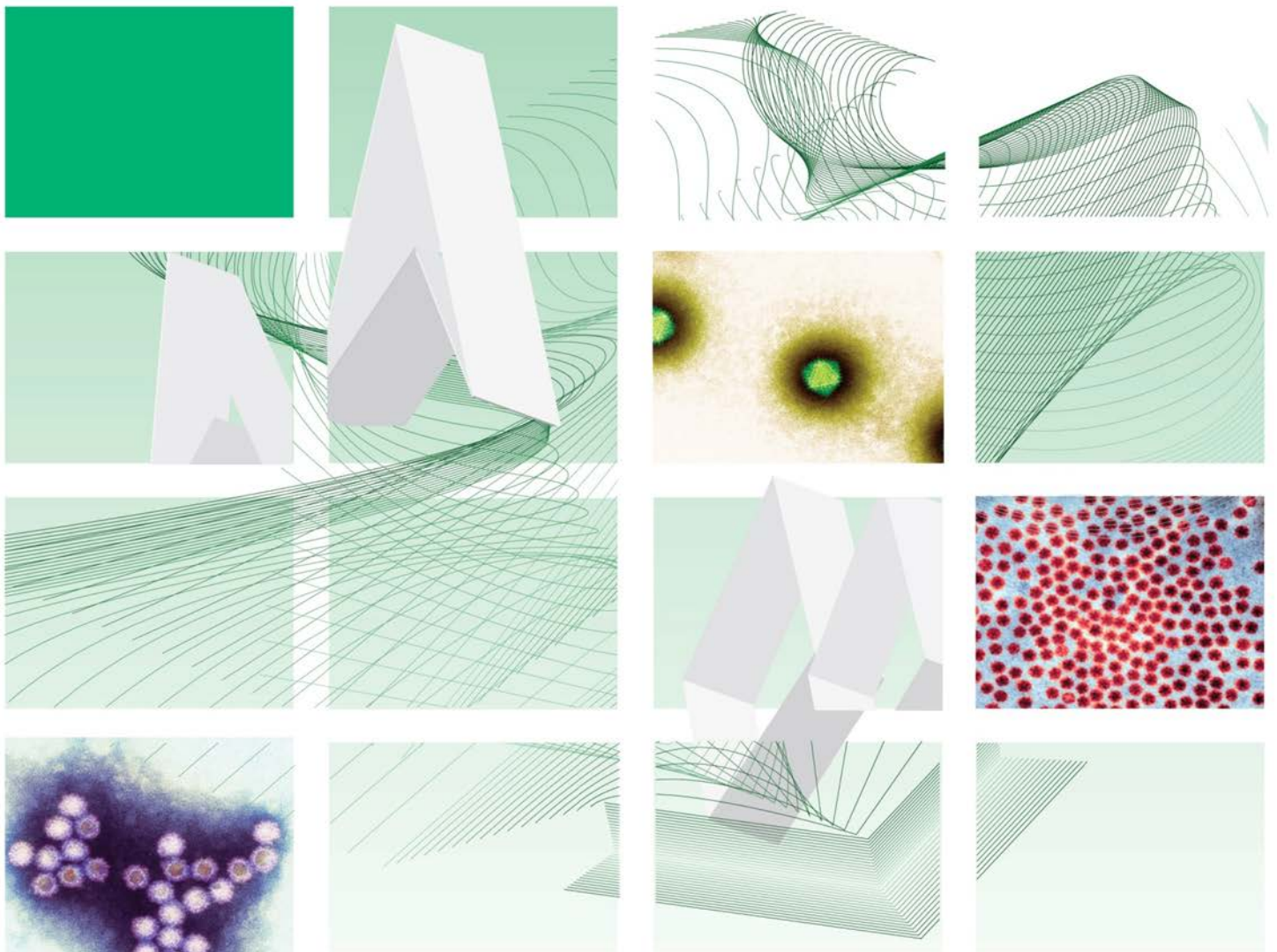


UK Standards for Microbiology Investigations

Investigation of cytomegalovirus infection



"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.

Issued by the Standards Unit, National Infection Service, PHE

Virology | V 28 | Issue no: 4 | Issue date: 26.06.19 | Page: 1 of 23

Contents

Amendment table	3
1. General information	4
2. Scientific information	4
3. Scope of document	4
4. Safety considerations	4
5. Specimen processing and procedure	4
6. Determination of CMV IgG status	6
7. Diagnosing CMV infection in symptomatic non-pregnant immunocompetent individuals	8
8. Diagnosing CMV infection in pregnant women	10
9. Diagnosing intrauterine and congenital infection	13
10. Interpreting and reporting laboratory results	16
11. References	21



"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**."

Amendment table

Each UK 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 number/date	6/26.06.19
Issue number discarded	3.1
Insert issue number	4
Anticipated next review date*	26.06.22
Section(s) involved	Amendment
Whole document.	Document restructured with new headings in line with new syndromic approach
Headings 1 and 2.	Link added to General Information and Scientific Information pages on gov.uk.
Document title.	Document renamed from "Cytomegalovirus Serology" to "Investigation of cytomegalovirus infection".
References.	References updated.
Flowcharts and footnotes.	Flowcharts and footnotes updated.
Screening flowchart.	"Screening Flowchart" renamed "Determination of CMV IgG status".
Immunocompetent host flowchart.	"Immunocompetent Host Flowchart" renamed "Diagnosing CMV infection in symptomatic non-pregnant immunocompetent individuals".
Pregnant women flowchart.	"Pregnant Women Flowchart" renamed "Diagnosing CMV infection in pregnant women".
Congenital infection flowchart.	"Congenital Infection Flowchart" renamed "Diagnosing intrauterine and congenital infection".

*Reviews can be extended up to five years subject to resources available.

1. General information

[View](#) general information related to UK SMIs.

2. Scientific information

[View](#) scientific information related to UK SMIs.

3. Scope of document

Cytomegalovirus (CMV) infection is common and usually harmless. It can cause serious disease in immunocompromised individuals and in babies who were infected in utero. This UK SMI is composed of four algorithms that cover the following situations:

- screening of blood donors and organ donors, and of individuals at risk of CMV disease^{1,2}
- diagnosing CMV infection in non-pregnant symptomatic immunocompetent individuals
- diagnosing CMV infection in immunocompetent pregnant women
- diagnosing congenital or intrauterine CMV infection

This document does not cover CMV diagnosis in immunocompromised individuals (including human immunodeficiency virus (HIV) infected, graft recipient, immunosuppressive treatment). In these patients serological methods are of limited use and molecular assays are the preferred tools for diagnosis and monitoring of CMV infection and related disease³. However, serological assays are used for pre-transplant assessment of the solid organ transplant donor and recipient and for screening donors of blood products to minimize risk of CMV infection in seronegative recipients³.

Refer to [Q 7 - Good practice when undertaking serology assays for infectious diseases](#) for information regarding good laboratory practice in serological testing.

This UK SMI should be used in conjunction with other UK SMIs.

4. Safety considerations

This guidance should be supplemented with local COSHH and risk assessments. Refer to current guidance on the safe handling of all organisms documented in this UK SMI.

5. Specimen processing and procedure

5.1 Specimen type

Blood, serum, plasma, urine, saliva, amniotic fluid.

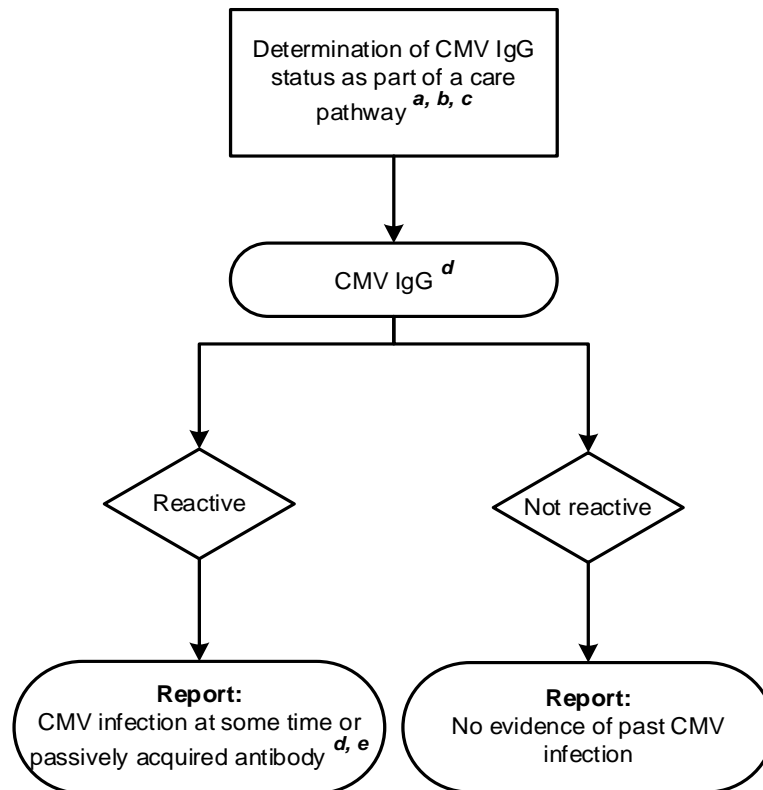
5.2 Specimen transport and storage conditions

Specimens should be collected in appropriate CE marked leak proof containers and transport in sealed plastic bags.

Specimens should be transported and processed according to manufacturer's instructions or local validation data⁴.

Samples should be retained in accordance with The Royal College of Pathologists guidelines 'The retention and storage of pathological records and specimens'⁵.

6. Determination of CMV IgG status

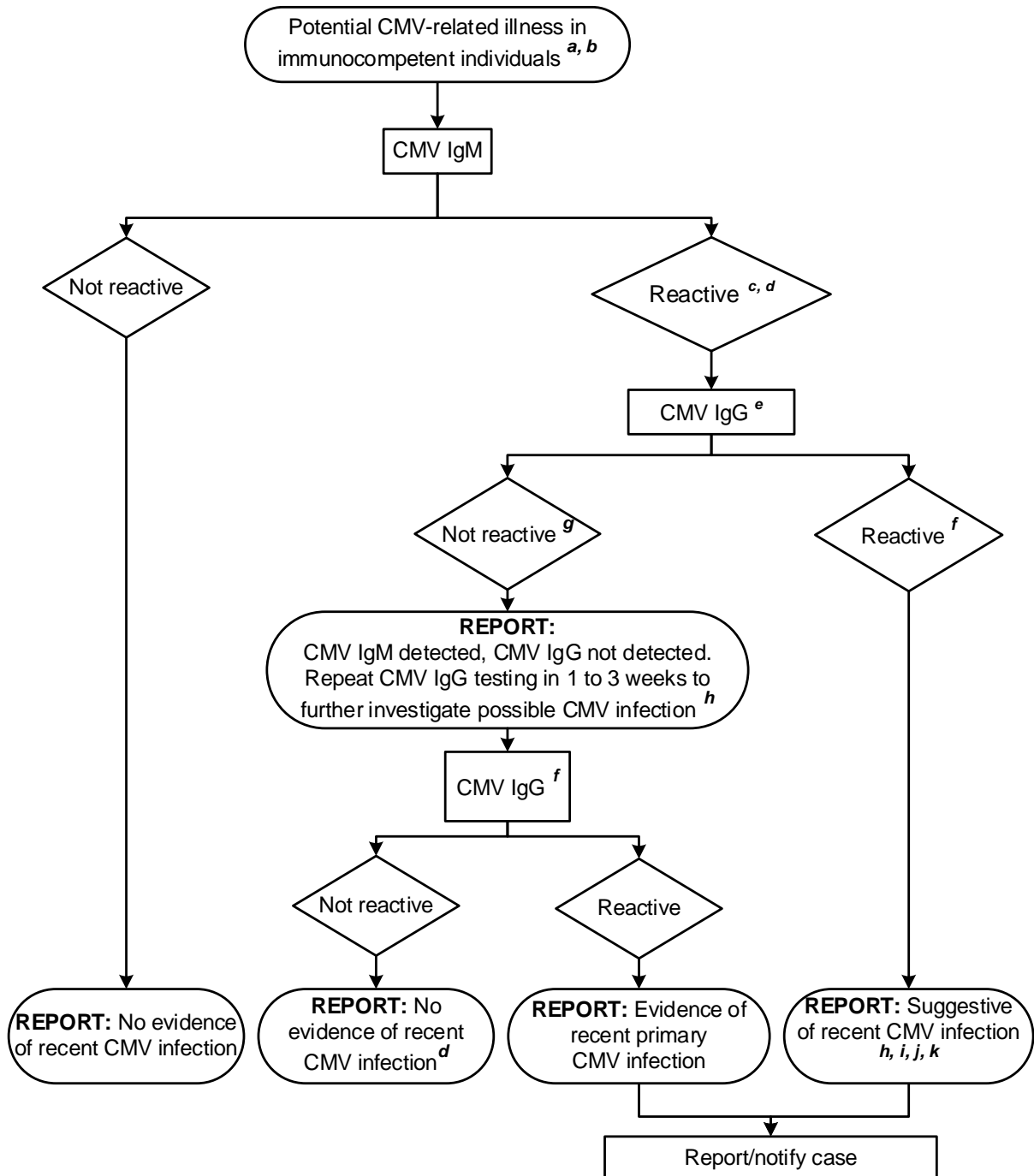


Please note: Equivocal results are not included in the above algorithm.

Footnotes relating to determination of CMV IgG status flowchart

- a) This includes blood donors and organ donors and individuals at risk of CMV disease¹.
- b) Individuals at risk of CMV disease include future graft recipients and individuals receiving (or due to receive) immunosuppressive treatment. CMV IgG antibody is one of the markers required to evaluate the risk of CMV infection or reactivation, and to implement appropriate control measures and pre-emptive or preventive treatment.
- c) Not all milk banks screen all potential breast milk donors as there may be effective treatment processes available that reduce or eliminate contamination⁶.
- d) Passively acquired CMV IgG may be detectable in patients who have recently received blood or blood products, including anti-D immunoglobulins, leading to misinterpretation of the CMV infection status through false seropositive or seroconversion results³. Passively acquired immunoglobulins decrease over time, with a half-life of approximately 3 weeks. If this data is not available at the time of transplantation the worst-case scenario must be considered in terms of preventing CMV infection.
- e) The detection of CMV IgG in blood and organ donors indicates potential infectivity of donations.

7. Diagnosing CMV infection in symptomatic non-pregnant immunocompetent individuals



Please note: Equivocal results are not included in the above algorithm.

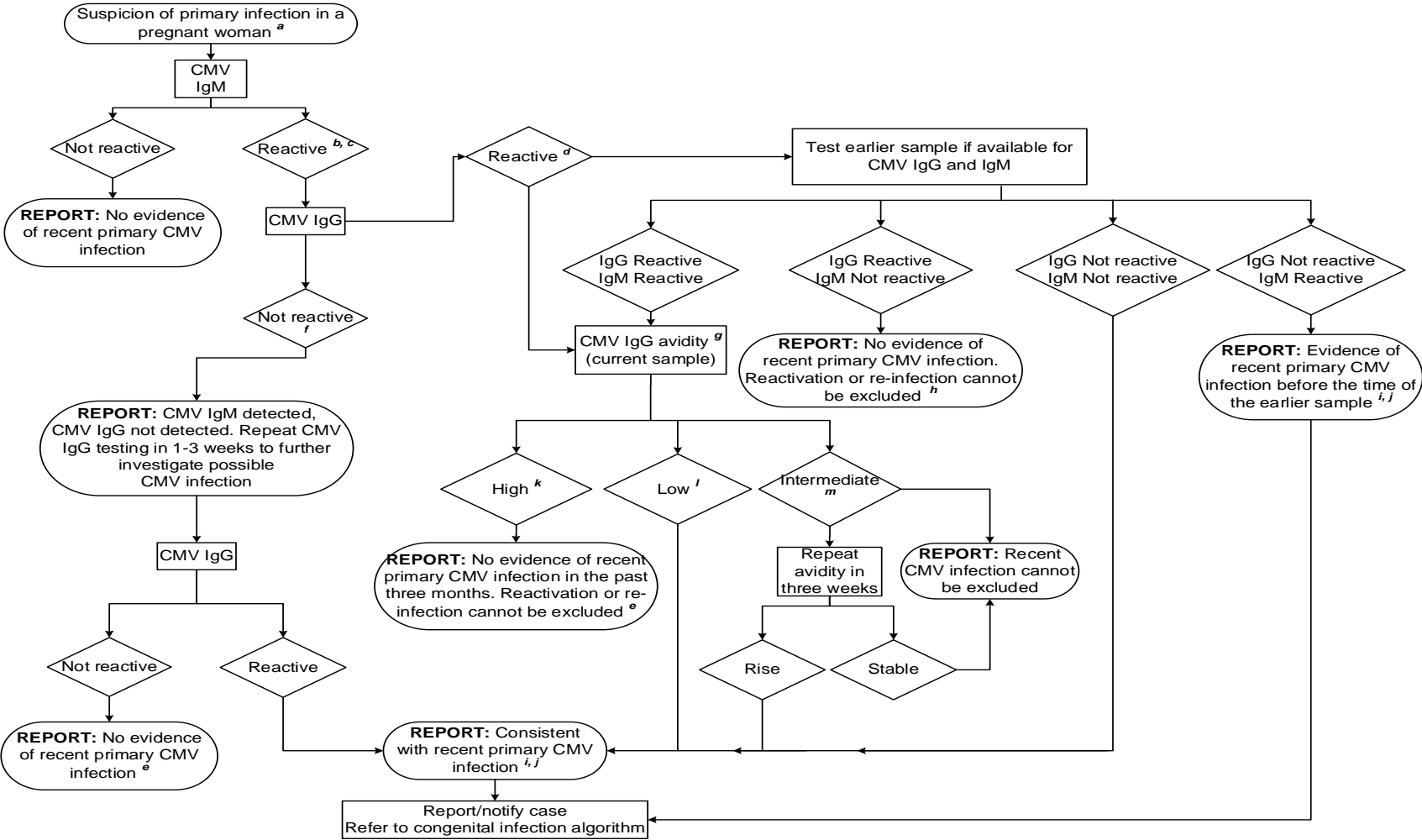
Footnotes relating to symptomatic non-pregnant immunocompetent individuals flowchart

- a) Clinical mononucleosis, fever, hepatitis or pyrexia of unknown origin in immunocompetent individuals.
- b) Immunocompetent women: where possible query pregnancy. If pregnant, refer to the algorithm for pregnant women.
- c) The presence of CMV IgM may indicate one of the following:
 - primary infection
 - re-infection
 - reactivation
 - false-positive test result

Therefore, the presence of CMV IgM cannot be used independently to diagnose primary CMV infection.

- d) Consider excluding false positive CMV IgM due to acute EBV infection by testing for heterophile antibody or EBV VCA-IgM. Refer to [V 26 – Epstein-Barr virus serology](#).
- e) Consider testing CMV IgG and IgM on an earlier sample, if available, to aid interpretation.
- f) Infants (<12 months): passively acquired maternal IgG may be present⁷. Determine the maternal IgG status and, if positive, consider testing for CMV in the infant's blood and/or urine. Refer to the algorithm for congenital infection if required^{3,8-10}.
- g) Consider CMV NAAT on the existing serum or plasma sample. A positive CMV NAAT indicates primary CMV infection. If the CMV NAAT is negative, primary CMV infection is unlikely but cannot be excluded, and the CMV IgG test should be repeated within 1 to 3 weeks.
- h) Review level of IgM reactivity and interpret results according to local assay experience.
- i) Recent infection includes primary infection or reinfection.
- j) Consider IgG avidity testing on the existing serum sample, especially where timing of primary infection is important eg pregnancy (refer to the algorithm for pregnant women).
- k) Where available, consider testing an earlier sample for IgG and IgM to differentiate between primary and secondary infection.

8. Diagnosing CMV infection in pregnant women



Please note: Equivocal results are not included in the above algorithm

Footnotes relating to pregnant women flowchart

- a) CMV infection should be suspected in symptomatic pregnant women presenting with clinical mononucleosis, fever, hepatitis or myalgia of unknown origin. If the woman is asymptomatic but concerns arise due to the foetus, refer to the congenital infection algorithm.
- b) The presence of CMV IgM may indicate one of the following:
 - primary infection
 - re-infection
 - reactivation
 - false-positive test result

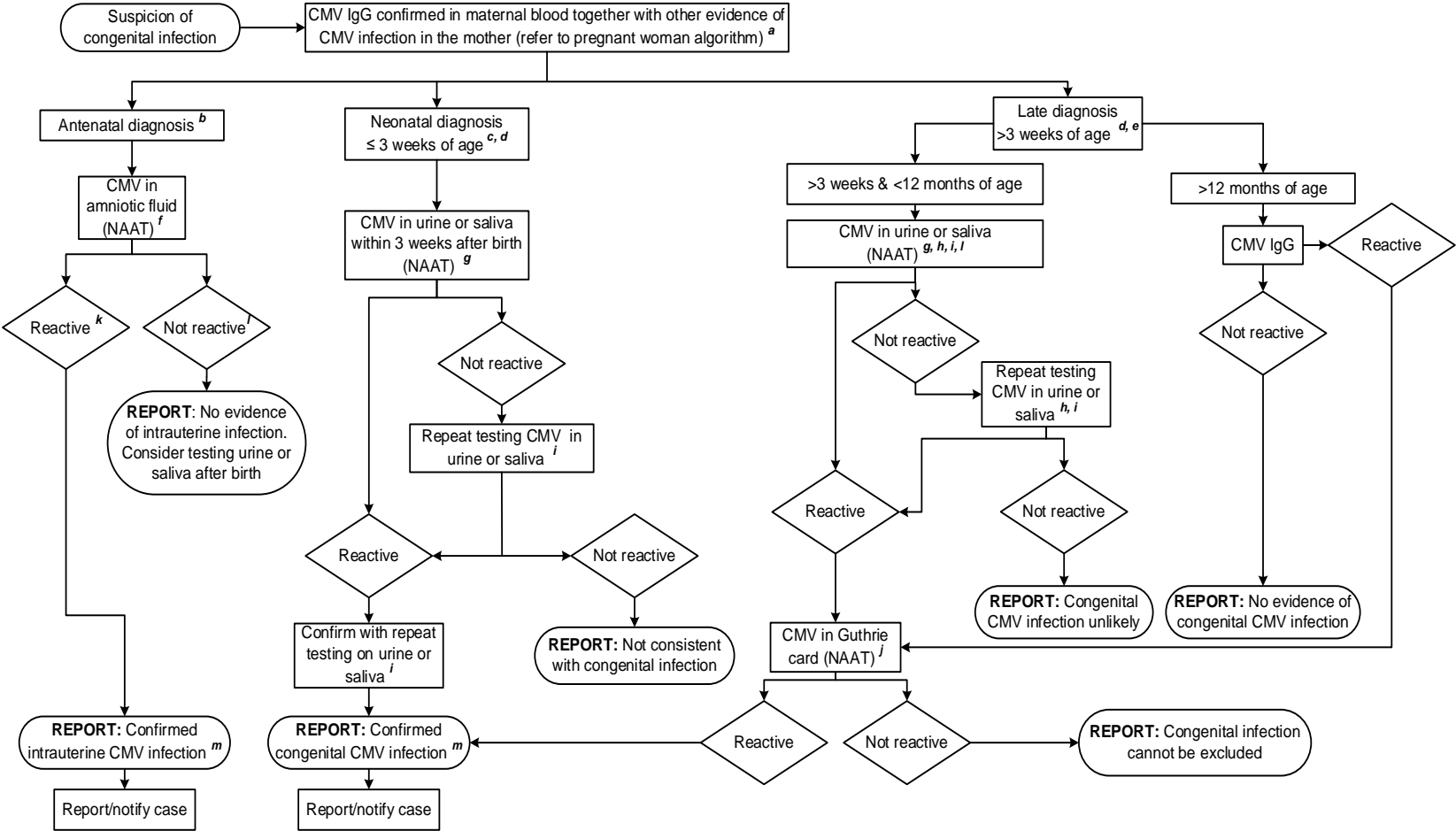
Therefore, the presence of CMV IgM cannot be used by itself to diagnose primary CMV infection.

- c) Consider excluding false positive CMV IgM due to concurrent EBV acute infection by testing for heterophile antibody or EBV VCA-IgM [V 26 – Epstein-Barr virus serology](#).
- d) Laboratories referring the sample for avidity testing may issue an interim report: 'Suggestive of recent CMV infection. CMV IgG avidity result will follow. Please send another sample in 1 to 3 weeks' time.'
- e) The presence of high-avidity CMV IgG antibodies before 16 weeks of gestation excludes primary infection in pregnancy; however, nonprimary infection is still a possibility⁸. Indications for prenatal testing in nonprimary infections are less clear, and decisions should be made on a case-by-case basis when sonographic findings are suggestive of intrauterine infection^{8,9}. Seek alternative causes which present with similar illness in pregnancy.
- f) Consider NAAT on blood or urine sample. A positive CMV NAAT indicates primary CMV infection. If the CMV NAAT is negative, primary CMV infection is unlikely but cannot be excluded, and the CMV IgG test should be repeated within 1 to 3 weeks.
- g) Low avidity index is associated with high risk of intrauterine infection, whilst high avidity index detected in the first trimester of gestation is associated with low risk of vertical transmission¹¹⁻¹⁴. If an earlier sample is available, test both samples (or the earlier sample only) for avidity. Increasing avidity results over time confirms acute infection around the time of the earlier sample; persistent low avidity results beyond 18 weeks (from the earliest sample tested) may be due to lack of specificity, and may require further confirmation with a different avidity assay¹⁵. CMV IgG avidity results cannot exclude or confirm a reactivation or a re-infection.
- h) Consider avidity testing on the earlier sample. Avidity is only recommended to be interpreted in the context of an IgM positive result; however, some experts may consider interpretation is possible where IgM is negative.
- i) Risk of intrauterine infection is about 32%¹⁶. Intrauterine infection can be confirmed prenatally by detecting CMV in amniotic fluid. For optimal results

amniocentesis must be performed at least 6 weeks after presumed time of maternal infection and after 21 weeks of gestation^{10,11,13}.

- j) Investigate CMV infection in the new born baby: perform CMV NAAT in urine or saliva within the first 3 weeks of life. Alternatively, a positive blood CMV IgM can confirm the infection however the test lacks sensitivity and NAAT should be performed in case of negative result¹⁷⁻¹⁹. Refer to the algorithm for congenital infection^{3,8}.
- k) High avidity: no evidence of recent infection in the past 3 months^{9,10,14,20,21}.
- l) Low avidity indicates recent infection of usually less than 3 months prior to sample date²¹.
- m) Interpretation of intermediate avidity is difficult and recent/relatively recent primary infection cannot be excluded, particularly in samples taken after the 1st trimester^{14,21}.

9. Diagnosing intrauterine and congenital infection



Please note: Equivocal results are not included in the above algorithm.

Footnotes relating to congenital infection flowchart

- a) Congenital CMV can be excluded if mother is CMV IgG negative. Congenital CMV infection can result from both primary and recurrent maternal infection. The risk of transmission is greater after primary infection (30-40%) than after recurrent infection (~1%)^{10,16}. Not all congenitally infected babies are symptomatic at birth or develop sequelae.
- b) Antenatal diagnosis can be requested when there is suspicion of recent maternal infection or when there are ultrasound features such as intrauterine growth retardation, ventricular dilatation, intracranial calcification, microcephaly, ascites, hepatomegaly, abdominal calcification, thickened placenta, echogenic bowel.
- c) Neonatal diagnosis is requested when clinical signs suggestive of intrauterine infection (such as sensorineural hearing loss, intrauterine growth retardation, microcephaly, hepatosplenomegaly, petechiae, jaundice, intracranial calcification, brain white matter disease, polymicrogyria, retinitis/retinal scarring) are present at, or prior to, birth. It is also indicated for those infants born to a mother with documented recent infection, inconclusive results or with typical fetal ultrasound abnormalities or when amniocentesis for suspected intrauterine CMV infection was declined.
- d) Detection of CMV by NAAT (in urine or saliva) within the first 3 weeks of life is considered the gold standard method for the diagnosis of congenital CMV infection. Note there is a risk of false positive detection of CMV by NAAT in the saliva of recently breast-fed infants; saliva swabs should be taken on two separate occasions, prior to a breast feed²².
- e) Late diagnosis is requested for infants and young children, usually asymptomatic at birth, who develop sequelae such as sensorineural hearing loss, mental retardation, delay of psychomotor development and visual impairment typically within a 5 to 7-year period but later in some cases²³.
- f) For optimal sensitivity, amniocentesis must be performed at a time that is at least 6 weeks after presumed time of maternal infection and after 21 weeks of gestation; however, there may be clinical reasons to conduct this earlier^{10,11,13,17-19}.
- g) Both urine and saliva of congenitally infected term neonates contain high levels of CMV and have equivalent sensitivity for diagnosis²⁴. Real time PCR performed on dried saliva specimens was shown to be a highly sensitive and practical tool to diagnose congenital CMV^{25,26}. Reactive CMV NAAT on samples taken after 3 weeks of age, cannot distinguish congenital from postnatal or perinatal infection (refer to the 'late diagnosis' branch of the algorithm).
- h) Viral excretion in urine and saliva lasts for several years with a steep decline after 5 years^{27,28}. Although there is some evidence to suggest that repeat testing should be carried out twice due to intermittent shedding, local policy may dictate that repeat testing once is acceptable²⁷.
- i) If the result is discordant, investigate possible laboratory error and consider request of a third sample to confirm. Note there is a risk of false positive detection of CMV by NAAT in the saliva of recently breast-fed infants.

- j) Sensitivity of NAAT performed from a dried blood spot (Guthrie card) has been reported to be between 70-80%^{29,30}.
- k) Investigate CMV infection in the neonate if pregnancy continues.
- l) Negative predictive values of between 92.7% and 95.7% are reported for CMV NAAT assays of amniotic fluid³¹.
- m) All babies and children with a confirmed congenital CMV infection must be followed up with regular paediatric examination and audiology assessment³². Symptomatic neonates with CNS disease and/or focal organ disease may receive valganciclovir³³. Treatment of neonates with neurological symptoms can prevent developmental delays and hearing deterioration^{34,35}.

10. Interpreting and reporting laboratory results

There are other combinations of results which have not been tabled but which do occur and require individual comments based upon profile and clinical setting, along with a further sample.

10.1 Immunocompetent host

	CMV IgM	CMV IgG	Interpretative Comment	Notes
1	Not reactive	Not reactive	No serological evidence of CMV infection at any time	
2	Not reactive	Reactive	Consistent with past CMV infection	
3	Reactive	Not reactive	CMV IgM detected, CMV IgG not detected. Repeat CMV IgG testing in 1 to 3 weeks to further investigate possible CMV infection	If IgG is reactive on the subsequent test this is evidence of primary infection. If IgG is not reactive on the subsequent test consider excluding false positive CMV IgM due to acute EBV infection by testing for heterophile antibody or EBV VCA-IgM
4	Reactive	Reactive	Suggestive of recent CMV infection	IgG avidity testing can be used to further investigate

10.2 Pregnant women, earlier antenatal serum sample not available

	CMV IgM	CMV IgG	CMV IgG avidity	Interpretative Comment	Notes
1	Not reactive	N/A	N/A	CMV IgM not detected. No evidence of recent primary CMV infection	
2	Reactive	Not reactive	N/A	CMV IgM detected. CMV IgG not detected. Repeat CMV IgG testing in 1 to 3 weeks to further investigate possible CMV infection	
3	Reactive	Reactive	High	No evidence of recent primary CMV infection in the past three months. Reactivation or reinfection cannot be excluded	
4	Reactive	Reactive	Intermediate	Recent primary CMV infection cannot be excluded. Repeat avidity in three weeks	A rise in avidity index on the repeat test is consistent with primary CMV infection. Recent primary CMV infection cannot be excluded if the repeat test is stable.
5	Reactive	Reactive	Low	Consistent with recent primary CMV infection within the preceding 3 months	

10.3 Pregnant women, earlier antenatal serum sample available

	CMV IgM	CMV IgG (current sample)	Earlier CMV IgG	Earlier CMV IgM	Interpretative Comment	Notes
1	Reactive	Reactive	Reactive	Reactive	IgG avidity test results: High: No evidence of recent primary CMV infection in the past 3 months Low: Consistent with recent primary CMV infection Intermediate: Recent CMV infection cannot be excluded. repeat avidity test: - Rise: interpret as low - Stable: Recent CMV infection cannot be excluded	IgG avidity test should be performed. Refer to serum sample not available reporting table
2	Reactive	Reactive	Reactive	Not reactive	No evidence of recent primary CMV infection. Reactivation or reinfection cannot be excluded	
3	Reactive	Reactive	Not reactive	Reactive	Evidence of recent primary CMV infection before the time of the earlier sample	
4	Reactive	Reactive	Not reactive	Not reactive	Consistent with recent primary CMV infection	

10.4 Intrauterine infection – antenatal diagnosis

The following reporting table is in the context of confirmed CMV IgG in maternal blood together with other evidence of CMV infection in the mother (refer to pregnant woman algorithm)

	CMV in amniotic fluid (NAAT)	Interpretive comment
1	Detected	Confirmed intrauterine CMV infection
2	Not detected	No evidence of intrauterine infection

10.5 Congenital infection – neonatal diagnosis (within 3 weeks of birth)

	CMV in urine or saliva within 3 weeks of birth	Interpretive comment
1	Detected	Confirmed congenital CMV infection
2	Not detected	Not consistent with congenital infection

10.6 Congenital infection – late diagnosis (between 3 weeks and 12 months of age)

	CMV in urine or saliva between 3 weeks and 12 months of age	CMV in Guthrie card	Interpretive comment
1	Detected	Detected	Confirmed congenital CMV infection
2	Detected	Not detected	Congenital infection cannot be excluded
3	Not detected	N/A	Congenital CMV infection unlikely

10.7 Congenital infection – late diagnosis (over 12 months of age)

	CMV IgG after 12 months of age	CMV in Guthrie card	Interpretive comment
1	Reactive	Detected	Confirmed congenital CMV infection
2	Reactive	Not detected	Congenital infection cannot be excluded
3	Not reactive	N/A	Congenital CMV infection unlikely

11. References

1. SaBTO Advisory Committee on the Safety of Blood Tissues and Organs. Guidance on the microbiological safety of human organs, tissues and cells used in transplantation. 1-60. 2017. **A, VI**
2. SaBTO Advisory Committee on the Safety of Blood Tissues and Organs. Cytomegalovirus tested blood components: Position Statement. 1-15. 2012. **A, VI**
3. Ross SA, Novak Z, Pati S, Boppana SB. Overview of the diagnosis of cytomegalovirus infection. *InfectDisordDrug Targets* 2011;11:466-74. **B, IV**
4. Baron EJ, Miller JM, Weinstein MP, Richter SS, Gilligan PH, Thomson RB, Jr. et al. A Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases: 2013 Recommendations by the Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM). *ClinInfectDis* 2013;57:e22-e121. **B, V**
5. The Royal College of Pathologists. The retention and storage of pathological records and specimens (5th edition). 1-59. 2015. **A, V**
6. National Institute for Healthcare and Clinical Excellence. Donor milk banks: service operation 2010. **A, VI**
7. Huygens A, Dauby N, Vermijlen D, Marchant A. Immunity to cytomegalovirus in early life. *Front Immunol* 2014;5:552. **A, IV**
8. Manicklal S, Emery VC, Lazzarotto T, Boppana SB, Gupta RK. The "silent" global burden of congenital cytomegalovirus. *ClinMicrobiolRev* 2013;26:86-102. **A, IV**
9. Lim Y, Lyall H. Congenital cytomegalovirus - who, when, what-with and why to treat? *J Infect* 2017;74 Suppl 1:S89-S94. **B, IV**
10. Tanimura K, Yamada H. Maternal and neonatal screening methods for congenital cytomegalovirus infection. *J Obstet Gynaecol Res* 2018. **B, IV**
11. Davis NL, King CC, Kourtis AP. Cytomegalovirus infection in pregnancy. *Birth Defects Res* 2017;109:336-46. **B, IV**
12. Yinon Y, Farine D, Yudin MH. Screening, diagnosis, and management of cytomegalovirus infection in pregnancy. *Obstet Gynecol Surv* 2010;65:736-43. **B, IV**
13. Yinon Y, Farine D, Yudin MH. No. 240-Cytomegalovirus Infection in Pregnancy. *J Obstet Gynaecol Can* 2018;40:e134-e41. **B, IV**
14. Kaneko M, Ohhashi M, Minematsu T, Muraoka J, Kusumoto K, Sameshima H. Maternal immunoglobulin G avidity as a diagnostic tool to identify pregnant women at risk of congenital cytomegalovirus infection. *J Infect Chemother* 2017;23:173-6. **B, IV**
15. Lumley S, Patel M, Griffiths PD. The combination of specific IgM antibodies and IgG antibodies of low avidity does not always indicate primary infection with cytomegalovirus. *JMed Virol* 2014;86:834-7. **B, II**
16. Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. *Rev Med Virol* 2007;17:253-76. **A, I**

17. Fabbri E, Revello MG, Furione M, Zavattoni M, Lilleri D, Tassis B et al. Prognostic markers of symptomatic congenital human cytomegalovirus infection in fetal blood. *BJOG* 2011;118:448-56. **A, II**
18. Kouri V, Correa CB, Verdasquera D, Martinez PA, Alvarez A, Aleman Y et al. Diagnosis and screening for cytomegalovirus infection in pregnant women in Cuba as prognostic markers of congenital infection in newborns: 2007-2008. *Pediatr Infect Dis J* 2010;29:1105-10. **B, II**
19. Romanelli RM, Magny JF, Jacquemard F. Prognostic markers of symptomatic congenital cytomegalovirus infection. *Braz J Infect Dis* 2008;12:38-43. **B, II**
20. Lagrou K, Bodeus M, Van Ranst M, Goubau P. Evaluation of the new Architect cytomegalovirus immunoglobulin M (IgM), IgG, and IgG avidity assays. *J Clin Microbiol* 2009;47:1695-9. **A, II**
21. Vauloup-Fellous C, Berth M, Heskia F, Dugua JM, Grangeot-Keros L. Re-evaluation of the VIDAS (®) cytomegalovirus (CMV) IgG avidity assay: determination of new cut-off values based on the study of kinetics of CMV-IgG maturation. *J Clin Virol* 2013;56:118-23. **B, II**
22. BAAP/BAPA. Guidelines for investigating infants with congenital hearing loss identified through the newborn hearing screening. *Best Practice Guidelines*, 2008. **A, V**
23. NHS Screening Programmes. *NHS Newborn Hearing Screening Programme 2009*. **A, VI**
24. Cardoso ES, Jesus BL, Gomes LG, Sousa SM, Gadelha SR, Marin LJ. The use of saliva as a practical and feasible alternative to urine in large-scale screening for congenital cytomegalovirus infection increases inclusion and detection rates. *Rev Soc Bras Med Trop* 2015;48:206-7. **B, II**
25. Boppana SB, Ross SA, Shimamura M, Palmer AL, Ahmed A, Michaels MG et al. Saliva polymerase-chain-reaction assay for cytomegalovirus screening in newborns. *N Engl J Med* 2011;364:2111-8. **A, II**
26. Pinninti SG, Ross SA, Shimamura M, Novak Z, Palmer AL, Ahmed A et al. Comparison of saliva PCR assay versus rapid culture for detection of congenital cytomegalovirus infection. *Pediatr Infect Dis J* 2015;34:536-7. **B, III**
27. Rosenthal LS, Fowler KB, Boppana SB, Britt WJ, Pass RF, Schmid SD et al. Cytomegalovirus shedding and delayed sensorineural hearing loss: results from longitudinal follow-up of children with congenital infection. *Pediatr Infect Dis J* 2009;28:515-20. **A, II**
28. Noyola DE, Demmler GJ, Williamson WD, Griesser C, Sellers S, Llorente A et al. Cytomegalovirus urinary excretion and long term outcome in children with congenital cytomegalovirus infection. *Congenital CMV Longitudinal Study Group. Pediatr Infect Dis J* 2000;19:505-10. **B, II**
29. Atkinson C, Emery VC, Griffiths PD. Development of a novel single tube nested PCR for enhanced detection of cytomegalovirus DNA from dried blood spots. *J Virol Methods* 2014;196:40-4. **B, III**
30. Wang L, Xu X, Zhang H, Qian J, Zhu J. Dried blood spots PCR assays to screen congenital cytomegalovirus infection: a meta-analysis. *Virol J* 2015;12:60. **B, I**
31. Enders G, Bader U, Lindemann L, Schalasta G, Daiminger A. Prenatal diagnosis of congenital cytomegalovirus infection in 189 pregnancies with known outcome. *Prenat Diagn* 2001;21:362-77. **A, II**

32. Kadambari S, Williams EJ, Luck S, Griffiths PD, Sharland M. Evidence based management guidelines for the detection and treatment of congenital CMV. *Early HumDev* 2011;87:723-8. **B, III**
33. Kimberlin DW, Jester PM, Sanchez PJ, Ahmed A, Arav-Boger R, Michaels MG et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. *N Engl J Med* 2015;372:933-43. **A, I**
34. Kimberlin DW, Lin CY, Sanchez PJ, Demmler GJ, Dankner W, Shelton M et al. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. *JPediatr* 2003;143:16-25. **A, I**
35. Oliver SE, Cloud GA, Sanchez PJ, Demmler GJ, Dankner W, Shelton M et al. Neurodevelopmental outcomes following ganciclovir therapy in symptomatic congenital cytomegalovirus infections involving the central nervous system. *J Clin Virol* 2009;46 Suppl 4:S22-S6. **B, II**