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Etiology of Prelingual Hearing Loss in the Universal Newborn Hearing Screening Era: A Scoping Review

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Abstract

Objective.—To conduct a scoping review on etiologic investigation of prelingual hearing loss among children <2 years of age in the era of universal newborn hearing screening (UNHS).

Data Sources.—PubMed, Embase, PsycInfo, CINAHL, and Cochrane Library databases.

Review Methods.—We searched for articles published from January 1, 1998, to February 19, 2020. We reviewed studies that (1) included children identified with either congenital or delayed-onset hearing loss before 2 years of age among cohorts who had undergone UNHS and (2) investigated ≥1 etiologies of hearing loss. We defined hearing loss as congenital when confirmed after UNHS failure and as delayed onset when diagnosed after ≥1 assessments with normal hearing.

Results.—Among 2069 unique citations, 115 studies met criteria for full-text assessment, and 20 met our inclusion criteria. Six studies tested children diagnosed with hearing loss for genetic etiology, 9 for congenital cytomegalovirus (CMV) infection, and 5 for both. Among 1787 children with congenital hearing loss and etiologic investigation, 933 (52.2%) were tested for genetic mutations and 1021 (57.1%) for congenital CMV infection. The proportion of congenital hearing

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Author Contributions

Ashley Satterfield-Nash, reviewed citations retrieved from literature search, selected studies for full-text assessment, reviewed selected studies for inclusion/exclusion, assessed validity of studies, abstracted data from selected studies, summarized and interpreted the findings, drafted manuscript, reconciled feedback from other authors, and approved the manuscript; **Ayesha Umrigar**, reviewed citations retrieved from literature search, selected studies for full-text assessment, reviewed selected studies for inclusion/exclusion, assessed validity of studies, abstracted data from selected studies, summarized and interpreted the findings reviewed manuscript critically for intellectual content, and approved the manuscript; **Tatiana M. Lanzieri**, conceptualized the literature review, reviewed citations retrieved, selected studies for full-text assessment, reviewed selected studies for inclusion/exclusion, assessed validity of studies, abstracted data from selected studies, summarized and interpreted the findings, reviewed manuscript critically for intellectual content, and approved the manuscript.

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Supplemental Material

Additional supporting information is available in the online version of the article.

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loss cases attributable to genetic etiology ranged between 7.7% and 83.3% and to congenital CMV infection between 0.0% and 32.0%.

Conclusion.—Data are lacking on the identification and etiology of delayed-onset hearing loss in children <2 years of age in the UNHS era. The proportion of congenital hearing loss cases attributable to genetic etiologies and congenital CMV infection appears to vary widely.

Keywords

prelingual hearing loss; universal newborn hearing screening; genetic hearing loss; congenital CMV; cytomegalovirus

Prelingual hearing loss is defined as hearing loss that occurs before the development of speech and language skills, typically before 2 years of age, and can be congenital or have delayed onset.[1] Prelingual hearing loss can have significant effects on speech, language, and academic and social-emotional development.[2–4] Early diagnosis and intervention are critical to minimize the developmental consequences of hearing loss.[5]

Universal newborn hearing screening (UNHS) has been adopted throughout many developed countries and greatly improved identification of infants with congenital hearing loss.[6] In the United States, the Joint Committee on Infant Hearing recommends that all infants, regardless of newborn hearing screening outcome, should receive ongoing monitoring for development of age-appropriate auditory behaviors and communication skills.[5] The committee also recommends that every infant with confirmed hearing loss be referred for otologic and other medical evaluations to determine the etiology of hearing loss, identify related conditions, and provide recommendations for treatment and referral for other services.[5]

In this study, we conducted a scoping review to determine the extent to which UNHS programs facilitated identification of delayed-onset hearing loss in infants and young children, and we investigated the etiology of prelingual hearing loss. Because data on identification and etiology of delayed-onset hearing loss in cohorts of children <2 years of age who had undergone UNHS were lacking, we describe the proportions of congenital hearing loss cases attributed to genetic etiology and congenital cytomegalovirus (CMV) infection.

Methods

In this scoping review, we followed a structured process similar to that of a systematic review but did not grade the evidence.[7,8] We searched PubMed, Embase, PsycInfo, CINAHL, and Cochrane Library databases for articles published in academic journals between January 1, 1998, and February 19, 2020, in English. The search strategy is described in Appendix 1 (available online).

Two authors read all titles and abstracts, flagging citations for full-text review, and identified additional studies by manual search. We included in this review studies that met the following criteria: (1) included children identified with either congenital or delayed-onset hearing loss before 2 years of age among cohorts who had undergone UNHS and (2) investigated ≥1 etiologies of hearing loss with appropriate methods. We defined hearing loss

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as congenital when confirmed after UNHS failure and delayed-onset when detected after ≥1 assessments with normal hearing. Although some authors consider hearing loss onset up to 4 to 5 years of age as prelingual, we chose the cutoff age of 2 years because of the greater developmental consequences of hearing loss occurring at an earlier age.[1] We excluded case reports and reviews. When articles or abstracts reported overlapping data from the same study, only the publication with the most complete data was included. To be included, a study had to systematically assess all children in the cohort for the etiologic causes of hearing loss for which it was designed. We adopted inclusion and exclusion criteria and definitions to minimize bias from studies among children identified with hearing loss in referral centers and/or at older ages. We also excluded studies reporting on cohorts of children with hearing loss that were not based on UNHS cohorts or were restricted to subsets of children with bilateral or more severe hearing loss, such as candidates for cochlear implant.

We abstracted the following data from studies meeting the inclusion criteria: country/state, study period, study type (prospective or retrospective), UNHS protocol (1- vs 2-stage screening) and method (eg, otoacoustic emissions, auditory brainstem response, or automated auditory brainstem response), and approaches and methods for etiologic investigation, which we would assess a priori as appropriate.

We classified approaches for etiologic investigation as concurrent screening, targeted screening, and following hearing loss diagnosis. We abstracted the number of newborns screened for hearing loss, the number of newborns who did not pass the hearing screening (referred or failed), and if available, the number of children diagnosed with hearing loss. We included only children with sensorineural hearing loss. Among children diagnosed with hearing loss, we abstracted the number of those who had etiologic investigations and were categorized as having genetic etiology (syndromic, nonsyndromic, and single–base pair mutation/chromosomal) or congenital CMV infection. Two authors abstracted the data independently and resolved discrepancies by discussion. We contacted corresponding authors of included studies to obtain missing information. A subject matter expert (A.U.) reviewed all studies reporting on genetic etiology for accuracy of interpretation. We entered abstracted data from each study into an Excel spreadsheet. We calculated proportions of hearing loss attributed to genetic etiology or congenital CMV infection based on the number of children with congenital hearing loss who had etiologic investigation. We used OpenEpi (v 3)[9] and the Wald method with normal distribution to calculate 95% CIs for each study. Because of the heterogeneity of the populations studied, summary measures were not applicable.

Results

Our search yielded 2069 unique citations, with 115 studies flagged for full-text assessment (Figure 1). Of 95 studies excluded after full-text assessment, 69 (72.6%) had a high risk of bias because they reported data for selected cohorts of children or did not systematically assess etiology of hearing loss, and 15 (15.8%) performed concurrent hearing and genetic or CMV screening but did not report the number of all children diagnosed with hearing loss. A total of 20 studies, published from 2004 to 2020, were included in this review. These studies

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were conducted from 1998 to 2018 and reported data on etiology of hearing loss among children who had undergone UNHS in the following countries: Australia,[10,11] Belgium,[12,13] Brazil,[14] China,[15] Croatia,[16] India,[17] Ireland,[18] Israel,[19] Italy,[20] Japan,[21] Norway,[22] Taiwan,[23,24] United Kingdom,[25] and the United States[26–29] (Table 1). Altogether, the 20 studies included 2149 children with congenital hearing loss, of which 1787 (83.2%) had etiologic investigation. Although 3 studies reported data on delayed-onset hearing loss,[13,21,22] we excluded the subgroup with delayed-onset hearing loss from 2 studies,[13,22] 55 and 10 children, because data for children <2 years of age could not be abstracted, and from 1 study that included 1 child with delayed-onset hearing loss that was diagnosed within 18 months of age (n = 22).[21] We also excluded 106 children with conductive or undetermined hearing loss diagnosed after failing the newborn hearing screening.[28] Thus, the etiology data summarized in this review refer to 1787 children with congenital hearing loss.

There were 15 prospective studies and 5 retrospective (Table 1). Of the 5 retrospective studies, 3 were based on retrospective chart review, but etiologic investigation was systematically conducted for children who did not pass the newborn hearing screening[19,26,28,29] or were diagnosed with hearing loss in a UNHS cohort.[18] Six studies had a 1-stage screening protocol (ie, infants who did not pass the initial hearing screening were referred for diagnostic audiologic evaluation)[10,18,19,21,25,26]; 12 had a 2-stage screening method (ie, infants who did not pass the initial hearing screening received a follow-up screening before being referred for further diagnostic evaluation)*; and 2 did not specify a particular screening protocol.[13,20] When reported, the number of newborns screened for hearing loss ranged from 1716 to 239,636 in 17 studies.[11,12,14–26,28,29] Three of the 20 studies reported that their cohorts were identified through UNHS but did not state the number of newborns screened.[10,13,27] The newborn hearing screening referral rate varied from 0.2% to 3.4%.[12,24] The prevalence of congenital hearing loss ranged from 1.0 to 6.4 per 1000 newborns screened.[17,22] The number of children diagnosed with hearing loss ranged from 6 to 548 (Table 2).[15,24] The proportion of those who had an etiologic investigation ranged from 23%[27] to 100% in 13 studies.†

Of the 20 studies, 8 conducted etiologic investigation after diagnosis of hearing loss‡; 7 after newborn hearing screening failure[11,13,19,25,26,28,29]; and 5 conducted concurrent newborn hearing screening with genetic and/or CMV screening[14,15,17,21,24] (Table 2). Six studies assessed genetic etiology of hearing loss[15,16,20,22,23,27]; 9 assessed congenital CMV infection§; and 5 assessed both.[12,17,18,21,24] Genetic testing methods included polymerase chain reaction (PCR) amplification and subsequent gene sequencing[12,15–18,20–24,27] or restriction digest,[16] liquid chromatography analysis,[12] or mass spectrometry.[15] Sequenced genes were *GJB2* (NM_004004.6) in 11 studies with genetic investigation.[12,15–18,20–24,27] Other genes sequenced included *GJB3* (MIM: 603324),[15,20,23] *GJB6* (MIM: 604418),[12,18,20,23] *SLC26A4* (NM_000441.1),[15,18,23,24] and mitochondrial DNA mutations m.1555A>G in *MT-RNR1*[15,18,27] and m.7445A>G in *MT-TS1*.[27] One study investigated

*References 11, 12, 14–17, 22–24, 27–29
†References 11, 13–15, 17–19, 21, 22, 24–26, 29
‡References 10, 12, 16, 18, 20, 22, 23, 27
§References 10, 11, 13, 14, 19, 25, 26, 28, 29

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mutations in 8 connexin genes and the *SLC26A4* gene.[23] CMV PCR testing was performed on saliva and urine[10,14,19]; saliva, urine, and/or dried bloodspot[11,18,25]; saliva or urine[24,29]; saliva[17,26,28]; urine[24]; or dried blood spot.[12,13] Two studies also performed CMV viral culture and serology.[12,13] Although CMV serology is not reliable for diagnosing congenital CMV infection, it was done for ruling out congenital CMV infection if CMV IgG was negative.[13] In 1 study based on retrospective chart review, infants with congenital hearing loss had etiologic investigations according to published best practice guidelines,[30] which included testing for mutations in the genes *GJB2, GJB6, SLC26A4*, and m.1555A>G in *MT-RNR1*, as well as for congenital CMV infection with PCR of saliva, urine, and/or dried bloodspot.[18]

Altogether, the 20 studies included 1787 children with congenital hearing loss and etiologic investigation, of whom 933 (52.2%) were tested for genetic mutations and 1021 (57.1%) were tested for congenital CMV infection. The proportion of congenital hearing loss cases attributable to genetic etiology varied widely across studies, ranging from 14.3% (95% CI, 0.0%–29.3%) in Japan,[21] as informed by the corresponding author of the study, to 83.3% (95% CI, 53.5%–100.0%) in Taiwan.[24] However, the populations were different; sample sizes varied; some studies did not investigate etiology in all children identified with hearing loss; and others had more comprehensive genetic testing. For example, 1 study in Taiwan included 6 children with congenital hearing loss[24]; thus, estimates are unstable. Another study in Taiwan, which included 26 (81.3%) of 32 children with hearing loss, found 7.7% (95% CI, 0.0%–17.9%) attributable to genetic etiology, despite more comprehensive genetic testing.[23] One study in the United States reported 41.7% (95% CI, 21.9%–61.4%) attributable to genetic etiologies but performed etiologic investigation among 24 (23.1%) of 104 children diagnosed with congenital hearing loss.[27] Studies conducted in Europe[12,13,16,18,20,22,25] found that the proportion of congenital hearing loss cases attributable to genetic etiologies ranged from 19.4% (95% CI, 7.2%–31.0%)[18] to 33.3% (95% CI, 23.4%–43.2%).[12] Finally, 1 study in China, which had the largest number of children with hearing loss (n = 548), found 33.2% (95% CI, 29.3%–37.2%) attributed to genetic etiology.[15]

Excluding the study from Taiwan,[24] the proportion of congenital hearing loss cases attributable to congenital CMV infection ranged from 3.6% (95% CI, 0.0%–8.6%) in Australia[11] to 32.0% (95% CI, 13.7%–50.3%) in Brazil.[14] A larger study in Australia, which included 323 children with congenital hearing loss, reported that 5.9% (95% CI, 3.3%–8.4%) were diagnosed with congenital CMV infection.[10] The proportion of congenital hearing loss cases attributable to congenital CMV infection in 3 studies conducted in the United States ranged from 4.5% (95% CI, 0.0%–13.3%)[29] to 9.7% (95% CI, 2.9%–16.6%).[28] In 1 study, despite testing for congenital CMV infection and various genetic mutations, about half of the children with congenital hearing loss remained with an unknown etiology.[18]

Discussion

Limited data are available on the prevalence and etiology of prelingual hearing loss in the era of UNHS, and data are lacking on identification and etiology of delayed-onset hearing

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loss before 2 years of age. We found that the proportion of congenital hearing loss cases attributed to specific genetic etiologies ranged between 7.7% and 83.3% and to congenital CMV infection between 0.0% and 32.0%.

Genetic mutations account for a considerable portion of hearing loss in newborns.[6] In this review, the proportion of hearing loss cases due to genetic mutations varied widely. All 11 studies assessing genetic mutations included testing for *GJB2.* Some studies also included testing for *GJB3, GJB6, SLC26A4, MT-RNR1*, and *MT-TS1.* The wide range in hearing loss cases with a known genetic etiology could have resulted from studies assessing different genetic mutations, as well as population differences and variable sample sizes. Although *GJB2* and *GJB6* mutations represent a significant portion of cases, diagnosing genetic hearing loss remains challenging due to the heterogeneity of genetic mutations.

In the United States, an estimated 14% to 23% of bilateral sensorineural hearing loss cases are attributable to congenital CMV infection, assuming a prevalence of congenital CMV infection of 0.7% and that 3% to 5% of infected children develop bilateral sensorineural hearing loss of 40 dB or greater.[31] Current prevalence estimates of congenital CMV infection in the United States are lower (4.5 per 1000 live births).[32] Many children with congenital CMV-associated hearing loss will have delayed-onset and/or progressive hearing loss[33–35]; some with unilateral mild hearing loss at birth may develop profound bilateral hearing loss.[36] Thus, even in the same population, the proportion of hearing loss cases attributable to congenital CMV infection will vary with age and severity of hearing loss. A study in France, for example, found that among children <3 years of age with bilateral hearing loss, a higher proportion of those with profound loss as compared with any severity (15.4% vs 8.0%) had congenital CMV infection.[37]

In this review, we summarized data for children diagnosed with congenital hearing loss, regardless of the severity and laterality of hearing loss. Studies in developed countries that included >20 children with unilateral or bilateral congenital hearing loss found 4.8% to 12.5% attributable to congenital CMV infection, except 1 study from Japan (19.0%), which conducted concurrent newborn hearing and CMV screening.[21] Although these studies identified cases of congenital hearing loss among cohorts of thousands of newborns, the number of children diagnosed with hearing loss was small, resulting in wide confidence intervals. The highest proportion of CMV-positive infants among those who were diagnosed with hearing loss was reported in the study in Brazil, which notably reported no delayed-onset hearing loss in CMV-positive children followed through median 3 years.[14] Whereas the prevalence of congenital CMV infection varies across populations, the variability in these findings could also result from differences in study methods, including specimen types for CMV PCR testing, which have variable sensitivity, and/or the algorithm for etiologic investigation.

A recent expert panel, which included members of the International Pediatric Otolaryngology Group, provided support for testing for mutations in *GJB2* for the workup of hearing loss in children and recommended that providers consider family goals and pretest counseling.[38] The panel also supported CMV testing for newborns who fail the hearing screening.[38] In studies included in this review, infants were systematically tested for

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congenital CMV infection concurrently with newborn hearing screening[14,17,21,24] or after failure,[11,13,19,25,26,28,29] with 3.6% to 32.0% CMV positive among those diagnosed with congenital hearing loss. The CMV-positive fraction among infants who did not pass the hearing screening, regardless of being diagnosed with hearing loss, ranges from 1% to 10%.[14,19,39–41] As expected, studies that tested infants for CMV after the diagnosis of hearing loss[10,12,18] had higher attrition rates than studies that conducted CMV screening for all newborns[14,17,21,24] or CMV testing for those who failed the newborn hearing screening.

The findings in this review are subject to limitations. Although we screened >2000 records and reviewed 115 studies, only 20 studies met the inclusion criteria. We identified numerous studies from countries in Latin America and Africa, and many studies were excluded mainly because the cohorts had not undergone UNHS, reflecting the lag in UNHS implementation in other parts of the world.[42] In contrast, several studies in Asia performed comprehensive genetic screening for hearing loss with or without hearing screening,[43–47] but only 3 studies[15,23,24] reported the number of children diagnosed with hearing loss. The findings across different regions of the world may not be generalizable to any specific population, because they may be influenced by the population prevalence of hearing loss, genetic etiologies, and congenital CMV infection. In some of the studies, etiology was not systematically investigated in all children, while other studies had comprehensive genetic testing performed. We identified a small number of studies that investigated the etiology of delayed-onset hearing loss. However, we were unable to extract data for children who underwent UNHS and were diagnosed with hearing loss before 2 years of age. Thus, those studies or cohorts were excluded from our review. One large study (n = 364) was excluded because children were diagnosed with hearing loss up to 3 years of age and, for nearly one-fourth of the cohort, either hearing screening was not performed or hearing screening outcome was unknown. In that study, 37.9% of hearing loss cases were attributable to genetic etiology and 7.7% to congenital CMV infection.[48]

Hearing loss may be associated with other clinical outcomes, such as vision loss and intellectual delay, as in certain cases of syndromic hearing loss[38] and congenital CMV infection. Thus, determining hearing loss etiology can help guide best care and intervention options for families and their children, as well as inform developmental prognosis.[5] Genetic testing may provide an opportunity for families and patients to meet with a medical geneticist in the context of a multidisciplinary audiology clinic to address concerns regarding likely sequelae and prognosis for future children.[49] CMV testing of specimens collected during the first 2 to 3 weeks of life may provide an opportunity for early diagnosis and antiviral treatment of infants with symptomatic congenital CMV disease[10] and increased identification of those who would be eligible for ongoing clinical trials.[50]

Advances in sequencing technologies have greatly increased the clinical utility of searching the entire exome or genome for mutations.[51,52] Studies performing comprehensive newborn hearing screening, including physiologic and genetic testing, might consider reporting data on audiologic follow-up of children, which will be useful to improve population-specific estimates of hearing loss attributable to genetic etiology and to understand the clinical significance of genetic findings. A relatively small study from Taiwan, which we included in this review, assessed the feasibility of incorporating genetic and CMV screening into the

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UNHS program.[24] The province of Ontario, Canada, recently rolled out an expanded hearing screening program to identify infants with risk factors for hearing loss, including a universal offer of dried bloodspot testing for genetic mutations associated with hearing loss, as well as congenital CMV infection, regardless of audiometric screening outcome.[53] However, the feasibility and benefits of comprehensive newborn hearing screening including physiologic and genetic testing, as well as CMV testing, have not been fully evaluated in large-scale studies.[54]

Conclusion

Limited data are available on identification and etiology of delayed-onset hearing loss in children <2 years of age in the era of UNHS. Estimates of congenital hearing loss attributable to genetic etiology and congenital CMV infection appear to vary widely and will likely improve as research progresses and policies for comprehensive or expanded newborn hearing screening are implemented. Additional research on the feasibility and impact of systematic investigation of etiologies of prelingual hearing loss can serve to inform future policy and practice efforts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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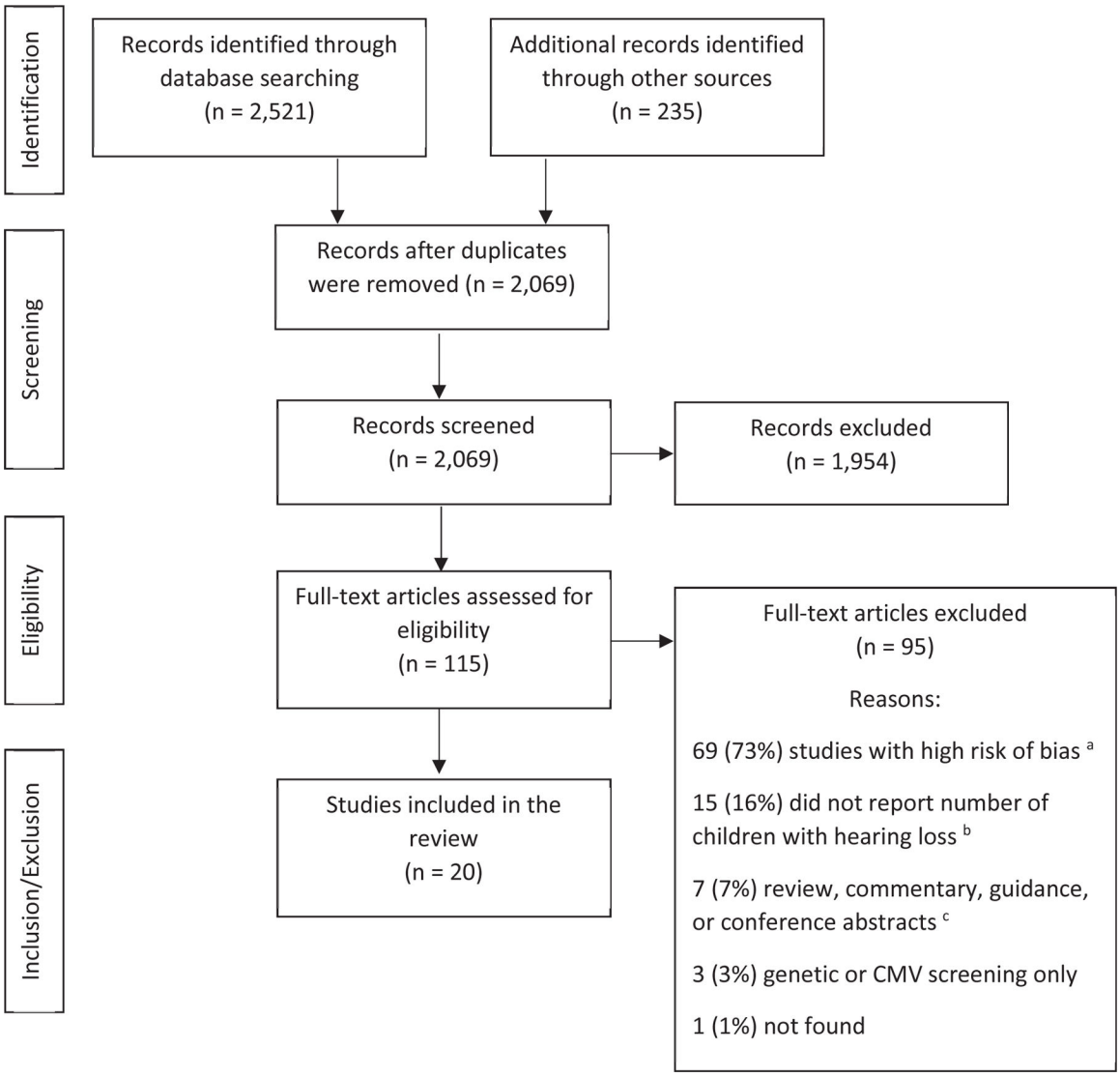

Figure 1.

Flow diagram.

[a]Studies reporting on selected cohorts of children who did not undergo universal hearing screening, had bilateral or more severe hearing loss (eg, candidates for cochlear implant), or identified with hearing loss at >2 years of age or studies that did not systematically assess etiology of hearing loss.

[b]Studies conducting concurrent hearing and genetic or cytomegalovirus (CMV) screening, including targeted screening, but not reporting on audiologic follow-up for diagnosis of hearing loss.

[c]Of the 4 conference abstracts, 3 studies described preliminary findings of other included studies, and 1 study was not found.

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Table 1.

Overview of Studies Included in the Review: Newborn Hearing Screening Methods, Referral Rate, and Prevalence of Hearing Loss.

First Author (Year)	Country	Study Period	Study Type	Screening Protocol	Screening Method	Newborns Screened, No.	Newborn Hearing Screening Referral Rate, %	Prevalence of Hearing Loss [a]
Rawlinson (2018)[10]	Australia	2009–2016	Prospective	1-stage	AABR			
Beswick (2019)[11]	Australia	2014–2016	Prospective	2-stage	AABR	28,286	1.2	1.9
Declau (2008)[12]	Belgium	1998–2006	Prospective	2-stage	AABR	~87,000	0.2	1.4
Boudewyns (2009)[13]	Belgium	2006–2008	Prospective					
Yamamoto (2019)[14]	Brazil	2013–2017	Prospective	2-stage	OAE and AABR	11,900	0.8	2.1
Guo (2020)[15]	China	2015–2018	Prospective	2-stage	OAE	239,636		2.3
Zaputovic (2005)[16]	Croatia	2002–2004	Prospective	2-stage	OAE	6019	1.4	2.3
Dar (2017)[17]	India	2010–2012	Prospective	2-stage	OAE	1720	2.3	6.4
Smith (2017)[18]	Ireland	2011–2014	Retrospective	1- or 2-stage (NICU)	OAE or OAE and ABR (NICU)	27,451		1.5
Roth (2017)[19]	Israel	2014–2015	Retrospective	1-stage	OAE or OAE and AABR (NICU)	19,830	1.0	1.8
Chinetti (2011)[20]	Italy	2006–2009	Prospective			178,690		
Yamaguchi (2017)[21]	Japan	2008–2015	Prospective	1-stage	ABR	22,229	0.8	1.0
Nelson (2015)[22]	Norway	2000–2009	Prospective	2-stage	OAE and AABR [b]	29,485	1.9	1.0
Chu (2015)[23]	Taiwan	2009–2013	Prospective	2-stage	OAE and AABR	15,345	1.0	2.1
Lu (2018)[24]	Taiwan	2016	Prospective	2-stage	AABR	1716	3.4	2.9
Williams (2014)[25]	UK	2010–2012	Prospective	1-stage	OAE or OAE and AABR (NICU)	46,242	2.4	
Stehel (2008)[26]	USA	1999–2004	Retrospective	1-stage	AABR	79,047	0.7	3.2
Dent (2004)[27]	USA	2001–2002	Prospective	2-stage	OAE			
Diener (2017)[28]	USA	2011–2015	Retrospective	2-stage		103,868	0.7	2.1
Vancor (2019)[29]	USA	2016	Retrospective	2-stage	OAE and ABR	10,964	1.6	2.0

Abbreviations: AABR, automated auditory brainstem response; ABR, auditory brainstem response; NICU, neonatal intensive care unit; OAE, otoacoustic emissions.

[a] Per 1000 infants screened.

[b] ABR before 2002.

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Table 2.

Overview of Studies Included in Review: Sample Size, Methods Used for Etiologic Investigation, and Proportion Attributed to Genetic Etiology and Congenital CMV Infection.

		Etiologic Investigation			Children With, No. (%, 95% CI)			
First Author (Year)	**Country**	**Approach**	**Genes Sequenced**	**CMV Testing Method**	**Congenital Hearing Loss**	**Etiologic Investigation**	**Genetic Hearing Loss**	**Congenital CMV Infection**
Rawlinson (2018)[10]	Australia	After hearing loss diagnosis		PCR on saliva and urine	502	323 (64)		19 (5.9, 3.3–8.4)
Beswick (2019)[11]	Australia	After UNHS failure		PCR on saliva, confirmed on urine, blood, or repeat saliva	55	55 (100)		2 (3.6, 0.0–8.6)
Declau (2008)[12]	Belgium	After hearing loss diagnosis	*GJB2, GJB6*	PCR on DBS, viral culture, or serology	116	87 (75)	29 (33.3, 23.4–43.2)	9 (10.3, 3.9–16.7)
Boudewyns (2009)[13]	Belgium	After UNHS failure		PCR on DBS, viral culture on urine and saliva	41[a]	41 (100)		3 (7.3, 0.0–15.3)
Yamamoto (2019)[14]	Brazil	Concurrent screening		PCR on saliva, confirmed on urine	25	25 (100)		8 (32.0, 13.7–50.3)
Guo (2020)[15]	China	Concurrent screening	*GJB2, GJB3, SLC26A4,* m.1555A>G in *MT-RNR1*		548	548 (100)	182 (33.2, 29.3–37.2)	
Zaputovic (2005)[16]	Croatia	After hearing loss diagnosis	*GJB2*		14	8 (57)	2 (25.0, 0.0–55.0)	
Dar (2017)[17]	India	Concurrent screening (CMV), after hearing loss diagnosis (genetic)	*GJB2*	PCR on saliva	11	11 (100)	0	2 (18.0, 0.0–41.0)
Smith (2017)[18]	Ireland	After hearing loss diagnosis	*GJB2, GJB6, SLC26A4,* m.1555A>G in *MT-RNR1*	PCR on saliva, urine, and/or DBS [b]	42	42 (100)	8 (19.4, 7.2–31.0)	2 (4.8, 0.0–11.2)
Roth (2017)[19]	Israel	After UNHS failure		PCR on saliva and urine	36	36 (100)		3 (8.3, 0.0–17.36)
Chinetti (2011)[20]	Italy	After hearing loss diagnosis	*GJB2, GJB3, GJB6*		178	129 (72)	36 (27.8, 20.2–35.7)	
Yamaguchi (2017)[21]	Japan	Concurrent screening	*GJB2*	PCR on urine	21[c]	21 (100)	3 (14.3, 0.0–29.6) [d]	4 (19.0, 2.3–35.8)
Nelson (2015)[22]	Norway	After hearing loss diagnosis	*GJB2*		31[e]	31 (100)	9 (29.0, 13.1–45.0)	

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First Author (Year)	Country	Etiologic Investigation			Children With, No. (%, 95% CI)			
		Approach	Genes Sequenced	CMV Testing Method	Congenital Hearing Loss	Etiologic Investigation	Genetic Hearing Loss	Congenital CMV Infection
Chu (2015)[23]	Taiwan	After hearing loss diagnosis	*GJB2, GJB4, GJA1P1, GJB6, GJB3, GJA1, GJB1, GJC3, SLC26A4*		32	26 (81)	2 (7.7, 0.0–17.9)	
Lu (2018)[24]	Taiwan	Concurrent screening	*GJB2, SLC26A4*	PCR saliva or urine, confirmed on DBS	6	6 (100)	5 (83.3, 53.5–100)	0
Williams (2014)[25]	UK	After UNHS failure		PCR on saliva, urine or DBS	24	24 (100)		3 (12.5, 0.0–25.7)
Stehel (2008)[26]	USA	After UNHS failure		PCR on saliva	256	256 (100)		16 (6.3, 3.3–9.2)
Dent (2004)[27]	USA	After hearing loss diagnosis	*GJB2*, m.1555A>G in *MT-RNR1*, m.7445A>G in *MT-TS1*		104	24 (23)	10 (41.7, 21.9–61.4)	
Diener (2017)[28]	USA	After UNHS failure		PCR on saliva	85[d,f]	72 (85)		7 (9.7, 2.9–16.6)
Vancor (2019)[29]	USA	After UNHS failure	PCR on saliva or urine		22	22 (100)		1 (4.5, 0.0–13.3)

Abbreviations: CMV, cytomegalovirus; DBS, dried bloodspot; PCR, polymerase chain reaction; UNHS, universal newborn hearing screening.

RefSeq numbers: *GJB2*: NM_004004.6. *GJB3*: NM_024009.3. *GJB6*: NM_001110219.3. *SLC26A4*: NM_000441.1. *MT-RNR1* and *MT-TS1*: NC_012920.1.

[a] Excluded 55 children with delayed-onset hearing loss diagnosed at mean ± SD age of 4.9 ± 3.2 years.

[b] Assessed by retrospective chart review of children with hearing loss and etiologic investigation conducted per the best practice guidelines of the British Association of Pediatricians in Audiology.

[c] Excluded 1 child with delayed-onset hearing loss, likely diagnosed within 18 months of age, who had congenital CMV infection.

[d] Information provided by corresponding author.

[e] Excluded 10 children with delayed-onset hearing loss diagnosed at median age of 36 months (range: 18–86 months).

[f] Excluded 130 children with hearing loss (87 conductive, 19 mixed, 19 undetermined, and 5 auditory neuropathy spectrum disorder).