UK National Screening Committee

Newborn Screening for Cytomegalovirus

An evidence map to outline the volume and type of evidence related to screening for cytomegalovirus 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

Contents

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

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Summary

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

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

Based on the findings of this evidence map, no further work on screening for CMV should be commissioned at the present time.

The UK National Screening Committee (UK NSC) will return to screening for CMV in 3-years' time.

Introduction and approach

Background and objectives

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

Screening for cytomegalovirus (CMV) is a topic currently due for an update external review.

CMV is a common virus resulting in mild/no symptoms in immunocompetent adults.[1-3] However, maternal transmission of CMV, known as congenital CMV (cCMV) can result in severe symptoms in some newborns.[3-5] CMV is one of the most prevalent congenital infections and is the leading non-genetic cause of childhood hearing loss and a significant cause of neurological impairment.[4-7]

Estimates of the incidence of CMV vary; the Report of the Cytomegalovirus Group in 2012 suggested that in the UK, approximately 50 to 60% of adults have been infected with CMV. According to this report, cCMV infection is present in about 3 in every thousand live births.[8] Approximately 90% of newborns with CMV are asymptomatic at birth,[9] and whilst many newborns will remain asymptomatic, between 10 to 15% of these (240 to 360 newborns per year) go on to develop mild to severe symptoms in the first two weeks of life, including neurological problems in around half of them (120 to 180 babies per year). Thus, while around 2,040 to 2,160 babies per year in the UK with be born with cCMV, the majority will remain asymptomatic while between 202 and 216 babies will be affected.[10]

The most common symptom, seen in nearly 14% of children with symptomatic cCMV infection is sensorineural hearing loss (SNHL).[3] Congenital CMV can also cause a variety of other symptoms including splenomegaly, hepatomegaly, jaundice, pneumonitis and microcephaly.[3] Mental retardation, spastic tetraplegia, and visual impairments have also been reported as a result of central nervous system (CNS) damage.[3] The mortality of symptomatic newborn CMV infection is between 10% and 30%.[8]

Screening and diagnosis

Universal CMV screening for pregnant women is currently not recommended in any nation.[11] An International Congenital Cytomegalovirus Recommendations Group was convened in 2015 and advised against CMV screening in pregnant women; this is in agree-

ment with much of the literature on the topic, as well as with various national guidelines.[11] However, if CMV is suspected, either because the mother has had known CMV infection during pregnancy or abnormalities associated with CMV are detected on the ultrasound, then testing may be encouraged.[11]

The most reliable method for testing prenatally for CMV is amniocentesis, which has high sensitivity and specificity. However, it comes with risks,[7] causing spontaneous miscarriages in about 1% of cases.[3] CMV can also be detected through fetal abnormalities in ultrasonography,[12] however, this has low sensitivity.[7]

Newborn Screening

Universal newborn screening is currently not recommended in any country, however, targeted screening of newborns who fail the auditory screen has been trialled or introduced in some countries/states, including the UK,[13] Australia,[14] Belgium[15] and US.[16, 17]

The most commonly used test is polymerase chain reaction (PCR) of urine or saliva grown cultures. Dried blood spots (DBS) could also be used, though the accuracy of the tests based on this material has been limited, compared with urine or saliva.[11] It has been argued that newborns with early diagnosis of hearing loss have a better prognosis later on, screening for CMV may be beneficial to identify those at higher risk of developing this complication.[18]

cCMV is usually detected due to the presence of symptoms, with newborn hearing screening often providing the first indication of cCMV. However, given the prevalence of late onset hearing loss, or different symptoms altogether, these tests often fail to detect CMV.[3, 19]

Treatment

The current treatments licensed for CMV disease in children are: ganciclovir, valaciclovir and valganciclovir.[20-22] Ganciclovir can be used for the prevention of CMV diseases, however, it is not licensed in neonates for cCMV infection of the CNS. There is still no established treatment for CMV in asymptomatic newborns, or during pregnancy.[23]

The 2017 UK NSC review identified a single placebo-controlled trial comparing 6 months of treatment with oral valganciclovir with 6 weeks of treatment in symptomatic newborns with cCMV with or without neurological manifestations. No evidence that prolonged treatment with oral valganciclovir improved short-term hearing outcomes was found and improvements in hearing and neurodevelopmental outcomes in the longer term at 12-24 months may have been due to statistical artefacts.[24]

Since the 2017 UK NSC review, there have been more studies into the efficacy of such treatments.[25-27] There are also currently a number of clinical trials underway investigating the efficacy of early valganciclovir treatment of symptomatic infants with hearing loss (ClinicalTrials.gov, NCT02005822; NCT01649869).

Importantly, whilst some studies have shown promising results in the treatment of symptomatic cCMV, none have looked at the effect of such treatment on asymptomatic or mildly symptomatic newborns and those at risk of developing late-onset sequelae.[28] Evidence on the effectiveness and safety of treatment of infants identified through screening, rather than testing has also not been found thus far.

Previous review on screening for cytomegalovirus

The UK NSC currently does not recommend population screening for CMV either in pregnant women or in newborns.[24]

Maternal screening was not included in the 2017 UK NSC review on CMV due to uncertainties relating to the risk of transmission and uncertainties relating to diagnosis highlighted by the 2012 UK NSC review; a scoping search of the literature in 2017 confirmed that no significant new evidence in support of antenatal screening was available. As such, antenatal screening is also not included in this 2021 evidence map.

For newborn screening, the 2017 UK NSC review concluded that PCR evaluation of saliva samples or viral cultures of saliva or urine samples is likely the best candidate for a screening test. Nevertheless, there was still uncertainty in how the test would affect management of cCMV-infected newborns and whether it had any effect on long-term outcomes. In addition, the review highlighted the following gaps in evidence:

1. It is not clear how to identify newborns that will develop long-term sequelae
2. The treatment offered to babies with asymptomatic cCMV infection is unclear
3. 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.

Aims of the evidence map

This evidence map has been developed to assess whether a more sustained review on screening for CMV should be commissioned and to evaluate the volume and type of evidence on key issues related to screening for CMV. The aim of this document is to present the information necessary for the UK NSC to decide this.

The evidence map aims to address the following questions:

1. Are there any markers that can distinguish which newborns with congenital cytomegalovirus will suffer long-term negative outcomes such as hearing loss or neurological impairments?
2. Is there evidence that screening for congenital cytomegalovirus impacts on morbidity (for example hearing) outcomes?

Due to a lack of understanding of the natural history of CMV it is difficult to identify asymptomatic infants to treat. An understanding of the effectiveness and safety of treatments given to asymptomatic or screen-detected infants with cCMV is also necessary. However, given the scarcity of this evidence in the 2017 UK NSC review, studies focusing on the treatment of asymptomatic newborns (not in the context of screening) are unlikely to be found. As such, any relevant studies would be expected to be performed in the context of screening and be identified through the second question.

Therefore, this evidence map concentrates on the gaps in the evidence related to the natural history of the condition and the benefits newborn screening.

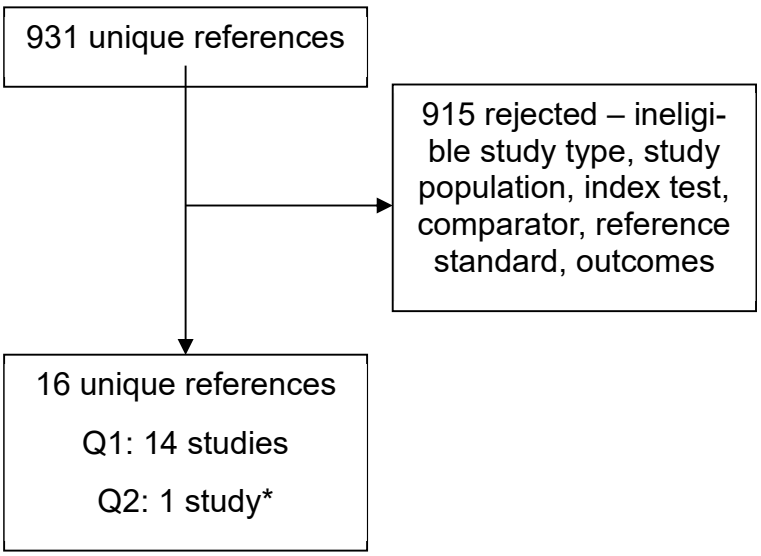
Search methods and results

Searches were conducted on 16 July 2021 in 4 databases: MEDLINE, Embase, Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL). The search period was restricted to 2016 to 2021. MEDLINE (including MEDLINE In-Process, MEDLINE Daily and Epub Ahead of Print) and Embase were searched simultaneously via the Ovid SP platform. The Cochrane Library databases (CDSR and CENTRAL) were searched via the Wiley Online platform.

The detailed search strategies, as well as the exclusion and inclusion criteria are available in **Error! Reference source not found.**. One reviewer screened all titles and abstracts. All references were reviewed at abstract level, though in some cases full texts were reviewed to clarify uncertain pieces of information. Decisions regarding the eligibility of all included studies and 10% of excluded studies were verified by a second, independent reviewer. A formal quality appraisal of the evidence was not required, given the remit of the evidence map.

The search returned 963 results across MEDLINE, Embase and the Cochrane library databases. After automatic and manual de-duplication, 931 unique references were reviewed for relevance to the review questions. 16 unique references reporting on 15 studies were included in the final evidence map. Of these, 14 studies were relevant to question 1 and one study (reported through two publications) was relevant to question 2. A flow diagram summarising the number of studies included and excluded is presented in **Figure 1**. Abstract reporting tables are available in **Error! Reference source not found.**.

Figure 1: Summary of included and excluded publications



*One study on Q2 was reported through 2 references

Summary of findings

Question 1: Are there any markers that can distinguish which newborns with congenital cytomegalovirus will suffer long-term negative outcomes?

Twenty-four studies were identified as potentially relevant for question 1, and for 22 of these, their full texts were consulted to determine relevance, whilst 2 studies were included on the basis of their abstract only. Of the 22 full texts checked, 10 were excluded and 12 included, giving a total of 14 studies included as relevant to question 1. No relevant randomised control trials (RCTs) were identified but 1 systematic literature review (SLR) was included. The most commonly included studies were retrospective cohort studies (n=9), followed by prospective cohort studies (n=4).

One of 14 studies included was an SLR, conducted in 2017, aimed to determine hearing and neurodevelopmental outcomes in asymptomatic infants infected with cCMV. Twenty-nine studies reporting hearing and 20 studies reporting neurodevelopmental outcomes were included in the SLR. Infants with asymptomatic cCMV were comparable to the healthy control group in neurodevelopmental assessments and performed better than symptomatic infants. The SLR concluded that no reliable virological prognostic markers were determined that could identify which infants will display clinical symptoms.[5]

Thirteen out of 14 studies included were primary studies, and none of these were conducted in the UK; 2 were in the Netherlands,[29, 30] 3 in Japan,[27, 31, 32] 2 in the USA,[33, 34] 1 in Spain,[35] Italy,[36] Finland,[37] Poland,[38] Canada[39] and China.[40] The population sizes of the studies ranged from 30 to 23,368. A variety of potential prognostic markers for cCMV sequalae were identified, including CMV viral load, CMV DNA copy number and genetic variants. The key findings of the studies relevant to question 1 are reported in

Table 1.

Ten studies identified viral load as a potential prognostic marker for determining cCMV sequelae.[27, 29-31, 34-37, 39, 40] As outlined in

Table 1, it was commonly (n=5) found that higher CMV viral load was associated with symptomatic cCMV infection, rather than lower CMV viral load.[31, 35, 36, 39, 40] By contrast, 5 studies found no substantial association between viral load and symptomatic cCMV infection.[27, 29, 30, 34, 37] As such, there is currently no clear direction in evidence regarding the use of viral load as a prognostic marker.

Table 1: Summary of findings reported by studies relevant to question 1

Study	Population	Outcome	Result
No differences found			
Koyano 2018[27]	72 CMV patients, 7% developed late-onset sequelae	Viral load in urine	No difference between those with late-onset sequelae and asymptomatic + symptomatic
Rovito 2018[30]	133 cCMV positive infants, 274 non-infected infants	Viral load in DBS	Not associated with individual CMV gene expression
Puhakka 2020[37]	40 cCMV positive infants: 4 with symptomatic and 36 with asymptomatic infection	Viral load in saliva	No difference between symptomatic and asymptomatic
Ross 2017[34]	313 cCMV positive infants	Viral load in saliva and DBS	No differences in viral load was found between infants with normal hearing and SNHL
Rovito 2017[29]	99 cCMV positive infants, 54 without cCMV	Molecular T and B cells and viral load in DBS	No differences between infected infants with or without LTIs, or between symptomatic and asymptomatic infants
Puhakka 2020[37]	40 cCMV positive infants: 4 with symptomatic and 36 with asymptomatic infection	Glycoproteins gH, gB, gN	Not associated with symptomatic infection
Differences found			
Blázquez-Gamero 2020[35]	4,097 newborns	Viral load in blood and saliva	Significantly higher viral load was associated with MRI abnormalities
Smiljkovic 2020[39]	47 cCMV positive infants	Viral load in blood	cCMV patients with moderate to severe symptoms had higher viral load than asymptomatic patients
Salomè 2020[36]	258 cCMV positive children, 125 asymptomatic	Viral load in urine and plasma	High urine vial load and positive viremia risk factors of delayed fluctuating SNHL
Wang 2021[40]	141 asymptomatic cCMV infants	Viral load in saliva	High CMV viral load is associated with increased risk of developing hearing loss
Yamaguhi 2017[31]	23,368 newborns	Viral load in urine samples	Urinary CMV may predict incidence of late-onset SNHL
Dobbins 2019[33]	30 cCMV positive infants: 13 with symptomatic and 17 with asymptomatic infection	Urinary CMV DNA	Genes UL33 and UL20 were closely associated with asymptomatic infants with SNHL
Jedlinska-Pijanowska 2020[38]	92 cCMV positive infants, 141 healthy controls	SNPs in urine	Association between clinical outcomes of cCMV and 4 SNPS
Nishida 2020[32]	42 cCMV positive infants	MRI findings	Infants with certain MRI abnormalities may be at higher risk of developing NDIs

Study	Population	Outcome	Result
Rovito 2017[29]	99 cCMV positive infants, 54 without cCMV	KRECs arrangement	cCMV positive infants that develop any LTI have lower percentages and numbers of KRECs arrangement than those who do not develop LTI
Rovito 2018[30]	133 cCMV positive infants, 274 non-infected infants	Gene expression	Antiviral genes, including ISG15 and RSAD2, were positivity associated with CMV viral load
Yamaguhi 2017[31]	23,368 newborns	Urinary CMV DNA copy numbers and MRI findings	Mean urinary CMV copy numbers are higher in infants with CNS abnormalities

Abbreviations: cCMV, congenital cytomegalovirus; CMV, cytomegalovirus; CNS, central nervous system; DBS, dried blood spots; DNA, deoxyribonucleic acid; KRECs, kappa-deleting recombination excision circles; LTI, long-term impairments; MRI, magnetic resonance imaging; NDI, neurodevelopmental impairments; SNHL, sensorineural hearing loss; SNPs: single nucleotide polymorphisms.

Three studies identified urinary CMV DNA copy number and viral load as a prognostic marker for long-term impairments (LTI), including SNHL and CNS damage.[31, 36, 40] Salomè 2020 reported that infants with fluctuating SNHL had higher urinary viral loads in comparison to infants with stable normal hearing.[36] Likewise, Yamaguhi 2017 reported a correlation between the quantification of urinary CMV load and the incidence of late-onset SNHL and neurodevelopmental disorders; they reported that the urinary cCMV DNA copy number of infected infants with SNHL was significantly higher than cCMV infected infants without SNHL.[31]

Five studies addressed genes and specific variants involved in cCMV clinical outcomes and their use as potential prognostic markers.[29, 30, 33, 37, 38] Of these studies, 5 different markers where investigated: SNPs (n=1), viral variants (n=1), B and T cells (n=1), transcriptomes from DBS (n=1) and glycoproteins (n=1). Rovito 2018 reported that there was no statistical association between specific individual gene expression in CMV infected patients and clinical outcomes and LTI; however, pathway analysis did suggest potential gene expression relating to viral load and LTI.[30] Alternatively, Rovito 2017 have identified kappa-deleting recombination excision circles (KRECs) as a potential marker for LTI. They found that cCMV infected children that go on to develop LTI were found to have a significantly lower percentage of cells containing T cell KREC arrangement ($p=0.04$); however, it was concluded that the discriminative power of KRECs as a marker for LTI needs further study.[29]

Two studies reported diagnostic findings during screening for cCMV using DBS, saliva and urine samples. Blázquez-Gamero 2020 reported 9 false positive results in saliva and urine samples out of 3,190 neonates tested.[35] Ross 2017 found that DBS PCR has low sensitivity and specificity for detecting children with SNHL; 42.3% and 73.3% respectively.[34] The study concluded that DBS PCR is not sufficient at identifying infants with CMV or CMV-associated SNHL.

Although some studies identified possible markers to distinguish which cCMV infected newborns will suffer long-term negative outcomes, there is currently no consensus about the predictive value of such markers or their reliability. As such, a further evidence summary is not recommended, as it is unlikely to lead to a change in the UK NSC's current position on screening.

Question 2: Is there evidence that screening for congenital cytomegalovirus impact on morbidity (e.g. hearing) outcomes?

Eight publications reporting on 7 unique studies were identified as potentially relevant to question 2 and the full texts were consulted for all 8 of these to determine their relevance. Two records reporting on 1 study were eventually included.

The included study, Yamada 2020, was prospective in design. While all of the treated newborns were referred to as symptomatic, some of these were considered to have subclinical symptoms, detected only due to those newborns having tested positive for cCMV and undergoing additional assessments. The authors found that 58% of treated infants had mild sequalae or normal development.[26] Of the cases with subclinical symptoms, all had normal development. Based on their results, Yamada 2020 concluded that due to the identification of potentially subclinical patients and subsequent treatment, neonatal urine screen and subsequent follow-ups could decrease neurological impairments of symptomatic cCMV infants.[26]

One of the studies included for question 1, Koyano 2018, also looked at treatment of newborns with cCMV infection. The study was not included in this question, as only symptomatic individuals were treated, it may, however, be noteworthy that they found no significant difference in the incidence of sequelae between treated and untreated groups within symptomatic cCMV (p=0.018).[27]

In summary, there is close to no evidence on the benefits of early treatment/interventions for cCMV compared to late treatment after the presentation of symptoms. The single study currently available is unsuitable for drawing conclusions on the effectiveness of the interventions and does no warrant conducting a further evidence summary.

Conclusions

The findings of this evidence map are unlikely to impact current recommendations on screening for cCMV as no new conclusive evidence was identified that would change those conclusions.

Recommendations

On the basis of this evidence map, the volume and type of evidence related to screening for cCMV is currently insufficient to justify an update review at this stage and so should be re-considered in 3-years' time.

Appendix 1 — Search strategy for the evidence map

Sources searched: Ovid MEDLINE® and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to 15 July 2021, Embase® 1974 to 15 July 2021, and the Cochrane Library (Cochrane Database of Systematic Reviews and Protocols, Issue 7 of 12, July 2021; Cochrane Trials, Issue 6 of 12, June 2021).

Dates of searches: Searches were run on 16 July 2021.

Table 2: Search terms for Ovid and the Cochrane Library

MEDLINE and Embase (searched simultaneously via the Ovid SP platform)
1. exp cytomegalovirus/ or exp cytomegalovirus infection/ or congenital CMV infection/ 2. (cytomegaly* and virus*).ti,ab,kw,kf. 3. (Cmv or cytomegalovirus).ti,ab,kw,kf. 4. or/1-3 5. Infant, Newborn/ or child/ or children/ 6. (newborn* or neonatal* or infant* or child*).ti,ab,kw,kf. 7. 5 or 6 8. dried blood spot testing/ 9. (dried blood spot or dry blood spot).ti,ab,kw,kf. 10. Saliva analysis/ or saliva/ch, cy or urinalysis/ or urine/ch, cy 11. (saliva analys#s or urine analys#s or urinalys#s).ti,ab,kw,kf. 12. (detect* or predict* or identif* or diagnos* or test*).ti. 13. mass screening/ or screen.ab. /freq=3 14. (Hearing loss or SNHL or asymptomatic infection or neurological or hepatosplenomegaly or thrombocytopenia or jaundice).ti,ab,kw,kf. 15. Asymptomatic infection/ or asymptomatic infections/ 16. or/8-15 17. ("Conference Abstract" or "Conference Review" or comment or editorial or note or case reports or news or news release).pt. 18. (case stud* or case report*).ti,ab. 19. historical article/ or case study/ 20. exp animals/ not exp humans/ 21. or/17-19 22. 4 and 7 and 16 23. 22 not 21 24. limit 23 to yr=2016-current 25. remove duplicates from 24
Cochrane Library (searched via the Wiley Online platform)
1. [mh cytomegalovirus] OR [mh "cytomegalovirus infection"] 2. (cytomegaly* and virus*):ti,ab,kw 3. (Cmv or cytomealovirus):ti,ab,kw 4. {OR #1-#3} 5. [mh "Infant, Newborn"] OR [mh child] 6. (newborn* or neonatal* or infant* or child*):ti,ab,kw 7. #5 OR #6 8. [mh "dried blood spot testing"]

9. (dried blood spot or dry blood spot):ti,ab,kw
10. [mh ^"Saliva analysis"] OR [mh ^saliva/ch,cy] OR [mh ^urinalysis] OR [mh ^urine/ch,cy]
11. ("saliva analysis" or "saliva analyses" or "urine analysis" or "urine analyses" or urinalysis or urinalyses):ti,ab,kw
12. (detect* or predict* or identif* or diagnos* or test*):ti
13. [mh ^"mass screening"] OR screen:ab
14. ("Hearing loss" OR SNHL OR "asymptomatic infection" OR neurological OR hepatosplenomegaly OR thrombocytopenia OR jaundice):ti,ab,kw
15. [mh "Asymptomatic infections"]
16. {OR #8-#15}
17. #4 AND #7 AND #16
18. #17 with Cochrane Library publication date Between Feb 2016 and Jul 2021, in Cochrane Reviews, Cochrane Protocols
19. #17 with Publication Year from 2016 to 2021, in Trials

Results by database:

MEDLINE and Embase	938
Cochrane Library	25
Total	963

Inclusions and exclusions:

Studies were included based on the eligibility criteria listed in Table 3 and Table 4 for question 1 and question 2, respectively.

Table 3: Eligibility criteria for question 1

PICOS domain	Inclusion criteria	Exclusion criteria
Patient population	Newborns, defined as <12 months of age.	• Children who are not newborns • Adults
Intervention	Any standalone test or any multiplex test used to screen or test for congenital cytomegalovirus using dried blood spots or saliva.	Any test that is not performed on newborn dried blood spots or saliva.
Comparator	Any or none	N/A
Outcomes	• Biological markers • Hearing loss in infants • Neurological impairments in infants • Thrombocytopenia and jaundice • Other long-term negative outcomes associated with cytomegalovirus, for example hepatosplenomegaly • Incidental findings, for example by products detected by the test • False positives/negatives	Outcomes that are not relevant to the desired clinical outcomes or reporting on the relevant diagnostic accuracy measures.

PICOS domain	Inclusion criteria	Exclusion criteria
Study design	**Tier 1:** • RCTs • SLR/(N)MAs of these study designs **Tier 2:** • Cohort studies (prospective or retrospective) • Case-control studies	Any other study design, including: • Case reports • Narrative reviews • Editorials • Commentaries • Conference abstracts • Other publication types that have not been peer-reviewed
Other considerations	• Articles published in the English language • Articles published since February 2016	• Studies with abstract not in the English language • Articles published before February 2016

Abbreviations: N/A, not applicable; (N)MA, (network) meta-analysis; SLR, systematic literature review.

Table 4: Eligibility criteria for question 2

PICOS domain	Inclusion criteria	Exclusion criteria
Patient population	Newborns, defined as <12 months of age.	• Children who are not newborns • Adults
Intervention	Screening for cytomegalovirus with any standalone or multiplex test using dried blood spots, urine or saliva.	Any test that is not performed on newborn dried blood spots, urine or saliva.
Comparator	No screening for congenital cytomegalovirus.	Any other method of measurement for congenital cytomegalovirus.
Outcomes	Morbidity outcome including but not limited to: • Hearing loss • Neurological impairments • Mortality	Any non-relevant outcomes, for example epidemiological, diagnostic or economic data.
Study design	**Tier 1:** • RCTs • SLR/(N)MAs of these study designs **Tier 2:** • Cohort studies (prospective or retrospective) • Case-control studies	Any other study design, including: • Case reports • Narrative reviews • Editorials • Commentaries • Conference abstracts • Other publication types that have not been peer-reviewed
Other considerations	• Articles published in the English language • Articles published since February 2016	• Studies with abstract not in the English language • Articles published before February 2016

Abbreviations: N/A, not applicable; (N)MA, (network) meta-analysis; SLR, systematic literature review.

Appendix 2 – Abstract reporting

Be sure to nest headings correctly – e.g. Heading 3 is followed by Heading 4, is followed by Heading 5 when using sub-headings.

Question 1: Are there any markers that can distinguish which newborns with congenital cytomegalovirus will suffer long-term negative outcomes?

Abbreviations: cCMV, congenital cytomegalovirus; CMV, cytomegalovirus; SNHL; sensorineural hearing loss.

TITLE	
Citation	*Blázquez-Gamero et al. (2020,) Prevalence and clinical manifestations of congenital cytomegalovirus infection in a screening program in Madrid (PICCSA Study), Pediatric Infectious Disease Journal; 1050–1056.*[35]
BACKGROUND	
Study type	*Prospective cohort study*
Objectives	*Investigate cCMV prevalence and clinical abnormalities in Spain.*
Components of the study	***Population:*** *4,097 neonates* ***Marker:*** *Viral load in blood and saliva* ***Comparator:*** *Clinical laboratory, auditory, visual and cerebral imaging assessments* ***Outcomes:*** *Prevalence of cCMV and associated clinical abnormalities*
OUTCOMES	
Outcomes reported	• *9 false positives were detected, easily determined due to lower viral loads in saliva* • *87% of cCMV infected infants exhibited a normal physical examination* • *No difference was found between gestations age at birth, days of life at time of screening, HC, birth weight between infants with and without cCMV* • *Children with MRI abnormalities presented higher viral loads in blood (p=0.04) and saliva (p=0.04)* • *Urine viral loads were not associated with MRI abnormalities* • *Most infants born with cCMV born after nonprimary infection during pregnancy (71.4%)*

Conclusions	*Association between MRI abnormalities and higher viral loads in blood and saliva. Their potential role as a prognostic factor in cCMV should be addressed in future studies. [Full text was consulted.]*

Abbreviations: cCMV, congenital cytomegalovirus; CMV, cytomegalovirus; HC, head circumference; MRI, magnetic resonance imaging.

TITLE	
Citation	*Dobbins et al. (2019) Association of CMV genomic mutations with symptomatic infection and hearing loss, BCM Infectious Diseases; 19(1).*[33]
BACKGROUND	
Study type	*Prospective cohort study*
Objectives	*To investigate viral diversity and viral variants that may be associated with symptomatic infection and SNHL.*
Components of the study	***Population:*** *30 infants (17 asymptomatic, 13 symptomatic)* ***Marker:*** *CMV DNA from urine specimens* ***Comparator:*** *CMV genomes* ***Outcomes:*** *Association between viral diversity and specific viral variants in infants with asymptomatic cCMV infection and SNHL*
OUTCOMES	

Outcomes reported	• *No association found between specific genes within variants and symptomatic infection*
	• *For glycoproteins gb(UL55) and gN(UL73)*
	  ○ *No correlation to symptomatic outcomes*
	  ○ *Symptomatic and HL outcomes had no unique consensus sequences in infants with SNHL or symptomatic infection*
	• *Phylogenetic analysis did not reveal any consequence sequence linked to SNHL*
	• *Mann Whitney Wilcoxon test found genes with increased nucleotide diversity associated with SNHL*
	• *UL33 and UL20 most closely associated with asymptomatic infants with SNHL*

Conclusions	*Genes and specific variants were identified that are associated with symptomatic and HL clinical outcomes. More research needed to determine if such genes and specific CMV polymorphisms could be used as markers for sequelae.* *[Full text was consulted.]*

Abbreviations: cCMV, congenital cytomegalovirus; CMV, cytomegalovirus; DNA; deoxyribonucleic acid; HL, hearing loss; SNHL, sensorineural hearing loss.

TITLE	
Citation	*Jedlinska-Pijanowska et al. (2020), Association between single nucleotide polymorphisms (SNPs) of IL1, IL2, IL28 and TLR4 and symptoms of congenital cytomegalovirus infection, Plos One; 27(5).*[38]
BACKGROUND	
Study type	*Prospective cohort study*
Objectives	*Investigate association between SNPs in genes and predisposition to cCMV infection, course of disease and symptoms.*
Components of the study	***Population:*** *92 infants with cCMV and 141 healthy control group, eight SNPs* ***Index test:*** *Urine sample* ***Comparator:*** *SNPs in genes encoding for cytokines and cytokine receptors* ***Outcomes:*** *Association between SNPS in genes encoding cytokines and cytokine receptors, and cCMV infection including course of the disease*
OUTCOMES	

Outcomes reported	• *No statistically significant association was identified between:*
	  ○ *Genotyped SNPs and the cCMV infection*
	  ○ *Genotyped SNPs and symptomatic course of cCMV infection*
	• *Polymorphism of IL12Brs3212227 linked to decreased risk of prematurity (OR=0.37;95%CI,0.14-0.98;p=0.025)*
	• *Polymorphism of IL1Brs16944 linked to reduced risk of splenomegaly (OR=0.36;95%CI,0.14-0.98;p=0.034)*
	• *Polymorphism of IL28Brs12979860 linked to thrombocytopenia (OR=2.55;95%CI,1.03-6.32;p=0.042)*
	• *Polymorphism of TLR4rs4986791 linked to hepatitis (OR=780;95%CI,1.49-40,81;p=0.024)*

Conclusions	*Associations identified between four SNPs and clinical outcomes of cCMV disease.* *[Full text was consulted.]*

Abbreviations: cCMV, congenital cytomegalovirus; CI, confidence interval; CMV, cytomegalovirus; OR, odds ratio; SNPs, single nucleotide polymorphisms.

TITLE	
Citation	*Koyano et al. (2018) Congenital cytomegalovirus in Japan: More than 2 year follow up of infected newborns, Pediatrics International; 60(1):57–62.*[27]
BACKGROUND	
Study type	*Retrospective cohort study*
Objectives	*Evaluate the outcome of cCMV infection, and observe clinical outcomes after treatment.*
Components of the study	***Population:*** *72 CMV patients* ***Index test:*** *Urine samples* ***Comparator:*** *Physical examination, laboratory tests, brain imaging echo, audiologic tests and CT and/or MRI* ***Outcomes:*** *Treatment of symptomatic patients resulted in favourable clinical outcomes*
OUTCOMES	
Outcomes reported	*Asymptomatic at birth* • *7% of infants developed late-onset sequelae* • *No significant differences between viral load at birth in patients with late-onset sequelae and those who were asymptomatic and symptomatic* *Symptomatic* • *All untreated symptomatic patients developed neurological sequelae* • *All patients in the untreated group had sequela within the follow-up period*
Conclusions	*About 1/10 cCMV infect newborns who are asymptomatic at birth develop certain sequelae. Identification of asymptomatic infants may facilitate early intervention for future disabilities.* *[Full text was consulted.]*

Abbreviations: cCMV, congenital cytomegalovirus; CMV, cytomegalovirus; CT, computed tomography; DBS, dried blood spot; MRI, magnetic resonance imaging.

TITLE	
Citation	*Nishida et al. (2020), Prediction of Neurodevelopmental Impairment in Congenital Cytomegalovirus Infection by Early Postnatal Magnetic Resonance, Neonatology; 117:460–466.*[32]

BACKGROUND	
Study type	*Retrospective cohort study*
Objectives	*To investigate the potential for brain MRI to predict NDIs in cCMV infection.*
Components of the study	***Population:*** *42 infants with cCMV from 2010 to 2018 in Japan* ***Index test:*** *MRI findings* ***Comparator:*** *NDIs, clinical presentations of cCMV* ***Outcomes:*** *Prevalence of NDIs between symptomatic and asymptomatic infants, Youden index values*
OUTCOMES	
Outcomes reported	• *Abnormal MRI findings were significantly more prevalent in infants with clinical symptoms than those without (p<0.01)* • *At least one abnormal MRI finding was detected in 28 infants (67%)* ○ *Abnormal findings included cerebellar hypoplasia (7%), migration disorders (17%), white matter abnormalities (62%), periventricular cysts (28%), hippocampal dysplasia (2%) and ventriculomegaly (48%)* • *Infants with at least 2 of the following abnormalities produced the highest Youden index value (0.78): ventriculomegaly, periventricular cysts, and white matter abnormality*
Conclusions	*cCMV infected infants with at least 2 of the stated MRI abnormalities may be at a high risk of developing NDIs. Additionally, abnormal MRI findings were more prevalent in symptomatic infants than asymptomatic infants.*

Abbreviations: cCMV, congenital cytomegalovirus; CMV, cytomegalovirus; MRI, magnetic resonance imaging; NDI, neurodevelopmental impairment.

TITLE	
Citation	*Puhakka et al. (2020), Viral shedding, and distribution of cytomegalovirus glycoprotein H (UL75), glycoprotein B (UL55), and glycoprotein N (UL73) genotypes in congenital cytomegalovirus infection, Journal of Clinical Virology, 125: 104287.*[37]
BACKGROUND	
Study type	*Retrospective cohort analysis*
Objectives	*To evaluate the viral shredding in a cohort of cCMV infected infants identified through newborn screening and*

	describe the distribution of viral genotypes in asymptomatic infants.
Components of the study	***Population:*** *Screening of 19,868 infants in Helsinki from September 2021 to January 2015; 40 cCMV positive infants sampled at age 3 and 18 months identified through newborn screening* ***Marker:*** *Viral load in saliva, urine and plasma* ***Reference standard:*** *Genotypes of envelope glycoproteins in CMV DNA* ***Outcomes:*** *Identification of symptomatic and asymptomatic infection through newborn CMV screening, association of genotypes with viral excretion, symptomatic infection, and neurodevelopmental outcomes* *The study also reports:* • *Comparison of the genotypes of the symptomatic infection cohort with existing literature*
OUTCOMES	
Outcomes reported	• *Symptomatic infection (n=4) and asymptomatic infection (n=36) were identified through newborn screening* o *Viral load of saliva samples did not differ between symptomatic and asymptomatic infants* o *Symptom manifestation included microcephaly (n=1) and calcifications seen in cerebral ultrasound (n=3)* o *Viral shedding was higher at 3 months of age compared to 18 months in saliva and plasma PCR; rates were the same in urine culture at both time periods* • *Biological markers:* o *Glycoproteins, gH, gB and gN were not associated with symptomatic infection or neurodevelopmental outcomes*
Conclusions	*There was no significant difference between the viral load of infants with symptomatic compared to asymptomatic infection. Additionally, viral shedding was found to be more persistent in urine samples compared to saliva samples in children with cCMV.* *[Full text was consulted.]*

Abbreviations: cCMV, congenital cytomegalovirus; CMV, cytomegalovirus; DNA, deoxyribonucleic acid; PCR, polymerase chain reaction.

TITLE	
Citation	*Ross et al. (2017), Newborn dried blood spot PCR to identify infants with congenital cytomegalovirus-associated sensorineural hearing loss, The Journal of Pediatrics; 184: 57–61.*[34]
BACKGROUND	
Study type	*Retrospective cohort analysis*
Objectives	*To evaluate the efficiency of DBS PCR in identifying infants with CMV-associated SNHL.*
Components of the study	***Population:*** *313 newborns from 7 American Hospitals between March 2007–March 2012 enrolled in the CMV and Hearing Multicenter Screening study* ***Marker****: Viral load in saliva and DBS* ***Comparator:*** *Infants with hearing loss* ***Outcomes:*** *Sensitivity, specificity, positive and negative likelihood ratios of DBS screening for CMV-associated SNHL, DBS viral loads between children with and without SNHL*
OUTCOMES	

Outcomes reported	*Clinical outcomes:*
	• *No differences in viral load were found between children with and without SNHL*
	• *In the asymptomatic cohort:*
	  ○ *DBS PCR was positive in 6/15 (40%) children with SNHL at birth compared to 75/270 (28.0%) with normal hearing*
	  ○ *DBS PCR was positive in 9/20 (45%) children who developed SNHL by 4 years of age compared to 70/257 (27%) with normal hearing*
	
	Diagnostic outcome for detecting CMV-associated SNHL through DBS PCRs:
	• *DBS PCR was positive in 9/28 (31,2%) symptomatic infants compared to 81/285 (25.9%) asymptomatic infants; p=0.7*
	• *Sensitivity and specificity were low at detecting children with SNHL: 42.3% and 73.3% respectively*
	• *Positive and negative likelihood ratios were 1.6% and 0.8% respectively*

	• *DBS PCR does not sufficiently identify the majority of infants with CMV or CMV-associated SNHL*
Conclusions	*The study summarised that neither DBS positivity nor viral load levels are useful prognostic markers for hearing outcomes in cCMV infected infants. Additionally, it was determined that a positive likelihood ratio close to 1 for SNHL at birth and at 4 years indicates that DBS positivity has poor diagnostic accuracy for detecting hearing loss in cCMV infected infants.* *[Full text was consulted.]*

Abbreviations: cCMV, congenital cytomegalovirus; CMV, cytomegalovirus; DBS, dried blood spot; LTI, long term impairment; PCR, polymerase chain reaction; SNHL, sensorineural hearing loss.

TITLE	
Citation	*Rovito et al. (2017), T and B Cell Markers in Dried Blood Spots of Neonates with Congenital Cytomegalovirus Infection: B Cell Numbers at Birth Are Associated with Long-Term Outcomes, The Journal of Immunology; 198:102–109.*[29]
BACKGROUND	
Study type	*Retrospective cohort study*
Objectives	*To investigate the role of immune regulation of cCMV and identify markers to predict LTIs.*
Components of the study	***Population:*** *99 children with cCMV, 54 without cCMV* ***Markers:*** *T and B cell numbers in neonatal DBS* ***Comparator:*** *Clinical symptoms at birth, LTI until 6 years of age, non-infected control cohort* ***Outcomes:*** *symptomatic versus asymptomatic cCMV infection, molecular markers relating to LTI*
OUTCOMES	
Outcomes reported	• *In cCMV infected cohort, 16 (16%) were symptomatic at birth and 22 (22%) had LTI* • *Viral loads did not differ significantly between cCMV infected children with or without LTI, or between asymptomatic and symptomatic patients* • *Neonates with cCMV infection had a higher number of γδ T cells and B cells* • *cCMV infected children that develop any LTI have lower percentages and numbers of KRECs arrangement (p=0.04, p=0.02 respectively), compared to those who do not develop LTI*

	• *No differences in B cell replication were observed in relation to LTI*
Conclusions	*There were no significant differences in the viral loads of cCMV infected infants with or without LTI. The discriminative power of KRECs as a marker for LTI needs further study.* *[Full text was consulted.]*

Abbreviations: cCMV, congenital cytomegalovirus; CMV, cytomegalovirus; DBS, dried blood spot; KREC, kappa-deleting recombination excision circles; LTI, long term impairment.

TITLE	
Citation	*Rovito et al. (2018), Impact of congenital cytomegalovirus infection on transcriptomes from archived dried blood spots in relation to long-term clinical outcome, PLoS ONE; 13(7): e0200652.*[30]
BACKGROUND	
Study type	*Retrospective cohort study*
Objectives	*To demonstrate the feasibility of RNA sequencing to determine the whole blood transcriptomes in relation to cCMV, CMV viral load and LTI development in infants at 6 years of age through RNA isolated from neonatal DBS.*
Components of the study	***Population:*** *133 children with cCMV, 274 non-infected* ***Index test:*** *CMV DNA PCR in neonatal DBS, viral load* ***Comparator:*** *cCMV positive infants with and without LTI* ***Outcomes:*** *Gene expression differences between controls and cCMV infected infants with and without LTI, RNA-sequence differences, differential expression pathways*
OUTCOMES	

Outcomes reported	• *No statistically significant difference found between individual gene expression and:*
	  ○ *cCMV infected compared to healthy controls*
	  ○ *Presence of LTI*
	  ○ *CMV viral load*
	• *Relationships were found between CMV viral load and LTI:*
	  ○ *Antiviral genes, including ISG15 and RSAD2, were positivity associated with CMV viral load*
	  ○ *Cytokine IL-4 was associated with cCMV infected infants that did not develop LTI*
	• *T cell exhaustion in infected infants with high viral load did not correlate with LTI*

	• *Increased expression of differentiation markers (CD57), transcription factor (T-bet) and effector markers (IFN-γ) observed in CMV infected group compared to the control* • *Differentiation markers, transcription factor and effected markers also compared according to viral load (high versus low), again these factors had increased expression for the CMV infected group compared to the control* ○ *However, no such trends were observed when comparing the cCMV infected group with those that developed LTI*
Conclusions	*Lack of statistical significance to determine individual gene expression relating to clinical outcomes and LTI. Pathway analysis suggested possible gene expression relating to viral load and LTI.* *[Full text was consulted.]*

Abbreviations: cCMV, congenital cytomegalovirus; CMV, cytomegalovirus; DBS, dried blood spot; DNA; deoxyribonucleic acid; IL, interleukin; LTI, long term impairment; PCR, polymerase chain reaction; RNA, ribonucleic acid.

TITLE	
Citation	*Salome et al. (2020), The Natural History of Hearing Disorders in Asymptomatic Congenital Cytomegalovirus Infection, Frontiers in Pediatrics; 8:217.*[36]
BACKGROUND	
Study type	*Prospective cohort study*
Objectives	*To evaluate the long-term audiological outcome in symptomatic and asymptomatic in children infected with cCMV.*
Components of the study	***Population:*** *258 cCMV infected children, 125 (48%) asymptomatic from 2002–2018 in Italy* ***Index test:*** *Viral DNA in urine and plasma by PCR* ***Comparator:*** *Neuroimaging, audiological assessment* ***Outcomes:*** *Comparison between symptomatic and asymptomatic viral load*
OUTCOMES	
Outcomes reported	• *SNHL was seen in 85/133 symptomatic children (64%), but no SNHL was seem in asymptomatic children* ○ *Plasma CMV DNA in normal hearing infants was 178–28,800 copies/mL compared with 263–49,600 copies/mL in fluctuating SNHL infants*

	○ *Urinary CMV DNA in normal hearing infants was 1,000–111,000,000 copies/mL compared to 45,000–36,300,00 copies/mL in fluctuating SNHL infants* • *No statistical difference in viremia according to the viral presence or CMV blood load at onset was found between symptomatic and asymptomatic infants* • *Infants with fluctuating SNHL had higher urine viral load than infants with stable normal hearing (p 0.002)*
Conclusions	*Asymptomatic cCMV infected children with no SNHL within their first month of life have low risk of developing hearing impairment. However, high urine viral load and positive viremia at birth are risk factors for delayed fluctuating SNHL. [Full text was consulted.]*

Abbreviations: cCMV, congenital cytomegalovirus; CMV, cytomegalovirus; DNA, deoxyribonucleic acid; PCR, polymerase chain reaction; SNHL, sensorineural hearing loss.

TITLE	
Citation	*Smiljkovic et al. (2020), Blood viral load in the diagnostic workup of congenital cytomegalovirus infection, Journal of Clinical Virology; 122.*[39]
BACKGROUND	
Study type	*Retrospective cohort study*
Objectives	*To determine if the level of CMV viremia at time of diagnosis could differentiate between symptomatic and asymptomatic infection.*
Components of the study	***Population:*** *47 cases of cCMV diagnosed between 2008 and 2016* ***Index test:*** *Saliva quantitative PCR* ***Comparator:*** *Using consensus classification criteria, infants were addressed on audiology, ophthalmology, neurological and neuroimaging evaluations, laboratory testing and clinical definitions* ***Outcomes:*** *CMV blood viral load and symptom severity*
OUTCOMES	
Outcomes reported	• *Median viral baseline was significantly higher in symptomatic infants compared with asymptomatic: 13,736 copies/mL versus 1,876 copies/mL, p<0.004* • *Median viral load was significantly higher amongst infants with any abnormal neurological findings, compared with those without:17,317 copies/mL versus 2,461 copies/mL, p=0.003*

	• *3 scenarios for patients with moderate-to-severe symptoms:*
	  ○ *Consensus criteria*
	  ○ *Infants with isolated SNHL included in moderate to severe symptoms (expanded criteria)*
	  ○ *Newborns with any abnormal neurological findings (neurological criteria)*
	• *In all three scenarios viral load was a predictor of the severity of symptoms*
	• *100,000 copies/ml resulted in a near 100% probability of reaching symptomatic criteria*

Conclusions	*cCMV infants with moderate to severe symptoms had a higher baseline viral load within their first month of life, as compared to asymptomatic infants. Further studies should be conducted to better understand the role of viral burden in CMV infected infants.* *[Full text was consulted.]*

Abbreviations: cCMV, congenital cytomegalovirus; CMV, cytomegalovirus; PCR, polymerase chain reaction; SNHL, sensorineural hearing loss.

TITLE	
Citation	*Wang et al. (2021), Late-onset Hearing Loss From Congenital Cytomegalovirus Infection After Newborn Period in a Highly Immune Population in China, The Pediatric Infectious Disease Journal; 40(1):70–73.*[40]
BACKGROUND	
Study type	*Retrospective cohort study*
Objectives	*To identify factors any maternal or childhood factors that are associated with increased risk of developing hearing loss in asymptomatic cCMV infants.*
Components of the study	***Population:*** *141 asymptomatic cCMV infants* ***Index test:*** *Viral load in saliva samples* ***Comparator:*** *cCMV infants without late-onset hearing loss* ***Outcomes:*** *Factors associated with cCMV and hearing loss*
OUTCOMES	
Outcomes reported	• *High saliva viral load was associated with an increased risk of developing hearing loss (p=0.03)* • *No other maternal or childhood factors were associated with a risk of developing hearing loss*
Conclusions	*Higher CMV viral load at birth is associated with an increased risk of developing hearing loss.*

Abbreviations: cCMV, congenital cytomegalovirus; CMV, cytomegalovirus.

TITLE	
Citation	*Yamaguhi et al. (2017), Screening for seemingly healthy newborns with congenital cytomegalovirus infection by quantitative real-time polymerase chain reaction using newborn urine: an observational study, BMJ Open; 7:e013810.*[31]
BACKGROUND	
Study type	*Retrospective cohort study*
Objectives	*To examine the relationship between urinary CMV load, SNHL and CNS damage.*
Components of the study	***Population:*** *23,368 newborns from Japan* ***Index test:*** *PCR screening in urine samples* ***Comparator:*** *Automated auditory brainstem response, MRI findings, CMV DNA copy numbers* ***Outcomes:*** *Relationship between the viral load in cCMV infected infants with and without SNHL and between cCMV infected infants with and without CNS abnormalities* *The study also reports:* • *Incidence of cCMV in Japan (60/23,368 newborns)*
OUTCOMES	

Outcomes reported	*Clinical manifestations of cCMV*
	• *All infected infants appeared normal at birth, aside from microcephaly*
	• *171 of 22,229 (0.769%) had hearing abnormalities*
	  ○ *5 cCMV infants had SNHL*
	• *83.0% of cCMV infants had CNS damage*
	  ○ *Urinary CMV load was greater in infants with CNS damage compared to those without (p=0.013)*
	
	Relationship between cCMV and SNHL
	• *Urinary CMV DNA copy number with SNHL ($3.23x10^7$ to $3.45x10^8$ copies/mL) was significantly higher than CMV infected infants without SNHL ($1.65x10^6$ to $3.86x10^6$ copies/mL)*
	• *Urinary CMV DNA copy number was still signifi-cantly higher at 7.7 weeks*
	
	Relationship between cCMV and MRI findings
	• *At 6 months, mean urinary CMV DNA copy number of newborns with CNS damage during screening did*

	not differ significantly to newborns without CNS damage • *At 18 months, mean urinary CMV DNA copy number of newborns with CNS damage (6.19x10^6 to 2.02x10^7 copies/mL) was significantly higher than those without (3.32x10^5 to 2.46x10^6 copies/mL)* • *Mean urinary CMV DNA copy number at 6 and 18 months for infants with CNS abnormalities was significantly higher than infants without* • *Urinary CMV viral load of infants with a change from normal to abnormal results were significantly higher than infants with normal results throughout*
Conclusions	*Quantification of urinary CMV load may predict the incidence of late-onset SNHL and neurodevelopmental disorders. It was suggested that newborns with a high urinary CMV DNA copy number during screening should be followed up with MRI.* *[Full text was consulted.]*

Abbreviations: cCMV, congenital cytomegalovirus; CMV, cytomegalovirus; CNS, central nervous system; DNA, deoxyribonucleic acid; MRI, magnetic resonance imaging; SNHL, sensorineural hearing loss.

Question 2: Is there evidence that screening for congenital cytomegalovirus impacts on morbidity (e.g. hearing) outcomes?

Title	
Citation	*Yamada et al. (2020). A cohort study of the universal neonatal urine screening for congenital cytomegalovirus infection, Journal of Infection and Chemotherapy; 26(8): 790–794.*[26] *Secondary publication: Nishida,2016.*[25]
BACKGROUND	
Study type	*Prospective cohort study*
Objectives	*Evaluate efficacy of universal neonatal urine screening.*
Components of the study	***Population:*** *56 neonates with symptomatic cCMV of 11,736 neonates* ***Index test:*** *Urine screening* ***Reference standard:*** *symptomatic/asymptomatic* ***Outcomes:*** *Neurological assessments*
OUTCOMES	
Outcomes reported	• *Symptoms of 19 symptomatic patients* ○ *Abnormalities on brain imaging (n=17), abnormal BAEP (n=15), thrombocytopenia*

	(n=8), SGA, (n=6), hepatitis (n=5), microcephaly (n=5) and ocular complications (n=5). • *Universal screening detected neonates with subclinical cases* • *37% of the treated infants had normal development without neurological impairment* • *21% mild sequelae*
Conclusions	*Universal neonatal urine screening for CMV along with diagnosis, workup for symptoms and early therapies may decrease neurological impairments in cCMV infected infants. [Full text was consulted.]*

Abbreviations: BAEP, brainstem auditory evoked potential; cCMV, congenital cytomegalovirus; CMV, cytomegalovirus.

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