UK National Screening Committee

Cytomegalovirus: an evidence map of antenatal screening

An outline of the volume and type of evidence related to antenatal screening for cytomegalovirus for the UK National Screening Committee

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Contents

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Abbreviations

cCMV	Congenital cytomegalovirus
CI	Confidence interval
CMV	Cytomegalovirus
DBS	Dried Blood Spot
ECCI	European Congenital Cytomegalovirus Initiative
ELISA	Enzyme-linked immunosorbent assay
HIG	Hyperimmune globulin
IgG,IgM	Immunoglobulin G/M
IU	International Units
MRI	Magnetic resonance imaging
NPV	Negative predictive value
NSC	National Screening Committee
PCR	Polymerase chain reaction
PPV	Positive predictive value
RCT	Randomised controlled trial
US	Ultrasound

Summary

This document discusses the findings of the evidence map on antenatal screening for cytomegalovirus (CMV).

Evidence maps are a way of scanning published literature to look at the volume and type of evidence in relation to a specific topic. They inform whether the evidence is sufficient to commission a more sustained analysis on the topic under consideration.

Based on the findings of this evidence map, there is sufficient published literature, including primary research and systematic reviews, to justify commissioning further work on antenatal screening for CMV in line with the UK NSC evidence review process.

With regard to screening for CMV infection, there is a good body of evidence to suggest that first trimester immunoglobulin testing using IgG and IgG avidity testing in combination with IgM testing could have good accuracy for detecting primary maternal CMV infection and so help to identify subsequent cCMV infection in the newborn. It should be noted that IgG avidity and IgM testing will not detect non-primary CMV infection. Evidence on other possible tests for CMV infection is limited.

There is a good body of evidence to show that treatment with oral valaciclovir substantially reduces the rate of transmission of CMV to the fetus. However, there is currently only 1 published randomised controlled trial on this topic. There is also a good body of evidence on hyperimmunoglobulin (HIG) treatment, but studies varied in their conclusions as to whether it was effective at reducing the rate of CMV transmission.

There is also a broad range of evidence on tests of fetuses with cCMV infection to detect long term harms after birth. There appears to be good evidence that fetal ultrasound, possibly in combination with fetal magnetic resonance imaging (MRI), could detect abnormalities indicative of long-term harm, and that a negative test result can “rule out” long-term harms. There is some, more limited, evidence that CMV viral load in the amniotic fluid could predict long-term harms.

Given the substantial extent of existing evidence of antenatal screening for CMV it is recommended that a full systematic review should be undertaken in this area. It may also be

desirable to combine any future review with new primary research to broaden the overall evidence base.

Introduction and approach

Background and objectives

The UK National Screening Committee (UK NSC) external reviews (also known as evidence summaries or evidence reviews) are developed in keeping with the UK NSC evidence review process to ensure that each topic is addressed in the most appropriate and proportionate manner. Further information on the evidence review process can be accessed online.

Antenatal screening for cytomegalovirus is a topic currently due for an update external review.

The condition

Cytomegalovirus (CMV) is a common virus which can cause mild flu-like symptoms or be asymptomatic in most immunocompetent adults. Around half of the UK population is infected by CMV at some point in their life.[1] However, if the virus is passed on to a fetus during pregnancy (through the placenta), the baby may be born with CMV infection, called congenital CMV (cCMV). In Europe, cCMV is the lead infectious cause of neurological disabilities in children.[2, 3] It is estimated that around 3-5 in 1000 babies are born with cCMV,[1] which equates to around 2,400 babies out of around 600,000 live births every year in the UK.[4] However, a very recent study examining the use of dried blood spots (DBS) to determine the incidence of cCMV in the UK, in London, found a rate of 0.66%, equating to around 3,960 infants with cCMV each year. [5] While the majority have no signs of illness at birth, around 10% of infected newborns will have clinically apparent signs of cCMV at birth, with symptoms such as jaundice, petechiae, hepatosplenomegaly, thrombocytopenia, chorioretinitis, intrauterine growth restriction, microcephaly, deafness, seizures and brain imaging abnormalities. Around half of these babies will experience long-term sequelae, primarily hearing and neurodevelopmental impairment. For those infected newborns who are asymptomatic at birth, outcomes are less clear, although around 10% are likely to develop hearing impairment during early childhood,[6] and a proportion may go on to have learning concentration and communication difficulties. Overall, each year around 202 to 216 babies born in the UK with cCMV will experience long-term problems.[7]

Primary maternal CMV infection occurs in women who acquire CMV for the first time in the periconceptual period or during pregnancy. Non-primary infection occurs in women who are already seropositive for Immunoglobulin G (IgG) before pregnancy and either have reactivation of latent virus during pregnancy or are infected by a different strain of the virus. CMV is transmitted through bodily fluids, most commonly through the saliva or urine of young children. Pregnant women in contact with young children are at heightened risk of having pregnancies complicated by cCMV. There is some evidence that implementation of hygiene-based interventions during pregnancy has the potential to prevent CMV transmission.[8, 9] The risk of fetal transmission is 30-35% with primary maternal infection, compared to around 3% or less with re-infection/reactivation. Infection occurring earlier in gestation, particularly in the first trimester, is associated with poorer fetal outcomes.[10]

Screening and treatment

An International Congenital Cytomegalovirus Recommendations Group was convened in 2015 and recommended against universal CMV screening in pregnant women. However, if CMV is suspected, either because a pregnant women develops an illness with influenza-like symptoms not attributable to another specific infection, or when imaging findings are suggestive of fetal CMV infection, then testing should be offered.[11] Routine antiviral therapy to prevent cCMV infection during pregnancy was not recommended, on the basis of insufficient evidence on safety and effectiveness.[11] However, new evidence on the use of high-dose valaciclovir to prevent vertical transmission in pregnant women with evidence of a recent primary infection in the periconception period / first trimester has recently become available.[12]

The updated consensus recommendations, from the European Congenital Cytomegalovirus Initiative (ECCI), recommend that maternal CMV serology should be performed as early as possible in the first trimester of pregnancy, and IgG seronegative women should be retested every 4 weeks until 14-16 weeks.[13] In cases of maternal primary infection in the periconceptional period or in the first trimester, oral valaciclovir (8 g/day) is recommended as early as possible after the diagnosis and until CMV polymerase chain reaction (PCR) in amniocentesis for the diagnosis of fetal CMV infection. Hyperimmune globulin (100 IU/kg every 4 weeks) is not recommended in pregnant women with primary CMV infection.[13] A major possible limitation of screening women for CMV in early pregnancy is that screening

can only identify primary infection, which, although it is associated with poorer fetal outcomes due to a higher transmission rate, may reflect less than half of CMV infections during pregnancy in European settings.[5]

The most reliable method of prenatal diagnosis of cCMV is amniocentesis, although this is an invasive test which is associated with a risk (although a very low risk) of spontaneous miscarriage.[11] Maternal antibody blood testing, such as enzyme-linked immunosorbent assay (ELISA) is a relatively non-invasive method for detecting primary maternal CMV infection.[14] Fetal ultrasound and magnetic resonance imaging (MRI) assessment in the third trimester are recommended in infected fetuses, to provide prognostic information.[13]

Current policy context and previous review on antenatal screening for cytomegalovirus

The UK NSC does not currently recommend population screening for CMV in pregnant women.[7] The 2012 UK NSC evidence review noted complexities around diagnosis of maternal and fetal CMV infection and a lack of available interventions to prevent transmission or development of cCMV disease. The 2017 review identified no significant new evidence to suggest that the UK NSC should reconsider screening in the antenatal period, therefore, the evidence review focussed on the postnatal period.[15]

Aims of the evidence map

Evidence maps are rapid evidence products which aim to gauge the volume and type of evidence relating to a specific topic.

This evidence map has been developed to assess whether a more sustained review on antenatal screening for CMV should be commissioned and to evaluate the volume and type of evidence on key issues related to screening pregnant women for CMV.

The evidence map aims to address the following questions:

1. What evidence exists on non-invasive antenatal screening tests to detect maternal C MV infection?

2. What evidence exists on the value of antenatal treatment to prevent cCMV infection, or cCMV-related morbidity and mortality?

3. What evidence exists on fetal tests to determine the severity of cCMV?

The findings of this evidence map will provide the basis for discussion to support decision making on whether there is sufficient evidence to justify commissioning a more sustained review of the evidence on antenatal screening for CMV.

The aim of this document is to present the information necessary for the UK NSC to decide this.

Search methods and results

The searches were conducted in January 2025. The following databases were searched: MEDLINE, Embase, Maternity and Infant Care Database, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Science Citation Index, Latin American and Caribbean Health Sciences Literature (LILACS), KSR Evidence and the Database of Abstract of Reviews of Effects (DARE). Unpublished, ongoing or grey literature was identified through searching the Conference Proceedings Citation index – Science, HTA database, International HTA database (INAHTA), PROSPERO, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, EU Clinical Trials Register and the websites of international HTA organisations. The search was limited to records published from 2009 onwards in order to update previous reviews undertaken for the UK NSC. No further limits were applied.

References retrieved for the newborn screening review (also conducted by the York group) that were flagged as potentially relevant for the antenatal map were also added to the search results. All search results were imported into EndNote 21 reference management software and deduplicated.

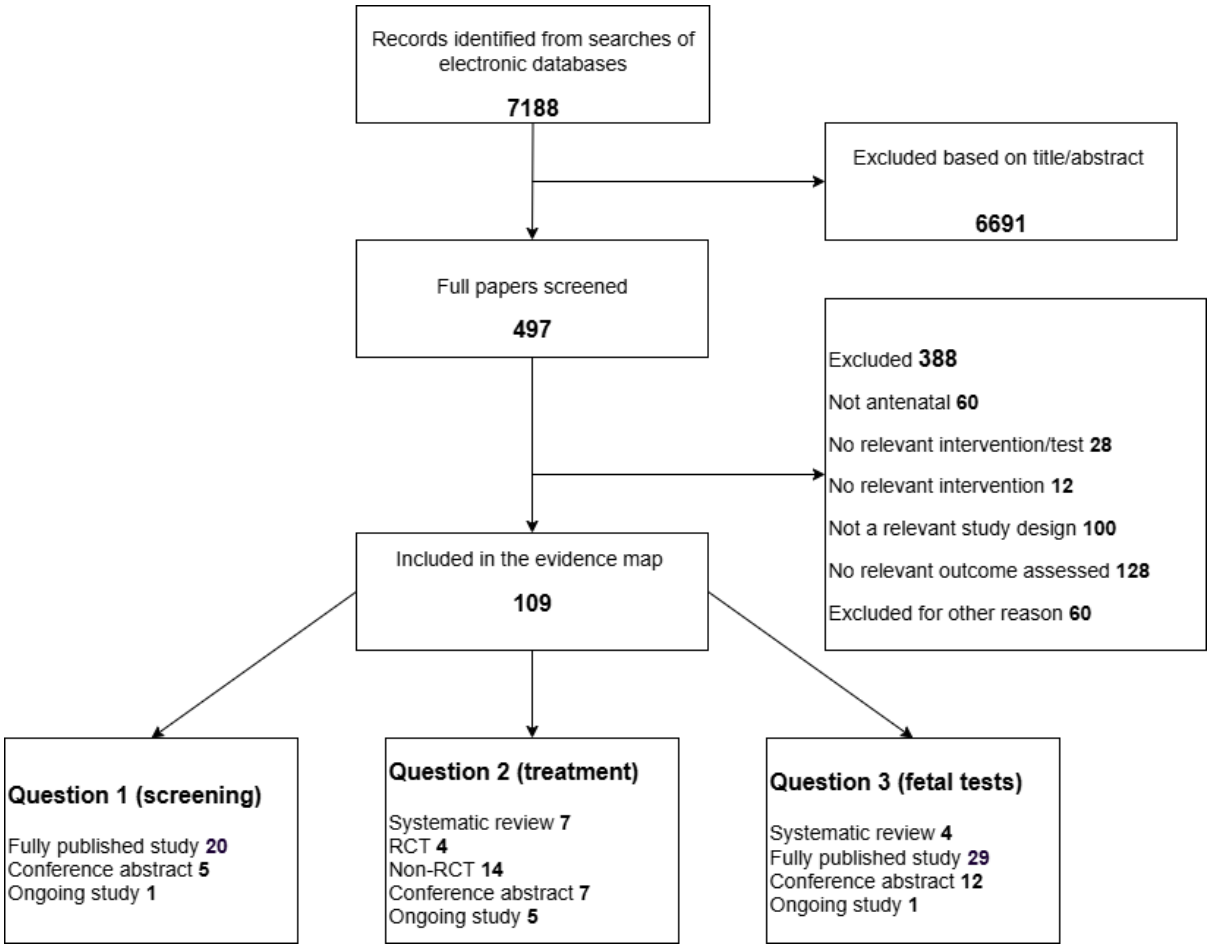
Deduplicated references were uploaded into EPPI-Reviewer for screening. The machine learning and text mining tool in EPPI-Reviewer (priority screening) was used to prioritise titles and abstracts for screening.[16] Just over 10% of prioritised records were independently screened by two reviewers to ensure eligibility criteria were applied consistently; disagreements between reviewers were resolved by discussion or, if necessary, a third independent reviewer. The remaining titles and abstracts were assessed by one reviewer. The full texts of potentially relevant studies were assessed independently by two reviewers, using the same process for resolution of disagreements as outlined above.

Supplementary searching included manual searches of the abstracts from the European Congenital Cytomegalovirus Initiative (ECCI) congresses 2022 and 2024, consulting with advisory group members for any additional studies that they were aware of, and checking the reference lists of all recent relevant systematic reviews.

The detailed search strategies, as well as the inclusion criteria are available in Appendix 1. A formal quality appraisal of the evidence was not required, given the remit of the evidence map.

The search returned 13849 results. After deduplication, 7188 unique references were reviewed for relevance to the questions and 109 references were included in the final evidence map. 26 studies were relevant to question 1, 37 studies were relevant to question 2 and 46 studies were relevant to question 3. A flow diagram summarising the number of studies included and excluded is presented in Figure 1.

Figure 1 Flow diagram of the study selection process



Summary of findings

Question 1: What evidence exists on non-invasive antenatal screening tests to detect maternal CMV infection?

A total of 26 of the included records were judged relevant to this question, consisting of 20 full study publications, 5 conference abstracts and 1 trial registration. Included studies were further categorised as: diagnostic studies of maternal CMV infection tests (7 studies)[17-23]; diagnostic accuracy studies of fetal or neonatal cCMV infection from maternal testing (6 studies)[24-29]; studies of assay accuracy (6 studies)[30-35]; surveys (1 study)[36]; and abstracts or trial records (6 records).[37-42] No systematic reviews, or studies conducted within the UK were identified.

Diagnostic accuracy studies of maternal CMV infection tests

Seven included studies reported the diagnostic accuracy of tests to detect maternal CMV infection and are summarised in Table 1.[17-23] The majority of evidence was retrospective with 5 studies using a retrospective design[18, 20-23], 1 prospective study[19] and 1 case-control study.[17] Population characteristics were generally poorly reported. No studies were conducted within the UK/NHS context. Sample sizes varied from 134 participants to over 30,000.

The screening tests used varied across studies: 3 used IgG and IgM in combination[17, 19, 22], 1 used IgM alone[20],1 used PCR testing[21], 1 used LAMP testing[23] and 1 used cell-free DNA sequencing.[18] Four of the studies used PCR results as the reference standard[17, 18, 22, 23]; and 2 used another CMV test.[20, 21]

Reporting of diagnostic accuracy data was generally poor and limited across the studies. Although no quality assessment was performed for this evidence map, this raises concerns as to the quality of the included studies. Where diagnostic accuracy was reported, the sensitivity to detect maternal CMV infection was high for all tests, and generally above 90%. Specificity data was only reported for 2 studies and was lower for IgG/IgM testing (72.7%)[17] but good for LAMP testing (97.2%).[23] PPV values were only reported in 3 studies.[17, 20, 23] For

both combined IgG/ IgM testing and LAMP the PPV was around 70%, so there will be some women who test positive for CMV who may not actually have the infection.

Most of the studies concluded that testing for CMV was sufficiently accurate to be used in practice, but 1 study[22] suggested that CMV screening should be restricted to women at high risk of transmitting CMV to the fetus.

Table 1 Summary of evidence evaluating the accuracy of maternal CMV tests

Study (Year), design, location	Population characteristics	Sample size (N with CMV)	CMV Index test	Reference standard	Findings
Al-Azam (2021)[17] Case control Iraq	91 pregnant women with previous abortion, controls 43 pregnant women without previous abortion. 15-48 years. All cases referred to hospital for caesarean. Gestational age unclear	134 (84)	IgM and IgG ELISA in serum or blood	RT-PCR	The ELISA sensitivity, specificity, PPV, NPV and diagnostic accuracy in HCMV cases were 95.65%, 72.73%; 90.25%, 86.37%, and 89.35%, respectively. The PCR sensitivity, specificity, PPV, NPV and diagnostic accuracy in HCMV cases were 98.53%, 100%, 100%, 93.84%, and 98.80% respectively. The paper concluded that all pregnant women, especially those with a history of abortion, should be screened for the presence of CMV IgM and IgG infections.
Faas (2024)[18] Retrospective The Netherlands	Pregnant women, gestational age 11-19 weeks	239 (112)	cfDNA sequencing data from database (collected non-invasively)	hCMV-qPCR	Overall true positives:36, false positives:76, true negatives:127, false negatives: 0. The paper concluded that large scale screening for both genetic fetal aberrations and active maternal CMV infections during pregnancy can be combined in one test.
Fourgeaud (2023)[19] Prospective & retrospective France	Pregnant women, gestational age 12-14 weeks	1516 (unclear)	LIAISON® CMV IgG II and LIAISON® CMV IgM II, followed by LIAISON® CMV IgG Avidity II and VIDAS® CMV IgG avidity II testing in cases with positive or equivocal IgM	Unclear: probably amniocentesis and saliva PCR in newborns	Sensitivity: 91.6%; NPV: 99.9%. The study concluded that a screening strategy based on IgM detection is preferable in terms of sensitivity and practicality. The performance of this strategy is highly dependent on the sensitivity of the IgM assay involved
Perillaud-Dubois (2020)[20] Retrospective France	Unclear	Group 1: 6550, Group 2: 30 (Group 1: 1074, Group 2: 11)	IgM in serum	IgG avidity	IgM testing had PPV:16.4 (95% CI 15.5 to 17.3) The study highlighted the importance of including CMV-IgG avidity in the diagnostic algorithm, to confirm or exclude a recent CMV primary infection in case of positive CMV-IgM.

Study (Year), design, location	Population characteristics	Sample size (N with CMV)	CMV Index test	Reference standard	Findings
Perillaud-Dubois (2022)[21] Retrospective France	Pregnant women for whom IgG avidity testing is not available. Gestational age unclear	57 in 72 serum samples (unclear)	CMV PCR in serum or whole blood	Seroconversion and/or avidity monitoring in serum	PCR of serum had sensitivity: 89% (95% CI 64 to 98), PCR of whole blood had sensitivity:100%. The study concluded that serum CMV PCR is reliable in confirming PI in cases when only IgM is detected. It is a valuable tool in introducing valaciclovir treatment as early as possible.
Tugrul (2023)[22] Retrospective Turkiye	Pregnant women, first trimester	31912 samples (28)	IgG, IgM, IgG avidity in serum	PCR,	The study concluded that CMV screening should be reserved to pregnant women with ultrasonographic findings at high risk of congenital CMV infection
Wang (2015)[23] Retrospective China	Unclear	336 (unclear)	LAMP in whole blood	RT-qPCR	Data were reported for multiple thresholds, the worst-case results were: sensitivity: 89.9%, specificity: 97.2%; PPV: 76.9% and NPV: 99.1%. The study concluded that a CMV LAMP method was sensitive, specific and efficient in the detection of HCMV infection.

Diagnostic studies of neonatal cCMV infection from maternal testing

Six included studies performed tests to detect maternal CMV infection, followed up with tests for cCMV infection in newborns.[24-29] As these studies assessed the accuracy of maternal testing to detect newborn cCMV they are not strictly studies of antenatal CMV infection. However, we have included them because of their relevance to antenatal screening for CMV in general. The studies are summarised in Table 2.

All 6 studies were performed in Japan, they all used IgG avidity tests with IgM tests to detect maternal CMV infection, and they all used urine testing to detect cCMV in newborns. We note there is therefore a possibility that the populations overlap across studies, but this is not certain. Four studies were prospective in design[26-29], and 2 retrospective.[24, 25] All studies were large, with sample sizes varying from 1,115 women to 19,435.

Four studies reported full diagnostic accuracy data of CMV testing to detecting newborn cCMV. In 2 studies diagnostic accuracy was high. In 1 study sensitivity and specificity were both over 80%.[24] In the other, sensitivity was 100% but specificity was only 35.6%.[25] This high accuracy related to first-trimester screening for primary CMV infection, with potentially lower accuracy for testing after 14 weeks' gestation.

The other 2 studies reporting diagnostic accuracy data found lower accuracy to detect newborn cCMV: as low as a sensitivity of 22.2% in one study[27] (and 62.5% in the other[28]), for specificities of 95% or more. This lower accuracy was because non-primary infections were included.

All 4 studies that reported diagnostic accuracy data found very low positive predictive values (PPV) ranging from 2.5 to 23.8%. This appears to be because not all women who test positive for CMV will have CMV infection, and among those infected, not all will transmit it to the fetus.

The studies generally concluded that testing for CMV using IgG , IgG avidity and IgM was sufficiently accurate for detecting neonatal cCMV infection. However, this relates only to first-trimester screening for primary maternal CMV infection. Many cCMV cases arising from non-primary infection will be missed. Test combinations and thresholds varied across studies.

One study concluded that the low PPV of maternal CMV testing meant it was not suitable as a test to identify cCMV in newborns.

Table 2 Summary of evidence evaluating accuracy of fetal or neonatal cCMV infection from maternal testing

Study (Year), design, location	Population characteristics	Sample size N with CMV or cCMV	CMV test	Reference standard	Findings
Kaneko (2017)[24] Retrospective Japan	Pregnant women with possible CMV or abnormal US. Gestational age: 7 to 37 weeks	1115 15 newborns with cCMV	IgG avidity, IgM sample < 14 weeks	Urine PCR	Sensitivity: 83.3%; Specificity: 83.8% PPV: 18.5%; NPV: 99.1% Lower accuracy at >15 weeks The study concluded that low IgG AI with IgM positivity at 14 weeks of gestation was a good indicator of congenital infection
Kitamura (2023)[25] Retrospective Japan	Pregnant women, mean age: 30 gestational age: 11 weeks	12832 7 newborns with cCMV	IgG avidity, IgM sample	Urine PCR	Sensitivity: 100%; Specificity: 35.6% PPV: 14.7%; NPV: 100% The study concluded that a revised IgM cutoff improves maternal screening in identifying primary infection and newborn cCMV
Shimada (2021)[26] Prospective Japan	Pregnant women, mean age: 30 gestational age: 11 weeks	19435 162 mothers considered to be CMV infected 23 newborns with cCMV	IgG avidity, IgM sample	Urine PCR or amniocentesis	*No diagnostic accuracy data* CMV IgM antibody has a high false-positive rate for primary infections: a diagnosis of primary CMV infection cannot be based on IgM alone A low IgG avidity result during first trimester suggests a primary infection during early-stage pregnancy.
Tanimura (2017)[27] Prospective Japan	Pregnant women, mean age 33.2 Gestational age: 17.9 weeks (+/- 8.5)	2193 92 mothers with CMV 10 newborns with cCMV	IgG avidity, IgM in serum, urine and uterine secretion samples	Neonatal cCMV	Sensitivity: 22.2%; Specificity: 95% PPV: 2.5%; NPV: 95.3% The study concluded that screening using CMV IgG and avidity index can identify pregnancies with cCMV from primary infection, but overlooks a number of those from nonprimary infection.
Torii (2019)[28] Prospective	Pregnant women. Gestational age: IgG reevaluated 22 weeks	11753 11 newborns with cCMV	IgG, IgM, unclear	Urine PCR	Sensitivity: 62.5%; Specificity: 96.5% PPV: 23.8%; NPV: 99.3%

Study (Year), design, location	Population characteristics	Sample size N with CMV or cCMV	CMV test	Reference standard	Findings
Japan			sample type		The study concluded that seroconversion of CMV IgG and high-titer IgM during early pregnancy are predictors of cCMV. Maternal screening offered insufficient positive predictive value for diagnosing cCMV.
Toriyabe (2017)[29] Prospective Japan	Pregnant women, median age 30 years Gestational age: median 11 weeks (range 4-13)	8469 17 newborns with cCMV	IgG avidity, IgM in serum	Urine PCR or amniocentesis	PPV: 17.1% The study concluded that high titer of CMV IgM during the first trimester in pregnant women with primary infection is a risk factor for congenital infection.

Studies of CMV assay accuracy

Six of the included records were categorised as studies of assay accuracy.[30-35] By this, we mean that studies were focused on establishing that a particular assay or test could detect CMV infection, rather than evaluating its value as a screening test. In particular, none used a formal reference standard for CMV, such as PCR testing. This limits their value and quality when assessing the diagnostic accuracy of the tests.

The studies categorised as studies of assay accuracy and are summarised in Table 3. Of these, 2 were case-control studies, 2 were retrospective designs, 1 was cross-sectional and 1 was prospective. None were conducted in the UK, although a majority were based in Europe. These investigated a variety of CMV assays, often combining them for comparison, and most used serum samples. Sample sizes varied from 60 to 837.

It is difficult to draw conclusions from these studies because of the variety of assays examined, and the inconsistency in reference standards. However, most studies reported high diagnostic accuracy for detecting maternal CMV infection, with sensitivity and specificity typically over 90%.

Table 3 Summary of evidence evaluating the accuracy of CMV assays

Study (year), design, location	Population characteristics	Sample size (N with CMV)	CMV test assay	Test sample/ Type	Reference standard or comparator test(s)	Findings
Carlier (2010) Cross-sectional Belgium	1346 random routine samples from pregnant women, 2a, 382 negative samples, 2b, 43 frozen samples with primary infection, 2c, 66 frozen samples with old infection. Gestational age unclear	837 (unclear)	IgG and IgM (ACCESS and VIDAS assays)	serum	Ref std: IgG VIDAS	IgG had sensitivity 97.2% and specificity 100% IgM sensitivity 100% and specificity 97.4%. The study concluded that the Access CMV IgG and IgM tests are suitable for screening prenatal CMV infections.
Daiminger (2024) Case-control USA	40 samples from pregnant women, 10 samples from non-pregnant patients, 100 samples from 39 pregnant women with CMV. Gestational age stratified, range 0 to >20 weeks.	89 (39 confirmed)	IgM (various assays)	serum	Ref std: from case/control recruitment	In the first 7 weeks (A), the sensitivity was 100% (95% CI: 85.8–100) in six assays (Medac, DiaSorin, Virion, EI-Lysate, EI-p52, and Vircell), whereas Aesku and Roche exhibited a sensitivity of 95.8% (95% CI: 78.9–99.9) and 91.7% (95% CI: 73.0–99.0), respectively. In period B (>7–12 weeks after onset), the EI-p52 and the Vircell showed a noticeable decrease of sensitivity to 76.2% (95% CI: 52.8–91.8) and to 85.7% (95% CI: 63.7–97.0), respectively. The study concluded that differences in the performance of the assays must be taken into account in CMV screening.
Rajasekariah (2013) Retrospective Australia	Pregnant women attending routine antenatal screening. Median age 34 yrs (range 19-48). Gestational age unclear	60 samples (60 with CMV)	Immunoblot	serum	Comparators: IgG avidity, IgM	IgM showed sensitivity 75%, specificity 62.5%, PPV of 81.8%, NPV 52.6%. IgG avidity assay had sensitivity 94.1%, with PPV 100% when identifying low avidity serum samples, and sensitivity100% with PPV 97.1% for high avidity serum samples.

Study (year), design, location	Population characteristics	Sample size (N with CMV)	CMV test assay	Test sample/ Type	Reference standard or comparator test(s)	Findings
						The study concluded that immunoblot is effective in detecting IgG and determining IgG avidity, but it showed no significant benefits as a diagnostic technique for primary CMV infection.
Revello (2012) Prospective Italy, France, Israel, Austria, Germany	Gestational age unclear	Group C: 80 (various samples) (80 with **CMV**)	Elecsys IgM and IgG		Comparators: Architect Anti-CMV-IgG, Anti-CMV-IgM, AxSYM CMV-igG- and IgM, Vidas CMV-IgG and CMV-IgM, ETI-CYTOK-G PLUS and ETI-CYTOk-M reverse PLUS ELISAs, Liaison CMV-IgG and CMV-IgM, Enzygnost A-CMV-IgG and A-CMV-IgM	Results presented for multiple sites. For primary CMV infection Elecsys typically had: sensitivity >91%; specificity >95% The study concluded that the Elecsys CMV IgM and IgG assays compare well with routinely used assays and are suitable for clinical use.
Vauloup-Fellous (2014) Retrospective Italy and France	Pregnant women. Gestational age unclear	61 (9)	Elecsys IgG	serum	Comparators: IgG avidity, IgM, IgG	Sensitivity ranged from 91.3% (95% CI 79.9-98.9%) to 96.1% (95% CI 89.0-99.2%) when excluding 'gray-zone' results. The study concluded that Elecsys CMV IgG avidity is an adequate predictor of the phase of infection.
Yasir (2020) Case-control Iraq	Pregnant women aged 15-45 years. Gestational age unclear	210 (97)	qRT-PCR, IgM, IgG	blood	Unclear	Enzyme immunoassays sensitivity 80.1%, specificity 96%, PPV 96.8% and NPV 76.1%. The study concluded that UL83 gene detection was successful, and more precise than HCMV isolated from serum samples.

Surveys

One further included paper was a survey of pregnant women on their perspectives regarding CMV testing.[36] It was the only study of this type to meet inclusion criteria and was conducted in Canada. It reported that the majority of pregnant participants wanted CMV screening during pregnancy, with significantly associated factors being the perceived risks and severity of cCMV.

Abstracts or trial records

Six relevant abstracts were identified.[37-42] Due to the sparsity of data, they are summarised in Appendix 2 Table 10. No further complete reports of these studies were identified.

Summary

We identified 26 studies, with 19 fully published, relevant to this question. The evidence suggests that combined IgG, IgG avidity and IgM testing could have sufficiently high diagnostic accuracy for detecting CMV infection in pregnant women, and subsequent cCMV infection in babies, to make it useful in antenatal screening. Other tests, such as cell-free DNA testing, may be suitable for use, but have very limited study evidence at present.

Concerns with the evidence are that it relates to primary CMV infection, and non-primary infections are not detected by screening. Many women who test positive using IgG and IgM testing will either not have CMV, or will not transmit it to the fetus, so the PPV of CMV testing may be low, raising issues about how to manage women with a positive CMV test. The quality of the studies is uncertain, and reporting of data was generally limited.

Overall, there appears to be a sufficient volume of evidence in this key area to justify commissioning an evidence summary.

Question 2: What evidence exists on the value of antenatal treatment to prevent cCMV infection, or cCMV-related morbidity and mortality?

The review identified 37 studies relevant to this question. This included 7 systematic reviews,[43-49] 4 randomised controlled trials (RCTs),[12, 50-52] and 14 non-RCTs,[53-66] which were published in full. There were also 6 conference abstracts,[67-72] 5 ongoing trials or reviews[73-77] and 1 review not in English.[78]

Secondary prevention treatment aims to prevent transmission of CMV to the initially uninfected fetus and does not include treatment to prevent maternal infection (primary prevention), nor treatment of an already-infected fetus (tertiary prevention). Three of the included studies evaluated both secondary and tertiary prevention,[57, 63, 79] but only data pertaining to the former have been included.

Systematic reviews

Of the 7 systematic reviews, 2 assessed the efficacy of valaciclovir alone,[43, 44] 2 evaluated hyperimmune globulin (HIG) alone,[45, 48] and 3 evaluated both valaciclovir and HIG.[46, 47, 49] These systematic reviews are summarised in Table 4 and briefly described below, where emphasis has been placed on the included RCTs.

Reviews of Valaciclovir

Chatzakis et al. (2024),[43] included 1 RCT[12] and 1 observational study. D'Antonio et al. (2023)[44] included 2 RCTs and six non-randomised studies. Of the 2 RCTs included by D'Antonio et al. (2023), only 1[12] was relevant to our review question.

On meta-analysis, which included non-randomised studies, both systematic reviews[43, 44] suggested that valaciclovir significantly reduces vertical transmission compared to control, withs odds ratios for vertical transmission of 0.34 (95% CI: 0.18 to 0.61) and 0.37 (95% CI: 0.21 to 0.64) respectively. This suggests that valaciclovir will reduce cCMV transmission rates by around 60%. Both reviews found that valaciclovir had a low rate of serious adverse events, of 2.1% and 3.2% respectively. D'Antonio et al. also found that valaciclovir increased

the likelihood of asymptomatic cCMV infection compared to control (OR: 2.98 (95%CI: 1.18 to 7.55)).

Reviews of HIG

El-Qushayri et al. (2021),[45] included 1 RCT[51] and 8 non-randomised studies. Hamilton et al. (2014)[48] included 6 RCTs (including two cluster RCTs) and 18 non-randomised studies. Of the 6 RCTs included by Hamilton et al. (2014), only 1[51] was relevant to our review question. It should also be noted that although Hamilton et al. evaluated valaciclovir as well as HIG, this was not in the context of secondary prevention.

Both systematic reviews[45, 48] demonstrated that HIG may reduce vertical transmission, and that it may have a reasonable safety profile. However, this was based on both RCT and non-RCT evidence. In the meta-analysis reported by El-Qushayri et al. HIG significantly reduced cCMV rates (OR 0.33 (95% CI 0.16 to 0.68)), but HIG had no significant effect on the prevalence of prematurity, intrauterine growth retardation or termination. Hamilton et al. did not perform any meta-analysis.

Reviews of both Valaciclovir and HIG

Three reviews evaluated both valaciclovir and HIG, as separate treatments, not in combination. Fitzpatrick et al. (2022)[46] included 3 RCTs[12, 50, 51] and 21 non-randomised studies. Perillaud-Dubois et al. (2021)[49] included 3 RCTs[12, 50, 51] and 27 non-randomised studies. Rybak-Krzyszkowska et al. (2023)[47] included 6 RCTs and 15 observational studies. Of the 6 RCTs included by Rybak-Krzyszkowska et al. (2023), only 4[12, 50-52] were relevant to our specific review question.

Both Fitzpatricket al. (2022)[46] and Rybak-Krzyszkowska et al. (2023)[47] suggested a possible benefit from both treatments on vertical transmission. However, this included non-RCT evidence. Fitzpatrick et al. reported a more consistent benefit for valaciclovir, whilst Rybak-Krzyszkowska et al. reported that both treatments showed inconsistent findings. Perillaud-Dubois et al. (2021)[49] did not report relevant results. None of the 3 reviews presented a meta-analysis of the included studies.

Table 4: Summary of the systematic reviews evaluating secondary prevention of valaciclovir and hyperimmune globulin (HIG)

Study (year)	Basic population characteristics	Review size	Drug / treatment given	Control intervention	Outcomes	Findings
Chatzakis, 2024[43]	Pregnant women with primary CMV infection in the periconceptional period or in the first trimester of pregnancy	1 RCT 2 non-RCTs 527 women	Valaciclovir	placebo or no intervention	Rates of cCMV at amniocentesis and birth (vertical transmission); termination; AEs	Valacyclovir reduced the vertical transmission rate of CMV compared to control: [adjusted pooled odds ratio (OR), 0.34 (95% CI: 0.18 to 0.61)]. Valacyclovir reduced the rate of termination of pregnancy compared to control: [pooled OR: 0.23; (95% CI: 0.22 to 0.24)]. The prevalence of severe adverse effects was 2.1%. The review concluded that valacyclovir reduced the vertical transmission rates of cytomegalovirus following primary maternal infection, with a low incidence of side effects.
D'Antonio, 2023[44]	Pregnancy with confirmed maternal CMV infection	2 RCTs 6 non-RCTs 620 women	Valaciclovir	No treatment	cCMV infection (amniocentesis); death; imaging anomalies; AEs	Valacyclovir reduced risk of congenital CMV infection compared to control [pooled OR: 0.37 (95% CI, 0.21–0.64); I^2 =0%; P<0.001]. Valacyclovir increased the likelihood of asymptomatic congenital CMV infection compared to control [pooled OR: 2.98 (95%CI, 1.18–7.55); I^2 =0%; P=0.021]. The prevalence of severe adverse effects was 3.17% (95% CI,1.24–5.93%), with 1.71%(95% CI, 0.41–3.39%) having acute renal failure (which resolved). The review concluded that valacyclovir administration in pregnancies with maternal CMV infection reduces the risk of congenital CMV infection.
El-Qushayri, 2021[45]	Pregnant women with CMV	1 RCT 8 non-RCTs 936 women	Hyperimmune globulin	No HIG	Rates of cCMV at birth (vertical transmission)	HIG significantly reduced cCMV rates [pooled OR (95% CI) = 0.33 (0.16–0.68). HIG had no significant effect on the prevalence of prematurity, intrauterine growth retardation or termination.

Study (year)	Basic population characteristics	Review size	Drug / treatment given	Control intervention	Outcomes	Findings
						The review concluded that there was promising efficacy of hyperimmunoglobulin therapy among pregnant women with primary infection, which fades on including secondary infection.
Hamilton, 2014[48]	Pregnancy with CMV infection	6 RCTs 18 non-RCTs 6,909 women	Hyperimmune globulin	No treatment	Narrative only	*No numerical data or meta-analysis.* The review concluded that HIG may be able to prevent cCMV and associated complications, with a low prevalence of serious adverse events.
Fitzpatrick, 2022[46]	Singleton and multiple pregnancies with evidence of either maternal infection on serology, fetal infection via amniocentesis, or neonatal infection utilizing polymerase chain reaction testing.	3 RCTs 21 non-RCTs N. women not reported	Hyperimmune globulin and valaciclovir (evaluated separately)	No treatment	Rates of cCMV at birth (vertical transmission)	*No meta-analysis performed.* Valaciclovir appeared to show a reduced rate of vertical transmission compared to control. across 3 studies. HIG appeared to have a less consistent benefit in terms of reduced vertical transmission across 5 studies, with one study suggesting a harm. The review concluded that valacyclovir to prevent vertical transmission has the highest quality evidence in favour of use.
Rybak-Krzyszkowska, 2023[47]	pregnant women and fetuses infected with CMV	6 RCTs 15 non-RCTs N. women not reported	Hyperimmune globulin and valaciclovir (evaluated separately)	No treatment	Rates of cCMV at birth (vertical transmission)	Although the systematic review generally suggested that both valacyclovir and HIG are successful for secondary prevention, meta-analysis yielded inconsistent and equivocal findings. *No clear conclusion presented.*
Perillaud-Dubois, 2021[49]	Maternal primary CMV infection	3 RCTs 27 non-RCTs N. women not reported	Hyperimmune globulin and valaciclovir	No treatment	Narrative only	*No results or conclusions relevant to this evidence map were reported.*

Study (year)	Basic population characteristics	Review size	Drug / treatment given	Control intervention	Outcomes	Findings
			(evaluated separately)			

RCTs

One RCT evaluated the efficacy of valaciclovir[12] and 3 evaluated HIG.[50-52] All 4 RCTs were included in the systematic reviews in Table 4, but have been described in detail again in this section because of their importance to the review question. These studies are summarised in Table 5.

Valaciclovir

One RCT[12] compared oral valaciclovir (n=45) at a dose of 8g per day to placebo (n=45) in women with serological evidence of a primary CMV infection. Treatment commenced at <16 weeks and the study evaluated the relative effects of treatment on rates of cCMV at birth (vertical transmission). Valaciclovir had a significant effect on reduction of vertical transmission compared to placebo (OR 0.29, 95% CI 0.09 to 0.90) in periconceptual and first trimester infections combined. A positive amniocentesis for CMV was also significantly less likely in the valaciclovir group, when restricting analysis to those with first trimester infections only.

HIG

Two RCTs[50, 51] compared HIG at monthly infusions of 100mg/kg to placebo in women with serological evidence of a primary CMV infection. Hughes et al [50] randomised 399 women and Revello et al [51] randomized 124 women. Both trials started treatment at <24 weeks or between 5-26 weeks gestation, and evaluated the relative effects of treatment on rates of cC MV at birth (vertical transmission), fetal loss, viral load or adverse events. Neither study demonstrated a significant benefit from HIG.

In a maternal population that was seronegative at study onset, 1 RCT[52] compared a strategy of CMV monitoring during pregnancy with provision of HIG at 200 mg/kg if seroconversion occurred, to routine prenatal care with CMV-serostatus testing at the end of pregnancy. Outcomes reported were rates of cCMV at birth (vertical transmission) and adverse events. No benefits were demonstrated from the CMV monitoring and HIG strategy over routine care.

Table 5: Summary of the RCTs evaluating secondary prevention of valaciclovir and hyperimmune globulin (HIG)

Study (year) and Location	Basic population characteristics	Gestational stage at start of treatment	Drug/treatment given (n)	Control (n)	Dose,frequency, duration	Outcomes	Findings
Shahar-Nissan, 2020[12] Israel	Pregnant women, with serological evidence of a primary CMV infection (acquired periconceptionally or during first trimester)	<16 weeks of gestation; mean around 80 days	Oral Valaciclovir (n=45)	placebo (n=45)	8 g per day, twice daily Until amniocentesis at 21 or 22 gestational weeks	Rates of cCMV at birth (vertical transmission)	For patients with periconceptual infection, or a primary infection during the first trimester, a positive amniocentesis for cytomegalovirus was significantly less likely in the valaciclovir group (OR: 0.29 (95% CI: 0.09-0.90). No clinically significant adverse events occurred. The trial concluded that valaciclovir is effective in reducing the rate of fetal cytomegalovirus infection after maternal primary infection acquired early in pregnancy.
Hughes, 2021[50] USA	pregnant women with primary CMV infection	<24 weeks; mean 16 weeks	Hyperimmune globulin (n=206)	placebo (n=193)	Monthly infusion of 100 mg/kg Until birth; follow up to 3 weeks post-natal	The primary outcome was a composite of cCMV infection or fetal/neonatal death if cCMV not measured; AEs	The primary outcome was more common in the HIG group [RR: 1.17 (95% CI: 0.80 to 1.72),p = 0.42]. Adverse events in the HIG group included a severe allergic reaction, as well as greater prevalence of headaches and shaking chills. The trial concluded that HIG starting before 24 weeks' gestation did not result in a lower incidence of a composite of cCMV infection or perinatal death than placebo.
Revello, 2014[51] Italy	pregnant women with primary CMV infection, within 6 weeks of presumed onset on infection	5-26 weeks gestation	Hyperimmune globulin (n=61)	placebo (n=63)	100 U (2.0 ml) per kg infusion - every 4 weeks Until 36 weeks, or detected CMV in amniotic fluid or spontaneous termination	Rates of cCMV at birth (vertical transmission); levels of virus-specific antibodies, T-cell mediated	The rate of cCMV was 30% in the HIG group and 44% in the placebo group [Risk difference: -14% (95% CI: −3% to 31%; p = 0.13]. The prevalence of obstetrical AEs was higher in the HIG group (13% versus 2%) The trial concluded that HIG did not significantly modify the course of primary CMV infection during pregnancy.

Study (year) and Location	Basic population characteristics	Gestational stage at start of treatment	Drug/treatment given (n)	Control (n)	Dose,frequency, duration	Outcomes	Findings
						response, viral DN; AEs	
Devlieger, 2021[52] Austria, Belgium, Germany, Hungary and Italy	CMV seronegative women <14 weeks GA	In those mothers that developed CMV, seroconversion was at a median 24 weeks, so this is likely to be close to the time that treatment was started.	CMV monitoring, with HIG administered if CMV became positive (n=45)	routine prenatal care with CMV-serostatus testing at end of pregnancy (8 chose off-label HIG) (n=35)	A dose of 200 U/kg, was given twice with an interval of 14 days; an optional third dose was given 28 days later, guided by IgG/IgG avidity levels	Rates of cCMV at birth (vertical transmission); AEs	cCMV rates were 35.6% in the monitoring/HIG group and 46.4% in the control arm (p = 0.46). The trial concluded that serial monitoring of CMV serostatus with HIG treatment was associated with a mild nonsignificant reduction in the vertical CMV transmission rate.

Non-randomised trials

Of the 14 eligible non-randomised trials, 4 evaluated the efficacy of valaciclovir,[53-56] and 10 studies evaluated HIG.[57-66] However, 10 of these 14 non-RCTs [54, 55, 57-61, 63, 65, 66] were also reviewed in the included systematic reviews. Because of the reduced internal validity of non-randomised compared to randomised evidence, these 10 primary studies have therefore not been reported in detail in this section, but are summarised in Appendix 2, Table 11. The four remaining non-randomised trials [53,56, 62, 64] that were not included in the systematic reviews have been discussed in detail below, and are summarised in Table 6.

Valaciclovir

The 2 valaciclovir studies compared 8g/day of valaciclovir to an unmatched historical placebo[53] or a non-treatment control group[56] in women with serological evidence of infection. One of the studies was retrospective, and one was prospective. Treatment onset was around 2 to 4 months gestation, and continued until amniocentesis or for approximately 2 months. Both studies were moderately large, ranging from 178 to 447 pregnant women. The main outcome evaluated was rates of cCMV at birth (vertical transmission). Both studies demonstrated a significant effect of valaciclovir in reducing vertical transmission, which supports the RCT findings from Shahar-Nissan, 2020.[12]

HIG

The 2 HIG studies were carried out in women with serological evidence of infection, and were single arm trials.[62, 64] Both trials were relatively small, with sample sizes of 36 and 107. The doses varied between 200 U/kg and 300 IU/kg every 4 weeks. Treatments started around 13 weeks gestation, continuing for around eight weeks until amniocentesis, although treatment duration was unclear in the Schirwani-Hartl (2023) study. The main outcome assessed was rates of cCMV at birth (vertical transmission).

Results in these studies were difficult to interpret, given the lack of a control group. Rates of vertical transmission in both studies were around 30%, which is similar to control group rates between 32.5% and 39.9% in comparative studies included in the systematic reviews[61, 63, 65](see Appendix 2, Table 11).

Table 6: Summary of the non-randomised studies evaluating secondary prevention of valaciclovir and hyperimmune globulin (HIG)

Study (design & location)	Basic population characteristics	Drug/treatment given (n)	Control (n)	Dose, frequency and duration	Outcomes	Findings
Amir, 2023[53] Retrospective Israel	Pregnant women with primary early CMV infection Gest. Age: 55 days if infected at periconception, and 93 days if infected in first trimester	Valaciclovir (n=178)	Historical placebo: Shahar-Nissan et al. (2020) trial (n=45)	8g/day until amniocentesis	cCMV infection (amniocentesis)	Amniocentesis was positive for CMV in only 7.9% of women treated with valaciclovir compared to 30% in the placebo of the previous study (p<0.001) The study concluded that valaciclovir prevents vertical transmission of CMV after primary maternal infection. Efficacy is improved with earlier treatment.
Zammarchi, 2023[56] Prospective Italy	Maternal primary (up to 24 weeks gestation) CMV infection Gest. Age: About 16 weeks for first trimester infections	Valaciclovir (n=205)	No valaciclovir (n=242)	8g/day, for mean 57.8 days	Rates of cCMV at birth (vertical transmission); Terminations; Symptomatic at birth	Valaciclovir resulted in a lower rate of cCMV at the time of amniocentesis [weighted OR: 0.39 (95% CI: 0.22 to 0.68), p=0.005] The study concluded that valacyclovir significantly reduces the rate of cCMV diagnosis, with a good tolerability profile, and reduces rates of termination of pregnancy and symptomatic cCMV at birth.
Karofylakis, 2024[62] Retrospective (Single arm) Greece	Maternal primary CMV infection Gest. Age: 13 weeks (10-15 weeks) at start of treatment	Hyperimmune globulin (n=107)	No comparator (single arm)	200 U/kg (IV) every 4 weeks (later members of the cohort received it every 2 weeks): until amniocentesis in 21st gestational week	Rates of cCMV at birth (vertical transmission)	Vertical transmission rate was 29.9% The study concluded that HIG was a safe, modestly effective strategy for cCMV prevention after primary infections.

Study (design & location)	Basic population characteristics	Drug/treatment given (n)	Control (n)	Dose, frequency and duration	Outcomes	Findings
Schirwani-Hartl, 2023[64] Retrospective (Single arm) Austria	Maternal primary CMV infection Gest. Age: 13.1 weeks at start of treatment	Hyperimmune globulin (n=36)	No comparator (single arm)	Either 300IE/kg every 4 weeks (n=26) or every 2 weeks (n=10), duration unclear	Rates of cCMV at birth (vertical transmission); death; imaging abnormalities	cCMV rates were 33.3% in those treated with HIG every 4 weeks and 30% in those treated every 2 weeks. There was no significant dose effect (p=0.850). The study concluded that there was no difference in the CMV transmission rates between HIG every 4 weeks versus every 2 weeks. HIG treatment is not effective in preventing maternal–fetal transmission.

Unpublished studies

The 6 unpublished studies comprised two observational comparisons of valaciclovir to a non-treatment group,[67, 68] three single arm evaluations of valaciclovir[69-71] and one case-control study[72] evaluating immunoglobulin to a non-treatment group in seropositive pregnant women. These have been briefly summarised in Appendix 2,

Table 12.

Ongoing reviews

Five possible ongoing systematic reviews of secondary prevention treatments have been identified from the PROSPERO database.[73-77]

Summary

This evidence map identified 37 studies of treatment for maternal CMV infection, including 7 systematic reviews. Valaciclovir and HIG were the only treatments identified.

There appears to be good evidence from across the systematic reviews that valaciclovir will substantially reduce the risk of transmission of CMV to the fetus, by up to 60%, when initiated following periconceptual or first trimester maternal primary CMV infection. However, there was only 1 RCT of valaciclovir, with all other studies being non-randomised.

Evidence on HIG was more mixed, with systematic reviews generally suggesting some benefit of HIG at reducing the rate of CMV transmission. However, the 3 RCTs found no evidence of any benefit of HIG use. This may be a consequence of the RCTs using lower doses and less frequent administration of HIG.

In summary, there appears to be a sufficient volume of evidence in this key area to justify commissioning an evidence summary. However, given the numerous recent reviews identified by this evidence map, it seems unlikely that the conclusions of any future review will differ in its findings, unless new trials, preferably RCTs, are conducted.

Question 3: What evidence exists on fetal tests to determine the severity of cCMV?

The review identified 46 studies relevant to this review question. Four were systematic reviews,[80-83] 29 were primary articles,[84-112] and 13 were unpublished abstracts or protocols in development.[113-125]

Systematic reviews

The four systematic reviews assessed the relationship between fetal testing and later outcomes indicative of cCMV severity in fetuses with confirmed cCMV. Table 7 summarises these studies.

Two reviews (Buca et al. (2021)[80] and Rybak-Krzyszkowska et al. (2023)[83]) evaluated fetal ultrasound, predominantly during the first or second trimester. They included 26 and 48 studies respectively. Subsequent severity outcomes included symptomatic infection at birth and hearing and developmental deficits. Buca et al. concluded that, for fetuses with congenital CMV infection in which no anomalies are detected on prenatal ultrasound, the likelihood of adverse outcomes is lower. In Rybak-Krzyszkowska et al. no direct associations between fetal US and subsequent findings relevant to severity outcomes were discussed, but it did conclude that ultrasonography is a reliable indicator of fetal anomalies due to cCMV.

One review (Kyriakopoulou et al (2020)[82]) evaluated both fetal US and MRI, either at regular intervals or in the second and third trimesters, and included 26 studies. It found that when both prenatal cerebral US and MRI are normal the negative predictive value (NPV) of poor outcome is high.

One review (Gilad et al (2024)[81]) evaluated viral load in the amniotic fluid at around 20 weeks. It concluded that amniotic fluid viral load has some association with post-natal sequelae.

Table 7 Summary of the systematic reviews investigating the capacity of fetal tests to predict cCMV severity

First author, year,	Number of included papers	Population characteristics	Fetal test details	Subsequent severity outcome(s)	Follow-up time	Findings
Buca, 2021[80]	26	Fetuses with congenital cytomegalovirus (CMV) infection and normal ultrasound at the time of diagnosis	Fetal US of CNS/non-CNS performed at diagnosis of cCMV. Mostly 1st/2nd trimester	An anomaly detected on a follow-up ultrasound scan, an anomaly detected on prenatal MRI but missed on ultrasound, an anomaly detected on postnatal assessment but missed prenatally, perinatal mortality, symptomatic infection at birth, neurodevelopmental outcome and hearing and visual deficits.	unclear	*No meta-analysis was presented* The review concluded that in fetuses with congenital CMV infection in which no anomalies are detected on prenatal ultrasound or MRI, the risk of adverse postnatal outcome is lower than that reported previously in the published literature when not considering the role of antenatal imaging assessment
Gilad, 2024[81]	8	Fetuses with congenital cytomegalovirus (CMV) infection	Viral load (in amniotic fluid) at around 20 weeks	Fetal and neonatal outcomes	unclear	Affected pregnancies had a higher viral load than unaffected: [Mean difference $2.2x10^7$, 95% CI $1.5x10^7$ to $2.8x10^7$] The review concluded that amniotic fluid CMV VL is associated with fetal sequelae in cCMV, with a higher VL conferring a greater risk for prenatal injury.
Kyriakopoulou, 2020[82]	26	Fetuses with congenital cytomegalovirus (CMV) infection	Fetal cerebral US or MRI, at varying times	'Poor outcome'	Up to 96 months	The review concluded that when both prenatal cerebral US and MRI are normal the negative predictive value of poor outcome is high
Rybak-Krzyszkowska, 2023[83]	48	Fetuses at risk of cCMV, not necessarily those with cCMV.	Any US of fetus. Timing unclear	Postnatal outcomes such as CP, cleft lip, etc. were discussed on a paper-by-paper basis	unclear	No statistical analysis or meta-analysis. In a narrative synthesis there was some discussion of theoretical links between US anomalies in the fetus and post-natal sequelae. The review concluded that ultrasonography is a reliable indicator of fetal anomalies due to cCMV.

Primary studies

Twenty-nine primary studies were found that evaluated the associations between test findings in fetuses with cCMV and subsequent outcomes reflecting the severity of cCMV infection. Of these, 17 studies [96-112] were already included in the 4 systematic reviews, and so these have not been further reviewed here, but are summarised in Appendix 2, Table 13. The remaining 12 studies[84-95] are reviewed below. These studies are summarized in Table 8.

Fetal tests for these studies were based on US scans alone,[92, 95] MRI scans alone,[84, 87-91] both US and MRI scans,[85, 86, 93] or blood sampling.[94]

US fetal tests

One study was a retrospective cohort study (Leruez-Ville (2021)[92]), whilst the other was retrospective (Tanimura (2023)[95]) both including fetuses with confirmed cCMV. Sample size was relatively small, ranging from 18 to 71 fetuses. Fetal US was undertaken once in the third trimester, or on a weekly basis (with unclear onset and cessation). Severity outcomes, which included long term sequelae were measured at around two years. Leruez-Ville (2021) showed that abnormal fetal US had good predictive capacity for later manifestations of severity, showing good sensitivity and NPV. Tanimura (2023) did not directly report associations between fetal imaging and later clinical manifestations of severity (although inferences may be made from tabulated data), but demonstrated a sensitivity of 80% and a specificity of 33.3% for prenatal US in predicting abnormalities associated with cCMV infection in the newborn. MRI was used as a gold standard, although this was ambiguously reported. These studies are summarized in Table 8.

MRI fetal tests

The 6 fetal MRI studies were of a retrospective[87-91] or case control design.[84] All were of small size, ranging from 10 to 58 fetuses with confirmed cCMV. Fetal MRI, which included unspecified scanning, or specific attention to white matter findings, temporal lobe T2 signals, brain volume or Apparent Diffusion Co-efficient values, was generally undertaken in the third trimester. Subsequent severity outcomes included response to valganciclovir, neurodevelopment, general development, hearing, cerebral palsy, size at birth, viral load at birth or post-natal MRI.

There were significant associations between MRI evidence of polymicrogyria and cerebral palsy,[87] between ADC values on fetal MRI and general development[90] and between pre-natal and post-natal MRI findings.[91] However there were also inconclusive findings,[88] or those suggesting no association.[84, 89, 91] These studies are summarized in Table 8.

US and MRI

One study was prospective[85] and the other 2 were retrospective.[86, 93] Study sizes were very small to moderate, ranging from 49 to 135 fetuses with confirmed cCMV. One study[85] provided targeted fetal US every 3-4 weeks until birth from 14 weeks of gestation onwards, with fetal MRI at 32-33 weeks if the US tests were positive for fetal brain lesions. Another study[86] provided fetal US every fortnight from referral (before 28 weeks) until birth or termination, and also MRI focussed on the brain at a median of 32 weeks of gestation. Likewise, another study[93] provided US at least once a month, most probably during the first and second trimesters, with some fetuses receiving additional MRI if appropriate at a median of 31 weeks gestation.

Outcomes included hearing loss or developmental delay measured around 4 years symptoms at birth and severe sequelae at up to 29 months or termination, fetal death, symptoms and mild or severe sequelae at an unreported timepoint.

One study showed excellent sensitivity of US and MRI to predict later outcomes, [86] and another showed a strong association between severity of prenatal imaging findings and the likelihood of subsequent adverse outcomes. However, another study showed no association between prenatal imaging and postnatal outcome.[85] These studies are summarized in Table 8.

Blood sampling

One retrospective study[94] evaluated 58 fetuses with confirmed cCMV, using fetal blood sampling at around 21-28 weeks gestation. The outcome was symptomatic infection at birth. At the defined thresholds, the blood sampling was predictive of moderate to severe symptoms at birth. This study is summarized in Table 8.

Table 8 Summary of the primary studies investigating the capacity of fetal tests to predict cCMV severity

First author, year, design, location	Population characteristics	Sample size	Fetal test details and gestational age	Subsequent severity outcome(s)	Follow-up time	Findings
Fetal US only						
Leruez-Ville, 2021[92] Retrospective France	CMV infected infants diagnosed prenatally	71 (diagnosed prenatally)	Routine fetal US Gest age: 20-24 weeks and 30-34 weeks	long term sequelae - mild or severe	median 24 months	Targeted ultrasound of known infected fetuses had 91% sensitivity, and 96% negative predictive value (NPV) for predicting any sequelae. For prediction of severe sequelae, both sensitivity and NPV were 100%. The study concluded that there was high performance of targeted prenatal US imaging in known cases of fetal infections.
Tanimura, 2023[95] Retrospective Japan	Fetuses with confirmed cCMV, with or without fetal growth restriction (FGR)	18	Fetal brain US performed weekly. Gest. age unclear	Post-natal sequelae	1.5 to 3 years	The diagnostic accuracy of "fetal US findings for morphological abnormalities associated with cCMV in newborns with prenatally confirmed cCMV" is 80% sensitivity and 33.3% sensitivity. It is unclear if these morphological abnormalities were related to sequelae associated with cCMV. The study did not present any conclusions clearly relevant to this assessment.
Fetal MRI only						
Barkai, 2024[84] Case-study Israel	Fetuses with confirmed cCMV	58	fbMRI to detect white matter hyperintense signals. Gest. age 33-34 weeks	Response to valganciclovir treatment; neurodevelopmental; hearing	Median 2.3 years in normal fbMRI group and 3.4 years in fbMRI group where white matter signals detected	The study found that fbMRI white matter findings are not associated with neurodevelopmental or hearing outcomes, but this result may be confounded by valganciclovir administration.

First author, year, design, location	Population characteristics	Sample size	Fetal test details and gestational age	Subsequent severity outcome(s)	Follow-up time	Findings
Goergen, 2020[87] Retrospective Australia	Whole study included fetuses with suspected cCMV, but predictive analysis focussed on those with confirmed cCMV	11 cCMV positive cases	Intrauterine MRI. Gest age. Median 28 weeks	Cerebral palsy, death, hearing, development	Ranges from a few months to over 4 years	The study found that iuMRI evidence of polymicrogyria in fetuses with confirmed cCMV, undetected with prenatal US, was associated with later development of CP
Gorenstein, 2021[88] Retrospective Israel	Fetuses with PCR-confirmed cCMV	29 confirmed with cCMV infection	Temporal lobe T2 MRI signal relative to amniotic fluid signal in fetus. Gest. age Median 28 weeks	SNHL	unclear	2/29 had SNHL, and of these 1/2 had an abnormal temporal T2 signal. Thus no clear findings. The study concluded that CMV infected fetuses do not present an increased signal when compared to age-matched controls.
Grinberg, 2019[89] Retrospective Israel	Fetuses with intrauterine CMV infection	42	Volumetric fetal MRI brain scans. Gest. age 30-34 weeks	VABS-II questionnaire (development, including communication, ADL, socialisation and motor skills), hearing, size at birth	unclear	No significant association between fetal brain volume on MRI and any post-natal outcome.
Kotovich, 2017[90] Retrospective Israel	CMV infected fetuses with originally unremarkable fetal MRI results	58 with cCMV	Apparent Diffusion Co-efficient values on fetal MRI Performed in al trimesters	VABS-II (Vineland Adaptive Behaviour Scales, 2nd Edn.)	unclear	Some significant correlation between ADC values on fetal MRI and later VABS-II findings in childhood. The study concluded that cCMV-infected children with unremarkable fetal MR imaging scans do not deviate from the healthy population in the VABS-II neurocognitive assessment.
Kyriakopoulou, 2023[91]	Children with confirmed cCMV who had	10	Fetal MRI	Viral load at birth; GA at birth; somatometric	At birth for clinical outcomes; postnatal MRI was	Neonatal blood viral load did not correlate with fetal MRI findings; No report of any correlation (strong, weak or non-existent) of the other clinical outcomes with pre-

First author, year, design, location	Population characteristics	Sample size	Fetal test details and gestational age	Subsequent severity outcome(s)	Follow-up time	Findings
Retrospective Greece	undergone both fetal and post-natal MRI		9 patients after 26 weeks, 1 patient at 23-25 weeks	measurements at birth, symptoms at birth; post-natal MRI	in 1st month of life for 7 patients, 2nd month of life for 2 patients and 3rd month of life for 1 patient.	natal MRI findings; High concordance between fetal and post-natal MRI, indicating that fetal findings are a good measure of later MRI findings. These may or may not relate to clinical indices. The study concluded that fetal MRI could potentially provide similar information to neonatal imaging.
Fetal US with MRI						
Elkan Miller, 2021[85] Prospective Israel	Fetuses with confirmed cCMV, infected in second or third trimester	135	Targeted US every 3-4 weeks until birth, and fetal MRI at 32-33 weeks if US tests positive for fetal brain lesions Gest. age 14 weeks	Post natal sequelae - hearing loss or developmental abnormalities	median 4 years	Serial prenatal US: Sensitivity 28.6%; specificity 80.6% PPV 10%; NPV 94% Serial prenatal MRI: Sensitivity 28.6%; specificity 83% PPV 12%; NPV 94% The study concluded that prenatal imaging failed to predict the development of childhood adverse outcomes
Faure-Bardon, 2020[86] Retrospective France	Fetuses infected with cCMV <14 weeks gestation	62	Fetal US (every fortnight), MRI (focussed on brain; frequency and timing unclear) US in 2nd trimester; MRI at median 32 weeks	Symptoms at birth, moderate to severe sequelae	29 months postnatally	Second trimester US with MRI to predict sequelae: Sensitivity 67%; specificity 93% PPV 67%; NPV 93% US and MRI of infected fetus have excellent sensitivity [based on study finding of NPV of 100%] for predicting neonatal and later outcomes.

First author, year, design, location	Population characteristics	Sample size	Fetal test details and gestational age	Subsequent severity outcome(s)	Follow-up time	Findings
						The study concluded that serial assessment in the second and third trimesters by ultrasound and MRI is necessary to predict the risk of sequelae
Massoud, 2023[93] Retrospective France	Fetuses infected with confirmed cCMV in first and second trimester	49	Cerebral and extracerebral fetal US at least once per month. Onset and cessation of imaging is unclear, but appears to have been in the first and second trimesters. MRI was optionally carried out subject to US findings (26/49 cases) at mean gestational age of 31 weeks.	Termination of pregnancy, fetal death, symptoms at birth, sensory deficits (visual, hearing and vestibular), motor delay, cognitive impairment	Unclear	Of 17 fetuses with severe imaging features, 12 were terminated, four died and one had severe postnatal sequelae. Of the 16 fetuses with mild imaging features, 5 had a normal postnatal outcome, 5 had mild postnatal sequelae and 6 were terminated. Of the 16 fetuses with normal prenatal imaging, 15 had a normal outcome and one had mild sequelae. The study concluded that fetuses with normal prenatal imaging have a low risk of postnatal sequelae, but fetuses with severe prenatal imaging features were at high risk of adverse sequelae.
Fetal blood sampling						
Pomar, 2024[94] Retrospective Switzerland	Fetuses with confirmed cCMV	58	Fetal blood sampling (thresholds for positive test are thrombocytes <120,000/mL, viremia >=5 log10/mL, and b2 macroglobulin >=12 mg/L) Gest. age 21-28 weeks	Symptomatic infection at birth	Outcome measured at birth	Fetal blood sampling with the described cutoffs had a negative predictive value of 100% for moderately to severely symptomatic infection. The study concluded that he combination of thrombocytes, b2-microglobulin, and CMV viral load in fetal blood can be used for prognosis determination, particularly in CMV-infected fetuses without severe brain abnormalities at the time of prenatal diagnosis.

Unpublished studies

Twelve unpublished abstracts were found that investigated the association of fetal tests with later indicators of cCMV severity in fetuses with cCMV[113-124]

These studies evaluated the ability of fetal MRI,[115, 120, 121] fetal US and MRI,[114, 117, 124] fetal US and viral load,[123] fetal MRI and blood tests,[113] fetal US/MRI and viral load,[122] viral load alone[118, 119] and blood tests alone[116] to predict later severity of infection. Further details are provided in Appendix 3, Table 14.

Studies in development

A protocol for a relevant systematic review evaluating the association between fetal US and postnatal outcome has been published on PROSPERO, which may be still in development.[125]

Summary

This evidence map identified 46 studies on fetal testing for later consequences of cCMV infection, including 4 systematic reviews. Most of this evidence related to fetal ultrasound or MRI testing, with more limited evidence on viral load testing of the amniotic fluid.

Across all the evidence there appears to be good evidence that fetal ultrasound, possibly in combination with fetal MRI, can detect long-term hearing and neurodevelopmental issues. In particular, a negative ultrasound appears to be a good “rule-out” test, as fetuses with a negative ultrasound appear very unlikely to have long-term sequelae. The diagnostic value of MRI without ultrasound is less certain.

Evidence on the use of CMV viral load testing in the amniotic fluid was more limited, but the one systematic review on this topic found some evidence that is a high viral load associated with a greater risk of fetal sequelae.

In summary, at present there is a sufficient volume of evidence in this key area to justify commissioning an evidence summary. However, given the numerous recent reviews identified by this evidence map, it is uncertain whether any future reviews could reach different conclusions.

Conclusions

On the basis of this evidence map, the volume and type of evidence for all 3 questions considered is sufficient to justify a more in-depth review.

There is a good body of evidence related to non-invasive antenatal screening tests to detect maternal CMV infection. This suggests that IgG testing combined with IgM testing has the potential to be able to detect primary maternal infection in the first trimester, with an accuracy suitable for use in screening. Evidence for other tests is limited, but some, such as cell-free DNA testing, may also have potential for use in screening. Therefore, further work to evaluate all available screening strategies would be justified.

There is a substantial body of evidence related to the benefits and harms of antenatal treatment to prevent cCMV infection, or cCMV-related morbidity and mortality. This suggests that oral valaciclovir is effective at reducing the rate of transmission of CMV to the fetus. Evidence on hyperimmunoglobulin (HIG) treatment is more uncertain, but suggests it is likely to be less effective. Hence there is sufficient evidence to justify a more in-depth review.

Finally, the volume and type of evidence on fetal tests to determine the severity of cCMV suggests that fetal ultrasound testing, possibly in combination with fetal MRI, has potential as a means of determining whether babies with cCMV will go on to have long-term hearing and developmental problems. Evidence on CMV viral load testing of the amniotic fluid is more limited, but it may also be a useful test. This suggests that there is sufficient evidence to justify a more in-depth review in this area.

Recommendations

On the basis of this evidence map, it is recommended that further work on antenatal screening for CMV should be commissioned.

Full systematic reviews are recommended for all three components of this evidence map (i.e. screening for maternal CMV infection, treatment of maternal CMV infection, and fetal testing to detect symptoms). It may also be desirable to expand any reviews to cover NSC criteria not covered by this evidence map; for example, to examine whether an antenatal CMV screening programme as a whole is clinically effective and cost-effective, and whether it is acceptable to pregnant women and the medical community.

Recommendations for primary research

Although the aim of this evidence map was to determine whether further review work is desirable, we note some key areas where additional primary research could strengthen the evidence base:

High-quality diagnostic accuracy studies are needed to fully determine the accuracy of combining IgG and IgM testing to detect maternal CMV infection. These should offer IgG and IgM testing to pregnant women in the first trimester and follow-up with some suitable reference testing for CMV infection, such as PCR testing. Ideally, studies should also test newborns for cCMV using urine testing and assess levels of symptoms (such as hearing loss) in newborns. Studies should examine a range of IgG and IgM cut-off levels to identify optimum tests for use in screening.

Further randomised controlled trials comparing valaciclovir to placebo (or alternatively to HIG) for women with confirmed or suspected CMV infection would be desirable, to confirm the findings of the 1 existing trial.

As the evidence suggests that antenatal screening for CMV may be feasible, studies to assess its feasibility and effectiveness would be desirable. These should offer IgG and IgM testing to pregnant women in the first trimester, with valaciclovir offered to women who test positive for CMV. Where feasible, fetal testing for CMV transmission (e.g. by amniocentesis) should be offered, and newborns should be tested for cCMV using urine testing, and assessed for hearing loss. Optimally, these would be cluster-randomised trials to compare screening to current practice without screening, but non-randomised studies would also be useful.

Appendix 1 — Search strategy and inclusion criteria for the evidence map

Databases and platforms searched

- MEDLINE ALL (Ovid)
- Embase (Ovid)
- Maternity and Infant Care Database (Ovid)
- CINAHL (Ebsco)
- Cochrane Database of Systematic Reviews (CDSR, Wiley)
- Cochrane Central Register of Controlled Trials (CENTRAL, Wiley)
- Science Citation Index (Web of Science)
- Conference Proceedings Citation index – Science (Web of Science)
- Latin American and Caribbean Health Sciences Literature (LILACS, https://pesquisa.bvsalud.org/)
- KSR Evidence (Ovid)
- Database of Abstract of Reviews of Effects (DARE, CRD databases)
- HTA database (CRD databases http://www.crd.york.ac.uk/CRDWeb/)
- International HTA database (INAHTA, https://database.inahta.org/)
- PROSPERO (https://www.crd.york.ac.uk/prospero/)
- ClinicalTrials.gov (https://clinicaltrials.gov/ct2/)
- WHO International Clinical Trials Registry Platform (https://trialsearch.who.int/)
- EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/)
- Websites of international HTA organisations

Search dates

The databases and resources listed above were searched in January 2025. A date limit restricting to records from 2009 onwards was applied.

Numbers of results for each database

One broad search strategy combining search terms for pregnancy or foetus with terms for CMV was used to identify evidence for Questions 1, 2 and 3. The number of records retrieved from each database and resource are reported in Table 9.

Table 9 Records identified from each database

Database/source	Number of records retrieved before deduplication
Records identified from newborn screening review	158
MEDLINE	2783
EMBASE	5533
Maternity and Infant Care	520
CINAHL	971
Science Citation Index Conference Proceedings Citation Index - Science	2999
CENTRAL	209
CDSR	6
KSR	56
DARE	3
HTA database	0
International HTA database	1
LILACS	224
ClinicalTrials.gov	95
WHO ICTRP	76
EU Clinical Trials Register	97
PROSPERO	114
HTA agency websites	4
Total	13849

Search strategies

MEDLINE ALL
via Ovid http://ovidsp.ovid.com/
Date range: 1946 to January 27, 2025
Date searched: 28th January 2025
Records retrieved: 2783

1 exp Pregnancy/ (1050684)
2 Pregnant Women/ (16354)
3 Mothers/ (60435)
4 pregnan$.ti,ab,kf. (658121)
5 gestation$.ti,ab,kf. (267534)
6 (mother$ or maternal$).ti,ab,kf. (534807)
7 (antenatal$ or ante natal$ or prenatal$ or pre natal$ or antepartum$ or ante partum$ or trimester$).ti,ab,kf. (239183)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (1529632)
9 Fetus/ (84552)
10 (f?etus$ or f?etal).ti,ab,kf. (374436)
11 9 or 10 (396030)
12 8 or 11 (1640497)
13 Cytomegalovirus/ (24035)
14 exp Cytomegalovirus Infections/ (29545)
15 cytomegalovir$.ti,ab,kf. (49829)
16 ((cytomegal$ or cyto megal$) adj6 (virus$ or viral$ or vir?emi$)).ti,ab,kf. (10105)
17 cytomegaloinfection$.ti,ab,kf. (1)
18 ((cytomegal$ or cyto megal$) adj infection$).ti,ab,kf. (11268)
19 ((cytomegaly$ or cyto megaly$) and (virus$ or viral$ or vir?emi$)).ti,ab,kf. (155)
20 (CMV or HCMV).ti,ab,kf. (37945)

21 cCMV.ti,ab,kf. (758)
22 human herpesvirus 5.ti,ab,kf. (37)
23 human herpes virus 5.ti,ab,kf. (14)
24 (HHV 5 or HHV5).ti,ab,kf. (68)
25 salivary gland virus$.ti,ab,kf. (59)
26 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 (66028)
27 12 and 26 (6007)
28 exp animals/ not humans.sh. (5300982)
29 27 not 28 (5679)
30 limit 29 to yr="2009 -Current" (2783)

Key:
/ = subject heading (MeSH heading)
sh = subject heading (MeSH heading)
exp = exploded subject heading (MeSH heading)
$ = truncation
? = optional wildcard – one or no characters
ti,ab,kf = terms in title or abstract or author keyword fields
adj = terms next to each other in order specified
adj6 = terms within six words of each other (any order)

Embase
via Ovid http://ovidsp.ovid.com/
Date range: 1974 to 2025 January 28
Date searched: 27th January 2025
Records retrieved: 5533

1 exp pregnancy/ (811858)
2 pregnant woman/ (127013)
3 mother/ or expectant mother/ (109955)
4 pregnan$.ti,ab,kw. (827500)
5 gestation$.ti,ab,kw. (373046)
6 (mother$ or maternal$).ti,ab,kw. (676979)
7 (antenatal$ or ante natal$ or prenatal$ or pre natal$ or antepartum$ or ante partum$ or trimester$).ti,ab,kw. (317912)
8 or/1-7 (1630526)
9 fetus/ (222126)
10 (f?etus$ or f?etal).ti,ab,kw. (462490)
11 8 or 9 or 10 (1792372)
12 Cytomegalovirus/ (41277)
13 exp human cytomegalovirus/ (8684)
14 exp cytomegalovirus infection/ (49625)
15 cytomegalovir$.ti,ab,kw. (62833)
16 ((cytomegal$ or cyto megal$) adj6 (virus$ or viral$ or vir?emi$)).ti,ab,kw. (13581)
17 cytomegaloinfection$.ti,ab,kw. (1)
18 ((cytomegal$ or cyto megal$) adj infection$).ti,ab,kw. (13793)
19 ((cytomegaly$ or cyto megaly$) and (virus$ or viral$ or vir?emi$)).ti,ab,kw. (174)
20 (CMV or HCMV).ti,ab,kw. (61824)
21 cCMV.ti,ab,kw. (868)
22 human herpesvirus 5.ti,ab,kw. (50)
23 human herpes virus 5.ti,ab,kw. (17)
24 (HHV 5 or HHV5).ti,ab,kw. (99)
25 salivary gland virus$.ti,ab,kw. (12)
26 or/12-25 (113974)
27 11 and 26 (8944)
28 animal/ or animal experiment/ (4892209)
29 (animal or animals or rat or rats or mouse or mice or murine or pig or pigs or piglet or piglets or porcine or rabbit or rabbits or hamster or hamsters or sheep or monkey or monkeys or macaque or macaques).ti,ab,hw. (7779137)
30 28 or 29 (7779137)
31 exp human/ or exp human experiment/ (27287212)
32 30 not (30 and 31) (5793412)
33 27 not 32 (8468)
34 limit 33 to yr="2009 -Current" (5533)

Key:
/ = subject heading (Emtree heading)
exp = exploded subject heading (Emtree heading)
hw = subject heading word
$ = truncation
? = optional wildcard – one or no characters
ti,ab,kw = terms in title or abstract or author keyword fields
adj = terms next to each other in order specified
adj6 = terms within six words of each other (any order)

Maternity and Infant Care
via Ovid http://ovidsp.ovid.com/
Date range: 1971 to January 21, 2025
Date searched: 28th January 2025
Records retrieved: 520

1 pregnan$.af. (153836)
2 gestation$.af. (67251)
3 (mother$ or maternal$).af. (139874)
4 (antenatal$ or ante natal$ or prenatal$ or pre natal$ or antepartum$ or ante partum$ or trimester$).af. (71116)
5 1 or 2 or 3 or 4 (234069)
6 (f?etus$ or f?etal).af. (71114)
7 5 or 6 (241030)
8 cytomegalovir$.af. (1066)
9 ((cytomegal$ or cyto megal$) adj6 (virus$ or viral$ or vir?emi$)).af. (190)
10 cytomegaloinfection$.af. (0)
11 ((cytomegal$ or cyto megal$) adj infection$).af. (581)
12 ((cytomegaly$ or cyto megaly$) and (virus$ or viral$ or vir?emi$)).af. (0)
13 (CMV or HCMV).af. (685)
14 cCMV.af. (99)
15 human herpesvirus 5.af. (0)
16 human herpes virus 5.af. (0)
17 (HHV 5 or HHV5).af. (1)
18 salivary gland virus$.af. (0)
19 or/8-18 (1125)
20 7 and 19 (910)
21 limit 20 to yr="2009 -Current" (520)

Key:
$ = truncation
? = optional wildcard – one or no characters
af = terms in any database fields
adj = terms next to each other in order specified
adj6 = terms within six words of each other (any order)

CINAHL
via Ebsco https://www.ebsco.com/
Date range: Inception to 20250128
Date searched: 28th January 2025
Records retrieved: 971

S1 (MH "Pregnancy+") 251,241
S2 (MH "Expectant Mothers") 16,383
S3 TI (pregnan* or gestation* or mother* or maternal* or antenatal* or ante-natal* or prenatal* or pre-natal* or antepartum* or ante-partum* or trimester*) OR AB (pregnan* or gestation* or mother* or maternal* or antenatal* or ante-natal* or prenatal* or pre-natal* or antepartum* or ante-partum* or trimester*) 338,988
S4 S1 OR S2 OR S3 427,952
S5 (MH "Fetus") 22,646
S6 TI (f#etus* or f#etal) OR AB (f#etus* or f#etal) 66,104
S7 S4 OR S5 OR S6 441,871
S8 (MH "Cytomegaloviruses") 1,692

S9 (MH "Cytomegalovirus Infections+") 3,854
S10 TI cytomegalovir* OR AB cytomegalovir* 5,218
S11 TI ((cytomegal* or cyto-megal*) N6 (virus* or viral* or vir#emi*)) OR AB ((cytomegal* or cyto-megal*) N6 (virus* or viral* or vir#emi*)) 1,099
S12 TI cytomegaloinfection* OR AB cytomegaloinfection* 0
S13 TI ((cytomegal* or cyto-megal*) N0 infection*) OR AB ((cytomegal* or cyto-megal*) N0 infection*) 1,546
S14 TI ((cytomegaly* or cyto-megaly*) and (virus* or viral* or vir#emi*)) OR AB ((cytomegaly* or cyto-megaly*) and (virus* or viral* or vir#emi*) 2
S15 TI (CMV or HCMV) OR AB (CMV or HCMV)3,169
S16 TI cCMV OR AB cCMV 154
S17 TI ("human herpesvirus 5" or "human herpes virus 5") OR AB ("human herpesvirus 5" or "human herpes virus 5") 0
S18 TI ("HHV 5" or "HHV5") OR AB ("HHV 5" or "HHV5") 0
S19 TI ("salivary gland virus" or "salivary gland viruses") OR AB ("salivary gland virus" or "salivary gland viruses") 1
S20 S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 7,030
S21 S7 AND S20 1,298
S22 MH animals+ 102,147
S23 MH (animal studies) 153,823
S24 TI (animal model*) 3,928
S25 S22 OR S23 OR S24 247,071
S26 MH (human) 2,870,625
S27 S25 NOT S26 212,458
S28 S21 NOT S27 Limiters - Publication Date: 20090101-20251231971

Key:
MH = CINAHL subject heading
MH with + = exploded CINAHL subject heading
* = truncation
# = wildcard - one or no characters
TI = title field
AB = abstract field
N6 = terms within six words of each other (any order)

Cochrane Library
via Wiley http://onlinelibrary.wiley.com/
Cochrane Central Register of Controlled Trials (CENTRAL): Issue 12 of 12, Dec 2024
Records retrieved: 209
Cochrane Database of Systematic Reviews (CDSR): Issue 1 of 12, Jan 2025
Records retrieved: 6
Date searched: 28th January 2025

#1 MeSH descriptor: [Pregnancy] explode all trees 34889
#2 MeSH descriptor: [Pregnant Women] this term only 1060
#3 MeSH descriptor: [Mothers] this term only 3461
#4 pregnan*:ti,ab,kw 93756
#5 gestation*:ti,ab,kw 35430
#6 (mother* or maternal*):ti,ab,kw 46204
#7 (antenatal* or (ante next natal*) or prenatal* or (pre next natal*) or antepartum* or (ante next partum*) or trimester*) 21789
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7 124908
#9 MeSH descriptor: [undefined] explode all trees 0
#10 (fetus* or foetus* or fetal or foetal):ti,ab,kw 19268
#11 #8 or #9 or #10 126937
#12 MeSH descriptor: [Cytomegalovirus] this term only 462
#13 MeSH descriptor: [Cytomegalovirus Infections] explode all trees 1063
#14 cytomegalovir*:ti,ab,kw 2690
#15 ((cytomegal* or cyto-megal*) near/6 (virus* or viral* or viremi* or viraemi*)):ti,ab,kw 371
#16 cytomegaloinfection*:ti,ab,kw 0
#17 ((cytomegal* or cyto-megal*) next infection*):ti,ab,kw 1811
#18 ((cytomegaly* or cyto-megaly*) and (virus* or viral*or viremi* or viraemi*)):ti,ab,kw 3
#19 (CMV or HCMV):ti,ab,kw 2380
#20 cCMV:ti,ab,kw 12
#21 "human herpesvirus 5":ti,ab,kw 0

#22 "human herpes virus 5":ti,ab,kw 0
#23 ("HHV 5" or "HHV5"):ti,ab,kw 0
#24 (salivary next gland next virus*):ti,ab,kw 0
#25 #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 3453
#26 #11 and #25 with Cochrane Library publication date Between Jan 2009 and Dec 2025, in Cochrane Reviews, Cochrane Protocols 6
#27 #11 and #25 with Publication Year from 2009 to 2025, in Trials 209

Key:
MeSH descriptor = subject heading (MeSH heading)
* = truncation
? = wildcard - zero or one characters
ti,ab,kw = terms in title, abstract or keyword fields
next = terms are next to each other
near/6 = terms within six words of each other (any order)

Science Citation Index (SCI)

Conference Proceedings Citation Index – Science (CP-SCI)

via Web of Science, Clarivate Analytics https://clarivate.com/

Date searched: 28th January 2025

Date range SCI: 1900 – present

Date range CP-SCI: 1990 – present

Records retrieved: 2999

1: TS=(pregnan* or gestation* or mother* or maternal* or antenatal* or ante-natal* or prenatal* or pre-natal* or antepartum* or ante-partum* or trimester*) Editions: WOS.SCI,WOS.ISTP Results: 1128338

2: TS=(fetus* or foetus* or fetal or foetal) Editions: WOS.SCI,WOS.ISTP Results: 395804

3: #1 OR #2 Editions: WOS.SCI,WOS.ISTP Results: 1294590

4: TS=(cytomegalovir*) Editions: WOS.SCI,WOS.ISTP Results: 57582

5: TS=((cytomegal* or cyto-megal*) NEAR/6 (virus* or viral* or vir$emi*)) Editions: WOS.SCI,WOS.ISTP Results: 12333

6: TS=(cytomegaloinfection*) Editions: WOS.SCI,WOS.ISTP Results: 0

7: TS=((cytomegal* or cyto-megal*) NEAR/1 infection*) Editions: WOS.SCI,WOS.ISTP Results: 19690

8: TS=((cytomegaly* or cyto-megaly*) and (virus* or viral* or vir$emi*)) Editions: WOS.SCI,WOS.ISTP Results: 118

9: TS=(CMV or HCMV) Editions: WOS.SCI,WOS.ISTP Results: 41099

10: TS=(cCMV) Editions: WOS.SCI,WOS.ISTP Results: 761

11: TS=("human herpesvirus 5" or "human herpes virus 5") Editions: WOS.SCI,WOS.ISTP Results: 43

12: TS=("HHV 5" or "HHV5") Editions: WOS.SCI,WOS.ISTP Results: 62

13: TS=("salivary gland virus*") Editions: WOS.SCI,WOS.ISTP Results: 74

14: #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 Editions: WOS.SCI,WOS.ISTP Results: 74099

15: #14 AND #3 Editions: WOS.SCI,WOS.ISTP Results: 5043

16: #14 AND #3 Editions: WOS.SCI,WOS.ISTP Timespan: 2009-01-01 to 2025-01-28 Results: 2999

Key:

TS = topic tag; searches in title, abstract, author keywords and keywords plus fields

* = truncation

$ = represents zero or one character

NEAR/6 = terms within six words of each other (any order)

Latin American and Caribbean Health Sciences Literature (LILACS)

via https://pesquisa.bvsalud.org/portal/advanced/?lang=en
Date range: Inception to current
Date searched: 28th January 2025

Records retrieved: 224

Advanced search screen used, terms searched in the title, abstract and subject fields. Filters applied: results from LILACS databases, publication year range: 2009-2025

1. (pregnan* OR gestation* OR mother* OR maternal* OR antenatal* OR ante-natal* OR prenatal* OR pre-natal* OR antepartum* OR ante-partum* OR trimester* OR fetus* OR foetus* OR fetal OR foetal)
AND
cytomegalovir* OR cytomegaloinfection* OR CMV OR HCMV OR cCMV OR "human herpesvirus 5" OR "human herpes virus 5" OR "HHV 5" OR "HHV5" OR "salivary gland virus" OR "salivary gland viruses"
116 records

2. pregnan* OR gestation* OR mother* OR maternal* OR antenatal* OR ante-natal* OR prenatal* OR pre-natal* OR antepartum* OR ante-partum* OR trimester* OR fetus* OR foetus* OR fetal OR foetal)
AND
(cytomegal* OR cyto-megal*) AND (infection* OR virus* OR viral* OR viremi* OR viraemi*)
108 records

Key:
* = truncation

KSR Evidence
via Ovid http://ovidsp.ovid.com/
Date range: 2015 to 2025 Week 04
Date searched: 28th January 2025

Records retrieved: 56

1 pregnan$.af. (12771)
2 gestation$.af. (5063)
3 (mother$ or maternal$).af. (9105)
4 (antenatal$ or ante natal$ or prenatal$ or pre natal$ or antepartum$ or ante partum$ or trimester$).af. (4096)
5 1 or 2 or 3 or 4 (18577)
6 (f?etus$ or f?etal).af. (3909)
7 5 or 6 (19005)
8 cytomegalovir$.af. (327)
9 ((cytomegal$ or cyto megal$) adj6 (virus$ or viral$ or vir?emi$)).af. (74)
10 cytomegaloinfection$.af. (0)
11 ((cytomegal$ or cyto megal$) adj infection$).af. (123)
12 ((cytomegaly$ or cyto megaly$) and (virus$ or viral$ or vir?emi$)).af. (0)
13 (CMV or HCMV).af. (284)
14 cCMV.af. (23)
15 human herpesvirus 5.af. (0)
16 human herpes virus 5.af. (0)
17 (HHV 5 or HHV5).af. (2)
18 salivary gland virus$.af. (0)
19 or/8-18 (398)
20 7 and 19 (56)
21 limit 20 to yr="2009 -Current" (56)

Key:
$ = truncation
? = optional wildcard – one or no characters
af = terms in any field
adj = terms next to each other in order specified
adj2 = terms within six words of each other (any order)

Database of Abstracts of Reviews of Effects (DARE)
Health Technology Assessment (HTA) database
via http://www.crd.york.ac.uk/CRDWeb/
Date range DARE: Inception – 31st March 2015
Date range HTA database: Inception – 31st March 2018
Date searched: 28th January 2025
Records retrieved: 3 (from DARE), 0 (from HTA)

1 MeSH DESCRIPTOR Pregnancy EXPLODE ALL TREES IN DARE,HTA 1855

2 MeSH DESCRIPTOR Pregnant Women IN DARE,HTA 25

3 MeSH DESCRIPTOR Mothers IN DARE,HTA 63

4 (pregnan* or gestation* or mother* or maternal* or antenatal* or ante-natal* or prenatal* or pre-natal* or antepartum* or ante-partum* or trimester*) IN DARE, HTA 3984

5 #1 OR #2 OR #3 OR #4 4009

6 MeSH DESCRIPTOR fetus IN DARE,HTA 51

7 (fetus* or foetus* or fetal or foetal) IN DARE, HTA 813

8 #5 OR #6 OR #7 4086

9 MeSH DESCRIPTOR Cytomegalovirus IN DARE,HTA 7

10	MeSH DESCRIPTOR Cytomegalovirus Infections EXPLODE ALL TREES IN DARE,HTA	31
11	(cytomegalovir*) IN DARE, HTA	61
12	((cytomegal* or cyto-megal*) adj6 (virus* or viral* or viremi* or viraemi*)) IN DARE, HTA	7
13	((virus* or viral* or viremi* or viraemi*) adj6 (cytomegal* or cyto-megal*)) IN DARE, HTA	9
14	(cytomegaloinfection*) IN DARE, HTA	0
15	((cytomegal* or cyto-megal*) adj1 infection*) IN DARE, HTA	46
16	(infection* adj1 (cytomegal* or cyto-megal*)) IN DARE, HTA	8
17	((cytomegaly* or cyto-megaly*) and (virus* or viral* or viremi* or viraemi*)) IN DARE, HTA	0
18	(CMV or HCMV) IN DARE, HTA	33
19	(cCMV) IN DARE, HTA	0
20	("human herpesvirus 5" or "human herpes virus 5") IN DARE, HTA	0
21	("HHV 5" or HHV5) IN DARE, HTA	0
22	("salivary gland virus" or "salivary gland viruses") IN DARE, HTA	0
23	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22	71
24	#8 AND #23	8
25	(#8 and #23) IN HTA FROM 2009 TO 2018	0
26	(#8 AND #23) IN DARE FROM 2009 TO 2015	3

Key:

MeSH DESCRIPTOR = subject heading (MeSH heading)

* = truncation

adj6 = terms within six words of each other (order specified)

International Health Technology Assessment (HTA) database
via https://database.inahta.org/
Date range: Inception – present
Date searched: 28th January 2025
Records retrieved: 1

(((CMV or HCMV or cCMV)[Title] OR (CMV or HCMV or cCMV)[abs] OR (CMV or HCMV or cCMV)[Keywords]) OR ((cytomegal* or cyto-megal*)[Title] OR (cytomegal* or cyto-megal*)[abs] OR (cytomegal* or cyto-megal*)[Keywords]) OR ((cytomegalovir*)[Title] OR (cytomegalovir*)[abs] OR (cytomegalovir*)[Keywords]) OR ("Cytomegalovirus Infections"[mhe]) OR ("Cytomegalovirus"[mh])) AND (((fetus* or foetus* or fetal or foetal)[Title] OR (fetus* or foetus* or fetal or foetal)[abs] OR (fetus*

or foetus* or fetal or foetal)[Keywords]) OR ((pregnan* or gestation* or mother* or maternal* or antenatal* or ante-natal* or prenatal* or pre-natal* or antepartum* or ante-partum* or trimester*)[Title] OR (pregnan* or gestation* or mother* or maternal* or antenatal* or ante-natal* or prenatal* or pre-natal* or antepartum* or ante-partum* or trimester*)[abs] OR (pregnan* or gestation* or mother* or maternal* or antenatal* or ante-natal* or prenatal* or pre-natal* or antepartum* or ante-partum* or trimester*)[Keywords]) OR ("Fetus"[mh]) OR ("Mothers"[mh]) OR ("Pregnant Women"[mh]) OR ("Pregnancy"[mhe]))

Limited to 2009 onwards = 1 hit

Key:

[Keywords] = search of keyword field

[abs] = search of abstract field

[Title] = search of title field

[mh] = subject heading search

[mhe] = exploded subject heading search
* = truncation

PROSPERO
via https://www.crd.york.ac.uk/prospero/
Date searched: 29th January 2025
Records retrieved: 114

#1	MeSH DESCRIPTOR Pregnancy EXPLODE ALL TREES	4314
#2	MeSH DESCRIPTOR Pregnant Women	272
#3	MeSH DESCRIPTOR Mothers	268
#4	pregnan* OR mother* OR maternal* OR antenatal* OR ante-natal* OR prenatal* OR pre-natal* OR antepartum* OR ante-partum* OR trimester*	33903
#5	#1 OR #2 OR #3 OR #4	34161
#6	MeSH DESCRIPTOR Fetus	186
#7	fetus* OR foetus* OR fetal OR foetal	6426
#8	#5 OR #6 OR #7	34721
#9	MeSH DESCRIPTOR Cytomegalovirus	23
#10	MeSH DESCRIPTOR Cytomegalovirus Infections EXPLODE ALL TREES	31
#11	cytomegalovir* OR cytomegaloinfection* OR CMV OR HCMV OR cCMV	408
#12	(cytomegal* OR cyto-megal*) adj6 (virus* OR viral* OR viremi* OR viraemi*)	92
#13	(cytomegal* OR cyto-megal*) adj1 infection*	131
#14	(cytomegaly* OR cyto-megaly*) AND (virus* OR viral* OR viremi* OR viraemi*)	3
#15	"human herpesvirus 5" OR "human herpes virus 5" OR "HHV 5" OR "HHV5"	4
#16	"salivary gland virus" OR "salivary gland viruses"	3
#17	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	412
#18	#8 AND #17	114

Key:
MeSH DESCRIPTOR = subject heading (MeSH heading)
* = truncation
adj6 = terms within six words of each other

ClinicalTrials.gov
https://clinicaltrials.gov/ct2/
Date searched: 28th January 2025
Records retrieved: 95

1. cytomegalovirus OR CMV OR cCMV OR HCMV OR "cytomegalovirus infection" OR "congenital cytomegalovirus" | Other terms: pregnant OR pregnancy OR mother OR maternal OR antenatal OR ante-natal OR prenatal OR pre-natal OR antepartum OR ante-partum OR trimester OR trimesters = 63 results

2. cytomegalovirus OR CMV OR cCMV OR HCMV OR "cytomegalovirus infection" OR "congenital cytomegalovirus" | Other terms: fetus OR fetuses OR foetus OR foetuses OR fetal OR foetal = 32 studies

WHO International Clinical Trials Registry Platform (ICTRP)
https://trialsearch.who.int/Default.aspx
Date searched: 28th January 2025
Records retrieved: 76

Basic search interface used. No date limits available in basic search interface, therefore results from all years downloaded and records pre-2009 removed in EndNote.

1. 56 records for 47 trials found for: (pregnan* OR mother* OR maternal* OR antenatal* OR ante-natal* OR prenatal* OR pre-natal* OR antepartum* OR ante-partum* OR trimester*) AND (cytomegalovir* OR CMV OR cCMV OR HCMV)

2. 20 records for 19 trials found for: (fetus* OR foetus* OR fetal OR foetal) AND (cytomegalovir* OR CMV OR cCMV OR HCMV)

EU Clinical Trials Register
https://www.clinicaltrialsregister.eu/ctr-search/search
Date of search: 29th January 2025
Records retrieved: 97

Advanced search
1. 84 result(s) found for: (cytomegalovirus OR CMV OR HCMV OR cCMV) AND (pregnant OR pregnancy OR mother OR maternal)
2. 3 result(s) found for: (cytomegalovirus OR CMV OR HCMV OR cCMV) AND (antenatal OR ante-natal OR prenatal OR pre-natal OR antepartum OR ante-partum OR trimester OR trimesters)
3. 7 result(s) found for: (cytomegalovirus OR CMV OR HCMV OR cCMV) AND (fetus OR fetuses OR foetus OR foetuses OR fetal OR foetal)

Also searched for EU clinical trials via the new portal Clinical Trials Information System (CTIS) https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en
Search terms: cytomegalovirus or CMV or HCMV or cCMV – scanned 48 results – 3 with a population of pregnancy or foetal

Websites of international HTA organisations
Date searched: 29th January 2025
Records retrieved: 4

Browsed or searched the following HTA Agency websites to check for additional reports not found through database searches. A date limit of 2009 was applied.

Agency for Healthcare Research and Quality (AHRQ), USA
1. https://www.ahrq.gov/research/findings/ta/index.html
Browsed list of technology assessments, topic refinements and archive of technology assessments – 0 relevant reports found
2. https://www.ahrq.gov/research/findings/evidence-based-reports/search.html
Searched by keyword cytomegalovirus, CMV, cCMV, HCMV – 0 relevant reports found

Adelaide Health Technology Assessment (AHTA), AUSTRALIA
https://health.adelaide.edu.au/adelaide-health-technology-assessment/research-services/publications/
Browsed following lists (2009 onwards):
reports and monographs – none relevant
protocols – none relevant
Technology Briefs and Prioritising summaries – none relevant
Presentations and abstracts – none relevant

Agency for Care Effectiveness – Singapore
https://www.ace-hta.gov.sg/
Browsed lists of technology guidance, horizon scanning reports, scientific publications – 0 relevant reports found

Austrian Institute for Health Technology Assessment
https://eprints.aihta.at/
cytomegalovirus – 32 hits browsed – 3 potentially relevant

Canadian Agency for Drugs and Technologies in Health (CADTH), CANADA
https://www.cadth.ca/
General search https://www.cadth.ca/search?s=&facets_query=&page=0
1. cytomegalovirus – 21 results, 0 potentially relevant

Browsed projects in progress page and topics under consideration page – none relevant

Health Information and Quality Authority, IRELAND HIQA
https://www.hiqa.ie/reports-and-publications/health-technology-assessments
Browsed all 152 health technology assessments – none relevant

Scottish Health Technologies Group
https://shtg.scot/our-advice/
cytomegalovirus – 0 results
in progress: https://shtg.scot/what-we-do/work-programme/
Browsed all – none relevant

Health Technology Wales
https://healthtechnology.wales/reports-guidance/
cytomegalovirus – 0 results

National Institute for Health and Care Excellence
https://www.nice.org.uk/
General search box:
1. cytomegalovirus – 8 results, 1 relevant

2. https://www.nice.org.uk/guidance/published Searched for cytomegalovirus - 2 results, none relevant
in development – none relevant
awaiting development – none relevant

National Institute for Health Research Journals Library
https://www.journalslibrary.nihr.ac.uk/journals-search
1. cytomegalovirus – 152 results browsed, none relevant

Belgian Health Care Knowledge Centre
https://www.kce.fgov.be/en/all-reports-0
Filtered to HTA reports – browsed 2009-2025 – none relevant

Inclusion criteria for mapping evidence on antenatal screening (Questions 1 and 3)

Population

The population of interest is pregnant women (Question 1) or fetuses (Question 3).

Index tests

The intervention of interest is any non-invasive screening test of a pregnant woman to detect active maternal CMV infection, e.g. Immunoglobulin tests or ELISA blood test. In addition, tests to determine the severity of cCMV in the fetus will be included (e.g. fetal ultrasound).

Comparators

The comparator is no antenatal screening test to detect active maternal CMV infection. Uncontrolled studies are also eligible for inclusion, if relevant outcome data are provided.

Reference standards

Any reasonable reference standard for active maternal CMV infection. This can include amniocentesis to detect fetal infection or cCMV testing of the newborn.

Outcomes

Outcomes of interest are:

- diagnostic accuracy of the test (including sensitivity, specificity, positive and negative predictive values)
- cCMV in the fetus or newborn
- use of additional tests and procedures
- pregnancy outcome (live birth, stillbirth, miscarriage or termination of pregnancy)
- cCMV-related morbidities (including hearing loss and neurological impairments in infants and other long-term negative outcomes associated with CMV)
- mortality
- incidental findings
- potential harms of screening
- health-related quality of life
- acceptability to individuals screened

Study designs

Clinical trials (including randomised and other controlled trials), prospective and retrospective cohort studies and case-control studies will be sought.

Inclusion criteria for mapping evidence on antenatal treatment (Question 2)

Population

The population of interest is pregnant women.

Interventions

The intervention of interest is any treatment used in a pregnant woman with active CMV infection to prevent vertical transmission or cCMV-related complications. The relevant treatments are antiviral medications used during pregnancy, such as valaciclovir, and other types of medication, such as passive immunisation with cytomegalovirus hyperimmunoglobulin.

Studies that include screening for maternal CMV infection combined with hygiene and educational interventions to prevent later infection in CMV negative pregnant women will also be included.

Comparators

The comparator is no antenatal treatment used in a pregnant woman with active CMV to prevent vertical transmission or cCMV-related complications. Uncontrolled studies are also eligible for inclusion, if relevant outcome data are provided.

Outcomes

Outcomes of interest are:

- cCMV in the fetus or newborn
- pregnancy outcome (live birth, stillbirth, miscarriage or termination of pregnancy)
- cCMV-related morbidities (including hearing loss and neurological impairments in infants and other long-term negative outcomes associated with CMV)
- mortality
- adverse events of antenatal treatment
- health-related quality of life
- acceptability of treatment to pregnant women

Study designs

Prospective clinical trials (including randomised and other controlled trials), cohort studies and case-control studies will be sought.

Appendix 2 – Additional tables

Table 10 Summary of evidence reported in abstracts and trial records relating to question 1

Author (Year)	Study details (design; location)	Sample size (N with CMV)	Test(s) performed	Test/Sample type	Report category	Findings
Fundacio (2023)	Trial Registry for prospective cohort; Spain	N/A	IgG, IgM, ultrasound	Various	N/A	N/A
Laze (2015)	Unclear; Albania	200 (50)	IgM	Serum	Assay accuracy	Both IgM assays showed sensitivity and specificity >90%. Authors report good concordance between assays.
Pavia (2015)	Retrospective; Italy	Unclear (40)	IgG, IgM, IgG avidity	Serum	Assay accuracy	Within 90 days of primary infection, sensitivity: 98%; after 120 days, sensitivity: 76.5%; after 150 days, sensitivity: 38%. Author conclude that the assay appears useful for accurate diagnosis of CMV in pregnancy.
Rawlins (2010)	Retrospective; USA	307 samples	IgM	Serum	Assay accuracy	Relative specificity: 99.7%. Authors conclude that the IgM assay showed good analytical performance for routine clinical testing.
Tairaku (2016)	Unclear; Japan	2224 (3)	IgG avidity	Serum	Diagnostic accuracy of fetal/neonatal cCMV in maternal testing	Sensitivity: 22%, specificity: 95%, PPV: 2.4%, NPV: 99.5%. Authors conclude that maternal serological screening to predict cCMV is limited.
Toriyabe (2020)	Unclear; Japan	26073 (13 congenital infections)	IgG avidity	Serum	Diagnostic accuracy of fetal/neonatal cCMV in maternal testing	Diagnostic outcomes not reported. Authors conclude that in the reported maternal CMV antibody screening programme, the introduction of IgM testing was valid to detect cCMV.

Table 11: Summary of the non-randomised studies included in the systematic reviews evaluating secondary prevention of valaciclovir and hyperimmune globulin (HIG)

First author	Study type and location	Basic population characteristics	Gestational stage at start of treatment	Drug/treatment given (n)	Control (n)	Dose & frequency	Duration of treatment	Outcomes	Findings
Egloff, 2023[54]	Retrospective Israel	Maternal primary CMV infection	13.6 weeks at start of treatment	Valaciclovir (n=59)	No valaciclovir (n=84)	8g/day	unclear	Rates of cCMV at birth (vertical transmission); AEs	Valaciclovir led to a lower rate of vertical transmission than control [OR: 0.4 (95% CI: 0.18 to 0.90), p=0.029]
Faure-Bardon, 2021[55]	Prospective France	Maternal primary CMV infection	12.7 weeks at start of treatment	Valaciclovir (n=65)	No valaciclovir (n=65)	8g/day	35 days	Rates of cCMV at birth (vertical transmission); AEs	After multivariable logistic regression, vertical transmission was lower in the valaciclovir group [OR: 0.32 (95% CI: 0.12 to 0.84), p=0.021]
Blazquez-Gamero, 2019[57]	Retrospective (Single arm) Spain	Maternal primary CMV infection	Around 21 weeks (median)	Hyperimmune globulin (n=17) [prevention arm only]	No comparator (single arm)	100 U (2.0 ml) per kg	unclear	Rates of cCMV at birth (vertical transmission); symptoms	21/30 fetuses were positive for CMV at amniocentesis. 24/36 babies were infected at birth.
Buxmann, 2012[58]	Retrospective (Single arm) Germany	Mothers with primary CMV infection	The time from diagnosis to the first treatment was up to 14 days for 16 mothers, 15 – 43 days for 14 mothers, and unknown for the remaining 7 mothers. Diagnosis was generally in the first trimester, so treatment was	Hyperimmune globulin (n=38) [prevention arm only]	No comparator (single arm)	50-270 U/kg; 2-5 times	unclear	Rates of cCMV at birth (vertical transmission)	9/39 children were positive for cCMV at birth in the secondary prevention group (where the fetuses had not been tested for CMV, or shown positive for CMV, prior to the first dose of HIG)

First author	Study type and location	Basic population characteristics	Gestational stage at start of treatment	Drug/treatment given (n)	Control (n)	Dose & frequency	Duration of treatment	Outcomes	Findings
			probably before 20 weeks in general.						
Chiaie, 2018[59]	Retrospective (Single arm) Germany	Pregnant women with primary CMV infection	Not stated when treatment started	Hyperimmune globulin (n=50)	No comparator (single arm)	At least two weight-based intravenous doses of CMV HIG (200 U/kg) every 2–3 weeks	unclear	Rates of cCMV at birth (vertical transmission); sequelae; AEs	cCMV infection was found in 19/53 children at birth or antenatally. The rates of sequelae were 10.5%. HIG was well-tolerated.
Kagan, 2019[60]	Prospective (historical non-treatment group) Germany	Maternal primary CMV infection	Treatments started at or before week 14; mean 11.1 weeks	Hyperimmune globulin (n=40)	No HIG treatment (historical matched cohort) (n=108)	200IU/kg biweekly	Until 20 weeks gestation (but on average until 16.6 weeks)	Rates of cCMV at birth (vertical transmission)	Vertical transmission by birth was 7.5%. A higher rate was found in the matched historical control group (32.5%). The difference between groups was significant (p<0.0001).
Kagan, 2021[61]	Prospective (single arm) Germany	Maternal primary CMV infection	Treatments started at mean 10.6weeks	Hyperimmune globulin (n=149)	No comparator (single arm)	200IU/kg biweekly	Until 17.9 weeks gestation (median)	Rates of cCMV at birth (vertical transmission)	At amniocentesis 10/153 fetuses were infected with CMV.
Minsart, 2018[63]	Retrospective (cohort, matched) Canada	Maternal primary CMV. Therapeutic groups also with positive CMV PCR for amniotic fluid, or US anomalies	Median 26 weeks +/- 6	Hyperimmune globulin (n=5) [prevention arm only]	No HIG (n=26) [prevention arm only]	150mg/kg monthly	unclear	Rates of cCMV at birth (vertical transmission); symptoms; AEs	After matching, there was no difference (p=0.631) in outcomes between HIG-treated (20%) and untreated (38.5%) women. HIG was well-tolerated.

First author	Study type and location	Basic population characteristics	Gestational stage at start of treatment	Drug/treatment given (n)	Control (n)	Dose & frequency	Duration of treatment	Outcomes	Findings
		suggesting cCMV							
Seidel, 2020[65]	Retrospective (281 un-matched CMV controls) Germany	Maternal primary CMV infection	17 weeks at start of treatment	Hyperimmune globulin (n=46)	Compared to data of people with CMV but no HIG treatment from Feldman et al. (2011) (n=281)	two or more infusions of 200IU/kg	Two doses given in a 2 week interval	Rates of cCMV at birth (vertical transmission); AEs	Vertical transmission was 23.9% in the HIG group and 39.9% in the untreated control group (p=0.026)
Visentin, 2012[66]	Prospective (unmatched historical) Italy	Early (pre week 17) maternal primary CMV infection	20-24 weeks at start of treatment	Hyperimmune globulin (n=31)	No HIG (n=36)	200 UI/kg in one IV administration	Single dose, between weeks 20-24	Rates of cCMV at birth (vertical transmission); sequelae	HIG treatment improved outcomes in children but the effect on vertical transmission was unclearly reported.

Table 12. Summary of the non-published secondary prevention treatment studies (all in abstract form)

First author	Study type (location)	Basic population characteristics	Gestational stage / trimester at start of treatment	Drug/treatment given	Control	Dose, frequency and duration	Outcomes	Key findings
D'Ambrosio, 2024[67]	Case-control Italy	Pregnant women with primary CMV infection	Diagnosed prior to the periconceptional period/first trimester	Valaciclovir (n=43)	No valaciclovir (n=37)	8g daily, "during pregnancy", implying until birth	Vertical transmission; US abnormalities; MRI abnormalities; AEs	Vertical transmission was lower in the valaciclovir group (7.9%) compared to the control group (34.5%) [p=0.006]. No adverse events were observed in the valaciclovir group.
Meogrossi, 2023[68]	Observational Italy	Confirmed maternal CMV infection	results stratified by gestational stage	Valaciclovir (n unclear)	No valaciclovir (n unclear)	No data	death; termination; anomalies on imaging; symptoms at birth	Vertical transmission was significantly lower in pregnancies receiving valaciclovir following first trimester infection (pooled OR 0.30, 95%CI 0.16-0.59, I2 = 0%, p = 0.001).
Salome, 2022[69]	Observational Italy	Pregnant women with CMV infection	Unclear	Valaciclovir (n=16)	No comparator	8g/day, until negative amniocentesis or birth (if positive amniocentesis and/or signs of fetal infection)	Vertical transmission; adverse events	16 women were treated, without significant adverse events. 10/12 newborns were negative for congenital infection. The 2/12 with vertical transmission were asymptomatic at birth and did not have sequelae.
Ville, 2021[70]	Single arm France	Maternal primary CMV infection with either unknown cCMV status (valacyclovir for secondary prevention), or	Treatment started prior to 14 weeks gestation	Valaciclovir (n=81)	No comparator	8g/day given in 4 divided doses per day, or 2 divided doses per day	Renal toxicity (compared between the 4 divided doses vs 2 divided doses regimens in both the	Acute renal failure occurred in one woman after 4 days of treatment using the two dose regimen. 7/42 (16%) on the four dose regimen had vertical transmission, and 2/33 (6%) had vertical transmission on the two dose regimen.

First author	Study type (location)	Basic population characteristics	Gestational stage / trimester at start of treatment	Drug/treatment given	Control	Dose, frequency and duration	Outcomes	Key findings
		known cCMV status (valacyclovir for tertiary prevention)					secondary and tertiary prevention strata).	
Yinon, 2023	Single arm Israel	Maternal primary CMV infection	unclear	Valaciclovir (n=75)	No comparator	8g/day, until amniocentesis at 21-22 weeks	vertical transmission	23% had vertical transmission, and there was a non-negligible rate of adverse events.
Nigro, 2012	Case-control Italy	Primary CMV infection	Unclear	immunoglobulin (n=32)	no immunoglobulin (n=32)	No data	Sequelae by 1-5 years (hearing deficit and/or psychomotor retardation). If sequelae, designated a case, otherwise control.	An analysis of the 32 matched case-control pairs revealed that the only independent risk factor for an affected child was the mother not receiving therapeutic immunoglobulin (P = 0.001).

Table 13. Summary of fetal testing studies included in the systematic reviews

First author	Study type	Location	Test type	N total	Author summary (in authors own words)
Birnbaum, 2017[96]	Retrospective	Israel	fetal neurosonography	81	Adding MRI in CMV-infected cases with a normal neurosonographic follow-up should be weighed against a nonnegligible rate of false positive and inconclusive finding
Cannie, 2016[97]	Prospective	Belgium	fetal MRI	121	Prediction of SNHL and neurological impairment is feasible by fetal MR imaging with a high negative predictive value and can equally be done at 27 or 33 weeks of gestation
Desveaux, 2016[98]	Prospective	France	Amniotic fluid peptide biomarkers	47	This classifier further yielded 89% sensitivity, 75% specificity and an area under the curve of 0.90 to segregate 9 severely symptomatic from 12 asymptomatic neonates in a validation cohort
Doneda, 2010[99]	Prospective	Italy	fetal US and MRI	38	MR imaging had higher sensitivity than US in detecting brain anomalies (92% vs 38%) and in predicting symptomatic infection (83% vs 33%)
Fabbri, 2011[100]	Retrospective	Italy	Blood sample markers	94	The determination of multiple markers in fetal blood, following virus detection in amniotic fluid samples, is predictive of perinatal outcome in fetuses with HCMV infection
Farkas, 2011[101]	Retrospective	Israel	fetal brain US	21	Normal neurosonographic examinations during pregnancy appear to predict a normal early neuropsychological outcome in fetuses with congenital CMV infection
Goegebuer, 2009[102]	Retrospective	Belgium	Viral load in amniotic fluid	282	A correlation between the CMV viral load in AF and the ... neonatal outcomes could not be demonstrated
Imafuku, 2020[103]	Prospective	Japan	fetal clinical factors and US	32	A combination of maternal fever/flu-like symptoms, ultrasound fetal abnormalities, or preterm birth at less than 34 gestational weeks as optimal predictive factors showed 90.6% sensitivity, 66.4% specificity
Kaneko, 2013[104]	Prospective	Japan	fetal US in conjunction with maternal factors	1163	Fetal US in conjunction with maternal factors enabled detection of infected fetuses having severe sequelae.
Leruez-Ville, 2016[105]	Retrospective	France	fetal ultrasound, amniotic fluid, and fetal blood analysis	82	Bivariate analysis combining ultrasound results and either adjusted viral load in amniotic fluid or fetal blood profile showed that these were independent prognostic factors of a symptomatic status at birth
Leyder, 2016[106]	Prospective	Belgium	fetal US	69	The PPV of targeted US screening for identifying infected fetuses that would subsequently present with clinical impairments was 83.3%

First author	Study type	Location	Test type	N total	Author summary (in authors own words)
Lipitz, 2010[107]	Prospective	Israel	fetal US and MRI	38	The outcome of congenital primary CMV infection with normal prenatal ultrasound and MRI exams is favourable. The prognostic value of subtle MRI findings is limited
Lipitz, 2013[108]	Prospective	Israel	fetal US and MRI	145	The risk of severe sequelae is significantly reduced in the presence of normal prenatal ultrasound and MRI findings.
Lipitz, 2020[109]	Prospective	Israel	fetal US and MRI	123	The risk of childhood sequelae after first-trimester fetal CMV infection is most often associated with abnormal prenatal imaging findings. However, normal imaging does not rule out the development of SNHL and minor neurodevelopmental abnormalities.
Picone, 2014[110]	Retrospective	France	fetal US	69	A possible specific sign is described: an anechogenic cavity located on the extremity of the occipital horn and/or near the temporal horn, in the region of the germinal zone that contains numerous proliferating and differentiating germinal cells
Roee, 2020[111]	Retrospective	Israel	Fetal US and MRI	27	When subtle imaging findings are isolated and nonprogressive the prognosis is probably favourable in the majority of cases.
Vorontsov, 2022[112]	Prospective	Israel	Amniotic fluid biomarkers	43	Amniotic fluid levels of Chemerin, Gal-3BP and CMV DNA load were each highly predictive of severe cCMV

Table 14. Summary of unpublished fetal testing studies

First author	Study type	Location	Test type	N total	Author summary (in authors own words)
Gabrielli, 2012[113]	Prospective	Italy	fetal MRI and blood markers	16	Foetal MR imaging does not contribute more information to US as a prognostic marker of adverse outcome, whereas foetal platelet count determination appears to be the only biological parameter in foetal blood associated significantly with the outcome
Hulsbosch, 2013[114]	Retrospective	Belgium	fetal/US MRI	18	Critical brain lesions were present on ultrasound in all cases of CMV infected fetuses ending in termination.
Katorza, 2019[115]	Retrospective	Israel	fetal MRI	42	There is a correlation between smaller cerebellar volume and lower VABS-II questionnaire scores, especially in the fields of daily living and communication skills
Meogrossi, 2023[116]	Prospective	Italy	Blood tests	104	Viral load in the amniotic fluid is a strong predictor of adverse perinatal outcome in congenital CMV infection
Miller, 2019[117]	Retrospective	Israel	fetal/US MRI	243	After exclusion of sonographic abnormalities, anatomical findings on MRI are not significantly associated with NDI, SNHL or composite outcome
Puccetti, 2009[118]	Retrospective	Italy	Viral load in amniotic fluid	603	A high viral load seems to be related with congenital symptomatic CMV infections. Low viral load (<500) in the AF can rule out fetal/neonatal damage.
Radan, 2023[119]	Retrospective	Unclear	Viral load in amniotic fluid	14	The data suggest poor predictive value of amniotic fluid VL for symptomatic CMV infection of the newborn
Stirnemann, 2017[120]	Prospective	France	fetal MRI	57	A white matter hyperintense T2 signal is independently associated with an adverse outcome following a reassuring mid-trimester assessment for cCMV. In asymptomatic fetuses, such a finding would suggest a 50% risk of hearing loss, whereas its absence strongly suggests a favourable outcome
Tassis, 2016[121]	Retrospective	Italy	fetal MRI	23	The incidence of minor abnormalities on postnatal brain MRI was very high and these were not clinically useful to predict neurodevelopment or hearing impairment
Van den Eede, 2024[122]	Retrospective	Belgium	fetal US/MRI/VL	473	Only 3% of patients with abnormal outcome were not detected on prenatal imaging
Vangoitsenhoven, 2020[123]	Retrospective	Belgium	fetal US / VL	181	In patients with less than 5 million copies, 52% had normal and 42.8% abnormal follow up.
Ville, 2019[124]	Retrospective	France	fetal US/MRI	62	PPV and NPV of second trimester prognostic assessment (STA) alone and STA+ MRI in predicting sequelae over mild hearing loss was 26% and 82% and 32% and 100% respectively.

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