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Guidance on the investigation, diagnosis and management of viral illness, or exposure to viral rash illness, in pregnancy

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339

Contents

Changes from previous guidance

1. Updates have been made to the epidemiology of rash illnesses in pregnancy and their sequelae.

2. Advice on post exposure prophylaxis for chickenpox and measles has been updated to reflect current guidance.

3. Advice on assessing immunity to rubella has been updated and the 10 IU/ml threshold for IgG antibody levels has been removed. The presence of antibodies at any level is sufficient to confirm immunity.

4. The section on antibody screening for rubella has been updated to note that universal antenatal screening is no longer offered.

5. A section has been added on the potential for restrictions to the use of varicella zoster immunoglobulin (VZIG) for pregnant women during times of VZIG shortage.

6. A section has been added on the management of a neonate born to a mother with rubella infection during pregnancy.

7. A section has been added on the management of inadvertent shingles immunisation in pregnancy. Unlike inadvertent immunisation in pregnancy with other live vaccinations, for which only reporting is encouraged, inadvertent vaccination with the live shingles vaccination should be treated as an exposure and assessed according to guidance on exposure to shingles.

1. Overview

This document updates and consolidates previous guidance, specifically the 2000 report of the Public Health Laboratory Service (PHLS) Working Group [1-3], and the Health Protection Agency (HPA), now Public Health England (PHE), guidance on the investigation, diagnosis and management of viral rash illness, or exposure to viral rash illness in pregnancy, published in 2011. This revised guidance has been circulated to PHE and external experts for comment and signed off by the PHE Vaccine Science and Surveillance Group.

This guidance aims to help decision making in the investigation, diagnosis and management of a pregnant woman who has, or is exposed to, rash illness. A rash illness is defined as “a rash compatible with a systemic viral illness”. This guidance should be read in conjunction with more detailed PHE guidance on prophylaxis for pregnant women exposed to measles and chickenpox.

This guidance is in 4 parts: the first part sets out the scope of the document and presents background information; the second part focuses on women who present with viral rash illness in pregnancy; and the third part focuses on pregnant women who have had contact with a viral rash illness. The fourth part provides advice on the management of susceptible women in the first 20 weeks of pregnancy who are working in occupational settings that may suggest increased risk of exposure highlights current antibody screening recommendations in pregnancy and discusses inadvertent immunisation in pregnancy.

The information presented by this guidance is intended to supplement, not substitute for, the expertise and judgement of healthcare professionals.

2. Scope and background

2.1 Introduction

This guidance focuses on the investigation and diagnosis of maculopapular rashes caused by rubella, parvovirus and measles and vesicular rash caused by chickenpox, in pregnant women or pregnant women in contact with such rashes.

Pregnant women may present with a generalised rash, or after contact with a person who has a generalised rash, the cause of which is not always clinically apparent. Therefore, the guidance includes a section on management from the first presentation. Sometimes the clinical and/or epidemiological features may be sufficient to directly implement disease specific investigation and management, for example, with chickenpox infection.

This guidance is largely aimed at the management of healthy pregnant women. For guidance on measles and chickenpox infection or contact in immunosuppressed individuals the PHE Immunoglobulin guidance should be referred to: www.gov.uk/government/publications/immunoglobulin-when-to-use. For the management of parvovirus B19 infection in immunosuppressed individuals, specialist advice should be sought.

2.2 Background and epidemiology of viral infections associated with a rash

Table 1 shows the characteristic features and incidence of those infections in the UK of particular significance for the fetus and where intervention can prevent or reduce the potential for adverse outcomes – parvovirus B19, measles, rubella and chickenpox. Any febrile illness, including those that can present with a rash, may be associated with an increased risk of fetal loss in the first trimester. The specific risk associated with each individual viral infection is therefore difficult to ascertain.

Streptococcal[1], meningococcal disease[2], syphilis[3], and imported rash causing infections such as Zika and dengue virus[4] are not considered further as clinical and epidemiological information would focus appropriate investigation and diagnosis in the field.

[1] https://www.gov.uk/government/collections/scarlet-fever-guidance-and-data
[2] https://www.gov.uk/government/collections/meningococcal-disease-guidance-data-and-analysis
[3] https://www.gov.uk/government/collections/syphilis-surveillance-data-and-management
[4] https://www.gov.uk/government/publications/zika-virus-interim-algorithm-for-assessing-pregnant-women-with-a-history-of-travel

Viral infections which commonly present with a generalised rash illness in the UK include:

- parvovirus B19
- measles
- rubella
- varicella
- human herpes virus 6 and 7 (HHV-6 and HHV-7)
- enterovirus

Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) rarely present as a rash illness but should be included as differential diagnoses.

The background and epidemiology of a range of viral rash illnesses is presented in this part but where management is already well established, relevant guidance, sources of further and background information are cited. This guidance does not attempt to embrace all aspects of management and focuses on the investigation and diagnosis of viral rashes where medical intervention can prevent or reduce the potential for adverse outcomes in a pregnant woman, the fetus or neonate. Human immunodeficiency virus (HIV) and herpes simplex virus (HSV) infection in pregnancy are not covered by this guidance and other established guidelines should be consulted. [5,6]

2.2.1 Parvovirus B19 (B19V)

There are a wide range of potential consequences of parvovirus B19 infection. These range from minor febrile illness to erythema infectiosum (fifth disease, slapped cheek syndrome), a generalised rash illness clinically indistinguishable from rubella, aplastic crises in patients with increased red cell turnover, arthropathy, and persistent infection in the immunocompromised. Infection in the first 20 weeks of pregnancy can lead to intrauterine death (average excess risk of 9%) [4]. Hydrops fetalis occurs in 3% of cases if infection is between 9-20 weeks gestation, about half of which die [4]. A more recent study reported fetal hydrops in 11% of pregnancies where infection occurred between 9 and 20 weeks gestation, 40% of whom died [5]. Fetal loss was seen in 7% of pregnancies, if maternal infection occurred at under 20 weeks gestation. Maternal infection after 20 weeks is rarely associated with developmental hydrops or fetal loss (<1%) [5]. These consequences usually occur some 3-5 weeks after the onset of maternal infection, but can be later. Permanent congenital abnormality and/or

[5] British HIV Association. BHIVA guidelines for the management of HIV infection in pregnant women 2012 (2014 interim review). http://www.bhiva.org/pregnancy-guidelines.aspx
[6] Royal College of Obstetricians and Gynaecologists. Management of Genital Herpes in Pregnancy (October 2014). https://www.rcog.org.uk/en/guidelines-research-services/guidelines/genital-herpes/

congenital anaemia have rarely been identified as a consequence of intrauterine infection [4;6;7;8].

In studies, parvovirus B19 reinfection has been shown after administration of high dose virus [9] and reactivation has been documented in the immunocompromised, but there is no evidence to suggest reinfection is a risk to the fetus.

Parvovirus B19 infection is common with some 50-60% of adults having been infected [10]. An increased incidence occurs every 3-4 years, largely in schoolchildren [11]. In 2013 and 2017/18, there was a particular increase in laboratory reported confirmed cases in women aged 15-44 years [11]. There is currently no licensed vaccine for parvovirus B19 and preventive measures are not available.

In 1998, guidance on the management of parvovirus B19 infection was issued by the PHLS (now Public Health England) after consultation with a range of authorities [1]. However, a number of areas in relation to management in pregnancy are outside the scope of that guidance.

2.2.2 Measles

The clinical features and complications of measles in the child and adult are well-established and include disseminated rash, coryza, conjunctivitis, pneumonia, otitis media and encephalitis [12]. The incubation period is 7-21 days and the patient is considered infectious from 4 days before to 4 days after the rash appears.

Measles in pregnancy is relatively uncommon but can be associated with severe maternal morbidity, as well as fetal loss and preterm delivery [13]. Maternal morbidity due to pneumonitis has been variously reported as 10% to 52% in case series [14]. There is no evidence to support an association with congenital infection and damage [14]. Although rare, neonatal measles has been associated with subacute sclerosing panencephalitis (SSPE) with a short onset latency and fulminant course and acquiring measles infection before one year of age is associated with an increased risk of SSPE [15].

Although indigenous measles was rare in the UK following introduction of MMR vaccine in 1988 and the MR vaccine campaign of 1994, fall in vaccine coverage in the late nineties and early 2000s contributed to a rise in the cohort of susceptible individuals, and an increase in the incidence of measles [16]. By 2007, the annual incidence of measles exceeded 1,000 cases for the first time in a decade and large outbreaks continued, leading to national catch up campaigns. In the last few years, coverage for the first and second dose of MMR has increased annually and the number of cases annually has remained below 1,000 since 2014. In 2016, the UK was certified as having

eliminated endemic measles transmission, which means that even though the UK continues to have measles cases, transmission is limited [17;18].

The UK SSPE register is co-ordinated by PHE and all cases are confirmed by the virology reference department. The reference laboratory receives samples from about 20 patients being investigated for SSPE annually. Between 2006 to 2017, only 2 cases of SSPE were identified with presumed UK measles acquisition [18].

2.2.3 Varicella

Primary chickenpox (varicella-zoster virus infection) presents as an illness characterised by vesicular rash and clinical diagnosis is highly specific, although not very sensitive as sub-clinical and mild cases occur. Chickenpox is endemic within the UK, with more than 85% of young adults having been infected [19], although there are variations in different ethnic groups [20]. The incubation period is 7-21 days. This can be prolonged if the patient is on steroids, immunosuppressed or has received VZIG (varicella zoster immunoglobulin). For investigation and consideration of VZIG, and contact management, the patient is considered infectious 48 hours before the rash appears and until all the vesicles crust over.

Reliable data on the incidence of chickenpox in pregnancy are not available but projecting from GP consultation rates for chickenpox in adults in 1996, Miller suggested an infection risk of approximately 2-3 per 1000 pregnancies and more recent data based on retrospective reviews of hospital admissions suggest an incidence between 5-6 per 10,000 deliveries [3;21;22]. In theory, as for rubella and parvovirus B19, the risk of chickenpox infection for susceptible women in a second or subsequent pregnancy may be higher due to exposure to their own young children or their peers. Non immune pregnant women should be advised to avoid exposure to chickenpox and shingles where practical. Chickenpox reinfection has been described, but is rare [23].

Historic estimates of pneumonitis in varicella cases in pregnancy have been between 10% to 14%, reported in small case series [24]. In a more recent US based study of almost 1,000 pregnant women with chickenpox admitted to hospital between 2003 and 2010, the proportion with pneumonitis was 2.5% and no maternal deaths were reported, probably reflecting improved medical care and use of aciclovir treatment [25]. Studies show that the risk of pneumonitis in pregnant women with chickenpox is increased towards term [26;27]. The highest risk of maternal pneumonitis appears to be associated with maternal infection after 18 to 20 weeks of pregnancy. Encephalitis is a rare complication with mortality of 5-10%. There is little evidence to suggest that pregnancies complicated by chickenpox in the first trimester are more likely to result in fetal loss [28;29].

The risk of fetal varicella syndrome is estimated to be 0.4% when maternal infection occurs between conception and week 12 of pregnancy, and nearly 2% when infection

occurs between weeks 12 and 20 [30]. Isolated case reports have indicated that fetal abnormality consistent with fetal varicella syndrome may occur following infections as late as 28 weeks in pregnancy [31] but the risk is likely to be substantially lower than that of the typical fetal varicella syndrome which occurs after maternal varicella in the first 20 weeks' gestation. The rare clinical manifestations of fetal varicella syndrome include low birth weight, severe multi-system involvement with neurological involvement, eye lesions, and skeletal anomalies, skin scarring and limb hypoplasia [32;33].

Babies born to those infected with chickenpox late in pregnancy (20-37 weeks) may develop shingles of infancy or early childhood (0.8 – 1.7% risk in first 2 years of life) [33]. This is thought to be due to reactivation of virus after a primary infection in utero.

Fetuses exposed to maternal chickenpox 7 to 20 days before delivery may develop neonatal chickenpox but this is usually less severe as transplacentally transmitted antibodies partially protect the fetus by this stage. If the mother develops a chickenpox rash between 7 days before and 7 days after delivery, the neonate may develop a severe disseminated haemorrhagic neonatal chickenpox known as purpura fulminans [21]. Death may occur in the neonatal period.

Localised shingles (herpes zoster) reflects reactivation of latent virus, and is usually dermatome restricted. There is a theoretical risk of postnatal transmission to the baby from maternal shingles on the chest, abdomen or in exposed areas. There is no other observed risk to the fetus or neonate of localised maternal shingles [34], although it is uncertain whether dissemination of shingles, as may occur in the immunocompromised, carries a fetal/neonatal risk.

2.2.4 Rubella

Rubella is extremely rare in the UK. Over the last 5 years (April 2013 - March 2018), of the nearly 1,500 oral fluid samples tested for rubella by the national reference laboratory as part of the enhanced surveillance programme, 7 cases have been confirmed [35]. Between 2003 and 2016, 31 rubella infections in pregnancy were diagnosed across the UK (0.23 infections per 100,000 pregnancies). Of these, 5 were considered to have been reinfections and 26 primary infections. Of those with primary infections, all women for whom a country of birth was available (n=20) were born outside the UK. Of the 22 women with known place of acquisition, 14 acquired their infection abroad. A total of 12 infants were born with congenital rubella syndrome (CRS) between 2003 and 2016. Five infants were born to women diagnosed with infection during pregnancy. A further 7 infants were diagnosed with CRS at birth but with no laboratory confirmation of maternal infection in pregnancy [36].

The clinical features and consequences for the fetus of primary rubella in pregnancy are well established [37]. The unreliability of a clinical diagnosis of rubella is accepted [38]. The risk to the fetus of primary rubella in the first 16 weeks gestation is substantial, with major and varied congenital abnormalities being associated with infection in the first trimester [37]. Rubella infection between 16 and 20 weeks gestation is associated with a minimal risk of deafness only [39] and rubella prior to the estimated date of conception or after 20 weeks carries no documented risk [37;40].

A rubella reinfection is defined as rubella infection in someone who has previously had either documented natural rubella virus infection or successful rubella immunisation [41]. Maternal reinfection is usually subclinical and diagnosed by changes in antibody concentration (IgG and/or IgM) only. The risk to the fetus of subclinical maternal reinfection in the first 16 weeks gestation has not been precisely determined, but an overview would suggest the risk of congenital damage is less than 10%, and probably less than 5% [42]. Maternal reinfection with a rash is very rare; it can be presumed to present a significant, but not quantified, risk to the fetus as viraemia will have occurred.

In the UK, rubella immunisation was introduced in 1970 for pre-pubertal girls and non-immune women of child-bearing age. The epidemiology of rubella changed substantially with the introduction of measles, mumps and rubella (MMR) vaccine in 1988 for males and females in the second year of life, which included a “catch-up” programme for children up to 5 years of age at that time. An increase in cases of measles in 1993 was followed by a measles/rubella vaccine campaign of school aged children in 1994. This campaign also allowed the cessation of the selective vaccination of young teenage girls against rubella when a two dose MMR schedule was introduced in 1996.

2.2.5 Human Herpes Virus (HHV)-6/7

HHV-6 and 7 are closely related to Cytomegalovirus (CMV). Primary infection with HHV-6 and 7 during infancy and early childhood is universal and characterised by a high fever with a subset of children developing roseola infantum [43]. After infection, the virus remains latent with periodic asymptomatic reactivation. HHV6 is integrated into the human genome in approximately 1% of the population. However no clinical implications have been identified and any long-term consequences of congenital infection with HHV-6 are yet to be defined.

2.2.6 Enteroviruses

Enterovirus infection (Coxsackie virus groups A and B; echovirus; enterovirus 68-71) may have a wide range of manifestations such as meningitis; rash; febrile illness; myocarditis; and Bornholm disease. Sporadic enterovirus infection is not uncommon, but major summer epidemics have not been seen in the UK for some years. Except for poliovirus, no vaccines are available.

Vertical transmission has been documented in pregnancy. Whilst infection with coxsackie virus during pregnancy has been associated with early onset neonatal hepatitis [44-46], congenital myocarditis [44;48-52], early onset childhood insulin dependent diabetes mellitus [47], abortion or intrauterine death [53], there is no clear causal relationship. There are no known treatments or preventative methods and these infections are not considered further in this guidance. Infection may be problematic in vulnerable infants, for example those in special care baby units (SCBU). Specialist advice should be sought from the PHE Virus Reference Department.

Hand, foot and mouth disease is an enteroviral infection characterised by vesicular lesions of hands, feet, and mouth; the latter soon break down to ulcers. Pregnant women presenting with the characteristic features of hand, foot and mouth, or who have been in contact with the infection may be reassured that there is no adverse consequence for the fetus.

2.2.7 Epstein-Barr virus

Infectious mononucleosis (IM) is a common presentation of primary Epstein-Barr virus (EBV) in young adults. IM is characterised by generalised lymphadenopathy, fever, sore throat and typical haematological and serological findings, including the detection of heterophil antibody. A generalised maculopapular rash may be an associated accompanying feature [54], particularly if ampicillin, or a similar antibiotic, has been taken.

Primary EBV infection in pregnancy (whether clinically-apparent as IM or asymptomatic) carries no specific risk to the fetus [55]. EBV infection results in a latent infection with persistent excretion in the throat of a proportion (c. 20%) of individuals. Hence exposure to EBV can occur irrespective of whether the contact patient has IM, and exposure to IM does not require investigation and the patient can be reassured.

Some 50% of young adults are susceptible to EBV, with higher rates in more affluent social groups, and some 2% or more of those susceptible become infected annually. About 50% of these infections will present with IM.

2.2.8 Cytomegalovirus (CMV)

CMV can be another cause of infectious mononucleosis, although primary infections are generally mild or even asymptomatic. Rarely patients may present with a generalised maculopapular rash. Following primary infection the virus remains latent and can periodically reactivate throughout life, and especially in pregnancy. The fetus can be infected either during primary or reactivation, and CMV infection is now the commonest cause of viral congenital infection [56]. It is estimated that the overall birth prevalence of congenital CMV infection in the UK is around 3/1000 [57]. However, there is no

treatment currently recommended to prevent or reduce mother-to-child transmission, and as presentation with a rash, or contact of a rash is rarely implicated, CMV infection is not considered further in this guidance. If primary infection or re-infection is suspected it should be appropriately investigated with CMV-specific assays and, if indicated, referral to an appropriate specialist unit.

2.3 Advice and information on rash illness for pregnant women

Information and advice to pregnant women should reflect the guidance set out in this document. At booking midwives should:

1. Check and document MMR vaccination status in the maternity records and offer postpartum doses to those with no, incomplete or uncertain vaccination history.
2. Check and document history of chickenpox and shingles, or vaccination against chickenpox and shingles, in the maternity records.
3. Enquire if women have had a rash illness or had contact with a rash illness during the current pregnancy. Those with a recent rash should be investigated according to this guidance.
4. Advise women that they should inform their midwife, GP or obstetrician urgently if they have contact at any time in pregnancy with someone who has a rash.
5. Advise women to inform their midwife, GP or obstetrician urgently if they develop a rash at any time in pregnancy. They should be advised to avoid any antenatal clinic or maternity setting until clinically assessed, to avoid exposing other pregnant women.

All pregnant women with rash illness, or contact with rash illness, should be referred for medical management and laboratory investigation in line with this guidance (Parts 2 and 3) should be initiated.

Before any testing or screening is undertaken women should be provided with information regarding screening and diagnostic tests, the meaning and consequences of both, what to expect in terms of results and further options for management.

3. A pregnant woman presenting with a rash illness

A full clinical history and examination should be undertaken for all pregnant women presenting with a rash. The appearance of the rash should be determined as vesicular or non-vesicular in order to direct laboratory investigation and management of the patient. Care must be taken in assessing the rash in a patient with a dark skin as the appearance may not be typical of that seen in those with a lighter skin. Those whose first language is not English may not be familiar with common terms, such as “German measles”, and hence relevant history obtained must be interpreted with care. Patients who have spent their childhood years in other countries may not have had the same exposure to natural infection or vaccination opportunities as those brought up in the UK; consequently, the risk estimates presented here may not apply to these groups as they may have a higher or lower level of susceptibility. If the nature of the rash is unclear they should be investigated for both vesicular and non-vesicular rash.

3.1 Laboratory investigation and management

All requests for laboratory investigation must clearly state that the patient is pregnant and give the following information to enable the results to be reported with the correct interpretation:

- full demographic details
- gestation of pregnancy
- date of onset, clinical features, type and distribution of any rash illness
- past relevant history of infection
- past relevant history of antibody testing
- past relevant history of vaccine administration (and dates/places)
- recent travel history and relevant dates
- any known contacts with rash illness or recent travel, and dates of contact

Booking sera or previous serum samples may be helpful and should be obtained if possible from the relevant laboratory. Antenatal screening sera should be retained for at least 2 years to assist diagnosis/exposure in later pregnancy and investigation of the neonate (UK National Screening Committee, Infectious Diseases in Pregnancy Screening Programme: Handbook for Laboratories: www.gov.uk/government/publications/infectious-diseases-in-pregnancy-screening-programme-laboratory-handbook. This may include exposure to chickenpox and parvovirus B19, when the availability of such sera for testing can be invaluable in rapidly assessing susceptibility. Although testing of amniotic fluid may be helpful where this has

been taken for other purposes it is not advocated specifically for investigation of these infections.

When any diagnostic testing is undertaken it should be made clear to the woman that:

- tests to establish the initial diagnosis will usually be on samples of blood
- the requirement for more invasive tests such as amniocentesis, is uncommon, and is only required in rare situations as advised by a specialist
- further testing may be necessary in order to confirm the diagnosis, which may prolong the time to result
- if investigation is commenced some weeks after rash or contact, it may not be possible to confirm or refute a particular diagnosis

In addition, minimum standards of information prior to any screening or diagnostic tests done to differentiate the origin of rash in pregnancy should include:

- how long the results will take (consult local laboratory)
- who will give the test results
- who will discuss future management of the pregnancy
- who they can contact if they have any unanswered queries or concerns

Written information should be provided to back up verbal advice or information given. The use of a competent adult interpreter for women who do not speak English and the use of translations and/or different media to reiterate verbal discussions are considered good practice. All discussions, advice and care management plans should be documented.

Decisions on management of a pregnant woman diagnosed with any of the infections potentially causing congenital pathology in her first 20 weeks of pregnancy are best made in a specialist fetal medicine unit, in consultation with the patient. This will enable patient access to counselling, serial ultrasound scanning and further follow up including investigations, treatment and referral to paediatrics, where appropriate.

3.2 Maculopapular rashes in pregnancy

Although parvovirus B19 and rubella infections predominantly have a specific impact on the fetus if infection occurs in the first 20 weeks gestation, investigation after 20 weeks is also strongly advised for the following reasons:

- Specific diagnosis would help in managing potential risk to contacts (eg in health care situations such as GP surgeries, antenatal clinics)
- It would confirm the date of infection related to gestational age
- estimate of the gestation may be wrong

- the mother may be reassured that a specific diagnosis has been reached or excluded, and may be helpful in the management of subsequent exposure
- measles infection can affect the pregnancy at any stage

Investigation will be directed by clinical/epidemiological information. For a non-vesicular rash, the probability of streptococcal and meningococcal infection, measles, enterovirus, syphilis and infectious mononucleosis (EBV or CMV) should be suggested by clinical features and would instigate appropriate specific investigation and management. Any doubt as to one of these diagnoses, or failure to confirm by laboratory investigation, must result in initiating specific investigation for rubella and parvovirus B19.

If features are compatible with rubella, parvovirus B19 or measles, appropriate laboratory investigation should be initiated, irrespective of past testing or immunisation. There is a remote possibility of past laboratory or documentation error, failed immunisation, or symptomatic reinfection.

Cases of measles and rubella diagnosed on the basis of clinical suspicion are notifiable diseases and should be reported to the local Health Protection Team (www.gov.uk/health-protection-team).

3.2.1 Parvovirus

Laboratory investigation of suspected parvovirus B19

In patients with a rash, recent parvovirus B19 infection can be confirmed or excluded by testing for parvovirus B19 specific IgM on the first serum obtained from the day after rash onset. Booking sera or other earlier serum samples may be available and may also aid in the diagnosis but the initial investigation should not be delayed.

Failure to detect parvovirus B19 specific IgM excludes infection in the 4 weeks prior to collection of the serum. Hence infection cannot be excluded if investigation commences more than 4 weeks after onset of rash illness (*vide supra*, rubella).

If parvovirus B19 IgM is detected in the first 20 weeks of pregnancy, confirmation is recommended by alternative assay, eg detection of high levels of B19V DNA or IgG seroconversion using an antenatal booking blood [58]. Testing a second sample may demonstrate a change in IgM reactivity and provide an additional confirmation method.

Management of confirmed parvovirus B19

The management of proven parvovirus B19 infection has become more active with the demonstration that intrauterine transfusion of the fetus improves the outcome [59;60;8]. On diagnosis of parvovirus B19 infection, specialist advice should be sought including

the need for serial ultrasound scanning and Doppler assessment to prevent the progression of hydrops fetalis.

Laboratory investigation of hydrops fetalis

In a pregnant woman presenting with hydrops fetalis without a rash history, the diagnosis of recent parvovirus B19 infection may be achieved by testing an acute sample for B19V-specific IgM or B19V viral load [58], or by testing the antenatal booking sample in parallel with the sample at presentation for parvovirus-specific IgG to show seroconversion. Inability to detect B19V-specific IgG in maternal blood at the time of hydrops excludes B19V as the aetiological agent. Parvovirus B19 infection as the cause of hydrops fetalis can be confirmed by detection of B19V DNA in amniotic fluid or fetal blood if available.

Management of hydrops fetalis following confirmed parvovirus B19

Following confirmation of parvovirus B19 in a pregnant woman presenting with hydrops fetalis, referral to a fetal medicine specialist is recommended if this has not already occurred. If a fetal blood sample is collected then examination by quantitative PCR to confirm fetal infection should be arranged.

Proven parvovirus B19 infection in the hydropic fetus will influence the management of the patient as it is important in establishing the aetiology of the hydrops and in excluding other causes so allowing appropriate counselling of the patient.

3.2.2 Measles

Measles is a notifiable disease, therefore, all suspected cases of measles should be reported to the local Health Protection Team.

Laboratory investigation of suspected measles

The serological diagnosis of measles is well established. A serum sample should be collected at first presentation and sent for laboratory testing for measles-specific IgM and IgG. Oral fluid should be collected at the same time, via the local Health Protection Team, for confirmation of the diagnosis by detection of viral RNA.

Recent measles infection can be confirmed or excluded by testing for measles-specific IgM on serum sample taken more than 4 days but within one month after the onset of rash.

Management of confirmed measles

When measles has been confirmed the management of the pregnancy should continue as normal. Given the risk of maternal pneumonitis, pregnant women must be closely monitored and asked to seek urgent advice if they develop respiratory symptoms.

Neonates born to measles infected mothers

Human normal immunoglobulin (HNIG) is recommended for neonates born to mothers who develop a measles rash 6 days before to 6 days after delivery. For neonates and infants exposed to measles, HNIG is recommended for up to and including 8 months of age.

The dosage for infants is described in the detailed guidance on post exposure prophylaxis for measles (www.gov.uk/government/publications/measles-post-exposure-prophylaxis).

3.2.3 Rubella

Rubella is a notifiable disease, therefore, all suspected cases of rubella should be reported to the local Health Protection Team.

Laboratory investigation of suspected rubella

If investigation for rubella is required, the request form must clearly state that:

- the woman is pregnant
- recent rubella is a possibility
- whether or not she has a rash and, if rash is present, date of rash onset
- and provide the other full clinical and epidemiological details given above (see 3.1)

It is recommended that, irrespective of a request for specific rubella or parvovirus B19 testing, all sera from women with rash illness are simultaneously investigated for both infections.

The serological diagnosis of rubella is well-established [61]. A serum at first presentation must be collected and sent for laboratory testing. Booking sera or other earlier serum samples may be available and may also aid in the diagnosis but the initial investigation should not be delayed. It is recommended that the laboratory investigates all cases of possible rubella by simultaneous testing for rubella-specific IgG (or total rubella antibody) and IgM.

Although positive rubella IgM results which do not reflect recent rubella (primary or reinfection) ('false positive') are infrequent, the control of rubella in the UK means that most rubella-specific IgM positive results do not reflect recent rubella. No pregnant woman should have rubella diagnosed on the basis of a single positive rubella-specific IgM alone. Results must be interpreted in relation to full clinical and epidemiological information. All rubella IgM-positive cases should be followed up by requesting a second sample and forwarding all samples to the PHE Virus Reference Department for confirmation. Confirmatory testing includes testing for rubella IgM with 2 different formats of assay, PCR testing for rubella RNA and/or rubella IgG avidity testing.

Unless seroconversion has been shown, further testing by alternative rubella-specific IgM tests, testing an acute sample and a sample taken 10-14 days later for rubella IgG, and measuring the strength of binding of specific IgG (avidity) is advised [61]. IgG avidity is low soon after a primary infection, but matures over a few weeks to become more strongly binding. If rubella-specific IgM positivity reflects a recent rubella episode (whether primary or reinfection), the degree of reactivity will usually change over the period of a few weeks, rather than persisting at a similar level.

When reporting the results of rubella serology, the laboratory must advise on any further sera/follow-up required, and give a definitive conclusion of their investigations, eg "No evidence of recent primary rubella".

Current methods developed for use on oral fluid must not be used alone for confirming or excluding rubella infection in pregnancy. Diagnosis must be made on serum sample(s).

Problems arise when investigation commences 4 weeks or more after the onset of rash illness. If rubella-specific IgG is detected, and specific IgM is not detected, rubella as a cause of the rash illness cannot be excluded serologically unless past sera can be tested to determine whether seroconversion has occurred recently. An assessment of probabilities has to be made based on recent epidemiology of rubella in the community, past history of vaccine and testing, characteristics of illness, etc.

Management of confirmed rubella – primary and reinfection

There is no specific treatment for rubella. Management depends on the gestation of pregnancy, the individual circumstances of the woman and the likelihood of congenital abnormalities (Table 1). Decisions on the management of a pregnant woman diagnosed with rubella in the first 20 weeks of pregnancy are best made in a specialist fetal medicine unit.

If a case of asymptomatic rubella reinfection is identified or suspected, management would, as for primary rubella, depend on the gestation of pregnancy and the individual

circumstances of the woman. Given the low but definite risk to the fetus of maternal rubella reinfection in the first 16 weeks of pregnancy, there may be occasions when consideration is given to further fetal investigation by PCR to ascertain if fetal infection has occurred.

The necessary virological techniques for fetal investigation are not widely available in the UK and the PHE Virus Reference Department should be consulted for advice if such approaches are being considered. It is strongly advised that management is based on risk assessment. Appropriate expert advice should also be obtained for the investigation of suspected cases of congenital rubella syndrome identified post-natally.

Management of the neonate born to mother infected during pregnancy

Neonates born to women with confirmed rubella infection in pregnancy or where rubella infection could not be ruled out during pregnancy, should be investigated at birth for congenital infection. Samples of cord blood, placenta, urine and an oral fluid should be taken from the infant soon after delivery and sent to the PHE Virus Reference Department. Congenital rubella infection (CRI) is confirmed by detection of rubella IgM in serum or oral fluid and/or detection of rubella RNA in body fluids [36].

Infants with congenital rubella infection are infectious. They excrete virus at birth and some may continue to excrete for more than a year. During the ante-natal period the health protection team should liaise with the hospital infection control team where the mother is booked and ensure there is an appropriate isolation plan for the neonate during and after birth. For infants diagnosed with CRI, isolation should be put in place for any subsequent healthcare attendance until the infant in no longer considered infectious. Samples to monitor duration of virus excretion as a marker of infectiousness should be arranged in discussion with the health protection team. Susceptible individuals should avoid contact with the infant and offered vaccination.

All suspected and confirmed cases of congenital rubella infection/syndrome should be reported to the local health protection team and to the National Congenital Rubella Surveillance Programme.

3.3 Generalised vesicular rash illness in pregnancy

Investigation will be directed by clinical/epidemiological information. A disseminated vesicular rash is highly suggestive of chickenpox.

3.3.1 Chickenpox

Laboratory investigation of suspected chickenpox

The diagnosis can be made clinically in many instances, but if there is doubt, confirmation of chickenpox should be sought. Laboratory diagnosis of active infection should be by DNA detection, virus antigen or electron microscopy of vesicle fluid.

Detection of VZV DNA in the amniotic fluid by polymerase chain reaction (PCR) can also be used for the confirmation of chickenpox infection in the fetus. However, this is not routinely advised. The precise predictive value is unknown and the norms for viral load relating to fetal varicella syndrome are also unknown. Therefore, this should only be requested by a specialist in fetal medicine and is usually requested in tandem with serial ultrasound scanning.

Management of confirmed chickenpox infection in a pregnant woman

Management has to take into account the possible effect on both mother and fetus. Pregnant women should be advised to consult their general practitioner at the first sign of chickenpox. They should avoid contact with others who might be at risk, such as other pregnant women and neonates, and the immunosuppressed.

All women require an urgent clinical assessment on presentation. If the woman shows evidence of severe disease at that stage or subsequently, she should be referred immediately for urgent assessment in a specialist isolation facility where she has access to the expertise of an obstetrician, infectious disease specialist and paediatrician.

If the chickenpox is uncomplicated, the woman can be reassured, offered acyclovir if appropriate and sent home with arrangements for daily review and for outpatient follow up for the fetus. The woman should be advised to seek help if the clinical picture deteriorates. Women who appear to have uncomplicated infections must be monitored closely for deterioration by an appropriate clinician.

If there is deterioration, or the fever persists, or the cropping of the rash continues after 6 days, or the woman develops respiratory symptoms, the woman should be referred for urgent hospital assessment. The general practitioner should have a low threshold for considering hospitalisation. The criteria indicating that hospitalisation is required are [3]:

Absolute indicators:

- respiratory symptoms
- neurological symptoms other than headache
- haemorrhagic rash or bleeding

- severe disease – dense rash/numerous mucosal lesions
- significant immunosuppression

Contributory factors:

- pregnancy approaching term
- bad obstetric history
- smoker
- chronic lung disease
- poor social circumstances
- GP unable to monitor patient closely

The time of onset of the rash is important for determining the likely effectiveness of antiviral treatment. Onset is timed from the first observable lesion. If the woman presents within 24 hours of the onset of the rash, and she has reached 20 weeks gestation, she should be offered oral antiviral treatment for 7 days (eg aciclovir 5x800mg per day) [24]. Aciclovir should be used cautiously before 20 weeks of gestation. It is reassuring that neither the US nor Danish studies found an increase in major congentical malformations following exposure to antiviral agents in pregnancy. The US based study was a prospective registry of over 1200 pregnancies that received either oral or IV aciclovir across all stages of pregnancy [62]. The Danish national cohort study reviewed 1804 pregnancies exposed to antiviral agents (aciclovir, valaciclovir, famciclovir) during the first trimester of pregnancy and found no evidence for an increased risk of major birth defects compared to an unexposed cohort [63].

If the woman presents more than 24 hours from the onset of rash and there are no indications of complications, antivirals are not routinely advised. There is no evidence that antivirals alter the natural history of uncomplicated chickenpox when given more than 24 hours after rash onset; however, this is a clinical decision [64;65]. VZIG has no place in treatment once the rash appears.

Intravenous treatment with aciclovir is indicated if the chickenpox is severe or there are any complications [66]. Treatment of pneumonia associated with chickenpox in hospital is with intravenous aciclovir 3x10mg/kg/day for 5-10 days [67]. Delivery by caesarean section may need to be considered. Detailed recommendations including the management of delivery are given by the Royal College of Obstetricians and Gynaecologists [24].

Management of proven chickenpox exposure in utero

There is a lack of evidence to support immunoglobulin and aciclovir treatment to prevent vertical transmission or fetal varicella syndrome [21].

Chickenpox during pregnancy does not justify termination without prior prenatal diagnosis as only a minority of fetuses will be infected and not all those infected will develop fetal varicella syndrome. The parents should be offered counselling in a specialist fetal unit and the option of abortion care following an early sonographic diagnosis of fetal varicella syndrome.

Management of the neonate exposed to chickenpox

PHE guidance on use of immunoglobulins (www.gov.uk/government/collections/chickenpox-public-health-management-and-guidance) recommends VZIG for neonates whose mothers develop chickenpox (but not shingles) in the period 7 days before to 7 days after delivery. VZIG can be given without VZV IgG antibody testing of the neonate or mother.

Prophylactic, intravenous aciclovir should also be considered in addition to VZIG for neonates whose mothers develop chickenpox in the period 4 days before to 2 days after delivery, as they are at the highest risk of a fatal outcome despite VZIG prophylaxis.

VZIG is not usually required for neonates born more than 7 days after the onset of maternal chickenpox, or in those whose mothers develop shingles before or after delivery as these neonates will have maternal antibody.

VZIG is not indicated for neonates (< 7 days old) whose mothers have been exposed during pregnancy and have been found to be VZV IgG negative, unless the mother develops chickenpox. VZIG is only indicated for the neonate if they are directly exposed postnatally. Any exposed pregnant women found to be IgG negative should be urgently assessed for post-exposure prophylaxis (PEP) as soon as exposure has occurred (see part 4).

If a neonate has possible exposure to chickenpox from someone other than their mother, refer to the VZIG guidance for risk assessment (www.gov.uk/government/collections/chickenpox-public-health-management-and-guidance).

If severe chickenpox develops in the neonate despite VZIG, high dose intravenous aciclovir treatment of 20mg/kg every 8 hours for at least 7 days should be started as soon as possible [68].

If other children in the family have chickenpox, and the mother has had chickenpox prior to this pregnancy or is shown to have varicella-zoster virus antibody, then there is no reason to prevent a new baby going home. If the mother is susceptible, contact with siblings with chickenpox should ideally be delayed until the new baby has reached 7 days of age. This is to prevent disease in the first month of life which carries a greater risk of severe disease [34]. If a new baby returns to a home where siblings are still in

the infectious phase of chickenpox, the risks must be clearly explained to the parent/s and every effort should be made to avoid significant contact with the siblings. VZIG is not a suitable alternative to avoiding such contact. The family should be advised to bring the infant back promptly if any chickenpox spots develop so that they can be treated with intravenous aciclovir at the earliest opportunity.

Mothers with chickenpox or shingles can breast feed safely. If they have lesions close to the nipple, they should express milk from the affected breast until the lesions have crusted; this expressed milk can be fed to the baby if he/she is covered by VZIG and/or aciclovir.

4. A pregnant woman in contact with a rash illness

Contact is defined as being in the same room (eg house or classroom or 2-4 bed hospital bay) for a significant period of time (15 minutes or more) or face-to-face contact. This definition is based on experience with VZV exposure. This definition of contact is probably practical for all nosocomial exposures in healthy pregnant women. In other settings, where exposure is less well defined, a less stringent definition of contact should be used, especially for measles. For parvovirus B19 infections household exposure is overwhelmingly the most important source of infections in pregnancy, followed by intense occupational exposure.

4.1 Contact with a maculopapular rash illness

The aetiology of a maculopapular rash in the contact may be diverse, and include non-infective causes. The possible causes which warrant consideration include measles, rubella and parvovirus B19. Other possible infective causes in the contact should await development of illness in a pregnant woman.

Suspected measles or rubella infection in contacts of a pregnant woman should be confirmed rapidly with oral fluid or serum testing. This can most readily be achieved through notification to the local HPT (www.gov.uk/health-protection-team). Through liaison with the local HPT, the Virology Reference Department or with the Immunisation Department at Colindale it may be possible to confirm whether or not the contact is a known case.

A risk assessment should be undertaken for measles, rubella and parvovirus for all pregnant women following contact with a maculopapular rash and appropriate investigation and treatment undertaken as set out in this section.

4.1.1 Contact with suspected parvovirus B19 (Figure One)

The pregnant woman should be investigated for asymptomatic parvovirus B19 infection. Investigation should not be delayed to ascertain if symptomatic infection occurs. This is because:

- maternal asymptomatic parvovirus B19 infection is at least as likely to infect and damage the fetus as symptomatic infection [4]
- active management of the infected fetus may reduce the risk of adverse outcome [59] (part 3)

Serum should be collected as soon after contact as possible and submitted to the laboratory with full clinical and epidemiological details, including date of contact (see part 3).

Serum should be tested for both B19V-specific IgG and IgM. If B19V-specific IgG is detected (c 50% probability), but IgM not detected, the woman should be reassured and a report issued, “Parvovirus B19 infection at some time, but not recently”. If specific IgG or IgM are not detected, further serum should be collected and tested one month after last contact. If, after one month testing, specific IgG and IgM are not detected, the woman should be reassured and a report issued “No evidence of recent parvovirus B19V infection, but is susceptible”. If B19V-specific IgM is detected, but B19V-specific IgG not detected, a further serum should be collected and tested immediately. If the sample is B19V-IgM positive further testing and management should be undertaken as in part 3 on suspected B19V infection in pregnancy.

4.1.2 Contact with suspected measles (Figure One)

Clinical features suggestive of measles are described in part 2. Additional factors that would increase the likelihood of measles are as follows:

- the contact is linked epidemiologically to a confirmed measles case
- the rash contact took place when the woman was abroad
- the contact had travelled abroad
- the contact has not received measles vaccine in the past
- the contact has been hospitalised recently

PHE guidance on human normal immunoglobulin (HNIG) for pregnant women should be consulted to determine if prophylaxis is warranted. The guidance is available here: www.gov.uk/government/publications/measles-post-exposure-prophylaxis.

The probability of measles immunity is considered in detail in this guidance on the basis of year of birth and clinical and immunisation history. This reflects changes in the epidemiology of measles and the age related susceptibility of the population determined by vaccine policy and coverage. If there is another exposure to measles 3 weeks or more after the first use of HNIG, the need for HNIG should be reassessed using the above guidance.

HNIG may not prevent measles, but has been shown to attenuate illness. There is no evidence that it prevents intrauterine death or pre-term delivery. [14]

4.1.3 Contact with suspected rubella (Figure One)

From 1 April 2016, antenatal rubella susceptibility screening ceased in England. If a woman has had one of the following she should be reassured that the likelihood of rubella is remote and that specific rubella investigation is not required but she must return if a rash develops:

- at least 2 documented doses of rubella containing vaccine
- at least one rubella antibody test (before or at the time of exposure) in which IgG antibody was detected

If the above criteria are not met, a serum should be obtained as soon after contact as possible and tested for IgM and IgG with a second sample 4 weeks later similarly tested if the patient is shown to be susceptible. Further testing may be required. Any evidence of seroconversion or IgM positivity should be referred to the PHE Virus Reference Department for confirmatory testing. Refer to part 3 for management of a patient who is subsequently confirmed as having rubella in pregnancy. Patients found to be IgG negative should be immunised with MMR vaccine after delivery, in line with national guidelines.

4.2 Contact with a vesicular rash illness

4.2.1 Contact with confirmed chickenpox (Figure One)

Healthy pregnant women who are exposed to chickenpox or shingles in pregnancy should seek medical advice promptly. The date, duration and nature of the contact, any past history of chickenpox infection, shingles or vaccination should be clarified. PHE guidance on post-exposure prophylaxis (PEP) for pregnant women should be consulted to determine if prophylaxis is warranted. The guidance is available here: www.gov.uk/government/publications/varicella-zoster-immunoglobulin.

If a woman has a past history of chickenpox or shingles or 2 doses of a varicella-containing vaccine, and is not immunosuppressed, protection can be assumed and reassurance given. If there is no history of past chickenpox or shingles and the woman is not fully vaccinated (2 doses), the woman’s susceptibility should be determined urgently.

Laboratory diagnosis of past infection is by VZV IgG antibody in serum. Serological assays for varicella antibody are of variable sensitivity [69]. Those with a negative or equivocal result from a qualitative assay require confirmatory testing with a quantitative assay. For immunocompetent pregnant women, a result of 100mIU/ml or less suggests susceptibility to infection.

Usually, VZIG is recommended for VZ antibody-negative pregnant contacts exposed at any stage of pregnancy, providing it can be given within 10 days of contact. However, when supplies of VZIG are short, issues to pregnant women may be restricted and revised guidance issued. Clinicians are advised to consult current guidance before offering VZIG to pregnant women (www.gov.uk/government/publications/varicella-zoster-immunoglobulin).

Where VZIG is indicated, it should be offered to eligible, susceptible women within 10 days of the exposure [70]. If urgent antibody testing is required for patients presenting late, VZIG can be ordered at the same time that blood is sent for testing and not used if the result is positive. VZV antibody testing should be available within 24 to 48 hours; advice should be obtained from the local NHS or PHE lab.

The clinical attack rates are similar whether VZIG is given within 72 hours or 4-10 days after contact [33]. 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. Where a woman is exposed in pregnancy, even if she has since delivered, VZIG should be administered within the 10 day period.[7]

The majority of adults will be VZV antibody positive. Lack of varicella-specific IgG antibody in a woman without a history of chickenpox is highly suggestive of susceptibility. If susceptibility in a pregnant woman has been confirmed using a quantitative assay then post-partum vaccination may be considered [24].

If a woman with a reliable history of chickenpox, shingles or full vaccination is inadvertently tested for antibody the following advice should be followed:

a) VZV IgG positive - reassure as PEP is not indicated.
b) VZV IgG equivocal or negative with a qualitative assay - retest using a quantitative assay. If time does not permit additional testing within 10 days of contact and the individual is VZV IgG negative then recommend appropriate PEP. If time does not permit additional testing within 10 days of contact and the individual is VZV IgG equivocal, then PEP is not recommended.
c) If less than 100mIU/ml with a quantitative assay then recommend PEP.

Pregnant women who have previously received VZIG or IVIG as VZV post-exposure prophylaxis require a new risk assessment if a second exposure occurs. If the second exposure occurs:

[7] The rationale for this is based on increased risk for severe respiratory complications in post-partum women with influenza (largely experience with H1N1), suggesting that increased risk does not subside immediately on delivery.

- within 3 weeks of administration of VZIG or IVIG, a further dose of VZIG is not required
- between 3 and 6 weeks following administration of VZIG or IVIG, further post-exposure prohylaxis should be administered without further testing
- more than 6 weeks following administration of VZIG or IVIG, retesting of a new sample is required

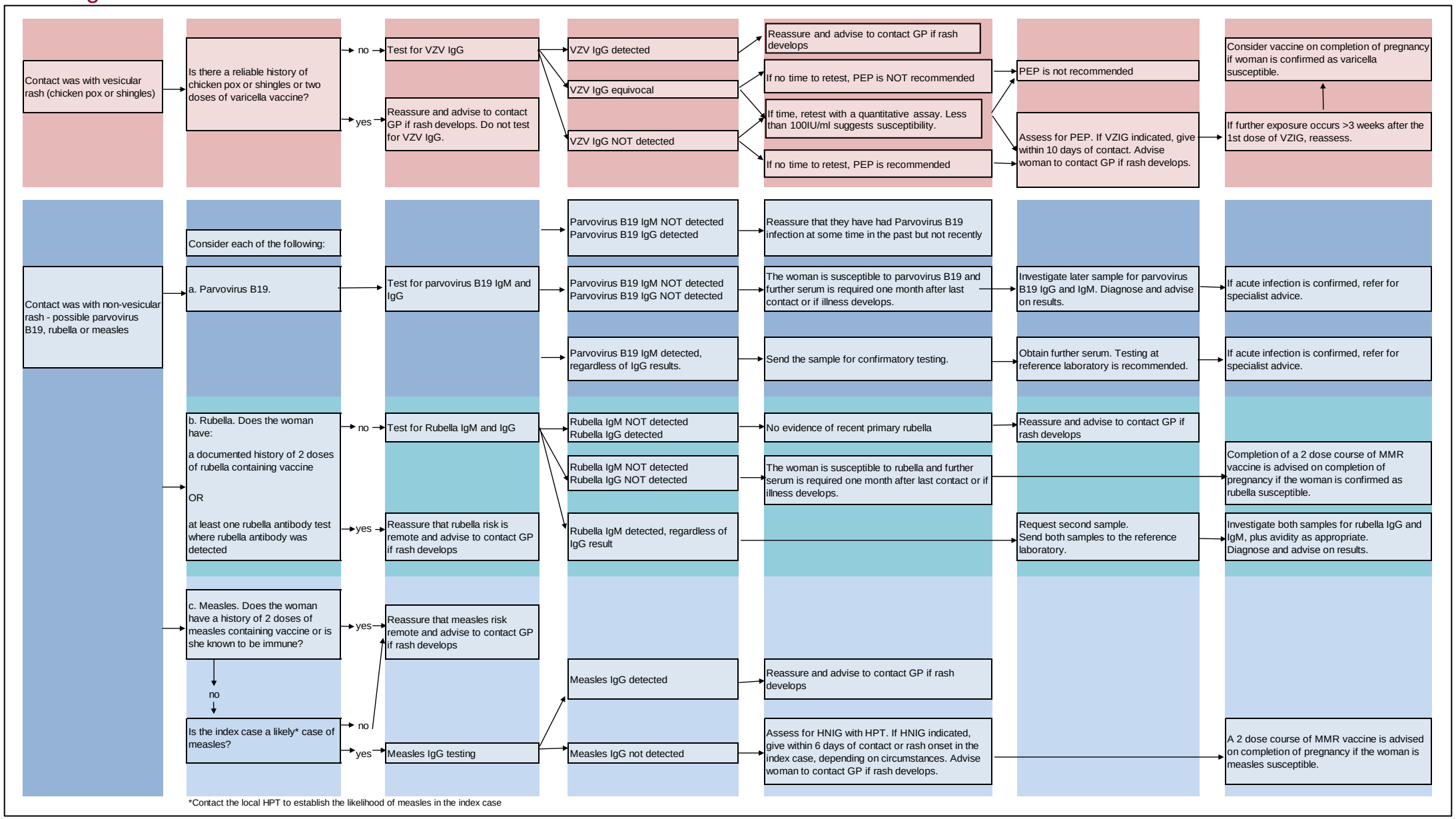
As post exposure prophylaxis does not always prevent chickenpox the woman should be managed as being possibly infectious 8-28 days after exposure and should be asked to contact her family doctor if she develops a rash. Up to 50% may develop a modified form of disease. Maternal pneumonitis associated with chickenpox infection has been reported in spite of timely VZIG administration.

The live chickenpox vaccine is contraindicated in pregnancy [72]. Confusion has been known to occur between the chickenpox vaccine and the varicella immunoglobulin. Staff should be trained to be aware of this known pattern of confusion and be extra careful when prescribing and administering the immunoglobulin. Inadvertent vaccination with chickenpox vaccine in pregnancy should be reported to Public Health England: www.gov.uk/guidance/vaccination-in-pregnancy-vip

4.2.2 VZIG restrictions for pregnant women during times of shortage

During times of severe shortage of VZIG, the issue of VZIG for pregnant women exposed to chickenpox may be restricted. In such circumstances, VZIG has normally been limited to susceptible pregnant women who have had significant exposure in the first 20 weeks (20+0) of pregnancy. For women exposed after 20 weeks who are found to be susceptible to chickenpox, prophylaxis with the oral anti-viral drug, aciclovir, is recommended. Valaciclovir may also be used. Clinicians are advised to consult current guidance before offering VZIG to pregnant women: www.gov.uk/government/publications/varicella-zoster-immunoglobulin

Figure One


Contact was with vesicular rash (chicken pox or shingles)
Is there a reliable history of chicken pox or shingles or two doses of varicella vaccine?
no
yes
Test for VZV IgG
Reassure and advise to contact GP if rash develops. Do not test for VZV IgG.
VZV IgG detected
VZV IgG equivocal
VZV IgG NOT detected
Reassure and advise to contact GP if rash develops
If no time to retest, PEP is NOT recommended
If time, retest with a quantitative assay. Less than 100IU/ml suggests susceptibility.
If no time to retest, PEP is recommended
PEP is not recommended
Assess for PEP. If VZIG indicated, give within 10 days of contact. Advise woman to contact GP if rash develops.
Consider vaccine on completion of pregnancy if woman is confirmed as varicella susceptible.
If further exposure occurs >3 weeks after the 1st dose of VZIG, reassess.
Contact was with non-vesicular rash - possible parvovirus B19, rubella or measles
Consider each of the following:
a. Parvovirus B19.
Test for parvovirus B19 IgM and IgG
Parvovirus B19 IgM NOT detected Parvovirus B19 IgG detected
Parvovirus B19 IgM NOT detected Parvovirus B19 IgG NOT detected
Parvovirus B19 IgM detected, regardless of IgG results.
Reassure that they have had Parvovirus B19 infection at some time in the past but not recently
The woman is susceptible to parvovirus B19 and further serum is required one month after last contact or if illness develops.
Send the sample for confirmatory testing.
Investigate later sample for parvovirus B19 IgG and IgM. Diagnose and advise on results.
Obtain further serum. Testing at reference laboratory is recommended.
If acute infection is confirmed, refer for specialist advice.
If acute infection is confirmed, refer for specialist advice.
b. Rubella. Does the woman have:
a documented history of 2 doses of rubella containing vaccine
OR
at least one rubella antibody test where rubella antibody was detected
no
yes
Test for Rubella IgM and IgG
Reassure that rubella risk is remote and advise to contact GP if rash develops
Rubella IgM NOT detected Rubella IgG detected
Rubella IgM NOT detected Rubella IgG NOT detected
Rubella IgM detected, regardless of IgG result
No evidence of recent primary rubella
The woman is susceptible to rubella and further serum is required one month after last contact or if illness develops.
Request second sample. Send both samples to the reference laboratory.
Reassure and advise to contact GP if rash develops
Completion of a 2 dose course of MMR vaccine is advised on completion of pregnancy if the woman is confirmed as rubella susceptible.
Investigate both samples for rubella IgG and IgM, plus avidity as appropriate. Diagnose and advise on results.
c. Measles. Does the woman have a history of 2 doses of measles containing vaccine or is she known to be immune?
yes
no
Is the index case a likely* case of measles?
no
yes
Reassure that measles risk remote and advise to contact GP if rash develops
Measles IgG testing
Measles IgG detected
Measles IgG not detected
Reassure and advise to contact GP if rash develops
Assess for HNIG with HPT. If HNIG indicated, give within 6 days of contact or rash onset in the index case, depending on circumstances. Advise woman to contact GP if rash develops.
A 2 dose course of MMR vaccine is advised on completion of pregnancy if the woman is measles susceptible.
*Contact the local HPT to establish the likelihood of measles in the index case

5. Other considerations for pregnant women

5.1 Occupational exposure

Parvovirus B19

Guidance on the management of pregnant women susceptible to parvovirus B19 has previously been published [1]. Exclusion is not routinely recommended of pregnant women susceptible to B19V from settings which may suggest a higher rate of exposure (eg nurseries and schools). Exposure to B19V is as likely to occur in the wider community, and more likely within the household setting. However, if there is a laboratory confirmed outbreak of B19V in a school or nursery, then an individual risk assessment should be undertaken, taking into account contact with other children outside the working environment.

Measles

Exclusion is not recommended of pregnant women susceptible to measles from settings which may suggest a higher rate of exposure (eg nurseries and schools). Exposure to measles is as likely to occur in the wider community. However, should there be a case or an outbreak of measles in that setting then an individual risk assessment should be undertaken.

Rubella

Exclusion is not recommended of pregnant women susceptible to rubella from settings which may suggest a higher rate of exposure (eg nurseries and schools). Rubella is now rare in children.

Chickenpox

Exclusion is not recommended of pregnant women susceptible to chickenpox from settings which may suggest a higher rate of exposure (eg nurseries, schools and hospitals). Exposure to chickenpox is as likely to occur in the wider community. However, should there be a case or an outbreak of chickenpox in that setting then an individual risk assessment should be undertaken.

5.2 Antibody screening

Parvovirus B19

Unselected screening of pregnant women for past infection with parvovirus B19 is not recommended as neither vaccine nor prophylaxis are available [73].

Measles

Unselected screening of pregnant women for adequate immunity to measles is not currently recommended.

Satisfactory evidence of protection would include documentation of having received 2 doses of measles containing vaccine or a positive antibody test for measles. All women without such evidence who need to be protected against measles should be offered MMR vaccine post-partum.

Rubella

Universal screening of all pregnant women is no longer recommended and was stopped in April 2016 [75]. Instead, rubella immunity should be established at booking by checking for documented evidence of 2 doses of a rubella-containing vaccine. All those without such evidence should be offered MMR vaccination post-partum.

Varicella

The National Screening Committee commissioned a review of antenatal screening for VZV susceptibility in 2016 which concluded that there was insufficient evidence to recommend the introduction of routine antenatal screening in the UK [74]. At present, it is good practice to establish and record whether there is a firm history of chickenpox or shingles at booking.

5.3 Inadvertent immunisation during pregnancy

MMR and chickenpox vaccines are live vaccines and as a matter of caution should not be given to women known to be pregnant. HPV vaccine, whilst inactivated, is also not advised in pregnancy. However, if a woman has been inadvertently immunised with these vaccines during pregnancy, termination should not be recommended. The woman should be reassured that no adverse effects have been identified from MMR, chickenpox or HPV vaccination during any stage in pregnancy.

The administration of shingles vaccine (Zostavax) is not recommended during pregnancy and inadvertent administration should be treated in the same way as natural

exposure to chickenpox. The woman's susceptibility should be urgently assessed (see part 4). [76].

Surveillance of inadvertent administration of vaccine shortly before conception or during pregnancy is being conducted by the Immunisation Department at PHE, to whom such cases should be reported (Tel: 07824 551 803 or 020 8200 4400: www.gov.uk/guidance/vaccination-in-pregnancy-vip

Table 1

	Parvovirus B19	Measles	Rubella	Chickenpox
Proportion seronegative in young adult females	40-50%	<5%	7% of all women screened antenatally, rising from nearly 3% in 2006 (2006-2014 NHSBT data)	1.2-14% Varies with country of origin
Incubation period	4-21 days	7-21 days	14-21 days	7-21 days
Infectivity period (days pre and post rash onset)	10 days before to day of onset of rash	4 days before onset of rash to 4 days after	7 days before to 10 days post onset of rash	2 days before onset of rash until cropping has ceased and all lesions crusted. Infectivity is prolonged by VZIG and HNIG
Infectivity – risk of transmission from close contact (household attack rate)	Medium (50%)	V high (99%)	High (90%)	High (70-90%)
Risk of adverse outcome for a pregnant woman	Arthropathy	Severe measles, including pneumonitis	Arthritis	Pneumonitis
Risk of intrauterine infection by gestational age	<4 weeks – 0% 5-16 weeks – 15% >16 weeks – 25-70%, increasing with gestation	Not known	<11 weeks – 90% 11-16 weeks – 55% >16 weeks – 45%	<28 weeks- 5-10% 28-36 weeks- 25% >36 weeks- 50%
Risk of adverse fetal outcome	<20 weeks – 9% excess fetal loss. 3% hydrops fetalis, of which about 50% die without treatment [4] >20 weeks - <1% [8]	Increased fetal loss. Premature delivery	<11 weeks- 90% 11-16 weeks - 20% 16 - 20 weeks – minimal risk of deafness only >20 weeks - no increased risk	Fetal varicella Syndrome risk: <13 weeks- 0.4% 13-20 weeks- 2%. Neonatal chickenpox risk in 4 days prior to 2 days post-delivery - 20%
Risk to the neonate	None	Risk of SSPE with a short onset latency and fulminant course	None	Risk of severe disseminated haemorrhagic chickenpox. An estimated 30 neonates at risk of severe neonatal infection per year
Interventions and benefit	Fetal hydrops – resolution of infection	HNIG to susceptible	Counselling for parents to make	PEP to exposed mother and neonate

	Parvovirus B19	**Measles**	**Rubella**	**Chickenpox**
	increased from 5% spontaneous resolution to 55% after intrauterine transfusion	women and neonates attenuates infection/illness	informed decision about whether to continue with the pregnancy	attenuates illness. Intravenous aciclovir or valcyclovir within 24 hrs of rash onset for mother. Intravenous aciclovir for infected neonates.
Number of infections in pregnancy per year	1 in 512 pregnancies [14] or seroconversion of 1.5 –13% among susceptibles	Total pregnant women for whom HNIG was requested post exposure- 30 between April 2014 and March 2018	1-2 confirmed infections in pregnancy	VZIG was issued for 580 susceptible, pregnant women in 2016/17. There are an estimated 2-3 infections per 1000 pregnancies, 6 per 10,000 deliveries or 2000 maternal infections per year.
Terminations of pregnancy	Unknown – not recommended	Unknown – not recommended	4 terminations between 2003 and 2016 [36]	Unknown
Number of babies born with congenital defects	An estimated 2-8 fetal hydrops per 100,000 pregnancies (14- 56 cases per year in UK) 12-48 per 100,000 spontaneous abortion (84-336 cases per year in UK)	None	Approx 1 per year	Approx 10 babies born with fetal damage per year, England and Wales

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