



Public Health  
England

Protecting and improving the nation's health

# Guidelines on Post-Exposure Prophylaxis for measles

## June 2019

The vial size of Subgam, the human normal immunoglobulin (HNIG) product issued by PHE stockholders, is being changed from 750mg to 1000mg. These updated guidelines provide doses based on the new vial size (1000mg).

As of 1<sup>st</sup> July 2019, some stockholders may still hold a limited number of 750mg vials. For those stockholders with 750mg vials, the following intra-muscular doses are recommended:

**Pregnant women:** approximately 3000 mg (4 vials)

**Infants:** 0.6ml/kg up to a maximum of 750mg (1 vial)

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Public Health England  
Wellington House  
133-155 Waterloo Road  
London SE1 8UG  
Tel: 020 7654 8000  
[www.gov.uk/phe](http://www.gov.uk/phe)  
Twitter: [@PHE\\_uk](https://twitter.com/PHE_uk)  
Facebook: [www.facebook.com/PublicHealthEngland](https://www.facebook.com/PublicHealthEngland)

Prepared by: Jamie Lopez Bernal, Gayatri Amirthalingam, Kevin Brown, Olivier le Polain, Mary Ramsay  
For queries relating to this document, please contact: [Immunisation.lead@phe.gov.uk](mailto:Immunisation.lead@phe.gov.uk)  
Telephone 0208 200 4000



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## Changes from the previous guidelines

### June 2019

New section on inadvertent vaccination with MMR in immunosuppressed individuals.

Update to doses of Human Normal Immunoglobulins following changes to vial sizes.

Updated logistics for ordering and issuing Human Normal Immunoglobulins from the Rabies and Immunoglobulins service at PHE Colindale.

### August 2017

The 2017 PEP guidelines updated the classification of immunosuppressed individuals (Groups A and B) and incorporate additional groups including individuals receiving newer immunosuppressive treatments such as biological therapies.

Recommendations for the post exposure management of infant contacts have been updated. Infants under 6 months of age who have had close contact with a likely or confirmed measles case should be offered HNIG without assessing maternal immune status. This reflects the fact that the majority of UK born pregnant women are protected through vaccination rather than natural exposure and therefore have lower levels of measles antibodies. As a result, their infants will become susceptible at a younger age.

Updated recommendations on the dose and mode of administration of immunoglobulins are summarised. Subcutaneous infusions are not considered practical for immunosuppressed individuals and so intravenous immunoglobulin (IVIG) is the recommended product to be used for post-exposure treatment. IVIG is not sourced from PHE but should be available through NHS hospital pharmacies.

A new section has been included detailing the logistics of ordering Human Normal Immunoglobulins (HNIG) from the Rabies and Immunoglobulins (RIgS) service at PHE Colindale and provides information on the service provided both in and out of hours.

# 1. Overview

Post-exposure prophylaxis (PEP) for measles has historically relied on use of normal immunoglobulin or measles vaccination of vulnerable contacts. However, the effectiveness of post exposure prophylaxis is limited and achieving high coverage with 2 doses of measles- mumps-rubella (MMR) vaccine in the general population remains the optimal way to protect individuals.

Despite this, because of the high risk of serious complications, contact tracing around reported measles cases should prioritise the identification of immunosuppressed individuals, followed by other vulnerable contacts (pregnant women and infants). The risk assessment for each identified contact will depend on their exposure risk and their likely susceptibility. For immunosuppressed contacts, an appropriate assessment of the nature and level of immunosuppression is central to a decision about PEP.

These guidelines describe the rationale for PEP and update the recommendations, including dosage and timing. Further details about the risk assessment of vulnerable contacts can be found in the PHE National measles guidelines.

## 2. Recommendations

In order to inform the decision to recommend post exposure prophylaxis, a local risk assessment should be undertaken to determine the likelihood of measles in the index case and the level of potential exposure of the vulnerable contacts. If the index case is laboratory confirmed, epidemiologically confirmed or considered likely to be measles by the local Health Protection Team (HPT), then the need for post exposure prophylaxis should be urgently addressed. Detailed information on the level and nature of exposure can be found in the [PHE National Measles Guidelines](#). For each identified contact, the decision to offer PEP is based on the level and timing of exposure and susceptibility to measles.

### 2.1 Immunosuppressed contacts

#### 2.1.1 Assessing 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 (16). 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  $\leq 3$  weeks 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 table 1), depending on their ability to maintain adequate antibody from past exposure or vaccination.

**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** 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/diagnosis and B(ii) individuals who require IVIG following an exposure without the need for testing. In principle, individuals should be vaccinated or have had their immunity against measles tested after completing their treatment.

**Other individuals** who do not meet the criteria for either Group A or B (for example HIV individuals with CD4 cell count  $> 200/\text{mm}^3$ , 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.

**Table 1 Classification of immunosuppression**

<b>Group A - individuals who should develop and maintain adequate antibody from past exposure or vaccination</b>	
<b>Manage on basis of evidence of protection at any time (prior to or since the diagnosis or treatment end)</b>	<ul style="list-style-type: none"> <li>• 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 HSCT)</li> <li>• Patients receiving systemic high-dose steroids, or who have received high dose steroids in the past 3 months. This would include:               <ul style="list-style-type: none"> <li>• Children who receive prednisolone, orally or rectally, at a daily dose (or its equivalent) of 2mg/kg/day for at least one week, or 1mg/kg/day for one month.</li> <li>• Adults who receive short term high-dose corticosteroids (&gt;40mg prednisolone per day or equivalent for more than 1 week)</li> <li>• Adults who receive long term lower dose corticosteroids (&gt;20mg prednisolone per day or equivalent for more than 14 days)</li> </ul> </li> <li>• Patients receiving high doses of non-biological oral immune modulating or other types of immunosuppressive drugs (alone or in combination with steroids) or who have received such therapy in the past 3 months. This would include:               <ul style="list-style-type: none"> <li>• Adults who receive methotrexate &gt;25mg per week</li> <li>• Adults who receive azathioprine &gt;3.0mg/kg/day or</li> <li>• Adults who receive 6-mercaptopurine &gt;1.5mg/kg/day</li> <li>• Adults on cyclosporin, cyclophosphamide, leflunomide AND</li> <li>• Children (&lt;16years) who receive any dose of the above drugs</li> </ul> </li> <li>• Patients with human immunodeficiency virus (HIV) infection: i) &gt;5 years of age and with a CD4 count &lt;200 cells/<math>\mu</math>l (but without a diagnosis of AIDS) or ii) aged 5 years or less, with a CD4 count &lt;500 cells/<math>\mu</math>l</li> </ul>



<b>Group B – individuals who lose or may not maintain adequate antibody levels from past exposure or vaccination</b>	
<b>B (i): Manage on basis of IgG obtained at the time of exposure (or since the diagnosis or treatment end)</b>	<ul style="list-style-type: none"> <li>• Patients on or after completion of immunosuppressive chemotherapy for acute lymphoblastic leukaemia (ALL)</li> <li>• Patients with lymphoproliferative disorders (including haematological malignancies such as indolent lymphoma, leukaemia and plasma cell lymphoma).</li> <li>• Patients who have received a solid organ transplant</li> <li>• Patients more than 12 months after receiving a haematopoietic stem cell transplant (HSCT)</li> <li>• Patients receiving or within 6 months of completing biological therapies (alone or in combination with steroids). These include: monoclonal antibodies, for example alemtuzumab, ofatumumab and rituximab cytokine inhibitors, for example etanercept</li> <li>• Patients with a diagnosis of acquired immunodeficiency syndrome (AIDs)</li> </ul>
<b>B (ii): Offer PEP regardless of status</b>	<ul style="list-style-type: none"> <li>• Patients who have received a haematopoietic stem cell transplant (HSCT) within the past 12 months</li> <li>• Patients with severe primary immunodeficiency*</li> </ul>

\* this group may already be on long term IVIG replacement, which should provide equivalent protection to post exposure immunoglobulin.

## 2.1.2 Management of immunosuppressed contacts

### 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 /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 (table 2).

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.

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.

### 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.

**Table 2 Assessing evidence of protection in immunosuppressed contacts of measles**

<b>Group A - individuals who should develop and maintain adequate antibody from past exposure or vaccination</b>		
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
<b>Group B – individuals who lose or may not maintain adequate antibody levels from past exposure or vaccination</b>		
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 Pregnant women

### 2.2.1 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 PHE Immunisation Department 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 (18). 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 PHE Virus Reference Department (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.

### 2.2.2 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 3. on the next page.

The main aim of measles PEP for pregnant women is attenuation of disease and therefore 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.

**Table 3: Assessment and treatment of pregnant women**

<b>Pregnant women</b>		
<b>Born before 1990</b>	<b>History of measles infection</b>	Assume immune
	<b>No history of measles infection</b>	Test and administer HNIG within 6 days only if measles antibody negative
<b>Born 1990 or later</b>	<b>Two measles vaccines</b>	Assume immune
	<b>One measles vaccine</b>	Test and administer HNIG within 6 days only if measles antibody negative
	<b>Unvaccinated</b>	Test and administer HNIG if measles antibody negative. If not possible to test within 6 days of exposure, offer HNIG.

### 2.3 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 transplacentally acquired antibodies tend to be low and to wane rapidly, generally in a few weeks after birth (1, 2). 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 (1, 2). 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 4

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.

**Table 4: Assessment and treatment of infants**

Infants		
<b>Infants &lt;6 months</b>	Assume susceptible and administer HNIG, ideally within 72 hours but up to 6 days, regardless of maternal status	
<b>Infants aged 6-8 months</b>	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
<b>Infants ≥9 months</b>	Administer MMR vaccine, ideally within 72 hours of exposure	

Where post-exposure vaccination is indicated (Table 4) 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.

Due to interference from maternal antibody, the efficacy of a dose of vaccine provided between 6 – 11 months of age is lower than that provided at 12 -13 months (19), and therefore doses offered before 1 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).

## 2.4 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.

PHE 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 is available at:

[www.gov.uk/government/publications/vaccine-in-pregnancy-advice-for-pregnant-women/mmr-measles-mumps-rubella-vaccine-advice-for-pregnant-women](http://www.gov.uk/government/publications/vaccine-in-pregnancy-advice-for-pregnant-women/mmr-measles-mumps-rubella-vaccine-advice-for-pregnant-women).

## 3. Dosage and administration of immunoglobulins

PHE has performed plaque neutralisation testing of 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 et al (7), the doses of intramuscular HNIG recommended in the past are not fully protective,(13) and therefore a fully protective dose cannot be realistically achieved using an intra-muscular injection (See Appendix 4 for more information). The following modified doses, allowing for the lowest levels of neutralising measles antibody observed in products available in the UK, are therefore recommended:

### 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 PHE stockholders. This would constitute a grey indication in the current National Demand Management plan (<http://www.igd.nhs.uk/>).

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 (80-330 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**.

### 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 3000 mg

**Infants:** 0.6ml/kg up to a maximum of 1000mg

Subgam® can be issued from PHE stockholders on request. Other HNIG products available in the NHS (including Cuvitru, Hizentra and Gammanorm) are available from local hospital pharmacies and have been shown to contain similar levels of measles antibody.



Subgam and Gammanorm can be administered via the intramuscular or subcutaneous route. Note that the current Subgam Summary of Product Characteristics (SPC) does not mention intramuscular administration. However, discussions with the manufacturer are ongoing to update the SPC to re-incorporate the intramuscular route of administration in line with previous SPCs. Cuvitru and Hizentra are currently only approved for subcutaneous administration.

### Interim doses for stockholders with 750mg vials of subgam

The vial size of Subgam, the human normal immunoglobulin (HNIG) product issued by PHE stockholders, is being changed from 750mg to 1000mg. These updated guidelines provide doses based on the new vial size (1000mg).

As of 1<sup>st</sup> July 2019, some stockholders may still hold a limited number of 750mg vials. For those stockholders with 750mg vials, the following intra-muscular doses are recommended:

**Pregnant women:** approximately 3000 mg (4 vials)

**Infants:** 0.6ml/kg up to a maximum of 750mg (1 vial)

### 3.3 Issuing HNIG from the Rabies and Immunoglobulin Services (RIgS) at PHE Colindale

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

### 3.4 In hours service at PHE Colindale

For practical purposes, requests that are made Monday-Friday will be ordered through Movianto for delivery to arrive on the next working day. Requests received after 1pm cannot be ordered/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.

For urgent requests, stock can be issued from Colindale during work hours for providers to collect using a courier service, paid by the provider. . The Colindale site is open for collection 24 hours a day, 7 days a week (see below).

Alternatively, HNIG can be issued from the nearest stockholder.

Further information on issuing of immunoglobulin is available at:

[www.gov.uk/government/publications/immunoglobulin-when-to-use/rabies-and-immunoglobulin-rigs-changes-to-the-current-service](http://www.gov.uk/government/publications/immunoglobulin-when-to-use/rabies-and-immunoglobulin-rigs-changes-to-the-current-service)

### 3.5 Out of hours service at PHE Colindale

PHE can issue products from Colindale between 2 and 3pm at weekends and bank holidays for the requestor to arrange collection using a courier. Therefore, for the majority of patients, arrangements should be made for collection and administration of the immunoglobulin the next day.

Further information on issuing of immunoglobulin is available at:

[www.gov.uk/government/publications/immunoglobulin-when-to-use/rabies-and-immunoglobulin-rigs-changes-to-the-current-service](http://www.gov.uk/government/publications/immunoglobulin-when-to-use/rabies-and-immunoglobulin-rigs-changes-to-the-current-service)

## 4. Appendix

### 4.1 Human Normal Immunoglobulin (HNIG)

The effectiveness of intra-muscular (IM) HNIG for measles prophylaxis was first established in young children in the 1940s. Janeway et al. (3) published a controlled study in children which demonstrated the effectiveness of gamma globulin in preventing disease if administered to household contacts within 4-5 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 43/46 (94%) compared to 18/62 (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 (4, 5) 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 96/237 (41%), 52/107 (49%) and 148/344 (43%) amongst children up to 5 years of age, those aged 6-12 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 24-48 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%) (6) 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 (7), Endo et al (7) found that in 14 children who received immunoglobulin (at the Japanese recommended dose of 0.33ml/kg) with a titre of < 16 IU/ml, 8 (57%) had clinically evident measles, whilst the 13 individuals who received immunoglobulin with a titre of >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(8), and antibody levels are lower in the absence of exposure to circulating measles(9). 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, (4, 7) 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 (<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010056.pub2/full>). 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 4-6 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**.

## 4.2 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 (10, 11) proposed that vaccine is effective in preventing secondary cases if given soon after exposure. In 1963, Watson (10) 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 1-5 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 (12), 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 (ie the maximum incubation period (13)) could be measles, although measles like symptoms can occur after vaccination. Oral fluid samples can be used to type the virus (ie vaccine or wild type) if taken within one week of onset.

### 4.3 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 (13). Seroprevalence studies suggest that fewer than 1% of individuals born before 1970 are susceptible to measles (14).

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.

Information on defining the nature and level of exposure is summarized in the PHE [National Measles Guidelines](#). This document focuses on the assessment of susceptibility for vulnerable contacts and the recommendations (dosage and timing) for immunoglobulin only.



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