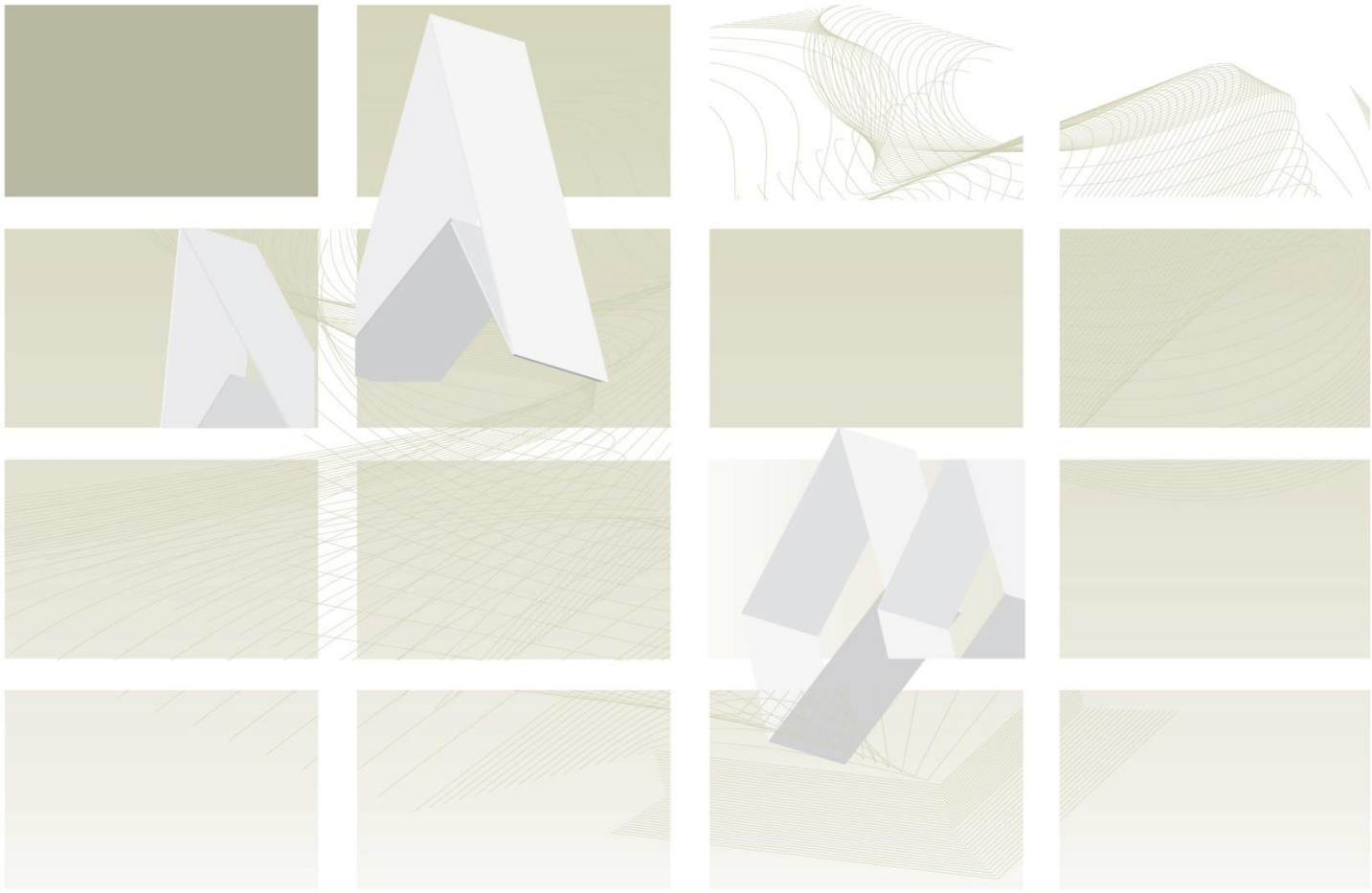
UK Standards for Microbiology Investigations

Review of users' comments received by
Working group for microbiology standards in clinical virology/serology

V 30: investigation of exposure to vesicular and non-vesicular rash in pregnancy



"NICE has renewed accreditation of the process used by **Public Health England (PHE)** to produce **UK Standards for Microbiology Investigations**. The renewed accreditation is valid until **30 June 2021** and applies to guidance produced using the processes described in **UK standards for microbiology investigations (UKSMIs) Development process, S9365', 2016**. The original accreditation term began in **July 2011.**"

This publication was created by Public Health England (PHE) in partnership with the NHS.
Recommendations are listed as ACCEPT/ PARTIAL ACCEPT/DEFER/ NONE or PENDING

Consultation:

04/03/2020 – 18/03/2020

04/08/2020 – 18/08/2020

Version of document consulted on: dm+

Proposal for changes

Comment number	1		
Date received	11/03/2020	**Lab name/Professional body (delete as applicable)**	Bristol PHL
Section	See below		
Comment			
Evidence			

1. I am not convinced by the 10 days, it was always 7 all other red rash causes independent of the algorithm title doesn't
2. Throughout the document there is an uncertain stance on whether to routinely investigate rubella when parvovirus is specifically requested, or vice versa.
3. Algorithm 1:Testing for Rubella will be subject to local epidemiology and decision except stated as mandatory in quoted PHE guidance
4. Algorithm 1: Immunity to varicella also defined by known IgG detected in past.
5. Algorithm 1: Second from right final box 'Reassure that measles risk is remote and advise to contact GP if rash develops'
6. Algorithm 2: Right hand rectangle- footnote c misplaced, already in earlier box.
7. Algorithm 2: Also footnote h is also incorrect here, since obtaining a further sample inevitably introduces delay so a report should always be issued; who has an alternative IgM assay? Virtually no lab I suggest; how does testing an earlier sample validate the current IgM reactivity- it will help define the time of infection.
8. Algorithm 3: Middle bacterium- confirm that a single rubella IgG positive is now final evidence of immunity, regardless of vaccination status.
9. Algorithm 3: Footnotes o in right diamond seem misplaced- offers local second IgM but says always send to ref lab;
10. Algorithm 3: Footnotes p doesn't need to be in twice in succession, and is there assuming the IgM is a false positive, is it?
11. Algorithm 4: Left final bacterium- footnote n misplaced, unless asking to test for all other red rash causes independent of the algorithm title
12. Algorithm 5: Footnote h seems misplaced- mentions IgM.
13. Footnote a: Although I'm not convinced by the 10 days, it was always 7 when I was younger. Is there a ref aside form PHE guidance?
14. Footnote c: An alternative is to test IgG and IgM on any timed earlier sample.

15. Footnote r: IgG results alone? 16. Rubella table: Consider NAAT **on what sample type? OF/TS/urine** if illness develops or seroconversion is observed on later samples	
Financial barriers	
Mandating of additional different parvovirus IgM assays	
Health benefits	
Should be beneficial to care of pregnant women.	
Are you aware of any interested parties we should consider consulting with on the development of this document?	
RCOG; RCGP; BIA; UK CVN	
Recommended action	1. **PARTIAL ACCEPT** Document amended to include range between 7 and 10 days. 2. **NONE** We are aware that practice varies throughout the UK and this has been reflected in the note to the algorithm 3. **NONE** Rubella testing is mandatory in woman with rash. This document covers only cases of pregnant people who were exposed to rash. 4. **ACCEPT** “Previous IgG” added to the diamond. 5. **ACCEPT** “If rash develops” added to box 6. **ACCEPT** Footnote c removed as duplicate 7. **PARTIAL ACCEPT** Footnote “h” has been retained, but the content of the triangle has been amended to clarify the need for interim report and the IgM testing: “Consider B19V NAAT or alternative IgM format assay. Consider testing an earlier sample, or alternatively obtain further serum 7 to 10 days after the initial sample, to confirm for IgG sero-conversion if the initial sample is IgG negative. Report indicated by results of additional testing”. 8. **ACCEPT** Report rephrased to read: “No evidence of recent primary rubella. Regard as immune, independently from vaccination status.” 9. **PARTIAL ACCEPT** The sentence: “Serology test results compatible with rubella infection” has been added to footnote “o” to clarify

	that compatible serology test should always be set to reference laboratory. 10. **ACCEPT** Removed duplicated footnote p 11. **ACCEPT** Footnote n removed 12. **ACCEPT** Footnote h removed 13. **ACCEPT** Sentence amended to include range from 7 to 10 following PHE guidance 14. **NONE** Footnote c gives indication on booking blood. Algorithm mentions an earlier sample. 15. **PARTIAL ACCEPT** The sentence: “Refer to PHE guidelines for post-exposure prophylaxis for measles” was added to footnote “r” to direct to the PHE guidance 16. **ACCEPT** Sample type added to the table

Comment number	2		
Date received	16/03/2020	**Lab name/Professional body (delete as applicable)**	Wirral and Chester Microbiology Service
Section	See below		
Comment			
1. Scope of document Suggest addition to line (p5 last paragraph) This document is restricted to virueses with clear management intervention during pregnancy. Rewite as This document is restricted to viruses with clear management intervention during pregnancy; bacterial rashes such as scarlet fever and syphilis have not been considered either. 2. Safety considerations p6 reference 3 - this Cuban paper did not have any perinatal HSV cases and does not differentiate primary and secondary CMV infections in the mothers, diagnosis of active infection is based on IgM testing. However it does give background information. Consider adding a couple of additional references on UK incidence or additional reviews (such as Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. Rev Med Virol. 2007;17: 253–276 and RCOG 2014 Management of Genital Herpesin Pregnancy)			

Specimen processing

3. Algorithm 1

   Suggest use of nomenclature 'parvovirus B19' throughout document rather than 'parvovirus'.

4. Algorithm 2

   rather than 'Consider B19V NAAT or...' suggest 'DO B19V NAAT AND alternative....'- in line with guidance from 2019 PHE rash in pregnancy (your reference 2)which says 'confirmation is recommended by alternative assay, eg detection of high levels of B19V DNA or IgG seroconversion using an antenatal booking blood'. It is the high level of DNA in recent B19V that is important as far as I am aware, as both IgM and (low level) B19V DNA can persist for long periods. Consider adding reference Maple PAC, Hedman L, Dhanilall P, Kantola K, Nurmi V, Soderland-Venermo M, et al. Identification of past and recent parvovirus B19 infection in immunocompetent individuals by quantitative PCR and enzyme immunoassays: a dual-laboratory study. J Clin Microbiol. 2014 Mar; 52947-56

5. Algorithm 3

   Suggest (right hand middle diamond) ...confirmatory IgM test AND Reference lab confirmation

6. Algorithm 4

   No comment

7. Algorithm 5

   Left hand lower lozenge - suggest add ....VZIG OR ANTIVIRAL

8. Interpreting and reporting laboratory results:

   p14 6. suggest change in line with comments on algorithm 2 above

Evidence
Financial barriers
Health benefits
Are you aware of any interested parties we should consider consulting with on the development of this document?

Recommended action	1. **ACCEPT** Added following sentence: “bacterial rashes such as scarlet fever and syphilis have not been considered” 2. **ACCEPT** Reference replaced with following two references:

	- Boppana SB, Fowler KB. Persistence in the population: epidemiology and transmission. In: Arvin A, Campadelli-Fiume G, Mocarski E, Moore PS, Roizman B, Whitley R et al., editors. Human Herpesviruses: Biology, Therapy, and Immunoprophylaxis. Cambridge; 2007. - Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. Rev Med Virol 2007;17:253-76. 3. **ACCEPT** Parvovirus B19 now used all through the document 4. **PARTIAL ACCEPT** Seroconversion and booking blood testing is covered in footnote "c". Regarding the use of PCR, the working group prefers not to stipulate that every laboratory will/should have PCR for testing. Triangle content has been rewritten to make clear that NAAT is recommended. 5. **PARTIAL ACCEPT** And/or added to diamond 6. **NONE** 7. **ACCEPT** Antiviral added. 8. **PARTIAL ACCEPT** Table in line with PHE guidance. Regarding use of NAAT, check point 4.

Comment number	3		
Date received	18/03/2020	**Lab name/Professional body (delete as applicable)**	NHLS South Africa
Section	See below		
Comment			
1. Scope of document In the viral causes I would suggest adding in Zika Virus. An acute onset of maculopapular rash (sometimes pruritic), arthralgia, conjunctivitis, fever (37.5 to 38.5). With relevant history of exposure which includes: • Current or recent residence in an area where mosquito-borne transmission of Zika virus infection has been reported • Recent travel to an area where mosquito-borne transmission of Zika virus infection has been reported.			

- Unprotected sexual contact with a person (male or female) who resides in or has traveled to an area where mosquito-borne transmission of Zika virus infection has been reported. Sexual contact may be vaginal, anal, or oral, and may involve shared sex toys.As safety measures, should be communicated to clinicians that patients with suspected viral rash disease should not sit in with other possibly pregnant or trying to conceive patients in the same waiting room to avoid transmission.

Safety considerations

2. Specimen processing

   I would like to also add; Nasophayngeal aspirates, skin scrapings from the base of the vesicle, whole blood, heparinized blood, plasma, amniotic fluid. chorionic villous samples: A reverse transcription-nested PCR assay has been used in small studies where it detects rubella virus in chorionic villous samples (CVS) and amniotic fluid samples of affected pregnancies. The largest study to date reported 34 cases where PCR detection of rubella was better in CVS samples than amniotic fluid samples.NB: viral transport medium where needed.

3. Algorithm 1

   In the non-vesicular rash category, concerning Zika Virus given screening,Cross-reactivity with other viruses — Serologic interpretation can be difficult in individuals who have resided in dengue endemic areas, because of the significant serologic cross-reactivity between Zika virus and other flaviviruses, especially dengue viruses 1 through 4. Preexisting dengue antibodies due to past symptomatic or asymptomatic infection may yield false-positive Zika antibody results. Similarly, Zika virus antibodies also cross-react with dengue antibodies and may yield false-positive dengue antibody results.Please see below CDC's diagnostic approach illustrated in the algorithm.

4. Algorithm 2

   Would like to amend the following comments:

   - Circulating IgM antibodies can be detected approximately 10 days after exposure and just prior to the onset of symptoms; they may persist for three months or longer 1 2.
   - However, reliance on a negative IgM serologic result alone can be misleading in a patient with a significant exposure history, because in some instances maternal IgM levels may be below the detection limit. In such cases, polymerase chain reaction can be useful. In a study utilizing serum samples from 101 pregnant women with confirmed B19-induced fetal hydrops, 15 percent of the patients who were seronegative for B19 IgM antibodies had evidence of viremia by maternal B19 DNA testing.

5. Algorithm 3

   - Serum should be obtained within 7 to 10 days after the onset of the rash and repeated two to three weeks later.
   - The reactive IgM could be falsely positive due to rheumatoid factor or other antibodies to infection which can cross react with the assay. Use of rubella specific avidity assay may be useful in these situations. Because of issues of

false-positivity, the Centers for Disease Control and Prevention in the United States discourages the use of rubella IgM for rubella screening in pregnancy3.

6. Algorithm 4

   A few points I'd like to add:

   1. Serology (anti-measles IgM) is the most common laboratory method used for diagnosis of measles virus infection. The detection of measles virus-specific IgM in serum or oral fluid is diagnostic of acute infection4.
   2. Anti-measles IgM is generally detectable three days after the appearance of the exanthem; it may be undetectable on the day the exanthem appears5. IgM is usually undetectable approximately 30 days after the exanthem.
   3. Anti-measles IgG is generally undetectable up to 7 days after rash onset but subsequently peaks about 14 days after the exanthem appears.

Evidence Please see uploaded document

Financial barriers

Health benefits

Are you aware of any interested parties we should consider consulting with on the development of this document?

Recommended action	1. **NONE** Zika virus is not in the remit of this document as it is vector-born and is not a risk in pregnant people if exposed to rash caused by Zika virus. 2. **NONE** This document is not aimed to diagnose viral rash when it has developed. The scope is narrowed to pregnant people exposed to viral rash. 3. **NONE** Zika virus is not in the remit of this document. 4. **NONE** We already request blood after a month. Regarding IgM, the algorithm suggests not only looking to IgM positivity but also interpreting the seroconversion from IgM to IgG. 5. **PARTIAL ACCEPT** 7-10 days added to triangle. IgM test is covered in footnote “g”: Caution should be taken when interpreting IgM results; low reactivity is often non-specific. Consider testing for potential cross reacting IgM and for recent EBV infection.

	6. **NONE** This document does not deal with diagnosis. The focus here is to assess immunity in people exposed to rash.

Comment number	4		
Date received	04/08/2020	**Lab name/Professional body (delete as applicable)**	Virology specialist centre public health Wales Cardiff
Section	See below		
Comment			
Scope of document The gov.uk has some useful sections on various diseases. Also nhs direct. There is useful rcog guidance on herpes and bash guidance on syphilis. Is it worth providing a list of conditions that might give a rash and/or a list of useful sites to direct readers as we get a lot of queries for other rashes such as hepatitis e, hand foot and mouth, zika, or management of congenital syphilis, perinatal herpes etc.			
Evidence			
Financial barriers			
Health benefits			
Are you aware of any interested parties we should consider consulting with on the development of this document?			
Recommended action	**NONE** This is outside the scope of this document and is covered by other resources available elsewhere. A non-exhaustive list is included in the document; however.		

Comment number	5		
Date received	11/08/2020	**Lab name/Professional body (delete as applicable)**	Dept of Virology, Hull University Teaching Hospitals NHS Trust
Section	See below		
Comment			
The table on p16 is incorrect regarding the interpretation of an equivocal qualitative VZV IgG assay (and contradicted by footnote 'u'). According to PHE immunoglobulin guidance, prophylaxis is not recommended for pregnant women who have an equivocal qualitative result and where a quantitative assay cannot be performed within 10d of contact.			
Evidence			
Financial barriers			
No			
Health benefits			
No			
Are you aware of any interested parties we should consider consulting with on the development of this document?			
Recommended action	**ACCEPT** Document has been updated in line with the PHE VZIG guidance on equivocal qualitative VZV IgG results.		

Comment number	6		
Date received	18/08/2020	**Lab name/Professional body (delete as applicable)**	PHE Virus Reference Department
Section	See below		
Comment			
Specimen processing			

The 'specimen types' section would benefit from being more specific according to the virus under investigation. For example: Oral fluids, Throat swabs, and Urine are not normally specimens taken for investigation of Parvovirus B19.
Evidence
Financial barriers
Health benefits
Are you aware of any interested parties we should consider consulting with on the development of this document?

Recommended action	**ACCEPT** Specimen type added for NAAT in the table.

Comment number	7		
Date received	18/08/2020	**Lab name/Professional body (delete as applicable)**	IBMS
Section	See below		

Comment
Section 5. Specimen processing and procedure **5.1 Specimen type** This section mentions a large list of sample types however, the algorithms are only for testing serum IgM and IgG. Therefore, the only samples that would or could be used for this are blood, serum and in some assays oral fluid. It is suggested that the other sample types are removed from the list. They could be used for the follow up NAATs testing, but those are not considered in this document.
Evidence
Financial barriers
Health benefits

Are you aware of any interested parties we should consider consulting with on the development of this document?	
Recommended action	**ACCEPT** Specimen types modified to reflect which one is used in which assay.

Respondents indicating they were happy with the contents of the document

Overall number of comments: 1			
Date received	07/03/2020	**Lab name/Professional body (delete as applicable)**	Medical laboratory scientist
Health benefits			