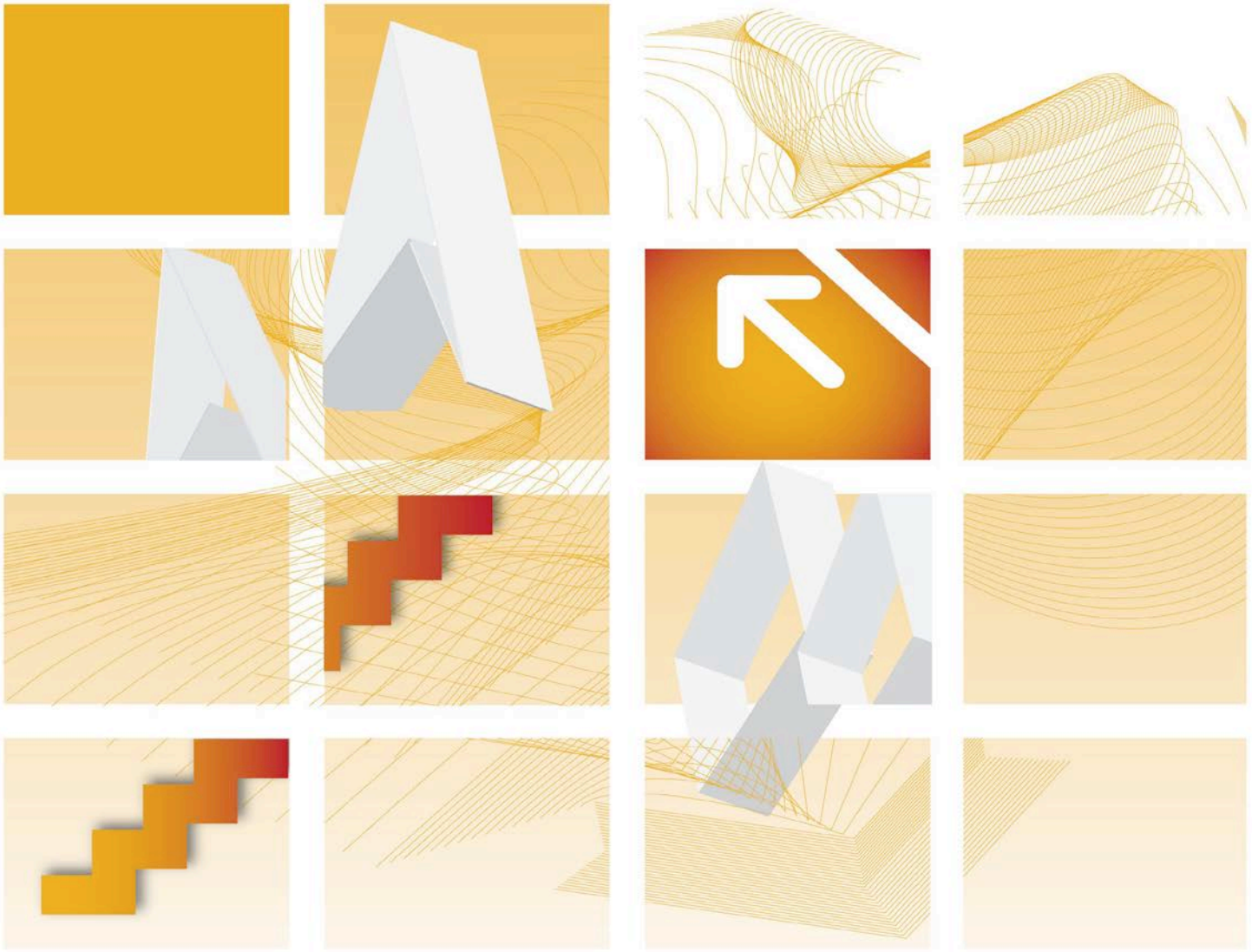
Public Health England

NHS

UK Standards for Microbiology Investigations

Investigation of Red Rash



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Acknowledgments

UK Standards for Microbiology Investigations (SMIs) are developed under the auspices of Public Health England (PHE) working in partnership with the National Health Service (NHS), Public Health Wales and with the professional organisations whose logos are displayed below and listed on the website http://www.hpa.org.uk/SMI/Partnerships. SMIs are developed, reviewed and revised by various working groups which are overseen by a steering committee (see http://www.hpa.org.uk/SMI/WorkingGroups).

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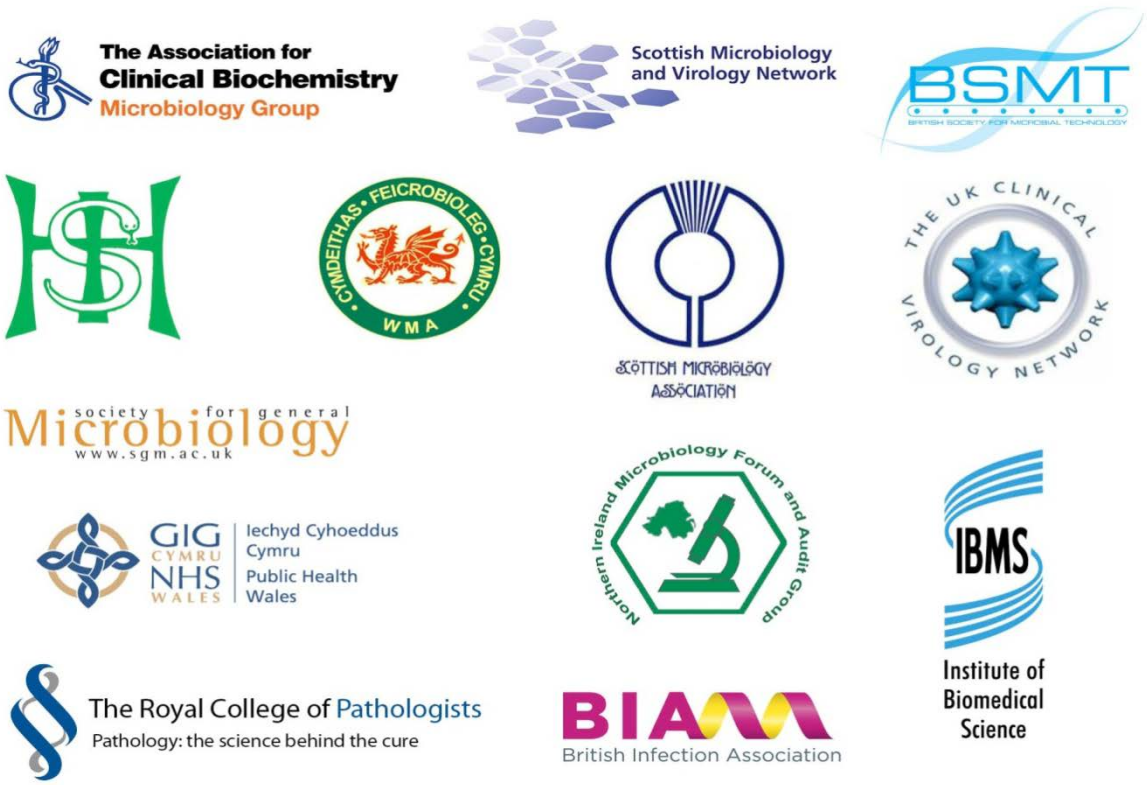

Contents

Amendment Table

Each SMI method has an individual record of amendments. The current amendments are listed on this page. The amendment history is available from standards@phe.gov.uk.

New or revised documents should be controlled within the laboratory in accordance with the local quality management system.

Amendment No/Date.	2/04.03.14
Issue no. discarded.	2
Insert Issue no.	2.1
Section(s) involved	**Amendment**
Whole document.	Document has been transferred to a new template to reflect the Health Protection Agency's transition to Public Health England. Front page has been redesigned. Status page has been renamed as Scope and Purpose and updated as appropriate. Professional body logos have been reviewed and updated. Scientific content remains unchanged.

Amendment No/Date.	1/11.11.11
Issue no. discarded.	1
Insert Issue no.	2
Section(s) involved	**Amendment**
Whole document.	Formerly QSOP 56 now G 7. Document presented in a new format.
Relevant NSM section.	Removed.
References.	References reviewed and updated.

UK Standards for Microbiology Investigations[#]: Scope and Purpose

Users of SMIs

- SMIs are primarily intended as a general resource for practising professionals operating in the field of laboratory medicine and infection specialties in the UK.
- SMIs provide clinicians with information about the available test repertoire and the standard of laboratory services they should expect for the investigation of infection in their patients, as well as providing information that aids the electronic ordering of appropriate tests.
- SMIs provide commissioners of healthcare services with the appropriateness and standard of microbiology investigations they should be seeking as part of the clinical and public health care package for their population.

Background to SMIs

SMIs comprise a collection of recommended algorithms and procedures covering all stages of the investigative process in microbiology from the pre-analytical (clinical syndrome) stage to the analytical (laboratory testing) and post analytical (result interpretation and reporting) stages.

Syndromic algorithms are supported by more detailed documents containing advice on the investigation of specific diseases and infections. Guidance notes cover the clinical background, differential diagnosis, and appropriate investigation of particular clinical conditions. Quality guidance notes describe laboratory processes which underpin quality, for example assay validation.

Standardisation of the diagnostic process through the application of SMIs helps to assure the equivalence of investigation strategies in different laboratories across the UK and is essential for public health surveillance, research and development activities.

Equal Partnership Working

SMIs are developed in equal partnership with PHE, NHS, Royal College of Pathologists and professional societies.

The list of participating societies may be found at http://www.hpa.org.uk/SMI/Partnerships. Inclusion of a logo in an SMI indicates participation of the society in equal partnership and support for the objectives and process of preparing SMIs. Nominees of professional societies are members of the Steering Committee and Working Groups which develop SMIs. The views of nominees cannot be rigorously representative of the members of their nominating organisations nor the corporate views of their organisations. Nominees act as a conduit for two way reporting and dialogue. Representative views are sought through the consultation process.

SMIs are developed, reviewed and updated through a wide consultation process.

[#] Microbiology is used as a generic term to include the two GMC-recognised specialties of Medical Microbiology (which includes Bacteriology, Mycology and Parasitology) and Medical Virology.

Quality Assurance

NICE has accredited the process used by the SMI Working Groups to produce SMIs. The accreditation is applicable to all guidance produced since October 2009. The process for the development of SMIs is certified to ISO 9001:2008.

SMIs represent a good standard of practice to which all clinical and public health microbiology laboratories in the UK are expected to work. SMIs are NICE accredited and represent neither minimum standards of practice nor the highest level of complex laboratory investigation possible. In using SMIs, laboratories should take account of local requirements and undertake additional investigations where appropriate. SMIs help laboratories to meet accreditation requirements by promoting high quality practices which are auditable. SMIs also provide a reference point for method development.

The performance of SMIs depends on competent staff and appropriate quality reagents and equipment. Laboratories should ensure that all commercial and in-house tests have been validated and shown to be fit for purpose. Laboratories should participate in external quality assessment schemes and undertake relevant internal quality control procedures.

Patient and Public Involvement

The SMI Working Groups are committed to patient and public involvement in the development of SMIs. By involving the public, health professionals, scientists and voluntary organisations the resulting SMI will be robust and meet the needs of the user. An opportunity is given to members of the public to contribute to consultations through our open access website.

Information Governance and Equality

PHE is a Caldicott compliant organisation. It seeks to take every possible precaution to prevent unauthorised disclosure of patient details and to ensure that patient-related records are kept under secure conditions.

The development of SMIs are subject to PHE Equality objectives http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317133470313. The SMI Working Groups are committed to achieving the equality objectives by effective consultation with members of the public, partners, stakeholders and specialist interest groups.

Legal Statement

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The evidence base and microbial taxonomy for the SMI is as complete as possible at the time of issue. Any omissions and new material will be considered at the next review. These standards can only be superseded by revisions of the standard, legislative action, or by NICE accredited guidance.

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Suggested Citation for this Document

Public Health England. (2014). Investigation of Red Rash. UK Standards for Microbiology Investigations. G 7 Issue 2.1. http://www.hpa.org.uk/SMI/pdf.

Scope of Document

Type of Specimen

Serum, throat swabs, peripheal blood lymphocytes, nasopharyngeal swabs, vesicle fluids, plasma, crevicula fluid, urine, PBMC, stools

Scope

This SMI describes the examination of Red Rash.

This SMI should be used in conjunction with other SMIs.

Introduction

This Clinical Guidance describes the identification of infection with those viruses that are capable of causing red rash as a major symptom of disease. Rashes may occur either as a direct result of infection of the skin, or as a secondary phenomenon due to the host immune response or an interaction between host immune response and virus in the skin. For the most part the rashes that arise from viruses that replicate in the skin are typically vesicular (poxviruses, herpes simplex, varicella-zoster), or nodular (papillomavirus) lesions[1].

Rashes may be morbilliform (erythematous macules and papules) or scarlatiniform (confluent blanching erythema)[1].

Viral rashes and drug reactions are usually morbilliform, while scarlatiniform rashes tend to be seen in bacterial infections which produce exotoxins.

The non vesicular ‘red rashes’ may be classified as follows[2]:

Centrally Distributed Maculopapular Rashes (Lesions Primarily on the Trunk)

a) Viral
   - Measles
   - Rubella
   - Erythema infectiosum (fifth disease)
   - Roseola infantum (exanthem subitum, sixth disease)
   - Infectious mononucleosis
   - Primary HIV infection
   - Arbovirus infections including dengue
   - Nonspecific enteroviral infections

b) Bacterial
   - Typhus
   - Typhoid
   - Lyme disease

c) Drug reactions

d) Collagen vascular diseases

- Rheumatic fever
- Still's disease
- Systemic lupus erythematosus

Peripheral Rashes (Beginning Peripherally and Extending Centripetally)

a) Viral

- Hand, foot and mouth disease
- Atypical measles

b) Bacterial

- Secondary syphilis
- Rocky Mountain spotted fever

Confluent Desquamative Erythemas

a) Scarlet fever

b) Staphylococcal toxic shock

c) Streptococcal toxic shock Rocky Mountain spotted fever

d) Kawasaki disease

The childhood exanthems have also been given a numerical classification based on the order in which they were accepted as separate entities. In this classification measles is First disease, scarlet fever Second, rubella Third, Filatow-Dukes disease (possibly staphylococcal scarlet fever) Fourth, erythema infectiosum Fifth disease, and Roseola infantum Sixth disease[3].

These agents are major causes of red rashes that are often diagnosed by virology laboratories. It should be noted that red rashes are a common presentation in many infections of viral aetiology eg EBV and CMV. It is also a common manifestation of other agents diagnosed in virology laboratories eg *Toxoplasma gondii* and in bacteriology laboratories eg *Streptococci*. The physician also needs to be aware of non-infectious causes of red rashes eg allergic reactions, Kawasaki Syndrome.

Diagnosis of Red Rashes (Exanthems)

It is essential that a good clinical history, including details of medication, recent travel and a description of the evolution of the rash and of any recent contact with individuals with rashes are obtained before considering the appropriate tests for laboratory confirmation of the clinical diagnosis. Many cases are diagnosed clinically if typical findings are present eg the slapped cheeks of erythema infectiosum, the typical measles case with coryza, conjunctivitis, fever and a widespread morbilliform rash. Accurate clinical diagnosis of rashes is notoriously difficult and laboratory diagnosis should be encouraged[4,5]. This is especially true of rashes in pregnancy where a laboratory confirmed diagnosis is mandatory. Laboratory results in this clinical setting need interpretation by experienced virologists as IgM testing can be prone to false

positive reactions in low prevalence settings as well as to the confounding effects of recent vaccination and the differentiation of primary infections from reinfections using avidity testing can be extremely important[5]. As many investigations are carried out on childhood rashes, saliva tests for IgM antibodies are widely used as well as blood tests[6].

1 Rubella

Rubella (German measles) is commonly asymptomatic, especially in children. Children often have few prodromal clinical symptoms but adolescents and adults usually present with a mild, febrile illness and an often painful lymphadenopathy affecting the postauricular, suboccipital and posterior cervical glands. Mild conjunctivitis and headache, malaise and coryza may occur. There may be a shortlived enanthem on the soft palate (Forchheimer spots). The transient erythematous exanthem appears on the face after a 16-18 day incubation period and spreads to the trunk and extremities. It is often pruritic but has faded from the body after about three days. The rash is maculopapular but the lesions tend not to coalesce as in measles. In all cases symptoms resolve spontaneously. Clinical diagnosis alone is unreliable, as there are no pathognomonic features. Arthralgia and arthritis sometimes occur in adults, commencing 1-6 days after the onset of the rash and taking sometimes weeks to resolve. Joint involvement is particularly common in women, with some 50% affected[7]. Joint inflammation is symmetric and involves fingers, wrists, knees and elbows[8].

The epidemiology of rubella has changed considerably since the introduction of MMR in 1988 and epidemics no longer occur in the UK. Until recently, the seroprevalence of antibody in children and adults was 97% to 98%. However, current unsubstantiated concerns about the hypothetical lack of safety of MMR vaccine have resulted in falling antibody levels in young children, to the extent that rubella epidemics are once more a possibility. People arriving in the UK from less developed countries lacking rubella vaccination programmes may be susceptible and at risk of infection.

Congenital rubella can follow primary infection in pregnancy. Severe foetal damage can occur if infection occurs in the first 16 weeks of gestation[9,10]. Re-infection is usually sub-clinical and the risk of congenital damage is rare. All pregnant women presenting with rash should be thoroughly screened and followed up (V 30 - Investigation of Pregnant Women Exposed to Rash Illness) to exclude recent infection. Laboratory diagnosis is essential, using validated sensitive assays.

Diagnosis of Rubella

The diagnosis of rubella is usually made serologically, using established criteria[11]. Commercial enzyme immunoassays usually make it possible to detect specific IgM within 4 days of onset of rash and for 4 to 24 weeks after, although there are reports of persistence for years in some individuals[12]. Where rubella specific IgM is detected in the presence of IgG or on its own, a further serum should be collected within 7 to 10 days and both samples should be tested in parallel and referred to a reference facility for confirmation and avidity testing as appropriate to allow differentiation of recent primary infection from re infection[13,14]. IgM assays can be of high specificity, but the low prevalence of rubella in the UK means that the predictive value of a positive IgM assay alone is now low. It is particularly important in pregnant women to establish the diagnosis with certainty. The collection of multiple blood samples to establish a rising level of IgG or the presence of low avidity antibody may be indicated to confirm a diagnosis of recent primary rubella. Confirmation of the IgM reactivity can be given by demonstrating IgG seroconversion especially by single radial haemolysis (SRH), or a significant rise in antibody titre by a quantitative enzyme immunoassay (EIA), haemagglutination inhibition (HAI) or latex agglutination titration (LA). Although HAI

antibodies may develop 1 to 2 days after onset of symptoms, this method is seldom used nowadays and is not widely available. Antibodies detected by EIA, LA or SRH may be delayed until 7 to 8 days. Subsequent re-exposure to rubella can cause a rapid rise in the titre of specific IgG antibodies, but the IgM titre does not usually rise as well. Rubella specific IgG and IgM antibodies may be detected in oral crevicular fluid using antibody capture immunoassays and results correlate well with serum antibodies[6-15]. Where crevicular fluid is used, antibody capture assays should be chosen for both IgG and IgM detection.

The presence of rubella IgG without rubella IgM is considered to indicate that the individual is immune to rubella; however the timing of collection of the sample in relation to onset of the rash should be considered before ruling out the possibility of rubella. Where neither rubella IgG nor IgM is detected the individual should be considered susceptible to rubella and a second sample requested one month later if thought to be in recent contact.

Rubella IgM assays in current use vary significantly in sensitivity and specificity. A recent comparison of seven commercial ELISAs for rubella IgM gave a range of 40-58% for sensitivity in the acute stages (<10 days from the onset of the rash) reaching 70-80% for sera collected later than 10 days. Specificity was between 86% and 97%[16]. Test selection and timing of samples are important considerations.

Rubella virus may be detected in throat swabs in the first day or two in most cases by isolation in cell culture in reference facilities in a range of cells including Vero. Rubella does not produce a CPE. Immunofluorescence with monoclonal anti-rubella antibody or detection of growth by rt-PCR have replaced the formerly used interference methods[17]. In rubella acquired postnatally, virus excretion is of greatest duration from the pharynx, typically commencing before the onset of clinical symptoms and continuing after the rash has faded but usually ceasing before lymphadenopathy has settled. Rubella rt-PCR is the test of choice for virus detection, from throat swab, from oral fluid, urine, or amniotic fluid for prenatal diagnosis of congenital infection[18-20].

Rubella samples requiring referral for PCR, sequencing and culture should be sent to PHE, Colindale, while serological confirmation is provided by PHE and by PHE Collaborating Centre, Microbiology Laboratory, Royal Preston Hospital.

2 Erythrovirus B19 (Parvovius B19) Virus Infection (Fifth Disease, Erythema Infectiosum)

Human B19 infection is commonly asymptomatic, but where symptoms do appear red rashes are the commonest signs. The illness is referred to as erythema infectiosum or fifth disease. The virus has been found in the respiratory secretions (eg, saliva, sputum, or nasal mucus) before the onset of rash, when the patient may appear to "just have a cold.". The virus is probably spread from person to person by direct contact with those secretions, such as sharing drinking cups or utensils. A susceptible person usually becomes ill 4 to 14 days after being infected with the virus, but may become ill as long as 20 days after infection.

In a household, as many as 50% of susceptible individuals exposed to a family member who has erythrovirus (parvovirus) B19 may become infected. During school outbreaks, 10% to 60% of students may get fifth disease. During school outbreaks of fifth disease, about 20% of adults and children who are infected with B19 virus do not

develop any symptoms. Furthermore, other individuals infected with the virus may have a non-specific illness that is not characteristic of fifth disease.

There is currently no vaccine that prevents erythrovirus infection; however people infected with the virus do develop lasting immunity.

Frequent hand washing is recommended as a practical and probably effective method to decrease the chance of becoming infected. Excluding people with fifth disease from work, child care centres, or schools is not likely to prevent the spread of the virus, since people are contagious before they develop the rash.

Infection due to B19 virus presents as a mild rash illness that occurs most commonly in children between 6 and 14 years of age. The ill child typically has a "slapped-cheek" rash on the face with a lacy red reticulate rash on the trunk and limbs appearing a little later. The facial rash is a bright red rash formed from coalescing papules. It is bilateral and symmetrical, involving the cheeks but sparing the perioral and perinasal areas[21]. The reticulate rash is seen on the trunk and especially the limbs when central clearing of a maculopapular rash occurs. The rash is occasionally pruritic. The rash may fade and reappear, often in association with exposure to sunlight or heat. The individual may have a low-grade fever, malaise, or a "cold" a few days before the rash breaks out. The patient is usually not very ill, and the rash resolves in 7 to 10 days.

A purpuric rash in a ‘glove and stocking’ distribution is sometimes seen in young adults with B19 infection. It affects the hands and feet (with a clear demarcation at the wrists and ankles) and there is pain, pruritus and swelling in the area involved[21]. Resolution occurs in about a week. Unlike erythema infectiosum the glove and stocking rash tends to appear before antibodies appear.

Joint pain and swelling may occur in B19 infection, particularly in adults. Joint involvement is bilateral and symmetrical, affecting the proximal interphalangeal joints and the knees and ankles. There is usually resolution without long-term disability.

Because B19 virus infection of red cell precursors causes arrest of haematopoiesis serious anaemia – aplastic crisis – can occur in people with conditions in which red cells have a reduced life span and haemoglobin levels are borderline, conditions such as hereditary spherocytosis, sickle cell disease, and thalassaemia. The typical rash of fifth disease is rarely seen in this group of patients. Once the infection is controlled by the immune response, the anaemia resolves. Patients who are immunocompromised may develop a chronic anaemia with B19 infection. This may respond to therapy with intravenous immunoglobulin[22].

Infection during pregnancy has a 30% risk of transplacental infection with 5-9% risk of foetal loss. There is a risk of hydrops fetalis, particularly with infection in the second trimester, so it is important to accurately diagnose B19 infection in pregnancy to allow foetal ultrasound monitoring of those babies at risk[23].

Diagnosis of Erythrovirus B19

For the routine laboratory diagnosis of B19 the use of commercially available immunoassays for the detection of specific IgG and IgM are acceptable for serum and plasma samples. In general commercial ELISA assays for B19 IgG and IgM have sensitivities and specificities of over 90%[24].

The presence of B19 IgG without B19 IgM is considered to show evidence that the individual has had previous B19 infection more than two months ago. This pattern of

results suggests likely immunity to B19 in the context of a rash contact. However a relatively recent B19 infection, over 2-3 months previously, cannot always be ruled out and this might have consequences in investigation of infection in pregnancy. Testing a blood sample for B19 IgG and IgM from earlier in the pregnancy or stored from a previous pregnancy should be considered if there is any doubt as to the timing of a possible B19 infection. Where neither B19 IgG nor IgM is detected the individual should be considered susceptible to B19 virus and if recent contact with a B19 case is suspected a second serum should be tested if symptoms appear, or one month after the contact date if the individual remains asymptomatic. Where B19 specific IgM is detected a further serum should be collected within 7 to 10 days and referred to a reference facility for confirmatory testing if felt appropriate. It is particularly important in pregnant women to establish the diagnosis with certainty.

In acute infection B19 DNA may be detected in serum in acute cases using PCR. Although the peak of B19 DNA in blood is reached before symptoms appear the levels are very high[25] and DNA can be detected for at least 2-6 months afterwards[26]. In pregnant women in one study where the onset date of infection was not known the levels detected by a Taqman B19 PCR ranged from 10^2 to 10^7 genome equivalents /mL[27]. Real time PCR for B19 DNA using the LightCycler is also used and has been reported to be more sensitive than nested PCR[28].

Sera requiring B19 serological confirmation should be sent to PHE, Colindale, while PCR for B19, both qualitative and quantitative, is available in several Specialist Virology Centres in the UK, including PHE.

3 Measles (Rubeola)

Measles is a highly contagious disease caused by a morbillivirus. It can be transmitted from 4 days prior to the onset of the rash to 4 days after the onset. Spread is mainly from the upper respiratory tract via large droplets, but the aerosol route is also important. The infected mucus can land in other people's noses or throats when they breathe or put their fingers in their mouth or nose after handling an infected surface. The virus remains active and contagious on infected surfaces for up to 2 hours. Some 90% of susceptible close contacts are likely to become infected following close contact with a case.

The incidence of measles in England and Wales has fallen since the National Vaccination campaign of 1994 when 92% of children between the ages of 5 and 16 were vaccinated. However current unsubstantiated concerns about the hypothetical lack of safety of MMR vaccine have potentially resulted in falling antibody levels in young children, to the extent that measles epidemics are once more a possibility. The group at highest risk is children aged 1 to 4 years who have not been vaccinated. Most cases in the UK in recent years have been among unvaccinated travellers and people coming from overseas; such cases have the potential to spread into poorly vaccinated local communities. People arriving in the UK from countries lacking measles vaccination programmes may be susceptible and at risk of infection[29].

Symptoms begin to appear about 10 to 12 days after exposure to the virus. The infected person first experiences a fever lasting about 2 to 4 days that can reach over 39°C around the time the rash appears. Respiratory symptoms are prominent early, with coryza and sneezing or cough. Conjunctivitis, often with eye pain or grittiness, is also a prominent feature. Malaise and irritability are common.

An enanthem, ‘Kopliks spots’, appears on the buccal mucosa 1-2 days before the exanthematous rash. Kopliks spots are pathognomonic for measles and are 1 mm blue-white spots on a red background. They have usually disappeared by the second day of the exanthem.

The morbilliform rash usually appears about 14 days after exposure and lasts 5 to 6 days. It begins at the hairline, with macules high on the forehead and behind the ears, and then involves the entire face and upper neck. Over the next 3 days, the rash gradually proceeds downward and outward, reaching the hands and feet, including palms and soles. Lesions coalesce[30]. In the immunocompromised the rash is often mild, atypical or even absent. Approximately 20% of reported measles cases experience one or more complications. These complications are more common among children under 5 years of age and adults over 20 years old.

Otitis media occurs in nearly one out of every 10 children who catches measles. As many as one out of 20 children with measles develops pneumonia, and about one child in every 1,000 who get measles will develop encephalitis. For every 1,000 children who become infected with measles, one or two will die from it. Infection in pregnancy may lead to miscarriage, premature birth, or low-birth-weight baby. Measles is the leading cause of blindness among African children, due largely to secondary bacterial or viral infection after the keratitis often present in measles[31].

In developing countries, where malnutrition and vitamin A deficiency are prevalent, measles has been known to kill as many as one out of four people. Measles formerly killed almost 1 million children in the world each year but recent vaccination programmes have reduced the mortality by an estimated 39% (46% in Africa) in the period 1999 to 2003, with latest estimates around 530,000 deaths annually worldwide[32].

Diagnosis of Measles

For the routine laboratory diagnosis of measles the use of commercially available immunoassays for the detection of specific IgG and IgM are acceptable for serum and plasma samples. Commercial IgM assays are reported to have sensitivities of approximately 88-97% with specificities of 95-99%[33]. Avidity testing may be useful in distinguishing between infection following secondary vaccine failure or CNS involvement and antibodies from primary infection[34,35]. Oral fluid is a useful diagnostic sample for measles IgM detection using capture immunoassays, with an optimal sampling time 1-5 weeks after the onset of illness[6].

Under circumstances where a more rapid result is required, immunofluorescent detection of measles antigen directly from clinical samples may be usedto provide a provisional result[36]. The most useful specimen is a nasopharyngeal aspirate or pernasal swab. The result should be confirmed by an alternative method when measles is at low prevalence. When possible, the polymerase chain reaction may be the method of choice.

Measles grows slowly in cell culture. Swabs from the respiratory tract are the samples of choice. In confluent monolayers the CPE appears more granular and non specific, often going on to syncytium formation. Some strains produce spindle-like CPE[37]. Confirmation of the identity of the viral isolate should be made by either direct or indirect IF employing a monoclonal antibody or by PCR on cell culture fluid.

Molecular diagnosis is preferred to virus isolation. A range of sensitive assays including real-time PCR assays is available[38]. Measles RNA is detectable in throat swabs of over 90% of infected individuals from 5 days before the onset of illness to 12 days after, while urine remains positive for measles RNA for 5 weeks from the onset in most cases[39]. The optimal diagnostic approach is to use oral fluid for measles IgM and PCR testing.

Presumptive measles positive samples should be referred to PHE, Colindale for confirmation and further investigation.

4 HHV-6 Infection (Roseola)[40]

HHV-6 infection is responsible for the rash illness known as roseola infantum, exanthem subitum or sixth disease, although some cases are caused by primary infection with HHV-7. Human herpesvirus 6 variant A (HHV-6A) and human herpesvirus 6 variant B (HHV-6B) are two closely related yet distinct viruses. These viruses, along with HHV-7 belong to the *Roseolovirus* genus of the *Betaherpesvirinae* subfamily; they are most closely related to human herpesvirus 7 and to human cytomegalovirus. The majority of people older than 2 years of age are seropositive for HHV-6 variants; current serologic methods are incapable of discriminating infection with one variant from infection with the other. Some 40% are infected in the first year of life, and by two years of age almost 80% have been infected. The majority of infections are asymptomatic. HHV-6B is the aetiologic agent of the common childhood illness roseola. The classic picture of roseola is seen in young children (under 1 year of age) and is characterized by high fever and the appearance of a maculopapular rash as the fever resolves after an average of 4 days. The rash (2 to 3mm in diameter macules which blanch on pressure) appears on the trunk and spreads to the face or appears on trunk and face simultaneously; it lasts around three to four days. Diarrhoea and mild respiratory symptoms may also be seen, and convulsions occur in 8%[41]. Roseola is only one manifestation of HHV-6 infection, and the classical roseola syndrome occurs in a minority of cases[42]. Fever, fussiness, and rhinorrhoea were the commonest symptoms at the time of HHV-6 acquisition in a recent Seattle study, with rash appearing in about 30%[43]. The incidence of roseola is 17% - 23%[43,44].

HHV-6 can infect the brain and various neurologic manifestations, such as convulsions including status epliepticus and encephalitis, can occur during primary HHV-6 infection or in patients who are immunocompromised. HHV-6 distribution in the central nervous system is altered in patients with multiple sclerosis; the significance of this is under investigation.

Diagnosis of HHV-6

The rash of roseola infantum is often misdiagnosed as measles or rubella, and laboratory confirmation is essential for accurate diagnostic assessment[45]. Commercially available immunofluorescent antibody tests are usually used and allow determination of HHV-6 IgG and IgM antibody status. There is some cross-reactivity with HHV-7 at low titres in these assays, and the use of Western Blot for serology is advocated by some as it permits differentiation of the two viruses. A diagnosis of acute primary HHV-6 infection in a rash illness can be made by detection of IgM antibody to HHV-6 and the presence of HHV-6 IgG of low avidity[46]. If a diagnosis is attempted using seroconversion to IgG positivity there is a risk of misdiagnosis through the cross reactivity of HHV-6 and HHV-7, and specific avidity studies are required to show

whether one or other antibody might have pre-existed. Detection of virus in tissue or blood can be attempted by virus culture in cord blood lymphocytes but PCR assays are widely available and the test of choice. A high viral load in blood was suggested to be 90-100% sensitive and 100% specific in acute HHV-6 infection[47]. The phenomenon of chromosomally-integrated HHV-6 which occurs in a minority of individuals and which is not yet known to be of clinical relevance also results in abnormally high viral loads. These viral loads are consistently >10^6 HHV-6 genome copies/ml in blood and ~50-fold lower in serum and are higher than transient viral loads associated with primary infection. Quantitative HHV-6 PCR of whole blood and serum can help in discriminating between integration and active replication during primary infection or reactivation. Antibody avidity studies may be needed to help interpretation if earlier samples are not available to exclude previous PCR positivity.

5 Enteroviral Rashes including Hand, Foot and Mouth Disease

The most commonly recognized enteroviral rash is that of hand, foot and mouth disease (HFMD), characterized by a tender and painful vesicular rash principally on the hands and feet, and in the mouth on the hard palate, tongue and buccal mucosaduring childhood and adolescence[1]. HFMD is caused by several enteroviruses including coxsackie A10, A16, B5 and enterovirus 71 (see G 6 – Investigation of Vesicular Rashes).

Infection is spread from person to person by direct contact with nose and throat discharges, saliva, fluid from blisters, or the stools of infected persons. A person is most contagious during the first week of the illness. HFMD is not transmitted to or from pets or other animals. The usual period from infection to onset of symptoms (“incubation period”) is 3 to 7 days. Fever is often the first symptom of HFMD.

Enteroviruses also cause non-specific red rashes. In recent studies 2.6-5% of children with morbilliform rashes were infected with enteroviruses[48,49]. In Finland 9% of children with fever and rash had serological evidence of enterovirus infection, cases occurring in late summer and early autumn[50].

Echovirus 7, 9, 16 and Coxsackie A4, A5, A9, and A16 are particularly described as causing rashes[51]. However rash was not uncommon in poliomyelitis in the past[52]. Echovirus 25 has been associated with outbreaks of an illness where there is a pink maculopapular rash over the trunk and face[53]. The rash of echovirus 9, seen in 50% of children under 5 years of age who are infected with echovirus 9, resembles rubella but is nonpruritic and is not associated with posterior cervical lymphadenopathy. It appears at the time of the fever and lasts 1-5 days[54]. Roseoliform rashes, where the rash appears at the time of defervescence, have been described with coxsackie B1 and B5 and echovirus 11 and 25 as well as in the classic echovirus 16 ‘Boston exanthem’ where discrete large macules were seen on the face and upper chest in young children[54].

Enterovirus infection is an important differential diagnosis in suspected meningococcal disease as some 7% of petechial rashes may be due to enteroviruses[55]. There are usually widespread micro-petechiae. The agents most associated with petechial rashes have been echovirus 9 and coxsackie A9[54].

In enteroviral infection in hospitalized infants less than 3 months of age rash has been reported in 23% of those infected by any enterovirus, in 28% of those who had echovirus infections and in 14% of those with coxsackie B virus infections. These rashes are erythematous macular or maculopapular rashes[56].

HFMD occurs mainly in children under 10 years old, but adults may also be at risk. Everyone is susceptible to infection, but not everyone who is infected becomes ill. Infection results in immunity to the specific virus, but a second episode may occur following infection with a different member of the enterovirus group.

Individual cases and outbreaks of HFMD occur worldwide, more frequently in summer and early autumn. In the recent past, major outbreaks of HFMD attributable to enterovirus 71 have been reported in some South East Asian countries[57,58].

HFMD is a common illness of infants and children. It is characterised by fever, sores in the mouth, and a rash with blisters. HFMD begins with a mild fever, poor appetite, malaise ("feeling sick"), and frequently a sore throat. 1 or 2 days after the fever begins, painful sores develop in the mouth. They begin as small red spots that blister and then often become ulcers. They are usually located on the tongue, gums, and inside of the cheeks. The skin rash develops over 1 to 2 days with flat or raised red spots, some with blisters. The rash does not itch, and it is usually located on the palms of the hands and soles of the feet. It may also appear on the buttocks. A person with HFMD may have only the rash or the mouth ulcers[59].

HFMD caused by coxsackievirus A16 infection is a mild disease and nearly all patients recover without medical treatment in 7 to 10 days. Complications are uncommon. Rarely, the patient with coxsackievirus A16 infection may also develop "aseptic" or viral meningitis, in which the person has fever, headache, stiff neck, or back pain, and may need to be hospitalized for a few days. Another cause of HFMD, EV71 may also cause viral meningitis and, rarely, more serious diseases, such as encephalitis, or a poliomyelitis-like paralysis. EV71 encephalitis may be fatal. Cases of fatal encephalitis occurred during outbreaks of HFMD in Malaysia in 1997 and in Taiwan in 1998[57,58].

Diagnosis of Coxsackievirus

Clinical diagnosis of enteroviral rashes other than HFMD is difficult except perhaps during a recognized outbreak of an enteroviral infection. Laboratory diagnosis is based on detection of virus by culture or by PCR, or by antibody detection. Traditionally cell culture has been the method of choice, using human diploid fibroblast lines such as MRC5 or WI38. The rhabdomyosarcoma line RD is a more sensitive cell line for coxsackie A viruses[60]. Cytopathic effects are seen between 3 and 7 days with non polio enteroviruses but further identification using neutralization or immunofluorescence should be undertaken (V 24 Isolation of Enteroviruses and Parechoviruses). Appropriate specimens for culture are faeces, throat swabs collected into virus transport medium, and tissue including skin biopsy (V 24). Typing of enteroviruses to exclude poliovirus must be undertaken and isolates are referred for this purpose to PHE, Colindale.

Enterovirus detection by PCR is increasingly used and can be carried out on throat swabs, faeces, blood or skin tissue. CSF samples are relevant in investigation of rashes in the neonate and in those with coincident neurological symptoms. Real-time assays can reduce the time to diagnosis to less than a day[61,62]. PCR on faeces may be especially valuable if acute phase samples are not available as, at least in enteroviral meningitis, positive results can be obtained in over 95% of cases even with

samples collected at 5-16 days after the onset of illness[63]. In the neonate enterovirus PCR on blood is positive in over 50% of cases[64].

Enteroviral serology has a limited role in diagnosis. Enterovirus IgM ELISAs are broadly reactive across a range of enteroviruses and although their sensitivity is poor in acute infection (28% IgM positive versus PCR positive from blood) the specificity is good (96%) and these assays can enable a diagnosis to be made when no suitable early samples are available for culture or PCR[65].

6 Epstein Barr Virus Infection

Maculopapular and morbilliform rashes may occur in acute infectious mononucleosis (IM). Rashes are not common in acute EBV infection but in association with fever, pharyngitis and lymphadenopathy, together with lymphocytosis, the differential diagnosis in a young person is likely to include EBV infection as one of the most likely causes. A morbilliform rash is commonly seen in patients with IM who are given ampicillin; over 70% of individuals with IM may respond in this way[66]. This rash is self-limiting and resolves within a few days of discontinuing the antibiotic. The mechanism is unclear. A similar rash has been described with many antibiotics including piperacillin-tazobactam, amoxicillin, cefalexin, minocycline, erythromycin and azithromycin[67,68].

Diagnosis of Epstein-Barr Virus

Infection can be made using heterophile antibody tests or by specific EBV serology including anti-EBV VCA IgM, anti-EBV VCA IgG, and anti-EBNA antibodies, as described in V 26 – Epstein-Barr Virus Serology.

7 HIV Infection

Acute HIV infection often presents with fever, headache, malaise and rash. Some 40-90% of patients infected with HIV have an acute influenza-like illness one to four weeks after exposure[69,70]. Fever occurs in 80-90%, and rash in 40-80%. The rash is maculopapular or morbilliform, nonpruritic, and is more prominent on the trunk, often with the neck and face involved. It disappears within 2 weeks[69,71]. This is also covered in G 2 - Microbiological Investigation of Patients with Acute Lymphadenopathy and Fever and V 11 – Anti-HIV Screening.

Diagnosis of Primary HIV Infection

At the time of the initial presentation antibodies to HIV are not present but serum p24 antigen testing will be positive. P24 antigen testing is specific but its sensitivity is relatively poor (79%) particularly at the time that antibody production is just beginning[70]. For this reason a combination test of antigen and antibody detection is now prefered. HIV RNA will invariably be detected in primary HIV infection at levels of >10000 copies/mL. Tests for proviral DNA are less sensitive than RNA testing in this situation[70].

8 Arbovirus Infections

Rashes are common in several arbovirus infections and although none of these is endemic in the UK the possibility of an arbovirus infection should be considered where there is an appropriate travel history. The commonest arbovirus infection seen in the UK in returning travellers is dengue, with most cases acquired in Asia, particularly Thailand, Malaysia, Indonesia, India and Sri Lanka. In 2002, 39 cases were confirmed by laboratory testing in the UK by positive IgM and positive PCR, and 56 cases were classed as probable (IgG and IgM both positive)[72].

9 Flavivirus Infections

Dengue Fever

Dengue is the most widespread arbovirus disease worldwide, with an estimated 50-100 million cases per year occurring in the tropics. Four types of dengue virus, DEN-1-4, flaviviruses with Aedes mosquito vectors, produce the disease, and in recent years both the range of classic dengue and an increase in dengue haemorrhagic fever have been noted[73]. Facial flushing is an early feature of dengue at all ages, and the classic picture of dengue includes fever, arthralgia and rash[73]. Dengue begins with the abrupt onset of high fever, headache, pain behind the eyes, and back pain. The fever may be biphasic ('saddleback' fever) and accompanied by myalgia, arthralgia and bone pain ('breakbone fever')[74]. A rash is seen in 50% of cases[75]. A transient mottling of the skin or a macular rash may occur in the first day or two of the illness, with a maculopapular or morbilliform rash appearing at the time of defervesence, around the third to the fifth day, starting on the trunk and spreading to the face and extremities (but sparing the palms and soles)[74]. This rash lasts up to 5 days; it is not itchy, and there may be desquamation as it resolves. Malaise is often a feature of dengue.

West Nile Fever

West Nile virus is transmitted principally by Culex mosquitoes and is widely distributed geographically[74]. Wild birds are a major reservoir of infection. Encephalitis is seen in a small proportion of cases but is more common in those over 50 years of age and has a poor prognosis. Many cases are asymptomatic or mild and non-specific. Symptomatic illness is similar to dengue, with fever (sometimes biphasic), arthralgia, and myalgia. A rash occurs in 50% of cases around the time of defeverescence. The rash is maculopapular and nonpruritic, and resolves without desquamation. It may resemble the rash of roseola. It typically affects the head, neck and trunk[76].

Diagnosis of Flavivirus Infection

Testing for arbovirus infection in the UK is generally undertaken at the Special Pathogens Reference Unit, Public Health England, Porton Down. For diagnosis of dengue commercial ELISA IgG and IgM assays are available. In the UK cases are recorded as confirmed when both IgM and PCR are positive, and as probable when IgG and IgM are both positive[72]. A combination of IgM and PCR detection offers the best sensitivity for early dengue diagnosis. Before the fifth day of symptoms dengue-specific IgM is positive in only 14%, but IgM is found in 75% after the fifth day using an IgM–capture ELISA[77]. Reverse-transcription PCR for dengue detects 78% before the fifth day of illness, and a combination of PCR and IgM testing gives at least 84%

positive rate in acute phase sera[77]. For West Nile infection the IgM ELISA has 90% sensitivity at 8 days; interpretation can be difficult however as antibody may persist for 6 months or more in West Nile fever and in alphavirus infections[76,78].

10 Alphavirus Infections

Human alphavirus infections typically present with fever, rash, and arthralgia. Alphavirus infections occur all over the world.

Chikungunya

Among the most widespread is chikungunya, one of the most important differential diagnoses for dengue. Chikungunya occurs throughout Asia and in much of Africa, and is transmitted by Aedes mosquitoes. It presents with a very sudden onset of fever, malaise, myalgia and arthralgia, without a prodrome. The joint and muscle pain are often incapacitating. A faint maculopapular rash appears either at the onset of illness or at the time of defevervescence. It begins on the trunk and face and then spreads to the extremities. The palms and soles can be involved. The rash often reappears some days after it has first faded[78]. O'nyong-nyong is a similar illness seen in East Africa, and is characterized by cervical lymphadenopathy.

Barmah Forest Disease

Barmah Forest disease is a mosquito-borne alphavirus infection which occurs in northern regions of Australia. The clinical presentation is similar to Ross River virus infection. Rash is a prominent feature in Barmah Forest disease, occurring in 68%-90% of cases. There is a non-specific erythematous maculopapular rash on the trunk and limbs, with facial erythema in 70%[79,80].

Ross River Virus (RRV)

Ross River Virus (RRV) is a mosquito-borne alphavirus endemic and enzootic in Australia and Papua New Guinea, where some 5000 cases a year are seen. Rash, fever and arthralgia make up the typical illness and can occur in any order. The typical symptomatic patient has symmetrical joint involvement affecting ankles, fingers, wrists and knees. About half of cases have a rash, mainly on the limbs and trunk, but sometimes seen on hands including the palms, the soles of the feet and the face. The rash is usually maculopapular and lasts for 5-10 days[81].

Kunjin Virus

Kunjin virus is seen in the tropical north of Australia. Like West Nile virus its reservoir is thought to be wild birds, and it is transmitted mainly by culicine mosquitoes. It can cause encephalitis, as well as milder febrile illness with rash, headache and arthralgia, and lymphadenopathy[82].

Sindbis Virus

Sindbis virus infection is seen in northern Europe and Scandinavia as well as in Africa, Asia and Australasia. The virus is maintained in birds and transmitted by culicine mosquitoes. Rash and arthralgia are seen as the presenting features. The arthropathy is symmetrical, affecting particularly knees, ankles, wrists, fingers and toes. The rash begins with discrete macules on the trunk and extremities, including the palms and

soles, and evolves to small papules. The face and head are usually spared[78]. The rash is sometimes pruritic[83].

Diagnosis of Alphavirus Infection

Testing for arbovirus infection in the UK is generally undertaken at the Special Pathogens Reference Unit, Public Health England, Porton Down. The standard tests for alphavirus diagnosis are ELISA tests for IgM antibody, and detection of RNA by PCR. Seroconversion to specific IgG antibody is diagnostic but a range of agents may need to be tested to exclude heterologous serological responses, such as cross reacting o'nyong-nyong antibodies in chikungunya. In chikungunya virus can usually be cultured from blood a day or two after the onset of illness, and up to 6 days from onset in o'nyong-nyong. Alphavirus diagnosis by PCR may be attempted on blood and on skin biopsies[78].

11 Rickettsial Infection

Increasing numbers of rashes due to rickettsial infections are seen in travellers to endemic areas. Of the 66 rickettsial notifications recorded in the UK between 1990 and 2002 the majority were associated with travel to Africa[84]. Recent European studies suggest that rickettsial infections imported from Southern Africa are among the more common potentially serious travel-related illnesses[85]. Tick-borne rickettsial infection typically presents with skin lesions, fever, headache, myalgia and rash, generally within two weeks of a tick bite. The initial skin lesion occurs at the bite site as a papule, which ulcerates and forms a black crust; this is called an eschar. The commonest travel-associated rickettsial infection nowadays is African tick bite fever due to *R. africae* which does not usually present with a red rash, although up to 30% may have a vesicular skin rash and mouth blisters[86]. The two main travel-related rickettsial infections with a red rash are *R. conori* and *O. tsutsugamushi* infection. Several other important rickettsial diseases are characterized by red rashes, notably murine typhus, louse-borne (epidemic) typhus, Rocky Mountain spotted fever (a rash is present in most but tends to be purpuric), and North Asian tick typhus. Discussion of the most common two in travellers follows:

Mediterranean Spotted Fever

This condition is caused by *Rickettsia conori* and is transmitted by dog ticks. The association with dogs makes this a disease which tends to be found in urban areas. Occasional transmissions have occurred in non endemic areas from dogs returning from abroad. It is endemic around the Mediterranean and Caspian Seas, as well as in the Middle East, India, and parts of sub-Saharan Africa.

Over 95% of cases have a generalized maculopapular rash and a single eschar at the site of the tick bite is seen in 70%[85].

Scrub Typhus

This rickettsial infection occurs in South East Asia, most cases in travellers arising in Thailand. The causative organism, *Orientia tsutsugamushi*, is transmitted by chiggers (larval trombiculid mites) and the primary eschar is seen on the lower extremities or genital area. Most patients initially experience sudden onset of fever, headache, and myalgia. Fever is frequently 40°C. About 5 days after the onset generalized

lymphadenopathy regularly occurs, together with a macular rash which appears on the trunk and spreads peripherally. The rash may only occur in about one third of patients[87].

Diagnosis of Rickettsial Infection

In the UK diagnostic testing is available at the Specialist Pathogens Reference Unit, Public Health England, Porton Down.

Rickettsial diagnosis can be made by isolation from buffy coat or from skin or eschar biopsy; this is a hazardous and difficult method. Molecular detection by PCR can be employed on blood and tissue culture. Serological diagnosis is usually made using the commercially available immunofluorescent antibody assay. The acute phase serum is tested in parallel with a convalescent serum taken 2 weeks later, with a 4-fold rise in titre being diagnostic of rickettsial infection. The antibody rise can be late (especially with *R. africae*) so a third serum at 4-6 weeks should be tested if there is no early rise. Rickettsiae are cross-reactive in IFA testing and confirmation and speciation requires Western blotting[86].

12 Syphilis

Rash is a prominent feature of syphilis in its secondary stages, generally 4-10 weeks after the primary infection, although the primary lesion may still be present at the time the rash appears[88]. Some 90% of cases have skin manifestations, especially macular, maculopapular, or pustular lesions. Secondary syphilis has become an increasingly relevant consideration in the differential diagnosis of rashes in young men as the incidence has increased in the UK over recent years[89]. The initial rash is a transient macular rash which is often overlooked, then a few days later a symmetrical papular rash appears on the trunk and extremities. The palms of the hands and soles of the feet are involved. At the same time other signs of dissemination of treponemes are seen including fever, malaise, headache, lymphadenopathy and mucosal lesions[88].

Diagnosis of Secondary Syphilis

In most cases the diagnosis of secondary syphilis is made serologically after an evaluation of the clinical picture and recognition of risk factors for syphilis. A combination of treponemal and non treponemal assays is recommended. Current UK practice is to use an anti-treponemal antibody EIA (preferably detecting both IgG and IgM) as the initial test, to confirm a positive result with a different treponemal test (usually TPPA or TPHA), and to also carry out a quantitative non treponemal test such as VDRL or RPR[90]. Treponemal IgM EIA may also be used to confirm recent active infection. Although dark ground microscopy is positive in 84% of cases positive by serology treponemal EIA is positive in 100% and most cases have RPR titres of >= 32[91]. Recently PCR detection of *T. pallidum* has been used in both primary and secondary syphilis[92].

13 Scarlet Fever

The scarlet fever or scarlatina rash is caused by infection with a group A streptococcus which produces erythrogenic toxin, usually erythrogenic exotoxin A. It usually occurs in association with streptococcal pharyngitis and affects mainly children

over the age of 3 years. The rash is fine and diffuse, and feels like sandpaper. It begins on the face and becomes generalized after 24 hours. The area around the mouth looks pale relative to the bright red of the cheeks –'circumoral pallor'. Erythema is often marked in flexor skin creases, especially the antecubital fossae (Pastia lines). The 'strawberry tongue' appearance results from prominent hypertrophied papillae on a white coated tongue[93]. The rash begins to fade within a few days, and is followed by desquamation occurs, starting on the face. Differential diagnosis of scarlet fever includes Kawasaki measles and staphylococcal toxic shock syndrome[94].

Diagnosis of Scarlet Fever

The clinical features of sore throat, tonsillar exudate, cervical lymphadenopathy, and a scarlatiniform rash are suggestive of the diagnosis but this should be confirmed by bacterial culture of a throat swab to isolate group A streptococcus. Rapid antigen detection tests for group A streptoccus detection are used in the primary care setting and can have sensitivity and specificity of well over 90%[95]. Serological diagnosis can be made by antistreptolysin O and anti-hyaluronidase testing; these are negative in the acute phase but a convalescent serum may show a rise in titre.

Appendix: Red Rash Chart

Condition or Illness	Causes	Incubation	Duration of infection	Mode of spread
Rubella	Rubella virus	Usually 16 - 18 days (Range 14 - 23 days)	Rash lasts 3 days, lymphadenopathy up to 1 week and joint pains up to 3 weeks.	Person to person through respiratory secretions. Congenital
Fifth Disease	Erythrovirus (parvovirus) B19	4 - 14 days	7 - 10 days from onset of rash, polyarthralgia can last from 3 weeks to over 2 years	Person to person by respiratory secretions, fomite, blood products. Congenital
Rubeola	Measles virus	10 - 12 days	4 days before rash to 4 days after	Respiratory, aerosol, and fomites
Roseola	Human herpes virus -6	10 - 14 days	Fever lasts 3 - 5 days then rash develops	Saliva - from mother to infant; from child to child. Intra uterine (rare)
Hand Foot and Mouth	enteroviruses eg Coxsackie virus A16	3 – 7 days	7 - 10 days after onset of symptoms	Person to person via nose and throat discharges, saliva, blister fluid or faeces
Infectious mononucleosis	Epstein-Barr virus	1 - 2 months	1 - 4 weeks (increases with age)	Close contact –aka ‘kissing disease’
HIV Infection	Human immunodeficiency virus	1 – 4 weeks after exposure	One study found the average length of ARS symptoms to be about 22 days.	Sexual transmission Bloodborne

Arbovirus Infection	Arbovirus: *Alphaviruses* Chikungunya Ross River virus Sindbis *Flaviviruses* Dengue West Nile Fever Yellow fever *Bunyaviruses* LaCrosse encephalitis Reoviruses		5 – 10 days dependent on virus, inability to work for up to 3/12 and rheumatic symptoms for up to 1 year	Mosquito
Rickettsial infection	Rickettsia *African Tick Bite fever* *Mediteranean Spotted fever* *Scrub typhus*	Within 2 weeks of bite	5 – 10 days dependent on virus	Tick bites
Syphilis	*Treponema pallidum*	Secondary syphilis appears 3 - 6 weeks after primary infection.	May persist for weeks to months	Sexual contact
Scarlet Fever	Bacterial infection (streptococcal)	Rash appears within 12 - 48 hours of the sore throat and prodromal symptoms	Skin rash fades after 6 – 7 days, but skin flaking and peeling may continue for 10 - 14 days.	Respiratory and droplet spread

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