



Congenital Cytomegalovirus Detected Through Universal Newborn Screening: A Narrative Review of What Universal Testing Finds That Targeted Testing Misses

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Abstract

Congenital cytomegalovirus is the commonest non-genetic cause of childhood hearing loss and is usually silent at birth. Targeted testing of babies who fail their hearing screen is cheap and logical, and it finds under half of the affected infants.

Objectives: *To review the published evidence on universal newborn screening for congenital cytomegalovirus: what universal testing detects that targeted testing does not, how many of those additional cases matter clinically, what treatment achieves, and what universal screening costs in return.*

Material and Methods: *Narrative review of universal and targeted screening programmes, randomised antiviral trials, cohort studies of hearing outcome and society guidance indexed in PubMed and the major paediatric, infectious disease and audiology journals. No new patient data were generated; every estimate quoted is one published by the original investigators.*

Results: *In a universal screening programme covering 48,556 infants (94.7 per cent of live births), congenital infection was identified in 176 newborns, a birth prevalence of 3.6 per 1000 (95% CI 3.1 to 4.2). One hundred of those 176 cases (57 per cent) would have been missed by expanded-targeted screening; of these, 8 per cent were moderately to severely symptomatic, 3 per cent were asymptomatic with sensorineural hearing loss, and 11 per cent received valganciclovir. Fifty-three per cent of cases with maternal infection type available were born to mothers with non-primary infection.*

Conclusion: *Universal screening roughly doubles case detection, and the additional cases include a minority who are clinically significant and treatable immediately. The majority are asymptomatic infants with normal hearing, for whom the benefit is surveillance and the cost is years of parental anxiety about a child who may never be affected.*

Abbreviations: *ABR – Auditory Brainstem Response, cCMV – Congenital Cytomegalovirus, CI – Confidence Interval, PCR – Polymerase Chain Reaction, SNHL – Sensorineural Hearing Loss, UNHS – Universal Newborn Hearing Screening.*

Keywords: *Congenital Cytomegalovirus; Newborn Screening; Sensorineural Hearing Loss; Valganciclovir; Targeted Screening*

Introduction

Congenital cytomegalovirus infection occurs in roughly 0.4 to 2 per cent of live births and is the commonest congenital infection worldwide [1,2,3]. It is the leading non-genetic cause of sensorineural hearing loss, accounting for approximately 20 per cent of hearing loss present at birth and rising to about 25 per cent by four years of age [3,4].

Most infected infants are asymptomatic at birth, and a substantial proportion of those who develop hearing loss do so after the newborn period, so they pass their hearing screen [5,6]. One multicentre study reported that 43 per cent of infants who went on to develop postnatal hearing loss were not identified by hearing-screen-triggered testing [3,7].

Two screening strategies are therefore in use: targeted testing of infants who fail newborn hearing screening, and universal testing of all newborns using saliva or urine polymerase chain reaction [8,9,10]. This review examines what the second finds that the first does not, and whether that difference justifies the programme.

Material and Methods

Search strategy: PubMed and the archives of the major paediatric, infectious disease and audiology journals were searched for studies of newborn screening for congenital cytomegalovirus. Search terms combined congenital cytomegalovirus with universal newborn screening, targeted screening, hearing loss, valganciclovir and birth prevalence. Reference lists of guidance and clinical pathways [8,11] were screened by hand for primary sources.

Eligibility: Studies were included if they reported detection rates or outcomes from a defined screening programme, evaluated antiviral treatment, or characterised hearing outcomes in identified infants. Studies of maternal screening and vaccination are cited for context and identified as such.

Data extraction and handling: Design, setting, screening method, denominator and the reported estimate were extracted as published. The screening strategy and its denominator are reported alongside every detection figure, because targeted and universal programmes describe different populations and the proportions are not comparable without them. No pooling or re-analysis was performed. Figures 1 to 4 and Tables 1 and 2 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

What universal screening detects: A universal programme screened 48,556 infants, 94.7 per cent of all live newborns in the catchment, using a pooled testing approach. Congenital infection was identified in 176 newborns, giving a birth prevalence of 3.6 per 1000 (95% CI 3.1 to 4.2). Pooling efficiency was 5.82 with a modest loss of analytical sensitivity [12].

The comparison that matters: One hundred of those 176 infants (57 per cent) would have been missed by expanded-targeted screening (Figure 1) [12]. Universal testing therefore identified more than twice as many cases as the targeted strategy would have. That is the central finding, and it is consistent with earlier work showing that a large share of cytomegalovirus-related hearing loss develops after the newborn hearing screen has been passed [5,7].

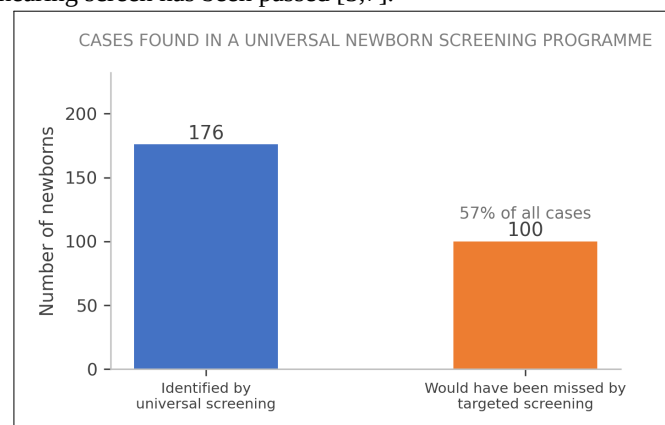


Figure 1: Cases identified by universal screening and the proportion targeted screening would have missed [12]

How many of the extra cases mattered: Among the 100 infants targeted screening would have missed, 8 per cent were classified as moderately to severely symptomatic, 3 per cent were asymptomatic with sensorineural hearing loss, and 11 per cent received valganciclovir (Figure 2) [12]. Restating that plainly: universal screening found roughly eleven additional infants per 48,556 births in whom antiviral treatment was started, and about eighty in whom no immediate clinical action followed.

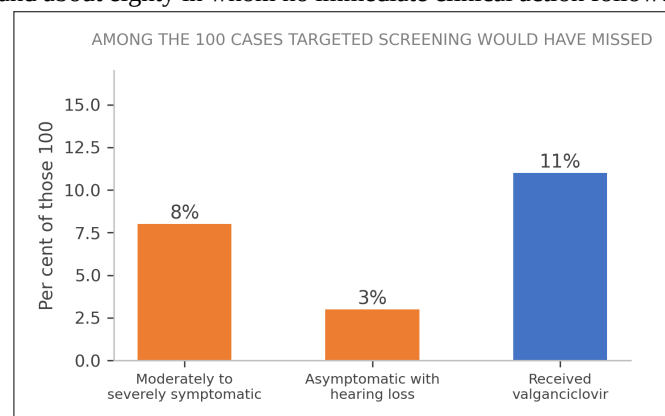


Figure 2: Clinical status of the 100 cases that targeted screening would have missed [12]

Maternal infection type: Of 158 cases with maternal infection type available, 84 (53 per cent) were born to mothers with non-primary infection and 74 (47 per cent) to mothers with primary infection, and these infants showed similar rates of moderate to severe symptoms, hearing loss, and one-year hearing or developmental sequelae (Figure 3) [12]. This matters because strategies built around identifying maternal seroconversion in pregnancy will miss roughly half of affected infants by design [13,14].

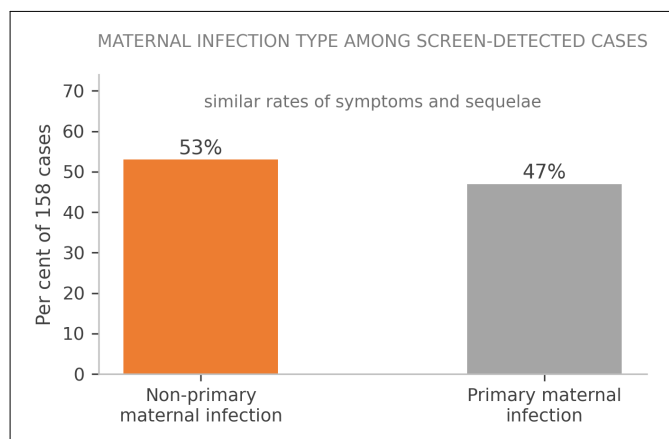


Figure 3: Maternal infection type among screen-detected cases [12]

The hearing burden: Congenital infection accounts for approximately 20 per cent of hearing loss present at birth, rising to around 25 per cent by four years (Figure 4) [3,4]. In a highly seropositive maternal population, 121 of 12,195 infants screened (1 per cent) were infected, 12 (10 per cent) were symptomatic at birth, and sensorineural hearing loss was observed in 10 of 102 assessed (9.8 per cent, 95% CI 5.1 to 16.7) [15].

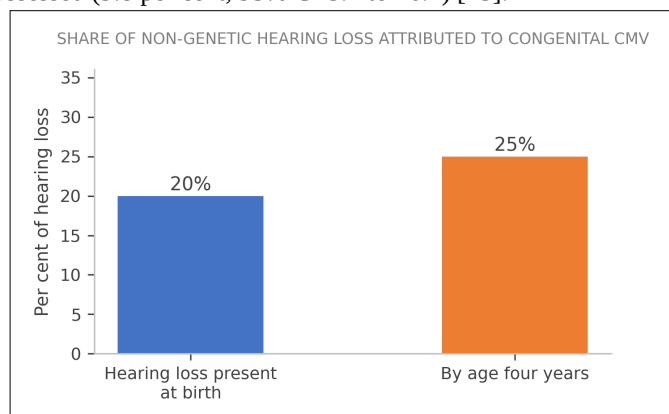


Figure 4: Share of non-genetic childhood hearing loss attributed to congenital cytomegalovirus [3,4]

Study	Design and cohort	Principal reported finding
Universal screening programme [12]	48,556 infants, pooled PCR	Prevalence 3.6/1000; 57% of cases missed by targeted screening
Same programme [12]	The 100 missed cases	8% moderate-severe, 3% asymptomatic with SNHL, 11% treated
Yamamoto et al. 2011 [15]	12,195 infants, high seroprevalence	1% infected; SNHL in 9.8% of those assessed
Kimberlin et al. 2015 [16]	RCT, valganciclovir in symptomatic disease	Six months superior to six weeks on hearing and development
Kimberlin et al. 2003 [17]	RCT, ganciclovir with CNS involvement	Established antiviral effect on hearing
Hearing screen cohort [18]	204,680 newborns, targeted testing	17 confirmed cases; 9 with confirmed hearing loss
Targeted screening study [19]	Multicentre, French settings	Targeted screening feasible; treatment started within days

Table 1: Principal studies reviewed, with the finding as reported by the original investigators

What treatment achieves: Randomised evidence supports antiviral therapy in symptomatic disease. Ganciclovir improved hearing outcomes in infants with central nervous system involvement [17], and six months of oral valganciclovir was superior to six weeks on hearing and neurodevelopmental outcomes in symptomatic congenital disease [16]. Guidance now extends treatment to clinically inapparent infants with isolated hearing loss [11,20]. The important gap is that the effect of antivirals in infants with isolated hearing loss and no other features has not been adequately assessed in randomised trials [21], although a non-randomised controlled trial has since addressed it [35], and hearing outcomes in asymptomatic infection have been described separately [27].

What targeted screening delivers: Targeted programmes are efficient at what they do. In one series, 204,680 newborns underwent hearing screening, 7147 (3.5 per cent) did not pass, and 17 had confirmed congenital infection, of whom 9 had confirmed hearing loss [18]. In a French multicentre evaluation, infected neonates had hearing loss confirmed within days and antiviral treatment started within about a fortnight [19]. The limitation is structural rather than operational: an infant who passes the hearing screen is never tested, and late-onset loss is the commonest pattern [5,7].

Consideration	Universal screening	Targeted screening
Cases detected	176 per 48,556 births	Would have found 76 of those 176 [12]
Late-onset hearing loss	Infant known and followed	Never tested if hearing screen passed [5,7]
Non-primary maternal infection	Detected equally	Also detected, but only if screen failed [12,13]
Immediate treatment	11% of the extra cases	Confined to those failing the screen [12,19]
Asymptomatic infants	Majority of extra cases	Not identified; no anxiety generated [12]
Operational burden	All newborns tested; pooling reduces cost	Tests about 3.5% of newborns [12,18]

Table 2: Universal against targeted screening on the dimensions that differ

Discussion

The arithmetic is clear and the interpretation is not. Universal screening found 176 cases where targeted screening would have found 76 [12]. If the question is how many infected infants are identified, universal screening wins decisively, and the explanation is structural: most cytomegalovirus-related hearing loss appears after the newborn period, so the hearing screen cannot be a gateway to a diagnosis it precedes [5,7].

The harder question is what those additional hundred infants gained. Eleven per cent received valganciclovir, which on the randomised evidence is a real benefit for hearing and development [12,16]. Eight per cent were moderately or severely symptomatic and would have been identified clinically before long, though earlier is better. Three per cent had hearing loss

without other features, which is precisely the group in whom antiviral benefit has not been established by randomised trial [21]. The remaining majority were asymptomatic infants with normal hearing.

For that majority, screening confers surveillance rather than treatment. That has real value, since audiological follow-up detects late-onset loss when amplification or implantation can still be offered within the window that matters for language [4,15,22]. It also has a cost that screening literature tends to under-record: parents told that their well newborn carries a virus that may damage hearing, facing years of appointments for a child who in most cases will never be affected. Anxiety is a harm, and a programme detecting mostly asymptomatic infants generates a great deal of it [23,24].

The finding with the widest implication is about maternal infection type. Fifty-three per cent of screen-detected cases arose from non-primary maternal infection, and those infants had similar rates of symptoms and sequelae to infants of mothers with primary infection [12]. Any strategy built on detecting seroconversion during pregnancy is therefore designed to miss about half the affected babies, and the common assumption that maternal immunity is protective does not survive this dataset [33]. Timing within pregnancy nonetheless shapes sequelae after primary infection [29].

Study limitations

The limitations belong to the underlying literature. The principal universal programme used pooled testing with a measurable loss of analytical sensitivity, so its prevalence estimate is a floor rather than a point value [12]. Follow-up in most screening studies is short relative to the age at which late-onset hearing loss declares, so sequelae rates are underestimated [4,15]. Symptom classification at birth is subjective and varies between programmes [1,12]. No randomised trial compares universal with targeted screening on child outcomes, and none is likely, so the comparison rests on modelled and observational data [8,10]. Antiviral benefit in isolated hearing loss without other features is unestablished, which is the group universal screening most distinctively identifies [21]. Parental anxiety and other harms of screening are rarely measured [23,24]. Cost-effectiveness estimates depend heavily on assumptions about late-onset loss and treatment efficacy [25,26]. And prevalence varies severalfold with maternal seroprevalence, so results do not transfer directly between populations [2,15,31,32]. European expert consensus and arguments for universal screening set out the remaining uncertainties [28,30,34].

Conclusion

Universal newborn screening for congenital cytomegalovirus finds roughly twice as many infected infants as testing only those who fail their hearing screen, and it does so for a structural reason that no refinement of targeted testing can fix: most of the hearing loss arrives after the screen has been passed. Of the extra cases, about one in nine was treated immediately and the rest entered surveillance. Whether that trade is worth making depends on how much weight is given to detecting late-onset loss early against the anxiety created in the families of well babies, and the published evidence measures the first far better than the second. What the data do settle is that half of affected infants are born to mothers who were already immune, so screening built around maternal seroconversion will always miss them.

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

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