregnant women: approximately 3,000mg
- infants: 0.6ml/kg up to a maximum of 1,000mg

Subgam® can be issued from UKHSA stockholders on request. Other SCIg products available in the NHS (including Cutaquig, Cuvitru, Hizentra and Gammanorm) are available from local hospital pharmacies and have been shown to contain similar levels of measles antibody. Products used for measles post exposure prophylaxis should contain a minimum of 150mg/ml of human normal immunoglobulin (IgG). A current list of available products is given in Annexe 3.

The current summary of product characteristics (SPC) covering these products may not mention intramuscular administration. Given the clinical imperative to treat these contacts urgently, it is reasonable to use available HNIG products intramuscularly so long as use via this route is acknowledged to be off-label. There are no specific contraindications to IM use listed for the products listed in annex 3, except for Cuvitru. If Cuvitru is the only immunoglobulin product available, subcutaneous administration would be suitable but due to slower absorption is likely to be associated with delayed action. Depending on clinical urgency, off-license IM administration based on a benefit-risk discussion would be a consideration. The functional biological activity of these produces is expected to be equivalent. In the absence of data from the manufacturers, users are asked to report back to UKHSA any concerns over tolerability with IM use.

2.3.3 Issuing HNIG from the Rabies and Immunoglobulin Services (RIgS) at UKHSA Colindale

HNIG (Subgam) can be issued by the Rabies and Immunoglobulin Service (RIgS) at UKHSA Colindale, and from a small number of stockholders across the country, the list of which is available.

In-hours service through UKHSA Colindale

For practical purposes, requests that are made Monday to Friday will be ordered through Movianto for delivery to arrive on the next working day.

Requests received after 1pm cannot be ordered or requested until the next working day.

Ordering of immunoglobulin on a Friday will only be possible if the delivery address is open on a Saturday. If this is not the case, a courier would need to be arranged or the issue would need to wait until the next working day.

Alternatively, HNIG can be issued from the nearest stockholder.

Further information on issuing of immunoglobulin is available online.

Out-of-hours service at UKHSA Colindale

Although UKHSA can issue products through Movianto at weekends and bank holidays to go to a named delivery site, if HNIG is required urgently it may be more practical to source it from the local trust.

Further information on issuing of immunoglobulin is available online.

3. Specific settings and situations

All staff working in healthcare settings with any contact with patients (including ambulance drivers and receptionists for example) should have their immune status assessed by their employer and, if non-immune or unclear, offered MMR vaccination. Satisfactory evidence of protection would include documentation of having received 2 doses of MMR or having had positive antibody tests for measles and rubella. Further details can be found in the Green Book: Immunisation of healthcare and laboratory staff: the green book, chapter 12.

Infection prevention and control guidance for clinical settings can be found at National Infection Prevention and Control Manual. Infection prevention and control measures for measles in healthcare settings may be found at: Guidance for risk assessment and infection prevention and control measures for measles in healthcare settings.

The Health and Safety Executive (HSE) publish advice for other settings.

3.1 Primary care settings

Whenever possible, signs should be placed in GP surgery waiting areas advising patients with any rash illness to report to reception. Receptionists should know that any patients with fever and rash are potentially infectious and, ideally, should attend at the end of surgery to minimise the risk of transmission. Where patients with a fever and rash attend when other patients are in the waiting room, they should be directed to a side room.

When a GP refers a suspected measles case to A&E or hospital they should inform the hospital staff ahead of time, so that the case can be appropriately isolated on arrival.

When a likely case of measles is reported from primary care, the HPT is responsible for undertaking the public health risk assessment identifying all the likely settings where vulnerable individuals may have been exposed. The HPT will be able to advise on infection control measures and, if for example the patient was not isolated on arrival to a primary care setting and exposed other patients in the waiting room, the surgery will be expected to identify vulnerable patients within the exposure window and clinically assess the risk to each patient based on their vaccine history and underlying condition or treatment. The HPT will support these assessments and advise on post-exposure measures as per current guidelines. The majority of exposed individuals will be assessed as low risk either because they are healthy or already protected and will simply require a warn-and-inform message from the surgery. A small number of vulnerable contacts may be at risk of serious measles infection, and the GP has a duty of care to these patients and is responsible for their clinical management.

3.2 Acute hospital settings

3.2.1 General control measures

Suspected measles cases that are hospitalised (wards or A&E) need to be appropriately isolated. The hospital Infection Control Team (ICT) should be informed of all suspected measles cases in their Hospital Trust so that they can undertake a risk assessment and provide appropriate advice. The ICT should help to assess the exposure of patients, with particular attention to identifying and managing immunosuppressed and vulnerable contacts. They should also liaise with occupational health to assess the status of any exposed health care staff . Hospital ICTs should have the main responsibility for identifying contacts exposed in the hospital setting and will need to work with HPTs on the follow up and management of those contacts who are now in the community.

3.2.2 Considerations for contact tracing through ‘warn and inform’ messages

When detailed information on the health and immune status of contacts is difficult to obtain (for example patients exposed in an emergency department waiting rooms), attempting to obtain detailed medical information on a large number of individuals at low risk could lead to unnecessary delay. In these situations, contact tracing through mass messaging (for example by email, text or letter) should be considered. This would involve the hospital infection control team contacting all individuals who were in the same area as the index case and providing information (for example, by using a link to a web page) about measles and advising individuals who may be vulnerable to seek medical advice. A template warn and inform letter, along with an easy read version, is provided online.

Similarly, this approach can be used by HPTs to contact large groups of individuals who may all have been exposed in the community, and for whom contact details exist (for example, passengers on a coach).

3.2.3 Considerations for health care workers

All healthcare workers (including receptionists, ambulance workers for example) should have satisfactory evidence of protection against measles to protect both themselves and their patients. Satisfactory evidence of protection includes documentation of having received 2 or more doses of measles containing vaccine and/or a positive measles IgG antibody test (32).

Health care workers (HCWs) who are exposed to a confirmed or likely case and do not have satisfactory evidence of protection should be excluded from work from the 5th day after the first exposure to 21 days after the final exposure. If HCWs are tested rapidly after exposure, they

can continue to work if found to be measles IgG positive within 7 days of exposure (as this is too early to be due to infection from the recent exposure).

Where MMR vaccine is given post-exposure, it is unlikely to prevent the development of measles but if the HCW remains symptom-free for at least 14 days after MMR vaccine was given, they can return at that stage. Health care workers with satisfactory evidence of protection can continue to work normally but should be advised to report to Occupational Health (OH) if they develop prodromal symptoms or a fever between 7 days after the first exposure and 21 days after the last exposure. Exposed HCWs that develop fever or rash should be excluded from all work until 4 full days after onset of the rash. Those HCWs should be treated as an epidemiologically confirmed case and laboratory confirmation and notification should be sought in the usual way.

3.3 Educational settings

Confirmed and likely cases should be excluded from nursery or school for the infectious period (from 4 days before rash onset and for a further 4 full days) Given the high risk of secondary infection following measles, it is advisable to return to nursery or school only after full recovery.

Susceptible contacts of cases (for example unvaccinated siblings) are at high risk of developing measles and should be advised to self-exclude from school for the incubation period.

Cases considered unlikely may be suffering from other infections, some of which may have public health implications (for example scarlet fever, roseola (HHV6 infection) – see differential diagnosis in Annexe 1) and therefore, general advice about staying away from school during the acute illness should be provided.

A health care staff member or appropriate senior staff at the institution (for example the school nurse and/or welfare officer, head teacher, health and safety officer or student health advisor) should be informed of all cases that are likely or confirmed. Schools should be asked whether they are aware of any vulnerable students or teachers, even if not yet exposed, so that their status can be assessed, and steps taken to reduce the risk of future exposure. Head teachers may wish to consider excluding unvaccinated pupils who have been exposed, because of the risk to other students. An appropriate letter or factsheet should be sent to the school or nursery for dissemination to parents (nursery or school) or students (higher education setting). The local NHS England Screening and Immunisation team and/or Director of Public Health (DPH) for the local authority should also be informed.

More detailed information about infection control in school settings can be found in the UKHSA guidance on infection control in schools and other childcare settings as well as in advice on measles and school trips.

3.4 International travel

All likely or confirmed cases linked to international travel, or who have travelled on aircrafts (including domestic travel) should be notified by email to the UK International Health Regulations (IHR) Focal Point – IHRNFP@phe.gov.uk – at UKHSA Colindale, and the national immunisation team via Immunisation.Lead@phe.gov.uk

For likely or confirmed cases who were infectious whilst abroad in a non-endemic country, or who are likely to have acquired their infection in a non-endemic country, contact with the relevant National Focal Point should be made through the IHR Focal Point and the national immunisation team at UKHSA Colindale.

Further information can be found in the International Health Regulations 2005: UK National Focal Point Communication Protocol.
Reporting of cases linked to international travel is an essential part of international surveillance and reporting should not be limited only to cases where immediate post-exposure interventions can be conducted. Classification of imported cases and identifying international links between cases is an important component of regional and global elimination and would be expected by most other countries.

3.4.1 Air travel

For a likely or confirmed case of measles who has travelled internationally during the infectious period, a risk assessment should be undertaken. The flight details should be collected and added as a context on HPZone/CIMS, so that colleagues across UKHSA can access the details if other linked cases are reported later.

In most instances, HPTs should make contact with the airline, and ask the airline to circulate a ‘warn and inform’ message to all passengers via text or email, with a link to further information about measles prevention and control, information about when and how passengers should contact their local HPT, and about what to do if they develop symptoms.

Full details about the assessment and public health action following a case of measles on aircrafts are provided in the UKHSA guidance for health protection staff managing cases that have undertaken international travel and travel by air.

3.4.2 Other modes of transport

For likely or confirmed cases of measles linked to travel other than by air during the infectious period, sending a ‘warn and inform message’ through the transport provider should be considered. If the transport provider does not have contact details of passengers, no further action is required, unless a defined group is known from the index case and can be contacted through other means (for example, children on a school trip).

More detailed guidance and template warn and inform messages are available in the UKHSA guidance for health protection staff managing cases that have undertaken international travel and travel by air.

3.5 Outbreaks

An outbreak is defined as 2 or more epidemiologically linked cases that occur within one incubation period of each other (that is the second case occurs between 7 and 21 days of the first case) (2).

While most outbreaks will occur within the household setting, an outbreak control team may need to be convened when transmission has occurred in other settings where a large number of people have been exposed (for example, school outbreak) or where the population exposed may be more vulnerable (for example hospital outbreak). If the reported number of measles cases across a local area or community is above the expected level, an outbreak control team should be considered to identify common factors and implement control measures.

3.5.1 Outbreak control team

An appropriate outbreak control team is likely to include, if appropriate:

- health protection specialist from the local HPT
- screening and immunisation team representative
- education representative from local authority
- school nurse or team leader
- GPs (if identifiable practices within community)
- local director of public health (DPH) or appropriate representatives
- local Integrated Care Board representative
- communications leads (UKHSA, local authority to liaise as necessary)
- acute trust representative (Director of Infection Prevention and Control; microbiologist (if different); infection control team, paediatric consultant or medical director, occupational health)

Hospital outbreaks or clusters will require close liaison with the Director of Infection Prevention and Control; microbiologist (if different), Infection Control Team, Clinical Directors or Service Managers, Occupational Health Manager, as well as the local DPH.

Expert advice can also be sought from the Virus Reference Department or the national Immunisation and Vaccine Preventable Diseases team at UKHSA Colindale.

3.5.2 Outbreaks in places of detention

Prisons and other places of detention have large populations of people living in close proximity who transfer in and out of the community and to other prisons frequently. Individuals are also likely to be vulnerable, to have complex medical needs and may also be under-vaccinated. Outbreaks of measles and other infectious diseases therefore present unique challenges. An outbreak of measles in a prison setting will require close liaison with UKHSA and NHS Health and Justice leads (Annexe 4).

3.5.2 Planning and response

Health protection teams should work with their local NHS England Screening and Immunisation teams to ensure that the necessary resources are available within their area to manage outbreaks. HPTs should know where to access urgent laboratory testing services (particularly measles IgG) and HNIG supplies. Access to a small stock of MMR vaccine should be available by the next day, including at weekends, and HPTs should ensure they know which walk-in clinics or out of hours GP services are available at the weekend to enable prompt administration of MMR vaccine or HNIG if required.

When outbreaks occur in an institutional setting such as a school, university or place of detention, all individuals in the setting who are susceptible or incompletely vaccinated should be offered MMR vaccine promptly, even if direct contact with the index case has not occurred. If a school with an outbreak is planning a school trip, all students who are not vaccinated or incompletely vaccinated should be vaccinated at least 2 weeks prior to departure. Similar considerations apply to students about to go on work placements, particularly in health care or with vulnerable patients.

Further information containing advice around school trips and international travel can be found in the Measles frequently asked questions for schools.

If an outbreak occurs in an institutional setting where vaccination coverage is known to be low, an urgent campaign should be considered. Vaccination of all susceptible students in a school for example, will limit the risk of tertiary transmission within the setting. Commissioners should have contracts in place to provide support for a vaccination campaign in defined settings, such as schools, and providers should have arrangements in place to source MMR vaccine promptly for outbreak control.

References

1. Moss WJ, Griffin DE. Measles. Lancet, 2012
2. Public Health England, Public Health Wales, Public Health Agency, Health Protection Scotland (2019). 'UK Measles and Rubella elimination strategy'
3. UKHSA. 'Risk assessment for measles resurgence in the UK'
4. Dar O, Gobin M, Hogarth S, Lane C, Ramsay M. 'Mapping the Gypsy Traveller community in England: what we know about their health service provision and childhood immunization uptake' Journal of Public Health (Oxford), 2013
5. Hanratty B, Holt T, Duffell E, Patterson W, Ramsay M, White JM and others. 'UK measles outbreak in non-immune anthroposophic communities: the implications for the elimination of measles from Europe' Epidemiology and Infection 2000
6. Baugh V, Figueroa J, Bosanquet J, Kemsley P, Addiman S, Turbitt D. 'Ongoing measles outbreak in Orthodox Jewish community, London, UK' Emerging Infectious Diseases 2013
7. Perry RT, Halsey NA. 'The Clinical Significance of Measles: A Review' The Journal of Infectious Disease 2004
8. WHO. 'Manual for the laboratory diagnosis of measles and rubella infection' Geneva: WHO Documents Production Services, 2007
9. UKHSA. Green Book (2005). Chapter 21: measles
10. Campbell H, Andrews N, Brown KE, Miller E. 'Review of the effect of measles vaccination on the epidemiology of SSPE' International Journal of Epidemiology 2007
11. Manikkavasagan G, Ramsay M. 'The rationale for the use of measles post-exposure prophylaxis in pregnant women: a review' Journal of Obstetrics and Gynaecology 2009
12. Manikkavasagan G, Ramsay M. 'Protecting infants against measles in England and Wales: a review' Archives of Disease in Childhood 2009
13. Marin M, Nguyen HQ, Langidrik JR, Edwards R, Briand K, Papania MJ and others. 'Measles transmission and vaccine effectiveness during a large outbreak on a densely populated island: implications for vaccination policy' Clinical Infectious Diseases 2006
14. Centers for Disease C, Prevention. 'Measles outbreak among school-aged children, Juneau, Alaska, 1996' Morbidity and Mortality Weekly Report 1996
15. Hope K, Boyd R, Conaty S, Maywood P. 'Measles transmission in health care waiting rooms: implications for public health response' Western Pacific Surveillance and Response Journal 2012
16. Bloch AB, Orenstein WA, Ewing WM, Spain WH, Mallison GF, Herrmann KL and others. 'Measles outbreak in a pediatric practice: airborne transmission in an office setting' Pediatrics 1985: volume 75, pages 676 to 683
17. Ehresmann KR, Hedberg CW, Grimm MB, Norton CA, MacDonald KL, Osterholm MT. 'An outbreak of measles at an international sporting event with airborne transmission in a domed stadium' The Journal of Infectious Diseases 1995
18. Sundell N, Dotevall L, Sansone M, Andersson M, Lindh M, Wahlberg T, Tyrberg T, Westin J, Liljeqvist J, Bergström T, Studahl M, Andersson L. 'Measles outbreak in

Gothenburg urban area, Sweden, 2017 to 2018: low viral load in breakthrough infections' Eurosurveillance

19. le Polain de Waroux O, Saliba V, Cottrell S, Young N, Perry M, Bukasa A and others. 'Summer music and arts festivals as hot spots for measles transmission: experience from England and Wales, June to October 2016' EuroSurveillance 2016
20. Ward KN, Gray JJ, Fotheringham MW, Sheldon MJ. 'IgG antibodies to human herpesvirus-6 in young children: changes in avidity of antibody correlate with time after infection' Journal of Medical Virology 1993
21. Ward KN, Turner DJ, Parada XC, Thiruchelvam AD. 'Use of immunoglobulin G antibody avidity for differentiation of primary human herpesvirus 6 and 7 infections' Journal of Clinical Microbiology 2001
22. Claesson BE, Svensson NG, Gotthardsson L, Gotthardsson L, Garden B. 'A foodborne outbreak of group A streptococcal disease at a birthday party' Scandinavian Journal of Infectious Diseases 1992
23. Rice PS, Cohen BJ. 'A school outbreak of parvovirus B19 infection investigated using salivary antibody assays' Epidemiology and Infection 1996
24. Joseph PR. 'Incubation period of fifth disease' Lancet 1986
25. UKHSA. Green Book Chapter 28: Rubella
26. Watson JC, Hadler SC, Dykewicz CA, Reef S, Phillips L. 'Measles, mumps, and rubella – vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: recommendations of the Advisory Committee on Immunization Practices (ACIP)' MMWR Recommendations and Reports 1998: volume 47, pages 1 to 57
27. Vyse AJ, and others. 'Interpreting serological surveys using mixture models: the seroepidemiology of measles, mumps and rubella in England and Wales at the beginning of the 21st century' Epidemiology and Infection 2006
28. Leuridan E, Hens N, Hutse V, Ieven M, Aerts M, Van Damme P. 'Early waning of maternal measles antibodies in era of measles elimination: longitudinal study' BMJ 2010
29. Waaijenborg S, Hahné SJ, Mollema L, Smits GP, Berbers GA, van der Klis FR, de Melker HE, Wallinga J. 'Waning of maternal antibodies against measles, mumps, rubella, and varicella in communities with contrasting vaccination coverage' The Journal of Infectious Diseases 2013
30. Klinge J, Lugauer S, Korn K, Heininger U, Stehr K. 'Comparison of immunogenicity and reactogenicity of a measles, mumps and rubella (MMR) vaccine in German children vaccinated at 9-11, 12-14 or 15-17 months of age' Vaccine 2000
31. Endo A, Izumi H, Miyashita M, Taniguchi K, Okubo O, Harada K. 'Current efficacy of postexposure prophylaxis against measles with immunoglobulin' The Journal of Paediatrics 2001
32. Janeway CA. 'Use of concentrated human serum gamma-globulin in the prevention and attenuation of measles' Bulletin of the New York Academy of Medicine 1945: volume 21, issue 4, pages 202 to 222
33. Stokes J, Maris EP, Gellis SS. 'Chemical, clinical, and immunological studies on the products of human plasma fractionation. Xi. The use of concentrated normal human

serum gamma globulin (human immune serum globulin) in the prophylaxis and treatment of measles' Journal of Clinical Investigation 1944

34. Black FL and Yannet H. 'Inapparent measles after gamma globulin administration' JAMA network 1960
35. King GE, Markowitz LE, Patriarca PA, Dales LG. 'Clinical efficacy of measles vaccine during the 1990 measles epidemic' The Paediatric Infectious Disease Journal 1991
36. Christenson B and Bottiger M. 'Measles antibody: comparison of long-term vaccination titres, early vaccination titres and naturally acquired immunity to and booster effects on the measles virus' Vaccine 1994
37. Ohsaki M, Tsutsumi H, Takeuchi R, Kuniya Y, Chiba S. 'Reduced passive measles immunity in infants of mothers who have not been exposed to measles outbreaks' Scandinavian Journal of Infectious Disease 1999
38. Watson GI. 'Protection after exposure to measles by attenuated vaccine without gamma-globulin' BMJ 1963
39. Ruuskanen O, Salmi TT, Halonen P. 'Measles vaccination after exposure to natural measles' The Journal of Pediatrics 1978
40. Rice P, Young Y, Cohen B, Ramsay M. 'MMR immunisation after contact with measles virus' The Lancet 2004

Annexe 1. Differential diagnosis

Roseola (exanthema subitum, sixth disease)

Pathogen

Human herpesvirus 6 (HHV6), occasionally HHV7.

Clinical presentation

Generally mild, often asymptomatic. When symptomatic, illness starts with 3 to 5 days of fever, which might be followed by a maculopapular rash, although most children have a viral illness without rash. Unlike measles, the onset of rash occurs when patients improve clinically and the fever recedes.

Epidemiology and transmission

Most infections occur in children aged 6 to 24 months. Transmission occurs through the respiratory route or droplet transmission. Seroprevalence studies have shown that by 2 years of age 90% of children are immune against HHV6 (20). Cases in older children may be due to HHV7, which tends to be acquired later in life, with seroprevalence studies showing that about 65% of children in the UK are immune by the age of 3 years (21). As HHV6 and HHV7 remain latent after infection, they can therefore reactivate among immunosuppressed individuals later on in life.

Incubation period

Around 5 to 15 days.

Scarlet fever

Pathogen

Group A streptococcus.

Clinical presentation

Sore throat, pharyngeal exudate, high fever. Cough is generally absent. The maculopapular rash typically appears about 12 to 48 hours after the start of symptoms. It generally starts on the abdomen, spreading to neck, back and limbs. A white coating of the tongue may be present (‘strawberry tongue’).

Epidemiology and transmission

Transmission occurs through the respiratory route or droplet transmission. It is most common during winter months or in early spring. Scarlet fever affects mostly children of school and pre-school age.

Incubation period

Around 2 days, ranging from 1 to 5 days (22).

More information on scarlet fever and its management can be found in the Scarlet fever: managing outbreaks in schools and nurseries guidelines.

Fifth disease ('slapped cheek' syndrome)

Pathogen

Parvovirus B19.

Clinical presentation

The infection generally presents with typical features of 'slapped cheeks', followed by a rash which is most visible on the extremities. There may be prodromal symptoms leading to the rash, such as coryza, fever or headache. Arthralgia and arthritis may be present – these are more common among adults.

Epidemiology and transmission

Transmission occurs through the respiratory route or droplet transmission. It is most common during winter months or in early spring. Children of all ages can be affected, and an infection among adults is not uncommon. Secondary attack rates among households and schools is high (23). Transmission occurs in the week preceding the rash and individuals are considered non-infectious when the rash appears.

Incubation period

Around 13 to 18 days (24).

Rubella (German measles)

Pathogen

Rubella virus.

Clinical presentation

Generally mild, asymptomatic in up to 50% of the cases (particularly in children). A prodromal phase of 1 to 5 days may precede the rash, with symptoms of malaise and coryza, with or without fever. Post-auricular and sub-occipital lymphadenopathy may be present. The rash is non-specific, generally mild and is most often seen on the face and behind the ears, where it starts before spreading.

Epidemiology and transmission

Rubella is prevented by MMR vaccination and few cases of rubella are now being reported. Most reported cases are imported.

Incubation period

14 days (range 12 to 21 days) (25).

Infectious mononucleosis (glandular fever)

Pathogen

Mostly Epstein-Barr virus (EBV). Rarely CMV, HHV6, HSV.

Clinical presentation

It mainly presents with a sore throat (pharyngitis or tonsillitis). Malaise and fever are common presentations. A rash only occurs in only about 10% of infected individuals and may not always be maculopapular. A more typical maculopapular rash frequently occurs after starting antibiotic treatment for pharyngitis.

Epidemiology and transmission

EBV is transmitted mostly through direct contact with saliva. About half of infections are asymptomatic but more so in young children than in adolescents and adults.

Incubation period

Thought to be about 30 to 50 days.

Other differential diagnoses to consider

Zika, Dengue, Chikungunya, primary HIV infection and syphilis.

Annexe 2. Classification of immunosuppression (measles)

In contrast to many other infections, protection from measles is primarily due to humoral or antibody-based immunity. The definitions of immunosuppression, therefore, will differ from those infections or diseases that are primarily controlled by cellular immunity.

Group A. Individuals who should develop and maintain adequate antibody from past exposure or vaccination

Manage on basis of evidence of protection at any time (prior to or since the diagnosis or treatment end):

Patients receiving or within 6 months of completing immunosuppressive chemotherapy or radiotherapy for malignant disease (other than those with all, 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.

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.

Group B. Individuals who lose or may not maintain adequate antibody levels from past exposure or vaccination

B (i)
Manage on basis of IgG obtained at the time of exposure (or since the diagnosis or treatment end):

- patients on or after completion of immunosuppressive chemotherapy for acute lymphoblastic leukaemia (all)
- patients with lymphoproliferative disorders (including haematological malignancies such as indolent lymphoma, leukaemia and plasma cell lymphoma)
- patients who have received a solid organ transplant
- patients more than 12 months after receiving a haematopoietic stem cell transplant (HSCT)
  patients receiving or within 6 months of completing biological therapies (alone or in combination with steroids); these include:
    - monoclonal antibodies, for example, alemtuzumab, ofatumumab
    - rituximab cytokine inhibitors, for example, etanercept
- patients with a diagnosis of acquired immunodeficiency syndrome (AIDs)

B (ii)
Offer PEP regardless of status:

- patients who have received a haematopoietic stem cell transplant (HSCT) within the past 12 months
- patients with persistent agammglobulinaemia (IgG less than 3g/L) due to primary immunodeficiency (for example, common variable immunodeficiency) or secondary to disease or therapy (this group may already be on long term IVIG replacement, which should provide equivalent protection to post exposure immunoglobulin)

Annexe 3. HNIG and MMR as post-exposure prophylaxis

HNIG

The effectiveness of intra-muscular (IM) HNIG for measles prophylaxis was first established in young children in the 1940s. Janeway and others (32) published a controlled study in children which demonstrated the effectiveness of gamma globulin in preventing disease if administered to household contacts within 4 to 5 days of exposure. In this study, families of index cases with 2 or more susceptible household contacts were divided into 2 groups; the groups were similar with respect to age and exposure history. The intervention group received intra-muscular human serum gamma globulin at a dose of 2.5mls for children below 5 years and 5mls for children over 5 years. The attack rate in the control group was 43 out of 46 (94%) compared to 18 out of 62 (29%) in the intervention group; consistent with an efficacy of 69%. In addition, 17 of the 18 children who developed measles in the intervention group compared to only 2 of 43 in the control group had a mild disease suggesting that immunoglobulin can also modify clinical measles.

Further uncontrolled studies in the USA (33, 34) confirmed the effectiveness of immunoglobulin as post-exposure prophylaxis against measles. In 1943, 891 susceptible household contacts (mainly children) received intramuscular injections of between 0.5 and 5mls of human serum gamma globulin within 7 days of exposure. The attack rate was 96 out of 237 (41%), 52 out of 107 (49%) and 148 out of 344 (43%) amongst children up to 5 years of age, those aged 6 to 12 years and older children and adults respectively. All subjects experienced a mild infection. Within the same age range, increasing the dose from 2 to 5mls increased the probability of preventing measles from 66% to 80%, suggesting that the total dose of measles antibody given was important. In 1960, 38 susceptible children received gamma globulin (within 24 to 48 hours from onset of rash in index case) during an outbreak in an institution for disabled male children. Nineteen (50%) did not develop any clinical signs of measles.

In 1990, an observational study in the US found the protective efficacy of post exposure HNIG given within 6 days of exposure (assumed to be 4 days prior to rash onset in the index case), was estimated at only 8% (95% CI 0, 59%) (35) One reason for the low observed effectiveness at this time may be due to changes in the measles antibody content of HNIG. This hypothesis is supported by the only more recent study to investigate immunoglobulin as post-exposure prophylaxis (31), Endo and others (31) found that in 14 children who received immunoglobulin (at the Japanese recommended dose of 0.33ml/kg) with a titre of less than 16 IU/ml, 8 (57%) had clinically evident measles, whilst the 13 individuals who received immunoglobulin with a titre of more than 40IU/ml were completely protected from disease.

There is currently no accepted minimum level of measles antibody required in HNIG in England and Wales. Human Normal Immunoglobulin (HNIG) is prepared from pooled plasma derived

from blood donations (sourced from outside the UK due to the theoretical risk of transmission of variant CJD). Levels of measles antibody are lower in people with vaccine-induced rather than naturally acquired immunity (36), and antibody levels are lower in the absence of exposure to circulating measles (37). As the proportion of vaccinated donors has risen, and as control of measles has improved in most countries, there is likely to have been a concomitant decline in measles neutralising antibodies derived from their plasma. As the dose of measles antibody given in HNIG appears to be important in providing efficacy (31, 33), it is likely that currently recommended products and doses are significantly less effective than observed in earlier studies. This explanation is also likely to apply to most of the studies cited in the 2014 Cochrane review, which were mainly conducted before 1960. In addition, most studies published to date have been conducted predominantly in young children. The appropriate dose of HNIG to provide sufficient antibody for adults exposed to measles in the UK has not been clearly established and must therefore be extrapolated from studies in children.

There is no consistent evidence regarding the efficacy of immunoglobulins provided 4 to 6 days after exposure and its use is primarily to reduce severity of disease in vulnerable contacts. Therefore, it is important to administer immunoglobulin to vulnerable contacts as soon as possible after exposure and ideally within the first 72 hours.

Measles mumps and rubella (MMR) vaccination

The evidence for the effectiveness of measles vaccine as post exposure prophylaxis is less well established, despite the current recommendation of use within 72 hours of exposure. Two early studies (38, 39) proposed that vaccine is effective in preventing secondary cases if given soon after exposure. In 1963, Watson (38) suggested prevention of clinical disease in family contacts from a single household when vaccine was administered one day after onset of rash in the index case. In the second study, protection amongst school contacts was suggested for up to 14 days after exposure.

During the 1990 US measles epidemic however, the protective efficacy of post exposure vaccination given to household contacts aged one to 5 years within 3 days of rash onset in the primary case, was estimated at only 4% (95% CI 0, 36%). In a more recent report (40), MMR vaccine failed to protect any of 4 contacts when given within 4 days of exposure in a UK nursery setting. The lower observed effectiveness in practice is likely to be partly explained by the timing and nature of exposure.

Overall, the limited evidence suggests that MMR may prevent disease, or reduce its severity, when administered soon after exposure (within 72 hours). Beyond this period, MMR should protect individuals from future measles exposures and provide protection against mumps and rubella. Importantly, in outbreak-prone settings such as schools and nurseries, MMR should prevent tertiary transmission in those who have not already been significantly exposed As neither immunoglobulin nor vaccine are fully effective in preventing measles, exposed individuals who receive post-exposure treatments will still be an infection control risk, for

example in health care settings. Any rash illness within the 21 days following exposure (the maximum incubation period (9)) could be measles, although measles like symptoms can occur after vaccination. Oral fluid samples can be used to type the virus (vaccine or wild type) if taken within one week of onset.

Assessing population susceptibility by age

In the absence of reliable information on the individual's history of measles infection and vaccination status, an assessment of susceptibility should take into account the exposure to natural disease. For example, individuals who were born before 1970 and grew up in the UK are very likely to have had natural exposure to measles, and although measles vaccination was introduced in 1968, coverage remained low until the mid-1980s and endemic measles continued to circulate (9). Seroprevalence studies suggest that fewer than 1% of individuals born before 1970 are susceptible to measles (27).

As vaccination coverage increased during the 1970s and 1980s, fewer individuals were exposed to circulating measles, and seroprevalence studies suggest that up to 10% of individuals born during that period are non-immune. Since 1990, relatively high vaccination coverage has resulted in little endemic measles circulation in the UK, with the exception of a few localised outbreaks. Individuals born in 1990 or after will therefore only be immune through vaccination, and if unvaccinated are highly likely to be susceptible.

For individuals who were born and raised abroad, the assessment is more difficult. With the exception of the US, where a measles vaccine was introduced in 1963 and where the incidence of measles was on the decline in the 1960s, all other countries have had pre-vaccine endemic measles circulation until 1970, or later. Most adults from countries where measles control is poor or where vaccination was introduced later are likely to be immune and following the guidelines for individuals born in the UK would therefore be a safe and conservative approach.

Human normal immunoglobulin products available, May 2023

	Brand	**Sizes available**
5% IVIg	Flebogamma DIF	2.5g, 5g, 10g, 20g
	Octagam 5%	2.5g, 5g, 10g
	Intratect 5%	2.5g, 5g, 10g
	Gammagard	10g
10% IVIg	Gammaplex 10%	5g, 10g, 20g
	Gamunex	5g,10g, 20g
	Intratect 10%	5g, 10g, 20g
	Iqymune	2g, 5g, 10g, 20g
	Octagam 10%	2g, 5g, 10g, 20g

	Brand	Sizes available
	Kiovig	1g, 2.5g, g, 10g, 20g, 30g
	Privigen	2.5g, 5g, 10g, 20g
SCIg	Cutaquig	1g, 1.65g, 2g, 3.3g, 4g, 8g
	Cuvitru	1g, 2g, 4g, 8g, 10g
	Hizentra	1g, 2g, 4g
	Hizentra PFS	1g, 2g, 4g
	Subgam	1g, 2g, 4g

NHS trusts are encouraged to use their local immunoglobulin stock where possible. This allows more timely administration and also ensures limited UKHSA stock can be reserved for use in the community. The NHS England Commissioning criteria policy for the use of therapeutic immunoglobulin (Ig) includes the use of Ig for measles (immunosuppressed individuals; pregnant women and infants) in line with the criteria detailed in the policy, available in the Commissioning criteria policy for the use of therapeutic immunoglobulin (Ig) England, 2021.

The acquisition cost of the immunoglobulin used in line with the policy will be reimbursed.

Annexe 4. Management of measles in prisons and other places of detention (PPD)

Please note that the text with blue font in this document within brackets refer to the main guidance.

This guidance provides operational recommendations to assist staff, local UK Health Security Agency (UKHSA) health protection teams (HPTs) and other stakeholders if an incident or outbreak of measles is reported in a prison or other place of detention (PPD). Operational practice may vary due to setting specific considerations.

The following establishments in England are included within the definition of PPDs used in this guidance:

- prisons (both public and privately managed)
- Immigration Removal Centres (IRC)
- Young Offender Institutions (YOI)
- Secure Children's Homes (SCH)
- Secure Training Centres (STC)
- Secure Schools (SS)

Vaccination

All residents entering PPD settings should have their vaccination history checked as part of reception screening. Those with an unknown or incomplete history of measles, mumps and rubella (MMR) vaccination should be offered MMR vaccination following national guidance.

Management of single cases

If an individual in a PPD is suspected to have measles they should be assessed by a clinical member of staff and rapidly isolated away from vulnerable and unvaccinated residents and staff. Steps should be taken to ensure the welfare of those who are isolated. The local health protection team must be notified if the clinician suspects measles and will support with public health management of the case, close contacts and wider risk assessment (see section 2.1) including advising on appropriate testing (section 2.1.1).

The following should be considered:

- standard Infection Prevention and Control (IP&C) measures should be implemented by all healthcare and operational staff including use of appropriate personal protective equipment (PPE)

- the individual should be isolated in a single room with toilet facilities and the door should remain closed
- a risk assessment should be conducted if in-room sanitation is not available, or there are other competing risks that make complete isolation inappropriate
- the impact of complete isolation on an individual's physical, mental health and wellbeing needs to be considered
- risk assessment by the healthcare team, with support from regional HPTs, should be undertaken to consider continued contact with individuals with known immunity to measles (for example, a roommate or member of staff who has a documented history of 2 doses of MMR)
- access to showers, food, medicine and outdoor exercise should be included in the risk assessment
- the local health protection team can assist with such risk assessments; for management of pregnant cases among individuals in PPDs including staff refer to section 2.2.4.2

The need for isolation must be carefully explained to the affected individual, including the nature of the infection, the mode of spread and its significance/implications for the individual.

Confirmed and suspected cases should be isolated for the duration of the infectious period which extends to the end of 4 full days after onset of rash (where the date of rash onset is day 0). Individuals who are immunosuppressed may be infectious for longer and may not display typical symptoms. In this instance the timing of isolation should be adjusted as appropriate in consultation with clinicians managing the case (section 2.3).

The clinical needs of the affected individual should be closely monitored, with admission to an inpatient setting if this is required for clinical care.

Contact tracing

Contact tracing should consider the whole infectious period, which is considered to span from 4 days prior to rash onset to the completion of 4 days after.

Contact tracing should be undertaken to identify individuals (including residents, staff, Prison Escort and Transport Services (PETS) and professional and domestic visitors) who have been in close contact with the case (see section 2.2), with a particular emphasis on identifying all vulnerable contacts (see section 2.2.2.1) who may be eligible for post exposure prophylaxis (PEP). The Health Protection Team will support the setting with this risk assessment. Unvaccinated close contacts of cases are at high risk of developing measles. MMR vaccine given with 72 hours of exposure may reduce the risk of measles infection and a timely offer should be prioritised. Exposed, susceptible individuals should avoid contact with vulnerable individuals (section 2.2.1) and a risk assessment should be conducted to agree the extent of isolation necessary for these contacts.

Staff exposed to a confirmed or likely case, who do not have satisfactory evidence of measles immunity, should be excluded from work from the fifth day after the first exposure to 21 days after the final exposure. If staff are tested rapidly after exposure, they can continue to work if found to be measles IgG positive within 7 days of exposure (as this is too early to be due to infection from the recent exposure). Where MMR vaccine is given post-exposure, it is unlikely to prevent the development of measles but if the staff member remains symptom-free for at least 14 days after MMR was given, they can return to work at that stage. Where staffing levels might lead to concerns for safety of individuals in PPDs the risk assessment should be jointly reviewed with the health protection team.

Given the risk of further cases, all vulnerable individuals in the relevant residential unit should be identified, even if not yet exposed, so that their status can be assessed, and steps taken to reduce the risk of future exposure. This should include staff and residents and careful consideration is required where Mother and Baby Units are part of the setting (section 2.2).

If a case or contact is due to attend a healthcare setting, for example an outpatient setting or emergency department, the setting and the IPC lead should be informed ahead, if possible, to support risk assessment, and if attendance is considered necessary, to ensure appropriate measures are in place to minimise risk.

Courts and custody

If a suspected or confirmed case, or an exposed, susceptible, and therefore potentially infectious contact, is due in court, a risk assessment should be undertaken. Consider rescheduling the appearance or proceed via video link with clear IPC measures in place.

Informing other residents and staff

Where an individual has been identified as having measles, warn and inform information should be provided to other residents and staff, including those in shared residential, education or work settings. The confidentiality of the case/s should be maintained.

Visitors

Information and advice should be readily available for individuals (domestic and professional) visiting the detained setting, including creche or other support settings. Visitors should be reminded not to attend the setting if they have a rash. Use posters and appropriate materials in waiting rooms. Warn and inform information should be provided to contacts.

Outbreaks

In the event of 2 or more cases being identified which are linked by time and place, with the second case occurring within 7 to 21 days of the first, the local HPT will consider convening and leading an urgent incident management team (IMT) to advise on actions and next steps. The IMT may consider vaccination and isolation of staff and residents (see section 3.5.2).

Contact details of your local health protection team are available online.

About the UK Health Security Agency

UKHSA is responsible for protecting every member of every community from the impact of infectious diseases, chemical, biological, radiological and nuclear incidents and other health threats. We provide intellectual, scientific and operational leadership at national and local level, as well as on the global stage, to make the nation's health secure.

UKHSA is an executive agency, sponsored by the Department of Health and Social Care.

Prepared by: Gayatri Amirthalingam and Kevin Brown
Updated by: Rebecca Cordery and Kevin Brown

For queries relating to this document, please contact: Immunisation and Vaccine Preventable Diseases Division at Immunisation@ukhsa.gov.uk

Issue number 5.0

Published: April 2024
Publishing reference: GOV-16347