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Long-term ocular and visual outcomes following symptomatic and asymptomatic congenital CMV infection: a systematic review protocol

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ABSTRACT

Introduction Cytomegalovirus (CMV) is one of the most common congenitally acquired infections worldwide. Visual impairment is a common outcome for symptomatic infants, with long-term ophthalmic surveillance often recommended. However, there are no clear guidelines for ophthalmic surveillance in infants with asymptomatic disease. We aim to conduct a systematic review to establish the overall prevalence and incidence of eye and vision related disorders following congenital CMV infection (cCMV).

Methods and analysis A systematic review and meta-analysis (pending appropriate data for analysis) of cross-sectional and longitudinal studies will be conducted. The PubMed, Embase and CINAHL databases will be searched up to 29 March 2022 without date or language restrictions. Studies will be screened by at least two independent reviewers. Methodological quality of included studies will be assessed using the Joanna Briggs Institute tool. The primary outcome measures will be incidence and/or prevalence of vision impairment or ophthalmic disorders in patients with symptomatic and asymptomatic cCMV infection. A narrative synthesis will be conducted for all included studies. The overall prevalence will be estimated by pooling data using a random-effects model. Heterogeneity between studies will be estimated using Cochran's Q and the I^2 statistics. Egger's test will be used to assess for publication bias.

Ethics and dissemination Ethical approval is not required as there is no primary data collection. Study findings will be disseminated at scientific meetings and through publication in peer-reviewed journals.

Trial registration number This is not a clinical trial, but the protocol has been registered: CRD42021284678 (PROSPERO)

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This protocol provides transparency to the proposed review and meta-analysis methodology and reduces the possibility of duplication.
⇒ The broad search strategy will result in a comprehensive examination of the literature on eye and vision outcomes following congenital cytomegalovirus infection.
⇒ The broad search strategy will result in a large number of titles and abstracts to screen, increasing the burden on reviewers, which may have a negative impact on review progress.

CMV seroprevalence ranges from 40% to 85%. Transmission rates are much higher in developing countries due to factors such as crowded living, with seroprevalence among women of childbearing age of 85%–100%.[1 2 4]

Intrauterine transmission of CMV to the developing fetus may occur with maternal primary or non-primary infection (exogenous infection or endogenous viral reactivation, respectively).[5 6] Estimates of congenital CMV prevalence in developed countries range from 0.6% to 0.7% of all live births, with approximately 60 000 infants born with congenital CMV each year in the USA and Europe.[5 7] Given the higher seroprevalence rates in developing countries, the congenital CMV burden is higher, affecting an estimated 1%–5% of all live births.[5 8]

Due to high CMV seroprevalence rates in mothers, while non-primary infections have low transmission rates of 1.1%–1.7%,[9] non-primary congenital infection accounts for two-thirds of cases.[10] Transmission rates for primary CMV infections are much higher, at 30%–35%.[9] Although the rate of vertical transmission is positively associated with older fetal gestational age at the time of infection,[11] there is a higher risk of fetal developmental malformations when infections occur earlier

INTRODUCTION

Cytomegalovirus (CMV) is the most common congenitally acquired infection worldwide.[1] Seroprevalence varies widely between and within populations, with higher rates being associated with factors such as socioeconomic vulnerability, or minority ethnic backgrounds.[2 3] In higher income countries

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Box 1 Consensus-based definition of symptomatic congenital cytomegalovirus (cCMV)[15]

'Mild' disease=isolated (one or two at most), otherwise clinically insignificant or transient findings: petechiae, mild hepatomegaly or splenomegaly or biochemical/haematological abnormalities (such as thrombocytopenia, anaemia, leucopenia, borderline raised liver enzyme abnormalities or conjugated hyperbilirubinaemia) or small for gestational age (weight for gestational age ≤2 SD) without microcephaly.

'Severe' disease=central nervous system involvement: abnormal neurological or ophthalmological examination, microcephaly or neuroimaging consistent with cCMV or with life-threatening disease.

'Moderate' disease=all non-severe, non-mild disease with at least two cCMV signs or symptoms.

Signs and symptoms of cCMV in neonates

Physical examination
  Hepatosplenomegaly.
  Petechiae, purpura or blueberry muffin rash in a newborn.
  Jaundice (prolonged or conjugated hyperbilirubinaemia).
  Microcephaly (head circumference ≤2SD, SD, for gestational age).
  Consider if symmetrically small for gestational age (≤2 SD for gestational age).

Laboratory parameters
  Prolonged jaundice with transaminitis.
  Conjugated hyperbilirubinaemia.
  Unexplained thrombocytopenia, consider if leucopenia or anaemia.

Neurology and neuroimaging
  Seizures with no other explanation.
  Intracranial calcification (often periventricular).
  Intracranial ventriculomegaly without other explanation.
  Consider in the case of periventricular cysts, subependymal pseudocysts, germinolytic cysts, white matter abnormalities, cortical atrophy, migration disorders, cerebellar hypoplasia, lenticulostriate vasculopathy.

Visual examination
  Abnormal findings on ophthalmological examination consistent with cCMV (eg, chorioretinitis).
  Consider if congenital cataracts.

Failed neonatal hearing screen

Maternal serology
  Evidence of maternal seroconversion.
  Consider in women with known CMV infection (known immunoglobulin G (IgG), IgG seropositive at start of pregnancy), particularly, if symptoms or virological examination consistent with suspected CMV reactivation/reinfection.

Prematurity

Signs and symptoms of cCMV in older children
  New diagnosis of sensorineural hearing loss.

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in gestation. Following primary infection in the first trimester, up to a third of neonates will develop symptomatic cCMV.[12 13]

At birth, the majority of infants with congenital CMV (cCMV) infection are asymptomatic, while 10%–15% are symptomatic with clinical manifestations of disease.[7 9] These multisystem manifestations include chorioretinitis, optic atrophy, cataracts, neurological disorders such as hearing impairments, microcephaly and intracranial calcification and other organ involvement (box 1).[7 14]

There is some heterogeneity within published literature around the definition of symptomatic disease, with some studies categorising low birth weight as symptomatic of cCMV, and some studies exclude a key health outcome, sensorineural hearing loss (SNHL), from the list of 'symptoms', classifying it instead as a diagnosis requiring specialised testing for detection.[15] In order to overcome this heterogeneity, which had resulted in a wide variation in reported rates of symptomatic disease, an international consensus on the definition of symptomatic disease now exists (box 1).[15]

Nearly 50% of symptomatic infants go on to develop long-term sequelae such as cerebral palsy, SNHL and other neurological problems.[5] There is also some evidence of long-term adverse effects in infants who were initially apparently asymptomatic.[7 16] The primary long-term adverse outcome for asymptomatic children is SNHL, which may be moderate or severe,[16 17] and which has been reported to present at median age of 44 months for children with asymptomatic cCMV.[18]

Visual impairment due to either neurological or ophthalmic manifestations of disease is another well recognised outcome for infants with symptomatic cCMV.[19–23] There is a growing body of evidence on the risk of long-term SNHL for initially asymptomatic infants, but there is a striking evidence gap on long-term visual outcomes for these infants. Currently, ophthalmic follow-up is recommended annually for preverbal children with clinically detectable disease at birth,[15] but there is an absence of consensus about the need for ophthalmic surveillance in children with asymptomatic disease.[15 23] Given that asymptomatic cCMV infection constitutes the majority of the disease burden (approximately 85%–90%), it is important to understand the current evidence on resultant ophthalmic manifestations to plan for optimal assessment and screening programmes. Therefore, the objective of this systematic review will be to describe the overall prevalence and incidence of eye or vision related disorders following diagnosis of asymptomatic cCMV, and to update the evidence base on visual sequelae of symptomatic cCMV.

METHODS AND ANALYSIS
We propose to undertake a systematic review and meta-analysis, pending appropriate data for analysis.

Data sources and search strategy
This systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) and has been developed in line with PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) recommendations.

This literature review and meta-analysis will be based on systematic evaluation of multiple literature databases, undertaken in accordance with PRISMA guidelines. We will search the PubMed, Embase and CINAHL databases, up to the date of 29 March 2022, without date or language

restrictions (full search strategy in online supplemental document S1) . We will include all studies that meet the inclusion criteria, and we will manually screen references cited within eligible articles in order to identify additional studies.

Inclusion and exclusion criteria

Original research articles will be included for data extraction if they fulfil the following criteria:

1. Study population comprises patients with symptomatic or asymptomatic cCMV.
2. Exposure is cCMV diagnosed by CMV PCR of urine obtained within 21 days of birth, or CMV DNA PCR of stored dried blood spot.
3. Outcomes include reported incidence or prevalence of visual or ophthalmic outcomes following cCMV infection.
4. Study design is a longitudinal study or a cross-sectional study.

Review articles will also be included for selection to undergo full-text review. This will enable manual hand searching of references to identify further eligible studies. Studies will be excluded if they are an animal study, case report, small case series (n<20) or conference abstract.

Screening and data extraction

The Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) will be used to store the included studies and screen for eligibility. Articles will initially be screened by title and abstract, followed by full-text articles to identify eligible studies. At least two authors will review all titles and abstracts. Discordant results will be resolved by discussion between the two authors, and in the event of a failure to reach consensus, the study will be included for free-text review. Free-text review for inclusion will also be undertaken by at least two authors. In the event of a failure to reach consensus on whether to include a paper in the review, the final decision will rest with the senior author (ALS).

At least two authors will independently review and extract data following full-text review using a piloted specific case report form (CRF) to ensure consistent data collection across all of the studies. The CRF for data extraction will include study information, such as publication year, study location, study period, study centre and sample size; and population characteristics, including gender, ethnicity, modality of CMV diagnosis, definition of symptomatic versus asymptomatic disease (including alignment with the definition within Luck *et al*),[15] follow-up duration, ophthalmic assessments undertaken, definitions used for vision impairment or vision disorder and prevalence or incidence of eye or vision disorders. Study authors will be approached if published data are incomplete or unclear. When multiple studies use the same data set or cohort, we shall exclude the duplicate studies with the smallest sample size or shortest follow-up duration.

Assessment of quality

The methodological quality of the included studies will be evaluated using the validated Joanna Briggs Institute tool.[24] Each study will be assessed according to whether the study ensured a representative sample, appropriate recruitment, adequate sample size, appropriate description and reporting of study subjects and setting, adequate data coverage of the identified sample, reliable and objective measurement of the condition, appropriate statistical analysis, and whether it identified and accounted for confounding factors (a total of 9 items).[24] Studies will be classified as having a low (>8 of the 10 items ensured, further research is very unlikely to change confidence in the estimate), moderate (6–8, further research is likely to have an important impact on confidence in the estimate and may change the estimate) or high (≤5, further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate) risk of bias on the basis of the overall score.

Data analysis

Analyses will be done in accordance with the PRISMA and the Meta-analysis of Observational Studies in Epidemiology guidelines.

The main outcomes will be vision impairment and ophthalmic disorder incidence or prevalence in patients with asymptomatic and those with symptomatic cCMV. The International Classification of Disease 11th revision definitions of visual impairment and blindness will be used to classify visual outcomes. Ophthalmic disorders will be defined as sight threatening structural or neuro-ophthalmic abnormalities outcome types (eg, degree of severity of visual impairment, moderate, severe or blindness; anatomical location of ocular abnormality) will be reported using descriptive analyses. The overall prevalence will be estimated by pooling the data using a random-effects model. We will estimate heterogeneity between studies using Cochran's Q statistic ($p<0.05$ indicates moderate heterogeneity) and the I^2 statistic ($\geq50\%$ or higher indicates moderate heterogeneity). Subgroup analyses will be done to investigate sources of heterogeneity, with tests for individual associations between the pooled estimates and the following covariates: diagnostic modality of cCMV, CMV symptom type (neurological vs other for symptomatic cCMV only), study period, country income, sample size, quality assessment score. Additionally, we will do a sensitivity analysis of prevalence for all methods of detection for vision or eye disorders, and for all methods of confirming CMV status. We will use separate random-effects model to pool the incidence and prevalence rates of vision or eye disorders among patients with symptomatic and asymptomatic cCMV. Egger's test will be used to assess studies for publication bias within the meta-analysis. All analyses will be performed separately for symptomatic and asymptomatic cCMV. The confidence in the cumulative evidence will be quantified using a modified GRADE (Grading of Recommendations, Assessment, Development and

Evaluations) scale: 'high', we are very confident that the true frequency (incidence or prevalence) lies close to that of the estimate; 'moderate', we are moderately confident that the true frequency is likely to be close to the estimate, but there is a possibility that it is substantially different; 'low', our confidence in the estimate is limited: the true frequency may be substantially different from the estimate; and 'very low', we have very little confidence in the estimate: the true frequency is likely to be substantially different from the estimate.[25]

Patient and public involvement

Patients and the public were not directly involved in the development of this systematic protocol. However, the 2013 James Lind Alliance Sight Loss and Vision Priority Setting Partnership identified 'How do we improve screening and surveillance from the ante-natal period through to childhood to ensure early diagnosis of impaired vision and eye conditions?' as a top three priority for research into childhood eye disorders.[26]

ETHICS AND DISSEMINATION

There are no requirements for ethical approval for this systematic review. Review findings will be disseminated in a peer-reviewed journal and shared with both the Royal Colleges of Ophthalmology and of Child Health in order to inform any future development of national guidelines on follow-up management of infants with cCMV.

DISCUSSION

Through this systematic review we aim to provide currently unavailable robust estimates of the burden of long-term ocular and visual sequelae following cCMV in asymptomatic as well as symptomatic children. A key strength of this study is the broad database search strategy. By using a broad inclusion strategy for search terms, the risk of missing studies is reduced, although this does increase the burden on reviewers, which may have a negative impact on review progress. Prior dissemination of a study protocol will enable a transparent and reproducible review process. Having multiple reviewers at each stage of the article review process will minimise reviewer bias and human error. A possible limitation to this systematic review is the potential difference in definition between studies for symptomatic and asymptomatic disease, but this will be overcome through comparison of study classification scheme with the consensus-based classification described by Luck *et al.*[15] As data will be extracted solely from full-text review of published studies, there is a risk of excluding data with grey literature and unpublished works. However, this is a conscious decision to minimise the effect of possible poor quality or unrepresentative data from non-peer-reviewed papers increasing the bias within the meta-analysis.

Effective screening requires that individuals are tested for a disorder for which there is an early intervention which can positively alter the disease course. While the ocular anomalies or neurodevelopmental disorders capable of causing poor vision in cCMV are not typically amenable to intervention, early detection of poor vision in these vulnerable children allows for early developmental support for the child and their family. This is of particular importance for a population who are also at risk of cCMV-related hearing impairment. However, recommendations for enhanced visual surveillance in children with hearing loss or with diagnosed neurodevelopmental impairments are already in place, and whole population childhood vision screening interventions are embedded within the UK's Health Child programme.[27] Consequently, in the absence of an evidence base suggesting that children with asymptomatic cCMV are at additional risk (over the general population) of ophthalmic or visual complications, it is questionable as to whether there is a need for additional surveillance for those children. This planned systematic review and meta-analysis will explore the available evidence to inform the development of optimum surveillance strategies for infants and children with symptomatic and asymptomatic CMV.

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