

# Hearing Loss in Children With Asymptomatic Congenital Cytomegalovirus Infection

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abstract

**OBJECTIVES:** To assess the prevalence, characteristics, and risk of sensorineural hearing loss (SNHL) in children with congenital cytomegalovirus infection identified through hospital-based newborn screening who were asymptomatic at birth compared with uninfected children.

**METHODS:** We included 92 case-patients and 51 controls assessed by using auditory brainstem response and behavioral audiometry. We used Kaplan–Meier survival analysis to estimate the prevalence of SNHL, defined as  $\geq 25$  dB hearing level at any frequency and Cox proportional hazards regression analyses to compare SNHL risk between groups.

**RESULTS:** At age 18 years, SNHL prevalence was 25% (95% confidence interval [CI]: 17%–36%) among case-patients and 8% (95% CI: 3%–22%) in controls (hazard ratio [HR]: 4.0; 95% CI: 1.2–14.5;  $P = .02$ ). Among children without SNHL by age 5 years, the risk of delayed-onset SNHL was not significantly greater for case-patients than for controls (HR: 1.6; 95% CI: 0.4–6.1;  $P = .5$ ). Among case-patients, the risk of delayed-onset SNHL was significantly greater among those with unilateral congenital/early-onset hearing loss than those without (HR: 6.9; 95% CI: 2.5–19.1;  $P < .01$ ). The prevalence of severe to profound bilateral SNHL among case-patients was 2% (95% CI: 1%–9%).

**CONCLUSIONS:** Delayed-onset and progression of SNHL among children with asymptomatic congenital cytomegalovirus infection continued to occur throughout adolescence. However, the risk of developing SNHL after age 5 years among case-patients was not different than in uninfected children. Overall, 2% of case-patients developed SNHL that was severe enough for them to be candidates for cochlear implantation.



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**WHAT'S KNOWN ON THIS SUBJECT:** The extent to which children with congenital cytomegalovirus infection who are asymptomatic at birth remain at risk for delayed-onset and progressive sensorineural hearing loss throughout childhood is not well established.

**WHAT THIS STUDY ADDS:** An estimated 2% of children with asymptomatic congenital cytomegalovirus infection develop severe enough sensorineural hearing loss to meet cochlear implantation candidacy, but their risk of developing hearing loss after age 5 years is not significantly increased compared to uninfected children.

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Congenital cytomegalovirus (CMV) infection causes a spectrum of impairments, including sensorineural hearing loss (SNHL), vision loss, and developmental delays. In the United States, an estimated 20 000 (0.5%) children are born with congenital CMV infection annually.<sup>1,2</sup> Although the majority (85%–90%) appear asymptomatic at birth, SNHL may be present at birth, progress in severity, or develop later.<sup>3</sup>

The burden of SNHL in children with asymptomatic congenital CMV infection at birth remains incompletely characterized, and the extent to which these children remain at risk for SNHL throughout childhood and adolescence is not well described. Previous studies have documented delayed-onset SNHL among children with asymptomatic congenital CMV infection up to age 15 years.<sup>4–7</sup> However, data from controlled studies with follow-up through adolescence are lacking. Studies that also included uninfected children had follow-up until 5 to 7 years of age and did not attempt to compare the risk of delayed-onset SNHL between children with asymptomatic congenital CMV infection and uninfected children.<sup>4–6,8,9</sup> In this study, we assessed the prevalence, characteristics, and risk of SNHL through age 18 years in children with congenital CMV infection identified through hospital-based newborn screening who were asymptomatic at birth compared with uninfected children.

## METHODS

From 1982 to 1992, 32 543 newborns delivered at Women's Hospital of Texas (Houston TX) were screened for congenital CMV infection via urine culture collected within 3 days of life, as described previously.<sup>10,11</sup> Of 135 (0.4%) CMV-positive newborns, 92 (68%) were enrolled in a longitudinal study as asymptomatic case-patients (eg, they had no CMV-related signs at

birth [purpura/petechiae, jaundice, hepatosplenomegaly, microcephaly, elevated liver enzymes, bilirubinemia, hemolytic anemia or thrombocytopenia]). Fifty-one uninfected newborns whose parents agreed to participate in the study were enrolled as controls, 42 (82%) were among CMV-negative newborns randomly preselected within 6 days of birth of a CMV-positive newborn ( $n = 298$ ), and 9 (18%) were siblings of referred CMV-positive infants or born to women diagnosed with CMV infection during pregnancy. We analyzed data from serial audiological assessments from birth to 18 years of age. The Institutional Review Board for Human Subject Research for Baylor College of Medicine and Affiliated Hospitals approved the study protocol.

Audiologic assessments were conducted by audiologists who were unaware of each subject's CMV status and included auditory brainstem response (ABR), behavioral audiometry (0.25–8 kHz), and tympanometry.<sup>10</sup> ABR testing included click and frequency-specific tone-burst stimuli. We combined the latter with frequency-specific pure-tone air conduction results obtained by behavioral audiometry after subtracting 10 dB for 0.5, 1, and 8 kHz, and 0 dB for 2 and 4 kHz from the tone-burst levels.<sup>12</sup> We defined SNHL as  $\geq 25$  dB hearing level (HL) for the ABR click or at any frequency for the corrected tone-burst or pure-tone air conduction results. Because middle ear disorder can cause transient conductive hearing loss, we excluded assessments with tympanometry type B.

We analyzed SNHL by age at onset, laterality, and progression. We categorized SNHL among case-patients for each ear as congenital/early-onset when detected in the first ABR assessment at age  $\leq 12$  months and confirmed in subsequent assessments, or as delayed-onset when detected after  $\geq 1$  assessments

with normal hearing. We classified SNHL as unilateral if it was present in 1 ear, or bilateral if it was present in both ears. We defined SNHL as progressive when a change to worse hearing occurred between the first detection of SNHL and the last assessment, or stable when there was no change between these 2 assessments. We defined fluctuations as changes to a worse or better HL between consecutive assessments: an absolute difference of  $\geq 20$  dB in  $\geq 1$  frequencies,  $\geq 10$  dB across any 2 or 3 adjacent frequencies,  $\geq 10$  dB in the average of the pure-tone thresholds at 0.5, 1, 2, and 4 kHz (4-frequency average), or a change from "hearing" to "no response" or vice versa at 3 adjacent frequencies.<sup>13</sup>

We categorized SNHL severity for each ear using the ABR click result or the 4-frequency average, as follows: slight (16–25 dB HL), mild (26–40 dB HL), moderate (41–55 dB HL), moderately severe (56–70 dB HL), severe (71–90 dB HL) and profound ( $\geq 91$  dB HL) hearing loss.<sup>14</sup> We classified children with  $\geq 25$  dB HL in any frequency without affecting the 4-frequency average as having SNHL at isolated frequencies. We described SNHL severity in the poorer- and better-hearing ears. For example, a child with unilateral SNHL could be categorized as having profound hearing loss in the poorer-hearing ear but normal hearing in the better-hearing ear. Characterization by poorer-hearing ear provides a more complete description of SNHL burden because it includes children with unilateral loss. However, eligibility criteria for health insurance coverage for audiological services may require bilateral loss,<sup>15</sup> which is described by better-hearing ear assessment. To estimate the need for audiological services, we assumed hearing aids would be recommended for children with unilateral or bilateral SNHL  $\geq 40$  dB HL, and cochlear implants for those with bilateral SNHL  $\geq 70$  dB HL.<sup>15</sup>

**TABLE 1** SNHL Among Children With Asymptomatic Congenital CMV Infection and Controls

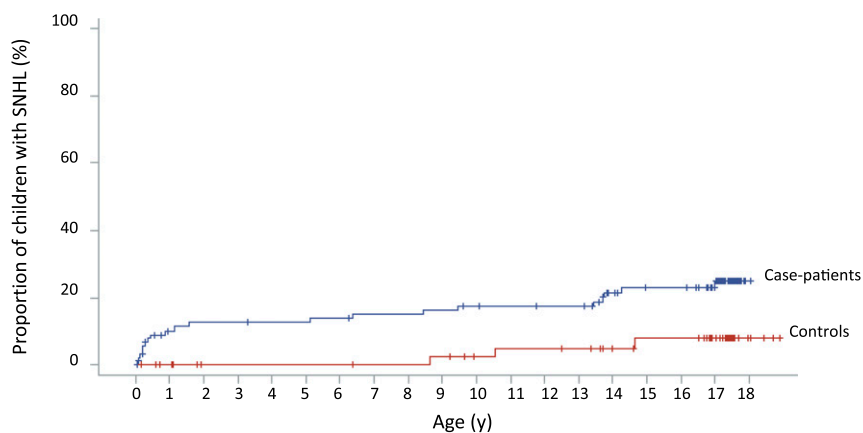
Age	Children With Asymptomatic Congenital CMV Infection ( <i>n</i> = 92)				Proportion of Controls With Any SNHL, ( <i>n</i> = 51) % (95% CI)
	Total With SNHL, <i>n</i> (%)	Total With Unilateral Loss, <i>n</i> (%)	Total With Bilateral Loss, <i>n</i> (%)	Proportion With Any SNHL, % (95% CI)	
3 mo	6 (30)	6 (100)	0 (0)	7 (3–14)	0
12 mo	9 (45)	7 (78)	2 (22)	10 (5–19)	0
24 mo	11 (55)	9 (82)	2 (18)	13 (7–22)	0
5 y	12 (60)	9 (75)	3 (25)	14 (8–23)	0
10 y	15 (75)	8 (53)	7 (47)	17 (11–27)	5 (1–18)
14 y	19 (95)	12 (63)	7 (37)	23 (15–34)	8 (3–22)
18 y	20 (100)	10 (50)	10 (50)	25 (17–36)	8 (3–22)

We compared demographic and birth characteristics among case-patients and controls using the  $\chi^2$  or exact test. To deal with loss to follow-up at varying ages, we used Kaplan–Meier survival analysis to estimate the proportion of children with SNHL by age. We calculated hazard ratios (HR) using Cox proportional hazards regression analyses to compare SNHL risk between groups. We considered results with a *P* value <.05 to be statistically significant. For analyses, we used SAS version 9.3 (SAS Institute, Inc, Cary, NC).

## RESULTS

The majority of the 92 case-patients and 51 controls were boys (58% vs 67%) and were born at  $\geq 37$  weeks' gestation (88% vs 98%) to mothers who were <30 years of age (63% vs 53%), non-Hispanic white (82% vs 86%), married (95% vs 100%), and multipara (78% vs 70%), with no statistically significant differences between the 2 groups (*P* > .05 for all). A higher proportion of the case-patients' mothers had  $\geq 1$  living child at the time of birth than mothers of those in the control group (68% vs 49%; *P* < .05).

Among the 92 case-patients, the median number of audiologic assessments was 7 (range: 1–17), and the median age at the first ABR evaluation was 2.4 months (range: 4 days to 11.5 months), after which 6 (6%) case-patients without SNHL were lost to follow-up. The remaining 86 (94%) case-patients had a median



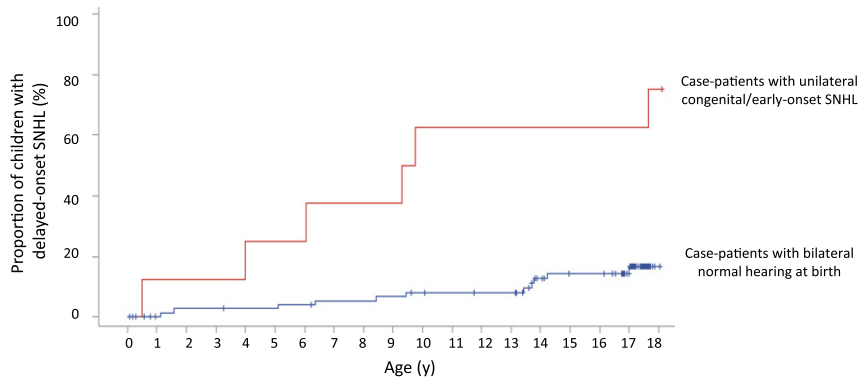
**FIGURE 1** SNHL among children with asymptomatic congenital CMV infection and controls.

of 8 assessments, with the last 1 at a median age of 17 years (range: 9 months to 18 years), 3 (3%) at 0 to 3 years, 5 (6%) at 6 to 9 years, and 78 (91%) at 12 to 18 years. Among the 51 controls, the median number of audiologic assessments was 3 (range: 1–8), and the median age at the first assessment was 3 years (range: 1 month to 14 years) of age. Among the 41 controls with  $\geq 2$  assessments, the median age at the last assessment was 17 (range: 1–18) years; 1 (2%) at 1 year, 2 (4%) at 6 to 9 years, and 38 (93%) at 12 to 18 years of age.

Using survival analysis, we estimated that the proportion of children with SNHL increased from 7% at age 3 months to 14% at age 5 years and 25% at age 18 years among case-patients, and from 0% at age 5 years to 8% at age 18 years among controls (Table 1). The SNHL risk from birth through age 18 years was fourfold greater among case-patients compared with controls

(HR: 4.0; 95% confidence interval [CI]: 1.2–14.5; *P* = .02). The SNHL risk from age 3 months to 18 years was threefold greater among case-patients compared with controls (HR: 3.0; 95% CI: 0.9–10.5; *P* = .08), but was not statistically significant. The SNHL risk from 6 to 18 years of age was 1.6-fold greater among case-patients compared with controls, but was not statistically significant (HR: 1.6; 95% CI: 0.4–6.1; *P* = .5) (Fig 1).

Among case-patients, 9 (10%) were ultimately classified with congenital/early-onset SNHL. Although 23 (25%) of the 92 case-patients had  $\geq 25$  dB HL detected at the first ABR (screening) assessment, 14 (61%) had normal hearing in both ears in subsequent assessments. Most (8/9) case-patients with confirmed congenital/early-onset SNHL presented with unilateral loss, but the majority (6/8) subsequently developed delayed-onset SNHL in the contralateral ear. In contrast,



**FIGURE 2** Delayed-onset SNHL among children with asymptomatic congenital CMV infection with and without unilateral congenital/early-onset hearing loss.

only 11 (14%) of 77 case-patients without congenital/early-onset SNHL who had  $\geq 2$  assessments had delayed-onset SNHL (Fig 2). Among case-patients, the risk of delayed-onset SNHL was significantly greater among those with unilateral congenital/early-onset loss than those without (HR: 6.9; 95% CI: 2.5–19.1). Overall, the proportion of case-patients with SNHL that had bilateral loss increased from 22% at age 12 months to 50% at the last assessment (Table 1). The median interval from unilateral to bilateral SNHL was 4 years (range: 4 months to 18 years).

Worsening of SNHL in affected ears was common; among 20 case-patients with SNHL, 13 (65%) had progressive loss in the poorer-hearing ear,

5 (25%) had stable loss, and 2 (10%) were indeterminate. Among 10 case-patients with bilateral SNHL, 4 (40%) had progressive loss in the better-hearing ear, 3 (15%) had stable loss without fluctuations, and 3 (15%) were indeterminate. Among 10 case-patients with SNHL who had fluctuations, progression occurred in all but 1. In all case-patients with SNHL, the initially poorer-hearing ears remained the more severely affected ear throughout follow-up.

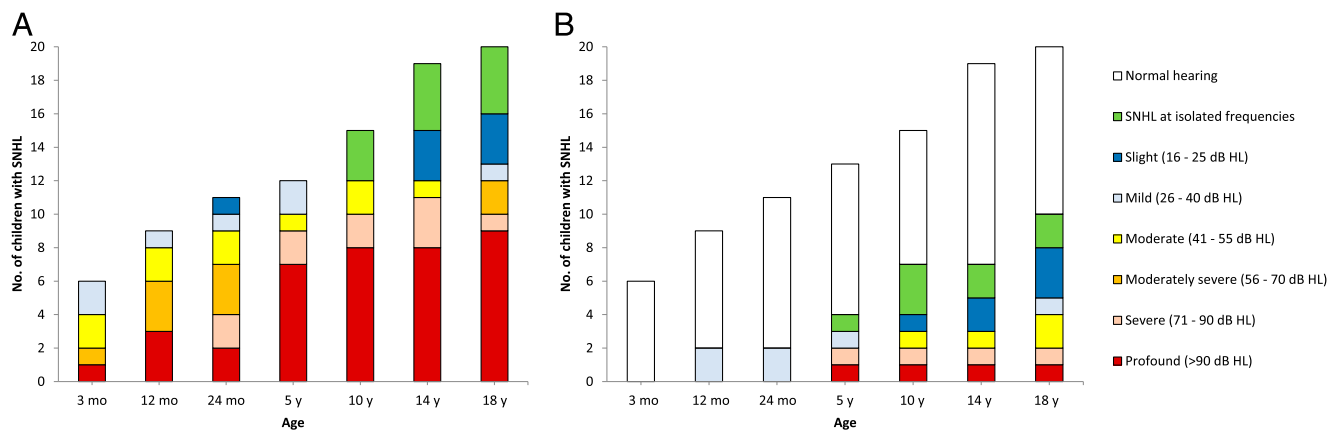
SNHL severity increased with age. At the last assessment, 12 (60%) of the 20 case-patients with SNHL had moderate or worse hearing loss in the poorer-hearing ear, and 4 of the 10 case-patients with bilateral SNHL had moderate or worse hearing loss

in the better-hearing ear (Fig 3). SNHL severity was greater among the 9 case-patients with congenital/early-onset SNHL, of whom 8 (89%) had profound hearing loss in the poorer-hearing ear at the last assessment. The 8 case-patients and 3 controls diagnosed with delayed-onset SNHL after age 5 years all had mild or a lesser degree of hearing loss in the poorer-hearing ear, among whom 3 (38%) and 1 (33%), respectively, had audiograms suggestive of noise-induced loss.

We estimated that the proportion of case-patients who would require hearing aids increased from 10% at age 12 months to 14% at age 18 years (Supplemental Table 2). The proportion of case-patients who would meet current candidacy criteria for cochlear implants increased from 1% at age 25 months to 2% at age 5 years and remained unchanged after that age. In considering more expansive criteria for cochlear implantation, 5% of case-patients had SNHL  $\geq 70$  dB HL in the poorer-hearing ear by age 12 months, increasing to 13% at age 18 years.

## DISCUSSION

In this study of children with congenital CMV infection identified



**FIGURE 3** Cumulative number of children with asymptomatic congenital CMV infection with SNHL ( $n = 20$ ) by age and SNHL severity in the poorer- (A) and better-hearing (B) ears.



through hospital-based newborn screening who were asymptomatic at birth, the prevalence and severity of SNHL increased throughout childhood. Children with asymptomatic congenital CMV infection who had unilateral congenital/early-onset SNHL were at a greater risk of subsequent delayed-onset loss in the normal-hearing ear compared with those without any SNHL in the first year of life. Many children with unilateral loss present with bilateral loss later and/or experience progressive hearing loss (eg, from mild/moderate to severe or profound hearing loss). Therefore, ongoing audiological monitoring is critical so that these children can receive appropriate interventions in a timely manner.

From age 3 months to 5 years, the prevalence of SNHL doubled among case-patients from 7% to 14%, but remained at 0% among controls. From 6 years to 18 years of age, the changes in SNHL prevalence were similar between the case-patients and controls: 11% and 8%, respectively. This finding is consistent with the 13% prevalence rate reported nationally among children 6 to 19 years of age in the United States.<sup>16</sup> Therefore, it appears that the risk of delayed-onset SNHL among school-aged case-patients was not appreciably higher than in the comparison group. Larger controlled studies will be important to confirm these findings and inform future guidance on the optimal duration of audiological monitoring for children with asymptomatic congenital CMV infection. The possibility that routine monitoring for SNHL may not be necessary beyond 5 years of age for children with congenital CMV infection who have normal hearing is of clinical importance.

We observed that 65% of our case-patients with SNHL had progressive hearing loss. Although we used strict criteria based on

ototoxicity monitoring studies<sup>13</sup> for categorizing SNHL as progressive, the proportion with progressive SNHL in our study was higher than the 20% estimated in a recent meta-analysis.<sup>17</sup> Referral bias in the studies included in the meta-analysis likely contributed to this difference. Some studies were based on cohorts of children identified with asymptomatic congenital CMV infection due to a diagnosis of SNHL at birth or primary maternal CMV infection during pregnancy.<sup>7,18-20</sup> Thus, some children were likely at a greater risk of more severe SNHL at onset than the entire population of infants with asymptomatic congenital CMV infection. In the same meta-analysis,<sup>17</sup> a higher proportion of children with asymptomatic congenital CMV infection and SNHL have bilateral severe to profound hearing loss compared with our study (42% vs 16% by age 5 years). Studies in which a larger proportion of children presented with profound hearing loss when SNHL was detected would have relatively fewer children who could experience SNHL progression.

CMV-related SNHL in children with congenital CMV infection who passed hearing screening tests in the first month of life has been detected at as early as 3 months of age.<sup>21</sup> Newborn hearing screening programs will not detect all infants with CMV-related hearing loss. In our study, at least 25% of case-patients with SNHL by age 5 years would not have been identified by newborn hearing screening. This proportion is lower than the 50% found in a large hospital-based newborn screening study with follow-up through age 6 years,<sup>21</sup> albeit higher than the 9% estimated in a recent meta-analysis.<sup>17</sup> Comparisons of delayed-onset SNHL among children with asymptomatic congenital CMV infection across studies are

complicated by heterogeneity in case ascertainment methods and duration of follow-up.<sup>22</sup> Currently, an estimated one-third of all children with bilateral SNHL  $\geq 40$  dB HL by age 4 years are not identified by newborn hearing screening.<sup>23</sup> The ongoing CMV and Hearing Multicenter Screening Study will provide population-based estimates of the prevalence of congenital CMV infection and CMV-related SNHL through age 4 years in the United States.<sup>24</sup> These data will be useful to inform the potential benefit of newborn screening for congenital CMV infection in identifying children at risk for delayed-onset SNHL who are missed by newborn hearing screening.

Identifying the etiology of hearing loss may affect clinical management and can provide reassurance to families.<sup>23</sup> The diagnosis of CMV-related SNHL depends on the diagnosis of congenital CMV infection, which requires laboratory testing on a specimen collected within the first 3 weeks of life. However, full audiologic evaluation to confirm or rule out hearing loss may not be conducted until later in infancy when laboratory testing can no longer confirm congenital infection. Thus, targeted CMV testing among newborns who fail hearing screening tests has been explored.<sup>25-28</sup> In the United Kingdom, this approach was found to be feasible and acceptable within the newborn hearing screening program, and did not appear to result in increased parental anxiety.<sup>28</sup> In Utah, which implemented a policy in 2013 mandating CMV testing for all infants who fail newborn hearing screening,<sup>26</sup> an improvement in follow-up rates of all infants who fail the hearing screening was reported. This testing strategy has the potential to increase identification of newborns with SNHL with symptomatic congenital

CMV infection who would be eligible for antiviral treatment and who might otherwise have gone unrecognized as well as infants with asymptomatic infection.<sup>29,30</sup> However, the efficacy of antiviral treatment in preventing hearing deterioration among children with asymptomatic infection has not been systematically studied. Therefore, antiviral treatment is not currently recommended for routine use in this population.<sup>29</sup> More data on the feasibility and benefits of targeted CMV testing are likely to become available as this approach is more widely adopted.

Our study has limitations. Our sample size was too small to detect statistically significant differences in SNHL risk after age 3 months. We may have underestimated SNHL risk among case-patients and controls because of loss to follow-up, particularly among children with only a single assessment at a younger age. Not all CMV-positive newborns identified through screening were enrolled. However, universal newborn hearing screening was not routinely done from 1982 to 1992, and thus, it is unlikely that there were systematic biases in the enrollment of participants by hearing status that would have affected our estimates. Although our control group had fewer audiological assessments and the first assessment occurred at an older age compared with case-patients, it does not affect our estimates of delayed-onset SNHL because the age at the last assessment was similar for both groups. Our control group included a small number of children selected among uninfected siblings of referred CMV-positive infants. Analyses including the control group consisting only of those selected among CMV-negative screened newborns resulted in similar findings. Thus, although the small number of controls may have

limited the power of the study to detect some statistically significant differences, the control group appears to have been appropriately valid for comparisons. We were unable to precisely determine if SNHL was congenital or delayed-onset because not all case-patients had hearing evaluations in the first month of life. In addition, some infants only had click-evoked ABR without frequency-specific tone burst stimuli, which can result in false-negative results. Other than ruling out the administration of gentamicin to premature case-patients, we were unable to fully investigate other etiologies of SNHL. Data on genetic testing and noise exposure were not available, and the audiologic assessments did not consistently include testing at 3 and 6 kHz, which could have aided in the evaluation of noise-induced SNHL.

## CONCLUSIONS

The burden of CMV-related SNHL is substantial considering the potential impact of SNHL on children's development and academic achievement and their need for ongoing audiologic monitoring and interventions. We estimate that ~5% of children with asymptomatic congenital CMV infection, about 900 children annually, have SNHL  $\geq 70$  dB HL in at least 1 ear by age 12 months, and half of these children meet current candidacy criteria for cochlear implantation. As cochlear implant technologies and indications for their use continue to evolve, the number of children with asymptomatic congenital CMV infection and SNHL who might be considered candidates for cochlear implants could increase. Newborn screening for congenital CMV infection has the potential to identify children at risk for CMV-related SNHL who currently go unrecognized and who might benefit from earlier intervention.<sup>31</sup>

Additional investigation into the age of onset and risk factors for SNHL in children with asymptomatic congenital CMV infection are needed to inform the evaluation of the potential costs and benefits of CMV screening.

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## ABBREVIATIONS

ABR: auditory brainstem response  
CI: confidence interval  
CMV: cytomegalovirus  
HL: hearing level  
HR: hazard ratio  
SNHL: sensorineural hearing loss

Congenital CMV Study, provided patient follow-up, conceptualized the analysis contained in this report, interpreted the data, and critically revised the manuscript; and all authors approved the final version.

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