Universal newborn screening for congenital cytomegalovirus infection

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Congenital cytomegalovirus (CMV) infection is the leading infectious cause of childhood disability, in particular sensorineural hearing loss (SNHL). Timeliness of diagnosis is crucial, since the presence of CMV in any compartment (eg, blood, urine, or saliva) after age 21 days can mean postnatal acquisition of infection, particularly in breastfed infants. Given these issues, there is considerable interest in implementation of screening programmes—either universal screening (where all newborns are tested) or targeted screening. Targeted screening is typically based on the outcome of a newborn hearing screen, and can be influenced in some strategies by findings of other signs suggestive of congenital CMV. Universal screening is likely to have the greatest overall benefit. Early identification of congenital CMV allows for interventions such as antiviral therapy (when indicated) and enables anticipatory audiological monitoring that facilitates timely detection of delayed-onset SNHL. However, there are debates about the effectiveness of screening programmes. Most infants with congenital CMV are unaffected and do not appear to be at risk for adverse neurodevelopment outcomes, except for SNHL. Screening can, therefore, raise unwarranted concern among parents and clinicians in these cases. The best clinical sample for diagnostic testing is unclear. PCR testing of saliva is sensitive but has a risk of yielding false-positive results in infants without congenital CMV. Resolving the technological issues has improved the sensitivity of dried blood spot (DBS) PCR but the technique remains suboptimum. An advantage to DBS PCR testing is that an infrastructure exists to add this test to existing newborn screening programmes. In this Review, the advantages and disadvantages of congenital CMV screening are discussed, along with high-priority areas for future research that will inform and direct this rapidly evolving field.

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Introduction

Congenital cytomegalovirus (CMV) infection is a condition of considerable public health importance, with CMV being the leading infectious cause of sensorineural hearing loss (SNHL)[1–3] and other neurodevelopmental sequelae[4] in children. Congenital infection must be differentiated from postnatally acquired CMV, which is usually acquired by breastfeeding[5] from a mother who is CMV-seropositive, and is shedding virus in breastmilk. Congenital CMV should be identified before age 21 days as the finding of CMV after this time can mean postnatal acquisition. Because of the crucial issue of timing, congenital CMV would seem to be an ideal candidate for universal newborn screening tests. However, although congenital CMV is the leading infectious cause of childhood disability globally, most infants with clinically inapparent congenital CMV infection appear to have no long-term health consequences, with the exception of a risk of SNHL.[6] Therefore, although several authors have voiced considerable enthusiasm for universal congenital CMV screening,[7–9] other experts have voiced caution in embracing such a policy until there is a better evidence base with respect to management of asymptomatic congenital CMV infection.[10] In this Review, we outline the advantages and disadvantages of congenital CMV screening programmes.

Epidemiology, clinical presentation, and symptomatic versus asymptomatic disease

The overall prevalence of congenital CMV infection has been reported to range from 0·2% to 2·5% in various studies[11–14] and the disease burden is substantial.[15] The frequency of congenital CMV transmission is higher in people who acquire primary CMV infection during pregnancy compared with those who have a non-primary infection.[16] However, since the seroprevalence of CMV is high in women aged approximately 16–45 years and preconception immunity does not fully protect against vertical transmission, most congenital CMV transmissions globally occur in women who are seropositive before

Key messages

- Most congenital cytomegalovirus (CMV) infections are clinically inapparent but can be associated with progressive sensorineural hearing loss and other neurodevelopmental sequelae.
- Early identification of congenital CMV enables efficient diagnosis (since congenital infection is difficult to confirm with certainty beyond age 21 days) and enhances prospective monitoring and therapy planning that can improve infant outcomes.
- Targeted and universal congenital CMV screening is increasingly being considered for implementation globally by various governmental health departments, newborn screening programmes, and legislative bodies.
- Universal screening has been shown to be a cost-effective strategy. Emerging evidence indicates that this approach identifies infants that are at risk for congenital CMV-associated sequelae who would have otherwise been missed by routine care or targeted screening.
- There remain unresolved questions about the optimal number and type of specimens needed to analyse for identification of congenital CMV. Other concerns centre around cost–benefit analyses, the ethics of screening for a condition that is typically asymptomatic, and the risks of overtreatment with unwarranted antivirals.
- As most infants with congenital CMV are asymptomatic and have a good prognosis, future studies must examine long-term outcomes in asymptomatic infants. Practitioner and parental acceptance of universal screening also requires careful scrutiny. Continued study of infant outcomes will inform and direct public policy decisions about uniform implementation of this practise in routine newborn care.

pregnancy.[17] Overall, congenital CMV prevalence is directly proportional to the maternal CMV seroprevalence rates in the population of interest.[18]

Most congenital CMV infections are clinically inapparent with CMV-related signs at birth reported to be present in only 13% of those with congenital CMV.[11] Newborns with symptomatic CMV can present with hepatosplenomegaly, jaundice, microcephaly, petechial or purpuric rash, neurological signs (such as hypotonia, seizures, or lethargy), or be small for gestational age.[19] Associated laboratory abnormalities in symptomatic infants include transaminitis, thrombocytopenia, neutropenia, and direct hyperbilirubinemia. Neuroimaging abnormalities include ventriculomegaly, periventricular calcifications, white matter abnormalities, and, in severe cases, manifestations of neuronal migration disruption (ie, lissencephaly, polymicrogyria, and cerebellar malformations).[4] The most severe manifestations of CNS injury are typically associated with first-trimester acquisition of CMV by the developing fetus.[20,21] Auditory brainstem response testing is warranted in all infants with confirmed congentical CMV infection, irrespective of the outcome on the newborn hearing screen.

There is no internationally accepted consensus on what constitutes symptomatic congenital CMV disease. Isolated SNHL in absence of any other clinical, laboratory, or neuroimaging abnormalities was defined by an international consensus committee as asymptomatic congenital CMV.[22] The Red Book Committee of the American Academy of Pediatrics generally follows these guidelines with respect to defining symptomatic disease,[22] whereas the European Society for Paediatric Infectious Diseases expert consensus panel has published a consensus statement that considers isolated CMV-associated SNHL as a manifestation of symptomatic congenital CMV infection involving the CNS.[23]

For the **American Academy of Otolaryngology–Head and Neck Surgery position statement** see https://www.entnet.org/resource/universal-newborn-congenital-cytomegalovirus-congenital CMV-screening/

Potential screening approaches

Targeted or hearing-targeted screening (also known in the UK as targeted testing) is based on the premise that some populations of newborns are at enhanced risk for congenital CMV infection, including newborns identified as having potential hearing deficits on the newborn hearing screen.[24–26] Hearing-targeted screening has been well received and has been implemented in many locations. Cost–benefit analyses, assuming a modest benefit of early antiviral therapy, indicate that this strategy can confer cost savings.[27] In 2013, Utah became the first state in the USA to legislatively mandate hearing-targeted congenital CMV screening.[28] Since that time, many other states have seen similar legislation passed.[29] Moreover, targeted screening is endorsed by the American Academy of Audiology, which noted in a 2023 position statement[30] that "implementation of a targeted cCMV screening program has potentially significant patient and family benefits".

Expanded-targeted congenital CMV screening goes a step beyond hearing-targeted screening, aiming to broaden the scope of testing to include more newborns in high-risk groups for congenital CMV infection, not just those that have a refer status on the newborn hearing screen. Expanded-targeted screening can include infants with other findings, such as atypical head size (eg, macrocephaly or microcephaly), small-for-gestational age birthweight, petechial rash, and other findings.[31–33] The list of indications that trigger a targeted-screening test includes many classic signs that most experienced clinicians would consider to be highly suggestive of congenital CMV infection, and might typically warrant definitive diagnostic testing, but as has been noted by Gantt and colleagues,[34] often these classic signs are overlooked.[35–37]

Universal screening tests every newborn for congenital CMV. The objective of universal newborn screening is to identify all children with congenital CMV at birth. This early identification aims to optimise follow-up care, facilitate the early diagnosis of related delayed hearing loss and neurological conditions, and ensure rapid access to rehabilitation and therapeutic strategies. We compared targeted screening, expanded-targeting screening, and universal screening (panel 1). In February, 2024, the American Academy of Otolaryngology–Head and Neck Surgery published a new position statement that recommended universal newborn congenital CMV screening, emphasising the impact on hearing outcomes and the value of early diagnosis.

Specimen selection for newborn congenital CMV screening

Experts concur that timing is crucial for specimen collection and specimens should be obtained within 21 days of birth. A key issue that has been extensively discussed is the question of which biological fluid should be used for universal congenital CMV screening. Urine, saliva, and dried blood spots (DBSs) have all been evaluated as potential sources of CMV DNA for PCR-based screening. We discuss the advantages and disadvantages of each method.

Urine PCR

Successful newborn screening studies have been conducted using newborn urine samples. Studies have focused on urine viral culture,[38] but PCR has equivalent sensitivity,[39] is faster, and is more cost-effective. In a cohort study in Japan, 11736 newborns underwent a universal urine PCR congenital CMV screening test; 56 (0·48%) were found to have congenital CMV.[40] Urine samples can be collected on filter discs,[41] filter paper,[42] or at home by parents.[43] Cost is also a consideration, because collection of urine samples by bag placement is very time-consuming and provider time is costly.[44] Bladder catheterisation, although less costly, is considered unacceptably invasive for infants.

***Panel 1*: Comparison of screening strategies**

Hearing-targeted screening

Advantages

- Can detect up to 7% of patients with congenital cytomegalovirus (CMV)
- Cost-effective; requires testing for fewer newborns
- Enables early diagnosis for sensorineural hearing loss (SNHL), hence avoids unnecessary testing for other syndromes and causes
- Hearing-targeted screening has improved compliance with ongoing hearing testing and evaluation of speech and language outcomes

Disadvantages

- Uncertainty regarding optimal specimen for CMV testing (eg, saliva, urine, or dried blood spot [DBS])
- High rate of false-positive referrals on newborn hearing screens
- Infants who test positive for congenital CMV and who refer on newborn hearing screens will often have a non-pathological assessment for other sequelae at time of definitive audiological evaluation; conversely, due to the high background prevalence of congenital CMV, there is possibility for an infant to have congenital CMV but have another explanation for finding SNHL
- Risk of overtreatment with antivirals

Extended-targeted screening

Advantages

- Captures infants with congenital CMV who might have been overlooked
- Defining criteria for expanded-targeted congenital CMV screening (targeted testing) increases overall knowledge and awareness
- Early detection enables accurate and timely diagnosis and avoids unwarrented additional diagnostic testing for other syndromes

Disadvantages

- Requires knowledge of maternal history and maternal HIV status for optimal implementation of this strategy
- Uncertainty regarding optimal specimen for CMV testing (eg, saliva, urine, or DBS)
- Criteria for screening incompletely defined; cost-effectiveness not studied

Universal screening

Advantages

- Captures patients with clinically inapparent congenital CMV at risk for sequelae, particularly SNHL
- Early identification allows for detailed, complete diagnostic testing to examine for other evidence of congenital CMV-associated disease
- Early identification enables consideration of antiviral therapy
- Cost-effective; enhanced cost savings per newborn from universal screening is from US$25·11 to $25·52 compared with $12·54 to $12·75 for targeted testing
- Potential for implementation into state, provincial, or national newborn screening infrastructure

Disadvantages

- Most infants are asymptomatic with good prognosis; might increase undue parental and clinician worry
- Risk of so-called vulnerable child syndrome; risk of overmedicalisation and excessive costs of diagnostic testing
- No evidence for benefit with use of antivirals in infants with clinically inapparent infection; risk of overtreatment with attendant drug toxicities
- There is increased investment in infrastructure to perform universal screening compared with hearing-targeted screening and expanded-targeted testing
- Uncertainty regarding optimal specimen for CMV testing (eg, saliva, urine or DBS)
- Little endorsement by expert groups and or regulatory agencies
- Controversy about whether universal congenital CMV screening fits traditional framework of conditions amenable to screening
- Shedding of CMV in specimens obtained beyond age 21 days cannot be interpreted as evidence of congenital CMV infection.

Saliva PCR

Saliva is easier to obtain than urine and has been advocated as an option for targeted and universal congenital CMV screening programmes.[45] The CHIMES study[46] (conducted at seven USA hospital nursery sites), screened 100 332 newborns from diverse populations. As a component of the CHIMES study, Boppana and colleagues[47] reported on the results of PCR of saliva (collected by mouth swab) from approximately 35 000 newborns at the seven hospitals. Sensitivity was reported as 100% for liquid-saliva PCR testing and 97·4% for dried saliva. In a follow-up report, additional data from 72 239 newborns who were screened for congenital CMV by rapid culture and real-time PCR of saliva samples were reported. 266 infants were found to have congenital CMV following the screen, of whom 14 were observed to have discordance between rapid culture and PCR. 13 of 14 infants were identified only by PCR, showing the superiority of the PCR assay.[48] A 2024 study[26] of pooled saliva samples indicated that this screening method is amenable to a high-throughput approach and, therefore, appropriate for universal screening.

There is concern that a false-positive PCR signal in infant saliva can occur due to presence of viral DNA in breastmilk from a mother who is CMV-seropositive, or

from CMV DNA in commercial donor breastmilk.[49] In research studies, the timing of an oral swab relative to breastfeeding can be controlled, but in routine practice the timing of the saliva sample after a breastfeed would be more difficult to predict; therefore, the false-positive rate might even be higher than in a research setting. In the original report by Boppana and colleagues,[47] false-positive test results were rare, with eight (0·045%) of 17 577 newborns for liquid-saliva PCR assays and eight (0·046%) of 17 251 for dried-saliva PCR assays. However, although these percentages are low, they should be considered against the denominator of any positive test. With this analysis, these positive PCR results were eight (8·6%) of 93 and eight (9·8%) of 82 of the total of all positive PCR results.[47] In a screening study conducted in five newborn nurseries in Minnesota, USA, the false-positive rate based on PCR testing of dried-saliva swabs was eight (0·064%) of 12 498, which was eight (13·3 %) of 60 of the positive results.

Saliva PCR has been evaluated as an approach for hearing-targeted screening.[50–53] Point-of-care testing at bedside for newborns that refer on their newborn hearing screen is appealing as a positive test could then trigger collection of a urine PCR, which ideally should be obtained before hospital discharge to clarify or confirm the infant's CMV status.

DBS PCR

Collection of saliva is fraught with concern for false-positive results. Urine collection is costly,[44] given the expense of a practitioner's time, making this an untenable approach, particularly in resource-limited settings. In light of the limitations and these intrinsic costs associated with newborn congenital CMV screening using urine and saliva samples, DBS-based screening is an option to consider. In many countries, infants have a DBS sample obtained at birth, which is collected well within the timeframe of 21 days necessary to make an accurate diagnosis of congenital CMV. Based on pioneering work done by Shibata and collagues,[54] Johansson and colleagues,[55] and Barbi and colleagues,[56] the use of DBS as a source for CMV DNA, detectable by PCR amplification, has been much discussed for over three decades. CMV DNA also appears to be highly stable in DBS,[57] enabling long-term storage amenable to purification and amplification after at least 10 years of sample retention.[58]

DBS PCR has been used for targeted congenital CMV screening. A study reported by Chung and colleagues[59] examined the DBS of 1374 infants with a refer status on the newborn hearing screen and found that 59 (4·3%) were CMV-positive—a rate eight times higher than the estimated birth prevalence of congenital CMV in the Netherlands. Infants identified in this study also had a high prevalence of neuroimaging findings with concomitant CMV disease. Leruez-Ville and colleagues[60] examined two different DBS PCR assays in a high-risk population of maternal–infant dyads in what could be described as expanded-targeted screening[31–33] or targeted testing. The authors used urine PCR testing of newborns as the gold standard of comparison and reported DBS sensitivities of 95·0–96·9%.[60]

To investigate the potential use of DBS-based screening for universal congenital CMV infection, the CHIMES study also evaluated DBS PCR for congenital CMV diagnosis,[61] comparing these results to the saliva-based screening data reported by Leruez-Ville and colleagues.[60] Using a single-primer set for DBS PCR, a sensitivity of 28·3% was reported. Using a two-primer DBS PCR approach augmented sensitivity only incrementally, with 34·4% sensitivity reported. The authors concluded that CMV testing with DBS real-time PCR had low sensitivity when compared with saliva rapid culture, and hence had little value as a screening test for congenital CMV. To reassess if improvements in nucleic acid purification techniques might enhance DBS sensitivity, a study was performed to compare the analytical sensitivity of DBS and dried-saliva PCR in an unselected cohort of infants from seven nurseries in Twin Cities, MN, USA.[62] The analytical sensitivity for PCR in identifying a congenital CMV infection was 93·1% for saliva, 73·2% for DBS in one laboratory, and 76·8% for DBS for another laboratory (combined sensitivity for both DBS primer sets was 85·7%). This increase in the sensitivity of the test, coupled with the existing infrastructure to collect DBS in newborns, has led some policy makers to implement this approach for universal congenital CMV screening programmes. However, more studies are needed to identify if this approach is sufficiently sensitive to be the reference test in a screening programme. Additionally, in many low-income and middle-income countries, there are no DBS collection-based metabolic screening programmes, so existing programmatic infrastructure cannot be used to implement a congenital CMV neonatal screening programme.

Advantages of universal congenital CMV screening for newborns

Screening newborns for congenital CMV infection enables early detection, facilitates anticipatory management, and provides an opportunity for improved outcomes. A considerable number of children with congenital CMV develop SNHL outside the neonatal period. CMV screening would allow for appropriate follow-up of these children and early intervention to help prevent late-onset hearing loss, as it is performed in the newborn hearing screening programme. One important consideration that is relevant to all approaches to CMV screening is the value of making a timely diagnosis with respect to the issue of considering antiviral therapy. A study sponsored by the National Institutes of Health Collaborative Antiviral Study Group,[63] CASG-112, showed audiological and neurodevelopmental benefits for infants with symptomatic congenital CMV infection involving

the CNS when antivirals were started by age 30 days. The CONCERT study[64] suggests that the timeframe for making a decision about starting antiviral therapy can be extended up to age 13 weeks. The CONCERT study, although non-randomised, also indicated that there was a benefit of 6 weeks of antiviral therapy for infants with otherwise asymptomatic congenital CMV who had isolated SNHL.[65]

Evidence supporting use of universal congenital CMV screening

At the current time, no public health organisation recommends universal congenital CMV screening. An analysis by Cannon and colleagues[9] in 2014 noted that "evidence of potential benefit for newborn CMV screening is limited by the scarcity of data to generate estimates" and that the authors were "unable to generate a precise estimate of potential benefit, and the numbers we provide should be considered approximate and provisional until more data become available". A review by the Canadian Agency for Drugs and Technologies in Health identified and summarised published evidence-based guidelines offering recommendations about the usefulness of congenital CMV screening.[2] evidence-based guidelines that made a positive recommendation favouring universal congenital CMV,[22] whereas the review found no support for recommending the implementation of universal screening for congenital CMV based on two other published analyses.[67,68]

However, there are robust new data that provide an evidence base supporting universal screening, with screening increasingly being implemented in several locations. Universal screening studies reported since 2022, with key evidence-based conclusions, have been summarised (table). A study in Italy of saliva-based screening identified 21 (0·7%) of 3151 newborns with congenital CMV; three (14·3%) of 21 had SNHL, and in one of these three newborns (4.7% of the overall total), hearing loss was not demonstrable until the infant was age 5 months.[69] A prospective screening study in Spain for congenital CMV evaluated 3190 infants, of whom 15 (0·47%) were confirmed to have congenital CMV. Only two of 15 infants were symptomatic at birth; therefore, the diagnosis would have been missed without a screening programme in most instances.[70] A study in Israel, performed over a 13-month period, screened 15 805 newborns with a pooled saliva-based PCR approach;[26] congenital CMV was identified in 54 (0·34%) newborns. In total, 30 (55.6%) of 54 infants identified with congenital CMV infection were asymptomatic at birth and would not have been identified as they were not otherwise targeted for screening, although the authors did not report if any of these infants had sequelae.

Other high-quality evidence for universal congenital CMV has come from evaluations comparing DBS and saliva, or with DBS alone. In an unselected universal screening study[71] comparing saliva PCR and DBS PCR in Minnesota, USA, 87 (0·37%) of 23 644 newborns screened were identified with congenital CMV. Analytical sensitivity was reported as 93·1% for saliva and 73·6% for DBS by the University of Minnesota laboratory, and 77·0% for DBS in the Centers for Disease Control and Prevention (CDC) laboratory. At birth, 68 (78%) of 87 newborns with congenital CMV were asymptomatic; six were moderately-to-severely symptomatic (two with SNHL); nine were mildly symptomatic; and four were asymptomatic with isolated SNHL. Four infants had delayed onset SNHL—two in the asymptomatic group and two in the symptomatic group.[71] Thus, without universal newborn CMV screening, some infants with congenital CMV who developed late neurological sequelae would not have been identified. Subsequent to this study, universal DBS-based congenital CMV screening was implemented in Minnesota, USA. In the first year of screening implementation, 184 (0·31%) of 60 115 infants had CMV detected, with three additional infants with congenital CMV who had negative DBS screening identified through routine care.[72] Of these 187 infants, 21 (12%) met the CDC definition for CMV disease. Clinical or laboratory evidence identified in the course of diagnostic evaluation following the positive screening test, consistent with symptomatic congenital CMV, was noted for seven infants identified through the newborn screening program. Two of these infants had CMV-related neuroimaging abnormalities. Importantly,

	Total newborns screened	Testing methodology	Congenital CMV prevalence	Key findings
Chiereghin et al (2022)[69]	3151	Saliva PCR	21 (0·7%)	75 newborns tested positive for congenital CMV with saliva PCR; 21 (28%) of 75 newborns were true positives; symptomatic congenital infection was observed in three (14·3%) of 21 infants; one (4·7%) infant developed moderate unilateral SNHL at 5 months after birth
Blázquez-Gamero et al (2020)[70]	3190	Saliva PCR	15 (0·47%)	Two infants with signs of congenital CMV infection at birth; eight infants with neuroimaging abnormalities
Merav et al (2024)[26]	15 805	Saliva PCR	54 (0·34%)	30 (55.6%) of 54 newborns who tested positive for congenital CMV with saliva PCR were asymptomatic at birth
Schleiss et al (2023)[71]	23 644	Comparison of saliva PCR and DBS PCR	87 (0·37%)	68 (78%) were asymptomatic; four infants with delayed-onset SNHL
Kaye et al (2024)[72]	60 115	DBS PCR (routine testing)	184 (0·31%)	21 (12%) with congenital CMV disease; seven infants with congenital CMV disease identified by newborn screening but missed by routine newborn examination

Data are N or n (%), unless stated otherwise. CMV=cytomegalovirus. DBS=dried blood spot. SNHL=sensorineural hearing loss.

Table: **Summary of universal congenital CMV screening studies**

none of these congenital CMV infections would have been identified in the context of routine newborn care.

Congenital CMV screening is cost-effective

Cost-effectiveness analyses have been performed for both hearing-targeted and universal congenital CMV screening. Most of the analyses are based on inferred or predicted benefits of early initiation of antiviral therapies, which, by mitigating the need for cochlear implantation and reducing the costs of other aspects of otolaryngological care, would result in a net cost savings.[73,74] Gantt and colleagues[27] modelled the cost-effectiveness of targeted and universal congenital CMV screening and noted that both interventions were cost-effective, although universal screening showed a greater financial benefit than targeted screening. In addition to offering larger net savings, universal screening offered the greatest opportunity to provide directed care.[27] Another study that compared hearing-targeted newborn congenital CMV screening with standard-of-care clinical diagnosis indicated that screening would result in reduced SNHL progression and would prevent progression of this condition at a very low cost.[75] A Markov model was used to estimate cost-effectiveness of targeted and universal screening in a high CMV seroprevalence population in China[76] and concluded that both screening strategies were cost-effective. A study in Japan, using a decision-tree model, also suggested enhanced cost-benefit for a universal congenital CMV screening policy when compared with a targeted screening approach.[77] A comprehensive economic analysis by Grosse and colleagues[78] called for more research before reaching firm conclusions about costs and benefits, but the available literature does support that all congenital CMV screening strategies provide cost savings. In an analysis of 96 785 newborns who had been tested for CMV as part of the CHIMES study,[46] a hierarchical, Bayesian generalised additive model was constructed to evaluate and adjust for geographical variability in the cost–benefit comparison of universal CMV screening with targeted screening. Universal screening was more cost-effective and afforded more averted instances of severe hearing loss than targeted testing and represented the most cost-effective option even in geographical areas with low congenital CMV prevalence. Cost savings per newborn from universal screening ranged from US$25·11 to $25·52 and from $12·54 to $12·75 for targeted testing.[79]

Universal congenital CMV screening can be helpful to parents

Lastly, much attention has been devoted to the question of whether congenital CMV screening might generate harm. Gievers and colleagues[80] have expressed reasonable concern that the diagnosis of CMV infection might cause considerable worry among parents, despite the fact that the likelihood for a good clinical outcome is generally high, particularly in a clinically inapparent infection. An analysis by Pesch and colleagues[81] challenged this viewpoint regarding undue parental concerns and worry in the context of asymptomatic congenital CMV. Studies in many populations show that, given the choice, parents support universal screening initiatives and would prefer to know their child has a congenital CMV infection, even in instances of uncertain prognosis with respect to sequelae, including SNHL.[82,83]

Disadvantages of universal congenital CMV screening for newborns

Newborn screening, maternal screening, or both?

A case can be made that, rather than a blanket endorsement of newborn congenital CMV screening, what is really needed is a better assessment of the presence—and importantly the timing—of maternal CMV infection during pregnancy. Antiviral therapies are now available for individuals who are pregnant and at high risk for congenital CMV transmission. Shahar-Nissan and colleagues[84] found in a randomised controlled trial that valaciclovir is effective in preventing fetal infection after a maternal primary infection periconceptionally or in first trimester of pregnancy (odds ratio 0·29, 95% CI 0·09–0·90). Other observational studies have shown similar results.[85–90] A maternal screening programme can, therefore, reduce the number of fetuses that acquire CMV in this high-risk period and, ultimately, the number of children with sequelae due to congenital CMV.

However, maternal screening has some limitations and potential risks. Prenatal screening programmes only detect primary infections and do not identify non-primary infections. Consequently, these programmes are not effective in areas with a high percentage of pregnant women who are already CMV-seropositive. Although IgG avidity index can be helpful, the molecular tests required to differentiate a primary from non-primary maternal infection during pregnancy are not available in clinical laboratories. Moreover, there is a fear of potential harm associated with maternal screening, such as unnecessary terminations of pregnancy in false-positive cases or in cases with no evidence of fetal CMV acquisition.[91]

If we perform both maternal and newborn screening, we might be able to know the time of maternal primary infection and possibly avoid unnecessary treatments in children at low risk of developing CMV-related sequelae. However, to date, most newborn screening programmes have started in regions (such as the USA) where there are no official recommendations for implementation of a maternal screening programme.[34]

DBS testing for CMV infection remains suboptimum

Despite improvements in the technology, there are still limitations to DBS testing. The CHIMES study[61] reported low sensitivity (34·4%) of DBS testing, with a high proportion of false-negative results. Moreover,

low sensitivity of DBS testing has been reported in some cohorts with a high proportion of symptomatic children.[92] In a study conducted in Spain, 101 newborns with congenital CMV (63% symptomatic at birth), DBS PCR had a sensitivity of 56%.[92] Even in ideal conditions, DBS sensitivity is only around 75% when a single test is performed.[62] There is a hypothesis that if 25% of children with false-negative test results are congentially infected but are not detected by PCR, this will be because they have a low blood viral load at birth and a lower risk of long-term sequelae than children with higher viral loads.

Ethical considerations of overtreatment

The ethical perspectives of the potential for excessive diagnostic studies on asymptomatic infants with congenital CMV and the possibility of overtreatment with unwarranted antiviral therapy raise substantial concerns in the context of congenital CMV newborn screening programmes. Balance among advantages and disadvantages in screening programmes should clearly show a positive benefit for infants. Most infants with congenital CMV do not develop any long-term sequelae; therefore, screening will mostly diagnose newborns at low risk of adverse consequences, an issue that many experts believe needs to be resolved before universal screening can be fully endorsed.

The stress on families of dealing with a positive screening test for congenital CMV (particularly in an asymptomatic infant) cannot be overemphasised. Parents confronting a positive result in CMV screening encounter a highly stressful situation, chiefly caused by coping with the uncertainty of the prognosis following the initial screening result. Moreover, there remains no clear consensus on which evaluations are required in infants who appear healthy and screen positive for congenital CMV. Even in the best scenario, what has been referred to by some authors in the literature as a vulnerable child syndrome[93] could be a concern for asymptomatic or mildly symptomatic infants with a low risk of long-term sequelae. Many infants will follow-up with multiple specialists during their first years of life.[81] There is concern that overmedicalisation[94] of children with congenital CMV can create stress for families, who might incorrectly blame the congenital CMV infection for all future medical or developmental issues their child might have.

Uncertainties about antiviral therapy

Overtreatment with antivirals (eg, ganciclovir and valganciclovir) is another risk for newborns identified as having congenital CMV through screening, particularly for asymptomatic infants with clinically inapparent infections. Antiviral treatment has shown modest benefits in randomised controlled trials of symptomatic infants, but data on asymptomatic infants or infants with mild disease is sparse.[63,95] A 6-month course of valganciclovir is undoubtedly beneficial to symptomatic infants with congenital CMV, but clinicians might be overusing the drug. Since the publication of the valganciclovir CASG-112 trial,[63] a higher proportion of infants with congenital CMV has been treated with antivirals in the USA (53%) than in previous years (38%), and valganciclovir use is steadily increasing.[96–98] Universal newborn screening might increase the number of children with congenital CMV receiving antivirals, exacerbating toxicities without clear evidence of benefit, despite scarce data on long-term safety.[99]

Time constraints regarding initiation of antivirals for newborns with congenital CMV are also a concern. Randomised controlled trials studying the effect of antivirals in preventing hearing deterioration have been designed to examine treatment commenced in the first 30 days of life.[63,95] Moreover, there is no evidence that any protective effect in preserving hearing in infancy and early childhood is sustained into later childhood and beyond. Lanzieri and colleagues[100] studied long-term hearing outcomes of children (age 11–13 years) with symptomatic congenital CMV treated with intravenous ganciclovir (n=17), compared with a similar group of untreated yet symptomatic children (n=27). Severe SNHL in best ear was present at the end of the follow-up in 12 (71%) of 17 children in the treated group versus 16 (59%) of 27 children in the untreated symptomatic group. This absence of sustained benefits of antiviral therapy should remind clinicians to be cautious, lest they overstate the benefits of antiviral therapy, particularly for children with mild disease.[101]

Summary and high-priority areas for future work

Diagnosing a substantial number of children who are asymptomatic and at low risk for congenital CMV sequelae could result in more harm than benefit. The concerns we have outlined stand out as a potential reason—offered by some experts—to defer universal congenital CMV screening until there is a consensus on the evaluation of clinically inapparent CMV infections. The management of congenital CMV has been defined by infections identified in the context of symptomatic CMV disease recognised by clinicians in the newborn period, but universal congenital CMV screening changes this outlook. Thus, the management of asymptomatic infants with clinically inapparent congenital CMV is yet to be thoroughly researched in the context of newborn screening. Large prospective newborn screening studies are needed to clarify evidence-based recommendations for the evaluation and management of asymptomatic infants. However, there are current evidence-based recommendations for diagnostic evaluation of infants who screen-positive for congenital CMV[72] and evidence-based consensus approaches to therapy for infants with suspected or confirmed disease due to congenital CMV[65,102] that should be used for clinical decision making until more data are available (figure).

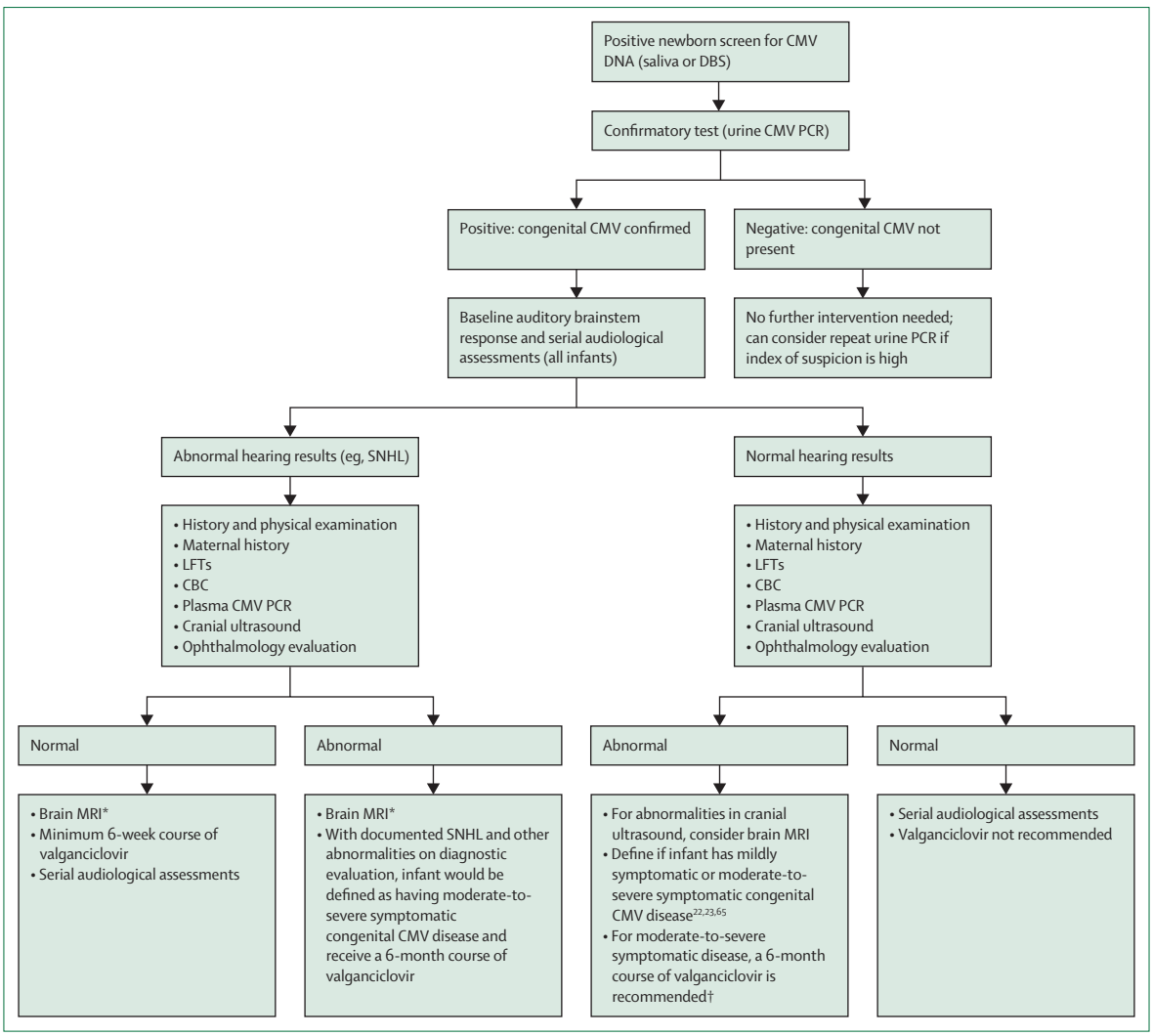

Figure: **Suggested universal congenital CMV screening algorithm**
Evaluation sequence for the infant identified by universal congenital CMV screening. This algorithm is informed by recent universal screening studies across a range of signs. The algorithm focuses on infants with clinically inapparent infections at birth, because these include most of the cases of congenital CMV identified by universal screening. Any positive screen should be confirmed by urine CMV PCR. The diagnostic evaluation of the infant with confirmed but clinically inapparent congenital CMV infection should centre around the need for early establishment of audiology care and baseline auditory brainstem response testing. Although an infant with SNHL might have an otherwise clinically inapparent infection, obtaining additional clinical diagnostic studies is important. All infants should undergo additional evaluation including examination of LFTs, CBCs, differential leukocyte count, platelet count, ophthalmological evaluation, and cranial ultrasound. We recommend consideration of MRI for infants with chorioretinitis; SNHL; abnormal physical examination; abnormal cranial ultrasound; and abnormal laboratory studies. Infants can be considered as having a clinical presentation fitting the following four categories: (1) congenital CMV with non-pathological hearing assessments and negative evaluation (ie, physical exam, laboratory studies, neuroimaging, and ophthalmological evaluation all within expected parameters; asymptomatic category); (2) congenital CMV with associated SNHL but with no other evidence of symptomatic disease (asymptomatic with SNHL); (3) congenital CMV with mildly symptomatic disease; or (4) congenital CMV with moderate-to-severe symptomatic disease (with or without SNHL). Infants with isolated SNHL and no other evidence of disease should be treated with at least 6 weeks of oral valganciclovir; some experts extend this course of therapy to 6 months. For moderate-to-severe symptomatic congenital CMV (with or without SNHL), evidence supports a full 6-month course of oral valganciclovir therapy. For mild symptomatic disease, valganciclovir can be considered on a case-by-case basis. CMV=cytomegalovirus. DBS=dried blood spot. SNHL=sensorineural hearing loss. LFTs=liver function tests. CBC=complete blood count. *Many experts recommend consideration of brain MRI in all infants with SNHL irrespective of cranial ultrasound findings. †Infants with congenital CMV and mildly symptomatic disease can be offered valganciclovir on a case-by-case basis in consultation with a paediatric infectious disease specialist.

Sustainability of early congenital CMV detection benefits

Sustainability of the long-term benefits of universal congenital CMV screening requires further study. The greatest benefit of universal congenital CMV screening is the facilitation of earlier recognition of auditory sequelae, as a high proportion (>40%) of newborns with SNHL caused by congenital CMV were not identified at the time of newborn hearing screen.[100,103–107] Lanzieri and colleagues[107] observed that delayed-onset SNHL in

***Panel 2*: Congenital CMV screening in relation to Wilson and Jungner[114] principles for mass screening for disease**

Specific screening criteria

1 *Important public health problem*
- Major viral cause of disability
- Most common cause of congenital viral infection globally

2 *Accepted treatment of those with recognised congenital cytomegalovirus (CMV) disease*
- Anticipatory guidance, monitoring, and serial audiology
- Valganciclovir for some infants

3 *Facilities for diagnosis and treatment should be available*
- Paediatricians; infectious diseases subspecialists; audiologists; otolaryngologists; neurologists; and developmental specialists (aligned to specific needs of the child)

4 *Latent or early symptomatic stage*
- Infants with asymptomatic congenital CMV can develop late-onset sensorineural hearing loss (SNHL)

5 *Suitable screening test available*
- Evidence not clear; dried blood spot (DBS) test has advantages of high-throughput and uses existing infrastructure in newborn screening programmes; saliva PCR has high sensitivity, however, there are false-positive results, and new sampling protocols should be developed to optimise the use of saliva for universal screening

6 *Testing is acceptable to the general public*
- Studies show acceptance of newborn congenital CMV screening among parents

7 *Natural history of the condition is known, from latent to declared disease*
- Evidence not clear; natural history for some children includes evolution from a non-pathological hearing assessment to SNHL that will be demonstrable at a follow-up evaluation; all children should, therefore, be regularly monitored

8 *Consensus protocols for determining who should be treated and what treatment should consist of*
- Consensus that all children with congenital CMV require audiological and developmental monitoring
- Evidence not clear regarding duration of follow-up of children
- Evidence not clear if asymptomatic children require paediatric infectious diseases consultation or should be followed by a primary care physician (with audiologist involvement)
- Evidence not clear which children are candidates for antiviral therapies

9 *Favourable cost–benefit analysis*
- Economic analyses suggest benefit for both targeted screening (targeted testing) and universal congenital CMV screening with more favourable results for universal screening

10 *Case-finding is a continuous process*
- Embedding congenital CMV screening in governmental newborn screening programmes ensures continuous monitoring for patients and optimises health equity

11 *Test is sensitive*
- Evidence not clear; DBS test has demonstrated steadily improving analytical sensitivity
- Evidence not clear; saliva PCR test has high sensitivity but has other associated problems such as false-positives results and high cost for implementation

asymptomatic children without hearing loss at birth might develop in up to 14% of children by age 18 years. Goderis and colleagues,[108] in a systematic review, reported that there was a 9% risk of delayed-onset SNHL in asymptomatic children. However, other cohort studies showed a low risk of delayed-onset SNHL in asymptomatic children. In a prospective cohort study of 157 children with congenital CMV (93% were asymptomatic), delayed-onset SNHL was present in only four (2·5%) children after excluding other risk factors.[109] De Cuypers and colleagues[110] found a similar rate of delayed-onset SNHL, being present in 31 (5·7%) of 548 ears of children with asymptomatic infection. If delayed-onset SNHL is shown in future studies to be less common than previously published, there could be a strong counterargument against endorsement of universal screening.

Long-term neurodevelopmental outcomes regarding subtle neuroimaging findings

The natural history of congenital CMV infection in symptomatic children has been well described.[111,112] However, the long-term prognosis of children with atypical neuroimaging abnormalities or incidental findings has not been well addressed, especially in the setting of mild symptoms or clinically inapparent infections. There is a consensus that performing a cranial ultrasound in all infants identified by universal screening, irrespective of the presence or absence of clinical signs, is a reasonable approach; however, the usefulness of brain MRI for asymptomatic children is unclear.[102,113] Data about long-term prognosis of children with subtle, possibly incidental, findings upon neuroimaging (eg, lenticulostriate vasculopathy, germinolysis, and mild white matter abnormalities) are still sparse.

Public policy, legislation, advocacy groups, and the Wilson and Jungner criteria

A challenging aspect in the implementation of universal congenital CMV screening is that there is no uniform endorsement by organisations and expert panels that establish newborn screening policy, even with advocacy groups having made substantial progress in getting congenital CMV screening incorporated into clinical

Panel 3: Priorities for future research in newborns with asymptomatic congenital cytomegalovirus infections identified by screening

Basic and translational research questions

Sequence analyses of viral strain variants

- Are there viral gene polymorphisms that are associated with an enhanced risk of long-term sequelae for infants with congenital cytomegalovirus (CMV)?

Profiling of potential host genetic variation and the relationship to pathogenesis and sequelae

- Is confirmation of a specific pathologial host genetic signature related to an enhanced risk for congenital CMV-induced sensorineural hearing loss (SNHL)[118] or related to enhanced risks for other neurodevelopmental sequelae?

Effect of congenital CMV on the microbiome

- Does congenital CMV affect the biology of the neonatal microbiome?
- Would virally induced alteration of the neonatal microbiome affect long-term neurodevelopmental outcome?

Maternal and infant immune response studies of congenital CMV infection

- Is there an immune response profile that can be elucidated in maternal–infant dyads where congenital CMV is identified by universal screening that predicts risk of sequelae?
- Does maternal vaccination before pregnancy affect the long-term outcome in infants with congenital CMV born to immunised mothers (once a vaccine is licensed)?
- Does the ontogeny of the evolving T-cell response in infants with congenital CMV identified by universal screening predict the risk of sequelae?

Clinical research questions

Neuroimaging findings in clinically inapparent congenital CMV infection

- Is cranial ultrasound the appropriate screening test for infants without clinical findings identified by universal screening?
- Is lenticulostriate vasculopathy identified by cranial ultrasound a disease-defining variant?
- Are subependymal cysts identified by cranial ultrasound of any clinical significance?
- What is the role of other non-classical or non-incidental findings noted by cranial ultrasound?
- Should any of these findings prompt a brain MRI examination?

Use and duration of antiviral therapy

- Should therapy for isolated SNHL in clinically inapparent infections become standard-of-care (CONCERT study;[64] 6 weeks of oral valganciclovir; commence up to age 13 weeks)?
- Are there any circumstances where therapy can be offered to infants with asymptomatic congenital CMV that have a non-pathological hearing assessment (ie, healthy auditory brainstem response)?
- Are there long-term risks associated with the overprescription of valganciclovir therapy?
- Are there alternatives to valganciclovir?
- Are there other novel antivirals for congenital CMV ready to enter clinical trials?

practice. In the USA, the well recognised criteria of Wilson and Jungner,[114] published in 1968, are often cited when considering addition of screenable disorders to the newborn screening panel. These criteria centre around ten principles that policy makers and health officials should consider, primarily focused on the relative importance of a health problem, the natural progression of the disease or condition, the characteristics of available screening tests and follow-up treatments, and the cost-effectiveness of screening.

The extent to which universal newborn screening for congenital CMV fulfils the Wilson and Jungner criteria has been analysed by Haller and colleagues.[24] These ten primary criteria, and the justifications for how they are considered in the context of congenital CMV screening, are summarised (panel 2). There are uncertainties in some areas such as an accepted treatment (criterion 2), suitability of screening test (criterion 5), acceptability of the screening test to the population (criterion 6), knowledge of natural history of the condition (criterion 7), and availability of consensus therapeutic protocols (criterion 8). Thus, until these uncertainties are resolved, an analysis of these criteria would lend credence to an argument opposed to implementation of universal congenital CMV screening.

Conclusion

In conclusion, congenital CMV screening will only become more commonplace in the years ahead. Many states and localities in the USA currently conduct targeted screening, and two US states (Minnesota[72] and New York) and two Canadian provinces (Ontario and Saskatchewan) are conducting universal congenital CMV screening based on PCR of DBS from newborns. The DBS method is a compelling option for universal screening, since infrastructure already exists in state health departments (in the USA) and at the provincial level in other countries (eg, Canada) to collect and process DBS samples. An unresolved question is whether the sensitivity of DBS PCR is adequate. At best, current DBS sensitivity is anticipated to range from 75% to 85%. Whether congenital CMV meets the other Wilson and Jungner criteria for a universal screening programme is debatable. There also exists an unresolved dilemma of how extensive the tests, evaluation, and treatment should

Search strategy and selection criteria

We searched the Cochrane Library, MEDLINE, and relevant specialty journals for articles published between Jan 1, 1990, and Aug 20, 2024, with the terms: "congenital cytomegalovirus screening", "targeted congenital cytomegalovirus screening", "universal congenital cytomegalovirus screening", and "newborn cytomegalovirus screening". We selected publications from 2004 to 2024, with an emphasis on those published after 2010, but we did not exclude commonly referenced and highly regarded older publications. We searched only for articles published in English, or those translated into English. We also searched reference lists of articles identified by this strategy and selected those we judged relevant. We included randomised controlled trials, observational studies, retrospective studies, meta-analyses, review articles, editorials, and case reports. We prioritised studies with superior methodological quality, including randomized controlled trials, intervention studies, meta-analyses, and systematic reviews. In the absence of such studies, observational studies, cohort studies, and case series were also included.

be for screened infants with congenital CMV who have a clinically inapparent infection.

Even as screening programmes move forward, recognising that many congenital CMV infections could be prevented by improved efforts on the part of physicians and public health agencies to educate women of reproductive age (approximately age 16–45 years) about the risks of acquiring CMV infection during pregnancy is essential. Education of people who are pregnant regarding sources of infection and methods of hygiene that can reduce maternal exposure to CMV are of utmost importance.[83,115,116] Counselling regarding prevention by obstetricians could probably reduce congenital CMV prevalence substantially. Newborn screening programmes created by legislative action are commonly accompanied by funding to enhance education about congenital CMV. As universal screening programmes develop, an exciting opportunity exists to combine these initiatives with studies of the effect of maternal education on transmission prevalence.

Basic virology and immunobiology research initiatives are also a priority. Studies of biomarkers that suggest a high risk of vertical CMV transmission should also be high-priority areas for future research. The pace of development of CMV vaccines should accelerate.[117] Licensure of a CMV vaccine will become a powerful argument for implementing universal congenital CMV screening, since such screening programmes offer the ability to assess the potential effectiveness of maternal immunisation on congenital CMV prevalence by comparing transmission rates before and after vaccination commences of women of reproductive age. Other high-priority areas for future research suggested by the authors of this Review, including the search for biomarkers that are predictive of adverse sequelae,[118] are highlighted (panel 3). Extramural funding agencies should provide resources to study these questions, and academic centres should lead the path toward a better understanding of this common, incompletely understood, and under-recognised infectious cause of paediatric disability.

Contributors

MRS and DB-G contributed to the literature search, design of this review, and writing and critical review of the manuscript.

Declaration of interests

MRS reports grant support to the University of Minnesota, but no personal honoraria, from Moderna. MRS reports advisory board consultancy work for GSK vaccines. DB-G reports consulting fees from Moderna and honoraria for lectures and educational activities from MSD and Medscape.

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