POST EXPOSURE PROPHYLAXIS FOR MEASLES: REVISED GUIDANCE
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BACKGROUND

The effectiveness of intra-muscular Human Normal Immunoglobulin (HNIG) for measles prophylaxis was first established in young children in the 1940s. Janeway *et al*.[1] 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 two 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,[2,3] 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 five 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 four days prior to rash onset in the index case), was estimated at only 8% (95% CI 0, 59%).[4] 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 recent study to investigate immunoglobulin as post-exposure prophylaxis; Endo *et al*[5] found that in 14 children who received immunoglobulin (at the Japanese recommended dose of 0.33ml/kg) with a titre of $\leq$ 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.

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[6,7] proposed that vaccine is effective in preventing secondary cases if given soon after exposure. In 1963, Watson 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,[8] MMR vaccine failed to protect any of four contacts when given within four 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.

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,[9] and antibody levels are lower in the absence of exposure to circulating measles.[10] 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,[2,5] it is likely that currently recommended products and doses are significantly less effective than observed in earlier studies. In addition, all 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.

CURRENT RECOMMENDATIONS

The Department of Health for England has published guidance[11] on the indications for the use of human normal immunoglobulin (HNIG), in cases where certain susceptible population groups have been exposed to measles. These include immunocompromised contacts, pregnant women, and infants under the age of 12 months. Based on very limited data to inform the timing of prophylaxis,[1,2,3] vaccine or HNIG were previously recommended for post-exposure prophylaxis within 72 hours and six days of exposure respectively.[11,14] This paper aims to provide additional guidance on post-exposure prophylaxis in these groups.

This guidance does not aim to define the nature or the level of exposure required before prophylaxis is considered. A local risk assessment of the index case and the exposure should take place. If the index case is confirmed, epidemiologically

linked or considered likely to be measles by the local health protection team, then the need for post exposure prophylaxis should be urgently addressed.

ASSESSING SUSCEPTIBILITY IN PREGNANT CONTACTS

According to recent seroprevalence studies, over 90% of UK adults have measurable measles antibody by commercial ELISA tests.[12] Such antibody tests are likely to be specific and therefore have a high positive predictive value in adult populations. Neutralisation assays performed by Centre for Infections (CfI) on samples from individuals who tested positive or equivocal for measles antibody on commercial assays have shown that all have detectable measles neutralisation antibody (data from CfI Virus Reference Department (VRD)) and therefore HNIG is likely to offer little benefit to antibody positive or equivocal individuals. As routine antibody tests lack sensitivity, however, a high proportion of those found to be antibody equivocal or negative are likely to be truly immune. Therefore for older women with a reliable history of measles, antibody testing is unnecessary and should be avoided.

According to recent seroprevalence studies 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 CfI Immunisation Department). For those born in the pre-vaccine era (before 1970), most will be immune due to natural exposure in childhood to measles. 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. Individuals born after 1990 are unlikely to have been exposed to natural measles and will mainly have acquired immunity via vaccination. Around 90% of individuals should respond to a single dose of measles-containing vaccine, whereas around 99% should be protected following two doses. Assessing the likelihood of prior exposure to natural or vaccine measles in

pregnant patients should be based upon a combination of age, history and / or antibody screening (table 1).

ASSESSING SUSCEPTIBILITY IN IMMUNOCOMPROMISED CONTACTS

All immunocompromised patients, as defined in chapter 6 of Immunisation against Infectious Disease, are at risk of severe measles and should be considered for immunoglobulin following exposure to measles. However, many adults and older children with immunosuppression will have immunity due to past infection or vaccination. A prophylactic dose of immunoglobulin is likely to offer little additional benefit to those who are positive for measles antibody using a commercial assay, as the latter group are likely to have antibody levels higher than those achievable with a prophylactic dose of immunoglobulin. For people with severe defects of cell mediated immunity, however, passive immunoglobulin may be indicated even in the presence of measurable antibody. 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 to be 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 two groups.

Group A would include 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 reliable history or antibody screening. This includes:

- all patients with malignant disease, other than those in group B, until at least six months after completion of immunosuppressive chemotherapy or radiotherapy

- patients who have received a solid organ transplant and are currently on immunosuppressive treatment
- patients receiving systemic high-dose steroids, until at least three months after treatment has stopped. This would include 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. For adults, an equivalent dose is harder to define but immunosuppression should be considered in those who receive at least 40mg of prednisolone per day for more than one week.
- patients with immunosuppression due to human immunodeficiency virus (HIV) infection who do not have a diagnosis of AIDS[13]
- patients receiving other types of immunosuppressive drugs (e.g. azathioprine, cyclosporin, methotrexate, cyclophosphamide, leflunomide, anti-TNF alpha and the newer cytokine inhibitors) alone or in combination with steroids, until at least six months after terminating such treatment.

For patients in the groups above who are likely to have developed an adequate response to vaccination or measles during childhood, 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. Measles antibody status should also be prospectively assessed for patients commencing chemotherapy. For those with unknown status at the time of exposure, management on the basis of history and, where possible, rapid antibody testing is recommended (table 1).

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. In most instances where measles control is poor or has only been established very recently, a high proportion of 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.[14]

Group B would include individuals who are unlikely to have developed or to maintain adequate antibody levels from past exposure or vaccination. It is recommended that, unless already on replacement immunoglobulin therapy, these patients would require urgent testing within three days of exposure, regardless of a past history or a previous positive measles antibody result (table 1). This group would include:

- patients with severe primary immunodeficiency (who would not be expected to have made a good initial response to vaccine or disease in childhood)
- patients who have received a bone marrow transplant until at least 12 months after finishing all immunosuppressive treatment, or longer where the patient has developed graft-versus-host disease
- patients with a diagnosis of Acquired Immunodeficiency Syndrome (AIDS)
- patients on treatment for ALL within and until at least six months after completion of immunosuppressive chemotherapy

Studies in children after treatment for ALL[15] and following bone marrow transplant,[16] found a reasonable proportion of those with prior vaccination retained protective antibody levels (>120mIU/ml). If current measles antibody levels can be established, therefore, immunoglobulin treatment can be avoided in those that are measles antibody positive. For those that cannot be shown to be antibody positive within three days of any exposure, immunoglobulin should be given without further delay.

Measles IgG antibody testing using commercial assays is now available in all HPA Regional Laboratories and in several NHS laboratories. Although not all

offer an out of hours or weekend service, antibody testing should be possible within one working day of receiving the serum sample.

ASSESSING SUSCEPTIBILITY IN INFANTS

A number of studies[17,18] have shown that maternally derived antibody decays more rapidly in infants of vaccinated mothers than in infants of naturally immune mothers. The evidence indicates whilst infants of naturally immune mothers are likely to have protective antibody levels until 6 months of age, a significant proportion of those born to vaccinated mothers may not have protective titres from birth.[19] This suggests that infants of vaccinated mothers should be offered HNIG at an earlier age than in the previous guidance.

The previous guidance also advises the use of MMR vaccine for post-exposure prophylaxis in infants from 9 months of age, as it is believed that low levels of maternal antibodies, lower than those associated with protection, will interfere with the immune response below this age.[20] Brugha *et al* found that whilst nearly 86% infants (born to vaccinated mothers) under 4 months of age had antibody levels that would interfere with vaccination, this fell to 50% amongst infants over 5 months. This implies that at least half of infants born to vaccinated mothers may respond to MMR vaccine from 5 months of age, without interference from maternal antibodies. In a Canadian prospective trial,[21] the serological response to single measles vaccine was evaluated in infants aged 6-8.5 months. As 76% of infants born to mothers who had received live measles vaccine seroconverted, the authors concluded that measles vaccine before 9 months of age is effective where you have a well vaccinated maternal population. In two smaller studies in the USA, all nine infants born to seronegative women[22] and 74% of infants born to vaccine-immune mothers[23] developed neutralizing antibody to measles vaccine at 6 months of age. In another US study, 14 premature infants who were seronegative received measles vaccine between 2 and 5 months of age and 11 (79%) seroconverted to measles IgG.[24] This suggests that most premature

infants and most infants born to seronegative or vaccinated mothers are able to respond to measles vaccination from six months of age.

Based on the evidence above, the use of post-exposure prophylaxis in infancy should now depend on a range of maternal factors (table 2). The vast majority of expectant UK mothers have now been eligible for measles-containing vaccine (introduced since 1968) and vaccine coverage has exceeded 75% in all cohorts born after 1985. Measles control has also improved since the late 1980s,[25,26] meaning that the opportunity for natural boosting of antibody levels,[27] is not present amongst younger UK born women.

Older women and those likely to have natural immunity may have higher levels of antibody. Their infants become susceptible to infection later (between three and six months), but the level of antibody may still be sufficient to interfere with response to vaccination until 9 months of age.[20] For infants in this category, a clinical decision to use either HNIG or MMR is required.(table 2) HNIG is preferred where there may be particular reasons to avoid measles (such as underlying lung disease or recent severe illness) or those who are exposed in the household setting when disease may be more severe.[28] Outside of the household, when ongoing exposure from further waves of infection are likely, MMR may be preferred as it should also provide longer lasting protection against subsequent exposures. This latter benefit is suggested by a study that investigated the effectiveness of a measles-containing vaccine during an outbreak, where the estimated vaccine effectiveness for infants aged 6-11 months was 73%.[29]

As the pattern of maternal antibody decay in infants shows significant geographical variation,[30] and as vaccination programmes were introduced at different times, this advice may not be applicable to infants of non-UK born mothers. An individual risk assessment would be required.

DOSE RECOMMENDATIONS FOR HNIG

Based on plaque neutralisation testing of the products currently available and applying the protective per/kg dose established by Endo et al, it is unlikely that the previously recommended doses of intramuscular HNIG are fully protective. The following modified doses, allowing for the lowest levels of neutralising measles antibody observed in products available in the UK, are therefore recommended:

Immunosuppressed patients

For immunosuppressed individuals, the protective dose will probably only be possible to administer by either intravenous or subcutaneous infusion. Based on testing results of products from three manufacturers the mean content of measles antibody by plaque neutralisation varies from 23 to 39 IU/ml for the subcutaneous products and 4 to 34 IU/ml (80-330 IU/g) for the intravenous products. A minimum protective dose of approximately 11 IU/kg measles antibody, should therefore be achievable using the following doses of any available product:

0.6 ml/kg of subcutaneous normal immunoglobulin or
0.15 g/kg of intravenous normal immunoglobulin.

The intravenous product is likely to be more easily obtained as it is held in most hospital pharmacies; facilities for delivery should be available in the same hospital. Consult the product literature for information about administration.

Subcutaneous products may be obtained either through hospital pharmacy or via HPA stockholders.

Immunocompetent infants and pregnant women

For immunocompetent infants and pregnant women, who are normally managed in the community where intravenous or subcutaneous infusion is not practical, lower doses of the subcutaneous product administered intramuscularly are still likely to attenuate an attack. These doses are compatible with those currently in use in the USA,[31] and higher than those previously recommended in the UK. The following intra-muscular doses are recommended.

Infants under 1	0.6 ml/kg up to maximum of 1 vial (5 ml)
Pregnant women	2250 mg (3 vials; 15 ml)

This product will be issued from HPA stockholders on request.

TIMING OF ADMINISTRATION

Patients with measles are considered infectious from four days before to four days after rash onset, and anyone exposed to the patient during this period should be considered for prophylaxis. For patients with continued exposure, for example in the household setting, exposure is likely to occur during the prodromal period, but for practical purposes the limit for administering prophylaxis should be timed from the onset of rash in the index case.

For immunosuppressed patients in group B or those in group A who are known or likely to be susceptible (table 1), administration should not be delayed (for example whilst awaiting test results) beyond three days after exposure. This because the effectiveness of immunoglobulin is likely to be higher where it is given as early as possible. As some attenuation of disease may occur when given later, however, immunoglobulin should be given until at least six days from exposure. Where exposure is recognised late, IVIG is likely to provide higher

levels of measles antibody more quickly than an intra-muscular or subcutaneous product.

For immunosuppressed patients in group A and born between 1970 and 1990, who are likely to be immune (table 1), antibody testing should be performed, ideally, within six days. Where antibody testing is found to be negative or equivocal, normal immunoglobulin should still be offered up to six days after exposure. Even at a later stage, however, testing is indicated to inform treatment and infection control for the patient, and for the management of future exposures.

For immunosuppressed patients where exposure is recognised late or who are found to be antibody negative or equivocal between six and eighteen 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 three weeks after a first dose of immunoglobulin, a further dose of immunoglobulin will need to be considered.

In susceptible pregnant patients and eligible infants, where the main aim of HNIG prophylaxis is attenuation of disease, HNIG will be issued up to six days after exposure, allowing time for assessment of immunity status in most instances. Where a second exposure occurs more than three weeks after a first dose of immunoglobulin, a further dose may need to be considered.

For infants and other healthy individuals where post-exposure vaccination is indicated,(table 2) MMR should ideally be given within three days after exposure. During the 1990 US measles epidemic, the effectiveness of post exposure HNIG given within two days of rash onset and of vaccination given within 3 days of rash onset were estimated at only 8% (95% CI 0, 59%) and 4% (95% CI 0, 36%) respectively. This experience suggests that 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 three days may provide protection from subsequent exposures.

As neither immunoglobulin nor vaccine are 100% effective in preventing measles, appropriate infection control procedures should be followed, for example in health care settings. Those receiving vaccine, however, may developing a vaccine-associated measles like rash. Carers should be advised, however, that any rash illness within the 18 days following exposure should be managed as if it is true measles. If such a rash does develop, oral fluid samples should be collected and sent to CfI VRD for confirmation and virus typing, ideally within one week of onset, and vaccination dates clearly documented on the request form.

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Table 1: Algorithm for assessing susceptibility in pregnant women and immunosuppressed contacts of measles

Age group	History	Pregnant	Immunosuppressed Group A	Immunosuppressed – Group B*
Born before 1970	**Of measles infection**	Assume immune	Assume immune	Regardless of history and even if known to be measles antibody positive previously, test again at time of exposure. Issue immunoglobulin if measles antibody negative or equivocal. If not possible to test within three days of exposure, offer immunoglobulin.
	No measles infection	Assume immune	Test and issue only if measles antibody negative or equivocal.	
Born between 1970 and 1990	**Of measles infection**	Assume immune	Test and issue only if measles antibody negative or equivocal.	
	No measles infection	Test and issue within six days only if measles antibody negative.	Test and issue if measles antibody negative or equivocal. If not possible to test within six days of exposure, offer immunoglobulin.	
Born after 1990	**One measles vaccine**	Test and issue within six days only if measles antibody negative.	Test and issue if measles antibody negative or equivocal. If not possible to test within three days of exposure, offer immunoglobulin.	
	Two measles vaccines	Assume immune.	Test and issue if measles antibody negative or equivocal. If not possible to test within three days of exposure, offer immunoglobulin.	
	Unvaccinated	Test and issue if measles antibody negative. If not possible to test within six days of exposure, offer immunoglobulin.	Offer immunoglobulin, ideally within three days.	

* excluding patients who are already on IVIG replacement therapy for either primary immunodeficiency or severe defects of cell mediated immunity

Table 2: Post exposure prophylaxis in infants of UK born mothers

Relevant infant history	Age of exposed infant (completed months)		
	0-2 months	**3-5 months**	**6-8 months**
Mother is the index case	HNIG	HNIG	MMR vaccine
Mother is known antibody negative or equivocal	HNIG	HNIG	MMR vaccine
Mother born before 1970	Nothing	HNIG	MMR vaccine or HNIG*
Mother born between 1970 and 1984 and has had natural measles	Nothing	HNIG	MMR vaccine or HNIG*
Mother born between 1970 and 1984 and is unsure of status	HNIG	HNIG	MMR vaccine or HNIG*
Mother has had measles vaccine or born after 1984	HNIG	HNIG	MMR vaccine
Infant born before 32 weeks gestation	HNIG	HNIG	MMR vaccine

* For those with less definite exposure, for example outside of the household setting, but likely to be at on-going risk, MMR is preferred to HNIG (see above). For infants exposed in the household or those where there may be particular reasons to avoid measles (such as underlying lung disease or recent severe illness) then HNIG is preferred.