UK National Screening Committee

# Congenital cytomegalovirus: a systematic review of newborn screening

## External review against programme appraisal criteria for the UK National Screening Committee

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**The UK National Screening Committee secretariat is hosted by the Department of Health and Social Care**

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# About the UK National Screening Committee (UK NSC)

The UK NSC advises ministers and the NHS in the 4 UK countries about all aspects of population screening and supports implementation of screening programmes.

Conditions are reviewed against evidence review criteria according to the UK NSC's evidence review process.

Read a complete list of UK NSC recommendations.

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www.gov.uk/uknsc

Blog: https://nationalscreening.blog.gov.uk/

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# Abbreviations

| | |
|---|---|
| cCMV | Congenital cytomegalovirus |
| CI | Confidence interval |
| CMV | Cytomegalovirus |
| CNS | Central nervous system |
| CSF | Cerebrospinal fluid |
| CT | Computed tomography |
| DBS | Dried blood spots |
| ECCI | European Congenital Cytomegalovirus Initiative |
| FN | False negative |
| FP | False positive |
| HTA | Health Technology Assessment |
| LSV | Lenticulostriate vasculopathy |
| MRI | Magnetic resonance imaging |
| NHS | Newborn hearing screening |
| NICU | Neonatal intensive care unit |
| NPV | Negative predictive value |
| NSC | National Screening Committee |
| PCR | Polymerase chain reaction |
| PPV | Positive predictive value |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| QUADAS | Quality Assessment of Diagnostic Accuracy Studies |
| RCT | Randomised controlled trial |
| SNHL | Sensorineural hearing loss |
| TN | True negative |
| TP | True positive |
| US | Ultrasound |
| WMA | White matter abnormalities |

# Plain English summary

Cytomegalovirus (CMV) is a common virus which usually causes mild flu-like symptoms, but sometimes causes problems in babies and people with a weakened immune system like elderly people and people undergoing transplants. If the virus is passed on to a fetus during pregnancy, the baby may be born with CMV infection, called congenital CMV (cCMV). Around 10% of babies with cCMV are born with symptoms and around half of these babies will develop long-term complications, such as hearing loss and developmental problems. Around 10-15% of those without early symptoms will develop problems later. Testing for cCMV at birth could enable treatment which could prevent or reduce long-term harm. Testing should ideally be done within three weeks of birth to avoid confusing cCMV with a CMV infection acquired after birth, which is less likely to cause long-term harm.

The UK National Screening Committee (UK NSC) does not currently recommend screening for cCMV. As part of its regular reviews on the evidence, the UK NSC commissioned York Evidence Synthesis Group to review existing studies to assess whether screening tests for newborn babies (defined as up to 28 days old in this review) can identify which babies are likely to develop long-term complications and would benefit from early treatment. We found 217 studies and extracted data from 171 studies that were reported in full.

We found 39 studies assessing how accurate saliva and dried blood spot testing were at detecting cCMV. These found that both tests were very accurate and will probably identify 90% or more of all cCMV cases. Hence both saliva and dried blood spot testing could be used to screen newborns for cCMV.

We found 97 studies that examined tests or characteristics of newborn babies with cCMV to identify who might experience long-term harm. The types of tests or characteristics varied, and evidence on most tests or characteristics was limited. The factor most clearly associated with long-term harm from cCMV was babies who showed symptoms of cCMV infection at birth, particularly hearing loss. There was some evidence that performing magnetic resonance imaging (MRI) scans on newborns can predict long-term developmental issues.

We found 37 studies that looked at newborn screening programmes to spot cCMV. None compared screening to current practice, so there is no evidence that screening for cCMV gives benefits when compared to what is currently done. Testing all newborns for cCMV ("universal screening") will identify almost all cCMV cases, but will identify lots of babies with no symptoms, most of whom will experience no long-term harms, but will undergo further examinations and possibly unnecessary treatment. Screening only babies who fail a newborn hearing test could identify most newborns who will have long-

term symptoms, but will miss some newborns with other types of symptoms, or where symptoms develop later.

Overall, although there is a lot of evidence on newborn screening for cCMV, it is not sufficient to conclusively recommend that it be used in practice. More studies comparing cCMV screening to standard medical practice without screening are needed to confirm exactly how children might benefit from screening.

# *Executive summary*

## Purpose of the review

This review aimed to assess whether there have been significant developments in the evidence base on screening for congenital cytomegalovirus (cCMV) since the previous full review of newborn screening for cCMV was conducted in 2017, and since the most recent evidence map in 2022. The review aimed to determine if sufficient evidence exists to support the establishment of a screening programme for cCMV in newborn infants.

## Background

Cytomegalovirus (CMV) is a common virus which usually causes mild flu-like symptoms. However, if the virus is passed on to a fetus during pregnancy, the baby may be born with CMV infection, called cCMV. cCMV is the lead infectious cause of neurological disabilities in children in Europe. In the UK, roughly 650,000 to 695,000 babies are born each year. Around 2,400 babies are born with cCMV every year in the UK; around 10% have symptoms at birth and around half of these babies will experience long-term sequelae, primarily hearing and neurodevelopmental impairment. In addition, around 10% of asymptomatic newborns develop hearing impairment throughout early childhood. Overall, each year around 400 babies born in the UK with cCMV will experience long-term problems. In the newborn infant, cCMV may be diagnosed by urine, saliva or blood polymerase chain reaction (PCR) assay in the first 21 days of life, to distinguish cCMV with CMV acquired after birth. Antiviral treatment is reserved for newborns with severe disease, central nervous system (CNS) related symptoms or sensorineural hearing loss (SNHL).

## Focus of the review

The aim of this project was to assess the value of initiating a screening programme for cCMV in newborns to reduce the long-term health burden caused by cCMV infection. A systematic review was undertaken to assess 4 key review questions:

1. What is the diagnostic accuracy of cCMV testing of saliva in newborns?
2. What is the diagnostic accuracy of cCMV testing of dried blood spots (DBS) in newborns?
3. What tests in newborns with cCMV identify which are likely to suffer long-term health consequences from cCMV, who would benefit from prompt treatment?

4. Can a screening programme for cCMV reduce the burden of cCMV-related morbidity and mortality?

## Recommendation under review

The UK National Screening Committee (UK NSC) does not currently recommend population or targeted screening for cCMV in newborns.

## Findings of this review and gaps in the evidence

A single overarching systematic search and review was conducted to answer all the key questions in this report, adapted to relate to the criteria set out by the UK NSC for assessing the suitability of a screening programme. These key questions will help answer the review questions above. A total of 171 published studies were included in the review. A summary of results for each criterion and key question is presented below.

### Criterion 4: There should be a simple, safe, precise and validated screening test.

*Key question 1 – What is the diagnostic accuracy of cCMV testing of saliva in newborns?*

*Key question 2 – What is the diagnostic accuracy of cCMV testing of dried blood spots (DBS) in newborns?*

The review included 39 studies relevant to these questions; 21 studies assessed saliva tests, 9 assessed DBS tests, 2 assessed both saliva and DBS tests, and 10 assessed other tests (3 of these also assessed saliva tests), including urine and cord blood testing. Individual studies and reviews were generally of good quality. Results from 1 systematic review (9 studies included in the meta-analysis) and our meta-analysis of 12 studies agreed that saliva screening can accurately detect cCMV with a sensitivity of about 93% for a specificity of over 99%. DBS testing was assessed in 1 systematic review and 10 further studies; results of the review and our meta-analysis of 4 studies demonstrated a similarly high accuracy to detect cCMV, with a sensitivity of between 84% and 90% for a specificity of over 99%. The positive predictive value of both tests was less certain, but may be low because cCMV infection is rare in most populations. Therefore, confirmatory testing for cCMV after a positive saliva or DBS test is probably needed. The 7 studies of urine testing confirmed that it is accurate enough to be considered a reference standard test for cCMV.

Overall, there is a substantial body of high-quality evidence for the accuracy of tests for cCMV. We conclude that saliva, DBS or urine testing could all be used for newborn screening for cCMV, and that further research on the accuracy of these tests is not required.

### Criterion 7: There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.

*Key question 3 – What tests in newborns with cCMV identify which are likely to suffer long-term health consequences from cCMV, who would benefit from prompt treatment?*

The review included 97 studies relevant to this question; 7 systematic reviews, 19 prognostic accuracy studies and 71 studies assessing the association between test results and/or antenatal and/or newborn characteristics and long-term health consequences. A range of tests and characteristics were assessed, however, much of the evidence is of limited quality.

Overall, the results indicate that the most reliable characteristics for predicting long-term sequelae in infants with cCMV are the presence of symptoms at birth and timing of maternal CMV infection. This concurs with current guidelines where newborns with more severe cCMV symptoms are likely to be offered antiviral treatment, but those with milder symptoms are not. Hence how to manage newborns with asymptomatic cCMV remains unclear.

Our results also indicate that the most useful test for predicting long-term hearing and neurodevelopmental sequelae is likely to be magnetic resonance imaging (MRI). Results of studies assessing viral load to predict long-term hearing sequelae are promising, particularly in newborns with asymptomatic cCMV, however, further research is required to confirm these findings. As the risk of long-term sequelae may depend on many factors, development of a multifactorial risk model for long-term harm in newborns with cCMV would be useful.

### Criteria 11 & 13: There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. The benefit gained by individuals from the screening programme should outweigh any harms for example from overdiagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications.

*Key question 4 – Can a screening programme for cCMV reduce the burden of cCMV-related morbidity and mortality?*

The review included 37 studies relevant to this question. No systematic reviews were identified and no studies compared newborn cCMV screening to current practice, or any management without screening. Therefore, it is not possible to conclude whether newborn screening leads to genuine benefits or harms for newborns, and the evidence available to address this question is of low quality.

Fifteen studies examined universal screening for all newborns. These found that universal screening would identify nearly all cases of cCMV, but most of these would be asymptomatic at birth and not likely to develop long-term sequelae. One study of a low-cCMV prevalence population in Finland found that the

rate of long-term sequelae in newborns with cCMV was not different to the rate in newborns without cCMV.

Twenty-two studies examined targeted screening, primarily screening newborns who fail a newborn hearing test. These studies found that targeted screening identifies newborns who will have long-term hearing loss, but will not detect cCMV in newborns with other types of symptoms, or where symptoms develop later.

Overall, there is insufficient evidence to demonstrate that newborns will benefit from cCMV screening when compared to current medical practice. Randomised or non-randomised studies comparing newborn screening to practice without screening are required in this area for both universal and targeted screening.

### Criterion 12: There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public.

The review included 5 studies relevant to this question. All were small surveys on the acceptability and feasibility of saliva testing, rather than newborn cCMV screening as a whole. The surveys mostly conclude that saliva testing was feasible and acceptable. Some concerns over screening increasing parental anxiety were raised. The evidence base is too small and of too limited quality to draw any meaningful conclusions.

## Recommendations on screening

There has been a substantial amount of new research on newborn screening for cCMV since the previous review conducted in 2017. In particular, there has been substantial new research on the accuracy of saliva, DBS and urine testing for cCMV. This new evidence appears to be of sufficient quantity and quality to show that all 3 tests could reasonably be used to test for cCMV as part of a screening programme.

While there have been many studies on tests and characteristics that may predict long-term harms in newborns with cCMV, the quality of the evidence is limited and is insufficient to draw definitive conclusions on their value within a screening programme. The only characteristic that is clearly associated with long-term harm is displaying cCMV-related symptoms at birth, such as hearing loss. This raises questions about how newborns who are asymptomatic might be managed, given their low rate of long-term harm.

A particular limitation of the evidence base is the lack of any randomised or non-randomised evidence comparing the outcomes of newborn cCMV screening to standard medical practice, or ad-hoc cCMV testing, without screening. All evidence on existing screening programmes is non-comparative and so of

low quality. Randomised trials may be difficult to conduct in this area, but trials or real-world evidence comparing screening to practice without screening are needed. Without such evidence, even if not randomised, it is not possible to determine to what extent newborns will benefit from cCMV screening, so universal or targeted cCMV screening cannot be recommended for implementation at this time.

## Limitations

Much of the evidence included in this systematic review is limited by the study design, size and quality. In addition, many of the included studies may not be applicable to the UK, owing to differences in health systems and the incidence of primary and non-primary maternal CMV infection in different countries. The evidence is too limited to draw definitive conclusions on the value of initiating a screening programme for cCMV in newborns to reduce the long-term health burden caused by cCMV infection.

## Evidence uncertainties

The main uncertainty in the evidence is the lack of evidence comparing cCMV screening to standard medical practice. Randomised trials, non-randomised studies, or other real-world studies comparing newborn cCMV screening to practice without screening are needed to properly demonstrate whether screening for cCMV will provide long-term benefits to children, as the current evidence is inconclusive.

In terms of further diagnostic investigation of newborns with cCMV to identify which infants are likely to benefit from prompt treatment, the results of studies assessing viral load to predict long-term sequelae appear promising, particularly in newborns with asymptomatic cCMV. Therefore, further research on the prognostic accuracy of viral load is recommended.

# Introduction and approach

## Background

### The condition

Cytomegalovirus (CMV) is a common virus which can cause mild flu-like symptoms or can 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 in the UK around 3-5 in 1000 babies are born with cCMV:[1] This equates to around 2,400 babies every year from approximately 600,000 live births.[4] 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 the symptomatic 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 throughout early childhood,[6] and a proportion may go on to have learning, concentration and communication difficulties. Overall, each year around 400 babies born in the UK with cCMV will experience long-term problems.[7] Other publications suggests a rate of long-term sequalae of around 17-20%,[8] or potentially around 900 babies per year experiencing long-term problems.[9]

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 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.[10, 11] The risk of fetal transmission is 30-35% with primary maternal infection, compared to around 3% or less with re-infection/reactivation. Primary maternal infection and infection occurring earlier in gestation are associated with higher rates of fetal transmission and earlier infection is also associated with poorer fetal outcomes.[12]

## Screening and treatment

In the newborn infant, cCMV may be diagnosed by urine, saliva or blood polymerase chain reaction (PCR) assay in the first 21 days of life; after 21 days it is not possible to distinguish cCMV from postnatal CMV infection. Previous research has shown that saliva testing may result in more false positive test results (from maternal CMV shed in breastmilk).[12] Research has also shown that newborn dried blood spot (DBS) testing may have lower sensitivity than saliva or urine;[7] however, it can be used to diagnose cCMV retrospectively after 21 days of age.

The European Expert Consensus Statement on Diagnosis and Management of Congenital Cytomegalovirus recommends that antiviral treatment should be reserved for babies with evidence of central nervous system (CNS) disease or other 'severe' disease.[13] Updated consensus recommendations from the European Congenital Cytomegalovirus Initiative (ECCI), published in May 2024, recommend treating newborns with isolated sensorineural hearing loss (SNHL), in addition to those with CNS related symptoms.[8] The reason for treatment in this scenario is to try to prevent late-onset SNHL in the other ear. Oral valganciclovir is the drug of choice and intravenous ganciclovir should be used in babies unable to tolerate oral drugs or where gastrointestinal absorption is uncertain. No treatment is recommended for babies with 'mild' disease. Whilst the definition of mild disease is not clear, the 2017 European Expert Consensus Statement states that mild disease includes those with isolated (1 or 2 at most) and otherwise clinically insignificant or transient findings. These can include petechiae, mild hepatomegaly or splenomegaly or biochemical/haematologic abnormalities (such as thrombocytopenia, anaemia, leukopenia, borderline raised liver enzyme abnormalities or conjugated hyperbilirubinemia), and babies who are small for gestational age (weight for gestational age <2 standard deviations) without microcephaly.[13] However, evidence on treatment effectiveness is limited, especially in babies who do not show signs of infection. Much of the debate around treatment relates to the potential adverse effects of antiviral drugs.[13] The updated consensus recommendations list the following indications for testing for cCMV infection in newborns: evidence of maternal primary CMV infection during pregnancy; presence of indicative features on prenatal ultrasonography or MRI; newborn clinical manifestations consistent with cCMV.[8]

# Current global landscape of newborn screening

In the USA, universal cCMV screening was introduced in 2023 in Minnesota and it is projected to be introduced in Connecticut in 2025. In addition, a National Institutes of Health study of universal screening in New York is underway and it is anticipated that screening will continue after this study has ended.[14] In Canada, 4 provinces are implementing universal newborn screening for cCMV, and 3 provinces have targeted screening programmes that offer cCMV testing to newborns who fail newborn hearing tests.[15] cCMV screening is also in use in Japan as part of wider newborn screening programmes.[16]

## Current policy context and previous reviews

The UK National Screening Committee (UK NSC) does not currently recommend population screening for cCMV in newborns.[17] This recommendation, based on an evidence review published in 2017,[18] concluded that there was insufficient evidence to recommend the introduction of newborn screening for cCMV because:

- It is not clear how to identify newborns that will develop long-term sequelae.
- The treatment offered to babies with asymptomatic cCMV infection is unclear.
- Screening is likely to identify a greater number of infants with cCMV, the majority of which are likely to have minimal symptoms or no symptoms. The management and treatment approach for these children is unclear, and it is unknown whether screening improves their outcomes.

A UK NSC evidence map on newborn screening for CMV, published in June 2022, concluded that no further work on screening for CMV should be commissioned at that time, but that the UK NSC would review the decision on screening for CMV in 3-years' time.[7]

## Objectives

This review aimed to assess whether there have been significant developments in the evidence base since the previous review was conducted in 2017, and if sufficient support exists for a screening programme for cCMV in newborns to reduce the long-term health burden caused by cCMV infection.

The overall objective was to undertake a systematic review to assess the clinical evidence on:

- newborn screening tests for identifying cCMV infection
- tests to determine which newborns are likely to develop long-term complications from cCMV
- whether a screening programme for cCMV can reduce the burden of cCMV-related complications

The review appraised evidence on the key questions in Table 1, adapted to relate to the criteria set out by the UK NSC for assessing the suitability of a screening programme. These key questions will help answer the review objectives above.

*Table 1: Key questions for the evidence summary and relationship to the UK NSC screening criteria*

| | Criterion | Key questions | Studies Included |
|---|---|---|---|
| **The Test** | | | |
| 4 | There should be a simple, safe, precise and validated screening test. | KQ1: What is the diagnostic accuracy of cCMV testing of saliva in newborns?<br><br>KQ2: What is the diagnostic accuracy of cCMV testing of dried blood spots (DBS) in newborns? | KQ1: 1 systematic review and 22 diagnostic accuracy studies<br><br>KQ2: 1 systematic review and 10 diagnostic accuracy studies<br><br>10 diagnostic accuracy studies assessed other tests, including urine |
| 7 | There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals. | KQ3: What tests in newborns with cCMV identify which are likely to suffer long-term health consequences from cCMV, who would benefit from prompt treatment? | 7 systematic reviews<br><br>19 prognostic accuracy studies<br><br>71 association studies |
| | **The screening programme** | | |
| 11 | There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. | KQ4: Can a screening programme for cCMV reduce the burden of cCMV-related morbidity and mortality? | 15 evaluations of universal screening programmes<br><br>22 evaluations of targeted screening programmes |
| 12 | There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public. | KQ4: Can a screening programme for cCMV reduce the burden of cCMV-related morbidity and mortality? | 5 studies with surveys reporting acceptability and feasibility of a screening programme |
| 13 | The benefit gained by individuals from the screening programme should outweigh any harms for example from overdiagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications. | KQ4: Can a screening programme for cCMV reduce the burden of cCMV-related morbidity and mortality? | 15 evaluations of universal screening programmes<br><br>22 evaluations of targeted screening programmes |

# Methods

The current review was conducted by York Evidence Synthesis Group, in keeping with the UK NSC evidence review process. Database searches were conducted in November 2024 to identify studies relevant to the questions detailed in Table 1.

The systematic review was conducted following the general principles recommended in the Centre for Reviews and Dissemination's guidance and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[19, 20] The systematic review was registered with PROSPERO, registration number CRD42024616064.

The York team were supported throughout the project, from inception to the writing of this report, by a broad advisory group. This consisted of representatives from UK NSC, experts in cCMV infection and newborn screening, representatives of the charity CMV Action, and families affected by cCMV.

## Databases/sources searched

The aim of the search was to systematically identify published, unpublished and ongoing studies of screening tests or programmes to detect cCMV in newborns, and additional screening tests to triage newborns with cCMV for antiviral treatment. Comprehensive searches of databases and trial registers were undertaken, supplemented by reference checking of relevant systematic reviews, manual searches of abstracts from relevant CMV conferences, and requests for relevant research from advisory group members.

A search strategy was designed in Ovid MEDLINE by an information specialist in consultation with the review team. The strategy combined terms for newborns with terms for CMV. Searches of the title, abstract and author keyword fields of database records along with relevant subject headings were included in the strategy. The search was limited to records published from 2013 onwards in order to update previous reviews undertaken for the UK NSC. No further limits were applied. The MEDLINE strategy was peer reviewed using aspects of the Peer Review of Electronic Search Strategies (PRESS) checklist,[21] and then translated to run on further databases and resources.

The following databases were searched in November 2024: MEDLINE ALL (Ovid), Embase (Ovid), Maternity and Infant Care Database (Ovid), Cochrane Central Register of Controlled Trials (CENTRAL, Wiley), the Science Citation Index (Web of Science), CINAHL (Ebsco), LILACS, Cochrane Database of Systematic Reviews (CDSR, Wiley), Database of Abstract of Reviews of Effects (DARE) and KSR Evidence (Ovid).

Unpublished, ongoing or grey literature was identified through searching the HTA database, International HTA database (INAHTA), websites of international HTA organisations, Conference Proceedings Citation index – Science (Web of Science), ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, EU Clinical Trials Register and PROSPERO. All search results were imported into EndNote 21 reference management software and deduplicated.

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 full search strategies can be found in Appendix 1.

# Eligibility for inclusion in the review

Deduplicated references identified by the electronic searches were uploaded into EPPI-Reviewer. The machine learning and text mining tool in EPPI-Reviewer (priority screening) was used to prioritise titles and abstracts for screening.[22] The first 40% of prioritised records were independently screened by 2 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 1 reviewer. It was initially planned to double screen at least 10% of records, however, owing to the complexity of the review question the level of agreement between reviewers was unacceptably low, therefore, double screening was continued until an acceptable level of agreement was reached. The full texts of potentially eligible studies were assessed independently by 2 reviewers, using the same process for resolution of disagreements as outlined above. Non-English language publications were eligible for inclusion and translated for data extraction. Eligible ongoing studies (e.g., reported in protocols and trial registers) without relevant outcome data reported at the time of data extraction were included and tabulated as 'Ongoing Studies'. Eligible studies published as conference abstracts were included and tabulated as 'Unpublished Studies'.

## Inclusion criteria

### Population

The population of interest for screening for cCMV infection was newborns, defined as up to 28 days old.

### Index tests and interventions

This assessment included any test used to detect cCMV in newborns, such as PCR assay of saliva, urine or blood. This assessment also included tests conducted in newborns for identifying which newborns who test positive for cCMV are likely to develop long-term complications, and so would benefit from prompt treatment. The relevant tests include CMV viral load tests, genetic tests and specific clinical or medical findings (e.g., newborn hearing tests and MRI). In addition, retrospective assessment of tests undertaken during pregnancy for maternal prognostic factors (i.e., assessment of booking bloods to determine timing of CMV infection) were included.

Both standalone and multiplex tests were eligible for inclusion. Tests that were only conducted after 28 days of life, or after initiation of antiviral treatment, were excluded.

### Comparators

Studies did not have to include any comparator group or test to be included. However, studies comparing a screening test or programme to no screening test for detecting cCMV were included, where available, as were studies comparing different screening tests.

## Reference standard

The reference standard for detecting cCMV infection was PCR urine testing. For studies reporting accuracy of tests to detect newborns likely to develop long-term complications from cCMV, the reference standard was confirmed clinical diagnosis of any morbidity (e.g., hearing loss, neurological impairment) in childhood, or absence of diagnosed morbidity in childhood. As newborns may be treated to prevent complications, which would interfere with this reference standard, alternatives were accepted, such as poor performance on newborn hearing tests, or other indicators of long-term morbidity.

## Outcomes

When considering the accuracy of screening tests to detect long-term health consequences the key outcomes were standard diagnostic accuracy measures (including sensitivity, specificity, positive and negative predictive values).

When considering the overall clinical value and effectiveness of screening the outcomes of interest were:

- cCMV-related morbidities
    - hearing loss, both at birth and later onset or deterioration
    - neurological impairments in infants, including brain imaging results
    - neurodevelopmental outcomes
    - any other long-term negative outcomes associated with cCMV infection
- mortality
- use of additional tests and procedures
- incidental findings, however defined
- potential harms from screening or treatment
- health-related quality of life (of children and their families)
- acceptability of screening

## Study designs

Clinical trials (including randomised and other controlled trials), prospective and retrospective cohort studies and case-control studies were sought. In addition, good quality, up to date, systematic reviews were included.

*Table 2: Inclusion and exclusion criteria for the key questions*

| Key question | Inclusion criteria | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Population** | **Target Condition** | **Intervention** | **Reference standard** | **Comparator** | **Outcome** | **Study type** |
| KQ1: What is the diagnostic accuracy of cCMV testing of saliva in newborns? | Newborns (<28 days) | cCMV | PCR testing of saliva for CMV | Urine PCR testing (or any other reasonable reference standard) | Not required (or comparison with any other cCMV test) | Detection of cCMV | Systematic reviews<br>Prospective or retrospective cohort studies<br>Case-control studies |
| KQ2: What is the diagnostic accuracy of cCMV testing of dried blood spots (DBS) in newborns? | Newborns (<28 days) | cCMV | DBS testing for CMV | Urine PCR testing (or any other reasonable reference standard) | Not required (or comparison with any other cCMV test) | Detection of cCMV | Systematic reviews<br>Prospective or retrospective cohort studies<br>Case-control studies |
| KQ3: What tests in newborns with cCMV identify which are likely to suffer long-term health consequences from cCMV, who would benefit from prompt treatment? | Newborns (<28 days) | Any long-term sequelae related to cCMV | Any test of newborns with cCMV to predict long-term sequelae | Clinical confirmation of symptoms | None | Any long-term sequelae (hearing loss, neurodevelopmental issues etc) | Systematic reviews<br>Prospective or retrospective cohort studies<br>Case-control studies |
| KQ4: Can a screening programme for cCMV reduce the burden of cCMV-related morbidity and mortality? | Newborns (<28 days) being screened for cCMV | cCMV and its long-term sequelae | Any screening test for cCMV (saliva, DBS or urine) | None | None, or outcomes without screening | Presence of cCMV<br>Antiviral treatment<br>Any long-term sequelae (hearing loss, neurodevelopmental issues etc) | Systematic reviews<br>RCTs<br>Other controlled trials<br>Prospective or retrospective cohort studies |

**Abbreviations:** cCMV, congenital cytomegalovirus; CMV, cytomegalovirus; DBS, dried blood spots; KQ, key question; PCR, polymerase chain reaction; RCTs, randomised controlled trials.

## Appraisal of studies for quality and risk of bias

Risk of bias and applicability of prognostic and diagnostic accuracy studies were assessed using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) checklist[23] by 1 reviewer and independently checked by a second reviewer (3 reviewers shared this work). Risk of bias in systematic reviews was assessed by 1 reviewer and independently checked by a second reviewer using the ROBIS tool.[23] Disagreements were resolved through discussion.

For studies that only assessed an association between test results/characteristics and health outcomes, study quality was briefly summarised, but not formally assessed. For non-comparative studies of screening programmes study quality was not formally assessed, but general quality issues across the studies were evaluated.

## Data extraction and methods of synthesis

A standardised data extraction form for study characteristics was developed and piloted. Data on the study design, patient characteristics, intervention(s), comparator(s) and relevant outcomes were extracted from included studies by 1 reviewer and independently checked by a second reviewer (4 reviewers shared this work). Disagreements were resolved through discussion.

The following diagnostic accuracy values were extracted or calculated for each test:

- the number of true positives (TP), which is the number of newborns with a positive cCMV test result who do have cCMV, i.e., the number of newborn babies correctly identified by the cCMV test as having cCMV
- the number of false positives (FP), which is the number of newborns with a positive cCMV test result who do not have cCMV, i.e., the number of newborn babies incorrectly identified by the cCMV test as having cCMV
- the number of true negatives (TN), which is the number of newborns with a negative cCMV test result who do not have cCMV, i.e., the number of newborn babies correctly identified by the cCMV test as not having cCMV
- the number of false negatives (FN), which is the number of newborns with a negative cCMV test result who do have cCMV, i.e., the number of newborn babies incorrectly identified by the cCMV test as not having cCMV

Measures of test accuracy are as follows:

- Sensitivity = TP / (TP + FN)

  This is the true positive rate, which is the probability that a newborn with cCMV receives a positive cCMV test result; in other words, the ability of a test to correctly classify a newborn baby with cCMV.

- Specificity = TN / (TN + FP)

  This is the true negative rate, which is the probability that a newborn without cCMV receives a negative cCMV test result; in other words, the ability of a test to correctly classify a newborn baby without cCMV.

- Positive predictive value (PPV) = TP / (TP + FP)

  This is the probability that a newborn who receives a positive cCMV test result has cCMV.

- Negative predictive value (NPV) = TN / (TN + FN)

  This is the probability that a newborn who receives a negative cCMV test result does not have cCMV.

These test accuracy measures were extracted or, where not directly reported, calculated from other reported data, where appropriate. Calculated measures, as opposed to directly reported measures, are identified as such in all results tables.

For ongoing studies or unpublished studies (conference abstracts or clinical trial/PROSPERO register records) that appeared to meet the review inclusion criteria, basic study details were extracted and are tabulated in Appendix 4.

Study characteristics and results are presented in structured tables (see Appendix 3) and as a narrative summary (see sections below). For diagnostic accuracy studies, where feasible, a joint bivariate meta-analysis of sensitivity and specificity was performed.[24] In cases where meta-analysis was performed the DerSimonian-Laird random-effects method was used, including assessment of heterogeneity using the $I^2$ statistic.[25, 26]

# Question level synthesis

## Overall review summary

A single overarching systematic search and review was conducted to answer all the key questions in this report. The overall review results are summarised briefly here, with discussion of findings for each key question in the sections below.

The electronic searches identified a total of 6,258 records after deduplication between databases. The full texts of 422 records were ordered for further review; 224 were excluded at full paper stage and are listed in Appendix 2, along with the reasons for their exclusion. Eighteen additional records were identified from screening abstract books of ECCI congresses (held in 2022 and 2024). One additional record was identified through consulting with advisory group members. No additional records were found from screening reference lists of relevant systematic reviews. A flow diagram of the study selection process is presented in Appendix 2.

A total of 217 records met the review inclusion criteria. There were 171 studies published in full; study characteristics are presented in Appendix 3. There were 8 ongoing studies and 38 studies only reported as conference abstracts; tabulated in Appendix 4.

# Criterion 4: There should be a simple, safe, precise and validated screening test.

## Previous work

The previous UK NSC evidence review by Bazian Ltd[18] included 1 systematic review and 2 prospective cohort studies that assessed diagnostic tests for the detection of cCMV. The systematic review (Wang et al., 2015)[27] was conducted on the screening of cCMV through the PCR assay of DBS and also included a meta-analysis. It included 14 studies and reported a sensitivity of 84% (95% confidence interval [CI]: 81 to 87) and a specificity of 100% (95% CI: 100 to 100) for detecting cCMV. The previous review concluded that while the specificity of the PCR assay of DBS was very high, the sensitivity was low, particularly when considering only the prospective studies (62%). The review was high-quality with generally a low risk of bias.

The 2 cohort studies assessed the usefulness of real-time PCR assays of both dried or liquid saliva[28] or PCR assays of liquid saliva.[29] Both cohort studies were found to have a high potential for verification bias as confirmatory testing was not conducted in the entire cohort. The previous review concluded that the value of saliva testing as a screening tool needed to be investigated further.

Bazian Ltd (2017)[18] also pointed out that even if DBS and saliva testing were able to detect cCMV reliably, it was not possible to correlate the likelihood of adverse outcomes as none of the studies reported longer-term disease outcomes.

The UK NSC evidence map of 2022[7] did not address this criterion.

## Description of the current evidence

There were 39 studies identified as relevant for this research question and included in the review. Systematic reviews were given priority, followed by diagnostic accuracy studies. Studies were categorised according to the sample-type being tested. Where possible a diagnostic bivariate meta-analysis was conducted for studies that had not been included in previous systematic reviews. If a 2x2 contingency table was not provided, it was calculated using the sensitivity and specificity reported. Meta-analyses were conducted using the web-based software MetaDTA.[30, 31]

## Question 1 – What is the diagnostic accuracy of cCMV testing of saliva in newborns?

This question included any prospective or retrospective cohort studies, or case-control studies, that reported the diagnostic accuracy of saliva testing for cCMV in newborns when compared to urine testing as a reference standard. Existing systematic reviews of relevant studies were also included. Full details of eligibility criteria are presented in Table 2.

### Description of the evidence

Database searches yielded 1 systematic review, and 22 diagnostic accuracy studies. Three identified studies were included in the previous UK NSC evidence review by Bazian Ltd.[18]

### Systematic Reviews

A systematic review assessed the diagnostic accuracy of PCR using saliva samples for newborns with cCMV (Zheng et al., 2022).[32] Nine studies,[28, 29, 33-39] published between 2006 and 2021, were included for quantitative analysis in this systematic review. The 2 studies included in the previous UK NSC evidence review[18] were included in the Zheng et al. (2022) review.[32] The index test was saliva PCR. Seven of the included studies used urine, assessed either by PCR or rapid culture, as the reference test. Bopanna et al. (2011)[28] used saliva rapid culture as the reference test and Alkhawaja et al. (2012)[33] used a culture of either saliva or urine.

The systematic review conducted by Zheng (2022) was of high quality overall with a low risk of bias. Of the studies included in the review, 4 were judged to be at high risk of bias, and the rest at moderate to low risk of bias.

The summary sensitivity and specificity of PCR saliva testing to detect cCMV infection were 91% (95% CI: 70 to 98) and 100% (95% CI: 100 to 100), respectively. A subgroup analysis was conducted where saliva PCR was compared with only urine culture. In this subgroup analysis the summary sensitivity and specificity were 97% (95% CI: 61 to 100) and 100% (95% CI: 99 to 100), respectively. Meta-analyses of PPV and NPV were not performed.

### Diagnostic accuracy studies

Twenty-two studies were identified on the diagnostic accuracy of saliva testing. Details of these studies are presented in Table 3. Of these, 3 studies[35, 38, 39] had been included in the Zheng et al. (2022) systematic review.[32]

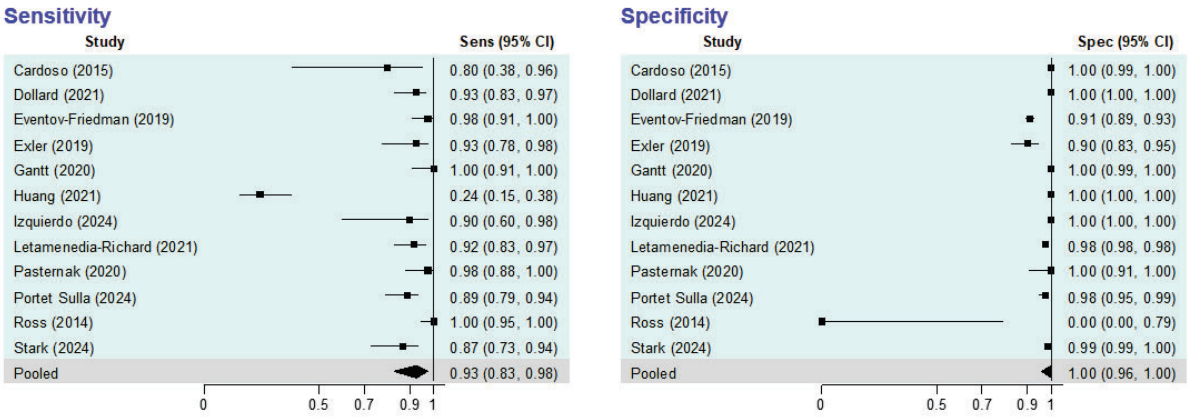
The studies were conducted in a wide variety of locations (7 in USA, 3 in France, 3 in Israel, 2 in China, 1 in Brazil, 1 in Germany, 1 in Turkey, 1 in Chile, 1 in USA and Italy, and 1 in Canada, USA, Italy and Australia), with only 1 from the UK. Most were prospective in design.

Most studies used urine PCR as the reference standard test, but some used repeated saliva testing. Studies varied substantially in size from 125 newborns to over 70,000. Diagnostic accuracy to detect cCMV was high, with reported sensitivities over 90% in most studies, and specificity generally close to 100%. There was considerable heterogeneity in PPV however, with estimates ranging from 12.9% to 100%.

Ten of the identified studies were not included in our meta-analysis. Eight[40-47] were not included as they used saliva as the reference standard, either through culture testing or repeated testing. Two[48, 49] were excluded from the meta-analysis as they did not report sufficient data for a bivariate meta-analysis.

The meta-analysis included 12 studies;[35, 38, 39, 50-58] the forest plots showing the results are presented as Figure 1. The pooled estimates from bivariate meta-analyses for sensitivity and specificity were consistent with those in Zheng (2022).[32] The pooled sensitivity was 93.2% (95% CI: 82.9 to 97.5) and the specificity was 99.5% (95% CI: 96.4 to 99.9). Meta-analyses of PPV and NPV gave results of 87% (95% CI: 63 to 96) and 100% (95% CI: 100 to 100), respectively. There was substantial heterogeneity in PPV values across studies, with some larger studies having positive predictive values below 50%.

*Figure 1 Bivariate meta-analysis of diagnostic accuracy of saliva testing*




**Abbreviations:** CI, confidence interval; Sens, sensitivity; Spec, specificity.

The quality of the studies was assessed using QUADAS-2 (Table 4). All studies generally had a low risk of bias across all domains. There was a high risk of bias in patient selection in Exler (2019)[50] and Stark (2024)[58] as both studies selected newborns using targeted screening based either on positive maternal cCMV tests during pregnancy (Exler 2019) or a pre-specified criteria for clinical symptoms (Stark 2024).

*Table 3: Results of the saliva studies*

| Study details | Study Type | Reference standard | Patient numbers | | Diagnostic accuracy, % (95% CI) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Total Screened | With cCMV | Sensitivity | Specificity | PPV | NPV |
| **Studies included in meta-analysis** | | | | | | | | |
| Cardoso (2015)[38]<br><br>*Location:* Brazil | Prospective | Urine | 333 | 5 | 80 | 100 | 100 | 99.7 |
| Dollard (2021)[39]<br><br>*Location:* USA | Prospective | Urine | 12554 | 56 | 92.9<br>(83.0 to 97.2) | 99.9<br>(99.9 to 100) | 86.7<br>(75.8 to 93.1) | 100<br>(99.9 to 100) |
| Eventov-Friedman (2019)[35]<br><br>*Location:* Israel | Prospective | Urine and Saliva | 856 | 58 | 98.3<br>(90.8 to 99.9) | 91.5<br>(89.3 to 93.3) | 45.6<br>(36.7 to 54.7) | 99.9<br>(99.2 to 99.9) |
| Exler (2019)[50]<br><br>*Location:* Germany | Retrospective | Urine | 133 | 29 | 93<br>(77 to 99) | 90<br>(83 to 95) | 73<br>(56 to 86) | 98<br>(93 to 100) |
| Gantt (2020)[51]<br><br>*Location:*<br>Canada/USA/Italy/Australia | Prospective and Retrospective | Saliva (composite) | 1480 | 39 | 100.0†<br>(100.0 to 100.0) | 99.8†<br>(99.4 to 100.0) | Not reported | Not reported |
| Huang (2021)[52]<br><br>*Location:* China | Prospective | Urine | 6234 | 49 | 24.5<br>(14.6 to 38.1) | 100<br>(99.9 to 100) | 100<br>(75.7 to 100) | 99.4<br>(99.2 to 99.6) |
| Izquierdo (2024)[53]<br><br>*Location:* Chile | Prospective | Urine | 2186 | 10 | 90†<br>(60 to 98) | 100†<br>(100 to 100) | 99.15 | 100 |
| Letamendia-Richard (2022)[54]<br><br>*Location:* France | Retrospective | Urine | 15341 | 63 | 92<br>(84 to 97) | 98<br>(95 to 100) | 90.5<br>(84.9 to 100) | Not reported |
| Pasternak (2020)[55]<br><br>*Location:* Israel | Prospective | Urine | 83 | 42 | 97.6<br>(87.4 to 100) | 100<br>(91.4 to 100) | Not reported | Not reported |

| Study details | Study Type | Reference standard | Patient numbers | | Diagnostic accuracy, % (95% CI) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Total Screened | With cCMV | Sensitivity | Specificity | PPV | NPV |
| Portet Sulla (2024)[56]<br><br>*Location:* France | Retrospective | Urine | 275 | 70 | 88 | 98 | 21.8 | Not reported |
| Ross (2014)[57]<br><br>*Location:* USA | Prospective | Saliva | 80 | Not reported | Not reported | Not reported | Not reported | Not reported |
| Stark (2024)[58]<br><br>*Location:* USA | Retrospective | Urine | 908 | 38 | 86.8<br>(71.9 to 95.6) | 99.4<br>(98.8 to 99.9) | 89.2<br>(75.5 to 95.7 | 99.4<br>(98.7 to 99.8) |
| **Studies not included in meta-analysis** | | | | | | | | |
| Atwood (2023)[40]<br><br>*Location:* USA | Prospective (part of screening) | Repeated testing | 696 | 5 | Not reported | 95.5<br>(93.7 to 96.9) | 13.9<br>(4.7 to 29.5) | Not reported |
| Dunn (2023)[41]<br><br>*Location:* USA/Italy | Prospective and Retrospective | Saliva (composite) | 1853 | 17 | 94.1†<br>(71.3 to 99.9) | 100.0†<br>(99.7 to 100.0) | Not reported | Not reported |
| Gunlemez (2023)[48]<br><br>*Location:* Turkey | Prospective | Urine or blood | 545 | Not reported | Not reported | 99.1<br>(97.9 to 99.7) † | Not reported | Not reported |
| Leruez-Ville (2017)[42]<br><br>*Location:* France | Prospective | Saliva (repeated) | 11740 | 51 | Not reported | Not reported | 58.6<br>(47.5 to 69.1) | Not reported |
| Pinninti (2015)[43]<br><br>*Location:* USA | Prospective | Saliva | 72239 | 266 | Not reported | Not reported | Not reported | Not reported |
| Ross (2018)[44]<br><br>*Location:* USA | Prospective | Saliva/DBS | 307 | 284 | Not reported | Not reported | Not reported | Not reported |

| Study details | Study Type | Reference standard | Patient numbers | | Diagnostic accuracy, % (95% CI) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Total Screened | With cCMV | Sensitivity | Specificity | PPV | NPV |
| Shlonsky (2021)[49]<br><br>*Location:* Israel | Prospective | Urine | 1000 | 6 | Not reported | 98.1 | 24 | 100 |
| Tan (2023)[45]<br><br>*Location:* UK | Prospective | Saliva | 100 | 70 | 93.3<br>(85.3 to 97.1) | 100<br>(86.7 to 100) | 100<br>(94.9 to 100) | 83.3<br>(68.2 to 92.1) |
| Wang (2017)[46]<br><br>*Location:* China | Prospective | Saliva | 7720 | 46 | 93.9<br>(82.1 to 98.4) | 99.9<br>(99.8 to 100) | 88.5<br>(75.9 to 95.2) | 100<br>(99.9 to 100) |
| Wunderlich (2023)[47]<br><br>*Location:* USA | Prospective | Repeated testing | 94 | Not reported | Not reported | Not reported | Not reported | Not reported |

**Abbreviations:** CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.
† Calculated using the 2 x 2 data provided in relevant publications.

*Table 4: Quality assessment results for the saliva studies*

| Paper | Domain 1: Patient selection | | Domain 2: Index tests | | Domain 3: Reference Standard | | Domain 4: Flow and timing |
|---|---|---|---|---|---|---|---|
| | | Applicability | | Applicability | | Applicability | |
| First author | Risk of bias from selection | Concerns about matching of patients to review question? | Risk of bias relating to index test | Concerns about matching of index tests to review question? | Risk of bias relating to reference test | Concerns about matching of reference test to review question? | Risk of bias from patient flow? |
| Cardoso (2015)[38] | Low | Low | Low | Low | Low | Low | Unclear |
| Dollard (2021)[39] | Low | Low | Low | Low | Low | Low | Unclear |
| Eventov-Friedman (2019)[35] | Low | Low | Low | Low | Low | Low | Low |
| Exler (2019)[50] | High | High | Low | Low | Low | Low | Low |
| Gantt (2020)[51] | Low | Low | Low | Low | Low | Low | Low |
| Huang (2021)[52] | Low | Low | Low | Low | Low | Low | Low |
| Izquierdo (2024)[53] | Low | Low | Low | Low | Low | Low | Low |
| Letamendia-Richard (2022)[54] | Low | Low | Low | Low | Low | Low | Low |
| Pasternak (2020)[55] | Unclear | Low | Low | Low | Low | Low | Low |
| Portet Sulla (2024)[56] | High | High | Low | Low | Low | Low | Unclear |
| Ross (2014)[57] | High | High | Unclear | Unclear | Unclear | Unclear | High |
| Stark (2024)[58] | High | Low | Low | Low | Low | Low | Low |
| Atwood (2023)[40] | Unclear | Unclear | Low | Low | Low | Low | Unclear |
| Dunn (2023)[41] | High | Unclear | Low | Low | Low | Low | Low |
| Gunlemez (2023)[48] | Low | Low | Unclear | Unclear | Unclear | Unclear | Unclear |

| Paper | Domain 1: Patient selection | | Domain 2: Index tests | | Domain 3: Reference Standard | | Domain 4: Flow and timing |
|---|---|---|---|---|---|---|---|
| | | Applicability | | Applicability | | Applicability | |
| First author | Risk of bias from selection | Concerns about matching of patients to review question? | Risk of bias relating to index test | Concerns about matching of index tests to review question? | Risk of bias relating to reference test | Concerns about matching of reference test to review question? | Risk of bias from patient flow? |
| Leruez-Ville (2017)[42] | Low | Low | Low | Low | Low | Low | Unclear |
| Pinninti (2015)[43] | Unclear | Low | Low | Low | Low | Low | Unclear |
| Ross (2018)[59] | Low | Low | Unclear | Unclear | Unclear | Unclear | Unclear |
| Shlonsky (2021)[49] | Low | Low | Low | Low | Low | Low | Low |
| Tan (2023)[45] | Unclear | High | Low | Low | Unclear | Low | High |
| Wang (2017)[46] | Low | Low | Low | Low | Low | Low | Unclear |
| Wunderlich (2023)[47] | Low | Low | Low | Low | Low | Low | Unclear |

## Question 2 – What is the diagnostic accuracy of cCMV testing of dried blood spots (DBS) in newborns?

This question included any prospective or retrospective cohort studies, or case-control studies, that reported the diagnostic accuracy of DBS testing for cCMV in newborns when compared to urine testing as a reference standard. Existing systematic reviews of relevant studies were also included.

### Description of the evidence

The review included 1 systematic review, and 10 diagnostic accuracy studies. The systematic review was included in the previous UK NSC review in 2017.[18]

### Systematic Reviews

No systematic reviews were identified after Wang (2015),[27] which was included in the previous UK NSC review.

As noted earlier, the Wang review was high-quality with generally a low risk of bias. It included 14 studies, all of which were published in or before 2012, so were not identified by our new review. Nine of the included studies were assessed as having a high risk of patient selection bias. The meta-analysis reported a sensitivity of 84% (95% CI: 81 to 87) and a specificity of 100% (95% CI: 100 to 100) for detecting cCMV. Sensitivity may have been lower in the prospective studies (62%) than in the retrospective studies (95%). The pooled positive predictive value (PPV) and negative predictive value (NPV) were 91% (95% CI: 84 to 95) and 99% (95% CI: 97 to 100)), respectively.

### Diagnostic accuracy studies

Ten studies[39, 46, 60-67] were identified that were published after the Wang (2015) review.[27] A summary of these studies is provided in Table 5. Six of the 10 included studies were prospective in design, and 4 were retrospective or case-control studies. Studies were conducted in a range of international locations (3 in USA, 1 in France, 1 in Japan, 1 in Iran, 1 in Belgium, 1 in Spain and 1 in China), with only 1 from the UK. Studies varied substantially in size from 60 newborns to over 12,000. Diagnostic accuracy to detect cCMV was variable but generally high, with most studies reporting a sensitivity over 80% and specificity of nearly 100%.

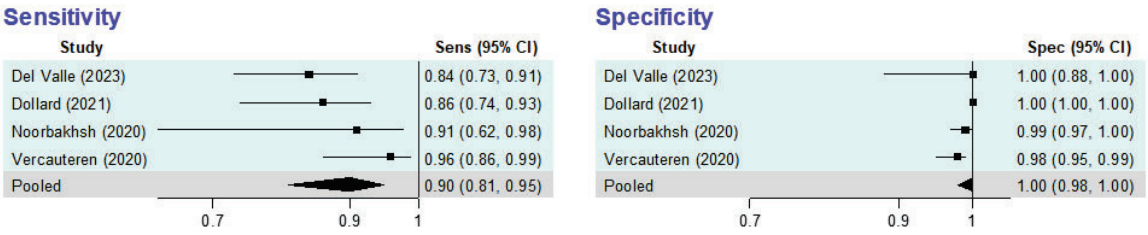
A meta-analysis was conducted to compare the diagnostic accuracy of testing DBS, using urine testing as a reference standard, as the latter is considered the gold standard. This meta-analysis included 4 of the included studies.[39, 61, 64, 66] Five studies[46, 60, 62, 63, 65, 67] were

not included in the meta-analysis as these studies compared the diagnostic accuracy of testing DBS to non-urine samples.

The results of the meta-analysis are shown in forest plots for sensitivity and specificity (Figure 2). The pooled sensitivity and specificity from the bivariate meta-analysis were 89.9% (95% CI: 81.3 to 94.8) and 99.9% (95% CI: 98.1 to 100).

These values were consistent with the estimates reported in the Wang (2015) systematic review. Meta-analyses for PPV and NPV gave results of 96% (95% CI: 86 to 99) and 99% (95% CI: 91 to 100), respectively. This is also broadly consistent with the Wang 2015 review.

*Figure 2 Bivariate meta-analysis of diagnostic accuracy of DBS*




**Abbreviations:** CI, confidence interval; DBS, dried blood spot; Sens, sensitivity; Spec, specificity.

The quality of the studies published after the Wang et al. (2015) systematic review was assessed using QUADAS-2 (Table 6). Generally, the included studies were at a low risk of bias across all domains.

*Table 5: Results of the dried blood spot studies*

| Study details | Study Type | Reference standard | Patient numbers | | Diagnostic accuracy, % (95% CI) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Total Screened | With cCMV | Sensitivity | Specificity | PPV | NPV |
| **Studies included in meta-analysis** | | | | | | | | |
| Del Valle (2023)[61]<br><br>*Location:* USA | Retrospective | Urine or Saliva | 89 | 62 | 83.9 | 100 | 100 | 73 |
| Dollard (2021)[39]<br><br>*Location:* USA | Prospective | Urine | 12554 | 56 | 85.7<br>(74.3 to 92.6) | 100<br>(100 to 100) | 98<br>(89.3 to 99.6) | 99.9<br>( 99.9 to 100) |
| Noorbakhsh (2020)[64]<br><br>*Location:* Iran | Prospective | Urine | 224 | 11 | 90.9<br>(58.7 to 99.7) | 99<br>(96.6 to 99.8) | 83.3<br>(51.5 to 97.9) | 99.5<br>(97.4 to 99.9) |
| Vercauteren (2020)[66]<br><br>*Location:* Belgium | Prospective | Urine | 276 | 48 | 95.8<br>(85.8 to 99.5) | 97.8<br>(95.0 to 99.3) | 90.2<br>(78.6 to 96.7) | 99.1<br>(97.0 to 99.9) |
| **Studies not included in meta-analysis** | | | | | | | | |
| Atkinson (2014)[60]<br><br>*Location:* UK | Retrospective / Case-Control | Not urine | Not reported | 26 | 81<br>(60.6 to 93.4) | 100 | Not reported | Not reported |
| Fourgeaud (2023)[62]<br><br>*Location:* France | Prospective | Saliva | 256 | Not reported | 95 | 33 | 21 | 97 |
| Moteki (2018)[63]<br><br>*Location:* Japan | Case-control | Cord blood | 48 | 12 | 83.3 | 97.2 | Not reported | Not reported |
| Ross (2017)[65]<br><br>*Location:* USA | Prospective | Saliva | 313 | 313 | Not reported | Not reported | Not reported | Not reported |

| Study details | Study Type | Reference standard | Patient numbers | | Diagnostic accuracy, % (95% CI) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Total Screened | With cCMV | Sensitivity | Specificity | PPV | NPV |
| Vives-Onos (2019)[67]<br><br>*Location:* Spain | Case-control | Any | 184 | 103 | 56<br>(47 to 65) | 98<br>(91 to 99) | Not reported | Not reported |
| Wang (2017)[46]<br><br>*Location:* China | Prospective | Saliva | 3953 | 11 | 39.3<br>(22.1 to 59.3) | 99.9<br>(99.8 to 100) | 78.6<br>(48.8 to 94.3) | 99.6<br>( 99.4 to 99.8) |
| **Abbreviations:** CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.<br>† Calculated using the 2 x 2 data provided in the publications. | | | | | | | | |

*Table 6: Quality assessment results for the dried blood spot studies*

| Paper | Domain 1: Patient selection | | Domain 2: Index tests | | Domain 3: Reference Standard | | Domain 4: Flow and timing |
|---|---|---|---|---|---|---|---|
| | | Applicability | | Applicability | | Applicability | |
| First author | Risk of bias from selection | Concerns about matching of patients to review question? | Risk of bias relating to index test | Concerns about matching of index tests to review question? | Risk of bias relating to reference test | Concerns about matching of reference test to review question? | Risk of bias from patient flow? |
| Del Valle (2023)[61] | Low | Low | Low | Low | Low | Unclear | Low |
| Dollard (2021)[39] | Low | Low | Low | Low | Low | Low | Unclear |
| Noorbakhsh (2020)[64] | Low | Low | Low | Low | Low | Low | Low |
| Vercauteren (2020)[66] | Low | Low | Low | Low | Low | Low | Unclear |
| Atkinson (2014)[60] | High | High | Low | High | Low | High | High |
| Fourgeaud (2023)[62] | Low | Low | Low | Low | Low | Low | Unclear |
| Moteki (2018)[63] | Low | Low | Low | Low | Low | Low | Low |
| Ross (2017)[65] | Low | Low | Low | Low | Unclear | Unclear | High |
| Vives-Onos (2019)[67] | Unclear | Low | Unclear | Low | Low | Low | High |
| Wang (2017)[46] | Low | Low | High | Unclear | High | Unclear | High |

# Additional material relating to Criterion 4

## Urine testing

The previous UK NCS evidence review by Bazian Ltd (2017)[18] did not include urine testing, even though it was considered to be the gold standard. This was stated to be due to the practical difficulties in collecting urine from newborns, limiting the role of urine testing in universal screening.

### Systematic Reviews

No systematic reviews of urine testing were identified.

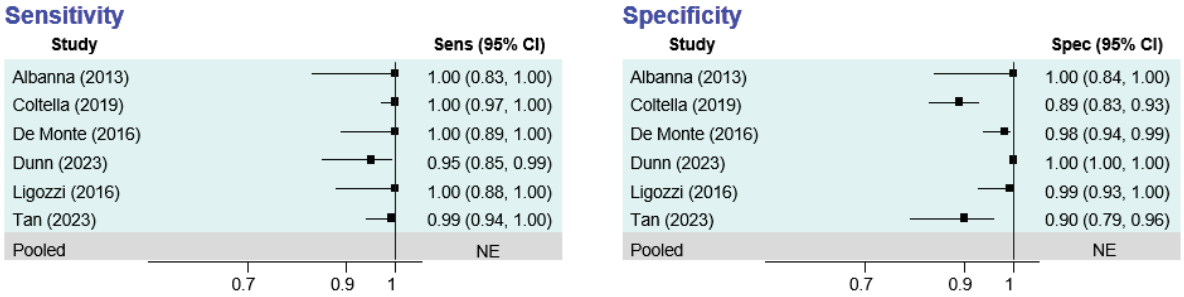
### Diagnostic accuracy studies

Seven studies were identified (Table 7).[41, 45, 52, 68-71] The studies were conducted in a wide variety of locations (2 in Italy, 1 in USA, 1 in France, 1 in Egypt, 1 in China), with only 1 from the UK. Three were prospective in design and 4 were retrospective or case-control studies. Four studies used urine viral cultures as the reference standard test. Studies were mostly small in size but varied from 58 newborns to just over 6,000. Diagnostic accuracy to detect cCMV was very high, with reported sensitivities and specificities at or close to 100% in most studies.

A meta-analysis was conducted on the studies that compared the diagnostic accuracy of urine PCR to urine viral cultures. Huang (2021)[52] was not included as it compared urine PCR to saliva PCR and had already been included in the meta-analysis for saliva testing.

The bivariate meta-analysis could not reliably estimate pooled values for sensitivity and specificity due to the very high sensitivities and specificities in all included studies, and consequent lack of convergence of the models (see Figure 3). However, separate meta-analyses of sensitivity and specificity suggested that the sensitivity was over 99% (95% CI: 96 to 100) and specificity was also over 99% (95% CI: 92 to 100).

*Figure 3 Diagnostic accuracy in studies of urine testing*




**Abbreviations:** CI, confidence interval; NE, not evaluable; Sens, sensitivity; Spec, specificity.

The quality of the studies was assessed using QUADAS-2 (Table 8). As De Monte (2016)[70] was a French language publication it was not possible to assess its quality. Generally, all included studies were at low risk of bias across all domains.

*Table 7: Results of the urine studies*

| Study details | Study Type | Reference standard | Patient numbers | | Diagnostic accuracy, % (95% CI) | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Total Screened | With cCMV | Sensitivity | Specificity | PPV | NPV |
| **Studies included in meta-analysis** | | | | | | | | |
| Albanna (2013)[68]<br><br>*Location:* Egypt | Case-control | Urine culture | 39 | 19 | 100 | 100 | 100 | 100 |
| Coltella (2019)[69]<br><br>*Location:* Italy | Retrospective | Urine viral culture | 255 | 107 | 100 | 89.19 | Not reported | Not reported |
| De Monte (2016)[70]<br><br>*Location:* France | Retrospective | Urine viral culture | 141 | 31 | 100<br>(86.9 to 100) | 98.2<br>(93.2 to 99.2) | Not reported | Not reported |
| Dunn (2023)[41]<br><br>*Location:*USA | Prospective | Urine composite | 1624: | 43 | 95.4†<br>(84.2 to 99.4) | 100.0†<br>(99.8 to 100.0) | Not reported | Not reported |
| Ligozzi (2016)[71]<br><br>*Location:* Italy | Retrospective | Shell viral culture | 110 | 29 | 100†<br>(88.1 to 100) | 98.8†<br>(93.3 to 100.0) | Not reported | Not reported |
| Tan (2023)[45]<br><br>*Location:* UK | Prospective | Urine LDT P CR | 148 | 96 | 99<br>(94.3 to 99.8) | 90.4<br>(79.4 to 95.8) | 95<br>(89.2 to 97.8) | 97.9<br>(87.0 to 99.7) |
| **Studies not included in meta-analysis** | | | | | | | | |
| Huang (2021)[52]<br><br>*Location:* China | Prospective | Saliva | 6234 | 49 | 28.6<br>(17.9 to 42.4) | 100<br>(99.9 to 100) | 100<br>(78.5 to 100) | 99.4<br>(99.2 to 99.6) |

**Abbreviations:** CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.
† Calculated using the 2 x 2 data provided in the publications.

*Table 8: Quality assessment results for the urine studies*

| Paper | Domain 1: Patient selection | | Domain 2: Index tests | | Domain 3: Reference Standard | | Domain 4: Flow and timing |
|---|---|---|---|---|---|---|---|
| | | Applicability | | Applicability | | Applicability | |
| First author | Risk of bias from selection | Concerns about matching of patients to review question? | Risk of bias relating to index test | Concerns about matching of index tests to review question? | Risk of bias relating to reference test | Concerns about matching of reference test to review question? | Risk of bias from patient flow? |
| Albanna (2013)[68] | Low | Low | Low | Low | Low | Low | Low |
| Coltella (2019)[69] | Low | Low | Low | Low | Low | Low | Low |
| De Monte (2016)[70] | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear |
| Dunn (2023)[41] | High | Unclear | Low | Low | Low | Low | Low |
| Ligozzi (2016)[71] | Unclear | Unclear | Low | Low | Low | Low | Low |
| Tan (2023)[45] | Unclear | Unclear | Low | Low | Low | Low | Unclear |
| Huang (2021)[52] | Low | Low | Unclear | Unclear | Unclear | Unclear | Unclear |

## Other testing for cCMV infection

### Systematic Reviews

No systematic reviews were identified.

### Diagnostic accuracy studies

An additional 3 studies[72-74] were identified that tested for cCMV using uncommon testing methods (Table 9). Wang (2013)[72] compared the accuracy of diagnosing cCMV using throat swabs to umbilical cord blood. Barkai (2013)[73] compared the diagnostic accuracy of umbilical cord blood (as an alternative to DBS) to urine testing. The sensitivity and specificity reported in Barkai (2013) was quite high. Reyes (2020)[74] also looked at umbilical cord blood but did not report diagnostic accuracy results.

As these 3 studies examine different tests, and are not tests likely to be used in routine screening, no quality assessment or synthesis of these studies was performed.

*Table 9: Results of the studies of other testing methods*

| Study details | Study Type | Testing Method | Reference standard | Patient numbers | | Diagnostic accuracy, % (95% CI) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Total Screened | With cCMV | Sensitivity | Specificity | PPV | NPV |
| Wang (2013)[72]<br><br>*Location:* China | Not reported | Throat swab | Cord blood (PCR) | Not reported | Not reported | 67 | 75 | 57 | 82 |
| Barkai (2013)[73]<br><br>*Location:* Israel | Retrospective (screening programme) | Cord blood | Urine | 8105 | 24 | 100<br>(84.6 to 100.0) | 99.1<br>(95.2 to 99.9) | Not reported | Not reported |
| Reyes (2020)[74]<br><br>*Location:* Spain | Retrospective | Cord blood (dried) | Mixed | 16 | 16 | Not reported | Not reported | Not reported | Not reported |
| **Abbreviations:** cCMV, congenital cytomegalovirus; CI, confidence interval; NPV, negative predictive value; PCR, polymerase chain reaction; PPV, positive predictive value. | | | | | | | | | |

## Summary of Findings Relevant to Criterion 4

### Criterion Met

There is now a large body of clinical evidence, including 2 systematic reviews and 39 diagnostic accuracy studies published since 2012, on the accuracy of newborn testing for cCMV. This evidence, both the systematic reviews and the primary studies, is generally of good quality. It seems unlikely that any future studies or reviews will substantially differ from the conclusions reached in this review.

This review identified 1 existing systematic review (Zheng, et al., 2022) and 22 diagnostic accuracy studies of newborn saliva PCR testing to detect cCMV infection. Both the review and the primary studies were generally of good quality and at low risk of bias. The meta-analyses of diagnostic accuracy conducted in the Zheng (2022) review and in this review were consistent in their results. Both found that saliva testing will detect over 90% of all cCMV cases, with a very low rate of false-positive results (around 0.2%). This very high accuracy suggests that saliva PCR testing is a sufficiently accurate test that could reasonably be used in a cCMV screening programme. It should be noted that this high detection rate refers to all cCMV cases, including those which are asymptomatic at birth and/or do not go on to develop long-term symptoms.

Despite the high accuracy of saliva testing the positive predictive value is predicted to be around 87%, so some newborns with a positive saliva test will not have cCMV infection. The exact proportion is currently uncertain, as it was highly variable across studies. This suggests that confirmatory testing after a positive saliva test may be required.

This review identified 1 existing systematic review (Wang, et al., 2015; included in the previous UK NSC review of this topic) and 10 diagnostic accuracy studies published after that review, of newborn DBS PCR testing to detect cCMV infection. The review and the primary studies were generally of good quality and at low risk of bias. The meta-analyses of diagnostic accuracy conducted in the Wang et al. (2015) review[27] and in this review were consistent in their results. Both found that DBS testing will detect most cCMV cases (around 80% to 90% of cases), with a very low rate of false-positive results (less than 1%). This high accuracy suggests that DBS PCR testing is a sufficiently accurate test that could reasonably be used in a cCMV screening programme. However, it does appear to be less accurate than saliva PCR testing.

This review did not find any studies comparing saliva and DBS testing, so it is uncertain which is preferable in practice. Although DBS seems to have a lower diagnostic accuracy

this would need confirming in studies directly comparing the 2 methods. Also, it is possible that, while DBS is less accurate overall, the cCMV cases detected may be the more serious cases requiring treatment, but that requires further research. DBS may also have some practical benefits over saliva testing, as DBS testing is already in use for other conditions.

This review found only 7 studies on the diagnostic accuracy of urine testing. This is probably because urine testing was already well established as a reference standard test for cCMV infection before this review was conducted. The results from the included studies confirm that urine testing is highly accurate, and so would be an appropriate confirmatory test after a positive saliva or DBS test result in any cCMV screening programme.

## Criterion 7: There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.

### What tests in newborns with cCMV identify which are likely to suffer long-term health consequences from cCMV, who would benefit from prompt treatment?

#### Previous work

The previous review included 3 cohort studies: Alarcon et al. (2013),[75] Bilavsky et al. (2015)[76] and Forner et al. (2015),[77] that assessed whether specific signs or symptoms were predictive of adverse long-term outcomes.[18] All 3 studies were also identified by our searches. The previous review identified several limitations to these studies, including the small sample sizes. The previous review concluded that the available evidence provides only limited new information about treatment indications and there remains a lack of clarity about which newborns with cCMV will go on to develop adverse outcomes and might benefit from treatment.

The previous review included 1 systematic review and 5 cohort studies that reinforced the previously established observation that symptomatic newborns are more likely to develop adverse outcomes than asymptomatic newborns.[18] One of these studies, was also identified by our searches.[78]

The Evidence Map of 2022[7] identified 14 studies, including 1 systematic review, relevant to this topic. Most examined the impact of viral load on long-term outcomes. The conclusion was that although some studies identified possible markers to distinguish which cCMV infected newborns will suffer long-term negative outcomes, there was no consensus about the predictive value of such markers or their reliability.

#### Description of the current evidence

Overall, 97 studies were identified as being relevant for this research question and were included in the review. Priority was given to systematic reviews, followed by “prognostic accuracy” studies, which we define as studies that formally assess the ability of a test to predict later health outcomes in terms of sensitivity and specificity or similar metrics. Other studies reported whether a test result, antenatal characteristic or newborn characteristic was associated with long-term health consequences, but without formal assessment of prognostic value. These are termed “association studies” in this report. These association

studies are only briefly summarised because of their large numbers, and because they are less informative as to the true clinical value of tests and their consequent lesser relevance to this assessment.

Owing to the large number of eligible studies, the evidence has been split according to the type of test or characteristic investigated.

## Neuroimaging (MRI and ultrasound)

### Systematic review evidence

One systematic review by Van de Walle et al.(2024)[79] assessed the value of MRI to predict clinical outcome in children with cCMV. This review included 20 studies. However, only 7 studies evaluated the associations between postnatal MRI and later clinical outcomes, and the review did not consider prognostic accuracy for detection of sequelae as an outcome. Critical appraisal of the systematic review revealed a high risk of bias. This was due to an unclear description of the prespecified study inclusion criteria in the absence of a published protocol, a limited search strategy, poor reporting of study characteristics and no attempt to narratively or quantitatively synthesise study findings.

No synthesis was undertaken, and associations between postnatal MRI and later outcomes were presented separately for each study. Therefore, studies included in this review are discussed in the sections below.

### Prognostic accuracy studies

Sixteen studies assessing the accuracy of neuroimaging (either used alone or in combination with non-imaging tests) to predict neurodevelopmental delay, epilepsy or hearing loss were identified.[75, 80-94] Full results from these studies are summarised in Table 10.

In general, neuroimaging tests demonstrated reasonable accuracy in predicting neurodevelopmental delay, epilepsy and hearing outcomes. The most accurate tests were MRI or ultrasound (and sometimes computed tomography) using the 'Alarcon' scoring. Using a threshold of 2 or more to predict neurodevelopmental delay, these tests yielded sensitivities from 77% to 94%, with specificities of 69% to 100%, in 2 studies.[80,81] MRI had good accuracy to detect epilepsy, with a sensitivity of 92% (95% CI: 62 to 99) at a specificity of 68% (95% CI: 44 to 87).[91]

Combining neuroimaging tests with other tests sometimes improved accuracy. A sensitivity of 87% at a specificity of 100%[75] for predicting neurodevelopmental delay was yielded by a test result involving a score of $\geq$2 on the Noyola scale or a cerebrospinal fluid (CSF) beta 2-

m concentration above a threshold of 7.9mg/L. In another study,[89] a composite test result of normal cerebral ultrasound, no hearing loss, and normal platelet count at birth predicted the absence of neurological or auditory sequelae with a sensitivity of 92% at a specificity of 83%.

In general, studies were small, and most studies had either a high or unclear overall risk of bias (see Appendix 3).

*Table 10: Summary of evidence evaluating the accuracy of neuroimaging tests to predict sequelae of cCMVinfection*

| Study properties | Sample size | Baseline tests performed | Long-term outcomes reported | Baseline test accuracy (threshold for positive test) |
|---|---|---|---|---|
| Alarcon et al. 2013[75]<br>Prospective<br>Spain<br>Follow-up: mean 8.7 years | With cCMV: 26<br>Symptoms at birth: 26<br>Long-term outcomes: 15 | Mixed (CSF, microcephaly, neuroimaging) | Neurodevelopmental delay (in terms of motor function, cognition, behaviour, hearing, vision, and epilepsy) at mean 8.7 years | **Neuroimaging (Noyola score of >=2) OR Adjusted microcephaly (threshold unclear)**<br>Sens: 66% Spec: 100%<br>**CSF concentration (>7.9mg/L) OR Neuroimaging (Noyola score of >=2) [A]**<br>Sens: 87% Spec: 100% |
| Alarcon et al. 2016[80]<br>Prospective<br>Spain<br>Follow-up: mean 8.7 years | With cCMV: 26<br>Symptoms at birth: 26<br>Long-term outcomes: 18 | MRI/ Ultrasound/CT | Neurodevelopmental delay (in terms of motor function, cognition, behaviour, hearing, vision, and epilepsy) at mean 8.7 years | **Neuroimaging with MRI/US/CT (Noyola scale >= 2)**<br>Sens: 61% Spec: 100%<br>**Neuroimaging with MRI/US/CT (Alarcon scale >= 2)**<br>Sens: 77% Spec: 100% |
| Alarcon et al. 2024[81]<br>Retrospective<br>Spain<br>Follow-up: median 4 years | With cCMV: 160<br>Symptoms at birth: 103<br>Long-term outcomes: 53 | MRI/ US | Moderate/severe disabilities: neurodevelopmental impairments (including hearing, CP, cognition, behavioral, epilepsy, visual) at median 4 years | **Neuroimaging with MRI/US (Alarcon scale >=2)**<br>Sens: 90% (95% CI: 78.2 to 96.7) Spec: 69% (95% CI: 58.1 to 78.5)<br>**TPWMA on MRI/US (1 or more present)**<br>Sens: 77.8% (95% CI: 40 to 97.2) Spec: 69.1% (95% CI: 52.9 to 82.4) |
| Blazquez-Gamero et al. 2019[82]<br>Prospective<br>Spain<br>Follow-up: 12 months | With cCMV: 107<br>Symptoms at birth: 77<br>Long-term outcomes: 37 | MRI/ symptoms at birth | Any sequelae (hearing or neurological) at 12 months | **Abnormal US and abnormal MRI (any category of symptoms at birth)**<br>Sens: 83.8% (95% CI: 68.0 to 93.8) Spec: 79.4% (95% CI: 62.1 to 91.3)<br>**Abnormal US and abnormal MRI (with symptoms at birth)**<br>Sens: 81.1% (95% CI: 64.8 to 92.0) Spec: 85.3% (95% CI: 68.9 to 95.1)<br>**Abnormal US and abnormal MRI (with NO symptoms at birth)**<br>Sens: 2.7% (95% CI: 0.7 to14.2) Spec: 94.1% (95% CI: 80.3 to 99.3) |
| Capretti et al. 2014[83]<br>Prospective<br>Italy<br>Follow-up: 6 years | With cCMV: 40<br>Symptoms at birth: 11<br>Long-term outcomes: 7 | MRI/ Ultrasound | Psychomotor development at 6 years | **US (pathological)**<br>Sens: 57% (95% CI: 20 to 88) Spec: 94% (95% CI: 78 to 96)<br>**MRI (pathological)**<br>Sens: 100% (95% CI: 56 to 100) Spec: 94% (95% CI: 78 to 98) |

| Study properties | Sample size | Baseline tests performed | Long-term outcomes reported | Baseline test accuracy (threshold for positive test) |
|---|---|---|---|---|
| Castellanos et al. 2022[84]<br>Retrospective<br>Spain<br>Follow-up: 4 years | With cCMV: 36<br>Symptoms at birth: 20<br>Long-term outcomes: 18 | MRI / Ultrasound | Neurological sequelae (WMA and other neuroimaging findings, delayed development, hearing loss) at 4 years | **US (pathological)**<br>Sens: 83.3% (95% CI: 58 to 100) Spec: 44.4% (95% CI: 18.7 to 70.2)<br>**MRI (Noyola score >=2)**<br>Sens: 94% (95% CI: 80 to 100) Spec: 66.6% (95% CI: 36 to 97.5) |
| Chebib et al. 2022[85]<br>Retrospective<br>France<br>Follow-up: 21 months | With cCMV: 130<br>Symptoms at birth: 94<br>Long-term outcomes: 83 | Antenatal infection point / fetal imaging | Inner ear impairment at median 21 months | **Infection in first trimester OR Imaging anomaly of fetus**<br>Sens: 91% (95% CI: 83 to 98) Spec: 48% (95% CI: 36 to 60)<br>**Infection in first trimester AND Imaging anomaly of fetus**<br>Sens: 38% (95% CI: 28 to 47) Spec: 92% (95% CI: 86-98) |
| Craeghs et al. 2021[86]<br>Prospective<br>Belgium<br>Follow-up: mean around 2.5 years | With cCMV: 411<br>Symptoms at birth: 164<br>Long-term outcomes: 75 | MRI / Ultrasound | Hearing loss at mean 2.5 years | **US (pathological)**<br>Sens: 43% (95% CI: 31 to 54) Spec: 84% (95% CI: 79 to 88)<br>**MRI (pathological)**<br>Sens: 39% (95% CI: 28 to 50) Spec: 78% (95% CI: 72 to 83) |
| De Juan et al. 2020[87]<br>Retrospective<br>Spain<br>Follow-up: mean 19 months | With cCMV: 60<br>Symptoms at birth: unclear<br>Long-term outcomes: 32 | US/MRI | Neurological sequelae at mean of 19 months | **US or MRI (score of 1 or more on Alarcon scale)**<br>Sens: 71.9% (95% CI: 53.3 to 86.3) Spec: 71.4% (95% CI: 51.3 to 86.8) |
| Foulon et al. 2019[88]<br>Prospective<br>Belgium<br>Follow-up: median 31 months | With cCMV: 173<br>Symptoms at birth: 9<br>Long-term outcomes: 20 | Trimester of infection / US/MRI | Hearing loss (mild or worse) at median 31 months | **US (abnormal)**<br>Sens: 47.1% (95% CI: 23 to 72.2) Spec: 92.5% (95% CI: 86.2 to 96.5)<br>**MRI (abnormal)**<br>Sens: 57.1% (95% CI: 18.4 to 90.1) Spec: 66.7% (95% CI: 43.0 to 85.4) |
| Fourgeaud et al. 2024[89]<br>Prospective<br>France<br>Follow-up: 24 months | With cCMV: 250<br>Symptoms at birth: 24<br>Long-term outcomes: 19 | *Lack of* risk factors for SNHL / psychomotor problems, as aimed to predict NO sequelae | *Lack of* SNHL (bilateral or unilateral) OR psychomotor sequelae (motor delay, psychomotor delay, autism, nystagmus) at 24 months | **No hearing loss at birth, normal cerebral ultrasound, and normal platelet count** (for detection of NO sequelae)<br>Sens: 92% Spec: 83% |

| Study properties | Sample size | Baseline tests performed | Long-term outcomes reported | Baseline test accuracy (threshold for positive test) |
|---|---|---|---|---|
| Gianattasio et al. 2018[90]<br>Retrospective<br>Italy<br>Follow-up: around 6 years | With cCMV: 170<br>Symptoms at birth: 112<br>Long-term outcomes: Unclear | US/MRI/CT | An impaired neurologic outcome was defined in the presence of 1 or more of the following problems: developmental/cognitive impairment, motor delay requiring rehabilitation, epilepsy and behavioural/ emotional problems. Follow up 1-6 years. | **US (Noyola >=1)**<br>Sens: 75.6% (95% CI: 62.2 to 86.7) Spec: 43.3% (95% CI: 31.7 to 56.7)<br>**CT (Noyola scale >=1)**<br>Sens: 66.7% (95% CI: 53.3 to 80) Spec: 85.7% (95% CI: 76.8 to 94.6)<br>**MRI (Noyola scale >=1)**<br>Sens: 42.6% (95% CI: 29.8 to 57.5) Spec: 89.1% (95% CI: 80 to 96.4)<br>**US (Alarcon >=1 )**<br>Sens: 88.9% (95% CI: 80 to 97.8) Spec: 40% (95% CI: 28.3 to 51.7)<br>**CT (Alarcon >=1)**<br>Sens: 88.9% (95% CI: 80 to 97.8) Spec: 62.5% (95% CI: 50 to 75)<br>**MRI (Alarcon >=1)**<br>Sens: 87.2% (95% CI: 76.6 to 95.7) Spec: 50.9% (95% CI: 38.2 to 63.6) |
| Kwak et al. 2018[91]<br>Retrospective<br>South Korea<br>Follow-up: mean 3.2 years | With cCMV: 31<br>Symptoms at birth: 31<br>Long-term outcomes: 11 | MRI | Epilepsy at mean 3.2 years | **MRI (>=2.5 points on un-named scale)**<br>Sens: 91.7% (95% CI: 61.5 to 99.8) Spec: 68.4% (95% CI: 43.5 to 87.4) |
| Lucignani et al. 2021[92]<br>Retrospective<br>Italy<br>Follow-up: 2 years | With cCMV: 44<br>Symptoms at birth: 27<br>Long-term outcomes: 30 | MRI | Development of adverse neurological outcomes [including hearing loss, severe neurological delay or CP ] by end of follow up at minimum of 2 years | **MRI (score >0 'old system')**<br>Sens: 93.3% (95% CI: 77.9 to 99.2) Spec: 50% (95% CI: 23.0 to 77.0)<br>**MRI (score >2 'new system')**<br>Sens: 70% (95% CI: 50.6 to 85.3) Spec: 80% |
| Nishida et al. 2020[93]<br>Prospective<br>Japan<br>Follow-up: 18 months | With cCMV: 42<br>Symptoms at birth: 23<br>Long-term outcomes: 19 | MRI / clinical symptoms | Neurodevelopmental impairment (NDI) was defined as a developmental quotient <80, hearing dysfunction, blindness, or epilepsy requiring anti-epileptic drugs at 18 months | **MRI (any brain abnormality)**<br>Sens: 89.5% (95% CI: 66.9 to 98.7) Spec: 52.6% (95% CI: 28.9 to 75.6)<br>**MRI (>=1 of the defined 3 MRI abnormalities of V, PVC or WMA)**<br>Sens: 89.5% (95% CI: 66.9 to 98.7) Spec: 52.6% (95% CI: 28.9 to 75.6)<br>**MRI (>=2 of the defined 3 MRI abnormalities)**<br>Sens: 89.5% (95% CI: 66.9 to 98.7) Spec: 89.5% (95% CI: 66.9 to 98.7) |

| Study properties | Sample size | Baseline tests performed | Long-term outcomes reported | Baseline test accuracy (threshold for positive test) |
|---|---|---|---|---|
| Vande Walle et al. 2024[94]<br>Retrospective<br>Belgium<br>Follow-up: up to 4 years | With cCMV: 255<br>Symptoms at birth: unclear<br>Long-term outcomes: 53 | MRI | Cognitive development (Bayley Scales of Infant and Toddler Development) Severe impairment < 50.<br>Motor development (AIMS). AIMS < P10 abnormal.<br>Hearing evaluation (ABR). ABR thresholds≤40 dB nHL considered normal. Follow up median 12 months | **MRI (Apparent Diffusion Coefficient of white matter [ADC] > 0.0497) – optimum threshold for predicting hearing impairment**<br>Sens: 86% Spec: 62%<br>**MRI (ADC > 0.0671) – optimum threshold for predicting cognitive impairment**<br>Sens: 83% Spec: 58%<br>**MRI (ADC > 0.159) – optimum threshold for predicting motor development**<br>Sens: 57% Spec: 72% |

**Abbreviations:** ABR, Auditory Brainstem Response; ADC, apparent diffusion co-efficient; AIMS, Alberta Infant Motor Scale; cCMV, congenital cytomegalovirus; CMV, Cytomegalovirus; CP, cerebral palsy; CSF, cerebrospinal fluid; CT, computed tomography; dB, decibels; DNA, deoxyribonucleic acid; MRI, magnetic resonance imaging; NDI, neurodevelopmental impairment; PCR, polymerase chain reaction; PVC, periventricular cyst; Sens, sensitivity; SNHL, sensorineural hearing loss; Spec, specificity; TPWMA, temporal pole white matter abnormalities; US, ultrasound; V, ventriculomegaly; WM, white matter; WMA, white matter abnormalities.

### Association studies

Seven studies that assessed the association between neuroimaging and long-term outcomes, but did not report prognostic accuracy data, were identified.[95-101] Studies evaluated US[95-99] and/or MRI.[96-98, 100, 101] Five studies were prospective[95, 96, 99-101] and 2 were retrospective.[97, 98] Sample sizes ranged from 11 to 211 infants with cCMV, and median follow-up ranged from 12 to 68 months. Studies were conducted in Italy, Switzerland, Netherlands, Belgium and Spain.

#### *M R I*

Vande Walle et al. (2023)[100] showed that white matter abnormalities (WMA) on MRI are associated with developing adverse motor sequelae and cognitive delay, but not late-onset hearing loss. Other studies demonstrated associations between abnormal MRI findings in the newborn period and subsequent hearing,[97] neurodevelopmental[96, 101] or neurodevelopmental and hearing[98] deficits, but these findings have either not been statistically tested[96, 98, 101] or have not demonstrated a significant effect.[97]

#### *Ultrasound*

Three studies[97-99] demonstrated that ultrasound abnormalities are predictors of hearing and neurodevelopmental sequelae. However, 4 studies[95-97, 99] found that ultrasound abnormalities were not significantly associated with hearing and neurodevelopmental sequelae, particularly after adjustment for confounding. These inconsistent findings suggest that ultrasound may be less useful than MRI for predicting sequelae.

## Antenatal characteristics – timing of maternal infection

### Systematic review evidence

Two relevant systematic reviews were found. The systematic review by Chatzakis et al. (2020)[102] included 17 studies. Of those, 6 studies (772 participants) evaluated the associations between timing of infection and sensorineural hearing loss (SNHL) or neurodevelopmental impairment at follow-up, and were included in meta-analyses.

The review had a low risk of bias. The protocol was published on PROSPERO and set appropriate inclusion criteria. Searches, data extraction and synthesis were all conducted appropriately.

Primary maternal infection in the first trimester led to a prevalence of SNHL or neurodevelopmental impairment of 22.8% (95% CI: 15.4 to 30.2; $I^2$=27.6%) at follow up. Primary maternal infection in the second and third trimesters led to smaller rates of 0.1% (95% CI: 0 to 0.8; $I^2$=24%) and 0% (95% CI: 0 to 2.1; $I^2$=0%) at follow up, respectively.

The systematic review by Buca et al. (2021)[103] included 26 studies, but only a subset were used in the relevant analyses. Two of the 26 included studies were included in our review.[104, 105] This review had a low risk of bias, with clear inclusion criteria, and good methods of searching, data extraction and synthesis. The pooled percentage of children with abnormal neurodevelopmental outcomes was 5.44% (95% CI: 2.3 to 9.8) in 7 studies evaluating first trimester infection, 0% (95% CI: 0 to 7) in 6 studies evaluating second trimester infection, and 0% (95% CI: 0 to 7.7) in 4 studies evaluating third trimester infection. The pooled percentage of children with hearing problems was 11.35% (95% CI: 6.7 to 17.1) in 7 studies evaluating first trimester infection, 7% (95% CI: 2.1 to 14.5) in 6 studies evaluating second trimester infection, and 0% (95% CI: 0 to 7.7) in 4 studies evaluating third trimester infection.

### Prognostic accuracy studies

Two studies were identified. Foulon et al. (2019)[88] (see Table 11) was included in the Chatzakis et al. (2020) review. It was a relatively large study (72 for this analysis) but had an unclear overall risk of bias (see Appendix 3). It found that primary infection during the first trimester had a sensitivity of 56% (95% CI: 21 to 86) at a specificity of 81% (95% CI: 69 to 90) for predicting hearing loss. Infection during the first *or* second trimester had a sensitivity of 89% (95% CI: 52 to 100) at a specificity of 33% (95% CI: 22 to 46) for predicting hearing loss. Neither of these thresholds are likely to be adequate in terms of avoiding unacceptably high levels of either false negative or false positive results.

Chebib et al. (2022)[85] was rated at serious risk of bias and so should be interpreted with caution (see Appendix 3). It showed primary infection in the first trimester *or* having an imaging anomaly of the fetus had a sensitivity of 91% (95% CI: 83 to 98) and specificity of 48% (95% CI: 36 to 60) for detecting inner ear dysfunction at 21 months. Similarly, a positive test defined by infection in the first trimester and having an imaging anomaly of the fetus had a sensitivity of 38% (95% CI: 28 to 47) and specificity of 92% (95% CI: 86 to 98) (Table 10).

*Table 11: Summary of evidence evaluating the accuracy of timing of infection to predict sequelae of cCMV infection*

| Study properties | Sample size | Baseline tests performed | Long-term outcomes reported | Baseline test accuracy (threshold for positive test) |
|---|---|---|---|---|
| Foulon et al. 2019[88]<br>Prospective<br>Belgium<br>Follow-up: median 31 months | With cCMV: 173<br>Symptoms at birth: 9<br>Long-term outcomes: 20 | Trimester of infection | Hearing loss (mild or worse) at median 31 months | **Trimester of infection (1st)**<br>Sens: 55.6% (95% CI: 21.2 to 86.3) Spec: 81% (95% CI: 69.1 to 89.8)<br>**Trimester of infection (1st or 2nd)**<br>Sens: 88.9% (95% CI: 51.8 to 99.7) Spec: 33.3% (95% CI: 22 to 46.3) |
| **Abbreviations:** cCMV, congenital cytomegalovirus; CI, confidence interval; MRI, magnetic resonance imaging; Sens, sensitivity; Spec, specificity; US, ultrasound. | | | | |

### Association studies

Sixteen studies that assessed the association between timing of maternal infection and long-term outcomes were identified.[98, 104-118] Three of these studies were included in the systematic review by Chatzakis et al. (2020).[107, 108, 111] Therefore, we have summarised the 13 additional association studies, not included in the Chatzakis review.

Six of these studies were prospective[104, 106, 115-118] and 7 were retrospective.[98, 105, 109, 110, 112-114] Sample sizes ranged from 27 to 753 infants with cCMV and follow-up ranged from 12 to 185 months (mean). Studies were conducted in Finland, Italy, Netherlands, Belgium, France, USA and Israel.

Five of these studies showed that primary infection in the first trimester significantly increased risk of long-term neurological and/or hearing sequelae.[105, 110, 112, 115, 116] Seven studies[98, 104, 106, 109, 113, 114, 117] demonstrated the same direction of effect, reporting a greater prevalence of long-term neurological and/or hearing sequelae with earlier infection. However, these effects were either not statistically tested,[98, 106, 109, 113, 117] or yielded a non-significant result.[104, 114] In contrast, 1 study[118] showed a greater prevalence of hearing sequelae in those with later infection, but this very small study did not conduct a statistical analysis.

## Antenatal characteristics – type of maternal infection

### Systematic review evidence

One systematic review by Maltezou et al. (2020)[119] compared long-term sequelae in children born following maternal primary or non-primary infection. The review reported data from 9 studies. Eight of these studies (835 persons) presented evidence assessing the association of the type of maternal infection and later outcomes. The review was at low risk of bias, with a protocol published on PROSPERO, and appropriate methods of searching, data extraction and synthesis.

Meta-analyses showed that maternal infection status (primary versus non-primary infection) did not influence the risk of developing unilateral SNHL (OR 0.80 (95% CI : 0.54 to 1.20)), bilateral SNHL (OR 0.66 (95% CI : 0.30 to 1.42)) or other neurologic outcomes (OR 0.73 (95% CI: 0.43–1.25)).

### Prognostic accuracy studies

No prognostic accuracy studies assessing type of maternal infection were identified.

### Association studies

Nine studies were identified.[111-113, 117, 118, 120-123] Three of these studies[111, 122, 123] were included in the systematic review by Maltezou et al. (2020).[119] We have summarised the other 6 studies.[112, 113, 117, 118, 120, 121] Four studies were prospective[117, 118, 120, 121] and 2 were retrospective.[112, 113] Sample sizes ranged from 22 to 186 infants with cCMV and follow-up ranged from 12 to 185 months (mean). The studies were from Finland, Italy, the USA and Iran.

Two studies[112, 113] found that a significantly higher proportion of infants born to mothers with non-primary infection (compared to primary infection) had long-term hearing or neurodevelopmental sequelae. Another study[118] found no numerical difference in the incidence of hearing sequelae between primary and non-primary maternal infection groups. Two studies[117, 120] found that prevalence of hearing sequelae was slightly higher in the primary infection group. Finally, 1 study[121] stated that there was no correlation between the type of infection and long-term visual sequelae, but no data were clearly presented to support this.

## Gestational age at birth

### Systematic review evidence

No systematic reviews were identified.

### Prognostic accuracy studies

No prognostic accuracy studies were identified.

### Association studies

Two studies[101, 124] evaluated the association between gestational age and hearing and neurodevelopmental sequelae. One study was prospective[101] and the other was retrospective.[124] Follow up was between 6 and 72 months. Sample sizes ranged from 11 to 102 infants with cCMV. The studies were from Italy and the Netherlands.

One study[124] showed that significantly more infants who developed long-term impairment were born premature, compared with infants who did not develop long-term impairment (p=0.024). The other study[101] suggested that neurodevelopmental sequelae were numerically more likely in infants with a lower gestational age.

## Symptoms at birth

### Systematic review evidence

Three relevant systematic reviews were found.[125-127] Smyrli et al. (2024)[125] assessed neurodevelopmental outcomes of children who had presented with asymptomatic cCMV at

birth. The review had a low risk of bias overall. The protocol was published on PROSPERO, and appropriate methods of data extraction and synthesis were used. The only limitation was the limited number of databases used in the search. All 28 studies in the systematic review evaluated the long-term outcomes for children with asymptomatic cCMV. The review included 28 studies, 19 of which reported analyses of outcomes in children who were asymptomatic at birth versus children who were symptomatic at birth. Sixteen of those 19 studies showed that adverse neurodevelopmental outcomes were less common among children with asymptomatic cCMV at birth. No formal meta-analyses were undertaken.

Vos et al. (2021)[126] assessed the association between symptomatic status at birth and childhood and late-onset hearing loss. The review included 65 studies, but only 17 were relevant to this assessment. The review had a low risk of bias overall, with a published protocol, and appropriate methods of searching, data collection and synthesis. The narrative review did not form any firm conclusions about an association between symptomatic status at birth and subsequent hearing loss in children with cCMV, although they found that hearing loss was associated with both symptomatic and asymptomatic disease.

Riga et al. (2018)[127] also evaluated the relationship between symptoms at birth and hearing loss, at up to 10 years of age. Eleven studies were included. The review was deemed to be at high risk of bias, principally because of limitations in the search strategy and synthesis methodology. Among asymptomatic newborns, SNHL was diagnosed in 8.9%, while for symptomatic newborns the percentage raised to 44.2%. This synthesis appeared to be a simple summation of study results rather than a proper meta-analysis.

### Prognostic accuracy studies

Nishida et al. (2020)[93] evaluated the accuracy of the existence of symptoms and found a sensitivity of 84% (95% CI: 60 to 97) at a specificity of 73.7% (95% CI: 49 to 91) (Table 12). The combination of 2 or more clinical symptoms and/or ventriculopathy, periventricular cysts and white matter abnormalities on imaging yielded a sensitivity of 90% (95%CI: 67 to 99) at a specificity of 75% (95% CI: 49 to 91) (Table 10). The combination of 3 or more clinical symptoms and/or ventriculopathy, periventricular cysts and white matter abnormalities on imaging yielded a sensitivity of 79% (95%CI: 54 to 94) at a specificity of 95% (95% CI: 74 to 100) (Table 10). More results are available in Appendix 3. This was a small (n=32) study, with a relatively short follow up of 18 months, and with unclear risk of bias (see Appendix 3).

Blazquez-Gamero et al. (2019)[82] evaluated symptoms at birth combined with neuroimaging to predict any hearing or neurological sequelae. Neuroimaging in symptomatic newborns had a sensitivity of 81% (95% CI: 65 to 92) at a specificity of 85% (95% CI: 69 to 95). Neuroimaging in asymptomatic newborns was not prognostic, with a sensitivity of 2.7% (95%

CI: 0.07 to 14) at a specificity of 94% (95% CI: 80 to 99). These results are summarised in Table 10. This moderately sized (n=71) study was at high risk of bias and there were concerns about applicability (see Appendix 3).

Alarcon et al. (2013)[75] assessed the accuracy of adjusted microcephaly for predicting neurodevelopmental delay, yielding a sensitivity of 44% and specificity of 100% (Table 12). The study also evaluated the accuracy of adjusted microcephaly in combination with positive neuroimaging findings (sensitivity of 66% at a specificity of 100%) and in combination with CSF beta2-m concentration (sensitivity of 82% at a specificity of 100) (Table 10). This small (n=26) study was also at high risk of bias and had concerns about applicability (see Appendix 3).

*Table 12: Summary of evidence evaluating the accuracy of symptoms at birth to predict sequelae of cCMV infection*

| Study properties | Sample size | Baseline tests performed | Long-term outcomes reported | Baseline test accuracy (threshold for positive test) |
|---|---|---|---|---|
| Alarcon et al. 2013[75]<br>Prospective<br>Spain<br>Follow-up: mean 8.7 years | With cCMV: 26<br>Symptoms at birth: 26<br>Long-term outcomes: 15 | Mixed (CSF, microcephaly, neuroimaging) | Neurodevelopmental delay (in terms of motor function, cognition, behaviour, hearing, vision, and epilepsy) at mean 8.7 years | **Adjusted microcephaly (threshold unclear)**<br>Sens: 44% Spec: 100% |
| Nishida et al. 2020[93]<br>Prospective<br>Japan<br>Follow-up: 18 months | With cCMV: 42<br>Symptoms at birth: 23<br>Long-term outcomes: 19 | Clinical symptoms | Neurodevelopmental impairment (NDI) was defined as a developmental quotient <80, hearing dysfunction, blindness, or epilepsy requiring anti-epileptic drugs at 18 months | **Clinical symptoms (present)**<br>Sens: 84.2% (95% CI: 60.4 to 96.6) Spec: 73.7% (95% CI: 48.8 to 90.9) |

**Abbreviations:** cCMV, congenital cytomegalovirus; CI, confidence interval; CSF, cerebrospinal fluid; NDI, neurodevelopmental impairment; Sens, sensitivity; Spec, specificity.

### Association studies

Thirty-six studies[78, 97, 99, 105, 114-118, 120-122, 124, 128-150] were identified. However, 8 of these studies[78, 136, 145-150] were included in the systematic reviews.[125-127] Therefore, we have summarised the 28 additional association studies. There were 16 prospective cohort studies and 12 retrospective cohort studies. Sample sizes ranged from 22 to 753 infants with cCMV, and follow-up ranged from 3 months to 18 years, where reported (most studies followed children up for over 2 years). Studies were conducted in Italy, Belgium, the Netherlands, the USA, Australia, Indonesia, China, Taiwan, Switzerland, Spain, Iran, Finland, and UK/Sweden.

Twenty-six of the studies compared the outcomes of children with symptomatic cCMV at birth with those with asymptomatic cCMV at birth.[97, 99, 105, 114-118, 120-122, 124, 128-135, 137-139, 142-144] Nine of these 26 studies showed that symptoms at birth were significantly associated with an increased risk of long-term visual,[121] hearing,[97, 114, 132] neurodevelopmental and hearing[128] and unspecified[116, 122 99, 105] long-term sequelae. In the other 17 studies statistical analyses were not carried out but the same direction of effect was evident, with a larger numerical prevalence of hearing,[115, 117, 118, 120, 131, 134, 135, 142] visual,[133, 137] language,[114] or neurodevelopmental/hearing[124, 129, 130, 138, 139, 143, 144] sequelae in the symptomatic groups.

Two studies[140, 141] did not compare outcomes in generally symptomatic and asymptomatic infants, instead focussing on the effects of specific baseline symptoms. One study[140] compared infants with CNS involvement against those without CNS involvement and those with only petechial rash. Significantly more infants in the CNS group had SNHL at birth, but the frequency of late-onset SNHL did not differ between groups. Significantly more children in the CNS group had an IQ below 70. The other study[141] compared infants who were small for gestational age with those appropriate for gestational age; long-term sequelae were only reported for the 14 symptomatic infants (all of whom had long-term sequelae). The study concluded that long-term outcomes do not seem to be affected by isolated impaired fetal growth, however, the study is severely limited by the very small sample size.

## Audiological screening result at birth

### Systematic review evidence

No systematic reviews were identified.

### Prognostic accuracy studies

Two studies evaluated the prognostic accuracy of audiological screening at birth. Dhondt et al. (2023)[151] assessed the accuracy of any hearing loss at birth for predicting vestibular function at 4 years. Although children who did not go on to develop vestibular dysfunction

rarely had hearing loss at birth, yielding a specificity 91% (95% CI: 86 to 95), only a small proportion of those who did develop vestibular function had baseline hearing loss, yielding a sensitivity 35% (95% CI: 15 to 59) (Table 13). This was a relatively large study (n=169), with good applicability but a high risk of overall bias (see Appendix 3).

Forgeaud et al. (2024)[89] also evaluated hearing loss as part of a composite test involving platelet count and US measurements at birth. The results (sensitivity 92% at a specificity of 83%) are discussed in more depth in the neuroimaging section and are presented in Table 10.

*Table 13: Summary of evidence evaluating the accuracy of audiological tests to predict sequelae of cCMV infection*

| Study properties | Sample size | Baseline tests performed | Long-term outcomes reported | Baseline test accuracy (threshold for positive test) |
|---|---|---|---|---|
| Dhondt et al. 2023 [151]<br>Prospective<br>Belgium<br>Follow-up: 4 years | With cCMV: 169<br>Symptoms at birth: 76<br>Long-term outcomes: 20 | Hearing loss at birth | Vestibular and motor function at 4 years | **Hearing loss at birth (present)**<br>Sens: 35% (95% CI: 15.4 to 59.2) Spec: 91.3% (95% CI: 85.5 to 95.3) |
| **Abbreviations:** cCMV, congenital cytomegalovirus; CI, confidence interval; Sens, sensitivity; Spec, specificity. | | | | |

### Association studies

Two studies[152, 153] were identified. Both were retrospective cohort studies. Sample sizes ranged from 44 to 61 infants with cCMV and follow-up ranged from 46 to 54 months (mean). Studies were conducted in Italy and the USA. Both studies[152, 153] found that a higher proportion of infants with a 'refer' result on newborn hearing screening developed SNHL than those with a bilateral 'pass' result. One study[152] found that worse hearing threshold at birth was a significant risk factor for progression of hearing loss (p=0.02).

## Viral load

### Systematic review evidence

No systematic reviews were identified.

### Prognostic accuracy studies

Yamaguchi et al. (2022)[154] assessed the accuracy of viral load (at a threshold of >2950 copies/ml) for detecting developmental delay at 36 months. The test was poor at predicting later developmental delay, with a sensitivity of 57% (95% CI: 18 to 90). However, the test was able to accurately predict a lack of developmental problems, with a specificity of 84% (95% CI: 60 to 97) (Table 14). This was a small study (n=26) which was at an overall high risk of bias (see Appendix 3).

*Table 14: Summary of evidence evaluating the accuracy of viral load to predict sequelae of cCMV infection*

| Study properties | Sample size | Baseline tests performed | Long-term outcomes reported | Baseline test accuracy (threshold for positive test) |
|---|---|---|---|---|
| Yamaguchi et al. 2022 [154]<br>Retrospective<br>Japan<br>Follow-up: 36 months | With cCMV: 39<br>Symptoms at birth: 21<br>Long-term outcomes: 7 | Viral load | Developmental delay at 36 months | **CMV DNA load (droplet digital PCR >=2950 copies/ml)**<br>Sens: 57.1% (95% CI: 18.4 to 90.1) Spec: 84.2% (95% CI: 60.4 to 96.6) |

**Abbreviations:** cCMV, congenital cytomegalovirus; CI, confidence interval; CMV, cytomegalovirus; DNA, deoxyribonucleic acid; PCR, polymerase chain reaction; Sens, sensitivity; Spec, specificity.

### Association studies

Eleven studies were identified.[56, 77, 105, 115, 155-161] There were 8 prospective cohort studies, 2 retrospective cohort studies and 1 *post hoc* analysis. Sample sizes ranged from 9 to 387 infants with cCMV and follow-up ranged from 6 months to 6 years, where reported. Studies were conducted in Italy, Belgium, France, the USA, China and Japan. Four studies included children with symptomatic cCMV,[155-157, 160] 3 studies included children with asymptomatic cCMV,[77, 158, 159] and 4 studies included a mixed population.[56, 105, 115, 161]

All 4 studies of infants with symptomatic cCMV found no significant association between viral load and SNHL severity. Of the 4 studies that included a mixed population, 3[56,161,115] found an association between higher viral load and the increased occurrence of SNHL and neurodevelopmental sequelae. The fourth reported no significant association between viraemia and neurodevelopmental sequelae, although no raw data were presented.

All 3 studies[77, 158, 159] that included only infants with asymptomatic cCMV found a statistically significant association between higher viral load at baseline and the development of late-onset sequelae.

## Genotypes and immune cell markers

### Systematic review evidence

No systematic reviews were identified.

### Prognostic accuracy studies

One study[162] showed that the sensitivity and specificity of a 16 gene signature to predict SNHL occurring at any point in a 3 year follow up period were 96% and 89%, respectively (Table 15). This study was deemed at a high risk of bias.

*Table 15: Summary of evidence evaluating the accuracy of genetic tests to predict sequelae of cCMV infection*

| Study properties | Sample size | Baseline tests performed | Long-term outcomes reported | Baseline test accuracy (threshold for positive test) |
|---|---|---|---|---|
| Ouellette et al. 2020[162]<br>Prospective<br>USA<br>Follow-up: 36 months | With cCMV: 80<br>Symptoms at birth: 49<br>Long-term outcomes: 24 | Genes | Late-onset SNHL at 3 years | **16 gene classifier signature (present)**<br>Sens: 95.8% Spec: 89.3% |
| **Abbreviations:** cCMV, congenital cytomegalovirus; Sens, sensitivity; SNHL, sensorineural hearing loss; Spec, specificity. | | | | |

### Association studies

Nine studies were identified.[99, 143, 144, 163-168] There were 6 prospective cohort studies and 3 retrospective cohort studies. Sample sizes ranged from 12 to 131 infants with cCMV and follow-up ranged from 6 months to 6 years of age. Studies were conducted in the Netherlands, Spain, Poland, the USA and China. Two studies included children with symptomatic cCMV,[163, 164] and 7 studies included a mixed population.[99, 143, 144, 165-168] A range of different genotypes were assessed in these studies and 3 of the studies assessed immune cell responses. Most of the genotype studies were limited by low patient numbers and missing data. Results were mixed, with many studies reporting no significant association between the genotypes assessed and long-term sequelae; those that reported an association stated that further studies are required. Studies that assessed immune cell markers reported an association between lower levels of T cells[99, 166] or B cells[144] and long-term sequelae.

## CNS involvement (CSF)

### Systematic review evidence

No systematic reviews were identified.

### Prognostic accuracy studies

Alarcon et al. (2013)[75] evaluated the prognostic accuracy of cerebrospinal fluid (CSF) beta 2-m concentration above a threshold of 7.9mg/L. Used alone, this test had a sensitivity of 69% at a specificity of 100%. When used in combination with microcephaly, accuracy improved to a sensitivity of 82% at a specificity of 100% (see Table 16). This was a small study (n=26) with concerns about applicability and a high overall risk of bias (see Appendix 3).

Results for a combination of CSF beta2-m concentration and neuroimaging have been described in the neuroimaging section and are summarised in Table 10.

*Table 16: Summary of evidence evaluating the accuracy of CSF tests to predict sequelae of cCMV infection*

| Study properties | Sample size | Baseline tests performed | Long-term outcomes reported | Baseline test accuracy (threshold for positive test) |
|---|---|---|---|---|
| Alarcon et al. 2013 [75]<br>Prospective<br>Spain<br>Follow-up: mean 8.7 years | With cCMV: 26<br>Symptoms at birth: 26<br>Long-term outcomes: 15 | Mixed (CSF, microcephaly, neuroimaging) | Neurodevelopmental delay (in terms of motor function, cognition, behaviour, hearing, vision, and epilepsy) at mean 8.7 years | **CSF concentration (>7.9mg/L)**<br>Sens: 69% Spec: 100%<br>**CSF concentration (>7.9 mg/L) OR adjusted microcephaly (threshold unclear)**<br>Sens: 82% Spec: 100% |
| **Abbreviations:** cCMV, congenital cytomegalovirus; CSF, cerebrospinal fluid; Sens, sensitivity; Spec, specificity. | | | | |

### Association studies

Two studies that assessed the association between CNS involvement (detection of CMV DNA in cerebrospinal fluid by PCR as a marker of CNS involvement) were identified.[169, 170] One was a prospective cohort study and 1 a retrospective cohort study. Sample sizes ranged from 136 to 168 infants with cCMV and follow-up ranged from 4-8 weeks to 6 months. Studies were conducted in Poland and Spain. One study[169] found that CNS involvement was associated with neurological abnormalities such as seizures at 4-8 weeks follow up, but the study with longer-term follow-up[170] found no association between a positive result and neurological sequelae or SNHL at 6 months of age. Both studies concluded that the test may not be a useful prognostic marker in clinical practice.

## Combination tests

### Systematic review evidence

No systematic reviews were identified.

### Prognostic accuracy studies

Four prognostic accuracy studies were identified that used combination tests.[75, 82, 85, 89] In 3 of these studies,[82, 85, 89] all the combination tests involved neuroimaging, and in the other study[75] 1 combination test involved neuroimaging, whilst the other covered CSF and symptoms. The combination tests involving neuroimaging have been presented in Table 10, and discussed in the appropriate sections. The CSF/symptom combination test has been presented in Table 16.

### Association studies

Many studies looked at the associations of more than 1 prognostic variable with sequelae, but analyses were usually carried out for each prognostic variable independently, and not in combination. Only 2 studies looked at the likelihood of sequelae in terms of the interactions between more than 1 variable.[76, 117]

Bilavsky et al. (2015)[76] evaluated the association between hearing sequelae and the combination of symptomatic status and presence of lenticulostriate vasculopathy (LSV). Broadly, the study found that that having LSV with no treatment leads to more long-term hearing loss than having LSV *with* treatment ($p<0.001$) or being asymptomatic ($p=0.008$). Although the study was moderately sized, with a reasonably long follow-up, the study was limited by the unknown LSV status of the asymptomatic group, who may not have had LSV status measured.

Demmler-Harrison et al. (2020)[117] looked at the association of hearing sequelae with the combination of symptomatic status and type of maternal CMV infection. Newborns were

more likely to develop hearing loss if symptomatic and the mother had a primary infection than if they were symptomatic and the mother had a non-primary infection. They were also more likely to develop hearing loss if asymptomatic and the mother had a primary infection than asymptomatic and the mother had a non-primary infection. However, these findings were not statistically analysed.

## Summary of Findings Relevant to Criterion 7

### Criterion Not Met

The review included 94 studies relevant to this question; 4 systematic reviews, 19 prognostic accuracy studies and 71 studies assessing the association between test results and/or antenatal and/or newborn characteristics and long-term health consequences. A range of tests and characteristics were assessed; however, much of the evidence is of limited quality.

Overall, the results indicate that the most reliable characteristics for predicting long-term sequelae in infants with cCMV are the presence of symptoms at birth and timing of maternal CMV infection. Newborns with more severe cCMV symptoms are likely to be offered antiviral treatment under current guidelines.[8] Our results indicate that the most useful test for predicting long-term hearing and neurodevelopmental sequelae is likely to be MRI. Results of studies assessing viral load to predict long-term hearing sequelae are promising, particularly in newborns with asymptomatic cCMV, however, further research is required to confirm these findings. As there appear to be multiple factors that affect the risk of long-term sequelae, research to generate a multifactorial risk model for long-term harms in newborns with cCMV may be useful.

A summary is presented below for each test/characteristic assessed.

#### Neuroimaging (MRI and ultrasound)

Fifteen prognostic accuracy studies and 7 other cohort studies assessed the accuracy of neuroimaging to predict long-term sequelae in infants with cCMV. In general, neuroimaging tests demonstrated reasonable accuracy in predicting neurodevelopmental delay, epilepsy and hearing outcomes. The most accurate tests were MRI or US (and sometimes CT) using 'Alarcon' scoring. In general, studies were small, and most studies had either a high or unclear risk of bias.

Studies assessing the association between US abnormalities and long-term sequelae had conflicting results; 3 studies reported an association between US abnormalities and hearing and/or neurodevelopmental sequelae, whilst 2 studies reported a numerically higher

prevalence of adverse outcomes in infants without abnormalities detected on US. Overall, MRI appears to be a more useful modality than US for predicting long-term sequelae.

### Antenatal characteristics (timing of maternal infection)

One good quality systematic review pooled evidence from 6 studies and found that primary maternal infection in the first trimester led to a much higher prevalence of adverse long-term sequelae than primary maternal infection in the second or third trimesters. However, we identified an additional 2 prognostic accuracy studies (of low quality) that did not demonstrate adequate accuracy of timing of maternal infection for predicting adverse hearing outcomes. Our review also included 13 cohort studies. Twelve of the studies demonstrated that infection in the first trimester significantly increased the risk of long-term neurological or hearing sequelae (5 of which reported a statistically significant association). Only 1 small study showed a greater prevalence of hearing sequelae in those with later infection.

Whilst some of these studies were limited by low patient numbers, missing data and relatively short-term follow-up, the finding that first trimester infection is associated with more severe long-term hearing or neurodevelopmental sequelae was generally consistent between studies and is likely to be valid.

### Antenatal characteristics (type of maternal infection)

One good quality systematic review pooled evidence from 8 studies and found that type of maternal CMV infection (primary or non-primary infection) did not influence the risk of developing SNHL or other neurological outcomes at follow-up. We identified an additional 6 cohort studies. Their results were inconsistent; 2 studies reported a statistically significant higher proportion of infants born to mothers with non-primary infection having long-term hearing and/or neurodevelopmental sequelae, 2 studies suggested the opposite direction of effect, and 2 studies reported no correlation between type of maternal infection and long-term sequelae. Confidence in these findings is limited by the small sample size in most studies and conflicting results. Overall, type of maternal CMV infection has not been shown to be a reliable predictor of long-term sequelae.

### Antenatal characteristics (gestational age)

Two cohort studies assessed the association between gestational age and long-term sequelae. As might be expected, both studies reported that more infants who were born premature developed adverse outcomes.

### Symptoms at birth

One good quality systematic review assessed neurodevelopmental outcomes of children who had presented with asymptomatic cCMV at birth. Most of the included studies that compared symptomatic and asymptomatic infants found that adverse neurodevelopmental outcomes were less common among children with asymptomatic cCMV at birth.

We identified an additional 30 cohort studies. Twenty-eight of the studies compared the outcomes of children with symptomatic cCMV at birth with those with asymptomatic cCMV at birth; all 28 studies showed that symptoms at birth were associated with an increased risk of long-term sequelae (9 of which reported a statistically significant association). Whilst some studies were limited by small sample sizes and/or short-term follow-up, the evidence was largely consistent, suggesting that there is an association between symptomatic cCMV at birth and poorer long-term outcomes, as might be expected.

### Audiological screening result at birth

Two prognostic accuracy studies assessed the accuracy of audiological screening at birth to predict hearing sequelae in infants with cCMV. One study (which was at a high risk of bias) did not demonstrate adequate accuracy of audiological screening at birth for predicting adverse hearing outcomes. The other study demonstrated a high level of accuracy for predicting SNHL or psychomotor sequelae. Our review also included 2 other small cohort studies, both studies found that a higher proportion of infants with a 'refer' result on newborn hearing screening developed SNHL than those with a bilateral 'pass' result.

### Viral load

One very small prognostic accuracy study (at a high risk of bias) assessed the accuracy of viral load for detecting developmental delay; the test was poor at predicting later developmental delay.

Our review also included 11 other cohort studies. Four of those studies included infants with symptomatic cCMV; all 4 studies found a trend towards lower baseline viral load and better hearing outcomes, but the findings did not reach statistical significance. Three studies included infants with asymptomatic cCMV; all 3 studies found a statistically significant association between higher viral load at baseline and the development of late-onset sequelae (primarily SNHL). Four studies included a mixed population of symptomatic and asymptomatic infants; 3 of the studies found an association between higher viral load and the development of hearing and/or neurodevelopmental sequelae.

Overall, viral load appears to be a promising test for predicting long-term hearing (and possibly neurodevelopmental) sequelae, particularly amongst asymptomatic infants.

### Genotypes and immune cell markers

One prognostic accuracy study (at a high risk of bias) reported a good level of accuracy of a 16 gene signature to predict SNHL. Our review also included 9 other cohort studies; 6 studies assessed a range of different genotypes and 3 studies assessed immune cell markers. Most of the genotype studies were limited by low patient numbers and missing data. Results were mixed, with many studies reporting no significant association between the genotypes assessed and long-term sequelae. Studies that assessed immune cell markers reported an association between lower levels of T cells or B cells and long-term sequelae. Study authors drew cautious conclusions and/or recommended further research. No firm conclusions can be drawn from any of the studies.

### CNS involvement (cerebrospinal fluid)

One very small prognostic accuracy study (at a high risk of bias) assessed the accuracy of CNS involvement, assessed using cerebrospinal fluid, for detecting neurodevelopmental delay; results indicated reasonable predictive accuracy, particularly when used in combination with microcephaly. Our review also included 2 cohort studies; both studies concluded that the test may not be a useful prognostic marker in clinical practice.

## Criteria 11 & 13: There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. The benefit gained by individuals from the screening programme should outweigh any harms for example from overdiagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications.

### Can a newborn screening programme for cCMV reduce the burden of cCMV-related morbidity and mortality?

#### Previous work

The most recent UK NSC evidence map[7] identified only 2 cohort studies that investigated the impact of screening on morbidity.[148, 171] Both studies were identified by our searches and are included in our assessment. The previous review concluded that the available evidence provides only limited new information and there was close to no evidence on the benefits of early treatment or interventions for cCMV compared to late treatment after the presentation of symptoms.

The earlier UK NSC evidence review from 2017[18] identified 1 study it judged to be relevant.[172] This study examined 178 newborns with symptomatic cCMV and found that newborns identified by screening were less likely to have long-term disease sequelae than newborns identified through routine referral (28% versus 51%, p=0.003). However, the review concluded that this study could not demonstrate whether this difference was due to the direct effect of screening. This study did not meet the inclusion criteria for the current review and so is not considered further.

#### Description of the current evidence

The aim was to identify all systematic reviews and randomised or non-randomised studies that reported evidence on an evaluation of screening for cCMV in practice. To be eligible for inclusion, studies had to report outcomes in line with the protocol, specifically: symptoms at birth (e.g. outcome of hearing test or results of neuroimaging); use of antiviral therapy; or long-term sequelae (e.g. long-term hearing loss or neurodevelopmental issues). Studies reporting acceptability of screening to physicians or parents were also included.

### Systematic reviews

The review identified 2 systematic reviews that investigated the value of newborn cCMV screening.

Hilditch al (2018)[173] included 2 studies of universal screening and 4 of targeted screening. All 6 studies were eligible for our review and were found in our searches. The Hilditch review did not perform any quantitative or qualitative synthesis of the studies, so is of limited value for this assessment. We therefore chose to examine the included studies as part of our review in the sections below. The Hilditch review concluded that newborn screening will identify asymptomatic newborns with cCMV that would otherwise have gone undiagnosed. They also stated that those newborns could benefit from antiviral therapy, but that treatment remains controversial. There may be other benefits of early diagnosis, including early intervention and hearing augmentation.

Pollick et al (2024)[174] included 12 studies: 3 of universal screening, 8 of targeted screening and 1 of pre-natal screening. Only 4 of the studies met the inclusion criteria for this review (and are included in our evaluation below), limiting the relevance of the Pollick review. The Pollick review found that universal screening will identify all cCMV cases, but is at risk of more false positives, and may be more costly and logistically burdensome. Hearing-targeted screening may be more cost-efficient but will miss asymptomatic cases and newborns with late-onset hearing loss. It concluded that continued research that examines the potential benefits and disadvantages of screening and how this may impact detection of hearing and other neurodevelopmental outcomes is required.

### Individual studies

Of the 422 papers considered at full text screening 36 studies met the inclusion criteria for this question. None of the included studies were randomised controlled trials (RCTs) and none were non-randomised studies comparing a screened population with a non-screened population. Therefore, strictly, there is no evidence to meet this criterion. However, the non-comparative studies which were identified are reported here.

There were 14 studies that evaluated universal screening (i.e. screening of all newborns regardless of symptoms, see Table 17), 12 studies evaluated targeted screening in newborns who had failed a newborn hearing screen (see Table 19), and 10 studies evaluated targeted screening in newborns who showed signs of cCMV at birth (including hearing loss) (see Table 21).

Presentation of results was limited in all studies, largely restricted to presenting numbers of c CMV diagnoses, and numbers with and without symptoms at birth. In the subset of studies

that reported long-term follow-up, reporting was mostly limited to numbers receiving antiviral therapy and numbers with long-term sequelae. Given the absence of comparative studies and the limitations of the results presented it was decided not to perform a quality assessment or risk of bias assessment of the included studies. However, we note the following general quality and risk of bias concerns across the studies:

- as there is no comparative evidence it is not possible to determine whether symptoms at birth, or long-term sequelae, are caused by CMV infection, or are unrelated to infection;
- it is not possible to evaluate which symptoms or long-term sequelae would have been identified, managed and treated in the absence of cCMV screening;
- as management protocols were not usually reported, there may have been differences in how symptomatic infection, asymptomatic infection and uninfected newborns were managed and followed-up;
- as use of antiviral therapy was not randomised or controlled it is not possible to determine whether treatment itself prevented or moderated long-term sequelae, or whether sequelae would have occurred without treatment;
- follow-up duration, where reported, was variable across studies; and
- studies were performed in a wide variety of locations with differing levels of cCMV prevalence. Therefore, results of the studies may not be applicable to the UK context.

Given the limitations in the evidence base, results presented in this report focus on summarising the overall conclusions and findings of the studies, and summarising event rates (such as frequency of long-term sequelae) using random-effects meta-analysis.

### Universal screening

The review identified 15 studies evaluating the performance of universal newborn screening for cCMV, using either saliva, DBS or urine testing. The characteristics and general conclusions of these studies are summarised in Table 17. Eight studies used primarily saliva testing to screen for cCMV, 3 used urine testing, 3 used DBS and 1 used a mix of tests.

Only 1 of these studies (Puhakka 2019)[175] included any comparative evidence. This study compared long-term outcomes in children with symptomatic infection, asymptomatic infection and no infection after saliva-based screening. It compared 40 cases of cCMV in Finland with 54 matched controls without cCMV. It found no difference in neurodevelopmental outcomes or in hearing between cases and controls after 18 months of follow-up (for example, 66% of cases and 76% of controls passed an audiological exam, p=0.572). It concluded that screening was unwarranted in Finland because of the low prevalence of cCMV infection.

Based on the reported conclusions of the 15 included studies, 4 were broadly in favour of implementing universal screening,[54, 148, 176, 177] 2 did not favour screening,[175, 178] 2 suggested more research is required or were neutral,[36, 179] 3 concluded that screening was feasible without stating if it should be used[171, 180, 181] and the 4 remaining studies did not conclude directly on whether screening should be used.[182-185] Therefore, there seems to be little consistency across the included studies as to whether universal screening should be implemented.

Arguments made in favour of universal screening included (see Table 17):

- most cCMV cases would not be diagnosed without universal screening;
- it identifies newborns with late neurological sequelae that would otherwise be missed;
- it identifies newborns who would benefit from ongoing audiologic surveillance;
- antiviral treatment of symptomatic cCMV leads to normal development or mild long-term sequelae; and
- it predicts late-onset SNHL and neurodevelopmental disorders.

Arguments made against current implementation of universal screening included (see Table 17):

- outcomes at 18 months of age in Finland did not differ between infected infants and healthy control infants;
- targeted cCMV screening among neonates who fail a hearing screen was preferable to universal screening;
- most newborns with cCMV had a normal cranial ultrasound; and
- universal urine screening likely identifies subclinical symptomatic cCMV.

Most studies concluded that universal screening, whichever test was used, was feasible and practical to implement. One study[183] reported that pooled saliva screening (in pools of 10 newborns) was beneficial and reasonable when compared to individual sample screening.

The included studies reported numbers of newborns who were diagnosed cCMV, numbers who had symptoms (including hearing loss and neuroimaging abnormalities), numbers given antiviral therapy, and numbers with long-term sequelae (hearing loss or neurodevelopmental issues). Table 18 summarises these data across the studies by presenting results from a meta-analysis of all studies reporting data on each outcome. This gives an “average” number of events that might be observed within a universal screening programme. Given the rarity of most events, results are presented as expected numbers of events per 10,000

babies screened, per 10,000 with cCMV, and, for antiviral therapy and long-term sequelae, per 10,000 with and without symptoms at birth. As this meta-analysis pools results across 3 types of screening (saliva, DBS and urine) and across a wide range of countries and settings, results are very heterogeneous, so should only be interpreted as a broad view of the consequences of universal screening.

The meta-analysis results in Table 18 demonstrate that, as expected, cCMV infection is rare, occurring in only 0.4% of newborns across the included universal screening studies. Symptomatic cCMV, and hence long-term sequelae, is very rare, at less than 0.1% of all newborns. Only 23% of newborns with cCMV displayed symptoms at birth, and cranial abnormalities may be more common than hearing loss. This concurs with claims made by the studies that universal screening will detect cCMV cases that will be missed by any other form of management. Antiviral therapy was only given to a minority of newborns with confirmed cCMV (around 11%), and around 18% of those with cCMV developed long-term sequelae.

Antiviral therapy was never given to children who were classified as being asymptomatic at birth, and only 6% of newborns with asymptomatic cCMV went on to develop long-term sequelae. This concurs with the findings of Puhakka (2019)[175] that it is unclear whether these findings can be distinguished from hearing loss and neurodevelopmental issues that are unrelated to cCMV. Among newborns with symptomatic cCMV, 69% received antiviral therapy, so there will still be some children with symptoms who do not receive therapy. Around 56% of these newborns will develop long-term sequelae.

*Table 17: Details of 15 studies relating to evaluation of universal cCMV screening performance*

| Study details | Screening test | Confirmation test | Follow-up beyond infancy | Number screened, Number with cCMV (Prevalence) | Results presented | Study conclusions |
|---|---|---|---|---|---|---|
| **Universal screening (15 studies)** | | | | | | |
| Dunn 2025[177]<br>Canada | DBS | Urine | No | 551,034<br>601 with cCMV | Symptoms at birth<br>Antiviral treatment | A lower than expected prevalence of cCMV. Screening identified many children who would otherwise not have been diagnosed and who would benefit from ongoing audiologic surveillance |
| Kaye 2024[179]<br>USA | DBS | Urine | No | 60115<br>184 with cCMV | Symptoms at birth<br>Antiviral treatment | Further evaluation of the newborn screening using dried blood spot sensitivity is warranted |
| Papaevangelou 2017[184]<br>Greece | DBS | Not stated | Yes<br>(5 years) | 2149<br>10 with cCMV | Symptoms up to 5 years | *No conclusions related to screening reported* |
| Barkai 2014[36]<br>Israel | Saliva | Urine | Yes | 9845<br>48 with cCMV | Hearing tests at birth and up to 18 months<br>Antiviral treatment | Saliva is a feasible and effective means of universal neonatal CMV screening that can detect affected infants who might benefit from treatment and follow-up. The long-term clinical significance of screening and its cost-effectiveness are yet to be determined |
| Chiereghin 2022[176]<br>Italy | Saliva | Urine or Saliva | Yes | 3151<br>21 with cCMV | Viral load<br>Symptoms at birth<br>Antiviral treatment | Without universal neonatal CMV screening, some infected infants who develop late neurological sequelae may not be recognized |

| Study details | Screening test | Confirmation test | Follow-up beyond infancy | Number screened, Number with cCMV (Prevalence) | Results presented | Study conclusions |
|---|---|---|---|---|---|---|
| Demortier 2021[182]<br>France<br>(Reunion/Mayotte) | Saliva | Urine | No | 1042<br>16 with cCMV | Symptoms at birth<br>Survey of healthcare workers (with limited response) | Parents found screening to be acceptable |
| Letamendia-Richard 2022[54]<br>France | Saliva | Urine | No | 15356<br>63 with cCMV | Viral load<br>Symptoms at birth<br>Survey of healthcare workers | Universal screening for cCMV on saliva samples is feasible and highly acceptable<br>62% would probably not have been diagnosed without universal screening |
| Merav 2024[183]<br>Israel | Saliva (pooled samples) | Saliva then urine | No | 15805<br>54 with cCMV | Performance of pooled versus individual screening | Wide feasibility and benefits of pooled saliva testing |
| Puhakka 2019[175]<br>Finland | Saliva | Urine | Yes<br>(up to 18 months) | 19868<br>40 with cCMV | Viral load<br>Neurological and hearing symptoms at 18 months<br>Comparison with uninfected control children | Outcomes at 18 months of age did not differ between the infected infants and healthy control infants. With such a low burden in Finland, universal newborn screening for cCMV seems unwarranted |
| Yamamoto 2020[178]<br>Brazil | Saliva | Urine | Yes<br>(median 36 months) | 11900<br>68 with cCMV | Hearing loss at birth<br>Hearing loss at long-term follow-up | Integrating targeted cCMV screening among neonates who fail a hearing screen could be a reasonable, cost-effective strategy to identify newborns with early-onset cCMV-related hearing loss |
| Zeytinoglu 2018[185]<br>Turkey<br>*(paper in Turkish)* | Saliva | Urine or blood | No | 1000<br>2 with cCMV | Symptoms at birth | *No conclusions related to screening reported* |
| Kruc 2024[180]<br>USA | Saliva or DBS | Urine | Yes<br>(up to 5 years) | 23644<br>87 with cCMV | Symptoms at birth | Among infants with cCMV identified in a universal screening study, the majority |

| Study details | Screening test | Confirmation test | Follow-up beyond infancy | Number screened, Number with cCMV (Prevalence) | Results presented | Study conclusions |
|---|---|---|---|---|---|---|
| | | | | | | had a normal cranial ultrasound |
| Koyano 2017[148]<br>Japan | Urine | Not stated | Yes<br>(Over 2 years) | 23405<br>72 with cCMV | Viral load<br>Symptoms at birth<br>Antiviral treatment<br>Symptoms at follow-up | Newborn urine–filter paper screening of congenital CMV infection is warranted |
| Yamada 2020[171]<br>Japan | Urine | Urine | Yes<br>(duration unreported) | 11736<br>56 with cCMV | Symptoms at birth<br>Neurological assessments on long-term follow-up | Universal urine screening and antiviral therapy for neonates with symptomatic cCMV may decrease neurological impairments, because 58% of the treated infants had normal development or mild sequelae. Universal urine screening likely identifies subclinical symptomatic cCMV |
| Yamaguchi 2017[181]<br>Japan | Urine | Not stated | Yes<br>(6 months) | 23368<br>60 with cCMV | Viral load<br>MRI at birth<br>MRI at follow-up | Urinary CMV load may effectively predict the incidence of late-onset SNHL and neurodevelopmental disorders |

**Abbreviations:** cCMV, congenital cytomegalovirus; CMV, cytomegalovirus; DBS, dried blood spots; MRI, magnetic resonance imaging; SNHL, sensorineural hearing loss.

*Table 18: Meta-analysis of event rates in 15 studies of universal screening*

| Event | Number of studies with data | Predicted rate per 10,000 screened newborns (95% confidence interval) | Predicted rate per 10,000 newborns with cCMV (95% confidence interval) |
|---|---|---|---|
| **Diagnosis of cCMV** | 14 | 37 (38 to 50) | x |
| **Has symptoms at birth (all symptoms)** | 13 | 8 (4 to 15) | 2293 (1379 to 3563) |
| **Has hearing loss at birth** | 9 | 3 (1 to 5) | 896 (601 to 1304) |
| **Has cranial MRI/US abnormalities at birth** | 7 | 5 (2 to 10) | 1676 (724 to 3419) |
| **Receives antiviral treatment** | 10 | 4 (2 to 6) | 1092 (682 to 1702) |
| **Has long-term sequelae** | 8 | 7 (4 to 11) | 1757 (970 to 2975) |
| **Has long-term hearing loss** | 8 | 4 (3 to 6) | 1225 (923 to 1609) |
| **Has long-term neurological or developmental issues** | 4 | 6 (3 to 12) | 1856 (694 to 4107) |
| | **Number of studies with data** | **Predicted rate per 10,000 newborns with symptomatic cCMV (95% confidence interval)** | **Predicted rate per 10,000 newborns with asymptomatic cCMV (95% confidence interval)** |
| **Receives antiviral treatment** | 6 | 6920 (5278 to 8187) | Zero |
| **Has long-term sequelae** | 5 | 5558 (2682 to 8101) | 585 (335 to 1002) |
| **Has long-term hearing loss** | 6 | 4085 (2340 to 6091) | 550 (334 to 891) |
| **Has long-term neurological or developmental issues** | 3 | 3495 (1788 to 5701) | 380 (158 to 886) |

**Abbreviations:** cCMV, congenital cytomegalovirus; MRI, magnetic resonance imaging; US, ultrasound.

## Targeted screening based on failure of newborn hearing screen

The review identified 12 studies evaluating the performance of targeted newborn screening for cCMV, among newborns who failed a newborn hearing screen (or equivalent hearing test), using either saliva, DBS or urine testing. The properties and general conclusions of these studies are summarised in Table 19. Six studies used saliva testing to screen for cCMV, 4 used saliva or urine testing, 1 used DBS and 1 used a mix of tests.

Based on the reported conclusions of the 12 included studies, 3 were broadly in favour of implementing targeted screening.[186-188] Two did not favour screening,[189, 190] although 1 of these was specifically in newborns in a neonatal intensive care unit.[189] Four suggested more research is required or were neutral.[191-194] Three concluded that targeted screening was feasible without stating if it should be used.[195-197] Hence the studies seem broadly to suggest

that targeted screening may be valuable, but some further evaluation is needed, such as clearly demonstrating its cost-effectiveness.

Arguments made in favour of targeted screening included (see Table 19):

- it identifies the majority of infants with cCMV-related SNHL at birth;
- it contributes to the early detection of infants born with cCMV-related SNHL who could benefit from treatment; and
- it ensures appropriate clinical, neurodevelopmental and audiological follow-up.

Arguments made against current implementation of targeted screening included (see Table 19):

- Many infants with CMV-related SNHL will not be detected using a newborn hearing screen; and
- it is problematic to perform in NICUs due to timing difficulties.

Most studies concluded that targeted screening, whichever test was used, was feasible and practical to implement.

As for universal screening, the included studies reported numbers of newborns who were diagnosed with cCMV, numbers who had symptoms, and numbers receiving antiviral therapy. None of the studies, however, reported any long-term follow-up data. Table 20 summarises these data across the studies by presenting results from a meta-analysis of all studies, as in Table 18 for universal screening.

The meta-analysis results in Table 20 demonstrate that cCMV infection is uncommon even in newborns who fail a hearing screen, occurring in 1.5% of newborns across the included studies. About 75% of newborns with confirmed cCMV displayed symptoms at birth (beyond failure of the hearing test in itself), although it is possible that some symptoms were diagnosed as a consequence of testing positive for cCMV. Antiviral therapy was only given to about half of newborns with cCMV (54%), representing just under 1% of those screened. It is perhaps surprising that antiviral therapy was given so infrequently, despite both a diagnosis of cCMV and failure of a hearing test; this may indicate issues with delayed diagnosis meaning treatment cannot be offered. No studies reported any long-term outcome data.

*Table 19: Details of 12 studies relating to evaluation of hearing loss-targeted cCMV screening performance*

| Study details | Screening test | Confirmation test | Follow-up beyond infancy | Number screened, Number with cCMV | Results presented | Study conclusions |
|---|---|---|---|---|---|---|
| **Screening in infants who fail a newborn hearing test (12 studies)** | | | | | | |
| Chung 2022[187] Netherlands | DBS | Not stated | No | 1374<br>59 with cCMV | Hearing loss and neuroimaging in infancy | Newborns who fail newborn hearing screening should be tested for CMV to ensure appropriate clinical, neurodevelopmental and audiological follow-up |
| Diener 2017[195] USA | Mixed | None | No | 314<br>21 with cCMV | Hearing loss at birth<br>Compliance with screening | Incorporating CMV screening into an established NHS program is a viable option |
| Ari-Even Roth 2017[186] Israel | Saliva | Urine | No | 187<br>4 with cCMV | Hearing loss at birth | Targeted cCMV screening contributed to the early detection of infants born with cCMV-related isolated SNHL who could potentially benefit from antiviral treatment |
| Beswick 2021[191] Australia | Saliva | Any | No | 489<br>4 with cCMV | Stakeholder interviews | cCMV screening alongside hearing tests is achievable, a number of barriers need to be addressed |
| Fourgeaud 2022[196] France | Saliva | Saliva + blood | No | 236<br>2 with cCMV | Hearing at birth<br>Antiviral use | Targeted cCMV screening is feasible |
| Kadambari 2015[194] UK | Saliva | Not stated | No | 203<br>2 with cCMV | Survey of screeners | Rapid diagnostic testing for cCMV needs a more detailed clinical and cost-effectiveness analysis |
| Ronner 2022[188] USA | Saliva | Not stated | Yes (duration not stated) | 891<br>8 with cCMV | Hearing at birth<br>Antiviral use<br>Hearing at follow-up | Implementation of a targeted screening program for CMV in children who do not pass the NHS resulted in significantly higher rates of CMV testing and earlier referral to infectious disease |
| Fowler 2017[192] USA | Saliva and DBS | Not stated | No | Unclear<br>(31 with cCMV failed hearing test) | Hearing tests at birth | A targeted CMV approach that tests newborns who fail their NHS identified the majority of infants with CMV-related SNHL at birth. However, |

| Study details | Screening test | Confirmation test | Follow-up beyond infancy | Number screened, Number with cCMV | Results presented | Study conclusions |
|---|---|---|---|---|---|---|
| | | | | | | 43% of the infants with CMV-related SNHL in the neonatal period and cCMV infants who are at risk for late-onset SNHL were not identified by NHS |
| Medoro 2021[189]<br>USA<br>(NICUs only) | Urine or saliva | Urine | No | 1498<br>3 with cCMV | Hearing tests at birth | Targeted CMV testing for failed hearing screen in the NICU is problematic |
| Rawlinson 2018[197]<br>Australia | Urine or saliva | Not stated | No | 336<br>19 with cCMV | Hearing test and MRI at birth | Timely CMV testing for newborns who fail NHS and who have permanent hearing loss confirmed, has been shown to be clinically practical |
| Vancor 2019[190]<br>USA | Urine or saliva | Not stated | No | 171<br>2 with cCMV | Symptoms at birth | Consideration should be given to other strategies for identifying children at risk of hearing loss as a result of cCMV infection |
| Williams 2014[198]<br>UK | Urine or saliva | Not stated | No | 407<br>6 with cCMV | Symptoms and neuroimaging at birth | Targeted salivary screening for cCMV within the NHS is feasible, acceptable and detects infants with cCMV-related SNHL who could benefit from early treatment |

**Abbreviations:** cCMV, congenital cytomegalovirus; CMV, cytomegalovirus; DBS, dried blood spots; MRI, magnetic resonance imaging; NHS, newborn hearing screening; NICU, neonatal intensive care unit; SNHL, sensorineural hearing loss.

*Table 20: Meta-analysis of event rates in 12 studies of hearing-loss targeted screening*

| Event | Number of studies with data | Predicted rate per 10,000 screened newborns (95% confidence interval) | Predicted rate per 10,000 newborns with cCMV (95% confidence interval) |
|---|---|---|---|
| **Diagnosis of cCMV** | 12 | 147<br>(80 to 269) | x |
| **Has symptoms at birth (all symptoms)** | 10 | 118<br>(69 to 202) | 7548<br>(6825 to 8400) |
| **Has cranial MRI/US abnormalities at birth** | *Insufficient data* | | |
| **Receives antiviral treatment** | 9 | 80<br>(53 to 118) | 5360<br>(3450 to 7170) |
| **Has long-term sequelae** | *Insufficient data* | | |
| **Abbreviations:** cCMV, congenital cytomegalovirus; MRI, magnetic resonance imaging; US, ultrasound. | | | |

## Targeted screening based on signs suggestive of cCMV infection

The review identified 10 studies evaluating the performance of newborn screening for cCMV, where screening was based on signs consistent with possible cCMV infection. Included signs varied across studies. Failure of hearing tests was consistently included, but other possible signs included known maternal CMV infection, microcephaly, baby being small for gestational age, among others. The properties and general conclusions of these studies are summarised in Table 21. One study used saliva testing to screen for cCMV, 5 used urine testing, 3 used saliva or urine testing, 1 used DBS testing.

Based on the reported conclusions of the 10 included studies, 3 were broadly in favour of implementing targeted screening.[199-201] One did not favour targeted screening.[152] Two were more neutral.[202, 203] Two concluded that it was feasible without stating if it should be used.[101, 204] Two did not report conclusions on the value of screening.[205, 206] Hence the studies seem broadly to suggest that targeted screening may be valuable, but findings were not consistent.

Arguments made in favour of targeted screening included (see Table 21):

- it helps lead to the diagnosis of cCMV infection that may otherwise be overlooked; and
- it allows for early recognition of asymptomatic cases with hearing loss.

Arguments made against current implementation of targeted screening included (see Table 21):

- it may overlook cCMV infection that is asymptomatic at birth; and

- a universal newborn screening programme should be adopted instead of targeted screening.

Most studies concluded that targeted screening, whichever test was used, was feasible and practical to implement.

As for universal screening, the included studies reported numbers of newborns who were diagnosed with cCMV, numbers who had symptoms, numbers receiving antiviral therapy, and numbers with long-term sequelae. Table 22 summarises these data across the studies by presenting results from a meta-analysis of all studies, as in Table 18 for universal screening.

The meta-analysis results in Table 22 demonstrate that cCMV occurred in 1.5% of newborns across the included studies. About 54% of newborns with confirmed cCMV (and 0.7% of newborns screened) were judged to be symptomatic at birth, and only 28% of newborns with confirmed cCMV received antiviral therapy, despite those babies having signs and symptoms consistent with infection. This is notably lower than the proportion receiving therapy when screening is based on failure of a hearing test only (Table 20), suggesting that expanding targeted screening beyond failure of a hearing test may be picking up more asymptomatic cases who do not receive antiviral therapy. About 18% of newborns with cCMV went on to have long-term sequelae. This is very similar to the proportion in the universal screening studies (Table 18).

*Table 21: Details of 10 studies relating to evaluation of symptom targeted cCMV screening performance*

| Study details | Screening test | Confirmation test | Follow-up beyond infancy | Number screened, Number with cCMV | Results presented | Study conclusions |
|---|---|---|---|---|---|---|
| **Screening in infants with symptoms suggestive of cCMV infection (10 studies)** | | | | | | |
| Lu 2018[204]<br>Taiwan | DBS | Urine or saliva | Yes<br>(3 months) | 1716<br>3 with cCMV | Hearing tests in infancy | Hearing, genetic, and CMV screenings are feasible |
| Webb 2024[206]<br>Australia | Saliva | Urine or saliva | Yes<br>(up to 6 months) | 96<br>1 with cCMV | Parent survey | Parent experiences of targeted cCMV screening were positive |
| Forli 2024[152]<br>Sweden | Urine | Not stated | Yes<br>(3-12 years) | 1615<br>25 with cCMV | Hearing loss at birth<br>Symptoms at birth<br>Hearing at follow-up | cCMV screening in newborns allows the detection of many cases; but many are still missed. Important to adopt a universal newborn screening program or a program extended to newborns at higher risk |
| Fujii 2017[202]<br>Japan | Urine | Urine | None | 575<br>20 with cCMV | Comparison with universal screening<br>Symptoms at birth | Urine test identifies cCMV cases efficiently. Risk-based and universal newborn screening strategies for cCMV infection each have advantages |
| Palma 2021[201]<br>Italy | Urine | Not stated | None | Not stated<br>20 with cCMV | Hearing loss at birth | Coupling cCMV screening and hearing screening is worthwhile as it allows early recognition of asymptomatic cases with hearing loss |
| Tan 2023[205]<br>Singapore | Urine | Not stated | Yes<br>(2-3 months) | 1220<br>11 with cCMV | Hearing loss | *No conclusions related to screening reported* |
| Zhang 2023[203]<br>Japan | Urine | Not stated | Unclear | 102<br>3 with cCMV | Symptoms at birth<br>Antiviral treatment | May overlook cCMV infection that is asymptomatic at birth; however, it is feasible and |

| Study details | Screening test | Confirmation test | Follow-up beyond infancy | Number screened, Number with cCMV | Results presented | Study conclusions |
|---|---|---|---|---|---|---|
| | | | | | | helps lead to the diagnosis of cCMV infection that may otherwise be overlooked |
| Masarweh 2021[199]<br>Israel | Urine or saliva | Not stated | Unclear | 693<br>18 with cCMV | Hearing loss at birth<br>Antiviral treatment | This examination policy can detect nearly all newborns with congenital CMV infection in whom therapy is indicated |
| Poletti 2024[101]<br>Italy | Urine or saliva | Not stated | Yes<br>(up to 36 months) | 940<br>11 with cCMV | Hearing loss at birth<br>Antiviral treatment<br>Hering loss at follow-up<br>Neurodevelopment at follow-up | Implementation of an expanded cCMV screening program appears feasible and of clinical value |
| McCrary 2020[200]<br>USA | Urine, saliva, DBS | Not stated | Unclear | 754<br>21 with cCMV | Symptoms at birth | An expanded targeted early CMV testing program has the potential to identify symptomatic cCMV infants who would not be identified otherwise |

**Abbreviations:** cCMV, congenital cytomegalovirus; CMV, cytomegalovirus; DBS, dried blood spots.

*Table 22: Meta-analysis of event rates in 10 studies of symptom targeted screening*

| Event | Number of studies with data | Predicted rate per 10,000 screened newborns (95% confidence interval) | Predicted rate per 10,000 newborns with cCMV (95% confidence interval) |
|---|---|---|---|
| **Diagnosis of cCMV** | 8 | 147<br>(82 to 262) | x |
| **Has symptoms at birth (all symptoms)** | 8 | 71<br>(29 to 172) | 5438<br>(3795 to 6991) |
| **Has hearing loss at birth** | 5 | 13<br>(3 to 69) | 1983<br>(704 to 4471) |
| **Has cranial MRI/US abnormalities at birth** | *Insufficient data* | | |
| **Receives antiviral treatment** | 5 | 43<br>(20 to 93) | 2828<br>(1472 to 4741) |
| **Has long-term sequelae** | 4 | 15<br>(6 to 38) | 1800<br>(964 to 3111) |
| **Abbreviations:** cCMV, congenital cytomegalovirus; MRI, magnetic resonance imaging; US, ultrasound. | | | |

# Summary of Findings Relevant to Criteria 11 and 13

## Criterion Not Met

The review identified 14 studies on universal cCMV screening and 22 studies of targeted cCMV screening relevant to this question. None of the studies were randomised, and only 1 study reported any form of non-randomised comparative evidence. The lack of comparative evidence inevitably limits the quality and value of the available evidence because it is not possible to determine whether symptoms at birth, or long-term sequelae, are caused by CMV infection, or are unrelated to infection. Nor is it possible to evaluate which symptoms or long-term sequelae would have been identified, managed and treated in the absence of cCMV screening. Given this fundamental limitation, there is currently no evidence to demonstrate that either universal or targeted screening of newborns for cCMV will provide long-term benefits to children with cCMV.

Key potential benefits of universal screening are that most cCMV cases would not be diagnosed without universal screening, because most newborns with cCMV do not have clear symptoms and because of potential issues with lack of awareness of cCMV among clinicians. It will also identify newborns with later development of neurological sequelae that would otherwise be missed. However, key concerns with universal screening are that most newborns with cCMV are asymptomatic at birth, without hearing loss and with a normal cranial ultrasound. Most of these babies will not develop long-term sequelae caused by cCMV. Universal screening also may identify many cases of subclinical symptomatic cCMV.

As asymptomatic newborns with cCMV are not currently offered antiviral therapy, the management pathway for most children diagnosed with cCMV is uncertain. The evidence suggests that only a minority of children diagnosed with cCMV through universal screening (perhaps around 11%) will receive antiviral therapy, and so the potential long-term clinical significance of universal screening and its cost-effectiveness are unknown. A further concern is that the only comparative study found that rates of long-term harms were similar between children with and without cCMV infection. This was in Finland, where primary maternal CMV infection rates are low, so the exact prevalence of cCMV could be an important factor in determining the clinical and cost-effectiveness of cCMV screening.

Key potential benefits of targeted screening after failure of a newborn hearing test are that it identifies the majority of infants with CMV-related SNHL at birth who could benefit from treatment. It allows for early recognition of asymptomatic cases with hearing loss. Key difficulties are that it will miss cases that are asymptomatic at birth, or who have symptoms that are not hearing loss. There may also be difficulties with timing, as both the hearing test and the cCMV test must be conducted quickly after birth if antiviral treatment is to be instigated promptly.

Unlike universal screening, most newborns who test positive for cCMV after targeted screening are symptomatic, and potentially go on to receive antiviral therapy. Hence targeted screening has a clearer treatment and management pathway than universal screening. However, it remains to be shown that targeted screening and subsequent antiviral therapy leads to better clinical outcomes than informal or ad-hoc testing for cCMV, or treating and managing sequalae caused by cCMV as symptoms emerge.

Adding additional signs or symptoms over hearing loss to targeted screening does not seem to have any clear benefits. The 12 studies that considered this were inconsistent in which symptoms were added to hearing loss. The overall impact appeared to be increasing the number of asymptomatic cases of cCMV that were detected, with a consequent reduction in the proportion of newborns who received antiviral treatment.

## Criterion 12: There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.

### Previous work

The acceptability of cCMV screening has not been assessed in any previous UK NSC evidence review on this topic.

### Description of the current evidence

The studies of universal or targeted screening described under Criteria 11 and 13 generally concluded that screening was feasible and practical. However, only 5 of those studies included any kind of formal survey of parents, doctors, nurses or other stakeholders. Demortier (2021)[182] and Letamendia-Richard (2022)[54] surveyed healthcare workers as part of a universal screening programme using saliva testing (see Table 17). Beswick (2021)[191], Kadambari (2015)[194] and Webb (2024)[206] surveyed stakeholders, screeners and parents, respectively, as part of a targeted screening programme using saliva testing (see Table 19 and Table 21).

As these were simple surveys, no quality assessment of these studies was undertaken.

Demortier (2021)[182] surveyed 9 healthcare workers in La Reunion and Mayotte. They agreed that screening was generally acceptable, although with some limitations due to time taken to obtain parental consent. Responses were mixed as to whether universal screening for cCMV was relevant and useful.

Letamendia-Richard (2022)[54] surveyed 72 healthcare workers, of which 92.7% found the salivary test easy to perform; 91.4% reported that time devoted to sample collection was acceptable. Time spent obtaining informed consent was also acceptable for 78.6% of the respondents.

Beswick (2021)[191] analysed feedback from an unstated number of stakeholders. They identified problems with limited funding for screening and training burdens. Nurses found that a cCMV diagnosis increased parental anxiety and found a lack of awareness of cCMV. The rarity of cCMV and its symptoms meant there was “study fatigue” and a reduced recruitment rate.

Kadambari (2015)[194] surveyed 24 screeners who generally felt that screening was a good idea and was feasible. They also generally felt confident explaining the screening process to parents.

Webb (2024)[206] surveyed 65 parents, most of whom thought that saliva testing for cCMV was easy to do (92%); that testing their baby for cCMV was a good idea (92.0%) and that they were glad their baby was screened for cCMV (96.9%).

## Summary of Findings Relevant to Criterion 12

### Criterion Not Met

Evidence on the acceptability of cCMV screening is extremely limited, covering only 5 studies, mostly of small size. The evidence base is therefore too small, and of too limited quality, to draw any reasonable conclusions.

Evidence was mostly from screeners and medical professionals who generally concluded that screening was feasible and acceptable. Some concerns over screening increasing parental anxiety were raised. Evidence from parents was available from only 1 small study, where parents were very supportive of screening.

The current evidence relates only to the acceptability of saliva testing, and there is no evidence on the acceptability of cCMV screening more broadly. For example, there is no evidence on the acceptability of screening where newborns are asymptomatic, or on the acceptability of antiviral treatment, general management of cCMV, or long-term follow-up.

# *Review summary*

## Conclusions and implications for policy

This report assesses newborn screening for congenital cytomegalovirus (cCMV) infection against select UK National Screening Committee (UK NSC) criteria for appraising the viability, effectiveness and appropriateness of a screening programme.

There has been considerable new research in this area since the previous evidence review in 2017 and the evidence map in 2022. This new evidence particularly demonstrates the high accuracy and practicality of saliva or DBS testing to detect cCMV infection in newborns. There has been an expansion in the evidence on tests or characteristics that will predict long-term sequelae of cCMV infection. Whilst this evidence is of limited quality, the results indicate that presence of cCMV symptoms at birth, and timing of maternal CMV infection, are both associated with long-term sequelae. There is also promising, but not yet conclusive, evidence that the use of MRI scans and assessment of CMV viral load may be useful in identifying newborns at higher risk of long-term sequelae. There have also been numerous studies reporting on the use of cCMV screening in practice, demonstrating its general feasibility and practicality.

However, despite the now substantial evidence base on cCMV screening, we conclude that further evidence is required before a change to the current recommendation can be made. This is primarily because there have been no studies, either randomised or non-randomised, that formally compare the outcomes of a cCMV screening programme to no screening or current clinical management, so there is, as yet, no conclusive evidence that newborn screening for cCMV will be beneficial. Therefore, newborn screening for cCMV is still not recommended.

## Evidence gaps and recommendations for research

The most substantial gap in the current evidence, where there is clear need for future clinical studies, is to properly compare the clinical impact of cCMV screening to current clinical practice without screening. Ideally this should consist of cluster randomised trials, where locations or medical centres are randomised to: universal cCMV screening, targeted screening after failing a newborn hearing screen, or standard practice without screening. Newborns should be tested using saliva, DBS or urine PCR, with a confirmatory urine test if required. Appropriate tests should be performed to identify cCMV symptoms and antiviral therapy offered to newborns with symptoms. Follow-up should be sufficient to identify long-term sequelae, as far as is possible, and confirm the impact of screening and antiviral treatment. Ideally,

trials should also survey parents and caregivers, to evaluate the acceptability of screening, treatment and long-term management.

As randomised trials may be impractical, non-randomised comparative studies may also be useful. We note that, with the introduction of cCMV screening in some Canadian provinces and US states, studies comparing locations that have adopted screening to those that have not may be useful.

This review has also identified some other areas where further clinical research would be useful. As MRI appears to be a promising means of predicting long-term sequelae, further studies evaluating the prognostic accuracy of MRI to detect long-term hearing, developmental and neurological outcomes would be useful, as well as studies evaluating the practical implications of using MRI scans as part of cCMV screening, such as identifying which newborns would most benefit from an MRI scan. Similarly, further studies assessing the predictive value of CMV viral load to identify newborns at risk of long-term sequelae would be useful. These could form part of the randomised trials of newborn cCMV screening.

Development of a tool to predict long-term sequelae that incorporates the full range of plausible predictors (such as symptoms at birth, trimester of infection, specific imaging findings, or viral load) would also be useful. This is because the causes of long-term sequelae are almost certainly multifactorial, and so an accurate test will need to cover a range of predictive variables. The design of such a tool could initially be informed by a large cohort study in a neonatal population with cCMV, investigating the magnitude of association of plausible predictors with sequalae using multivariable logistic regression. Such a risk tool could then be validated in a separate cohort, to establish how well it can predict sequelae.

We note that there is now a substantial evidence base on the accuracy of both saliva and DBS testing for cCMV, with both covered by extensive systematic reviews (including ongoing reviews, listed in Appendix 4). We therefore suggest that further diagnostic accuracy studies are not required. However, there may still be value in studies comparing the accuracy and practicality of saliva screening with DBS screening.

## Limitations

Many of the included studies were limited in terms of their design, size and quality. In addition, very few studies were conducted in the UK, limiting their applicability to UK practice, owing to differences in health systems and the prevalence of maternal CMV in different countries.

## Acknowledgments

The York Evidence Synthesis group would like to thank all those who supported and provided advice for this review. Specifically, all those at UK NSC, all clinical advisers, CMV Action and all parent representatives.

# Appendix 1 — Search strategy

## Electronic databases and resources

The search strategy included searches of the databases shown in Table 1. All searches were restricted to literature published from 2013 onwards.

*Table 23 Databases and resources searched*

| Database/resource | Platform | Date of search | Date range/segment |
|---|---|---|---|
| MEDLINE ALL | Ovid | 19/11/2024 | 1946 to Nov 18, 2024 |
| Embase | Ovid | 19/11/2024 | 1974 to 2024 Nov 18 |
| Maternity and Infant Care | Ovid | 19/11/2024 | 1971 to Nov 05, 2024 |
| CINAHL | Ebsco | 19/11/2024 | Inception to 20241119 |
| LILACS | https://pesquisa.bvsalud.org/portal/advanced/?lang=en | 19/11/2024 | Inception to last update (date unavailable) |
| Cochrane Central Register of Controlled Trials (CENTRAL) | Cochrane Library, via Wiley | 19/11/2024 | Issue 10 of 12, Oct 2024 |
| Cochrane Database of Systematic Reviews (CDSR) | Cochrane Library, Wiley | 19/11/2024 | Issue 11 of 12, Nov 2024 |
| Science Citation Index (SCI) | Web of Science, Clarivate Analytics | 19/11/2024 | 1900 – 2024-11-16 |
| Conference Proceedings Citation Index – Science (CP-SCI) | Web of Science, Clarivate Analytics | 19/11/2024 | 1990 – 2024-11-16 |
| KSR Evidence | Ovid | 19/11/2024 | 2015 to 2024 Week 45 |
| Database of Abstracts of Reviews of Effects (DARE) | CRD databases | 19/11/2024 | Inception – 31st March 2015 |
| Health Technology Assessment (HTA) database | CRD databases | 19/11/2024 | Inception – 31st March 2018 |
| International Health Technology Assessment (HTA) database | https://database.inahta.org/ | 19/11/2024 | Inception – last update (date unavailable) |
| PROSPERO | https://www.crd.york.ac.uk/prospero/ | 19/11/2024 | Inception – last update (date unavailable) |
| ClinicalTrials.gov | https://clinicaltrials.gov/ct2/ | 19/11/2024 | Inception – last update (date unavailable) |
| WHO International Clinical Trials Registry Platform (ICTRP) | https://trialsearch.who.int/Default.aspx | 19/11/2024 | Inception – last update (date unavailable) |
| EU Clinical Trials Register | https://www.clinicaltrialsregister.eu/ctr-search/search | 20/11/2024 | Inception – last update (date unavailable) |
| HTA Agency websites | Various (see below for individual HTA agency URLs accessed) | 19/11/2024 | Inception – last update (date unavailable) |

## Search Terms and structure

Search terms included combinations of free text and subject headings (e.g. Medical Subject Headings [MeSH] for MEDLINE, and Emtree terms for Embase). The search strategy was structured using aspects of the population, combined using the Boolean operator AND:

- Population: age – newborns (0-28 days)

  AND

- Population: health condition – CMV

Individual search strategies for each database and resource can be viewed below.

Database search strategies

**MEDLINE ALL**
via Ovid http://ovidsp.ovid.com/
Date range: 1946 to November 18, 2024
Date searched: 19th November 2024
Records retrieved: 2638

1 exp Infant, Newborn/ (696555)
2 Neonatology/ (3278)
3 (newborn$ or new born$ or newly born$).ti,ab,kf. (212956)
4 (neonat$ or neo nat$).ti,ab,kf. (334932)
5 (infant$ or infancy).ti,ab,kf. (579331)
6 (baby$ or babies).ti,ab,kf. (88964)
7 at birth.ti,ab,kf. (61025)
8 (preterm or preterms or pre term or pre terms).ti,ab,kf. (104600)
9 (preemie$ or premie or premies).ti,ab,kf. (239)
10 (low adj2 (birthweight$ or birth weight$)).ti,ab,kf. (43582)
11 (lbw or vlbw or elbw).ti,ab,kf. (11240)
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (1297214)
13 Cytomegalovirus/ (23937)
14 exp Cytomegalovirus Infections/ (29425)
15 cytomegalovir$.ti,ab,kf. (49521)
16 ((cytomegal$ or cyto megal$) adj6 (virus$ or viral$ or vir?emi$)).ti,ab,kf. (10032)
17 cytomegaloinfection$.ti,ab,kf. (1)
18 ((cytomegal$ or cyto megal$) adj infection$).ti,ab,kf. (11208)
19 ((cytomegaly$ or cyto megaly$) and (virus$ or viral$ or vir?emi$)).ti,ab,kf. (156)
20 (CMV or HCMV).ti,ab,kf. (37691)
21 cCMV.ti,ab,kf. (739)
22 human herpesvirus 5.ti,ab,kf. (37)
23 human herpes virus 5.ti,ab,kf. (14)
24 (HHV 5 or HHV5).ti,ab,kf. (66)
25 salivary gland virus$.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 (65657)
27 12 and 26 (7380)
28 exp animals/ not humans.sh. (5278373)
29 27 not 28 (7098)
30 limit 29 to yr="2013 -Current" (2638)

**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
adj2 = terms within two words of each other (any order)

**Embase**
via Ovid http://ovidsp.ovid.com/
Date range: 1974 to 2024 November 18
Date searched: 19th November 2024
Records retrieved: 4804

1 newborn/ (632221)
2 baby/ (14822)
3 neonatology/ (6041)
4 (newborn$ or new born$ or newly born$).ti,ab,kw. (243697)
5 (neonat$ or neo nat$).ti,ab,kw. (442847)
6 (infant$ or infancy).ti,ab,kw. (624640)
7 (baby$ or babies).ti,ab,kw. (127181)
8 at birth.ti,ab,kw. (81954)
9 exp low birth weight/ (65734)
10 exp prematurity/ (138950)
11 (preterm or preterms or pre term or pre terms).ti,ab,kw. (145796)
12 (preemie$ or premie or premies).ti,ab,kw. (393)
13 (low adj2 (birthweight$ or birth weight$)).ti,ab,kw. (55243)
14 (lbw or vlbw or elbw).ti,ab,kw. (15481)
15 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (1435440)
16 Cytomegalovirus/ (41472)
17 exp human cytomegalovirus/ (8760)
18 exp cytomegalovirus infection/ (45608)
19 cytomegalovir$.ti,ab,kw. (63173)
20 ((cytomegal$ or cyto megal$) adj6 (virus$ or viral$ or vir?emi$)).ti,ab,kw. (13634)
21 cytomegaloinfection$.ti,ab,kw. (1)
22 ((cytomegal$ or cyto megal$) adj infection$).ti,ab,kw. (13895)
23 ((cytomegaly$ or cyto megaly$) and (virus$ or viral$ or vir?emi$)).ti,ab,kw. (181)
24 (CMV or HCMV).ti,ab,kw. (61625)
25 cCMV.ti,ab,kw. (863)
26 human herpesvirus 5.ti,ab,kw. (51)
27 human herpes virus 5.ti,ab,kw. (16)
28 (HHV 5 or HHV5).ti,ab,kw. (99)
29 salivary gland virus$.ti,ab,kw. (13)
30 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 (113281)
31 15 and 30 (9938)
32 animal/ or animal experiment/ (4904537)
33 (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. (7805171)
34 32 or 33 (7805171)
35 exp human/ or exp human experiment/ (27309330)
36 34 not (34 and 35) (5829658)
37 31 not 36 (9328)
38 limit 37 to yr="2013 -Current" (4804)

**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
adj2 = terms within two words of each other (any order)

**Maternity and Infant Care**
via Ovid http://ovidsp.ovid.com/
Date range: 1971 to November 05, 2024
Date searched: 19th November 2024
Records retrieved: 404

1 (newborn$ or new born$ or newly born$).af. (48922)
2 (neonat$ or neo nat$).af. (77600)
3 (infant$ or infancy).af. (116339)
4 (baby$ or babies).af. (42172)
5 at birth.af. (11025)
6 (preterm or preterms or pre term or pre terms).af. (36985)
7 (preemie$ or premie or premies).af. (72)
8 (low adj2 (birthweight$ or birth weight$)).af. (17959)
9 (lbw or vlbw or elbw).af. (4041)
10 or/1-9 (178316)
11 cytomegalovir$.af. (1060)
12 ((cytomegal$ or cyto megal$) adj6 (virus$ or viral$ or vir?emi$)).af. (188)
13 cytomegaloinfection$.af. (0)
14 ((cytomegal$ or cyto megal$) adj infection$).af. (579)
15 ((cytomegaly$ or cyto megaly$) and (virus$ or viral$ or vir?emi$)).af. (0)
16 (CMV or HCMV).af. (681)
17 cCMV.af. (99)
18 (human herpesvirus 5 or human herpes virus 5).af. (0)
19 (HHV 5 or HHV5).af. (1)
20 salivary gland virus$.af. (0)
21 or/11-20 (1118)
22 10 and 21 (795)
23 limit 22 to yr="2013 -Current" (404)

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

**CINAHL**
via Ebsco https://www.ebsco.com/
Date range: Inception to 20241119
Date searched: 19th November 2024
Records retrieved: 783

| | | | |
|---|---|---|---|
| S1 | (MH "Infant, Newborn+") | 162,261 | |
| S2 | (MH "Neonatology") | 1,542 | |
| S3 | TI ( (newborn* or new-born* or (newly N0 born*) ) OR AB ( (newborn* or new-born* or (newly N0 born*) ) | | 39,452 |
| S4 | TI ( neonat* or neo-nat* ) OR AB ( neonat* or neo-nat* ) | 86,610 | |
| S5 | TI ( infant* or infancy ) OR AB ( infant* or infancy ) | 139,479 | |
| S6 | TI ( baby* or babies ) OR AB ( baby* or babies ) | 38,698 | |

| | | |
|---|---|---|
| S7 | TI ( preterm or preterms or pre-term or pre-terms ) OR AB ( preterm or preterms or pre-term or pre-terms ) | 43,268 |
| S8 | TI ( preemie* or premie or premies ) OR AB ( preemie* or premie or premies ) | 355 |
| S9 | TI ( low N2 (birthweight* or birth-weight*) ) OR AB ( low N2 (birthweight* or birth-weight*) ) | 15,037 |
| S10 | TI ( lbw or vlbw or elbw ) OR AB ( lbw or vlbw or elbw ) | 4,174 |
| S11 | S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 | 315,539 |
| S12 | (MH "Cytomegaloviruses") | 1,701 |
| S13 | (MH "Cytomegalovirus Infections+") | 3,874 |
| S14 | TI cytomegalovir* OR AB cytomegalovir* | 5,216 |
| S15 | 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*) ) | 1,092 |
| S16 | TI cytomegaloinfection* OR AB cytomegaloinfection* | 0 |
| S17 | TI ( (cytomegal* or cyto-megal*) N0 infection* ) OR AB ( (cytomegal* or cyto-megal*) N0 infection* ) | 1,544 |
| S18 | 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 |
| S19 | TI ( CMV or HCMV ) OR AB ( CMV or HCMV ) | 3,174 |
| S20 | TI cCMV OR AB cCMV | 152 |
| S21 | TI ( "human herpesvirus 5" or "human herpes virus 5" ) OR AB ( "human herpesvirus 5" or "human herpes virus 5" ) | 0 |
| S22 | TI ( "HHV 5" or "HHV5" ) OR AB ( "HHV 5" or "HHV5" ) | 0 |
| S23 | TI ( "salivary gland virus" or "salivary gland viruses" ) OR AB ( "salivary gland virus" or "salivary gland viruses" ) | 1 |
| S24 | S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 | 7,044 |
| S25 | S11 AND S24 | 1,308 |
| S26 | MH animals+ | 102,528 |
| S27 | MH (animal studies) | 158,518 |
| S28 | TI (animal model*) | 4,039 |
| S29 | S26 OR S27 OR S28 | 252,096 |
| S30 | MH (human) | 2,840,690 |
| S31 | S29 NOT S30 | 217,272 |
| S32 | S25 NOT S31 | 1,289 |
| S33 | S25 NOT S31 Limiters - Publication Date: 20130101-20241231 | 783 |

**Key:**
MH = CINAHL subject heading
MH with + = exploded CINAHL subject heading
* = truncation
# = wildcard - one or no characters
TI = title field
AB = abstract field
N2 = terms within two 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: 19th November 2024
Records retrieved: 233

Advanced search screen used, terms searched in the title, abstract and subject fields. Filters applied: results from LILACS databases, publication year range: 2013-2024
1. newborn* OR new-born* OR "newly born" OR neonat* OR neo-nat* OR infant* OR infancy OR baby* OR babies OR "at birth" OR preterm OR preterms OR pre-term OR pre-terms OR preemie* OR premie OR premies OR lbw OR vlbw OR elbw OR "low birthweight" OR "low birthweights" OR "low birth-weight" OR "low birth-weights"
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"
123 records

2. newborn* OR new-born* OR “newly born” OR neonat* OR neo-nat* OR infant* OR infancy OR baby* OR babies OR “at birth” OR preterm OR preterms OR pre-term OR pre-terms OR preemie* OR premie OR premies OR lbw OR vlbw OR elbw OR “low birthweight” or “low birthweights” or “low birth-weight” or “low birth-weights”
AND
(cytomegal* OR cyto-megal*) AND (infection* OR virus* OR viral* OR viremi* OR viraemi*)
110 records

**Key:**
* = truncation

**Cochrane Library**
via Wiley http://onlinelibrary.wiley.com/
**Cochrane Central Register of Controlled Trials (CENTRAL)**: Issue 10 of 12, Oct 2024
Records retrieved: 192
**Cochrane Database of Systematic Reviews (CDSR):** Issue 11 of 12, Nov 2024
Records retrieved: 6
Date searched: 19th November 2024

#1 MeSH descriptor: [Infant, Newborn] explode all trees 24460
#2 MeSH descriptor: [Neonatology] this term only 63
#3 (newborn* or (new next born*) or (newly next born*)):ti,ab,kw 37964
#4 (neonat* or (neo next nat*)):ti,ab,kw 30453
#5 (infant* or infancy):ti,ab,kw 81631
#6 (baby or babies):ti,ab,kw 12265
#7 (at next birth):ti,ab,kw 39722
#8 (preterm or preterms or (pre next term) or (pre next terms)):ti,ab,kw 18139
#9 (preemie* or premie or premies):ti,ab,kw 57
#10 (low near/2 (birthweight* or birth weight*)):ti,ab,kw 12915
#11 (lbw or vlbw or elbw):ti,ab,kw 2022
#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 121007
#13 MeSH descriptor: [Cytomegalovirus] this term only 461
#14 MeSH descriptor: [Cytomegalovirus Infections] explode all trees 1061
#15 cytomegalovir*:ti,ab,kw 2682
#16 ((cytomegal* or cyto-megal*) near/6 (virus* or viral* or viremi* or viraemi*)):ti,ab,kw 370
#17 cytomegaloinfection*:ti,ab,kw 0
#18 ((cytomegal* or cyto-megal*) next infection*):ti,ab,kw 1803
#19 ((cytomegaly* or cyto-megaly*) and (virus* or viral*or viremi* or viraemi*)):ti,ab,kw 3
#20 (CMV or HCMV):ti,ab,kw 2368
#21 cCMV:ti,ab,kw 12
#22 "human herpesvirus 5":ti,ab,kw 0
#23 "human herpes virus 5":ti,ab,kw 0
#24 ("HHV 5" or "HHV5"):ti,ab,kw 0
#25 (salivary next gland next virus*):ti,ab,kw 0
#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 3438
#27 #12 and #26 with Cochrane Library publication date Between Jan 2013 and Nov 2024, in Cochrane Reviews, Cochrane Protocols 6
#28 #12 and #26 with Publication Year from 2013 to 2024, in Trials 192

**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/2 = terms within two 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: 19th November 2024
Date range SCI: 1900 – 2024-11-16
Date range CP-SCI: 1990 – 2024-11-16
Records retrieved: 2606

1: TS=(cytomegalovir*) Editions: WOS.SCI,WOS.ISTP Results: 57207

2: TS=((cytomegal* or cyto-megal*) NEAR/6 (virus* or viral* or vir$emi*)) Editions: WOS.SCI,WOS.ISTP Results: 12259

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

4: TS=((cytomegal* or cyto-megal*) NEAR/1 infection*) Editions: WOS.SCI,WOS.ISTP Results: 19533

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

6: TS=(CMV or HCMV) Editions: WOS.SCI,WOS.ISTP Results: 40762

7: TS=(cCMV) Editions: WOS.SCI,WOS.ISTP Results: 748

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

9: TS=("HHV 5" or "HHV5") Editions: WOS.SCI,WOS.ISTP Results: 60

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

11: #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 Editions: WOS.SCI,WOS.ISTP Results: 73539

12: TS=(newborn* or new-born* or "newly born*") Editions: WOS.SCI,WOS.ISTP Results: 196051

13: TS=(neonat* or neo-nat*) Editions: WOS.SCI,WOS.ISTP Results: 341407

14: TS=(infant* or infancy) Editions: WOS.SCI,WOS.ISTP Results: 550643

15: TS=(baby* or babies) Editions: WOS.SCI,WOS.ISTP Results: 76840

16: TS=("at birth") Editions: WOS.SCI,WOS.ISTP Results: 56577

17: TS=(preterm or preterms or pre-term or pre-terms) Editions: WOS.SCI,WOS.ISTP Results: 126050

18: TS=(preemie* or premie or premies) Editions: WOS.SCI,WOS.ISTP Results: 229

19: TS=(low NEAR/2 (birthweight* or birth-weight*)) Editions: WOS.SCI,WOS.ISTP Results: 52040

20: TS=(lbw or vlbw or elbw) Editions: WOS.SCI,WOS.ISTP Results: 11324

21: #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 Editions: WOS.SCI,WOS.ISTP Results: 991736

22: #11 and #21 Editions: WOS.SCI,WOS.ISTP Timespan: All years (Publication Date) Results: 5492

23: #21 AND #11 Editions: WOS.SCI,WOS.ISTP Timespan: 2013-01-01 to 2024-11-19 Results: 2606

**Key:**
TS = topic tag; searches in title, abstract, author keywords and keywords plus fields
* = truncation
$ = represents zero or one character
NEAR/2 = terms within two words of each other (any order)

**EB Health - KSR Evidence**
via Ovid http://ovidsp.ovid.com/
Date range: 2015 to 2024 Week 45
Date searched: 19th November 2024
Records retrieved: 60

1 (newborn$ or new born$ or newly born$).af. (2142)
2 (neonat$ or neo nat$).af. (5888)
3 (infant$ or infancy).af. (7028)
4 (baby$ or babies).af. (1475)
5 at birth.af. (772)
6 (preterm or preterms or pre term or pre terms).af. (3846)
7 (preemie$ or premie or premies).af. (2)
8 (low adj2 (birthweight$ or birth weight$)).af. (1490)
9 (lbw or vlbw or elbw).af. (426)
10 or/1-9 (13134)
11 cytomegalovir$.af. (311)
12 ((cytomegal$ or cyto megal$) adj6 (virus$ or viral$ or vir?emi$)).af. (71)
13 cytomegaloinfection$.af. (0)
14 ((cytomegal$ or cyto megal$) adj infection$).af. (119)
15 ((cytomegaly$ or cyto megaly$) and (virus$ or viral$ or vir?emi$)).af. (0)
16 (CMV or HCMV).af. (274)
17 cCMV.af. (22)
18 (human herpesvirus 5 or human herpes virus 5).af. (0)
19 (HHV 5 or HHV5).af. (2)
20 salivary gland virus$.af. (0)
21 or/11-20 (380)
22 10 and 21 (61)
23 limit 22 to yr="2013 -Current" (60)

**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 two 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: 19th November 2024
Records retrieved: 1

1 MeSH DESCRIPTOR Infant, Newborn EXPLODE ALL TREES IN DARE,HTA 1057
2 MeSH DESCRIPTOR Neonatology IN DARE,HTA 5

3 (newborn* or new-born* or "newly born") IN DARE, HTA 1332
4 (neonat* or neo-nat*) IN DARE, HTA 1352
5 (infant* or infancy) IN DARE, HTA 2740
6 (baby* or babies) IN DARE, HTA 428
7 ("at birth") IN DARE, HTA 128
8 (preterm or preterms or pre-term or pre-terms) IN DARE, HTA 828
9 (preemie* or premie or premies) IN DARE, HTA 0
10 (low adj2 (birthweight* or birth-weight*)) IN DARE, HTA 317
11 ((birthweight* or birth-weight*) adj2 low) IN DARE, HTA 22
12 (lbw or vlbw or elbw) IN DARE, HTA 43
13 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 3498
14 MeSH DESCRIPTOR Cytomegalovirus IN DARE,HTA7
15 MeSH DESCRIPTOR Cytomegalovirus Infections EXPLODE ALL TREES IN DARE,HTA 31
16 (cytomegalovir*) IN DARE, HTA 61
17 ((cytomegal* or cyto-megal*) adj6 (virus* or viral* or viremi* or viraemi*)) IN DARE, HTA 7
18 ((virus* or viral* or viremi* or viraemi*) adj6 (cytomegal* or cyto-megal*)) IN DARE, HTA 9
19 (cytomegaloinfection*) IN DARE, HTA 0
20 ((cytomegal* or cyto-megal*) adj1 infection*) IN DARE, HTA 46
21 (infection* adj1 (cytomegal* or cyto-megal*)) IN DARE, HTA 8
22 ((cytomegaly* or cyto-megaly*) and (virus* or viral* or viremi* or viraemi*)) IN DARE, HTA 0
23 (CMV or HCMV) IN DARE, HTA 33
24 (cCMV) IN DARE, HTA 0
25 ("human herpesvirus 5" or "human herpes virus 5") IN DARE, HTA 0
26 ("HHV 5" or HHV5) IN DARE, HTA 0
27 ("salivary gland virus" or "salivary gland viruses") IN DARE, HTA 0
28 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 71
29 #13 AND #28 9
30 (*) IN DARE, HTA FROM 2013 TO 2015 20407
31 #29 AND #30 1

**Key:**
MeSH DESCRIPTOR = subject heading (MeSH heading)
* = truncation
adj2 = terms within two words of each other (order specified)

**International Health Technology Assessment (HTA) database**
via https://database.inahta.org/
Date range: Inception – 18th November 2024
Date searched: 19th November 2024
Records retrieved: 1

(("Cytomegalovirus Infections"[mhe]) OR ("Cytomegalovirus"[mh]) OR (("human herpesvirus 5" OR "human herpes virus 5" OR "HHV 5" OR "HHV5" OR "salivary gland virus" OR "salivary gland viruses")[Title] OR ("human herpesvirus 5" OR "human herpes virus 5" OR "HHV 5" OR "HHV5" OR "salivary gland virus" OR "salivary gland viruses")[abs] OR ("human herpesvirus 5" OR "human herpes virus 5" OR "HHV 5" OR "HHV5" OR "salivary gland virus" OR "salivary gland viruses")[Keywords]) OR ((CMV or HCMV or cCMV)[Title] OR (CMV or HCMV or cCMV)[abs] OR (CMV or HCMV or cCMV)[Keywords]) OR ((cytomegaloinfection*)[Title] OR (cytomegaloinfection*)[abs] OR (cytomegaloinfection*)[Keywords]) OR (((cytomegal* or cyto-megal*)[Title] OR (cytomegal* or cyto-megal*)[abs] OR (cytomegal* or cyto-megal*)[Keywords]) AND ((infection* or virus* or viral* or viremi* or viraemi*)[Title] OR (infection* or virus* or viral* or viremi* or viraemi*) [abs] OR (infection* or virus* or viral* or viremi* or viraemi*)[Keywords])) OR ((cytomegalovir*)[Title] OR (cytomegalovir*)[abs] OR (cytomegalovir*)[Keywords])) AND ((("low birthweight" or "low birthweights" or "low birth-weight" or "low birth-weights")[Title] OR ("low birthweight" or "low birthweights" or "low birth-weight" or "low birth-weights")[abs] OR ("low birthweight" or "low birthweights" or "low birth-weight" or "low birth-weights")[Keywords]) OR ((preterm or preterms or pre-term or pre-terms or preemie* or premie or premies or lbw or vlbw or elbw)[Title] OR (preterm or preterms or pre-term or pre-terms or preemie* or premie or premies or lbw or vlbw or elbw)[abs] OR (preterm or preterms or pre-term or pre-terms or preemie* or premie or premies or lbw or vlbw or

elbw)[Keywords]) OR (("at birth")[Title] OR ("at birth")[abs] OR ("at birth")[Keywords]) OR ((newborn* or new-born* or "newly born" or neonat* or neo-nat* or infant* or infancy or baby* or babies)[Title] OR (newborn* or new-born* or "newly born" or neonat* or neo-nat* or infant* or infancy or baby* or babies)[abs] OR (newborn* or new-born* or "newly born" or neonat* or neo-nat* or infant* or infancy or baby* or babies)[Keywords]) OR ("Neonatology"[mh]) OR ("Infant, Newborn"[mhe]))

Date limit 2013 onwards applied – 1 record retrieved

**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: 19th November 2024
Records retrieved: 106

| | | |
|---|---|---|
| #1 | MeSH DESCRIPTOR Infant, Newborn EXPLODE ALL TREES | 1301 |
| #2 | MeSH DESCRIPTOR Neonatology | 2 |
| #3 | newborn* or new-born* or (newly adj1 born*) | 4750 |
| #4 | neonat* or neo-nat* | 9274 |
| #5 | infant* or infancy or baby* or babies | 14476 |
| #6 | "at birth" | 1923 |
| #7 | preterm or preterms or pre-term or pre-terms or preemie* or premie or premies | 5738 |
| #8 | low adj2 (birthweight* or birth-weight*) | 2359 |
| #9 | lbw or vlbw or elbw | 480 |
| #10 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 | 21414 |
| #11 | MeSH DESCRIPTOR Cytomegalovirus | 23 |
| #12 | MeSH DESCRIPTOR Cytomegalovirus Infections EXPLODE ALL TREES | 31 |
| #13 | cytomegalovir* | 290 |
| #14 | (cytomegal* or cyto megal*) adj6 (virus* or viral* or viremi* or viraemi*) | 89 |
| #15 | cytomegaloinfection* | 0 |
| #16 | (cytomegal* or cyto megal*) adj infection* | 150 |
| #17 | (cytomegaly* or cyto megaly*) and (virus* or viral* or viremi* or viraemi*) | 3 |
| #18 | CMV or HCMV or cCMV | 289 |
| #19 | "human herpesvirus 5" or "human herpes virus 5" or HHV5 or "HHV 5" | 4 |
| #20 | "salivary gland virus" or "salivary gland viruses" | 3 |
| #21 | #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 | 398 |
| #22 | #10 AND #21 | 106 |

**Key:**
MeSH DESCRIPTOR = subject heading (MeSH heading)
* = truncation
TI,KW,RQ = terms in title, keyword or research question field
adj2 = terms within two words of each other

**ClinicalTrials.gov**
https://clinicaltrials.gov/ct2/
Date searched: 19th November 2024
Records retrieved: 504

1. cytomegalovirus OR CMV OR cCMV OR HCMV OR "cytomegalovirus infection" OR "congenital cytomegalovirus" | 0 Days to 28 Days old =114 studies

2. cytomegalovirus OR CMV OR cCMV OR HCMV OR "cytomegalovirus infection" OR "congenital cytomegalovirus" | 0 Months to 1 Months old =121 studies

3. cytomegalovirus OR CMV OR cCMV OR HCMV OR "cytomegalovirus infection" OR "congenital cytomegalovirus" | 0 Weeks to 4 Weeks old =114 studies

4. cytomegalovirus OR CMV OR cCMV OR HCMV OR "cytomegalovirus infection" OR "congenital cytomegalovirus" | Other terms: newborn* OR new-born* OR "newly born" OR neonat* OR neo-nat* OR infant* OR infancy OR baby* OR babies OR "at birth" =109 studies

5. cytomegalovirus OR CMV OR cCMV OR HCMV OR "cytomegalovirus infection" OR "congenital cytomegalovirus" | Other terms: preterm OR preterms OR pre-term OR pre-terms OR preemie* OR premie OR premies OR lbw OR vlbw OR elbw OR "low birthweight" OR "low birthweights" OR "low birth-weight" OR "low birth-weights" = 46 studies

**WHO International Clinical Trials Registry Platform (ICTRP)**
https://trialsearch.who.int/Default.aspx
Date searched: 19th November 2024
Records retrieved: 66

Basic search interface used. No date limits available in basic search interface, therefore results from all years downloaded and records pre-2013 removed in EndNote.

1. 65 records for 58 trials found for: (newborn* OR new-born* OR "newly born" OR neonat* OR neo-nat* OR infant* OR infancy OR baby* OR babies) AND (cytomegalovir* OR CMV OR cCMV OR HCMV)

2. 8 records for 8 trials found for: ("at birth" OR preterm OR preterms OR pre-term OR pre-terms OR preemie* OR premie OR premies OR lbw OR vlbw OR elbw OR "low birthweight" OR "low birthweights" OR "low birth-weight" OR "low birth-weights") AND (cytomegalovir* OR CMV OR cCMV OR HCMV)

**EU Clinical Trials Register**
https://www.clinicaltrialsregister.eu/ctr-search/search
Date of search: 20th November 2024
Records retrieved: 38

Advanced search
1. 38 result(s) found for: cytomegalovirus OR CMV OR HCMV OR cCMV  filter applied: infant, newborn, preterm

Also searched for EU clinical trials via the new portal Clinical Trials Information System (CTIS) https://euclinicaltrials.eu/search-for-clinical-trials/?lang=en
1. cytomegalovirus – scanned 18 results – 0 with a population of newborns
2. CMV – scanned 32 results – 0 with a population of newborns
3. HCMV – 0 results
4. cCMV – 0 results

Website searches

**HTA Agencies**
Date searched: 19th November 2024
Records retrieved: 3

Browsed or searched the following HTA Agency websites to check for additional reports not found through database searches. A date limit of 2013 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 (2013 onwards):
reports and monographs – none relevant
protocols – none relevant
Technology Briefs and Prioritising summaries – non 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 – 1 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, 2 potentially relevant
Browsed projects in progress page and topics under consideration page – 0 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, none relevant.
4. https://www.nice.org.uk/guidance/published Searched for cytomegaloviurs - 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/search/#/
1. cytomegalovirus – 7 results browsed, none relevant

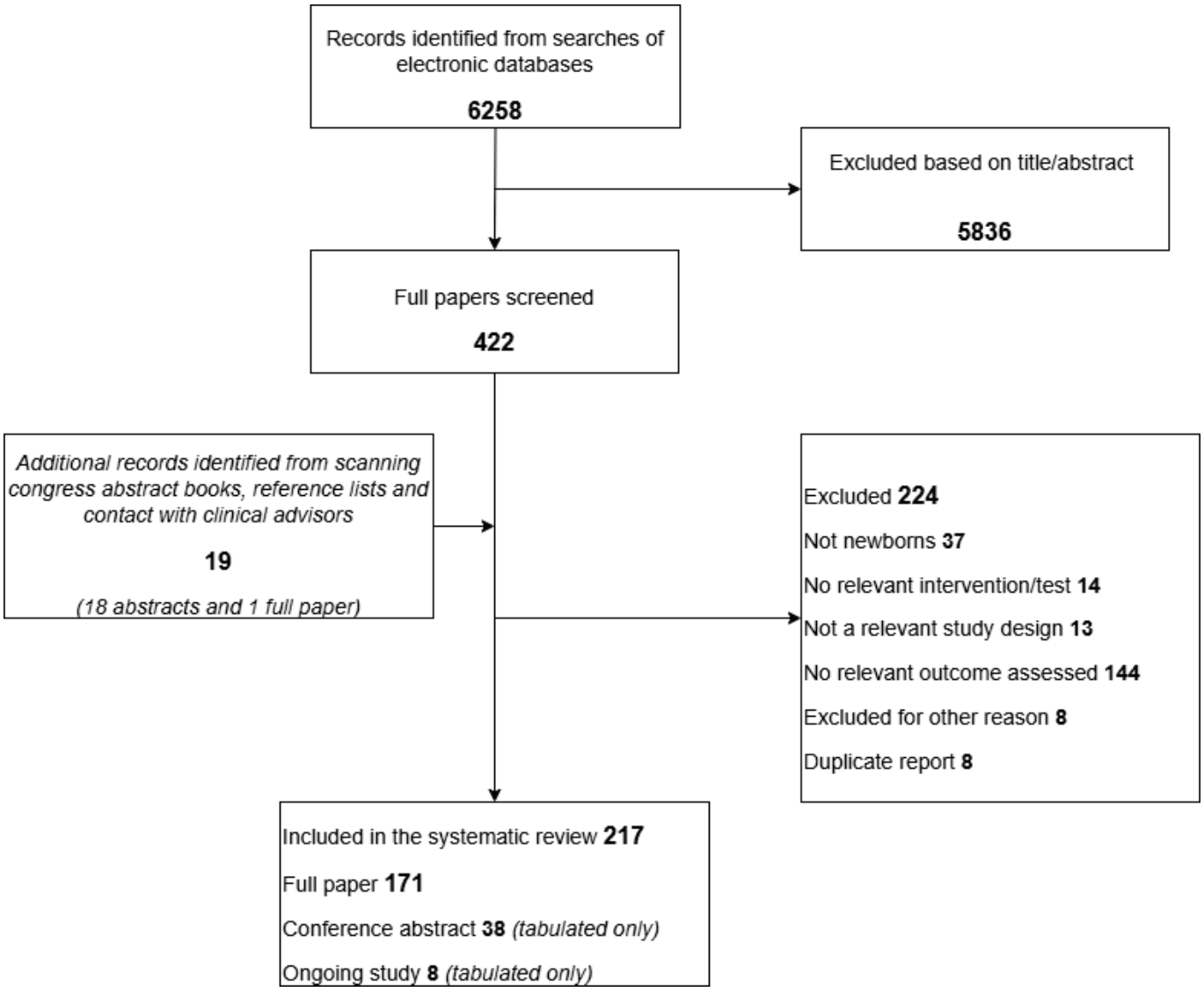
**Belgian Health Care Knowledge Centre**
https://www.kce.fgov.be/en/all-reports-0
Filtered to HTA reports – browsed 2013-2024 – none
Results from the above searches were imported into Endnote 21 and duplicates removed.

# *Appendix 2 — Included and excluded studies*

## PRISMA flowchart

Figure 4 summarises the volume of studies included and excluded at each stage of the review. A total of 217 studies were ultimately judged to be relevant to 1 or more review questions; 171 studies were published in full and were data extracted. There were 8 ongoing studies and 38 studies only reported as conference abstracts; these are tabulated in Appendix 4. Publications that were included or excluded after the review of full text articles are detailed in the tables below.

*Figure 4: Flow diagram of the study selection process*



# Publications included after review of full text articles

The 171 publications included after review of full texts are summarised in Table 24 below.

*Table 24: Summary of publications included after review of full text articles, and the question(s) each publication relates to*

| Study | The test | The screening programme | Implementation criteria | Comments |
|---|---|---|---|---|
| Atwood et al., 2023[40] | Q1 | | 4 | Diagnostic accuracy study |
| Cardoso et al., 2015[38] | Q1 | | 4 | Diagnostic accuracy study |
| Dollard et al., 2021[39] | Q1 & Q2 | | 4 | Diagnostic accuracy study |
| Dunn et al., 2023[41] | Q1 | | 4 | Diagnostic accuracy study |
| Eventov-Friedman et al., 2019[35] | Q1 | | 4 | Diagnostic accuracy study |
| Exler et al., 2019[50] | Q1 | | 4 | Diagnostic accuracy study |
| Gantt et al., 2020[51] | Q1 | | 4 | Diagnostic accuracy study |
| Gunlemez et al., 2023[48] | Q1 | | 4 | Diagnostic accuracy study |
| Huang et al., 2021[52] | Q1 | | 4 | Diagnostic accuracy study |
| Izquierdo et al., 2024[53] | Q1 | | 4 | Diagnostic accuracy study |
| Leruez-Ville et al., 2017[42] | Q1 | | 4 | Diagnostic accuracy study |
| Letamendia-Richard et al., 2022[54] | Q1 | Q4 | 4, 11, 12 & 13 | Diagnostic accuracy study and Screening evaluation |
| Pasternak et al., 2020[55] | Q1 | | 4 | Diagnostic accuracy study |
| Pinninti et al., 2015[43] | Q1 | | 4 | Diagnostic accuracy study |
| Portet Sulla et al., 2024 [56] | Q1 & Q3 | | 4 & 7 | Association study and diagnostic accuracy study |
| Ross et al., 2014[57] | Q1 | | 4 | Diagnostic accuracy study |
| Ross et al., 2018[44] | Q1 | | 4 | Diagnostic accuracy study |
| Shlonsky et al., 2021[49] | Q1 | | 4 | Diagnostic accuracy study |
| Stark et al., 2024[58] | Q1 | | 4 | Diagnostic accuracy study |
| Tan et al., 2023[45] | Q1 | | 4 | Diagnostic accuracy study |
| Wang et al., 2017[46] | Q1 & Q2 | | 4 | Diagnostic accuracy study |
| Wunderlich et al., 2023[47] | Q1 | | 4 | Diagnostic accuracy study |
| Zheng et al., 2022[32] | Q1 | | 4 | Systematic review |
| Atkinson et al., 2014[60] | Q2 | | 4 | Diagnostic accuracy study |
| Del Valle Penella et al., 2023[61] | Q2 | | 4 | Diagnostic accuracy study |
| Fourgeaud et al., 2023[62] | Q2 | | 4 | Diagnostic accuracy study |
| Moteki et al., 2018[63] | Q2 | | 4 | Diagnostic accuracy study |
| Noorbakhsh et al., 2020[64] | Q2 | | 4 | Diagnostic accuracy study |
| Ross et al., 2017[65] | Q2 | | 4 | Diagnostic accuracy study |
| Vercauteren et al., 2020[66] | Q2 | | 4 | Diagnostic accuracy study |
| Vives-Onos et al., 2019[67] | Q2 | | 4 | Diagnostic accuracy study |
| Wang et al., 2015[27] | Q2 | | 4 | Systematic review |
| Albanna et al., 2013[68] | | | 4 | Diagnostic accuracy study |
| Barkai et al., 2013[73] | | | 4 | Diagnostic accuracy study |
| Coltella et al., 2019[69] | | | 4 | Diagnostic accuracy study |
| De Monte et al., 2016[70] | | | 4 | Diagnostic accuracy study |
| Ligozzi et al., 2016[71] | | | 4 | Diagnostic accuracy study |
| Reyes et al., 2020[74] | | | 4 | Diagnostic accuracy study |
| Wang et al., 2013[72] | | | 4 | Diagnostic accuracy study |
| Airlangga et al., 2024 [128] | Q3 | | 7 | Association study |
| Alarcon et al., 2013[75] | Q3 | | 7 | Prognostic accuracy study |
| Alarcon et al., 2016[80] | Q3 | | 7 | Prognostic accuracy study |
| Alarcon et al., 2024[81] | Q3 | | 7 | Prognostic accuracy study |
| Amir et al., 2016 [104] | Q3 | | 7 | Association study |
| Auriti et al., 2022 [129] | Q3 | | 7 | Association study |
| Bartlett et al., 2018 [147] | Q3 | | 7 | Association study |
| Bilavsky et al., 2015 [76] | Q3 | | 7 | Association study |

| Study | The test | The screening programme | Implementation criteria | Comments |
|---|---|---|---|---|
| Blazquez-Gamero et al., 2019[82] | Q3 | | 7 | Prognostic accuracy study |
| Buca et al., 2021[103] | Q3 | | 7 | Systematic review |
| Capretti et al., 2014[83] | Q3 | | 7 | Prognostic accuracy study |
| Capretti et al., 2017 [121] | Q3 | | 7 | Association study |
| Capretti et al., 2021[130] | Q3 | | 7 | Association study |
| Castellanos et al., 2022[84] | Q3 | | 7 | Prognostic accuracy study |
| Chatzakis et al., 2020[102] | Q3 | | 7 | Systematic review |
| Chebib et al., 2022[85] | Q3 | | 7 | Prognostic accuracy study |
| Chen et al., 2019 [163] | Q3 | | 7 | Association study |
| Coscia et al., 2020 [112] | Q3 | | 7 | Association study |
| Craeghs et al., 2021[86] | Q3 | | 7 | Prognostic accuracy study |
| Czech-Kowalska et al., 2021 [169] | Q3 | | 7 | Association study |
| De Cuyper et al., 2024 [115] | Q3 | | 7 | Association study |
| De Juan et al., 2020[87] | Q3 | | 7 | Prognostic accuracy study |
| Demmler-Harrison et al., 2020 [117] | Q3 | | 7 | Association study |
| Dhondt et al., 2021 [131] | Q3 | | 7 | Association study |
| Dhondt, 2023[151] | Q3 | | 7 | Prognostic accuracy study |
| Dong et al., 2023 [164] | Q3 | | 7 | Association study |
| Elkan Miller et al., 2021 [106] | Q3 | | 7 | Association study |
| Faure-Bardon et al., 2019 [107] | Q3 | | 7 | Association study |
| Forli et al., 2024 [152] | Q3 | | 7 | Association study |
| Forner et al., 2015 [77] | Q3 | | 7 | Association study |
| Foulon et al., 2019[88] | Q3 | | 7 | Prognostic accuracy study |
| Fourgeaud et al., 2024[89] | Q3 | | 7 | Prognostic accuracy study |
| Giannattasio et al., 2017 [123] | Q3 | | 7 | Association study |
| Giannattasio et al., 2017[95] | Q3 | | 7 | Association study |
| Giannattasio et al., 2018[90] | Q3 | | 7 | Prognostic accuracy study |
| Goderis et al., 2016 [78] | Q3 | | 7 | Association study |
| Goycochea-Valdivia et al., 2017 [170] | Q3 | | 7 | Association study |
| Hu et al., 2024 [132] | Q3 | | 7 | Association study |
| Jin et al., 2019 [133] | Q3 | | 7 | Association study |
| Kabani et al., 2023 [161] | Q3 | | 7 | Association study |
| Kakei et al., 2024 [157] | Q3 | | 7 | Association study |
| Kasztelewicz et al., 2017 [165] | Q3 | | 7 | Association study |
| Kawada et al., 2015 [160] | Q3 | | 7 | Association study |
| Korndewal et al., 2017 [146] | Q3 | | 7 | Association study |
| Keymeulen et al., 2023 [116] | Q3 | | 7 | Association study |
| Koyano et al., 2018 [148] | Q3 | | 7 | Association study |
| Kwak et al., 2018[91] | Q3 | | 7 | Prognostic accuracy study |
| Lanzieri et al., 2018 [134] | Q3 | | 7 | Association study |
| Lipitz et al., 2013 [108] | Q3 | | 7 | Association study |
| Lo et al., 2022 [135] | Q3 | | 7 | Association study |
| Lucignani et al., 2021[92] | Q3 | | 7 | Prognostic accuracy study |
| Maes et al., 2017 [150] | Q3 | | 7 | Association study |
| Maltezou et al., 2020[119] | Q3 | | 7 | Systematic review |
| Mardegan et al., 2024 [97] | Q3 | | 7 | Association study |
| Marsico et al., 2019 [155] | Q3 | | 7 | Association study |
| Massoud et al., 2023 [109] | Q3 | | 7 | Association study |
| Medoro et al., 2024 [166] | Q3 | | 7 | Association study |
| Meyer et al., 2017 [156] | Q3 | | 7 | Association study |
| Minsart et al., 2020 [145] | Q3 | | 7 | Association study |
| Nigro et al., 2020 [110] | Q3 | | 7 | Association study |

| Study | The test | The screening programme | Implementation criteria | Comments |
|---|---|---|---|---|
| Nishida et al., 2020[93] | Q3 | | 7 | Prognostic accuracy study |
| Noorbakhsh et al., 2022 [120] | Q3 | | 7 | Association study |
| Oosterom et al., 2015 [98] | Q3 | | 7 | Association study |
| Ouellette et al., 2020[162] | Q3 | | 7 | Prognostic accuracy study |
| Pati et al., 2013 [167] | Q3 | | 7 | Association study |
| Pinninti et al., 2016 [140] | Q3 | | 7 | Association study |
| Poletti de Chaurand et al., 2024[101] | Q3 | Q4 | 7, 11 & 13 | Association study and screening evaluation |
| Puhakka et al., 2017 [111] | Q3 | | 7 | Association study |
| Puhakka et al., 2022 [118] | Q3 | | 7 | Association study |
| Riga et al., 2018[127] | Q3 | | 7 | Systematic review |
| Rohren et al., 2024 [153] | Q3 | | 7 | Association study |
| Rovito et al., 2017a [143] | Q3 | | 7 | Association study |
| Rovito et al., 2017b [144] | Q3 | | 7 | Association study |
| Rovito et al., 2017c [124] | Q3 | | 7 | Association study |
| Rovito et al., 2018 [168] | Q3 | | 7 | Association study |
| Royackers et al., 2013[136] | Q3 | | 7 | Association study |
| Salome et al., 2020 [158] | Q3 | | 7 | Association study |
| Salome et al., 2023 [137] | Q3 | | 7 | Association study |
| Scaramuzzino et al., 2022 [113] | Q3 | | 7 | Association study |
| Seneviratne et al., 2022 [138] | Q3 | | 7 | Association study |
| Simonazzi et al., 2014 [141] | Q3 | | 7 | Association study |
| Smyrli et al., 2024[125] | Q3 | | 7 | Systematic review |
| Soriano-Ramos et al., 2024 [99] | Q3 | | 7 | Association study |
| Tapasak et al., 2022 [142] | Q3 | | 7 | Association study |
| Topham et al., 2019[149] | Q3 | | 7 | Association study |
| Townsend et al., 2013 [122] | Q3 | | 7 | Association study |
| Turriziani Colonna et al., 2020 [114] | Q3 | | 7 | Association study |
| Vande Walle et al., 2023 [100] | Q3 | | 7 | Association study |
| Vande Walle, 2024[79] | Q3 | | 7 | Systematic review |
| Vande Walle, 2024[94] | Q3 | | 7 | Prognostic accuracy study |
| Vila-Bedmar et al., 2024 [96] | Q3 | | 7 | Association study |
| Vos et al., 2021[126] | Q3 | | 7 | Systematic review |
| Wang et al., 2021[159] | Q3 | | 7 | Association study |
| Yamaguchi et al., 2022[154] | Q3 | | 7 | Prognostic accuracy study |
| Zavattoni et al., 2014 [105] | Q3 | | 7 | Association study |
| Zavattoni et al., 2016 [139] | Q3 | | 7 | Association study |
| Ari-Even Roth et al., 2017[186] | | Q4 | 11 & 13 | Screening evaluation |
| Barkai et al., 2014[36] | | Q4 | 11 & 13 | Screening evaluation |
| Beswick et al., 2021[191] | | Q4 | 11, 12 & 13 | Screening evaluation |
| Chiereghin et al., 2022[176] | | Q4 | 11 & 13 | Screening evaluation |
| Chung et al., 2023[187] | | Q4 | 11 & 13 | Screening evaluation |
| Demortier et al., 2021[182] | | Q4 | 11, 12 & 13 | Screening evaluation |
| Diener et al., 2017[195] | | Q4 | 11 & 13 | Screening evaluation |
| Dunn et al., 2025[177] | | Q4 | 11, & 13 | Screening evaluation |
| Forli et al., 2024[207] | | Q4 | 11 & 13 | Screening evaluation |
| Fourgeaud et al., 2022[196] | | Q4 | 11 & 13 | Screening evaluation |
| Fowler et al., 2017[192] | | Q4 | 11 & 13 | Screening evaluation |
| Fujii et al., 2017[202] | | Q4 | 11 & 13 | Screening evaluation |
| Hilditch et al., 2018[173] | | Q4 | 11 & 13 | Systematic review |
| Kadambari et al., 2015[194] | | Q4 | 11, 12 & 13 | Screening evaluation |
| Kaye et al., 2024[179] | | Q4 | 11 & 13 | Screening evaluation |
| Kruc et al., 2024[180] | | Q4 | 11 & 13 | Screening evaluation |
| Lu et al., 2018[204] | | Q4 | 11 & 13 | Screening evaluation |

| Study | The test | The screening programme | Implementation criteria | Comments |
|---|---|---|---|---|
| Masarweh et al., 2021[199] | | Q4 | 11 & 13 | Screening evaluation |
| McCrary et al., 2020[200] | | Q4 | 11 & 13 | Screening evaluation |
| Medoro et al., 2021[189] | | Q4 | 11 & 13 | Screening evaluation |
| Merav et al., 2024[183] | | Q4 | 11 & 13 | Screening evaluation |
| Palma et al., 2021[201] | | Q4 | 11 & 13 | Screening evaluation |
| Papaevangelou et al., 2019[184] | | Q4 | 11 & 13 | Screening evaluation |
| Pollick et al., 2024[174] | | Q4 | 11 & 13 | Systematic review |
| Puhakka et al., 2019[175] | | Q4 | 11 & 13 | Screening evaluation |
| Rawlinson et al., 2018[197] | | Q4 | 11 & 13 | Screening evaluation |
| Ronner et al., 2022[188] | | Q4 | 11 & 13 | Screening evaluation |
| Tan et al., 2023[205] | | Q4 | 11 & 13 | Screening evaluation |
| Vancor et al., 2019[190] | | Q4 | 11 & 13 | Screening evaluation |
| Webb et al., 2024[206] | | Q4 | 11, 12 & 13 | Screening evaluation |
| Williams et al., 2014[198] | | Q4 | 11 & 13 | Screening evaluation |
| Yamada et al., 2020[171] | | Q4 | 11 & 13 | Screening evaluation |
| Yamaguchi et al., 2017[181] | | Q4 | 11 & 13 | Screening evaluation |
| Yamamoto et al., 2020[178] | | Q4 | 11 & 13 | Screening evaluation |
| Zeytinoglu et al., 2019[185] | | Q4 | 11 & 13 | Screening evaluation |
| Zhang et al., 2023[203] | | Q4 | 11 & 13 | Screening evaluation |

## Publications excluded after review of full text articles

Of the 422 publications included after the review of titles and abstracts, 224 were ultimately judged not to be relevant to this review. These publications, along with reasons for exclusion, are listed in Table 25.

*Table 25: Publications excluded after review of full text articles*

| Reference | Reason for exclusion |
|---|---|
| Akiko et al., 2021[208] | Population |
| Akiva et al., 2023[209] | Outcome |
| Albano et al., 2014[210] | No eligible test |
| Albano et al., 2016[211] | Outcome |
| Albano et al., 2017[212] | Outcome |
| Alifieraki et al., 2022[213] | Outcome |
| Almeida et al., 2023[214] | Outcome |
| Alwan et al., 2019[215] | Outcome |
| Amin et al., 2021[216] | Population |
| Annabelle et al., 2023[217] | Outcome |
| Anonymous, 2016[218] | Other (erratum for other study) |
| Arancibia et al., 2023[219] | No eligible test |
| Arellano-Galindo et al., 2014[220] | Outcome |
| Banjac et al., 2022[221] | Study design |
| Barriga et al., 2024[222] | Outcome |
| Ben Shoham et al., 2023[223] | Outcome |
| Berg et al., 2019[224] | Population |
| Bergevin et al., 2015[225] | No eligible test |
| Beswick et al., 2019[226] | No eligible test |
| Bilavsky et al., 2016[227] | Population |
| Bilavsky et al., 2017[228] | Outcome |
| Blazquez-Gamero et al., 2020[229] | Outcome |
| Blazquez-Gamero et al., 2021[230] | Duplicate report |
| Boppana et al., 2016[231] | Population |
| Boscarino et al., 2024[232] | No eligible test |

| Reference | Reason for exclusion |
|---|---|
| Branas et al., 2015[233] | Outcome |
| Brunet, 2024[234] | Study design |
| Campione et al., 2022[235] | No eligible test |
| Canadian Agency for Drugs and Technologies in Health, 2024[236] | Outcome |
| Central Hospital Nancy France, 2023[237] | Outcome |
| Chasqueira et al., 2023[238] | Outcome |
| Chauhan et al., 2021[239] | Outcome |
| Chiereghin et al., 2017[240] | Outcome |
| Chisholm et al., 2013[241] | Outcome |
| Chisholm et al., 2014[242] | Population |
| Choudhary et al., 2015[243] | Population |
| Correa et al., 2016[244] | Outcome |
| Cushing et al., 2022[245] | Outcome |
| Czech-Kowalska et al., 2021[246] | Outcome |
| Dallaire et al., 2021[247] | Outcome |
| Dallaire et al., 2022[248] | Population |
| Dar et al., 2017[249] | Outcome |
| De Cuyper et al., 2023[250] | Outcome |
| de Vries et al., 2013[251] | Population |
| Del Valle Penella et al., 2023[252] | Outcome |
| Demmler-Harrison G J, 2021[253] | Study design |
| Dharnidhar et al., 2019[254] | Outcome |
| Dimopoulou et al., 2020[255] | Outcome |
| Dobbins et al., 2019[256] | Outcome |
| Dougherty et al., 2022[257] | Population |
| Dreher et al., 2013[258] | Outcome |
| Dreher et al., 2014[172] | No eligible test |
| Ebrahimi-Rad et al., 2017[259] | Outcome |
| Eres Saritas et al., 2023[260] | Outcome |
| Eventov-Friedman et al., 2014[261] | Outcome |
| Farnan et al., 2023[262] | Outcome |
| Faure-Bardon et al., 2020[263] | Population |
| Fernandes et al., 2021[264] | No eligible test |
| Folkins et al., 2013[265] | Outcome |
| Gandhoke et al., 2013[266] | Population |
| Gantt et al., 2018[267] | Study design |
| Garnham et al., 2023[268] | Outcome |
| Gillespie et al., 2023[269] | Study design |
| Goderis et al., 2013[270] | Duplicate report |
| Goel et al., 2018[271] | Outcome |
| Goetzl et al., 2019[272] | Population |
| Gonzalez Lopez et al., 2015[273] | Outcome |
| Gorzer et al., 2015[274] | Outcome |
| Gunes et al., 2024[275] | Outcome |
| Gunkel et al., 2014[37] | Population |
| Gupta et al., 2023[276] | Population |
| Gutierrez Posso et al., 2023[277] | Outcome |
| Gwee et al., 2014[278] | Outcome |
| Hadar et al., 2016[279] | Outcome |
| Hadar et al., 2017[280] | Outcome |
| Hamid et al., 2022[281] | Outcome |
| Hamilton et al., 2014[282] | Population |
| Hasan et al., 2021[283] | Outcome |
| Hernandez-Alvarado et al., 2023[284] | No eligible test |
| Hirth et al., 2018[285] | Other (insufficient information to screen against inclusion criteria) |
| Hirth et al., 2021[286] | Other (no data relating to review questions) |
| Hranilovich et al., 2016[287] | Outcome |

| Reference | Reason for exclusion |
|---|---|
| Hranilovich et al., 2020[288] | Population |
| Hu et al., 2021[289] | Outcome |
| Huang et al., 2024[290] | Other (no relevance to review questions) |
| Ikuta et al., 2013[291] | Other (no relevance to review questions) |
| Imafuku et al., 2020[292] | Outcome |
| Ishida et al., 2015[293] | Study design |
| Ismail et al., 2013[294] | Outcome |
| Izquierdo et al., 2023[295] | Duplicate report |
| Javid et al., 2016[296] | Outcome |
| Jedlinska-Pijanowska et al., 2020[297] | Outcome |
| Jedlinska-Pijanowska et al., 2021[298] | Outcome |
| Kachramanoglou et al., 2021[299] | Outcome |
| Kakkar et al., 2015[300] | Other (insufficient information to screen against inclusion criteria) |
| Karamchandani et al., 2022[301] | Outcome |
| Karimi et al, 2023[302] | Outcome |
| Kawano et al., 2016[303] | Outcome |
| Keymeulen et al., 2022[304] | Outcome |
| Khalil et al., 2016[305] | Outcome |
| Kim et al., 2023[306] | Population |
| Kipfmueller et al., 2018[307] | Outcome |
| Kitamura et al., 2022[308] | Population |
| Kobayashi et al., 2015[309] | Outcome |
| Kohmer et al., 2019[310] | Population |
| Koontz et al., 2015[311] | Population |
| Korndewal et al., 2016[312] | Outcome |
| Kravchenko et al., 2015[313] | Population |
| Kravchenko et al., 2021[314] | Outcome |
| Krishna et al., 2020[315] | No eligible test |
| Kruc et al., 2022[316] | Outcome |
| Kyriakopoulou et al., 2023[317] | Outcome |
| Lakhan et al., 2023[318] | Outcome |
| Lam et al., 2017[319] | Outcome |
| Lee et al., 2013[320] | Population |
| Leruez-Ville et al., 2013[321] | Population |
| Leruez-Ville et al., 2020[322] | Outcome |
| Levit et al., 2020[323] | Outcome |
| Lewald et al., 2023[324] | Outcome |
| Liao et al., 2023[325] | Outcome |
| Lilleri et al., 2023[326] | Outcome |
| Lim et al., 2013[327] | Population |
| Lipitz et al., 2020[328] | Outcome |
| Lopez et al., 2017[329] | Outcome |
| Luck et al., 2016[330] | Outcome |
| Mack et al., 2017[331] | Study design |
| Mahajan et al., 2018[332] | Outcome |
| Maltezou Panagiota et al., 2019[333] | Duplicate report |
| Mappa et al., 2023[334] | Population |
| Mareri et al., 2013[335] | Outcome |
| Martinez et al., 2021[336] | Outcome |
| Mastutik et al., 2022[337] | Population |
| Matsuo et al., 2014[338] | Outcome |
| McCrary et al., 2019[339] | Outcome |
| Medoro et al., 2017[340] | Duplicate report |
| Medoro et al., 2019[341] | Other (insufficient information to screen against inclusion criteria) |
| Medoro et al., 2019[342] | Outcome |
| Medoro et al., 2020[343] | Outcome |
| Melamed et al., 2020[344] | Outcome |

| Reference | Reason for exclusion |
|---|---|
| Meogrossi et al., 2023[345] | Population |
| Merino-Hernandez et al., 2023[346] | Outcome |
| Minami et al., 2021[347] | No eligible test |
| Mirsalehi et al., 2024[348] | Outcome |
| Morimoto et al., 2023[349] | Study design |
| Mu et al., 2023[350] | Population |
| Mujtaba et al., 2016[351] | Outcome |
| Nagel et al., 2020[352] | Outcome |
| Namdeo et al., 2013[353] | Outcome |
| Nishida et al., 2016[354] | Outcome |
| Nishida et al., 2016[355] | Outcome |
| Niz Xavier et al., 2015[356] | Outcome |
| Noorbakhsh et al., 2020[357] | Outcome |
| Noorbakhsh et al., 2023[358] | Outcome |
| Norton et al., 2020[359] | Study design |
| Ohyama et al., 2019[360] | Outcome |
| Oneko et al., 2020[361] | Outcome |
| Orb et al., 2024[362] | Outcome |
| Palma et al., 2019[363] | Outcome |
| Palma et al., 2023[364] | Outcome |
| Paradowska et al., 2013[365] | Outcome |
| Paradowska et al., 2014[366] | Outcome |
| Paradowska et al., 2019[367] | Outcome |
| Parsons et al., 2021[368] | Other (insufficient information to screen against inclusion criteria) |
| Pathirana et al., 2019[369] | Outcome |
| Pellegrinelli et al., 2019[370] | Population |
| Peterson et al., 2020[371] | Outcome |
| Pitlick et al., 2015[372] | Outcome |
| Rahniayu et al., 2022[373] | Population |
| Raynor et al., 2021[374] | Outcome |
| Reina et al., 2014[375] | Outcome |
| Renaud et al., 2018[376] | Outcome |
| Reynders et al., 2024[377] | Outcome |
| Ronchi et al., 2020[378] | Outcome |
| Roy et al., 2024[379] | Population |
| Rymer-Haskel et al., 2019[380] | Outcome |
| Sahiner et al., 2015[381] | Outcome |
| Sakamoto et al., 2015[382] | Outcome |
| Sarkar et al., 2019[383] | Outcome |
| Schleiss et al., 2023[384] | Population |
| Schleiss et al., 2023[385] | Population |
| Shahar-Nissan et al., 2022[386] | Outcome |
| Shahrokhi et al., 2020[387] | Outcome |
| Shears et al., 2022[388] | Outcome |
| Smiechura et al., 2014[389] | Outcome |
| Smiljkovic et al., 2017[390] | Outcome |
| Smiljkovic et al., 2019[391] | Outcome |
| Smiljkovic et al., 2020[392] | Outcome |
| Smyrli et al., 2022[393] | Duplicate report |
| Southern Illinois University, 2016[394] | Outcome |
| Spalletti-Cernia et al., 2016[395] | No eligible test |
| Ssentongo et al., 2021[396] | Outcome |
| Stoyell et al., 2024[397] | Outcome |
| Stoykova et al., 2022[398] | Outcome |
| Suarez et al., 2023[399] | Outcome |
| Thompson et al., 2020[400] | Outcome |
| Torii et al., 2024[401] | Outcome |
| Torre et al., 2016[402] | Outcome |

| Reference | Reason for exclusion |
|---|---|
| Turner et al., 2014[403] | Outcome |
| Uematsu et al., 2016[404] | Outcome |
| Vande Walle et al., 2021[405] | Outcome |
| Vargas et al., 2022[406] | No eligible test |
| Viswanathan et al., 2019[407] | Outcome |
| Vives-Onos et al., 2014[408] | Outcome |
| Wang et al., 2017[409] | Population |
| Wang et al., 2022[410] | Outcome |
| Waters et al., 2014[29] | Outcome |
| Webb et al., 2022[411] | Duplicate report |
| Wei et al., 2014[193] | Outcome |
| Williams et al., 2015[412] | Study design |
| Wissel et al., 2017[413] | Study design |
| Wolf, 2024[414] | Study design |
| Wu et al., 2022[415] | Outcome |
| Wu et al., 2022[416] | Population |
| Wujcicka et al., 2017[417] | Outcome |
| Yamaguchi et al., 2023[418] | Outcome |
| Yamaguchi et al., 2023[419] | Outcome |
| Yang et al., 2021[420] | Outcome |
| Yao, 2018[421] | Outcome |
| Zavattoni et al., 2014[422] | Study design |
| Zavattoni et al., 2018[423] | Outcome |
| Zeng et al., 2017[424] | Population |
| Zhang et al., 2013[425] | No eligible test |
| Zhang et al., 2016[426] | Outcome |
| Zheng et al., 2022[427] | Duplicate report |

# *Appendix 3 — Summary and appraisal of studies relating to Criterion 7*

## Data Extraction

Detailed characteristics of studies relevant to criterion 7 are tabulated below.

*Table 26: Systematic reviews relevant to criterion 7*

| Study details | Test/characteristic assessed (of relevance to this review) | Population (of relevance to this review) | Outcome (and timeframe) | Results/conclusions and comments |
|---|---|---|---|---|
| Vande Walle, 2024[79] | Postnatal brain MRI. A 1.5 or 3T scanner was used in the axial, coronal and/or sagittal planes. Sequences included T2 (+ fat saturation), T1, DWI (with ADC) and FLAIR. Mild sedation, anaesthesia or a vacuum mattress were sometimes used to reduce motion artefacts. Postnatal scoring systems described in some studies.<br><br>Prenatal MRI was included in the paper, but details of prenatal MRI have not been | Newborns and children with cCMV. No definition of upper age limit for baseline MRI. | Neurodevelopmental impairments (cognitive and motor), sensorineural hearing loss, epilepsy, behavioural problems, visual impairments.<br><br>Timeframes not consistently described. | An analysis of the associations between prenatal MRI and later outcomes was included in the paper, but details of these associations have not been included in this review as they are out of scope.<br><br>Out of the 20 studies included in the SR, only 7 studies covered the relevant analyses between post-natal MRI and the outcomes below. No quantitative or narrative synthesis were undertaken, and associations between postnatal MRI and later outcome were merely given per study. These results have been summarised below. The numbers of participants in each included study were not presented in the SR [Vande Walle (2024)]. Other reporting deficits described below relate to perceived limitations in the SR, but some may be related to similar reporting limitations in the original sources.<br><br><u>Neurodevelopmental outcomes</u><br>*Kwak et al*: MRI score was associated with epilepsy (p=0.004). Polymicrogyria on MRI was associated with epilepsy (p=0.012) and neurodevelopmental impairment (NDI) (p=0.01). Ventriculomegaly (p=0.045), calcification (p=0.006), and white matter abnormalities (no p value given) on MRI each associated with epilepsy. For all outcomes, outcome follow up length was not presented in the SR, and presence of any statistical adjustment was unclear. |

| Study details | Test/characteristic assessed (of relevance to this review) | Population (of relevance to this review) | Outcome (and timeframe) | Results/conclusions and comments |
|---|---|---|---|---|
| | included in this review as they are out of scope. | | | *Nishida et al*: Ventriculomegaly (p<0.001), periventricular cysts (p<0.005), and white matter abnormalities (p=0.02) were associated with NDI. NDI could be predicted (Youden index of 0.78) by presence of 2 out of the 3 MRI abnormalities. For all outcomes, follow up length was not presented in the SR, and presence of statistical adjustment was unclear.<br>*Vande Walle*: Isolated white matter abnormalities were associated with lower motor scores (p=0.01), and impaired mental development (p=0.07). For all outcomes, follow up length was not presented in the SR, and presence of statistical adjustment was unclear.<br><br><u>Hearing outcomes</u><br>*Alarcon*: Temporal pole lesions (but not white matter lesions) were significantly associated with sensorineural hearing loss (SNHL), but follow up length was not presented in the SR. Results appear to be based on an adjusted regression analysis.<br>*Craeghs*: There was a [presumably univariate] significant association between abnormal MRI and hearing loss (p=0.007), but follow up length was not presented in the SR. On multivariate analysis only calcifications were associated with hearing loss.<br>*De Cuyper*: Periventricular cysts were independently and significantly associated with hearing loss, but follow up length was not presented in the SR.<br>*Kwak*: No associations between MRI abnormalities and SNHL were observed, but follow up length was not presented in the SR.<br>*Vande Walle*: Associations between white matter lesions and hearing loss (p=0.008) were observed, but follow up length was not presented in the SR.<br><br><u>Combined neurodevelopmental/hearing loss outcomes</u><br>*Blazquez-Gamero*: Abnormal MRI was strongly associated with NDI/hearing loss sequelae (p=0.028) at 12 months. This was an adjusted association, based on multivariable logistic regression.<br><br><u>Other information</u><br>MRI was also compared to US, but only in terms of the anomalies detected by each. No analysis was made of the differential ability to predict later outcomes. |

| Study details | Test/characteristic assessed (of relevance to this review) | Population (of relevance to this review) | Outcome (and timeframe) | Results/conclusions and comments |
|---|---|---|---|---|
| | | | | No data on predictive accuracy of post-natal MRI were presented.<br><br>Protocol not published as far as is known. |
| Chatzakis, 2020[102] | Timing of infection: first vs second vs third trimester | Neonates of pregnant women with confirmed primary CMV infection in the immediate preconception period (up to 12 weeks preconception) or during pregnancy were included. | The only outcome relevant was severe sensorineural hearing loss (SNHL) or neurodevelopmental impairment at follow-up (from 6 months to 5 years). | Although 17 studies were included in the review, only 6 studies[88, 107, 108, 111, 428, 429] contained the relevant outcome of sensorineural hearing loss (SNHL) and/or neurodevelopmental impairment at follow-up, and so only results relating to these are included here.<br><br>Data from these 6 studies (comprising 738 participants) were synthesised using meta-analysis to evaluate the association of time of maternal infection and severe SNHL or neurodevelopmental impairment at follow-up. Maternal infection in the first trimester resulted led to a pooled prevalence of SNHL or neurodevelopmental impairment of 22.8% (95% CI: 15.4-30.2;$I^2$=27.6%) at follow up. Maternal infections in the second and third trimesters led to smaller rates of 0.1% (95% CI: 0-0.8; $I^2$ =24%) and 0% (95% CI: 0-2.1; $I^2$ =0%) at follow up, respectively. No evidence of sub-grouping or meta-regression by potential outcome modifiers was presented. The meta-analyses were flawed by not evaluating the between-group effects (for example a more valid approach might have analysed the odds ratios for later impairment of each of second and third trimester groups with reference to the first trimester group), and instead provided the within-group prevalences. Although this approach prevents a rigorous analysis of group difference, the large magnitude of effect in this analysis provides some evidence that timing of infection may be an important factor determining the likelihood of neurodevelopmental and hearing sequelae.<br><br>A further (sensitivity) meta-analysis restricted to the 4 studies that were conducted prospectively, and had used IgG avidity assays for the timing of maternal infection produced similar results.<br><br>No data on predictive accuracy of timing of infection were presented.<br><br>Protocol published on PROSPERO. |

| Study details | Test/characteristic assessed (of relevance to this review) | Population (of relevance to this review) | Outcome (and timeframe) | Results/conclusions and comments |
|---|---|---|---|---|
| Maltezou, 2020[119] | Type of maternal infection: primary infection (PI; where the mother is initially infected during the index pregnancy) or non-primary infection (NPI; where the mother is initially infected before the index pregnancy). | Congenitally CMV infected children born following maternal PI or NPI | Relevant outcomes were unilateral SNHL, bilateral S NHL, or other neurologic outcomes. Follow up ranged from 1-5 years (set at a minimum of 12 months in SR protocol). | The paper reported some results for analyses from 9 studies (n=879) that are not reported here as they are outside the scope of the current review. However, 8 of these studies (n=835) produced data that were relevant to the meta-analyses of 'later outcomes'.<br><br>Meta-analyses showed that maternal infection status (primary versus non-primary infection) did not influence the risk of developing unilateral SNHL [pooled OR of 8 studies = 0.80 (95 % CI 0.54–1.20, p = 0.282) $I^2$=0%], bilateral SNHL [pooled OR of 5 studies = 0.66 (95 % CI 0.30–1.42, p = 0.283) $I^2$=36.2%] or other neurologic outcomes [pooled OR of 4 studies = 0.73 (95 % CI 0.43–1.25, p = 0.518) $I^2$=0%]. This paper suggests that type of maternal infection is not an important factor determining hearing or neurological outcomes at follow up.<br><br>No data on predictive accuracy of type of maternal infection were presented.<br><br>Protocol published on PROSPERO. |
| Smyrli, 2024[125] | Children with asymptomatic cCMV at birth. | Children with asymptomatic and symptomatic cCMV | Neurodevelopmental outcomes. Age at last follow up ranged from 1 month to 18 years. | All 28 studies (number of participants unclear) in the SR evaluated the outcomes for children with asymptomatic cCMV.<br><br>For the 19/28 studies (number of participants unclear) that included an analysis of asymptomatic versus *symptomatic cCMV*, 16/19 studies showed that adverse neurodevelopmental outcomes were less common among children with asymptomatic cCMV at birth.<br><br>Where reported, antivirals were received by children with asymptomatic cCMV in 6 studies and by children with symptomatic cCMV in 11 studies. Although this might create bias, the bias would favour the symptomatic group, which would be expected to reduce rather than augment the overall finding that asymptomatic children have better long-term outcomes.<br><br>No formal meta-analyses were undertaken, as a narrative approach had been decided pre-hoc based on the anticipated heterogeneity between studies.<br><br>No data on predictive accuracy of type of maternal infection were presented. |

| Study details | Test/characteristic assessed (of relevance to this review) | Population (of relevance to this review) | Outcome (and timeframe) | Results/conclusions and comments |
|---|---|---|---|---|
| | | | | Protocol published on PROSPERO. |
| Buca,2021[103] | Trimester of infection | Children with cCMV and normal prenatal US at diagnosis | Neurodevelopment/ hearing. Age at last follow up ranged from 1 month to 10 years (median) | 26 studies were included in the systematic review, but only a proportion of these were relevant to the subgroup analysis of the association between trimester of infection and neurodevelopmental/hearing sequelae. It is unclear which (or how many) of these eligible studies there were, as the number of studies with data on trimester of infection in the study characteristics table does not tally with the number of studies with relevant data in the results section.<br><br>The pooled proportion of children with abnormal neurodevelopmental outcome was 5.4% (95% CI: 2.3 to 9.8) in 7 studies evaluating first trimester infection, 0% (95% CI: 0 to7) in 6 studies evaluating second trimester infection, and 0% (95% CI: 0 to 7.7) in 4 studies evaluating third trimester infection. The pooled proportion of children with hearing problems was 11.4% (95% CI: 6.7 to 17.1) in 7 studies evaluating first trimester infection, 7% (95% CI: 2.1 to14.5) in 6 studies evaluating second trimester infection, and 0% (95% CI: 0 to 7.7) in 4 studies evaluating third trimester infection.<br><br>No data on predictive accuracy of timing of maternal infection were presented.<br><br>No evidence that the protocol was published. |
| Vos, 2021[126] | Symptoms at birth | Children with cCMV | Late-onset hearing loss, up to 18 years | 65 articles were included, but only 17 were relevant for assessing the association between cCMV symptoms at birth and late-onset hearing loss. Other studies were not relevant as they covered post-natal CMV, hearing loss at birth, or did not analyse the association between symptoms at birth and outcomes.<br><br>This narrative review did not form any firm conclusions about an association between symptomatic status at birth and subsequent hearing loss in children with cCMV; late-onset permanent childhood hearing loss occurred in children in all cCMV subgroups (symptomatic, asymptomatic and unspecified).<br><br>No data on predictive accuracy of symptoms at birth were presented. |

| Study details | Test/characteristic assessed (of relevance to this review) | Population (of relevance to this review) | Outcome (and timeframe) | Results/conclusions and comments |
|---|---|---|---|---|
| | | | | Protocol published on PROSPERO. |
| Riga, 2018[127] | Symptoms at birth | Children with cCMV | CMV-induced hearing loss, up to 6-10 years of age | 11 articles were included. It is unclear how many of these were included in the synthesis of results.<br><br>A synthesis was carried out on a pooled population of 1089 children with cCMV. Among asymptomatic participants SNHL was diagnosed in 8.9% (70/784), while for symptomatic children the percentage raised to 44.2% (107/242). This synthesis appears to be a simple summation of study results rather than a proper meta-analysis.<br><br>No data on predictive accuracy of symptoms at birth were presented.<br><br>No evidence that the protocol was published. |

*Table 27: Prognostic accuracy studies relevant to criterion 7*

| Study | Details of neonatal sample, cCMV diagnosis method/timing and timing of baseline predictive tests | Specific sequelae predicted with follow up | Baseline test(s) to predict the defined sequelae, with thresholds defining a positive test | n | TP | FN | FP | TN | Sen (%) | Spec (%) | PPV (%) | NPV (%) | AUC |
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| Alarcon et al. 2013[75] | Symptomatic neonates only.<br>3 deaths during follow-up. 15 with at least 1 sequel of neurodevelopmental delay<br>17/26 patients received antivirals<br>Identification of CMV or viral DNA in urine or blood, or detection of CMV IgM or viral antigen in blood during first 2 weeks.<br>CSF baseline tests performed at mean 8.5 days. Timing of other baseline tests unclear. | Neurodevelopmental delay (in terms of motor function, cognition, behaviour, hearing, vision, and epilepsy) at mean 8.7 years | adjusted microcephaly (threshold unclear) | 26 | - | - | - | - | 44 | 100 | 100 | 44 | 0.72 |
| | | | CSF conc. >7.9mg/L | 26 | - | - | - | - | 69 | 100 | 100 | 63 | 0.84 |
| | | | Neuroimaging (on any of MRI, US or CT) score of ≥2 on Noyola scale#* | 26 | - | - | - | - | 61 | 100 | 100 | 53 | 0.80 |
| | | | CSF conc. >7.9mg/L OR adjusted microcephaly (threshold unclear) | 26 | - | - | - | - | 82 | 100 | 100 | 70 | 0.91 |
| | | | adjusted microcephaly (threshold unclear) OR neuroimaging (on any of MRI, US or CT) score of ≥2 on Noyola scale | 26 | - | - | - | - | 66 | 100 | 100 | 57 | 0.83 |
| | | | CSF>7.9mg/L OR neuroimaging (on any of MRI, US or CT) score of ≥2 on Noyola scale | 26 | - | - | - | - | 87 | 100 | 100 | 77 | 0.92 |
| Alarcon et al. 2016[80] | Symptomatic neonates only.<br>3 deaths during follow-up. 15 with at least 1 sequel of neurodevelopmental delay<br>17/26 patients received antivirals<br>Identification of CMV or viral DNA in urine or blood, or detection of CMV IgM or viral antigen in blood during first 2 weeks.<br>Timing of baseline tests unclear. | Neurodevelopmental delay (in terms of motor function, cognition, behaviour, hearing, vision, and epilepsy) at mean 8.7 years | Neuroimaging (on any of MRI, US or CT) ≥ score of 2 on 'new scale' ** (contains additional characteristics in each scoring category, allowing more scores of 2 or above) | 26 | - | - | - | - | 77 | 100 | 100 | 66 | 0.88 |
| | | | Neuroimaging (on any of MRI, US or CT) score of ≥2 on Noyola scale#* | 26 | - | - | - | - | 61 | 100 | 100 | 53 | 0.80 |

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| Alarcon et al. 2024[81] | 103 symptomatic, 57 asymptomatic<br>41 with moderate/severe disability at follow up<br>96/160 received antivirals<br>Diagnosis method of cCMV not reported.<br>Baseline neuroimaging in first 3 months of life | Moderate/severe disabilities: neurodevelopmental impairments (including hearing, CP, cognition, behavioral, epilepsy, visual) at median 4 years | Neuroimaging (US or MRI) composite score (as 'new' score in Alarcon, 2016**) ≥ score of 2 | 160 | - | - | - | - | 90 | 69 | 63 | 92 | 0.89 |
| | | | One or more temporal pole white matter abnormalities (TPWMAs) observed | 160 | - | - | - | - | 78 | 69 | 35 | 94 | 0.73 |
| Blazquez-Gamero et al. 2019[82] | 77 symptomatic, 30 asymptomatic<br>37 with sequelae during follow up.<br>96/107 received antivirals<br>Only children diagnosed with cCMV during the fetal period or at birth (first 14 days of life) were included in this study. Retrospective DBS after 14 days<br>Excluded.<br>MRI done in first 3 months of life. | Any sequelae (hearing or neurological) at 12 months | Abnormal US AND Abnormal MRI (with any category of symptoms at birth).## | *71* | *31* | *6* | *7* | *27* | *84* | *79* | *82* | *82* | - |
| | | | Abnormal US AND Abnormal MRI (WITH symptoms at birth). ## | *71* | *30* | *7* | *5* | *29* | *81* | *85* | *86* | *81* | - |
| | | | Abnormal US AND Abnormal MRI (with NO symptoms at birth). ## | *71* | *1* | *36* | *2* | *32* | *03* | *94* | *33* | *47* | - |
| Capretti et al. 2014[83] | 11 symptomatic and 29 asymptomatic<br>7 with pathological psychomotor development at follow up<br>7/40 had antivirals<br>Shell-vial procedure for CMV identification from infant | Psychomotor development at 6 years | cUS: cUS scans were defined pathological if they showed ventriculomegaly, pseudocysts, cerebral or cerebellar hypoplasia, hippocampal dysplasia, neuronal migration abnormalities, white matter abnormalities or calcifications. | 40 | *4* | *3* | *2* | *31* | 57 | 94 | 66 | 91 | - |

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| | urine, within first 2 weeks of life.<br>US performed in first 2 weeks and MRI at week 4. | | cMRI: Cerebral MRI scans were defined as pathological if they showed intracranial calcification, ventriculomegaly, pseudocysts or cerebellar hypoplasia | 40 | *7* | *0* | *2* | *31* | 100 | 94 | 78 | 100 | - |
| Castellanos et al. 2022[84] | Patients being followed up in a pediatric neurology department.<br>20 symptomatic, 16 asymptomatic<br>18 with neurological sequelae at follow up<br>20/36 had antivirals<br>Congenital CMV infection was confirmed by positive PCR or urine culture findings for CMV in the first 15 days of life or positive DBS in first 48 hours of life.<br>Timing of MRI and US tests not reported. | Neurological sequelae (WMA and other neuroimaging findings, delayed development, hearing loss) at 4 years | Brain MRI, categorized by modified Noyola score. Threshold of score used is unclear, but appears to be ≥2 | 29 | *15* | *1* | *4* | *9* | 94 | 67 | 80 | 88 | - |
| | | | Transfontanellar US. Pathological brain ultrasound findings were defined as intracranial calcifications, ventriculomegaly, germinolytic cysts, and/or lenticulostriate vasculopathy | 30 | *10* | *2* | *10* | *8* | 83 | 44 | 50 | 80 | - |
| Chebib et al. 2022[85] | 94 symptomatic, 36 asymptomatic<br>83 with inner ear impairment at 21 months<br>No data on numbers using anti-virals<br>No clear information on cCMV test or timing<br>Index tests were both antenatal | Inner ear impairment at median 21 months | Infection in first trimester OR Imaging anomaly of fetus | | | | | | 91 | 48 | | | |
| | | | Infection in first trimester AND imaging anomaly of fetus | | | | | | 38 | 92 | | | |

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| Craeghs et al. 2021[86] | 164 symptomatic, 247 asymptomatic<br>75 with hearing loss at follow up.<br>No data on number using antivirals<br>Diagnosis of cCMV infection made by PCR on a urine sample in first 2 weeks of life.<br>MRI and US done at neonatal stage but precise timing not reported. | Hearing loss at mean 2.5 years | MRI. Pathological if 1 or more of: WM injury, WM injury with cyst formation, periventricular pseudocysts, intraventricular adhesions, gyration disorders, calcifications, vermis hypoplasia, cortical atrophy, ventriculomegaly, or other abnormalities. | 275 | *29* | *46* | *45* | *155* | 39 | 78 | 39 | 77 | - |
| | | | US. Pathological if 1 or more of: intraventricular adhesions, periventricular, WM injury with or without cyst formation, lenticulostriatal vasculopathy, calcifications, vermis or even cerebellar hypoplasia, hyperechogenic caudal pit, ventriculomegaly, or other abnormalities. | 342 | *32* | *43* | *44* | *223* | 43 | 84 | 11 | 92 | - |

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| De Juan et al. 2020[87] | Not reported how many were symptomatic<br>32/60 with neurological sequelae<br>Number using antivirals not reported<br>Patients diagnosed with CMV infection within the first 3 weeks of birth with positive urine or blood PCR tests. Patients older than 3 weeks of age with positive serology (CMV-specific IgM) or viral load in plasma or a blotting paper blood sample from newborn screening were also included<br>Unclear when the US and MRI tests were used. | Neurological sequelae at a mean of 19 months | Ultrasonography and 1.5 Tesla MRI were used. Noyola et al. classification used (score of 1 or more used as threshold by reviewers) | 60 | *23* | *9* | *8* | *20* | *72* | *71* | *74* | *69* | |
| Dhondt et al. 2023[151] | 76 symptomatic, 93 asymptomatic<br>20 with vestibular impairment at follow up.<br>No data on numbers using anti-virals<br>No information on cCMV test or timing<br>Hearing test conducted at birth | Vestibular function at 4 years | Hearing loss at birth | 169 | *7* | *13* | *13* | *136* | 35 | 91 | 35 | 91 | - |
| Foulon et al. 2019[88] | 9 symptomatic and 146 asymptomatic<br>20 with mild or worse SNHL at follow up | Hearing loss (mild or worse) at median 31 months | Trimester of infection: positive was first trimester | 72 | 5 | 4 | 12 | 51 | *56* | *81* | *29* | *93* | - |
| | | | Trimester of infection: positive was first or second trimester | 72 | 8 | 1 | 42 | 21 | *89* | *33* | *16* | *95* | - |

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| | Number on antivirals not provided<br>Method of cCMV diagnosis not described.<br>Timing of US/MRI not reported | | US: 'abnormal' was: intracranial calcifications, migrational abnormalities, white matter disease, periventricular cysts, cerebral atrophy, ventriculomegaly, ventricular adhesions, and lenticulostriate vasculopathy. | 137 | 8 | 9 | 9 | 111 | *47* | *93* | *47* | *93* | -- |
| | | | MRI: 'abnormal' was: intracranial calcifications, migrational abnormalities, white matter disease, periventricular cysts, cerebral atrophy, ventriculomegaly, ventricular adhesions, and lenticulostriate vasculopathy. | 28 | 4 | 3 | 7 | 14 | *57* | *67* | *36* | *82* | - |

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| Fourgeaud et al. 2024[89] | Prediction tool developed in a cohort of 227 neonates with cCMV, but the accuracy of the developed tool was tested in a separate validation cohort of n=102.<br>24 symptomatic and 78 asymptomatic in validation cohort<br>19 in validation cohort had sequelae during follow up<br>Number on antivirals from validation cohort not reported.<br>Newborns <1 month of age with cCMV diagnosed in the first 10 days of life were recruited during routine care diagnosis.<br>Imaging and tests appear to have been assessed at birth. | SNHL (bilateral or unilateral) OR psychomotor sequelae (motor delay, psychomotor delay, autism, nystagmus) at 24 months | Risk factors for SNHL / psychomotor problems: Hearing, US, platelets). This DA analyses the detection of NO sequelae, so the index test is also detecting normality; thus the threshold is no hearing loss at birth, normal cerebral ultrasound, and normal platelet count | 102 | - | - | - | - | 92 | 83 | 63 | 97 | 0.94 |
| Giannattasio et al. 2018[90] | 112 symptomatic and 58 asymptomatic, but only symptomatic included in the diagnostic accuracy analysis<br>Unclear how many had impaired neurologic outcomes. | An impaired neurologic outcome was defined in the presence of 1 or more of the following problems: developmental/cognitive impairment, motor | Noyola Brain MRI: Noyola score of 1 or more. | 102 | - | - | - | - | 43 | 89 | - | - | - |
| | | | Noyola US: threshold was a Noyola score of 1 or more. | 105 | - | - | - | - | 76 | 43 | - | - | - |
| | | | Noyola CT: threshold was a Noyola score of 1 or more | 101 | - | - | - | - | 67 | 86 | - | - | - |
| | | | Alorcon Brain MRI: 'new' Alorcon** score of 1 or more | 102 | - | - | - | - | 87 | 51 | 40 | 91 | - |
| | | | Alorcon US: Threshold was an Alorcon score of 1 or more. | 105 | - | - | - | - | 89 | 40 | 34 | 90 | - |

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| | 19 ganciclovir, 28 valganciclovir and 29 with both treatments<br>Diagnosis of cCMV infection was based on virus detection by polymerase chain reaction assay in urine samples collected within 2 weeks of birth.<br>Timing of neuroimaging unclear. | delay requiring rehabilitation, epilepsy and behavioral/ emotional problems. Follow up 1-6 years. | Alorcon CT: Threshold was an Alorcon score of 1 or more | 101 | - | - | - | - | 89 | 63 | 48 | 95 | - |
| Kwak et al. 2018[91] | 31 symptomatic only.<br>12 developed epilepsy during follow up.<br>17 using antivirals.<br>Diagnosis confirmed by urine CMV culture or DNA polymerase chain reaction within 4 weeks after birth.<br>MRI at mean of 33 days (but up to 375 days) | Epilepsy at mean 3.2 years | Brain MRI. One point given to each of the following findings: ventriculomegaly, white matter abnormality, polymicrogyria, and calcification. Threshold for a positive test was >=2.5 MRI points | 31 | *11* | *1* | *6* | *13* | 92 | 68 | *65* | *93* | 0.87 |
| Lucignani et al. 2021[92] | 27 symptomatic and 17 asymptomatic<br>30 with adverse neurological outcomes<br>22 received antivirals<br>Congenital CMV infection was defined by PCR urine/blood and IgM CMV in the serum in first 2 weeks of life in neonates born to CMV infected mothers.<br>Brain MRI at mean of 1.2 years. | Development of adverse neurological outcomes [including hearing loss, severe neurological delay or CP ] by end of follow up at minimum of 2 years | Brain MRI. Scores assigned based on presence of lesions involving 3 different locations (cerebral cortex, white matter, cerebellum), presence of calcifications and ventricular dilatation, and/or presence of ventriculomegaly. A positive test is >0 points | 44 | *28* | *2* | *7* | *7* | *93* | *50* | *80* | *78* | - |
| | | | Brain MRI. 'New score', based on weight at birth, new maternal infection or recurrent infection, trimester of infection and symptoms at birth. Threshold for positive test >=2. | 44 | *21* | *9* | *3* | *11* | 70 | 80 | *88* | *55* | - |

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| Nishida et al. 2020[93] | 19 symptomatic, 23 asymptomatic<br>19 with neurodevelopmental impairment outcomes<br>20 with antiviral therapy<br>Diagnosis of cCMV in urine within 3 weeks of birth.<br>MRI within 3 months of birth (median 24 days) | Neurodevelopmental outcomes(Neurodevelopmental impairment (NDI) was defined as a developmental quotient <80, hearing dysfunction, blindness, or epilepsy requiring anti-epileptic drugs at 18 months | MRI – any of the 3 brain MRI abnormalities (V, PVC, WMA) | 38 | *17* | *2* | *9* | *10* | *89* | 53 | *65* | *83* | - |
| | | | MRI – ventriculomegaly (V) | 38 | *16* | *3* | *3* | *16* | 84 | 84 | *84* | *84* | - |
| | | | MRI – periventricular cyst (PVC) | 38 | *11* | *8* | *1* | *18* | 58 | 95 | *92* | *69* | - |
| | | | MRI – white matter abnormality (WMA) | 38 | *16* | *3* | *8* | *11* | 84 | 58 | *67* | *79* | - |
| | | | MRI – V and/or PVC | 38 | *17* | *2* | *3* | *16* | *89* | 84 | *85* | *89* | - |
| | | | MRI - V and/or WMA | 38 | *17* | *2* | *9* | *10* | 89 | 53 | *65* | *83* | - |
| | | | MRI – PVC and/or WMA | 38 | *17* | *2* | *8* | *11* | 89 | 58 | *68* | *85* | - |
| | | | MRI - >=1 of the MRI abnormalities | 38 | *17* | *2* | *9* | *10* | 89 | 53 | *65* | *83* | - |
| | | | MRI - >=2 of the MRI abnormalities | 38 | *17* | *2* | *2* | *17* | 89 | 89 | *89* | *89* | - |
| | | | Clinical symptoms (CS) - hepatosplenomegaly, liver dysfunction, thrombocytopenia, eye complications, and hearing dysfunction | 38 | *16* | *3* | *5* | *14* | 84 | 74 | *76* | *82* | - |
| | | | CS and/or V | 38 | *18* | *1* | *6* | *13* | 95 | 68 | *75* | *93* | - |
| | | | CS and/or PVC | 38 | *16* | *3* | *5* | *14* | 84 | 74 | *76* | *82* | - |
| | | | CS and/or WMA | 38 | *18* | *1* | *10* | *9* | 95 | 47 | *64* | *90* | - |
| | | | CS and/or V and/or PVC and/or WMA | 38 | *18* | *1* | *1* | *18* | 95 | 47 | *95* | *95* | - |
| | | | >=2 of CS and/or MRI abnormalities | 38 | *17* | *2* | *5* | *14* | 89 | 74 | *77* | *88* | - |
| | | | >=3 of CS and/or MRI abnormalities | 38 | *15* | *4* | *1* | *18* | 79 | 95 | *94* | *82* | - |

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| Ouellette et al. 2020[162] | 49 symptomatic and 31 asymptomatic<br>24 with vestibular impairment at follow up<br>19 on antivirals<br>cCMV infection was defined as a positive culture or PCR test of urine (88%) and/or a positive PCR from saliva (12%) samples obtained in the first 21 days of age. Positive saliva samples were all confirmed by CMV urine culture or PCR<br>Biomarkers appear to be collected soon after birth, but unclear | Late-onset SNHL at 3 years | Biomarkers: 16-gene classifier | 52 | - | - | - | - | 96 | 89 | - | - | 0.98 |
| Vande Walle et al. 2024[94] | No data on number symptomatic.<br>18 known to have developed cognitive impairment by follow up.<br>35 known to have developed a motor impairment by follow up.<br>Unclear how many with hearing impairment at follow up.<br>No report of number on antivirals<br>Viral isolation and/or PCR on urine or saliva within the first 3 weeks. Retrospective diagnosis (after age of 21 days) made by PCR on DBS. | Cognitive development: assessed using the Bayley Scales of Infant and Toddler Development. Severe impairment below 50. Follow up median 12 months. | Apparent Diffusion Coefficient (ADC) values of the white matter in MRI at threshold of >= 0.0671 | *242* | - | - | - | - | 83 | 58 | - | - | 0.74 |
| | | Motor development. assessed using AIMS. AIMS below P10 was considered abnormal. Follow up median 12 months. | Apparent Diffusion Coefficient (ADC) values of the white matter in MRI at threshold of >= 0.159 | *239* | - | - | - | - | 57 | 72 | - | - | 0.64 |

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| | MRI evaluated at a median 21 days. | Hearing evaluation using ABR. ABR thresholds≤40 dB nHL were considered normal. Follow up median 12 months | Apparent Diffusion Coefficient (ADC) values of the white matter in MRI at threshold of >= 0.0497 | *250* | - | - | - | - | 86 | 62 | - | - | 0.79 |
| Yamaguchi et al. 2022[154] | 21 symptomatic and 18 asymptomatic<br>7 with developmental delay at 36 months.<br>Number using antivirals not reported<br>All patients were diagnosed with cCMV by qPCR of their blood or urine within 21 days of age.<br>Viral loads measured at diagnosis (i.e. at or before 21 days) | Developmental delay at 36 months | CMV DNA load using droplet digital PCR >=2950 copies/ml | 26 | 4 | 3 | 3 | 16 | 57 | 84 | 57 | 84 | 0.74 |

Data in italics have been calculated or inferred by the reviewer from data provided in the paper.

Abbreviations: ABR, Auditory Brainstem Response; ADC, apparent diffusion co-efficient; AIMS, Alberta Infant Motor Scale; AUC, Area under the curve; cCMV, congenital cytomegalovirus; cMRI, cranial MRI; CMV, Cytomegalovirus; CP, cerebral palsy; CS, clinical symptoms; CSF, cerebrospinal fluid; CT, computed tomography; cUS, cranial US; dB, decibels; DBS, dried blood spot; DNA, deoxyribonucleic acid; FN, false negatives; FP, false positives; Ig, immunoglobulin; MRI, magnetic resonance imaging; NDI, neurodevelopmental impairment; NPV, negative predictive value; PCR, polymerase chain reaction; PPV, positive predictive value; PVC, periventricular cyst; sen, sensitivity; SNHL, sensorineural hearing loss; spec, specificity; TN, true negatives; TP, true positive; TPWMA, Temporal pole white matter abnormalities; US, ultrasound; V, ventriculomegaly; WM, white matter; WMA, white matter abnormalities.

*Table 28: Association studies relevant to criterion 7*

| Study details | Test/characteristic assessed | Population | Outcome (and timeframe) | Results/conclusions and comments |
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| **Neuroimaging (n=3 studies)** | | | | |
| Giannattasio et al., 2017[95]<br>Prospective cohort study<br>Italy | Head ultrasound (lenticulostriated vasculopathy; LSV) within the first month of life | Infants with cCMV<br>N=161 (105 symptomatic) | Neurodevelopment and hearing outcomes<br>Follow-up: mean 4.5 years | Head ultrasound (HUS) was abnormal in 77/105 (73%) symptomatic infants and 18/56 (32%) asymptomatic infants. Of those with abnormal HUS (n=95), neurodevelopmental impairment was observed in 25/64 (39%) patients with LSV and in 17/31 (55%) patients without LSV (p>0.05). Hearing impairment was observed in 24/64 (38%) patients with LSV and in 14/31 (45%) patients without LSV (p>0.05); indicating that presence of LSV (alone or with other findings) is not a risk factor for unfavourable outcome. There was also no correlation between presence of LSV and outcomes when restricting the analysis to symptomatic patients, or to asymptomatic patients.<br>The authors concluded that "Although LSV is a common HUS finding in infants with cCMV infection, its presence is not predictive of an adverse outcome. Our data suggest that HUS as a single neuroimaging investigation is unreliable in selecting candidates for antiviral therapy, mainly in the presence of LSV as isolated finding".<br>This conclusion appears appropriate and is based on a reasonable size cohort of infants with cCMV and abnormal HUS. The study methods and length of follow-up were acceptable. |
| Vande Walle et al., 2023[100]<br>Prospective cohort study<br>Belgium | MRI performed within the first 45 days of life (median age at MRI was 21 days) | Newborns with cCMV<br>N=211 (13/207 patients [6.3%] were clinically symptomatic) | Hearing and neuromotor evaluation<br>Follow-up: median 12 months | White matter was normal in 121 patients, doubtful in 62 and abnormal in 28. Neonatal hearing loss occurred in 4/27 (14.8%) patients with abnormal, 1/118 (0.8%) patients with normal and 1/62 (1.6%) patients with doubtful white matter (p<0.01). Nine patients had late-onset hearing loss; all of whom had normal white matter on neonatal brain MRI. Impaired cognitive development was seen in 3/27 (11.1%) patients with abnormal, 3/114 (2.6%) patients with normal and 1/59 (1.7%) patients with doubtful white matter (no significant difference). Alberta Infant Motor Score (AIMS) was below P75 in 21/26 (80.8%) patients with abnormal, 73/114 (64%) patients with normal and 36/57 (63.2%) patients with doubtful white matter. In a subgroup of 77 patients with ≥18 months follow-up, AIMS score was below P75 in 10/13 (76.9%) patients with abnormal, 13/34 (38.2%) patients with normal and 7/20 (35%) patients with doubtful white matter (p<0.05). |

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| | | | | The authors concluded that “Abnormal white matter was associated with neonatal hearing loss and mild, lower motor scores. A tendency towards impaired cognitive development was seen. Patients with doubtful white matter did not show worse clinical outcome”.<br><br>This conclusion appears appropriate and is based on a relatively large cohort of infants with cCMV, although only 28 infants had white matter abnormalities. The length of follow-up was relatively short, with only 77 patients having follow-up ≥18 months (of which, only 13 had white matter abnormalities).<br><br>This study is included in the Vande Walle 2024 systematic review of MRI. |
| Vila-Bedmar et al., 2024[96]<br><br>Prospective cohort study<br><br>Spain | Ultrasound (US) and MRI performed within the first 2 weeks of life | Newborns with cCMV diagnosed through a screening programme<br><br>N=15 (2 symptomatic) | SNHL, neuro-developmental disorders, chorioretinitis and epilepsy<br><br>Follow-up: median 68 months | Brain abnormalities were found on 4/15 US and 10/15 MRI; white matter abnormalities (WMA) were the most common finding on MRI. Eight children were treated with antivirals. Two children were diagnosed with psychomotor delay and 2 with attention-deficit hyperactivity disorder; all of them presented brain abnormalities on MRI, especially severe and extensive WMA, that were not detected by US (2 children were symptomatic at birth). All 5 children with normal MRI developed normally without long-term sequelae.<br><br>The authors concluded that “Children with isolated WMA without other clinical symptoms showed overall good outcomes, although more studies with a larger sample and a control group should be performed. Interobserver agreement about the presence of abnormalities in MRI was good”.<br><br>The methods and length of follow-up appear appropriate. However, this was a very small study, therefore, the authors’ conclusion that further research is required appears appropriate. |
| **Antenatal characteristics (n=10 studies)** | | | | |
| Amir et al., 2016[104]<br><br>Retrospective cohort study<br><br>Israel | First trimester infection vs second trimester infection (diagnosed by positive amniotic fluid findings) | Infants infected with CMV in 1st or 2nd trimester with normal fetal imaging<br><br>N=98 (60 symptomatic) | Late-onset SNHL (and motor and cognitive delay)<br><br>Follow-up: median 32 months (27 months for infants infected during the first trimester and 45 months for those infected in the second trimester) | Fifty-two infants were treated with an antiviral agent, the main indication for treatment was abnormal cranial ultrasound finding. Fifty-two infants were infected in the first trimester and 46 in the second trimester. Moderate and severe hearing losses were associated more often with first-trimester infection than second-trimester infection (p=0.053); 6/104 ears vs 0/92 ears at the time of the last test. 95/104 (91.4%) infants had normal hearing in the first trimester group vs 91/92 (98.9%) in the second trimester group.<br><br>The authors concluded that “First trimester infection is associated with a trend towards more severe hearing loss than second trimester infection. |

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| | | | | Overall, the outcome of these infants is good, with a low rate of sequelae on short-term follow-up and intermediate-term follow-up".<br><br>This conclusion appears appropriate and is based on a reasonable size cohort of infants with cCMV and acceptable methods and length of follow-up. |
| Elkan Miller et al., 2021[106]<br><br>Prospective cohort study<br><br>Israel | Second trimester infection vs third trimester infection (mostly diagnosed by amniocentesis, according to patient preference) | Newborns with cCMV<br><br>N=127 (proportion symptomatic at birth not reported) | Hearing and neurodevelopmental outcome<br><br>Follow-up: median 4 years | Maternal infection was during the second trimester in 100/127 infants and third trimester in 27/127 infants. 7/100 (7%) infants had long-term sequelae (hearing loss or neurodevelopmental impairment) following second trimester infection vs 1/27 (3.7%) following third trimester infection. Twenty-one (21%) second trimester infection infants received antiviral therapy vs 3 (11%) third trimester infection infants.<br><br>The authors concluded that "Second trimester infection is associated with a slight risk of developing mild childhood sequelae, mostly partial unilateral hearing loss, which may develop late in childhood."<br><br>This conclusion appears appropriate and is based on a relatively large cohort of infants with second trimester infection. The study methods and length of follow-up were acceptable. |
| Faure-Bardon et al., 2019[107]<br><br>Prospective cohort study<br><br>France | Trimester of infection (based upon serial measurements of immunoglobulin (Ig) M and IgG and on IgG avidity in sera collected at each trimester) | Newborns with cCMV<br><br>N=234; 19 lost to follow-up (70 symptomatic) | SNHL and neurological sequelae<br><br>Follow-up: median 24 months | 126 newborns were infected in the first trimester, 72 in the second trimester and 36 in the third trimester. SNHL and/or neurological sequelae were only seen in children infected following a primary infection in the first trimester of pregnancy (32.4% vs 0% infants infected in the second or third trimester; $p<0.0001$).<br><br>The authors concluded that "These results suggest that a CMV infection can be severe only when the virus hits the fetus in the embryonic or early fetal period. Recent guidelines recommend auditory follow-ups for at least 5 years for all infected children. This raises parental anxiety and generates significant costs. We suggest that auditory and specialized neurologic follow-ups may be recommended only in cases of a maternal infection in the first trimester".<br><br>This conclusion appears appropriate and is based on a relatively large cohort of infants with first or second trimester infection (only 36 infants had third trimester infection). The study methods and length of follow-up were acceptable.<br><br>This study is included in the Chatzakis 2020 systematic review of time of maternal infection. |

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| Lipitz et al., 2013[108]<br>Prospective cohort study<br>Israel | First trimester infection vs second trimester infection (based upon seroconversion or presence of IgG and IgM antibodies associated with low IgG avidity) | cCMV (diagnosed as fetus)<br>N=137 (proportion symptomatic at birth not reported) | Hearing loss and neurodevelopmental delay<br>Follow-up: median 27 months of age | Maternal infection was during the first trimester in 66 infants and second trimester in 71 infants. Mothers with first-trimester infection were significantly more likely to have infants with auditory or neurodevelopmental sequelae than patients with second-trimester infection (13/66 infants [19.7%] vs 4/71 infants [5.6%]; p=0.01).<br>The authors concluded that "The risk of sequelae is higher following first- than second-trimester CMV infection".<br>This conclusion appears appropriate and is based on a relatively large cohort of infants. The study methods and length of follow-up were acceptable.<br>This study is included in the Chatzakis 2020 systematic review of time of maternal infection. |
| Massoud et al., 2023[109]<br>Retrospective cohort study<br>France | First trimester infection vs second trimester infection (mostly determined using maternal CMV IgG and IgM and IgG avidity test) | cCMV (diagnosed as fetus)<br>N=27 surviving to infancy (out of the original sample of 49, 22 were terminated or had an intrauterine death) (proportion symptomatic at birth not reported) | Ophthalmological or sensorineural deficit, motor delay and/or cognitive impairment<br>Follow-up: mean 51 months | Maternal infection was during the first trimester in 15 infants and second trimester in 12 infants. 9/15 first-trimester infection infants had a normal outcome, 5/15 had mild sequelae and 1/15 had severe sequelae. 11/12 second-trimester infection infants had a normal outcome and 1/12 had mild sequelae. Mild sequelae were mostly hearing loss.<br>The authors summarised that "Fetuses infected with cytomegalovirus during the first trimester of pregnancy have significant risks of sequelae, which may persist into the second trimester, particularly for sensorineural disorders".<br>This was a small study investigating both prenatal imaging and trimester of infection in pregnant women with CMV infection. Most of the results reported related to prenatal imaging, with few results reported relating to trimester of infection. |
| Nigro et al., 2020[110]<br>Prospective cohort study<br>Italy | Timing of maternal seroconversion (first trimester infection confirmed by positive amniotic fluid findings) | Infants of pregnant women diagnosed with primary CMV infection<br>N=108 with cCMV (106 with long-term follow-up; proportion symptomatic at birth not reported) | Hearing loss, psychomotor retardation, cerebral palsies, visual impairment<br>Follow-up: mean 4 years | Twenty-one infants had abnormalities and 85 were categorised as 'normal' at long-term follow-up. In a multivariate logistic regression, odds of later abnormalities were lower if maternal infection occurred in later gestation (mean 16.2 weeks) compared to earlier gestation (mean 10.1 weeks) [adjusted odds ratio 0.9 (95% CI: 0.83 to 0.98); p=0.017].<br>The authors concluded that "Maternal viremia predicts fetal infection and neonatal outcome. This may help patient counselling. High-dose HIG may prevent fetal infection and disease, and is associated with the resolution of DNAemia". |

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| | | | | This study investigated several factors predictive of infant outcome, including HIG administration, fetal ultrasound and timing of maternal infection; few results were reported relating to timing of maternal infection. |
| Giannattasio et al., 2017[123]<br><br>Prospective cohort study<br><br>Italy | Primary maternal infection vs non-primary maternal infection | Children with cCMV<br><br>N=158 (88 symptomatic) | Hearing and neurodevelopmental assessment<br><br>Follow-up: Beyond 3 years of age | Ninety-three infants were born to mothers with primary CMV infection and 65 to mothers with non-primary infection. Fifty-one symptomatic infants received antiviral treatment; 25 in the primary infection group and 26 in the non-primary infection group. Frequency of impaired neurodevelopmental outcome (23.7% vs 24.6%) and hearing loss (25.8% vs 26.2%) did not differ between the primary infection and non-primary infection groups.<br><br>The authors concluded that "Neurodevelopmental and hearing sequelae are not affected by the type of maternal CMV infection. Preventing strategies should be developed for both primary and non-primary infections".<br><br>This conclusion appears appropriate and is based on a relatively large cohort of infants. The study methods and length of follow-up were acceptable.<br><br>This study is included in the Maltezou 2020 systematic review of type of maternal infection and the Smyrli 2024 systematic review of impact of symptoms. |
| Coscia et al., 2020[112]<br><br>Retrospective cohort study<br><br>Italy | Trimester of infection and primary vs non-primary maternal infection | Newborns with cCMV at Neonatal Care Unit<br><br>N=91 (results presented for infants where timing (n=52) and type (n=49) of maternal infection could be determined) | Hearing and neurodevelopment<br><br>Follow-up: 12 months (asymptomatic infants) and 24 months (symptomatic infants) | Data regarding the trimester of infection were missing for 39 patients. Determined cases accounted for 40% patients infected in the first trimester, 29% in the second trimester and 16% in the third. Data regarding type of infection were missing for 42 patients. Determined cases included 86% patients with primary infection and 14% with non-primary infection. A higher proportion of first-trimester infection infants had long-term sequelae, however, the difference between groups was only statistically significant for 'need for cochlear implant'; 28% vs 0% (p=0.003). A higher proportion of infants born to mothers with non-primary infection had long-term sequelae, however, the difference between groups was only statistically significant for 'need for cochlear implant'; 43% vs 10% (p=0.05).<br><br>The authors concluded that "We underline the possibility of re-infection in previously immunized mothers (non-primary infection) with unfavorable neonatal and long-term outcomes".<br><br>Data on timing and type of maternal infection were missing for a large proportion of patients; therefore, the results are based on a small number of infants with relatively short-term follow-up. |

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| Puhakka et al., 2017[111]<br>Retrospective cohort study<br>Finland | Timing of infection and primary vs non-primary maternal infection | Infants with symptomatic cCMV<br>N=26 (all symptomatic) | Hearing, vision and neurology<br>Follow-up: mean 21.7 months (vision), 44.6 months (hearing), 47.2 months (neurology) | Fourteen infants had non-primary maternal infection, 7 had primary infection in the first trimester or near conception and 5 during the second or third trimester. Long-term sequelae (SNHL, neurologic abnormality and/or visual impairment) occurred in 15 infants: 6/7 after primary infection in the first trimester, 0/5 after primary infection in the second or third trimester and 9/14 after non-primary infection.<br>The authors concluded that "In this register-based cohort, non-primary infections caused the majority of symptomatic congenital CMV infections, and resulted in significant morbidity".<br>This was a very small study with missing data on long-term outcomes for some patients (particularly hearing and ophthalmologic examinations). Therefore, the results should be interpreted with caution.<br>This study is included in the Chatzakis 2020 systematic review of time of maternal infection and the Maltezou 2020 systematic review of type of maternal infection. |
| Scaramuzzino et al., 2022[113]<br>Retrospective cohort study<br>Italy | Primary maternal infection vs secondary maternal infection and trimester of infection | Babies with symptomatic cCMV<br>N=53 (all symptomatic) | SNHL and neurodevelopmental impairment<br>Follow-up: Mean 37.2 months (primary infection) and 55 months (secondary infection) | Forty babies were born to mothers with primary infection and 13 to mothers with secondary infection. Of those with primary infection, 18 were infected during the first trimester, 13 were infected during the second trimester and 8 were infected during the third trimester (1 unknown timing of infection). Treatment was given to 57.5% primary infection babies and 84.6% secondary infection babies. There was a higher rate of long-term sequelae (tetraparesis, epilepsy, motor and speech delay, and unilateral SNHL) in children of mothers with secondary infection, which was statistically significant for tetraparesis (p=0.002) and unilateral SNHL (p=0.009). Only children born to mothers with primary infection presented bilateral SNHL (6 vs 0; p=not significant). 66.7% first-trimester infected babies had neurodevelopmental and auditory sequelae vs 23% second-trimester infected and 12.5% third-trimester infected babies.<br>The authors concluded that "Our data suggest that the risk of symptomatic cCMV and long-term sequelae is similar in children born to mother with primary and secondary CMV infection; it is important to pay appropriate attention to seropositive mothers in order to prevent reinfection and to detect and possibly treat infected babies".<br>The methods and length of follow-up appear appropriate. However, this was a small study and the number of children suffering some of the long-term |

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| | | | | sequelae reported (particularly tetraparesis, epilepsy and cognitive delay) was very small. |
| **Symptoms/characteristics at birth (n=23 studies)** | | | | |
| Airlangga et al., 2024[128]<br>Prospective cohort study<br>Indonesia | Symptomatic vs asymptomatic cCMV | Newborns with cCMV<br>N=26 (9 symptomatic) | Hearing function and central auditory neuroanatomy evaluation<br>Follow-up: 3 months and 6 months | The proportion of children with global developmental delay was significantly higher in infants with symptomatic cCMV infection (88.9% vs 47.1%; p<0.001). The proportion of children with abnormal hearing function at 3 months old was significantly higher in infants with symptomatic cCMV infection (69.6% vs 30.4%; p<0.001).<br>The authors concluded that "SNHL along with its fluctuation and progression are common in cCMV-infected infants. cCMV infection may induce structural changes in the central auditory pathway".<br>This was a very small study with short-term follow-up. |
| Auriti et al., 2022[129]<br>Retrospective cohort study<br>Italy | Symptomatic vs asymptomatic cCMV | Infants with acquired infection (CMV, toxoplasma or syphilis)<br>N=84 with cCMV (29 symptomatic) | Cognitive, motor, audiological, visual and language outcomes<br>Follow-up: At least 24 months | Thirty-one (36.9%) newborns received antiviral treatment. At 1 year of age, 12/29 (41.4%) infants who were symptomatic at birth had 1 sequela and 4/29 (13.8%) had 2 or more sequelae, compared with 6/55 (10.9%) and 0/55 (0%) in asymptomatic infants, respectively. Of 69 infants with longer term follow-up (2-4 years of age), 14/27 (51.9%) symptomatic infants had 1 sequelae and 5/27 (18.5%) had 2 or more sequelae, compared with 8/42 (19.0%) and 0/42 (0%) asymptomatic infants, respectively.<br>The authors concluded that "Infected babies symptomatic at birth have a worse prognosis than asymptomatic ones. Long-term sequelae may occur in infected children asymptomatic at birth after the first year of life. Multidisciplinary follow-up until 4-6 years of age should be performed in all infected children, regardless of the presence of symptoms at birth".<br>The methods and length of follow-up appear appropriate. However, this study was small, with only 29 symptomatic infants. |
| Bartlett et al., 2018[147]<br>Retrospective cohort study<br>Australia | Symptomatic vs asymptomatic cCMV | Infants with cCMV<br>N=302 (214 symptomatic) | Hearing loss and developmental delay<br>Follow-up: Not reported | Fifty-eight (19.2%) infants received antiviral treatment. Of 257 cCMV cases born in the era of universal neonatal hearing screening, hearing loss was reported in 75/178 (42.1%) symptomatic (49/75 cases reported ≤30 days of age, 17/75 reported >30 days of age and 9/75 had uncertain timing) and 21/79 (26.6%) asymptomatic cases. Developmental delay was reported in 30/178 (16.9%) symptomatic (6/30 cases reported ≤30 days of age, 18/30 |

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| | | | | reported >30 days of age and 5/30 had uncertain timing) and 1/79 (1.3%) asymptomatic cases.<br><br>The authors concluded that “There appears to be under-reporting and under-recognition of congenital CMV despite increasing use of antiviral therapy. Universal newborn CMV screening should be considered to facilitate follow-up of affected children and targeted linkage into hearing and developmental services, and to provide population-level infant CMV epidemiology to support research and evaluation of antiviral and adjunctive therapies”.<br><br>Whilst this appears to be a large, well conducted study, it is unclear how long patients were followed up for and the conclusion does not relate to the association between symptomatic cCMV infection and long-term sequelae.<br><br>This study is included in the Smyrli 2024 systematic review of impact of symptoms. |
| Capretti et al., 2021[130]<br><br>Prospective cohort study<br><br>Italy | Symptomatic vs asymptomatic cCMV | Newborns with cCMV<br><br>N=30 (10 symptomatic) | SNHL and neurodevelopmental delay<br><br>Follow-up: median 30 months | All 10 symptomatic infants received antiviral therapy. 6/10 symptomatic infants had SNHL and 1/10 had neurodevelopmental delay, whereas none of the 20 asymptomatic infants had SNHL or neurodevelopmental delay.<br><br>The authors concluded that “A detectable CMV-specific CD8 + T-cell response, evaluated using the QuantiFERON-CMV assay, correlates with the lack of CMV-related symptoms and the control of CMV DNAemia”.<br><br>This was a very small study investigating immune monitoring using QuantiFERON-CMV assay; few results were reported relating to the association between symptomatic cCMV infection and long-term sequelae. |
| Dhondt et al., 2021[131]<br><br>Prospective cohort study<br><br>Belgium | Symptomatic vs asymptomatic cCMV | cCMV infected children<br><br>N=93 (41 symptomatic) | SNHL and vestibular function<br><br>Follow-up: average 10.2 months | Thirty-two symptomatic infants received antiviral therapy. Delayed onset SNHL occurred in 3/52 asymptomatic and 2/41 symptomatic patients (12 symptomatic patients had hearing loss at birth). The median age of diagnosis of delayed onset hearing loss was 13 months (range 2-20 months).<br><br>The authors concluded that “cCMV can impair not only the auditory but also the vestibular function. Similar to the hearing loss, vestibular loss in cCMV can be highly variable. It can be unilateral or bilateral, limited or extensive, stable or progressive, and early or delayed in onset. As the vestibular function can deteriorate over time and even normal-hearing subjects can be affected, vestibular evaluation should be part of the standard otolaryngology follow-up in all children with cCMV”. |

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| | | | | Whilst this appears to be a reasonable sized study, the length of follow-up was relatively short and the conclusions do not relate to the association between symptomatic cCMV infection and long-term sequelae. All symptomatic infants received antiviral therapy, whilst none of the asymptomatic infants did, which could confound the finding relating to delayed onset SNHL |
| Goderis et al., 2016[78]<br><br>Prospective cohort study (Flemish CMV registry)<br><br>Belgium | Symptomatic vs asymptomatic cCMV | Children with cCMV<br><br>N=379 (123 symptomatic) | Hearing loss<br><br>Follow-up: not reported (mean age at diagnosis of delayed onset hearing loss was 18 months) | Fifty-six symptomatic infants received antiviral treatment. Delayed onset hearing loss occurred in 10.6% symptomatic patients and 7.8% asymptomatic patients; 63% symptomatic patients and 8% asymptomatic patients had hearing loss overall. Almost half of the symptomatic patients who developed delayed onset hearing loss had preexisting contralateral hearing loss. Mild hearing loss was more frequent in asymptomatic (52% ears) vs symptomatic (23.5% ears) infants, compared with moderate, severe or profound hearing loss.<br><br>The authors concluded that "Symptomatic and asymptomatic cCMV infections are a major cause of hearing loss in childhood. Reliable estimates of the long-term outcome of cCMV infection are mandatory to increase vigilance, especially among pregnant women and to draw attention to preventive measures, vaccine development, and prenatal and postnatal therapy. Universal screening of newborns for cCMV infection should be initiated and combined with longitudinal audiometric follow-up".<br><br>This study included a relatively large cohort of infants with cCMV, the methods and length of follow-up appear to have been acceptable. The conclusion that symptomatic and asymptomatic cCMV infections are a major cause of hearing loss appears appropriate. |
| Jin et al., 2019[133]<br><br>Retrospective subanalysis of a prospective cohort study<br><br>USA | Symptomatic vs asymptomatic cCMV | Infants with cCMV<br><br>N=186 (77 symptomatic)<br><br>Follow-up: mean 11-12 years | Visual impairment and SNHL | Eleven symptomatic patients developed cortical visual impairment (CVI) (11/77; 14.3%), compared to no asymptomatic patients (0/109; 0%). Comparisons were made between these 11 patients and the remaining 66 symptomatic patients who did not develop CVI; All 11 patients with CVI also had SNHL, compared with 69.7% patients without CVI. Microcephaly, white matter abnormality, seizure at birth, intracranial calcifications, encephalomalacia and dilatation of ventricles occurred more frequently in patients with CVI than without. Five predictive models based on 11 variables were created using logistic regression to predict which symptomatic patients would have developed CVI. Model 5 showed the variables of microcephaly, seizure at birth, optic atrophy, chorioretinitis/retinal scars, strabismus, intracranial calcifications, neonatal hearing loss and severe visual impairment |

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| | | | | were predictors of CVI; this model correctly identified 10/11 cases of CVI, giving the lowest false-positive rate (23.1%), overall accuracy 94.8%.<br><br>The authors concluded that "CVI may result from symptomatic congenital CMV infection. The relationship of CVI and its risk factors in patients with CMV suggests the potential to predict the development of CVI through predictive modelling in future research. Early screening of CVI in children born with symptomatic congenital CMV can facilitate educational, social, and developmental interventions".<br><br>Whilst this was a reasonable sized study with long-term follow-up, it focussed on comparing symptomatic cCMV patients with (n=11) and without (n=66) CVI. The models proposed would need to be prospectively validated in a much larger study. |
| Korndewal et al., 2017[146]<br><br>Retrospective cohort study<br><br>Netherlands | Symptomatic vs asymptomatic cCMV | Infants with cCMV diagnosed retrospectively using dried blood spot PCR and healthy controls<br><br>N=133 with cCMV (26 symptomatic) | SNHL, visual impairment and neurological impairment<br><br>Follow-up: up to 6 years of age | Long-term impairment, diagnosed in the first 6 years of life, was more frequent in symptomatic than asymptomatic cCMV infection: multiple domains 19.2% vs 8.4%; SNHL 7.7% vs 2.8%; epilepsy 7.7% vs 0%; autism spectrum disorder 7.7% vs 1.9%; cognitive impairment 15.4% vs 3.7%; fine motor impairment 19.2% vs 7.5%; gross motor impairment 15.4% vs 8.4%; language disorder 23.1% vs 7.5% (other results presented).<br><br>This study concluded that "Children with cCMV were twice as likely to have long-term impairment up to the age of 6 years, especially developmental delays and sensorineural hearing loss, than cCMV-negative comparison children, with a risk difference of 12.8%. These insights into the risk of cCMV-associated impairment can help optimize care and stimulate preventive measures".<br><br>This was a large study comparing long-term impairment between children with cCMV vs those without, as well as those with symptomatic cCMV vs asymptomatic cCMV. The authors' conclusions appear appropriate. However, only 26 children had symptomatic cCMV, therefore, the number of children in the comparison of interest to this review was small.<br><br>This study is included in the Smyrli 2024 systematic review of impact of symptoms. |
| Koyano et al., 2018[148] | Symptomatic vs asymptomatic cCMV | Infants with cCMV<br><br>N=60 (17 symptomatic) | Hearing, development and 'other' (including death, epilepsy, autism spectrum disorder and | Ten of the 17 symptomatic infants received antiviral treatment. All 7 untreated symptomatic infants had long-term sequelae (100%), including hearing loss (4), developmental delay (3), death (1), epilepsy (2) and autism spectrum disorder (1). Seven of the 10 treated symptomatic infants had long- |

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| Prospective cohort study<br>Japan | | | attention deficit-hyperactivity disorder)<br>Follow-up: At least 2 years | term sequelae (70%), including hearing loss (7), developmental delay (3) and epilepsy (2). Five of the 43 asymptomatic infants had long-term sequelae (12%), including hearing loss (1), speech delay (2), autism spectrum disorder (1) and attention deficit-hyperactivity disorder (1).<br>The authors concluded that "The rate of late-onset sequelae observed in Japan is similar to that reported in the USA and Europe. The treatment of symptomatic patients with antiviral agents results in favorable clinical outcomes. Thus, newborn urine-filter paper screening of congenital CMV infection is warranted".<br>The methods and length of follow-up appear appropriate (outcomes of symptomatic infants who received antiviral treatment were reported separately from those who did not receive treatment). However, this was a relatively small study including only 17 symptomatic infants.<br>This study is included in the Smyrli 2024 systematic review of impact of symptoms. |
| Lanzieri et al., 2018[134]<br>Prospective cohort study<br>USA | Symptomatic vs asymptomatic cCMV | Patients with cCMV<br>N=168 (76 symptomatic) | SNHL<br>Follow-up: up to 18 years of age | Seventy-eight (51%) ears of symptomatic patients were diagnosed with congenital/early-onset SNHL, compared with 10 (5%) ears of asymptomatic patients. Twenty-five (17%) ears of symptomatic patients were diagnosed with delayed-onset SNHL, compared with 20 (11%) ears of asymptomatic patients. Forty-nine (32%) and 154 (84%) ears had normal hearing, respectively. In affected ears, all frequency-specific hearing thresholds worsened with age. At the end of follow-up, 56 (74%) symptomatic patients and 20 (22%) asymptomatic patients had SNHL, among whom 47 (84%) and 10 (50%) had bilateral SNHL, respectively.<br>The authors concluded that "Congenital/early-onset SNHL frequently resulted in severe to profound loss in symptomatic and asymptomatic case patients. White matter lucency in asymptomatic case patients was significantly associated with SNHL by age 5 years".<br>This conclusion appears appropriate and is based on a relatively large cohort of infants. The study methods and length of follow-up were acceptable. However, it is unclear whether the results/conclusion relating to white matter lucency related to delayed-onset SNHL or congenital/early-onset SNHL |
| Lo et al., 2022[135] | Symptomatic vs asymptomatic cCMV | Infants with cCMV<br>N=39 (10 symptomatic, 20 | SNHL | SNHL developed in 60% of children who were initially symptomatic and 34.5% of children who were initially asymptomatic (with normal hearing or isolated hearing loss). Of the 10 symptomatic infants, 4 had SNHL at birth (as |

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| Prospective cohort study<br>Taiwan | | asymptomatic with normal hearing and 9 asymptomatic with isolated hearing loss) | Follow-up: median 4 years | well as other symptoms) and 2 patients subsequently developed late-onset SNHL. One asymptomatic infant with normal hearing subsequently developed late-onset SNHL. All 9 asymptomatic infants with isolated hearing loss had SNHL. All 13 infants who failed newborn hearing screening (NHS) developed SNHL, along with 3 infants who passed NHS. Initial viral loads were higher in children who were symptomatic at birth, who failed NHS, and who developed SNHL.<br>The authors concluded that "The presence of cCMV-related symptoms at birth, failure in NHS, and blood viral load might be the prognostic factors for hearing outcomes. Regular audiologic examinations are necessary in all children with cCMV infection even after CMV DNAemia clearance".<br>The methods and length of follow-up appear appropriate. However, this was a small study including only 10 symptomatic infants. |
| Maes et al., 2017[150]<br>Prospective cohort study<br>Belgium | Symptomatic vs asymptomatic cCMV | Infants with cCMV, Connexin 26 mutation and controls<br>N=40 (24 with cCMV; 8 symptomatic with impaired hearing, 8 symptomatic with normal hearing and 8 asymptomatic) | Motor performance and vestibular function<br>Follow-up: 6 months of age | Six symptomatic children with normal hearing and 4 hearing-impaired symptomatic children received antiviral treatment. Mean values for gross and fine motor performance were lower for symptomatic children than asymptomatic children, particularly gross motor performance, where the mean score for the symptomatic hearing-impaired group was significantly lower than the asymptomatic cCMV group (p=0.034).<br>The authors concluded that "The weakest gross motor performance was found in symptomatic hearing-impaired cCMV-infected children with absent cVEMP responses. These results suggest that abnormal saccular responses are a major factor for this delayed motor development, although more work is needed including comprehensive vestibular function testing to verify this".<br>This was a very small study with short-term follow-up, therefore, the results should be interpreted with caution.<br>This study is included in the Smyrli 2024 systematic review of impact of symptoms. |
| Rovito et al., 2017c[124]<br>Retrospective cohort study<br>Netherlands | Symptomatic vs asymptomatic cCMV | Children retrospectively diagnosed with cCMV from neonatal DBS | Long-term impairments (hearing, visual, neurological, motor, cognitive, speech-language)<br>Follow-up: 6 years of age | Ten of the 18 (55.6%) symptomatic infants developed 1 or more long-term impairment vs 15/84 (17.9%) asymptomatic infants. Eleven infants were born premature and 91 were term. Significantly more infants who developed long-term impairment were born premature, compared with infants who did not develop long-term impairment (24% vs 6.5% respectively; p=0.024). All 6 premature infants with birthweight <2500g developed long-term impairment vs only 1 premature infant with birthweight ≥2500g. |

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| | | N=102 with cCMV (18 symptomatic) | | The authors concluded that “Although these findings demonstrate limitations in the use of routine neonatal screening data as predictors for long-term cCMV outcome, a possible influence of cCMV in the amino acids metabolism of preterm neonates, and of higher viral loads in the metabolism of longer chain fatty acids were shown. Finally, by considering the use of routine neonatal screening data, this study represents a first step in identifying prognostic markers for cCMV outcome”.<br><br>The conclusion does not specifically relate to the association between symptomatic cCMV infection and long-term sequelae. The finding of an association between symptomatic cCMV (including prematurity and birthweight) and the development of long-term impairment appears to be credible, although only 18 children in the study had symptomatic cCMV. |
| Royackers et al., 2013[136]<br><br>Prospective cohort study<br><br>Belgium | Symptomatic vs asymptomatic cCMV | Infants with cCMV<br><br>N=98 (24 symptomatic) | Late-onset hearing loss<br><br>Follow-up: average 5.4 years | Eight symptomatic children with hearing loss at birth were treated with ganciclovir. Two symptomatic children with normal hearing at birth developed late-onset hearing loss (detected within 5 months of birth). One asymptomatic child with normal hearing at birth developed late-onset hearing loss (detected at the age of 2 years and 9 months).<br><br>The authors concluded that “Hearing loss caused by congenital cytomegalovirus infection cannot be defined unequivocally either with respect to the level of hearing loss or its evolution over time. Treating symptomatic children with ganciclovir leads to a better prognosis during the first year of life, after which progression or fluctuation again becomes more likely. However, overall, progression is more common in the untreated symptomatic group. Asymptomatic children with SNHL are more likely to have a stable hearing status”.<br><br>The methods and length of follow-up appear appropriate. However, this was a small study including only 24 symptomatic infants and only 3 cases of late-onset hearing loss. |
| Salome et al., 2023[137]<br><br>Prospective cohort study<br><br>Italy | Symptomatic vs asymptomatic cCMV | Infants with cCMV<br><br>N=250 (123 symptomatic) | Long-term visual impairment<br><br>Follow-up: median 4.7 years (symptomatic infants) and 2.9 years (asymptomatic infants) | Fundoscopic abnormalities were identified in the neonatal period in 16/123 (13%) symptomatic infants and in none of the asymptomatic infants. Chorioretinitis was the most common finding (10/16 cases), with the others presenting with chorioretinal scars. Fifteen of the 16 infants with ocular involvement received antiviral therapy. Seven of the 16 showed normal psychomotor development, 8/16 developed severe psychomotor delay and 1/16 showed speech delay and mild psychomotor delay. No patient (symptomatic or asymptomatic) developed new/late-onset retinal lesions. |

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| | | | | Throughout follow-up, 5/16 infants with ocular involvement at birth were diagnosed with visual impairment.<br><br>The authors concluded that “Chorioretinal lesions are a fairly common finding at birth in neonates with symptomatic cCMV, often associated with long-term visual impairment. Asymptomatic infants do not show ophthalmological abnormalities in the short or long term. This information is relevant both to parental counselling and to cost-effective patient management”.<br><br>Whilst this was a large study with relatively long-term follow-up, the results focussed on the 16 infants with ocular involvement in the neonatal period. No patients (symptomatic or asymptomatic) developed new/late-onset retinal lesions. |
| Seneviratne et al., 2022[138]<br><br>Retrospective cohort study<br><br>Australia | Symptomatic vs asymptomatic cCMV | cCMV cases<br><br>N=45 (25 diagnosed within 3 weeks of birth and 20 diagnosed >3 weeks from birth; 35 symptomatic) | Developmental delay, SNHL, cerebral palsy, death<br><br>Follow-up: 24 months | Thirteen symptomatic newborns received antiviral therapy. A degree of developmental delay during the first 24 months of follow-up was reported in 22 newborns: 9/13 (69.2%) symptomatic treated newborns; 10/22 (45.5%) symptomatic untreated newborns; and 3/10 (30%) asymptomatic newborns. SNHL: 3/13 (23.1%) symptomatic treated newborns, 5/22 (22.7%) symptomatic untreated newborns and 0 asymptomatic newborns. Cerebral palsy: 2/13 (15.4%) symptomatic treated newborns, 2/22 (9.1%) symptomatic untreated newborns and 0 asymptomatic newborns. One child died (symptomatic untreated).<br><br>The authors concluded that “Up to half of the neonates with cCMV were at risk of developing a degree of developmental delay at our centre. Whether these outcomes are related to CMV infection or are confounded by the co-existence of prematurity is unclear and needs further evaluation in prospective studies”.<br><br>This was a small study, in which 20 of the newborns were diagnosed >3 weeks from birth, so may not have had congenital cytomegalovirus, therefore, the results should be interpreted with caution. |
| Topham et al., 2019[149]<br><br>Prospective cohort study<br><br>USA | Symptomatic vs asymptomatic cCMV | Children with symptomatic or asymptomatic cCMV (and controls)<br><br>N=112 with cCMV (36 symptomatic) and 29 controls | Inattention and hyperactivity (also lifetime hearing loss)<br><br>Follow-up: at least 6 years | Children with symptomatic cCMV had a higher proportion of elevated Attention Problems T-scores at follow up compared with the asymptomatic cCMV group (39% vs 17%; p=0.012). There were no differences in the proportions of children with elevated Hyperactivity T-scores at follow up between symptomatic cCMV and asymptomatic cCMV groups (28% vs 20%). Children with symptomatic cCMV had higher mean Attention Problems T-scores at follow up versus those with asymptomatic cCMV (scores of 56.0 vs 50.6; p=0.006) and higher mean Hyperactivity T-scores versus those with |

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| | | | | asymptomatic cCMV (scores of 54.3 vs 50.3; p=0.031). After adjusting for IQ, differences in mean Attention Problems or Hyperactivity T-scores were no longer significant. Significantly more symptomatic children had lifetime hearing loss: 28/36 (78%) vs 16/76 (21%) asymptomatic children; p<0.001. Mean IQ score was significantly lower in symptomatic vs asymptomatic children (90.5 vs 109.2; p<0.001).<br><br>The authors concluded that "Children with asymptomatic cCMV are not at increased risk of inattention or hyperactivity compared with controls. However, our study suggests an increased prevalence of inattention and hyperactivity among children with symptomatic cCMV. Differences in IQ were confirmed to have a confounding effect. Evaluation for attention-deficit/hyperactivity disorder may be warranted in this population".<br><br>This conclusion appears appropriate and is based on a reasonable sized cohort of infants and relatively long-term follow-up.<br><br>This study is included in the Smyrli 2024 systematic review of impact of symptoms. |
| Zavattoni et al., 2016[139]<br><br>Retrospective cohort study<br><br>Italy | Symptomatic vs asymptomatic cCMV | Newborns with cCMV<br><br>N=46 (36 live births; 8 symptomatic) | Long-term sequelae<br><br>Follow-up: Not reported | Long-term sequelae were reported in 3/7 (42.8%) symptomatic (1 lost to follow-up) and 7/22 (31.8%) asymptomatic (5 lost to follow-up, 1 died) newborns. In the symptomatic cCMV group, 1 had communicative disorders, 1 neurodevelopmental deficits and 1 motor and language disabilities. In the asymptomatic cCMV group, 2 had hearing loss, 3 had language disabilities, 1 had diabetes and 1 had cognitive impairment.<br><br>The authors conclusions are unclear (there is no conclusions section).<br><br>This was a very small study with only 8 symptomatic infants, unclear length of follow-up and no clear conclusions drawn. |
| Minsart et al., 2020[145]<br><br>Retrospective cohort study<br><br>Canada | Symptomatic (moderate to severe symptoms) vs asymptomatic cCMV | Mother-child pairs referred to Women and Children's Infectious Diseases Center with confirmed cCMV | Hearing function and neurodevelopmental symptoms<br><br>Follow-up: median 2.1 years hearing, median 29.5 months neurodevelopmental symptoms | Fifty-one of the 77 infants received antiviral therapy. There were 3 neonatal deaths attributed to CMV disease. Among 74 children who survived the neonatal period, 50 had normal hearing initially; 5/50 (10%) developed late-onset SNHL after a median time of 1.2 years, all of whom had symptoms at birth. Nine out of 59 symptomatic children developed severe neurodevelopmental symptoms, all of which had moderate to severe symptoms at birth. No asymptomatic children had severe neurodevelopmental symptoms.<br><br>The authors concluded that "Outcome of cCMV infection in a setting without routine CMV screening and third-trimester scan varies according to the |

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| | | N=77 with cCMV (59 symptomatic) | | reason for screening and timing of diagnosis. Late detection of prenatal ultrasound anomalies and postnatal diagnosis following neonatal symptoms represented more than half of the series, and remain challenging situations. Awareness of this should help perinatologists to recognize cCMV patterns and ensure optimal management".<br><br>The methods and length of follow-up appear appropriate. However, this was a relatively small study including only 18 asymptomatic infants.<br><br>This study is included in the Smyrli 2024 systematic review of impact of symptoms. |
| Hu et al., 2024[132]<br><br>Prospective cohort study<br><br>China (non-English language publication) | Symptomatic vs asymptomatic cCMV (and severity of symptoms) | Newborns with cCMV<br><br>N=176 (79 asymptomatic, 12 mildly symptomatic, 85 moderately to severely symptomatic) | SNHL<br><br>Follow-up: not reported | Fifty cases had SNHL at birth, with different degrees of severity: 30 mild, 9 moderate, 5 severe and 6 extremely severe SNHL. Among the 50 infants with SNHL, 29 (58%) completed hearing follow-up; 19 (65.5%) had improved hearing thresholds, 7 (24.1%) remained stable and 3 (10.3%) progressed. Among 121 infants with normal hearing at birth, 52 (43%) completed hearing follow-up; 2 (1.7%) exhibited late-onset hearing loss. Univariate logistic regression analysis showed that disease grade at birth, SNHL, abnormal neuroimaging, and premature birth were all associated with poor hearing outcomes (all $p<0.1$). Multivariate logistic regression analysis found that SNHL and premature birth were independent risk factors for poor hearing outcomes (all $p<0.05$).<br><br>The authors concluded that "SNHL resulting from cCMV infection presents symptoms at birth and can be improved by antiviral therapy. Poor hearing outcomes are associated with SNHL and prematurity".<br><br>This information has been extracted from the Chinese publication using the English abstract and a crude translation of the text (using Google Translate™). Therefore, the results and assessment of validity are very limited. Only 81/176 (46%) infants completed at least 1 hearing follow-up (at 3, 6, 12 and 24 months of age). |
| Tapasak et al., 2022[142]<br><br>Retrospective cohort study<br><br>USA | Symptoms at birth, gender and race/ethnicity | cCMV patients<br><br>N=170 (153 symptomatic) | SNHL<br><br>Follow-up: 50.6 months (average follow-up for the 83 infants with SNHL eligible for evaluation) | In this cohort, 46% symptomatic children and 41% asymptomatic children developed SNHL. Of the 170 infants with cCMV, 83 were determined to have SNHL eligible for evaluation. Newborn hearing screening (NBHS) results were available for 69/83 infants, of which 26 passed. 22/26 (85%) eventually developed SNHL by their last visit. Over the monitoring period, 3/20 (15%) children with unilateral SNHL progressed to bilateral SNHL. After excluding those with profound hearing loss at detection, 32/68 (47%) had deterioration in hearing. Within our cohort, females with cCMV were significantly more likely |

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| | | | | to have SNHL than males with cCMV (48/77 [62.3%] vs 35/93 [37.6%]; p<0.01). Otherwise, there were no statistically significant differences in incidence of SNHL, CNS involvement, or radiographic evidence of disease between race/ethnicity or gender.<br><br>The authors concluded that "Approximately one half of children with symptomatic cCMV in our cohort developed SNHL related to CMV. This hearing loss progression may manifest as a worsening in severity and/or progression from unilateral to bilateral hearing loss. The majority of children with symptomatic cCMV eventually end up with severe to profound range loss in at least one ear. Children with symptomatic cCMV are at high risk of delayed onset and progressive hearing loss and should be monitored closely".<br><br>This conclusion appears appropriate and is based on a relatively large cohort of infants, although only 17 infants had asymptomatic cCMV. The authors note that their results on the proportion of asymptomatic patients with hearing loss are higher than in previous research and attribute this discrepancy to the very low presence of asymptomatic patients in their study. |
| Pinninti et al., 2016[140]<br><br>Prospective cohort study<br><br>USA | CNS involvement vs no CNS involvement (transient findings) and a group with only petechial rash | Infants with symptomatic cCMV<br><br>N=160 | Hearing and neurodevelopment<br><br>Follow-up: average 4.6 years | Infants with microcephaly, seizures, lethargy/hypotonia, poor suck and/or neuroimaging findings, with or without other findings, were categorised as the CNS group (n=84). Infants with jaundice, purpura, hepatosplenomegaly, elevated aspartate aminotransferase or thrombocytopenia with or without petechial rash and without CNS involvement were considered as the transient findings group (n=53). Infants with petechial rash without other findings comprised the third group (n=23). None of the included infants received antiviral therapy. Significantly more infants in the CNS group had SNHL at birth (58.2% vs 37.7% in the transient symptoms group and 21.7% in the petechiae group; p=0.0007). Of those with SNHL, bilateral SNHL and moderate-profound hearing loss were more frequent in the CNS group and transient symptom group than the petechiae group, but the differences were not statistically significant. The frequency of late-onset SNHL did not differ between groups: 16% in the CNS group vs 13.2% in the transient symptoms group and 8.7% in the petechiae group. Of those assessed for cognitive outcome, significantly more children in the CNS group had IQ<70 (23/39; 59%) than in the transient symptom group (8/39; 20%); p<0.0001. None of the 10 children in the petechiae group had IQ<70.<br><br>The authors concluded that "In infants with symptomatic cCMV, those with evidence of CNS involvement at birth are at significantly higher risk for SNHL and cognitive deficits than those with transient symptoms or a petechial rash |

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| | | | | suggesting a direct relationship between the severity of disease at birth and the risk for adverse outcomes".<br><br>This conclusion appears appropriate and is based on a relatively large cohort of infants. However, only 88 children had cognitive outcome data, so the finding relating to cognitive deficit is less certain. The study methods and length of follow-up were acceptable. |
| Simonazzi et al., 2014[141]<br><br>Retrospective cohort study<br><br>Italy | Small for gestational age vs not small for gestational age | Infants born to CMV infected mothers<br><br>N=119 with cCMV (14 symptomatic) | Long-term sequelae (hearing impairment and neurodevelopmental delay)<br><br>Follow-up: not reported | Eight of the 119 infants with cCMV were small for gestational age (SGA). SGA was defined as birth weight less than the 10th centile. Of the 14 symptomatic newborns, 2 were SGA and 12 were appropriate for gestational age (AGA). Both SGA newborns had long-term sequelae; 1 had monolateral deafness and 1 had monolateral deafness and speech disability. All 12 AGA newborns had long-term sequelae; 4 had hearing loss, 1 had monolateral deafness, 5 had bilateral deafness, 1 had learning disability and 1 had speech disability and learning disability.<br><br>The authors concluded that "Congenital CMV infection does not seem to be associated with a higher incidence of SGA, and long-term outcomes do not seem to be affected by isolated impaired fetal growth".<br><br>The length of follow-up was not reported and long-term sequelae were only reported for the 14 symptomatic newborns, of which only 2 were SGA, therefore, the results should be interpreted with caution. |
| **Audiological screening result at birth (n=2 studies)** | | | | |
| Forli et al., 2024[152]<br><br>Retrospective cohort study<br><br>Italy | Newborn hearing screening result – refer vs pass | Children diagnosed with cCMV through newborn hearing screening or symptoms<br><br>N=61 (35 symptomatic) | SNHL, ophthalmological and neurodevelopmental abnormalities<br><br>Follow-up: mean 54 months | Nineteen symptomatic newborns received antiviral treatment. At newborn hearing screening, 39 newborns were 'pass' bilaterally, 8 were 'refer' unilaterally and 14 were 'refer' bilaterally. Twenty children (32.7%) developed SNHL (10 symptomatic and 10 asymptomatic at birth); 17 (85%) were 'refer' at newborn hearing screening and 3 (15%) were 'pass'. In 5 patients (25%) a progression of the hearing threshold was observed (mean age at progression 26 months); risk factors for progression were worse final hearing threshold (p=0.0001) and worse hearing threshold at birth (p=0.02). 4/61 children (6.6%) presented with ophthalmological disorders compatible with cCMV and 16/40 (40%) were diagnosed with neurodevelopmental abnormalities.<br><br>The authors concluded that "This study highlights the diverse and significant long-term sequelae of cCMV infection detected through early screening. With a significant proportion of cCMV children developing sensorineural hearing loss, ophthalmological and neurodevelopmental issues, the results |

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| | | | | emphasize the importance of continuous, multi-disciplinary follow-up. Early identification and tailored interventions are crucial for improving the long-term health and quality of life of children affected by cCMV'.<br><br>This conclusion appears appropriate and is based on a reasonable sized cohort of infants. The study methods and length of follow-up were acceptable. Whilst only 22 infants were given a 'refer' newborn hearing screening result, the results indicate that infants with a 'refer' result are more likely to develop SNHL than those with a 'pass' result. |
| Rohren et al., 2024[153]<br><br>Retrospective cohort study<br><br>USA | Newborn hearing screening result – refer (bilateral/unilateral) vs pass | Children with cCMV<br><br>N=44 | SNHL<br><br>Follow-up: mean age 46 months | Twenty children received antiviral therapy. 33/44 (75%) children had SNHL of varying degree and age at onset (mean age at hearing loss detection 13 months). 17/44 (39%) received a bilateral 'refer' result on universal newborn hearing screen (UNHS). 17/44 (39%) children passed bilaterally; of which 6/17 (35%) acquired SNHL, detected at a mean age of 20 months. 10/44 children had a unilateral 'refer' result; 5/10 (50%) acquired SNHL in the contralateral ear, detected at a mean age of 24 months.<br><br>The authors concluded that "Among children with cCMV included in this study who passed UNHS in both ears, 35% demonstrated delayed-onset SNHL. Notably, of those children who referred unilaterally, 50% later demonstrated SNHL in the contralateral ear. These findings have implications for audiological monitoring, and potentially antiviral therapy, of children with cCMV. As implementation of universal cCMV screening moves forward, a key aspect of follow-up will be appropriate long-term audiologic monitoring".<br><br>This conclusion appears appropriate; the methods and length of follow-up were acceptable. However, this was a small study with only 17 and 10 children in the unilateral 'refer' and 'pass' groups, respectively. |
| **Viral load (n=7 studies)** | | | | |
| Marsico et al., 2019[155]<br><br>Post hoc analysis<br><br>USA | Whole blood viral load (determined by real-time PCR before and during therapy) | Infants with symptomatic cCMV enrolled in 2 prospective studies of antiviral treatment<br><br>N=120 (all symptomatic), of which baseline | Hearing and neurodevelopmental assessment<br><br>Follow-up: up to 24 months | All patients received antiviral treatment (73 for 6 weeks and 47 for 6 months). In patients treated for 6 months, a lower baseline viral load was associated with better hearing outcome at 12 months; median baseline viral load was 3.56 log for children with improved/protected hearing vs 3.93 log for those with worsened hearing or maintenance of the same degree of hearing loss ($p \leq 0.02$). However, clinically meaningful viral load thresholds predictive of SNHL were not identified. No significant association was found between baseline viral load and 6 and 24-month hearing outcome. No significant association was found between baseline viral load and 6, 12 or 24-month hearing |

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| | | samples were available for 114 infants | | outcome in patients treated for 6 weeks. No significant association was found between baseline viral load and neurodevelopmental outcome at 12 or 24 months.<br><br>The authors concluded that “In infants with symptomatic congenital cytomegalovirus disease, higher whole blood viral load before initiation of antiviral therapy has no clinically meaningful predictive value for long-term outcomes”.<br><br>This conclusion appears appropriate and is based on a relatively large cohort of infants. The study methods and length of follow-up were acceptable. |
| Meyer et al., 2017[156]<br><br>Retrospective cohort study<br><br>USA | Viral load in DBS | Children with SNHL<br><br>N=15 with cCMV (of 57 children with unexplained SNHL) | SNHL<br><br>Follow-up: 3 months to 10 years of age | When viral load was evaluated in the dried blood spots (DBS) of infants with retrospectively diagnosed cCMV, it was found to be $8.3 \pm 4.1 \times 10^4$ copies/µg DNA. No statistically significant correlation was found between viral load and SNHL severity at follow up.<br><br>The authors concluded that “A retrospective DBS analysis demonstrated that 26% of patients presenting with unexplained SNHL in childhood had cCMV. DBS testing is useful in the retrospective diagnosis of cCMV, and may provide definitive diagnostic information about the etiology of SNHL”.<br><br>This was a small retrospective study investigating causes of unexplained SNHL in children; only 15 children had cCMV and few results were reported relating to viral load and long-term sequelae. |
| Kakei et al., 2024[157]<br><br>Prospective cohort study<br><br>Japan | Viral load in blood and urine | Infants with cCMV<br><br>N=24 (all symptomatic) | Response to treatment (hearing)<br><br>Follow-up: at 6 months of treatment | All infants received antiviral treatment for 6 months. 4/24 infants had normal hearing on assessment of the ear with best hearing. Of those without normal hearing at baseline, hearing improved in 13/20 infants (responders) and remained the same in 7/20 infants (non-responders) after 6 weeks of treatment. After 6 months of treatment, 14/20 patients were responders and 6/20 were non-responders. The plasma CMV loads at baseline were significantly higher in non-responders than in responders at 6 weeks ($p=0.028$); the difference was no longer significant at 6 months ($p=0.124$). There was a trend of higher blood and urine CMV loads at baseline in non-responders than in responders.<br><br>The authors concluded that “Infants with a low plasma viral load at screening tend to have an improvement in hearing impairment. Clinicians should be aware of neutropenia during valganciclovir treatment particularly in patients with a low neutrophil count during screening”. |

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| | | | | This was a small study that compared baseline characteristics between responders (improved hearing) and non-responders to antiviral treatment. The authors' conclusions that infants with a low plasma viral load tend to have an improvement in hearing impairment appears appropriate, but the study was very small with short-term follow-up. |
| Portet Sulla et al., 2024[56]<br><br>Prospective cohort study<br><br>France | Viral load in saliva | Newborns with cCMV detected by screening<br><br>N=70 with cCMV (7 symptomatic) | Neurologic/hearing assessments<br><br>Follow-up: 3-6 years | 3/7 (42.8%) symptomatic infants later developed sequelae. 5/63 (7.9%) asymptomatic infants later developed sequelae; mainly SNHL and neurodevelopmental impairment.<br><br>Overall, the occurrence of sequelae was associated with viral load in saliva, whether expressed as copies/mL (p=0.039) or copies/million cells (p=0.006). Amongst asymptomatic infants, the difference was only statistically significant when expressed as copies/million cells (p=0.0044; when expressed as copies/mL p=0.0765).<br><br>The authors summarised that "Our results confirm that saliva swab is a suitable sample for universal neonatal screening. However, identifying newborns that will develop sequelae remains an issue in the management of cCMV infection".<br><br>This study assessed the diagnostic accuracy of saliva swabs for cCMV screening and the association between viral load in saliva and symptomatology/outcome of cCMV. Whilst an association was found between viral load in saliva and the occurrence of sequelae, only 3 symptomatic infants and 5 asymptomatic infants developed sequelae, so the results are based on a very small number of children. |
| Forner et al., 2015[77]<br><br>Prospective cohort study<br><br>Italy | Viral load in blood and urine (determined by real-time PCR) | Asymptomatic newborns with cCMV<br><br>N=33 (none symptomatic) | Audiological, neurodevelopment and visual assessment<br><br>Follow-up: 6 years of age | Ten of 33 infants developed late-onset sequelae between the age of 3 months and 5 years; SNHL (8 children) and/or psychomotor retardation (2 children), right-side hemiparesis (1 child). The mean viral load at birth was 17,045 copies/mL in babies who developed late-onset sequelae vs 1,770 copies/mL in those who remained symptom-free (p=0.0002). Multivariate logistic regression revealed that the risk of clinical disease crossed the level of 50% with a DNAemia at birth of ≥12,000 copies/mL (p=0.0002) and the risk of hearing deficit crossed the level of 50% with a DNAemia at birth of ≥17,000 copies/mL (p=0.0001).<br><br>The authors concluded that "Asymptomatic newborns with a CMV DNAemia at birth of ≥12,000 copies/mL were more likely to experience CMV-related |

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| | | | | sequelae. The risk of hearing deficit increased with a viral load in blood of ≥17,000 copies/mL".<br><br>The methods and length of follow-up appear appropriate. However, this was a small study including only 10 infants that developed long-term sequelae. |
| Salome et al., 2020[158]<br><br>Prospective cohort study<br><br>Italy | Viral load in blood and urine and clearance time | Newborns with asymptomatic cCMV<br><br>N=125; 102 of which had follow-up of at least 12 months so included in study (none symptomatic) | SNHL<br><br>Follow-up: median 2.8 years | Time to viral clearance was 104 days (range 11-659) in blood and 1,437 days (range 230-2,756) in urine. No infant developed a stable delayed SNHL and 88/102 children (86%) presented normal hearing function at all assessments. Only 14/102 (14%) presented a fluctuating hearing impairment, which was bilateral in 7 babies. The transient SNHL was mild in 12 children and moderate in 2. Children with fluctuating SNHL had a significantly higher urine viral load at baseline (p=0.002) and more often positive viremia (p=0.015) than children with stable normal hearing. None of the infants developed later sequelae such as neurologic disorders, visual loss, thrombocytopenia or liver disease during the follow-up period.<br><br>The authors concluded that "CMV infected, asymptomatic neonates have a low risk of transient SNHL later in infancy. Positive viremia and high urine viral load at onset are significant risk factors for delayed fluctuating SNHL. These data are relevant for an appropriate follow up plan of these patients".<br><br>The conclusions appear appropriate, however, only 14 children presented a fluctuating hearing impairment, so the comparison of viral load between those with stable normal hearing and fluctuating SNHL were based on a small number of children.<br><br>This study is included in the Smyrli 2024 systematic review of impact of symptoms. |
| Wang et al., 2021[159]<br><br>Prospective cohort study<br><br>China | Viral load in saliva | '"Likely asymptomatic" (based on the absence of symptoms, without neuroimaging or ophthalmic assessment) newborns with cCMV | Late-onset hearing loss<br><br>Follow-up: Not reported (beyond 4 years for some children) | 4/141 (2.8%) children had late-onset SNHL (2 bilateral and 2 unilateral, ranging from mild to moderate), diagnosed at 1-4 years of age. Children with late-onset SNHL had higher median CMV salivary viral loads at birth than children without hearing loss (median 5.3 vs 3.5 $\log_{10}$ copies/mL; p=0.03). Other maternal or childhood factors did not significantly differ between children with or without late-onset SNHL<br><br>The authors summarised that "After following 141 children with likely asymptomatic congenital cytomegalovirus infection in a highly immune population in China, 4 children (2.8%) were found to have late-onset hearing loss. No maternal or childhood factors, except higher saliva cytomegalovirus |

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| | | N=141 (none symptomatic) | | viral load at birth (p=0.03), were associated with increased risk of developing a hearing loss".<br><br>This study compared baseline characteristics between children with and without late-onset hearing loss. The conclusions appear appropriate, however, only 4 children had late-onset SNHL, so the comparisons were based on a very small number of children. |
| **Genotype (n=6 studies)** | | | | |
| Chen et al., 2019[163]<br><br>Prospective cohort study<br><br>China (non-English language publication) | CMV gH1 genotype vs CMV gH2 genotype | Newborns with cCMV in NICU<br><br>N=21 (all newborns were hospitalised in NICU, therefore, probably all symptomatic) | Clinical manifestations, laboratory examinations, hearing loss and neurological prognosis<br><br>Follow-up: 3-5 years | 14/21 (67%) infants were gH1 type and 7 (33%) were gH2 type. 20 infants (40 ears) had severe hearing loss; it was higher in gH1 group than gH2 group (4/22 vs 0/18 ears; p=0.023). The imaging Alarcon score was lower in the gH1 group than the gH2 group (0.4 vs 1.3; p=0.024). No significant difference was found in the probability of motor or language development lag in gH1 and gH2 groups.<br><br>The authors concluded that "Compared with gH2 infection, gH1 infection in children has a younger gestational age. The major type of hearing loss in neonatal period is gH1 infection. Children with gH2 congenital infections are more likely to suffer from nervous systems damage".<br><br>All infants were hospitalised in the neonatal intensive care unit, so represent a subgroup of cCMV infants. This information has been extracted from the abstract of this non-English language publication. Therefore, it is not possible to assess the validity of the results presented, although the number of infants in the different genotype groups was very small. |
| Dong et al., 2023[164]<br><br>Prospective cohort study<br><br>China | gB, gH and gN genotypes | Newborns with cCMV<br><br>N=42 (all symptomatic) | Hearing loss and developmental delay<br><br>Follow-up: Up to 3 years of age | The UL55 (gB), UL75 (gH) and UL73 (gN) genes were successfully sequenced for 32/42 (76%), 37/42 (88%) and 28/42 (67%) newborns, respectively. No significant association was found between CMV gB, gH or gN genotypes and hearing loss or developmental delay. No significant association was found between CMV genotypes and urine viral loads.<br><br>The authors concluded that "Our findings demonstrate the overall distribution of gB, gH and gN genotypes in infants with symptomatic cCMV infection in Shanghai for the first time. The findings in our study may suggest a possible association between gH1 genotype and early infancy hearing loss. gB3 genotype was associated with a 6.5-fold increased risk of petechiae while gN4a strongly correlated with chorioretinitis due to cCMV infection. No |

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| | | | | significant correlation was found between urine viral loads and CMV genotypes or hearing impairment in cCMV infected infants".<br><br>Infants underwent audiological assessment within the first month of life and at 3, 6, 12 and 18 months of age. However, it is unclear whether the hearing loss results relate to newborn hearing loss or longer-term hearing loss (the outcome of interest to this review). Children underwent developmental assessment at least every 6 months; whilst the timing of diagnosis of developmental delay was not presented, it can be assumed that it was beyond the newborn period. The number of patients with different genotypes was very small (0 to 2), limiting the reliability of the study results. |
| Kasztelewicz et al., 2017[165]<br><br>Prospective cohort study<br><br>Poland | 11 single nucleotide polymorphisms | Infants at a children's hospital<br><br>N=72 with cCMV (61 symptomatic) | SNHL<br><br>Follow-up: 6 months | A panel of 11 candidate single nucleotide polymorphisms (SNPs) was genotyped: TNF rs1799964, TNF rs1800629, TNFRSF1A rs4149570, IL1B rs16944, IL1B rs1143634, IL10 rs1800896, IL10RA rs4252279, IL12B rs3212227, CCL2 rs1024611, CCL2 rs13900, and CCR5 rs333. 22/72 newborns had early-onset SNHL No significant association was found between severity of cCMV disease (i.e., illness score) and SNPs. However, when analysis was performed according to hearing outcome at birth as well as at the age of 6 months, a significant association between polymorphisms within CCL2 gene (rs13900) and SNHL was observed. In particular, carriers of CT or TT genotype of CCL2 rs13900 had increased risk of hearing loss (OR=3.38; p=0.033 and OR=4.0; p=0.04, for hearing status at birth and at age 6 months, respectively).<br><br>The authors concluded that "The results of the present study suggest for the first time that polymorphisms in cytokine genes may influence the pathogenesis of cCMV infection. It has been shown that genetic polymorphisms in IL1B and TNF may modulate the susceptibility to intrauterine CMV infection, whereas CCL2 polymorphisms may influence the hearing outcome in children with cCMV infection. Further, larger studies and functional assessment of the SNPs are required to confirm their pathogenic role".<br><br>Whilst this was a reasonable sized study, the length of follow-up was relatively short and 16/72 infants who underwent hearing screening at birth did not have auditory brainstem response (ABR) data available for confirmation of hearing loss. In addition, 14 babies (7 with early-onset SNHL and 7 with normal hearing) were lost by the 6-month follow-up assessment. |

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| Medoro et al., 2024[166]<br>Prospective cohort study<br>USA | T-cell cytokine responses | Infants with cCMV (and uninfected controls)<br>N=30 with cCMV (22 symptomatic) | Neurodevelopmental outcomes<br>Follow-up: at least 12 months | 21/30 (70%) infants received antiviral therapy. 14/30 (47%) had any neurodevelopmental impairment; 9/30 (30%) had developmental delay, 9/30 (30%) had SNHL and 1 (3%) had 'unknown' neurodevelopmental impairment. Infants with subsequent developmental delay lacked detectable CMV-specific T cell responses, with patterns resembling those of uninfected infants, whereas those with normal developmental outcomes had high frequencies of the differentiated memory CD8+ T cells. Two children with progressive SNHL had high frequencies of PD-1+CD8+ T cells over the first year compared with children with nonprogressive SNHL and normal hearing.<br>The authors concluded that "… a lack of in utero T cell differentiation was associated with developmental delay, and high frequencies of PD-1+CD8+ T cells persisted only in children with progressive SNHL. Further work is needed to define the specificity of these T cells and the mechanistic connection to these outcomes".<br>A number of infants who had at least 12 months clinical follow-up had incomplete data on T-cell responses; therefore, the results are based on a small number of infants with relatively short-term follow-up. |
| Pati et al., 2013[167]<br>Prospective cohort study<br>USA | Genotype (UL55 (gB), UL73 (gN) and UL75 (gH)) and mixed vs non-mixed genotype | Children with cCMV from CHIMES study and another cohort<br>N=131 (37 symptomatic) | Hearing<br>Follow-up: mean 29.6 months | The UL55, UL75 and UL73 genes were successfully amplified and genotype assigned for 118/131 (90%), 118/131 (90%) and 109/131 (83%) infants, respectively. No particular genotype of UL55, UL73, UL75 or US28 was associated with symptomatic disease or SNHL at birth. In the cohort of 52 infants with long-term hearing outcome data, 5 had hearing loss (3 at birth and 2 developed late-onset hearing loss at 12.4 months and 16.4 months of age). 3/5 (60%) children with hearing loss at follow up had infection with multiple strains, compared with 16/48 (33%) children with normal hearing at follow up (p=0.23).<br>The authors concluded that "Mixed infection is common in infants with cCMV but is neither associated with symptomatic infection nor with SNHL".<br>This conclusion appears appropriate and is based on a reasonable sized cohort of infants. However, only 52 infants had long-term hearing outcome data, of which only 5 had hearing loss. The study methods and length of follow-up were acceptable. |
| Rovito et al., 2018[168] | Gene expression differences and viral load | Children retrospectively diagnosed with cC | Long-term impairments (hearing, visual, neurological, motor, | Differential expression of individual genes was compared between children with cCMV who developed long-term impairment and those that did not; there were no statistically significant differences between the groups. The |

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| Retrospective cohort study (same cohort as Korndewal et al., 2017[ref])<br><br>Netherlands | | MV from neonatal DBS<br><br>N=12 with cCMV (5 symptomatic) | cognitive, speech-language)<br><br>Follow-up: 6 years of age | differences in gene expression were assessed in relation to the logarithm of CMV viral load a continuous variable; there were no statistically significant differences observed. Pathway analysis suggested the involvement of innate immune response with higher CMV viral loads, and of anti-inflammatory markers in cCMV infected children who did not develop long-term impairments. The T cell exhaustion observed in infected newborns, in particular with higher viral load, did not correlate with long-term impairment, therefore other mechanisms are likely to be involved in the long-term immune dysfunction.<br><br>The authors summarised that "Despite these data demonstrate limitation in determining prognostic markers for LTI by means of transcriptome analysis, this exploratory study represents a first step in unravelling the pathogenesis of cCMV, and the aforementioned pathways certainly merit further evaluation".<br><br>This was a very small study which included 12 children retrospectively diagnosed with cCMV using neonatal DBS (from a previous retrospective cohort study by Korndewal et al., 2017[ref]); 6 children with long-term impairments were compared against 6 children without long-term. Therefore, the results should be interpreted with caution. |
| **Cerebrospinal fluid (CNS involvement) (n=2 studies)** | | | | |
| Czech-Kowalska et al., 2021[169]<br><br>Prospective cohort study<br><br>Poland | Detection of CMV DNA in cerebrospinal fluid (CSF) by PCR (CSF-CMV-PCR) as a marker of<br><br>CNS involvement | Newborns with cCMV<br><br>N=168 (162 symptomatic) | Clinical and laboratory assessment<br><br>Follow-up: after 4-8 weeks of treatment. Audiologic assessment lasted at least 5 months | Antiviral treatment was used in 149 infants. Twenty-three (13.7%) infants had positive CSF-CMV-PCR results and 145 (86.3%) infants had negative CSF-CMV-PCR results. After 4-8 weeks of treatment, infants with positive CSF-CMV-PCR presented with a higher prevalence of the following clinical abnormalities: splenomegaly, microcephaly, seizures and opisthotonos. There were no differences between groups according to laboratory results apart from thrombocytopenia. The CSF-CMV-PCR results were negative in 15 infants, still positive in 5 infants and not available for 3 infants.<br><br>The authors concluded that "The detection of CMV DNA in CSF is associated with a higher rate of CNS damage including abnormal MRI neuroimaging and severe hearing loss. Therefore, detection of CMV DNA in CSF may be considered as a marker of severe CNS injury in cCMV infection. However, the very low prevalence of the positive CSF-CMV-PCR results, even in infants with proven CNS involvement, may imply its limited role in clinical practice.<br><br>This study reported very few results relating to longer term outcomes; clinical abnormalities after 4-8 weeks of treatment were presented only for infants |

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| | | | | with positive CSF-CMV-PCR results. The authors' cautious conclusion appears appropriate. |
| Goycochea-Valdivia et al., 2017[170]<br>Retrospective cohort study<br>Spain | Detection of human CMV DNA in CSF by PCR as a marker of CNS involvement (lumbar puncture performed at a median age of 5 days) | Newborns with cCMV<br>N=136 (77 symptomatic) | Audiological and neurological outcomes<br>Follow-up: 6 months | Antiviral treatment was used in 105 infants (all symptomatic infants and 28 asymptomatic infants). Twenty-one (15.4%) infants had positive CSF hCMV-PCR results and 115 (84.6%) had negative results. Significantly more infants in the positive group were symptomatic (17/21 [81%] vs 60/115 [52.2%] in the negative group; p=0.01). There were no differences between groups regarding the rate of microcephaly, neuroimaging abnormalities, neurological sequelae at 6 months of age or plasma viral load. SNHL at birth was associated with a positive CSF hCMV-PCR result (OR=3.49; p=0.04), although no association was found at 6 months of age (OR=2.89; p=0.07).<br>The authors concluded that "A positive hCMV-PCR result in CSF is associated with symptomatic cCMV and SNHL at birth. However, no differences in neuroimaging studies, plasma viral load, or outcomes at 6 months were found. These results suggest that hCMV-PCR in CSF may not be a useful prognostic marker in cCMV.<br>The authors' conclusion appears appropriate and is based on a relatively large cohort of infants, although only 21 infants had positive CSF hCMV-PCR results. |
| **Multiple tests/characteristics assessed (n=18 studies)** | | | | |
| Poletti de Chaurand et al., 2024[101]<br>Prospective cohort study<br>Italy | Antenatal characteristics and clinical characteristics at birth | Infants screened for cCMV (targeted screening)<br>N=11 with cCMV (7 symptomatic) | Hearing, cognitive, motor and speech<br>Follow-up: 6-36 months | An adverse clinical outcome was observed in 2/11 infants (1 infant died on day 11 and the other had cognitive delay and motor impairment). These 2 infants had the lowest gestational age (just under 34 weeks) of the cohort and both had abnormalities detected on neuroimaging (fetal or neonatal MRI). Two additional infants had mild abnormalities. All 4 infants with abnormalities were symptomatic at birth.<br>The authors formed no conclusions in relation to associations between baseline factors and sequelae, as the study was not designed to investigate this.<br>This was a very small study, without any formal analysis, and so findings related to associations between baseline factors and clinical sequelae should be interpreted with caution. |

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| Puhakka et al., 2022[118]<br>Prospective cohort study<br>Finland | Primary vs non-primary maternal infection and trimester of infection and symptoms at birth | Children with cCMV from a newborn screening study<br>N=32 (3 symptomatic) | Hearing<br>Follow-up: median age 3.1 years | Five children had unilateral hearing loss and 27 children had normal hearing. Unilateral hearing loss at 3-4 years of age was not associated with the type of maternal infection: 3/15 (20%) children born to mothers with non-primary infection had hearing loss at 3-4 years, compared to 2/10 (20%) children with primary maternal infection. In both infants with hearing loss following primary maternal infection, the infection was during the second to third trimester (2/4 infants infected in the second/third trimester had hearing loss vs 0/6 infants infected in the first trimester). Finally, unilateral hearing loss at 3-4 years of age appeared to have some association with symptoms at birth: 1/3 (33%) children who were symptomatic at birth had hearing loss at 3-4 years, compared to 4/29 (14%) children who were asymptomatic at birth. No attempt was made to examine interactions between the baseline variables and sequelae (for example, assessing if a particular combination of characteristics has an effect on outcome, that is over and above what could be inferred from the univariate results).<br>The authors' conclusion was, "Adverse hearing outcome occurred both in children born to mothers with primary infection after the first trimester, and non-primary infection during pregnancy."<br>This was a small study, in which only 5 infants had long-term hearing loss. Findings should therefore be treated with caution. |
| Noorbakhsh et al., 2022[120]<br>Prospective cohort study<br>Iran | Symptoms at birth and primary vs non-primary maternal infection | Newborns with cCMV admitted to NICU and from 2 other prospective screening studies in Iran<br>N=22 (8 symptomatic) | SNHL<br>Follow-up: 24 months of age | Hearing loss at follow up occurred in 2/8 (25%) children that were symptomatic at birth and in 1/14 (7.1%) children that were asymptomatic at birth. However a statistical analysis was not performed. Meanwhile, there was no significant association between the type of maternal infection and later hearing loss, with hearing loss in 1/6 (16.5%) children whose mothers had primary infection and in 1/11 (9.1%) children whose mothers had non-primary infection (p=0.4). There were also no significant associations observed between later hearing loss and each of maternal age (p=0.9), sex (p=0.3), preterm birth (p=0.7), jaundice at birth (p=0.9) or intrauterine growth restriction (p=0.2). No attempt was made to examine interactions between the different baseline variables and sequelae. Antivirals were provided to 5/8 symptomatic infants.<br>The authors' conclusion was, "neonates with symptomatic CMV infection are more prone to develop HL." |

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| | | | | The authors' conclusion is difficult to unequivocally support. This was a very small study, and a lack of statistical analysis for the primary outcome, along with the failure to adjust for confounding, were major limitations. |
| Townsend et al., 2013[122]<br>Prospective cohort study<br>UK and Sweden | Symptoms at birth and primary vs non-primary maternal infection | Newborns with cCMV (and controls)<br>N=176 with cCMV (19 symptomatic) | Neurological sequelae<br>Follow-up: at least age 5 | 8/19 (42%) children symptomatic at birth had sequelae (mild, moderate or severe), compared to 19/135 (14%) of those asymptomatic at birth (p = 0.006). 5/73 (6.8%) newborns whose mothers had presumed or confirmed primary infection had moderate or severe sequelae, compared to 9/39 (23.1%) newborns whose mothers had presumed or confirmed non-primary infection. This was not subjected to statistical analysis, and no interactions between variables were examined. No infants received antivirals.<br>The authors concluded that, "Nonprimary infections contributed substantially to the burden of childhood congenital CMV disease".<br>This relatively large study was weakened by the limited statistical analysis and the lack of adjustment, making the authors' conclusion somewhat speculative. In addition, no outcomes were reported for 22/176 (12.5%) children and the type of maternal infection was unknown for 42/154 (27.3%) of the children with outcomes reported.<br>This study is included in the Maltezou 2020 systematic review of type of maternal infection. |
| Demmler-Harrison et al., 2020[117]<br>Prospective cohort study<br>USA | Primary vs non-primary infection; symptomatic vs asymptomatic cCMV; time of maternal infection [first half vs second half]. The study also compared with 51 uninfected controls but these results are not included here. | Newborns with cCMV (and uninfected controls)<br>N=186 with cCMV (77 symptomatic) | SNHL<br>Follow-up: mean 15.4 years | 57/77 (74.0%) children who were symptomatic at birth had hearing loss, compared to only 22/109 (20.2%) who were asymptomatic. In addition, 23/63 (36.5%) children whose mothers had primary infection had later hearing loss, compared to 2/22 (9.1%) whose mothers had non-primary infection.<br>When considering the interaction between primary/non-primary and symptomatic/non-symptomatic, newborns were more likely to develop hearing loss if symptomatic and the mother had a primary infection (9/12) than symptomatic and the mother had a non-primary infection (0/4); and more likely to develop hearing loss if asymptomatic and the mother had a primary infection (14/51) than asymptomatic and the mother had a non-primary infection (2/18).<br>Finally, 8/19 (42.1%) children whose mothers were infected in the first half of pregnancy had later hearing loss, compared to 14/38 (36.8%) whose mothers were infected in the second half of pregnancy. Statistical analyses were not conducted for these specific analyses. |

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| | | | | The authors' conclusions were, "Sensorineural hearing loss occurred in children born to mothers with both primary and non-primary CMV infections, and in both asymptomatic and symptomatic congenital CMV infection, but was more common after maternal primary infection".<br><br>The authors' conclusions appear plausible in this relatively large study, despite the lack of statistical analysis or adjustment for confounding. |
| Turriziani Colonna et al., 2020[114]<br><br>Retrospective cohort study<br><br>Italy | Symptomatic vs asymptomatic cCMV and trimester of infection | Newborns with cCMV treated with VGC<br><br>N=36 (12 symptomatic) | Long-term clinical, audiological, visual, neurocognitive and behavioural outcome<br><br>Follow-up: average age 4.23 years | There were some associations between symptoms at birth and a greater risk of later SNHL and language disorders: 5/12 (41.7%) symptomatic newborns went on the develop SNHL, compared to 1/24 asymptomatic newborns (4.2%) [p=0.012], whilst 3/12 (25%) symptomatic newborns went on the develop language disorders, compared to 3/24 asymptomatic newborns (12.5%). However, there were also associations favouring symptomatic newborns: 2/12 (16.7%) symptomatic newborns went on to present abnormal neuropsychological tests, compared to 9/12 (75%) asymptomatic newborns. Likewise, 2/12 (16.7%) symptomatic newborns went on to present abnormal behavioural test results, compared to 6/12 (50%) asymptomatic newborns. Cognitive impairment was equivalent between groups, being developed by 1/12 (8.4%) symptomatic newborns and 2/24 (8.4%) asymptomatic newborns.<br><br>There were also associations between the trimester of maternal infection and abnormal performance on the neurocognitive and behaviour tests: 9/15 (60%) newborns whose mothers were infected in the 1st trimester had abnormal responses, compared 4/9 (44.4%) newborns whose mothers were infected in the 3rd trimester. The difference between 1st and 3rd trimester was non-significant [p>0.05].<br><br>No interactions between variables were considered. All infants received antivirals (VGC).<br><br>The authors' conclusions were, "Our study shows that both symptomatic and asymptomatic newborns with cCMV infection develop long-term sequelae, particularly in the behavioural and communicative areas, independently from the trimester of maternal infection."<br><br>The authors' conclusion appears to be partially backed up by the evidence from this small study for the specific association between symptoms at birth and later hearing outcomes. However, the analyses of most other sequelae were not subjected to statistical analysis and adjustment for confounding was not carried out in any analyses. |

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| Zavattoni et al., 2014[105]<br><br>Retrospective cohort study<br><br>Italy | Timing of maternal infection, symptomatic vs asymptomatic cCMV and other fetal and neonatal parameters | Newborns with cCMV<br><br>N=150 with cCMV (28 symptomatic) of which 115 had long-term data | Physical and clinical progress, hearing, neurologic and cognitive assessment and fundus oculi<br><br>Follow-up: until school age | 9/26 (34.6%) children who were symptomatic at birth developed sequelae, compared to 12/89 (13.5%) who were asymptomatic at birth [p=0.021]. 15/58 (25.9%) children whose mothers were infected in the 1st trimester developed sequelae, compared to 6/57 (10.5%) children whose mothers were infected later [p=0.05]. No significant effects on the risk of sequelae were seen for other fetal baseline variables (HCMV DNA in amniotic fluid and antigenaemia, viraemia, HCMV DNAemia, and IgM in fetal blood) and other neonatal variables (antigenaemia, HCMV DNAemia, IgM). No interactions were examined.<br><br>The authors' conclusions were, "single clinical, virological, or instrumental features are poor predictors of clinical symptoms at birth and long-term sequelae, but the combined evaluation of maternal, fetal, and neonatal findings may increase prognostic significance."<br><br>The authors' conclusions are a cautious but accurate summary of the findings. However, this large and well-conducted study appears to provide good evidence of the association of sequelae with symptoms at birth and timing of maternal infection. |
| Bilavsky et al., 2015[76]<br><br>Retrospective cohort study<br><br>Israel | Neuroimaging (brain ultrasound for detecting lenticulated vasculopathy [LSV]), hearing at birth and treatment | Infants with cCMV<br><br>N=141 (89 symptomatic)<br><br>This study contained 4 cCMV groups: group 1 had solitary LSV (without antiviral treatment), group 2 had solitary LSV (with antiviral treatment), group 3 had solitary LSV with abnormal hearing at birth (with antiviral treatment) and group 4 were asymptomatic. | Hearing deterioration/loss<br><br>Follow-up: more than 1 year (up to 4 years) | For the 3 groups where there had been no hearing loss at birth, later hearing loss was observed in 11/13 (84.6%) in group 1, 0/51 in group 2, and 5/52 (9.6%) in group 4. Hearing deterioration was significantly higher in group 1 than in group 2 ($p<0.001$) and group 4 ($p<0.001$) and also in group 4 than in group 2 ($p=0.008$).<br><br>The authors concluded that, "Lenticulostriated vasculopathy is a relatively common finding in infants with symptomatic cCMV, a sign of central nervous system involvement and further hearing deterioration."<br><br>This conclusion is not fully supported by the data. Because the groups differed from each other by more than 1 independent variable (e.g., groups 2 and 3 received antiviral treatment) it is difficult to form conclusions about the effects of any single independent variable, apart from the likelihood that symptomatic infection leads to more long-term hearing loss than asymptomatic infection. |

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| Mardegan et al., 2024[97]<br>Retrospective cohort study<br>Switzerland | Neuroimaging (ultrasound and MRI) and symptoms at birth | Infants with cCMV<br>N=66 (56 symptomatic) | SNHL and developmental delay<br>Follow-up: median age 34 months | Symptoms at birth (axial hypotonia [p=0.04] or petechia [p=0.004]) were associated with SNHL at follow up. There were also trends for an association between abnormal baseline US [p=0.06] or abnormal baseline MRI [p=0.1] with later SNHL<br>Vacuolization of anterior temporal lobe and ventricular septation on baseline MRI were associated with developmental delay [both p=0.05]. No US findings showed an association with this outcome.<br>Microcephaly [p=0.05] and abnormal MRI [p=0.03] at baseline were associated with the composite later outcome of SNHL, developmental delay and/or abnormal vestibular function.<br>Interactions between baseline variables were not evaluated. 20 infants received antivirals until 6 months of age (19 symptomatic and 1 asymptomatic)<br>The authors' conclusions are, "this study highlights factors that are directly linked to a poor long-term outcome, including microcephaly and MRI abnormalities."<br>The authors' conclusions are plausible, but adjustment for confounding was not performed in this moderately-sized study. |
| Oosterom et al., 2015[98]<br>Retrospective cohort study<br>Netherlands | Timing of maternal infection and MRI/ultrasound | Infants diagnosed with cCMV admitted to NICU or maternity unit<br>N=36 (26 symptomatic) | Developmental outcome and hearing loss<br>Follow-up: until 5 years of age for hearing | Trimester of infection was known in 17/36 (47%) infants. Any adverse sequelae were observed in 8/10 (80%) children whose mothers had been infected in the first trimester, compared to 1/7 (14.3%) children whose mothers had been infected in the 2nd or 3rd trimester.<br>Neurodevelopmental (ND) sequelae were observed in 15/15 (100%) children with severe US abnormalities at baseline, compared to 1/21 (4.8%) children with mild or no abnormalities. SNHL at follow up was observed in 7/15 (46.7%) children with severe US abnormalities at baseline, compared to 2/21 (9.5%) children with mild or no abnormalities. 6 children died; all had severe US abnormalities.<br>ND sequelae were observed in 13/13 (100%) children with severe MRI abnormalities at baseline, compared to 2/7 (28.6%) children with mild abnormalities. SNHL at follow up was observed in 7/13 (53.8%) children with severe MRI abnormalities at baseline, compared to 2/7 (28.6%) children with mild abnormalities. |

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| | | | | No interactions between baseline variables were assessed. 5 children received antivirals, but no information was provided on which risk factor groups these belonged to.<br><br>The authors concluded as follows: “Infants with a first trimester cCMV infection are most at risk of severe cerebral abnormalities and neurological sequelae. MRI, and not cUS, enables an early diagnosis of migrational disorders, which can improve prediction of outcome”<br><br>All infants were admitted to a neonatal intensive care unit or maternity unit, so represent a subgroup of cCMV infants. This was a small study, with no adjustments for confounding, and so the conclusions of this study should be interpreted with caution. |
| Kabani et al., 2023[161]<br><br>Prospective cohort study<br><br>USA | Viral load in saliva and urine and symptoms at birth | Newborns with cCMV<br><br>N=384 (39 symptomatic) | SNHL<br><br>Follow-up: up to 48 months of age | Newborn saliva viral load was associated with the development of SNHL (viral load in those developing SNHL = $7.4x10^6$IU/mL; viral load in those with normal hearing at birth = $1.74x10^6$IU/mL; p=0.004). A significant effect was not observed in separate symptomatic or asymptomatic sub-groups [SYMPTOMATIC: viral load in symptomatic children with SNHL = $4.4x10^7$IU/mL; viral load in symptomatic children with normal hearing at birth = $4.1 x10^6$IU/mL; p=0.09); ASYMPTOMATIC: viral load in asymptomatic children with SNHL = $4.2x10^6$IU/mL; viral load in asymptomatic children with normal hearing at birth = $1.74 x10^6$IU/mL; p=0.19). These data do not permit an evaluation of interactions between symptoms at birth and viral load.<br><br>The authors concluded that, “VL is not a useful marker for hearing loss in cCMV, and should not be used for counseling patients and families regarding outcomes of cCMV.”<br><br>Although a relatively large study, the analysis of data did not adjust for confounding. The most significant limitation of the study was the ambiguity concerning the timing of SNHL measurement; whilst the paper implies that the SNHL value used in the analysis is measured at follow up this is not explicitly stated. This ambiguity is further increased by the comparator group being made up of ‘people with normal hearing *at birth*.’ A more useful comparator in terms of predicting *later* hearing loss would be ‘people with normal hearing at *follow up*.’ |
| Rovito et al., 2017a[143] | Symptomatic at birth vs asymptomatic at birth and genotype | Children retrospectively diagnosed with cC | Long-term impairments (hearing, visual, neurological, motor, | Long-term impairments (LTI) in the child were more likely when mothers were HLA-G del/del than otherwise (OR 3.542, 95% CI 1.397–8.977, p = 0.008). HLA-C and HLE-E genotypes in the mother were not associated with LTI in |

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| Retrospective cohort study (same cohort as previous Rovito 2017)<br>Netherlands | | MV from neonatal DBS<br>N=96 (19 symptomatic) | cognitive, speech-language)<br>Follow-up: 5 years of age | the child. None of the HLA-G, HLA-C or HLA-E genotypes in the child were related to LTI in the child.<br>11/19 (57.9%) symptomatic newborns went on to get 1 or more LTIs, compared to 16/77 (20.8%) asymptomatic newborns.<br>Interactions between baseline variables were not evaluated.<br>The authors' conclusion is as follows: "the potential role of<br>maternal–child HLA in controlling CMV infection and cCMV-related disease, and the clinical value as predictor for long-term outcome certainly deserve further evaluation".<br>The authors' tentative conclusion seems appropriate for this moderately sized and unadjusted study. |
| Rovito et al., 2017b[144]<br>Retrospective cohort study (same cohort as previous Rovito 2017)<br>Netherlands | Symptomatic at birth vs asymptomatic at birth and T and B cell markers | Children retrospectively diagnosed with cC MV from neonatal DBS<br>N=99 with cCMV (16 symptomatic) | Long-term impairments (hearing, visual, neurological, motor, cognitive, speech-language)<br>Follow-up: 5 years of age | Children who had lower numbers of B cells at birth (as measured by KREC copies per ml) were more likely to develop LTI than those with higher numbers of B cells (p=0.005).<br>8/16 (50%) symptomatic newborns went on to get 1 or more LTIs, compared to 14/83 (16.9%) asymptomatic newborns.<br>Interactions between baseline variables were not evaluated.<br>The authors' conclusion is as follows: "the potential protective role of B cells in controlling cCMV-related disease and the clinical value of this marker as a predictor of long-term outcome merit further evaluation".<br>The authors' tentative conclusion seems appropriate for this moderately sized and unadjusted study. |
| Kawada et al., 2015[160]<br>Prospective cohort study<br>Japan | Viral load in blood and urine at diagnosis | Infants referred for CMV testing because of failed newborn hearing screening or suspected to have cCMV because of other clinical abnormalities | SNHL<br>Follow-up: 1 year of age | Mean CMV viral load at diagnosis in whole blood was $6.6\times10^2$ copies/mL in newborns with SNHL at 1 year, and $4.2\times10^2$ copies/mL in those without SNHL at 1 year (p>0.05).<br>Mean CMV viral load at diagnosis in urine was $8.8\times10^5$ copies/mL in newborns with SNHL at one year and $2.6\times10^4$ copies/mL in those without SNH L at 1 year (p>0.05).<br>No baseline interactions were investigated. All 9 patients were treated with antivirals for 6 weeks. |

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| | | N=9 with cCMV (all symptomatic) | | The authors' conclusion was, "Our results suggest that CMV load at diagnosis cannot predict the hearing outcome".<br><br>This was an extremely small study, and so there is a possibility that type II errors may explain the lack of significant findings. |
| Capretti et al., 2017[121]<br><br>Prospective cohort study<br><br>Italy | Clinical, laboratory and instrumental evaluations, including neuroimaging; symptomatic vs asymptomatic | Infants with cCMV<br><br>N=48 (18 symptomatic) | Ophthalmological abnormalities and/or visual impairment<br><br>Follow-up: mean 35 months | Visual impairment at last follow-up was suspected or detected in 4/18 (22%) symptomatic children and in 0/30 (0%) asymptomatic children (p = 0.01). Visual impairment was also associated with signs of central nervous system (CNS) involvement (p<0.001). No association was found with the type of maternal infection. 12/18 (67%) symptomatic infants had SNHL; in 8 infants it was diagnosed at birth, while it was late-onset in 4 cases. No cases of SNHL were reported among asymptomatic infants. No interactions were described. 8/8 infants in the symptomatic group with ocular findings at birth were provided with antivirals (it is unclear whether infants with other symptoms at birth received antivirals).<br><br>The authors concluded that, "ocular involvement seems to be common, even if often not severe, among symptomatic infants, while is rare among asymptomatic infants. Ophthalmological involvement is more common in infants with CNS involvement at birth, and both primary and non-primary maternal infections may be associated with symptomatic infections and ocular disease."<br><br>This unadjusted study suggests that symptomatic newborns are at a slightly greater risk of visual impairment. The sample size was relatively small, but, despite this, findings were statistically significant. |
| De Cuyper et al., 2024[115]<br><br>Prospective cohort study (Flemish CMV registry)<br><br>Belgium | Antenatal characteristics, clinical findings, imaging, viral load, hearing status at birth | Newborns with untreated cCMV<br><br>N=387 (113 symptomatic) | Hearing evolution (long-term neurodevelopmental and audiological follow-up)<br><br>Follow-up: at least 4 years | Children born to mothers infected in their first trimester had a greater odds of late-onset hearing loss than those born to mothers in their second or third trimester [OR (95% CI): 10.10 (2.90 to 34.48)]. None of the children born to mothers infected in their third trimester developed late-onset hearing loss.<br><br>Late-onset hearing loss occurred in 12/135 ears (8.9%) of children with symptomatic infection and 31/548 ears (5.7%) of children with an asymptomatic infection. Children with unilateral hearing loss at birth had greater odds of developing late-onset hearing loss than those with normal hearing at birth [OR (95% CI): 2.68 (0.98-7.29)].<br><br>Children who went on to develop late-onset hearing loss had a higher viral load at baseline than those who did not develop such sequelae, though this was not statistically significant [Hedges g, 0.22 (-0.60 to 1.04)]. |

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| | | | | Interactions between baseline variables were not assessed. None of the newborns received antiviral treatment.<br><br>The authors concluded that, “Findings of this cohort study support that ongoing audiological follow-up for untreated children with congenital hearing loss is important, as the majority of patients had hearing deterioration. The timing of seroconversion was associated with the risk of developing late-onset hearing loss.”<br><br>The conclusion that hearing loss at birth is a risk factor for late-onset hearing loss is not fully supported by the evidence, which was uncertain. However the conclusion that the timing of maternal infection is related to late-onset hearing loss is supported by the data. However, the lack of adjustment for confounding prevents any assumption of causality.<br><br>This study is included in the Vande Walle 2024 systematic review of MRI. |
| Keymeulen et al., 2023[116]<br><br>Prospective cohort study (Flemish CMV registry)<br><br>Belgium | Timing of seroconversion, fetal ultrasound and MRI, clinical features at birth, US, MRI, antiviral therapy | Children with cCMV<br><br>N=753 (261 symptomatic) | Neurodevelopmental outcome<br><br>Follow-up: most followed up beyond 1 year of age | Any long-term impairment was more likely in those who were severely symptomatic at birth (104/190) compared to those who were not severely symptomatic (99/533) (p<0.001). Any long-term impairment was also more likely in those children whose mothers were infected in the first trimester (95/233) compared to those who were not (44/262) (p<0.001). No interactions between baseline variables were investigated. Antivirals were received by 180/261 symptomatic children.<br><br>The authors concluded that, “both symptomatic and asymptomatic children can develop sequelae, independent of the timing of seroconversion.”<br><br>This large study did not adjust for confounding. However, the authors’ conservative conclusions are supported by their findings. |
| Soriano-Ramos et al., 2024[99]<br><br>Prospective cohort study<br><br>Spain | Type of maternal infection, newborn symptoms, US and MRI, T-cell immune responses | Newborns with cCMV<br><br>N=64 (42 symptomatic) | Hearing loss and neurological impairment<br><br>Follow-up: median age 25.3 months | Long-term sequelae were associated with the following baseline variables on a bivariate analysis: symptomatic cCMV (p=0.012), presence of abnormal physical examination at birth (p=0.006), abnormal findings in first cUS (p=0.016), presence of white matter abnormalities in cUS (p=0.008), and a failed hearing screening test (p<0.001). Sequelae were also associated with a lower total lymphocyte count (p=0.013), a lower CD4+ T-cell count (p=0.020), and a lower CD4+/ CD8+ ratio (p=0.03). No relationship was observed with CMV-specific IFN-g-CD8+ or CD4+ lymphocyte levels. No interactions between baseline variables were investigated. 38 children received antivirals (17/18 with sequelae and 21/46 without sequelae). |

| | | | | |
|---|---|---|---|---|
| | | | | Multivariable analysis showed that sequelae were independently associated with lower total lymphocyte count (adjusted OR 0.549, 95% CI 0.323-0.833, p=0.012). There was also a trend toward an association with higher absolute count of CD8+ T cells (p=0.090).<br><br>The authors concluded that, “CMV-specific IFN-g-CD4+ and CD8+ T-lymphocyte responses in neonates with cCMV were not predictive of long-term sequelae.”<br><br>This study was enhanced by its rigorous analysis, though it is unclear if the moderate sample size was sufficient for such a large multivariable analysis. The authors’ cautious conclusion is therefore justified, and further work in this area is warranted. |

# Appraisal of study quality and risk of bias

Table 29 presents the results of the ROBIS assessment of included systematic reviews (for reviews relevant to Criterion 7 and the Zheng review, relevant to Criterion 4). Table 30 presents the results of the QUADAS-2 evaluation of all included prognostic accuracy studies relevant to Criterion 7.

*Table 29: ROBIS assessment of all included systematic reviews*

| STUDY | DOMAIN APPRAISAL | |
|---|---|---|
| Vande Walle, 2024[79] | **DOMAIN 1: STUDY ELIGIBILITY CRITERIA**<br>**Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified:** | |
| | Did the review adhere to pre-defined objectives and eligibility criteria? | **PN** |
| | Were the eligibility criteria appropriate for the review question? | **PY** |
| | Were eligibility criteria unambiguous? | **N** |
| | Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)? | **PN** |
| | Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)? | **PN** |
| | Concerns regarding specification of study eligibility criteria | **HIGH CONCERN** |
| | **DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES**<br>**Describe methods of study identification and selection (e.g. number of reviewers involved):** | |
| | Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? | **Y** |
| | Were methods additional to database searching used to identify relevant reports? | **N** |
| | Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? | **PN** |
| | Were restrictions based on date, publication format, or language appropriate? | **PN** |
| | Were efforts made to minimise error in selection of studies? | **PN** |
| | Concerns regarding methods used to identify and/or select studies | **HIGH CONCERN** |
| | **DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL**<br>**Describe methods of data collection, what data were extracted from studies or collected through other means, how risk of bias was assessed (e.g. number of reviewers involved) and the tool used to assess risk of bias:** | |
| | Were efforts made to minimise error in data collection? | **PY** |
| | Were sufficient study characteristics available for both review authors and readers to be able to interpret the results? | **N** |
| | Were all relevant study results collected for use in the synthesis? | **PY** |
| | Was risk of bias (or methodological quality) formally assessed using appropriate criteria? | **Y** |
| | Were efforts made to minimise error in risk of bias assessment? | **PN** |
| | Concerns regarding methods used to collect data and appraise studies | **HIGH CONCERN** |

| STUDY | DOMAIN APPRAISAL | |
|---|---|---|
| | **DOMAIN 4: SYNTHESIS AND FINDINGS**<br>**Describe synthesis methods:** | |
| | Did the synthesis include all studies that it should? | **PN** |
| | Were all pre-defined analyses reported or departures explained? | **NI** |
| | Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies? | **Y** |
| | Was between-study variation (heterogeneity) minimal or addressed in the synthesis? | **NA** |
| | Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses? | **NA** |
| | Were biases in primary studies minimal or addressed in the synthesis? | **NA** |
| | Concerns regarding the synthesis and findings | **UNCLEAR** |
| | **OVERALL RISK OF BIAS IN THE REVIEW** | **HIGH RISK OF BIAS** |
| Chatzakis, 2020[102] | **DOMAIN 1: STUDY ELIGIBILITY CRITERIA**<br>**Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified:** | |
| | Did the review adhere to pre-defined objectives and eligibility criteria? | **PY** |
| | Were the eligibility criteria appropriate for the review question? | **PY** |
| | Were eligibility criteria unambiguous? | **PN** |
| | Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)? | **Y** |
| | Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)? | **Y** |
| | Concerns regarding specification of study eligibility criteria | **LOW CONCERN** |
| | **DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES**<br>**Describe methods of study identification and selection (e.g. number of reviewers involved):** | |
| | Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? | **PY** |
| | Were methods additional to database searching used to identify relevant reports? | **N** |
| | Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? | **PN** |
| | Were restrictions based on date, publication format, or language appropriate? | **PY** |
| | Were efforts made to minimise error in selection of studies? | **PY** |
| | Concerns regarding methods used to identify and/or select studies | **LOW CONCERN** |
| | **DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL**<br>**Describe methods of data collection, what data were extracted from studies or collected through other means, how risk of bias was assessed (e.g. number of reviewers involved) and the tool used to assess risk of bias:** | |
| | Were efforts made to minimise error in data collection? | **Y** |
| | Were sufficient study characteristics available for both review authors and readers to be able to interpret the results? | **Y** |
| | Were all relevant study results collected for use in the synthesis? | **PY** |
| | Was risk of bias (or methodological quality) formally assessed using appropriate criteria? | **Y** |

| STUDY | DOMAIN APPRAISAL | |
|---|---|---|
| | Were efforts made to minimise error in risk of bias assessment? | **Y** |
| | Concerns regarding methods used to collect data and appraise studies | **LOW CONCERN** |
| | **DOMAIN 4: SYNTHESIS AND FINDINGS**<br>**Describe synthesis methods:** | |
| | Did the synthesis include all studies that it should? | **PY** |
| | Were all pre-defined analyses reported or departures explained? | **PY** |
| | Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies? | **PN** |
| | Was between-study variation (heterogeneity) minimal or addressed in the synthesis? | **Y** |
| | Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses? | **N** |
| | Were biases in primary studies minimal or addressed in the synthesis? | **PY** |
| | Concerns regarding the synthesis and findings | **LOW CONCERN** |
| | **OVERALL RISK OF BIAS IN THE REVIEW** | **LOW RISK OF BIAS** |
| Maltezou, 2020[119] | **DOMAIN 1: STUDY ELIGIBILITY CRITERIA**<br>**Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified:** | |
| | Did the review adhere to pre-defined objectives and eligibility criteria? | **Y** |
| | Were the eligibility criteria appropriate for the review question? | **Y** |
| | Were eligibility criteria unambiguous? | **Y** |
| | Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)? | **Y** |
| | Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)? | **PN** |
| | Concerns regarding specification of study eligibility criteria | **LOW CONCERN** |
| | **DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES**<br>**Describe methods of study identification and selection (e.g. number of reviewers involved):** | |
| | Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? | **PN** |
| | Were methods additional to database searching used to identify relevant reports? | **Y** |
| | Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? | **PN** |
| | Were restrictions based on date, publication format, or language appropriate? | **PN** |
| | Were efforts made to minimise error in selection of studies? | **PY** |
| | Concerns regarding methods used to identify and/or select studies | **LOW CONCERN** |
| | **DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL**<br>**Describe methods of data collection, what data were extracted from studies or collected through other means, how risk of bias was assessed (e.g. number of reviewers involved) and the tool used to assess risk of bias:** | |
| | Were efforts made to minimise error in data collection? | **PY** |
| | Were sufficient study characteristics available for both review authors and readers to be able to interpret the results? | **PY** |

| STUDY | DOMAIN APPRAISAL | |
|---|---|---|
| | Were all relevant study results collected for use in the synthesis? | **Y** |
| | Was risk of bias (or methodological quality) formally assessed using appropriate criteria? | **Y** |
| | Were efforts made to minimise error in risk of bias assessment? | **NI** |
| | Concerns regarding methods used to collect data and appraise studies | **LOW CONCERN** |
| | **DOMAIN 4: SYNTHESIS AND FINDINGS**<br>**Describe synthesis methods:** | |
| | Did the synthesis include all studies that it should? | **Y** |
| | Were all pre-defined analyses reported or departures explained? | **Y** |
| | Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies? | **Y** |
| | Was between-study variation (heterogeneity) minimal or addressed in the synthesis? | **Y** |
| | Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses? | **PY** |
| | Were biases in primary studies minimal or addressed in the synthesis? | **N** |
| | Concerns regarding the synthesis and findings | **LOW CONCERN** |
| | **OVERALL RISK OF BIAS IN THE REVIEW** | **LOW RISK OF BIAS** |
| Smyrli, 2024[125] | **DOMAIN 1: STUDY ELIGIBILITY CRITERIA**<br>**Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified:** | |
| | Did the review adhere to pre-defined objectives and eligibility criteria? | **Y** |
| | Were the eligibility criteria appropriate for the review question? | **Y** |
| | Were eligibility criteria unambiguous? | **Y** |
| | Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)? | **Y** |
| | Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)? | **Y** |
| | Concerns regarding specification of study eligibility criteria | **LOW CONCERN** |
| | **DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES**<br>**Describe methods of study identification and selection (e.g. number of reviewers involved):** | |
| | Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? | **PN** |
| | Were methods additional to database searching used to identify relevant reports? | **N** |
| | Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? | **Y** |
| | Were restrictions based on date, publication format, or language appropriate? | **Y** |
| | Were efforts made to minimise error in selection of studies? | **Y** |
| | Concerns regarding methods used to identify and/or select studies | **LOW CONCERN** |
| | **DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL**<br>**Describe methods of data collection, what data were extracted from studies or collected through other means, how risk of bias was assessed (e.g. number of reviewers involved) and the tool used to assess risk of bias:** | |

| STUDY | DOMAIN APPRAISAL | |
|---|---|---|
| | **Questions** | |
| | Were efforts made to minimise error in data collection? | **Y** |
| | Were sufficient study characteristics available for both review authors and readers to be able to interpret the results? | **Y** |
| | Were all relevant study results collected for use in the synthesis? | **Y** |
| | Was risk of bias (or methodological quality) formally assessed using appropriate criteria? | **Y** |
| | Were efforts made to minimise error in risk of bias assessment? | **NI** |
| | Concerns regarding methods used to collect data and appraise studies | **LOW CONCERN** |
| | **DOMAIN 4: SYNTHESIS AND FINDINGS**<br>**Describe synthesis methods:** | |
| | Did the synthesis include all studies that it should? | **PY** |
| | Were all pre-defined analyses reported or departures explained? | **Y** |
| | Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies? | **PN** |
| | Was between-study variation (heterogeneity) minimal or addressed in the synthesis? | **NA** |
| | Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses? | **NA** |
| | Were biases in primary studies minimal or addressed in the synthesis? | **NA** |
| | Concerns regarding the synthesis and findings | **LOW CONCERN** |
| | **OVERALL RISK OF BIAS IN THE REVIEW** | **LOW RISK OF BIAS** |
| Buca,2021[103] | **DOMAIN 1: STUDY ELIGIBILITY CRITERIA**<br>**Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified:** | |
| | Did the review adhere to pre-defined objectives and eligibility criteria? | **Y** |
| | Were the eligibility criteria appropriate for the review question? | **Y** |
| | Were eligibility criteria unambiguous? | **Y** |
| | Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)? | **Y** |
| | Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)? | **Y** |
| | Concerns regarding specification of study eligibility criteria | **LOW CONCERN** |
| | **DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES**<br>**Describe methods of study identification and selection (e.g. number of reviewers involved):** | |
| | Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? | **Y** |
| | Were methods additional to database searching used to identify relevant reports? | **Y** |
| | Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? | **PY** |
| | Were restrictions based on date, publication format, or language appropriate? | **PY** |
| | Were efforts made to minimise error in selection of studies? | **Y** |
| | Concerns regarding methods used to identify and/or select studies | **LOW CONCERN** |

| STUDY | DOMAIN APPRAISAL | |
|---|---|---|
| | **DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL**<br>**Describe methods of data collection, what data were extracted from studies or collected through other means, how risk of bias was assessed (e.g. number of reviewers involved) and the tool used to assess risk of bias:** | |
| | Were efforts made to minimise error in data collection? | **Y** |
| | Were sufficient study characteristics available for both review authors and readers to be able to interpret the results? | **Y** |
| | Were all relevant study results collected for use in the synthesis? | **PY** |
| | Was risk of bias (or methodological quality) formally assessed using appropriate criteria? | **Y** |
| | Were efforts made to minimise error in risk of bias assessment? | **Y** |
| | Concerns regarding methods used to collect data and appraise studies | **LOW CONCERN** |
| | **DOMAIN 4: SYNTHESIS AND FINDINGS**<br>**Describe synthesis methods:** | |
| | Did the synthesis include all studies that it should? | **NI** |
| | Were all pre-defined analyses reported or departures explained? | **NI** |
| | Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies? | **NI** |
| | Was between-study variation (heterogeneity) minimal or addressed in the synthesis? | **Y** |
| | Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses? | **Y** |
| | Were biases in primary studies minimal or addressed in the synthesis? | **PY** |
| | Concerns regarding the synthesis and findings | **LOW CONCERN** |
| | **OVERALL RISK OF BIAS IN THE REVIEW** | **LOW RISK OF BIAS** |
| Vos, 2021[126] | **DOMAIN 1: STUDY ELIGIBILITY CRITERIA**<br>**Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified:** | |
| | Did the review adhere to pre-defined objectives and eligibility criteria? | **Y** |
| | Were the eligibility criteria appropriate for the review question? | **Y** |
| | Were eligibility criteria unambiguous? | **Y** |
| | Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)? | **Y** |
| | Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)? | **Y** |
| | Concerns regarding specification of study eligibility criteria | **LOW CONCERN** |
| | **DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES**<br>**Describe methods of study identification and selection (e.g. number of reviewers involved):** | |
| | Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? | **Y** |
| | Were methods additional to database searching used to identify relevant reports? | **NI** |
| | Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? | **PY** |
| | Were restrictions based on date, publication format, or language appropriate? | **Y** |

| STUDY | DOMAIN APPRAISAL | |
|---|---|---|
| | Were efforts made to minimise error in selection of studies? | **Y** |
| | Concerns regarding methods used to identify and/or select studies | **LOW CONCERN** |
| | **DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL**<br>**Describe methods of data collection, what data were extracted from studies or collected through other means, how risk of bias was assessed (e.g. number of reviewers involved) and the tool used to assess risk of bias:** | |
| | Were efforts made to minimise error in data collection? | **Y** |
| | Were sufficient study characteristics available for both review authors and readers to be able to interpret the results? | **N** |
| | Were all relevant study results collected for use in the synthesis? | **PY** |
| | Was risk of bias (or methodological quality) formally assessed using appropriate criteria? | **Y** |
| | Were efforts made to minimise error in risk of bias assessment? | **Y** |
| | Concerns regarding methods used to collect data and appraise studies | **LOW CONCERN** |
| | **DOMAIN 4: SYNTHESIS AND FINDINGS**<br>**Describe synthesis methods:** | |
| | Did the synthesis include all studies that it should? | **PY** |
| | Were all pre-defined analyses reported or departures explained? | **PY** |
| | Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies? | **Y** |
| | Was between-study variation (heterogeneity) minimal or addressed in the synthesis? | **NA** |
| | Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses? | **NA** |
| | Were biases in primary studies minimal or addressed in the synthesis? | **PY** |
| | Concerns regarding the synthesis and findings | **LOW CONCERN** |
| | **OVERALL RISK OF BIAS IN THE REVIEW** | **LOW RISK OF BIAS** |
| Riga, 2018 [127] | **DOMAIN 1: STUDY ELIGIBILITY CRITERIA**<br>**Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified:** | |
| | Did the review adhere to pre-defined objectives and eligibility criteria? | **PY** |
| | Were the eligibility criteria appropriate for the review question? | **Y** |
| | Were eligibility criteria unambiguous? | **PN** |
| | Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)? | **Y** |
| | Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)? | **PY** |
| | Concerns regarding specification of study eligibility criteria | **LOW CONCERN** |
| | **DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES**<br>**Describe methods of study identification and selection (e.g. number of reviewers involved):** | |
| | Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? | **PY** |
| | Were methods additional to database searching used to identify relevant reports? | **Y** |

| STUDY | DOMAIN APPRAISAL | |
|---|---|---|
| | Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? | **PN** |
| | Were restrictions based on date, publication format, or language appropriate? | **PY** |
| | Were efforts made to minimise error in selection of studies? | **PY** |
| | Concerns regarding methods used to identify and/or select studies | **HIGH CONCERN** |
| | **DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL**<br>**Describe methods of data collection, what data were extracted from studies or collected through other means, how risk of bias was assessed (e.g. number of reviewers involved) and the tool used to assess risk of bias:** | |
| | Were efforts made to minimise error in data collection? | **Y** |
| | Were sufficient study characteristics available for both review authors and readers to be able to interpret the results? | **PY** |
| | Were all relevant study results collected for use in the synthesis? | **Y** |
| | Was risk of bias (or methodological quality) formally assessed using appropriate criteria? | **Y** |
| | Were efforts made to minimise error in risk of bias assessment? | **NI** |
| | Concerns regarding methods used to collect data and appraise studies | **LOW CONCERN** |
| | **DOMAIN 4: SYNTHESIS AND FINDINGS**<br>**Describe synthesis methods:** | |
| | Did the synthesis include all studies that it should? | **PY** |
| | Were all pre-defined analyses reported or departures explained? | **PY** |
| | Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies? | **N** |
| | Was between-study variation (heterogeneity) minimal or addressed in the synthesis? | **N** |
| | Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses? | **NI** |
| | Were biases in primary studies minimal or addressed in the synthesis? | **PY** |
| | Concerns regarding the synthesis and findings | **HIGH CONCERN** |
| | **OVERALL RISK OF BIAS IN THE REVIEW** | **HIGH RISK OF BIAS** |
| Zheng (2022)[32] | **DOMAIN 1: STUDY ELIGIBILITY CRITERIA**<br>**Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified:** | |
| | Did the review adhere to pre-defined objectives and eligibility criteria? | **Y** |
| | Were the eligibility criteria appropriate for the review question? | **Y** |
| | Were eligibility criteria unambiguous? | **PN** |
| | Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)? | **Y** |
| | Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)? | **PY** |
| | Concerns regarding specification of study eligibility criteria | **LOW CONCERN** |
| | **DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES**<br>**Describe methods of study identification and selection (e.g. number of reviewers involved):** | |

| STUDY | DOMAIN APPRAISAL | |
|---|---|---|
| | Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? | **Y** |
| | Were methods additional to database searching used to identify relevant reports? | **N** |
| | Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? | **PY** |
| | Were restrictions based on date, publication format, or language appropriate? | **PY** |
| | Were efforts made to minimise error in selection of studies? | **NI** |
| | Concerns regarding methods used to identify and/or select studies | **LOW CONCERN** |
| | **DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL**<br>**Describe methods of data collection, what data were extracted from studies or collected through other means, how risk of bias was assessed (e.g. number of reviewers involved) and the tool used to assess risk of bias:** | |
| | Were efforts made to minimise error in data collection? | **Y** |
| | Were sufficient study characteristics available for both review authors and readers to be able to interpret the results? | **PY** |
| | Were all relevant study results collected for use in the synthesis? | **PY** |
| | Was risk of bias (or methodological quality) formally assessed using appropriate criteria? | **Y** |
| | Were efforts made to minimise error in risk of bias assessment? | **Y** |
| | Concerns regarding methods used to collect data and appraise studies | **LOW CONCERN** |
| | **DOMAIN 4: SYNTHESIS AND FINDINGS**<br>**Describe synthesis methods:** | |
| | Did the synthesis include all studies that it should? | **PY** |
| | Were all pre-defined analyses reported or departures explained? | **PY** |
| | Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies? | **Y** |
| | Was between-study variation (heterogeneity) minimal or addressed in the synthesis? | **PY** |
| | Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses? | **Y** |
| | Were biases in primary studies minimal or addressed in the synthesis? | **PY** |
| | Concerns regarding the synthesis and findings | **LOW CONCERN** |
| | **OVERALL RISK OF BIAS IN THE REVIEW** | **LOW RISK OF BIAS** |
| Y = yes; PY = probably yes; PN = probably no; N = no; NI= no information | | |

*Table 30: QUADAS-2 evaluation of all included prognostic accuracy studies*

| Paper | Domain 1: Patient selection | | Domain 2: Index tests | | Domain 3: Reference Standard | | Domain 4: Flow and timing |
|---|---|---|---|---|---|---|---|
| | | Applicability | | Applicability | | Applicability | |
| First author | ROB from selection (L/H/U) | Concerns about matching of patients to review question? (L/H/U) | ROB relating to index test (L/H/U) | Concerns about matching of index tests to review question? (L/H/U) | ROB relating to reference test (L/H/U) | Concerns about matching of reference test to review question? (L/H/U) | ROB from patient flow? (L/H/U) |
| Alarcon et al. 2013[75] | L | H | H | L | L | L | U |
| Alarcon et al. 2016[80] | L | H | U | L | L | L | U |
| Alarcon et al. 2024[81] | L | L | U | L | U | L | U |
| Blazquez-Gamero et al. 2019[82] | L | H | U | L | U | L | U |
| Capretti et al. 2014[83] | L | L | U | L | U | L | L |
| Castellanos et al. 2022[84] | L | L | U | L | U | L | L |
| Chebib et al. 2022[85] | L | L | H | L | U | L | L |
| Craeghs et al. 2021[86] | L | L | U | L | U | L | L |
| De Juan et al. 2020[87] | L | L | H | L | U | L | L |
| Dhondt et al. 2023[151] | L | L | U | L | U | L | H |
| Foulonet al. 2019[88] | L | L | U | L | U | L | U |
| Fourgeaud et al. 2024[89] | L | L | U | L | U | L | U |
| Giannattasio et al. 2018[90] | L | L | U | L | U | L | L |
| Kwak et al. 2018[91] | L | H | U | L | U | L | L |

| Paper | Domain 1: Patient selection | | Domain 2: Index tests | | Domain 3: Reference Standard | | Domain 4: Flow and timing |
|---|---|---|---|---|---|---|---|
| | | Applicability | | Applicability | | Applicability | |
| First author | ROB from selection (L/H/U) | Concerns about matching of patients to review question? (L/H/U) | ROB relating to index test (L/H/U) | Concerns about matching of index tests to review question? (L/H/U) | ROB relating to reference test (L/H/U) | Concerns about matching of reference test to review question? (L/H/U) | ROB from patient flow? (L/H/U) |
| Lucignani et al. 2021[92] | L | L | H | L | L | L | L |
| Nishida et al. 2020[93] | L | L | U | L | U | L | U |
| Ouellette et al. 2020[162] | L | L | H | L | U | L | L |
| Vande Walle et al. 2024[94] | L | L | H | L | U | L | U |
| Yamaguchi et al. 2022[154] | L | L | H | L | U | L | U |
| L = low; H =High; U = unclear; ROB = risk of bias | | | | | | | |

# Appendix 4 – Relevant ongoing studies and unpublished studies

There were 8 ‘ongoing’ studies identified from clinical trial registers and PROSPERO (the international prospective register of systematic reviews), summarised in Table 31. Whilst most of these studies appear to have been completed (the study completion date has passed), no publications were identified relating to them.

*Table 31: Summary of ongoing studies*

| Study details | Participant information | Intervention/ characteristic | Outcome (primary) |
|---|---|---|---|
| **Ongoing systematic reviews** | | | |
| Abrahao et al. 2022[430]<br><br>The congenital cytomegalovirus infection screening by urine: is it worthy? A systematic review<br><br>PROSPERO: CRD42022326424<br><br>Anticipated completion date: 31/12/23 | Newborns (without a known risk factor) within the first 2 weeks of life | Urine screening for cC MV | Hearing function (Brainstem Evoked Response Audiometry) |
| Wu et al. 2022[431]<br><br>Meta-analysis of HCMV viral load level and the occurrence and outcome of hearing impairment<br><br>PROSPERO: CRD42022301633<br><br>Anticipated completion date: 01/03/22 | Children under the age of 18 who were diagnosed with cytomegalovirus infection | Viral load in different types of specimens such as saliva, blood, urine, and dried blood spots | Sensorineural hearing loss |
| Lopes et al. 2023[432]<br><br>Impact of congenital cytomegalovirus infection on motor development in children: systematic review<br><br>PROSPERO: CRD42023404868<br><br>Anticipated completion date: 01/11/24 | Children with cCMV infection up to 5 years | Assessment of motor development (aspects of cCMV infection – diagnostic method, symptomatic or asymptomatic at birth and which symptoms, will be extracted) | Motor development: presence or absence of delay in motor development |

| Study details | Participant information | Intervention/ characteristic | Outcome (primary) |
|---|---|---|---|
| Shetty et al. 2024[433]<br><br>Evaluation of salivary sample in diagnosis, screening and management of cytomegalovirus (CMV) infection in newborns-systematic review and metanalysis<br><br>PROSPERO: CRD42024603785<br><br>Anticipated completion date: 31/12/25 | Neonates with cytomegalovirus | Salivary markers and screening test (including using pooled salivary samples) compared with gold standard tests on urine | Diagnostic accuracy (sensitivity, specificity, positive and negative predictive values) |
| Wang et al. 2023[434]<br><br>Accuracy and implementability of dried blood spot polymerase chain reaction assays for screening congenitalcytomegalovirus infection: Systematic review and meta-analysis<br><br>PROSPERO: CRD42023397836<br><br>Anticipated completion date: 30/06/24 | Infants | Dried blood spot PCR assays collected among the first week of life compared with standard methods | Diagnostic accuracy (sensitivity, specificity, positive and negative likelihood ratios, positive and negative predictive values) |
| **Ongoing primary studies** | | | |
| Prognostic Value of Neonatal Markers for the Development of Neurosensorial Sequelae in Children Infected by Cytomegalovirus in Utero (CYMEPEDIA)[435]<br><br>Clinical trial identifier: NCT01923636<br><br>Study completion date: 16/05/22 | Neonates less than 1 month with cCMV infection at birth objectified by the detection of CMV in a urine sample, in saliva or blood obtained in the first 10 days of life (n=254) | Prognostic score for the development of neurosensorineural sequelae, based on clinical, radiological and laboratory (virological and immunological) standardized reports | Prognostic value of neonatal markers (clinical, imaging and biological) for the development of neurosensorial sequelae at 1 year and 2 years of age |
| Markers for neurocognitive impairment in congenitally CMV infected infants: MARVELYS study[436]<br><br>Clinical trial identifier: NL-OMON43495<br><br>Study completion date: not reported (start date 17/05/16) | Neonates younger than 10 days of life with positive CMV PCR in urine or blood and/or positive CMV PCR in dried blood spot in children older than 10 days of age (n=100) | CSF and blood parameters | Neurocognitive performance, deviations in neuroimaging parameters, audiological and ophthalmologic measurements at the age of 1, 2, 5 and 8 years |

| Study details | Participant information | Intervention/ characteristic | Outcome (primary) |
|---|---|---|---|
| Targeted Screening for Congenital Cytomegalovirus-related Hearing loss in infants in Western Australia[437]<br><br>Clinical trial identifier: ACTRN12621000484842<br><br>Study completion date: not reported (date of last data collection 07/12/22) | Infants born in Western Australia undergoing newborn hearing screening which results in a 'refer' (fail) result in 1 or both ears | Targeted testing of infants for congenital cytomegalovirus (cCMV). Infants are targeted using the newborn hearing screen result. | To assess whether targeted congenital cytomegalovirus testing is able to be completed by day 21 of life in Infants at high-risk of the virus across Western Australia. |

Abbreviations: cCMV = congenital cytomegalovirus; CMV = cytomegalovirus; CSF = cerebrospinal fluid; PCR = polymerase chain reaction.

The electronic searches and supplementary searching identified 38 studies that have only been published as conference abstracts, summarised in Table 32. These studies have been cross-checked against the identified published studies, but do not appear to have been published in full.

*Table 32: Summary of unpublished studies*

| Study details | Title |
|---|---|
| **Criterion 4** | |
| Brophy et al. 2024[438] | Congenital CMV ANd HEARing in Ontario: Optimizing screening to improve child health outcomes (CAN HEAR ONTARIO) |
| Churyukina et al. 2023[439] | Predictive value of cytokines for preservation neurologic semiology in neonatal cytomegalovirus infection |
| Del Valle Penella et al. 2022[440] | Performance of dried blood spot (DBS) for the diagnosis of congenital cytomegalovirus (cCMV) in a single center: a real-world experience |
| Kakkar et al. 2024[441] | Feasibility of dried urine on filter paper for universal congenital CMV screening |
| Kim et al. 2023[442] | CMV PCR agreement between blood and dried blood spots in infants with congenital cytomegalovirus infection |
| Kruc et al. 2021[443] | Does cytomegalovirus (CMV) viral load correlate with disease severity in the setting of congenital CMV (CCMV) infection? results from a universal CCMV screening study |
| Lazzarotto et al. 2013[444] | Pre-and post-natal diagnosis of congenital cytomegalovirus infection |
| Rohde et al. 2017[445] | Analytical and clinical performance of a real-time screening PCR assay identifying congenital CMV infection |
| **Criterion 7** | |
| Alarcon et al. 2022[446] | Isolated white matter abnormalities at birth as prognostic markers in congenital cytomegalovirus infection |
| Boscolo et al. 2024[447] | Correlation between neurodevelopemental outcomes and brain MRI severity score in patients with congenital cytomegalovirus infection: a monocentric restrospective study |
| Buonsenso et al. 2024[448] | Prognostic factors of late-onset hearing loss in infants with congenital cytomegalovirus and normal audiological assessment at birth |
| Castells Vilella et al. 2016[449] | Risk factors associated with hearing loss and neurologic impairment in the Spanish network of infants with congenital cytomegalovirus infection (REDICCMV) |
| Chung et al. 2024[450] | Predicting outcome in clinically inapparent congenital cytomegalovirus infection with hearing loss |
| Churyukina et al. 2021[451] | Early predictors of preservation neurologic semiology in neonatal cytomegalovirus infection |
| Czech-Kowalska et al. 2022[452] | Predictors of sensorineural hearing loss in newborns with congenital CMV infection – a single-center experience |
| Eleni Loizou et al. 2024[453] | Vestibular dysfunction in asymptomatic children with congenital cytomegalovirus infection |
| Faure-Bardon et al. 2018[454] | Neonatal outcome and long-term sequelae in CMV infected neonates according to the timing of primary maternal infection |
| Fernandez-Rueda et al. 2024[455] | Risk factors associated with hearing loss in children with congenital cytomegalovirus infection |
| Fourgeaud et al. 2024[456] | Sequelae of congenital cytomegalovirus following maternal primary infections are limited to those acquired before 12 weeks |

| Study details | Title |
|---|---|
| Karagiannidou et al. 2024[457] | Delayed onset hearing loss (DOHL) in asymptomatic newborns with congenital cytomegalovirus infection (cCMV) |
| Kravchenko et al. 2014[458] | The outcome of cerebral pathology by the end of the first year of life in newborn babies with cytomegalovrus infection |
| Kravchenko et al. 2016[459] | Prognosis for the preservation of neurological symptoms by the end of the first year of life in Newborn babies, who had cytomegalovirus infection |
| Medoro et al. 2022[460] | Neonatal immune phenotypes and neurodevelopmental outcomes in infants with congenital cytomegalovirus infection (cCMV) |
| Morioka et al. 2017[461] | Neurological outcomes at 18 months of age and neonatal risk factors for severe sequelae in congenitally cytomegalovirus-infected infants treated by antiviral treatment early in life |
| Nosan et al. 2022[462] | Genetic variations in toll-like receptor 2 gene in Slovenian newborns with congenital human cytomegalovirus infection |
| Salome et al. 2024[463] | Can viral load predict a symptomatic congenital CMV infection? A systematic review and meta-analysis |
| Sandoval Carmona et al. 2022[464] | Viral load kinetics as a prognostic indicator of outcomes among children with congenital cytomegalovirus infection in the Montreal cohort |
| Smiljkovic et al. 2016[465] | Use of quantitative polymerase chain reaction in blood and cerebrospinal fluid as a predictor of severity in congenital cytomegalovirus infection |
| Smithers-Sheedy et al. 2014[466] | Cerebral palsy attributed to congenital cytomegalovirus infection is associated with spastic quadriplegia and female sex |
| Vanwinkel et al. 2016[467] | Congenitally infected CMV fetuses following first trimester maternal infection: Neonatal and short-term outcome |
| Villaverde et al. 2024[468] | Association between congenital cytomegalovirus infection and autism spectrum disorder |
| Vossen et al. 2016[469] | Long-term impairment attributable to congenital cytomegalovirus infection |
| **Criteria 12 and 13** | |
| Carrillo-Marquez et al. 2017[470] | Programmatic congenital CMV universal screening programme |
| Landers et al. 2024[471] | Analysis of dried blood spot and saliva PCR screening for detection of congenital cytomegalovirus infection informs implementation of a novel universal newborn screening program |
| Lund et al. 2024[472] | Targeted screening for congenital CMV in the capital region of Denmark |
| Penton et al. 2019[473] | Adherence to follow-up and CMV testing in infants who failed newborn hearing screens: Evaluation of new protocol to ensure follow-up and testing |
| Syridou et al. 2022[474] | Diagnostic ability of targeted and universal neonatal screening for cCMV-infection, to provide timely diagnosis of cCMV-infection associated neurodevelopmental delay |
| Webb et al. 2024[475] | Exploring parents' experiences of completing targeted congenital cytomegalovirus screening during their infant's newborn hearing screening |

# Appendix 5 – UK NSC reporting checklist for evidence summaries

All items on the UK NSC Reporting Checklist for Evidence Summaries have been addressed in this report. A summary of the checklist, along with the page or pages where each item can be found in this report, is presented in Table 33.

*Table 33 UK NSC reporting checklist*

| Section | Item | Page no. |
|---|---|---|
| Title and summaries | | |
| Title Sheet | Identify the review as a UK NSC Evidence summary | Title page |
| Plain English summary | Plain English description of the executive summary. | 7 |
| Executive summary | Structured overview of the whole report. To include: the purpose/aim of the review; background; previous recommendations; findings and gaps in the evidence; recommendations on the screening that can or cannot be made on the basis of the review | 8 |
| Introduction and Approach | | |
| Background and objectives | Background – Current policy context and rationale for the current review – for example, reference to details of previous reviews, basis for current recommendation, recommendations made, gaps identified, drivers for new reviews | 14 |
| | Objectives – What are the questions the current evidence summary intends to answer? – statement of the key questions for the current evidence summary, criteria they address, and number of studies included per question, description of the overall results of the literature search. | 16 |
| | Method – briefly outline the rapid review methods used. | 18 |
| | | 15 |
| | | 17 |

| Section | Item | Page no. |
|---|---|---|
| Eligibility for inclusion in the review | State all criteria for inclusion and exclusion of studies to the review clearly(PICO, dates, language, study type, publication type, publication status etc.) To be decided a priori | 18 |
| Appraisal for quality/ risk of bias tool | Details of tool/ checklist used to assess quality, e.g. QUADAS 2, CASP, SIGN, AMSTAR. | 22 |
| Search strategy and study selection | | |
| Databases/ sources searched | Give details of all databases searched (including platform/ interface and coverage dates) and date of final search. | 17 |
| Search strategy and results | Present the full search strategy for at least one database (usually a version of Medline), including limits and search filters if used.<br>Provide details of the total number of (results from each database searched), number of duplicates removed, and the final number of unique records to consider for inclusion. | Appendix 1<br>Appendix 2, Figure 4 |
| Study selection | State the process for selecting studies – inclusion and exclusion criteria, number of studies screened by title/abstract and full text, number of reviewers, any cross checking carried out. | 18, 24 and Appendix 2 |
| Study level reporting of results (for each key question) | | |
| Study level reporting, results and risk of bias assessment | For each study, produce a table that includes the full citation and a summary of the data relevant to the question (for example, study size, PICO, follow-up period, outcomes reported, statistical analyses etc.).<br>Provide a simple summary of key measures, effect estimates and confidence intervals for each study where available.<br>For each study, present the results of any assessment of quality/risk of bias. | 30-46 (Criterion 4): Tables 3-9<br>Criterion 7: Tables 10-16 & Appendix 3<br>Criteria 11, 12, 13): Tables 17-21 |
| Additional analyses | Describe additional analyses (for example, sensitivity, specificity, PPV, etc.) carried out by the reviewer. [Remove if not performed] | 23 |
| Question level synthesis | | |

| Section | Item | Page no. |
|---|---|---|
| Description of the evidence | For each question, give numbers of studies screened, assessed for eligibility, and inclusion in the review, with summary reasons for exclusion | Criterion 4:<br>25 onwards<br>Criterion 7:<br>46 onwards<br>Criteria 11, 12, 13:<br>75 onwards<br><br>See also Appendix 2 |
| Combining and presenting the findings | Provide a balanced discussion of the body of evidence which avoids over reliance on one study or set of studies.<br>Consideration of four compartments should inform the reviewer's judgement on whether the criterion is "met", "not met" or "uncertain": quantity; quality; applicability and consistency. | onwards25 to 94 |
| Summary of findings | Provide a description of the evidence reviewed and included for each question, with reference to their eligibility for inclusion.<br>Summarise the main findings including the quality/ risk of bias issues for each question.<br>Have the criteria addressed been "met", "not met" or "uncertain"? | 44 (Criterion 4)<br>71 (Criterion 7)<br>91 (Criteria 11 & 13)<br>94 (Criterion 12) |
| Review Summary | | |
| Conclusions and implications for policy | Do findings indicate whether screening should be recommended?<br>IS further work warranted?<br>Are there gaps in the evidence highlighted by the review? | 10911 & 95 |
| Limitations | Discuss limitations of the available evidence and of the review methodology if relevant. | 11012 & 96 |

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