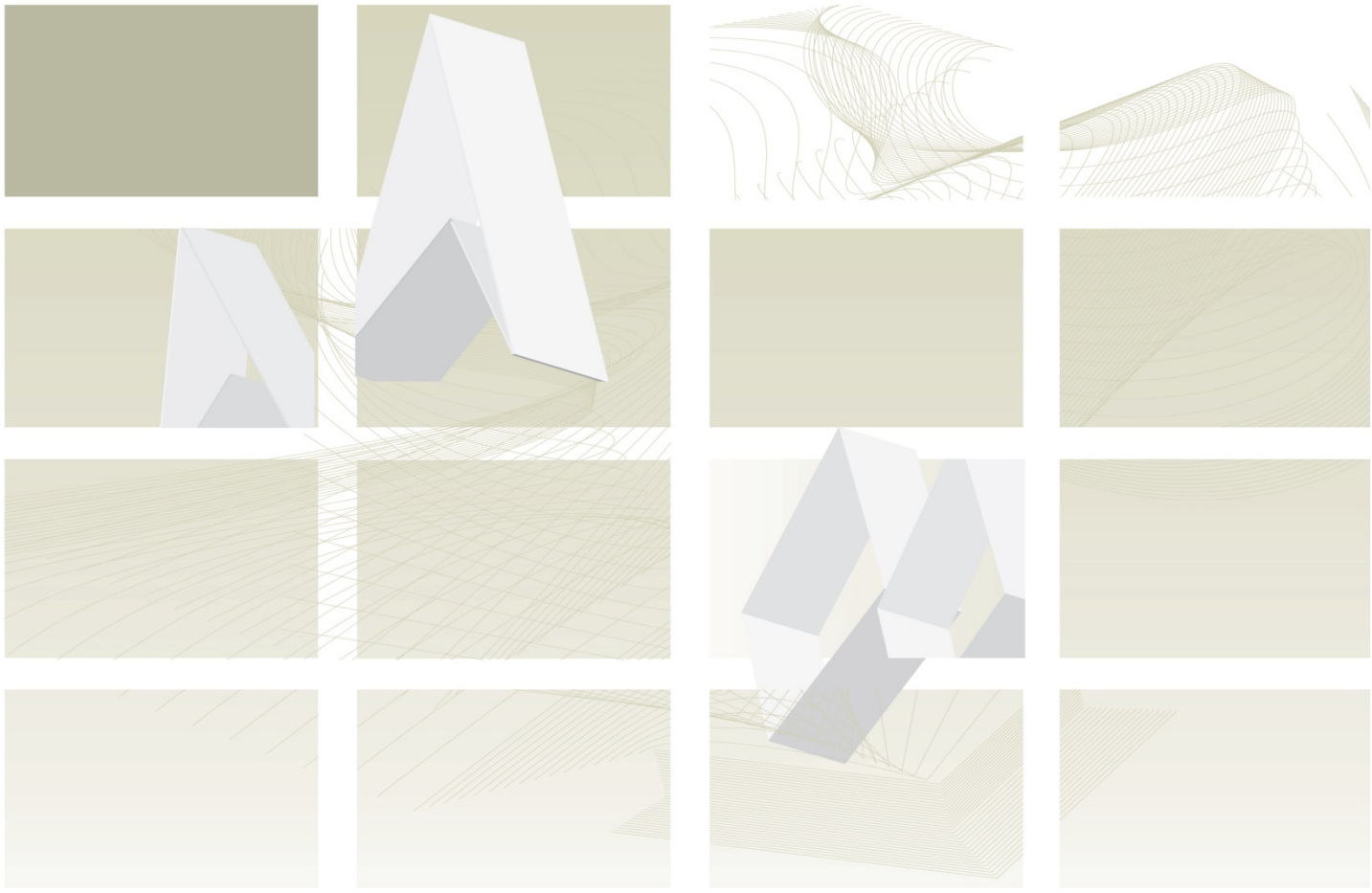
UK Standards for Microbiology Investigations

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

V 28 Investigation of cytomegalovirus infection



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: 10/12/2018 – 27/12/2018

Version of document consulted on: V 28dk+

Proposal for changes

Comment number	1		
Date received	13/12/2018	**Lab name/Professional body**	Dundee
Section	9 and 10.3		
Comment			
a. Diagram section 9 diagnosing congenital infection: Diagram twice mentions culture, and this seems at odds with footnote d which indicates that NAAT is gold standard. My feeling is that PCR is the standard and widely available and that studies such as references 26 and 27 have shown equivalence with culture. Recommend removing culture from diagram. b. Table 10.3 Pregnant woman, earlier antenatal serum sample available Heading of second column is CMV IgM and IgM, should this be IgG and IgM? Row 1: having no interpretative comment seem unsatisfactory, even while awaiting avidity results. It says see note but does not even indicate which notes are most relevant.			
Evidence			
Not completed.			
Financial barriers			
No.			
Health benefits			
No.			
Are you aware of any interested parties we should consider consulting with on the development of this document?			
No.			
Recommended action	a. **ACCEPT** Removed culture from diagrams. b. **ACCEPT** Table amended.		

Comment number	2		
Date received	17/12/2018	**Lab name/Professional body**	Dept of Microbiology, Hull and East Yorkshire NHS Trust

Section	6
Comment	
In footnote a) to the flow chart in section 6, a travel history is mentioned. It seems unlikely that this would be a relevant factor in CMV screening.	
Evidence	
Not completed.	
Financial barriers	
No.	
Health benefits	
No.	
Are you aware of any interested parties we should consider consulting with on the development of this document?	
No.	
Recommended action	**ACCEPT**

Comment number	3		
Date received	19/12/2018	**Lab name/Professional body**	British Association of Paediatricians in Audiology
Section	a. Page 13 Section 'c' b. Page 13 section 'f' - late diagnosis.....'who develop sequelae within a 5-7 year period'		
Comment			
a. I think a 'sensorineural hearing loss' should be added to the clinical signs suggestive of congenital infection as it is an important sign which, with the newborn hearing screen, is very often picked up in the neonatal period but can also be absent in many children and develop later on. It is however mentioned in a further paragraph in this section. b. Professionals working with children who develop a sensorineural hearing loss at a later stage beyond the time of performing the newborn hearing screen have found, in areas where the Guthrie card can be tested beyond 5 years of age, that children older than 7 years have been found to have congenital cytomegalovirus infection. There are also children/young adults who request investigations into their hearing loss at a time when they wonder about it, usually as late teenagers, when it has not been investigated (for whatever reason - such as parents not wanting investigations to be performed when the child was young) at an earlier date.		
Evidence			

a. Aetiological investigations are logged onto our database for hearing loss - eSP and SMART4Hearing - which will have the cause of the hearing loss inserted if it has been found.

b. Simone Walters, Consultant Audiovestibular Physician, St Helier's Hospital, Sutton has recently performed a survey on this. In uploaded paper - (Longitudinal Investigation of Hearing Disorders in Children with Congenital Cytomegalovirus, by Dahle et al.)- Table 3 on page 285 indicates that a percentage of children with congenital cytomegalovirus were found to have a hearing loss AFTER the age of 7 years.

Have you got any suggestions on how UK SMIs can be improved? (Do you have suggestions on:) = Allowing Guthrie cards to be stored longer than 5 years and up to at least 25 years (the upper age of a young adults; Are you aware of any inconsistencies in the UK SMIs? (Do you have suggestions on:) = In some areas in the country Guthrie cards are destroyed at 5 years of age but page 13 section 'f' talks about sequelae up to the age of 7 years - we feel that the sequelae can go well beyond the age of 7 years.

Financial barriers

No.

Health benefits

If Guthrie cards were not destroyed at the age of 5 years and we were able to test the Guthrie cards for congenital cytomegalovirus infection for children older than 5 years, on those children/young adults who developed a hearing loss or were investigated for a hearing loss at an older age, they would benefit from this information.

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

Not completed.

Recommended action	a. **ACCEPT** Sensorineural hearing loss to be added. b. **PARTIAL ACCEPT** Noted that sequelae can occur later than 7 years in some cases.

Comment number	4		
Date received	20/12/2018	**Lab name/Professional body**	Newcastle upon Tyne Hospitals NHS Foundation trust
Section	See below		
Comment			

a. Algorithm 7: Diagnosing CMV in the immunocompetent. We responded similarly in a previous consultation however we feel this issue is worthy of further review. CMV cannot be reliably diagnosed on IgM testing alone without either showing

seroconversion or testing for CMV IgG avidity; these should be integral to the algorithm rather than a footnote. As stated in the algorithm IgM can be false positive, or due to reinfection or reactivation (the latter two being of unlikely significance in this patient group). It is the diagnosis of primary infection that needs to be made. This can only be made in IgG positive patients by testing an earlier sample or CMV avidity. Without such confirmatory testing there is limited value to doing the IgM in the first place. b. Algorithm 9: Diagnosing congenital infection. We responded similarly in a previous consultation however we feel this issue is worthy of further review. We do not feel testing for IgM is justified in this algorithm. We have previously audited this and confirmed the accepted fact that IgM is more commonly negative in PCR proven congenital infection. We also showed that despite requests for urine sample on negative IgM reports these were rarely received. We feel testing and providing a negative result may provide false re-assurance, and is of no clinical benefit.
Evidence
Not completed.
Financial barriers
No.
Health benefits
No.
Are you aware of any interested parties we should consider consulting with on the development of this document?
No.

Recommended action	a. **NONE** Confirmatory testing only required for pregnant women; will retain current footnotes. b. **ACCEPT** Remove IgM testing from algorithm.

Comment number	5		
Date received	21/12/2018	**Lab name/Professional body**	University College London
Section			
Comment			
This document is generally accurate, but I have a few specific suggestions for clarifications. a. Page 10 j) the risk of congenital infection is 32% not 40% b. Page 14 k) a discordant saliva/urine result may be caused by breast milk contaminating the baby's mouth.			

c. Page 14 l) modern extraction and amplification methods detect congenital CMV in 70% to 80% of cases.

d. Page 14 n) a negative amniotic fluid PCR result may be associated with subsequent delivery of congenital CMV, possibly explained by intrauterine transmission of CMV in late pregnancy.

e. Page 17 the heading of the left-hand column should be IgG and IgM (not IgM and IgM).

f. Page 17 comment for scenario 2: before the time instead of at the time.

g. Page 18 comment for scenario 1: confirmed intrauterine infection (not congenital infection, because congenital infection is only diagnosed at birth).

h. Page 18 comment for scenario 2: no evidence of intrauterine infection

Evidence

a. Kimberlin DW, Jester PM, Sanchez PJ, Ahmed A, Arav-Boger R, Michaels MG, et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. The New England journal of medicine. 2015 Mar 5;372(10):933-43. PubMed PMID: 25738669. Pubmed Central PMCID: 4401811.

b. Atkinson C, Emery VC, Griffiths PD. Development of a novel single tube nested PCR for enhanced detection of cytomegalovirus DNA from dried blood spots. JVirolMethods. 2014;196:40-4.

Financial barriers

No.

Health benefits

Health benefits from diagnosing more cases of cCMV so that treatment can be considered.

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

Yes. It is important that dried blood spots (Guthrie) are retained for many years to allow retrospective diagnoses. There is a current consultation on destroying these.

Recommended action	a. **ACCEPT** Replace 40% by 32%. b. **ACCEPT** Note regarding pre-breastfeed swab to be added. c. **ACCEPT** Updated to 70-80% and references updated. d. **PARTIAL ACCEPT** Note will be added to reporting table only. e. **ACCEPT** Table amended. f. **ACCEPT** “at” amended to “before”.

	g. **ACCEPT** “intrauterine” to be used where appropriate. h. **ACCEPT** “intrauterine” to be used where appropriate.

Comment number	6		
Date received	23/12/2018	**Lab name/Professional body**	RCPCH, GMC and BAAP (British Association of Audiovestibular Physicians
Section	Page 13 point f and Page 14 point l		
Comment			

a. Page 13 point f The 5- 7 year period is not long enough. We know from clinical practice and from studies such as Dahle's 2000 longitudinal follow up study that SNHL can start in the teenage years (see Ref). Other late effects such as epilepsy can start with puberty. The timing of investigation is often much later than the date of onset of the condition being investigated. Hearing loss and balance disorders tend to present late to the relevant professionals. It is essential that the Guthrie card/blood spot is available for testing for older children and young adults, who may not have had the chance to have the test before. (There is no universal screening for congenital CMV and it is not routinely tested for in developmental delay or autism). The hearing loss occurs after the newborn hearing screen in 50% of cases and may start and/or present late. We have collected data in the UK this past year which demonstrates the clinical need for this test for up to 25 year olds and submitted this to PHE. Also the bloodspot CMV test needs to be available for the transition group with CMV symptoms, so they can have the opportunity of consenting for blood spot CMV testing (EHCP covers up to 25 years, WHO definition of young people = 10-24 years). Suggest add in the list of 'sequelae': balance disorder, autism, epilepsy

b. Page 14 point l The blood spot CMV test sensitivity quoted is far too low (28%) which gives a falsely negative impression of the usefulness of the test (approx. 80% UK data and higher in other studies in Europe). Please see Professor Paul Griffiths and Claire Atkinson's work on this. This test is an integral part of the NICE approved national guideline on the aetiological investigation from BAAP (a compulsory investigation to offer for all children with sensorineural hearing loss- see references). In over 1years of age the protocol is to test child/young person's IgG and if positive to test the Guthrie card (unless maternal IgG is negative). (See ref 6 below.)

Are there any gaps in the UK SMI repository that you would like filled? (Do you have suggestions on:) = no; Have you got any suggestions on how UK SMIs can be improved? (Do you have suggestions on:) = no; Are you aware of any inconsistencies in the UK SMIs? (Do you have suggestions on:) = The PHE policy of Guthrie card destruction at age 5 years contradicts this document which state a 5-7 year period. In fact, CMV effects can occur much later, even in teenage years. See above,

Evidence	
References a. Goderis, J et al. Hearing loss and congenital CMV infection: a systematic review. Pediatrics, 2014. 134(5): p. 972-82. b. Dahle AJ (2000) Fowler, KB Wright JD et al Longitudinal investigation of hearing disorders in children with congenital cytomegalovirus. J Am Acad Audiol; 11:283-2903. S Bernard et al. Vestibular disorders in children with congenital cytomegalovirus Infection. Pediatrics. 2015 Oct;136(4):e887-95. doi: 10.1542/peds.2015-0908. Epub 2015 Sep 74. Sakamoto A, Moriuchi H, Matsuzaki J, Motoyama K, Moiriuchi M. 'Retrospective diagnosis of congenital cytomegalovirus infection in children with autism spectrum disorder but no other major neurologic deficit. Brain Dev 2015 Feb; 37 (2):200-5. doi: 10.1016/j.braindev.2014.03.016. Epub 2014 Apr 24. 5. Standard 6 NDCS Quality Standards in Transition Oct 2011 6.http://www.baap.org.uk/Resources/Documents,GuidelinesClinicalStandards.aspx7. Atkinson C, Walter S, Sharland M, Tookey P, Luck S, Peckham C, Griffiths P, Use of stored dried blood spots for retrospective diagnosis of congenital CMVJ Med Virol 2009 Aug;8 (8):1394-8	
Financial barriers	
No, if a diagnosis of congenital CMV can be made retrospectively it saves money and time spent testing for alternative explanations for symptoms. Sometimes these tests are costly and invasive eg metabolic tests, neurological and genetics tests to investigate white matter abnormalities on brain MRI scans. This investigation standard and the guideline on bloodspot storage should be complementary, as this one demonstrates the important role of this test in the retrospective diagnosis of congenital CMV, which supports the storage for as long as it is clinically useful.	
Health benefits	
There is a risk of not being able to diagnose congenital CMV if the blood spots are not stored for long enough, and this affects clinical management of the patient. (In some areas they are being destroyed at age 5 years already, and this is denying patients chance of a diagnosis). Families and physicians have reported the importance of being able to diagnose congenital CMV using the blood spots and once the diagnosis can be made, knowledge and research in this field can further develop.	
Are you aware of any interested parties we should consider consulting with on the development of this document?	
CMV Action. National Deaf Children's Society. British Paediatric Allergy, Immunity and Infection Group Professor Paul Griffiths and Dr Claire Atkinson of the Royal Free virology Centre, as they are UK experts in CMV. (I think they may have also responded).	
Recommended action	a. **PARTIAL ACCEPT** Noted that sequelae can occur later than 7 years in some cases. b. **ACCEPT** Percentage changed and reference added.

Comment number	7		
Date received	24/12/2018	**Lab name/Professional body**	Bristol PHL
Section	All		

Comment

First, this clearly took a lot of thought, well done. The division into different clinical settings is very helpful for the user. I have some comments for most of the sections, which I will try and describe in text as annotation of the actual document is difficult. Most are not evidence based, just my version of logic or opinion.

a. p5, section 6- footnote d would be better in the left diamond.

b. Footnote e- couldn't find that in the latest SaBTO document, regardless, I think the use of 'consider' in UK SMI is unhelpful as these are typically use to inform laboratory and clinical practice- in order to consider, what evidence is being suggested, and what is the advantage or disadvantage of adopting either choice?

c. p7, section 7, algorithm- footnote e better in the first right hand diamond.

d. Central lozenge report comment repeat testing in 1-3 weeks- which is it? Is 4 weeks too late? If the seroconversion time from true IgM detection to IgG detection is known then that is the minimum gap- something like retest as soon as possible but no earlier than 2 weeks after the current sample date? Note- 3 weeks is chosen later in the document without a range.

e. Footnote d should be added to the left report comment 'no evidence of recent CMV infection'; in the HEV algorithm there is a statement of false positive IgM, consider adding for consistency.

f. p9, section 8- retesting for seroconversion is 3 weeks here. Left side, screen IgM reactive, IgG negative, retest showing seroconversion ends with action to repeat IgG and IgM on the 'same' sample- logically both samples should be retested, or avidity could be done on the later one for confidence. This algorithm seems to mandate avidity on current samples and testing earlier- this is good practice but can generate discrepancy- high avidity but recent seroconversion- suggest a troubleshooting comment. Central report 'no evidence of recent primary CMV in the past 3 months.....' has no advisory action. Suggest adding, baby should be tested for congenital infection as soon as possible after birth, and no later than 3 weeks of age.

g. Footnote e- 'excludes primary infection in pregnancy; however....'

h. p12, section 9- generally fab. Left report lozenge- Congenital infection unlikely BUT still suggest testing neonate.

i. Right hand side, urine negative by NAAT in first year of life, congenital infection unlikely- very helpful, but any idea what unlikely is in percentage terms, as the clinical team need to derive an action from this- e.g. no follow up.

j. Footnote j- not sure of relevance. Thanks.

Evidence

Opinion only.

Financial barriers

No.	
Health benefits	
No.	
Are you aware of any interested parties we should consider consulting with on the development of this document?	
CMV society.	
Recommended action	a. **ACCEPT** Footnote d to be included in left diamond. b. **ACCEPT** Reference and footnote removed. c. **ACCEPT** Footnote f also moved to first right hand diamond. d. **ACCEPT** “at least two weeks” to be used in both instances. e. **NONE** f. **PARTIAL ACCEPT** High avidity but recent seroconversion case does not occur within the algorithm. “Repeat IgG and IgM on the same sample to confirm seroconversion” box removed. g. **ACCEPT** Wording amended. h. **ACCEPT** Consider testing urine or saliva after birth” added to report. i. **NONE** No evidence to support more specific terminology. j. **ACCEPT** Footnote J removed.

Comment number	8		
Date received	26/12/2018	**Lab name/Professional body**	Imperial College Healthcare NHS Trust
Section			
Comment			
I am a paediatric Infectious Disease's consultant and I look after a large number of children with congenital CMV infection. Please see the notes which I have added to the			

consultation draft document, particularly in relation to the antenatal and postnatal diagnosis sections.

I am have no other experience of this unit, but of concern, the list of references for this document, does not have any references after 2014, and there are plenty of relevant articles since then regarding congenital CMV, its diagnosis and its treatment.

a. p7 - note freezing may reduce, but does not destroy CMV in breast milk
b. p11 - does it have to be after 21 weeks, surely can be done earlier?
c. p12 - I don't think that serology is useful in the neonate, and waiting for and IgM result could delay getting the useful diagnostic test, ie CMV PCR urine and saliva. If it is done, then should always be WITH PCRs.
d. p13 - see my comment above, should only be done as an adjunct to PCRs, and waiting for the serology should definitely not delay sending them
e. p13 - who does culture these days?
f. p13 - see comment above re Guthrie cards.
g. p13 - check maternal booking blood serology for evidence of sero-conversion / previous in infection. I would also repeat the PCRs in blood urine and saliva to confirm
h. p13 - I would test blood, urine and saliva for DNA PCR. Not necessary to test the Guthrie card if <3 weeks of age.
i. p14 - add - echogenic bowel
j. p14 - failed new born hearing screening, intracranial calcification, brain white matter disease, polymicrogyria, retinitis / retinal scarring etc
k. p14 - The risk of false positive saliva PCR in recently breast fed infants should be highlighted, ideally saliva swabs should be taken just before a breastfeed.
l. p14 - Samples for PCR testing are easy to obtain, IgM should only be done as a secondary test, it risks delaying getting a diagnostic PCR result.
m. p14 - mostly within this time frame but can even be later in childhood.
n. p14 - How many years are booking bloods kept for? I don't think most labs keep for this length of time.
o. p14 - see above my query about this, in some cases could be done earlier.
p. p15 - blood CMV PCR should also be tested
q. p15 - In the UK more like 85% sensitive, but this is not just due to the sensitivity of the test, a significant proportion of babies with congenital CMV (symptomatic and asymptomatic at birth) may no longer be viraemic at birth.
r. p15 - note all babies with congenital CMV should be referred to their local Paediatric Infectious Diseases Service for assessment for treatment, and registration with the national registry - see European guidelines PIDJ 2017. Note treatment is now with oral valganciclovir for 6 months,
s. p15 - references 34-36 are out of date. see N Engl J Med. 2015 Mar 5;372(10):933-43. doi: 10.1056/NEJMoa1404599. Valganciclovir for symptomatic congenital cytomegalovirus disease.
t. p17 - At the same time could do blood / urine PCR for CMV to try to confirm infection.

u. p18 - presumably meant to be IgG and IgM?

v. p18 - unless sample taken too soon after infection (< 6 weeks) 2)

w. p19 - I'm not sure how this scenario would happen? Why would a repeat test be sent, unless the clinicians were concerned the first test result was wrong?

x. p20 - test maternal booking blood for evidence of sero-conversion

y. p20 - see my comment above 10.5 -2, not sure when this would occur

z. p21 - I note that there are no reference for congenital CMV after 2014, this is concerning, as this is a fast moving field with new data available since then.

Evidence

Please see the notes which I have added to the consultation draft document, particularly in relation to the antenatal and postnatal diagnosis sections.

Financial barriers

None known.

Health benefits

This SMI could help to make sure that more children are diagnosed with congenital CMV, within a timely manner (ie before 21 days of life), so that treatment options and can be offered within a timely manner (ie before 28 days of life).

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

BPAIIG.

Recommended action	a. **ACCEPT** b. **PARTIAL ACCEPT** Will note that 21 weeks is considered optimum, but there may be clinical reasons to do earlier. c. **ACCEPT** Serology to be removed. d. **ACCEPT** Serology to be removed. e. **ACCEPT** Culture to be removed. f. **PARTIAL ACCEPT** Noted that sequelae can occur later than 7 years in some cases. g. **NONE** Not required within algorithm. h. **ACCEPT** Guthrie card testing not required under neonatal diagnosis, but will be retained under late diagnosis.

	i. **ACCEPT** Echogenic bowel to be added. j. **ACCEPT** List of sequelae to be updated. k. **ACCEPT** Need for pre-breastfeed saliva swabs to be indicated; two salivary samples to resolve false positive. l. **ACCEPT** Serology to be removed. m. **ACCEPT** Sequelae mostly occur within this timeframe, but can occur later. n. **NONE** Reference to booking bloods removed. o. **ACCEPT** Amniocentesis may be done earlier for clinical reasons. p. **NONE** Not used to resolve discordance. q. **ACCEPT** Percentage to be updated with new references. r. **ACCEPT** Valganciclovir to be mentioned. s. **ACCEPT** References to be updated. t. **NONE** u. **ACCEPT** Heading amended. v. **PARTIAL ACCEPT** Amend report wording to “no evidence of congenital CMV infection, consider testing urine or saliva after birth”. w. **ACCEPT** Table amended. x. **NONE** y. **ACCEPT** Table amended. z. **ACCEPT** Table amended.