UNIVERSITEIT GENT

FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

Academiejaar 2015 – 2016

Hearing Loss and Congenital CMV Infection: A Systematic Review

Julie GODERIS

Promotor 1: Prof. dr. I. Dhooge

Promotor 2: Dr. H. Van Hoecke

Masterproef voorgedragen in de master in de specialistische geneeskunde
Neus-, Keel en Oorheelkunde

UNIVERSITEIT GENT

FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

Academiejaar 2015 – 2016

Hearing Loss and Congenital CMV Infection: A Systematic Review

Julie GODERIS

Promotor 1: Prof. dr. I. Dhooge

Promotor 2: Dr. H. Van Hoecke

Masterproef voorgedragen in de master in de specialistische geneeskunde
Neus-, Keel en Oorheelkunde

Voorwoord

Deze review is voor mij een werk van bloed, zweet en tranen geweest. 50 jaar literatuur samenvatten bleek geen eenvoudige opdracht te zijn. Maar ondanks alle hindernissen is het wel een werk geworden waar ik trots op ben. Mijn oprechte dank gaat dan ook uit naar Prof. Dr. I. Dhooge, voor haar coördinatie, haar verbeteringen, advies en haar steun. Verder wens ik ook alle andere coauteurs te bedanken voor hun medewerking. Tenslotte bedank ik ook graag de commissarissen, Prof. Dr. A. Boudewyns en Prof. Dr. K. Smets voor hun interesse en kritische blik op mijn proefstuk.

Ik hoop dat dit een referentiewerk mag worden voor alle onderzoekers en clinici die geboeid worden door het onderwerp congenitale CMV infectie.

Julie Goderis

Maart 2016

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Hearing Loss and Congenital CMV Infection: A Systematic Review

Julie Goderis, Els De Leenheer, Koenraad Smets, Helen Van Hoecke, Annelies Keymeulen and Ingeborg Dhooge

Pediatrics 2014;134;972; originally published online October 27, 2014;
DOI: 10.1542/peds.2014-1173

Hearing Loss and Congenital CMV Infection: A Systematic Review

abstract

BACKGROUND AND OBJECTIVE: Hearing loss caused by congenital cytomegalovirus (cCMV) infection was first observed in 1964. Today cCMV is the most common cause of nonhereditary sensorineural hearing loss in childhood. Our objective was to provide an overview of the prevalence of cCMV-related hearing loss, to better define the nature of cCMV-associated hearing loss, and to investigate the importance of cCMV infection in hearing-impaired children.

METHODS: Two reviewers independently used Medline and manual searches of references from eligible studies and review articles to select cohort studies on children with cCMV infection with audiological follow-up and extracted data on population characteristics and hearing outcomes.

RESULTS: Thirty-seven studies were included: 10 population-based natural history studies, 14 longitudinal cohort studies, and 13 retrospective studies. The prevalence of cCMV in developed countries is 0.58% (95% confidence interval, 0.41–0.79). Among these newborns 12.6% (95% confidence interval, 10.2–16.5) will experience hearing loss: 1 out of 3 symptomatic children and 1 out of 10 asymptomatic children. Among symptomatic children, the majority have bilateral loss; among asymptomatic children, unilateral loss predominates. In both groups the hearing loss is mainly severe to profound. Hearing loss can have a delayed onset, and it is unstable, with fluctuations and progression. Among hearing-impaired children, cCMV is the causative agent in 10% to 20%. Despite strict selection criteria, some heterogeneity was found between selected studies.

CONCLUSIONS: This systematic review underscores the importance of cCMV as a cause of sensorineural hearing loss in childhood. *Pediatrics* 2014;134:972–982

AUTHORS: Julie Goderis, MD,[a] Els De Leenheer, MD, PhD,[a] Koenraad Smets, MD, PhD,[b] Helen Van Hoecke, MD, PhD,[a] Annelies Keymeulen, MD,[b] and Ingeborg Dhooge, MD, PhD[a]

[a]Department of Otorhinolaryngology and [b]Neonatal ICU, University Hospital Ghent, Ghent, Belgium

KEY WORDS

cytomegalovirus, congenital infection, hearing, auditory, prevalence, symptomatic infection, systematic review

ABBREVIATIONS

cCMV—congenital cytomegalovirus
CI—confidence interval
DBS—dried blood spots
PCR—polymerase chain reaction
SNHL—sensorineural hearing loss
UNHS—universal neonatal hearing screening

Dr Goderis designed this review, performed the literature search, drafted the initial manuscript, and improved revised versions; Drs De Leenheer, Smets, Van Hoecke, and Keymeulen revised the analysis and interpretation of data and critically reviewed the manuscript; Dr Dhooge conceptualized this review, coordinated and supervised the process, approved the literature search and selection, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2014-1173

doi:10.1542/peds.2014-1173

Accepted for publication Aug 27, 2014

Address correspondence to Julie Goderis, MD, Department of Otorhinolaryngology, University Hospital Ghent, De Pintelaan 185, 9000 Ghent, Belgium. E-mail: julie.goderis@ugent.be

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

The first article on hearing loss by congenital cytomegalovirus (cCMV) infection was published in 1964 by Medearis et al.[1] Over the past 50 years, numerous studies explored the relationship between cCMV infection and hearing loss. Today cCMV is acknowledged as the most common nongenetic cause of childhood sensorineural hearing loss (SNHL) and an important cause of neurodevelopmental delay.[2–7]

Worldwide, cCMV infection affects 0.2% to 2.5% of all live-born neonates.[8–11] In industrialized countries, the average prevalence of cCMV infection is 0.64% to 0.70%.[4,12] The incidence of cCMV infection is highest in developing countries, 1% to 5% of all live births, and is probably driven by nonprimary maternal infections.[13] The prevalence of cCMV infection increases with increasing maternal CMV seroprevalence. Most European countries have a maternal CMV seroprevalence ranging from 40% to 60%. In developing countries it is >90%.[13,14] Maternal seroprevalence depends on age, socioeconomic status, and parity.[15–17] But between industrialized countries there are clear differences in prevalence, probably because of race-bound predilection in addition to differences in sexual behavior, day care attendance, breastfeeding, and profession.[18,19] Spreading of CMV occurs through close contact with infected body fluids. Children aged 1 to 2 years are the most important source of infection for women of reproductive age.[20,21]

In seropositive mothers, reactivation of a latent virus or reinfection with a new CMV strain can cause cCMV disease as well, with or without permanent sequelae.[22–30] The risk of vertical transmission seems to be higher in primary infections than in nonprimary infections. In a meta-analysis, Kenneson and Cannon[12] found rates of vertical transmission of 32% and 1.4% for primary and nonprimary infections, respectively. The rate of vertical transmission increases with older gestational age at infection, but there is a significantly higher risk of fetal anomalies and symptomatic disease when maternal infection occurs during the preconceptional and periconceptional period and during the first trimester of pregnancy.[31,32]

Approximately 10% to 15% of children with cCMV are symptomatic at birth. Outcomes for these infants are poor, and most survivors suffer from severe neurologic sequelae.[4,33–35] The overall mortality rate is <5%.[10,27,35,36] The majority of children with cCMV are asymptomatic and therefore not diagnosed at birth. However, 7% to 15% of clinically asymptomatic patients may develop late sequelae, including SNHL, which is by far the most common sequela.[5,37–39]

Because the majority of children are asymptomatic at birth and because there is no systematic newborn screening, the impact of cCMV is ill defined. Population-based natural history studies that accurately estimate the prevalence of disease and morbidity burden are scarce, but the economic burden is estimated to be similar to that for congenital rubella before the introduction of vaccination.[13,40,41] Because SNHL is the most common sequela of cCMV infection, it is a major contributor to disease burden. Reliable estimates of the hearing loss caused by cCMV are needed to increase vigilance among health care workers and the public.

Retrospective studies performed on a population of deaf children report frequencies of cCMV-related hearing loss ranging from 2% to 18%.[42–45] However, it is assumed that the importance of asymptomatic cCMV as a cause of hearing loss may be higher than currently believed.[3,46,47]

This systematic review provides an overview of the prevalence of cCMV-related hearing loss based on the literature of the past 50 years and aims at better defining the nature of cCMV-associated hearing loss and the importance of cCMV among patients with childhood hearing loss.

METHODS

A systematic literature search was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.[48] The Medline database was searched for relevant articles published from inception to December 2013. In order to find all articles about hearing loss and cCMV infection, we used the following subject headings: congenital cytomegalovirus AND (hearing OR deafness OR auditory), combined with the results for perinatal cytomegalovirus AND (hearing OR deafness OR auditory) in all fields. This resulted in 476 citations, of which titles and abstracts were read by 2 reviewers independently. A manual search of reference lists of the retrieved articles resulted in 8 additional articles. Duplicates and non-English articles were excluded, because omission of non-English articles has been shown to have minimal impact on the results. Also, nonrelevant papers, defined as not focusing on the topic as indicated by the abstract, were excluded. A total of 101 articles were read in detail and narrowed to 37 relevant studies (Fig 1).

Variable definitions of symptomatic cCMV are found in the literature. The most common definition of symptomatic disease is the presence of ≥1 of the following symptoms at birth: petechiae, jaundice with conjugated hyperbilirubinemia, hepatosplenomegaly, thrombocytopenia, chorioretinitis, seizures, microcephaly, and intracranial calcifications.[3,4,28,34,49] Only studies that mentioned ≥3 of these symptoms were included. If there was no description or definition, studies were nevertheless included if there was a reference to an article with a similar definition. Diagnosis of cCMV had to be confirmed by virus isolation or polymerase chain reaction (PCR) of CMV in urine or saliva, collected within 3 weeks of birth to distinguish it from postnatally acquired infections.[18,50]

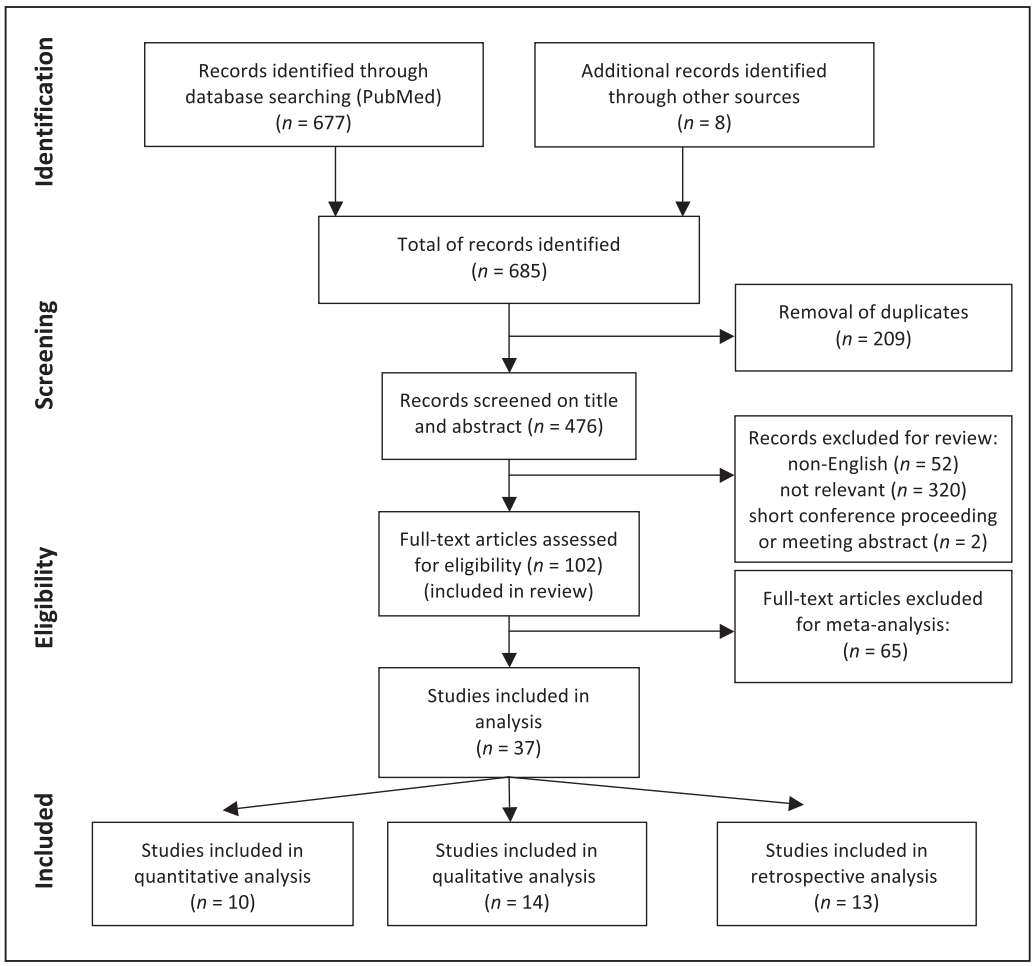


FIGURE 1
PRISMA flowchart of literature search.

Only articles with data from primary sources were included. In case of multiple reports from 1 research group, the most recent or the most detailed report was chosen. Methods for hearing evaluations were not standardized across the studies, nor were follow-up protocols. Only studies where transient middle ear pathology was excluded by otoscopy, admittance measurements, and absence of air–bone gap were included. Hearing loss includes both unilateral and bilateral SNHL, with thresholds >20 dB. Individual study quality was assessed through evaluation of study design, number of evaluations, length of follow-up, outcome measurement method, and reporting of confounding factors for hearing loss. Selected articles were divided according to 3 different approaches.

Quantitative Approach

To determine the prevalence of cCMV-associated hearing loss on a population level, we selected studies where cCMV infection was diagnosed through universal newborn screening for cCMV. The following articles were included: original peer-reviewed articles where screening for cCMV was done in all newborns during a given period and studies where the diagnosis of cCMV was made by virus isolation or PCR of CMV in urine or saliva, collected within 3 weeks of birth. Studies with cases identified by immunoglobulin M detection in blood samples were not included because such assays lack sensitivity.[27,51,52] The use of the aforementioned definition of symptomatic cCMV was required. We were especially interested in studies with a longitudinal prospective design. Data on the number of symptomatic and asymptomatic patients and the associated hearing loss had to be available. Studies with children treated with ganciclovir or valganciclovir were excluded to determine the exact number of affected children in the natural course of infection.

Qualitative Approach

To determine the nature of cCMV-associated hearing loss, we selected cohort studies with a longitudinal audiological follow-up. Those studies include children detected by systematic cCMV screening or diagnosed because of known seroconversion of the mother, or children with clinical signs suggestive of the disease. We selected all studies that

conducted longitudinal testing in a group of ≥20 children with cCMV infection. The use of the aforementioned definition of symptomatic cCMV was mandatory. Children had to have ≥2 audiological evaluations during follow-up. In such studies an overrepresentation of symptomatic children is expected, so to stratify the results according to symptomatic or asymptomatic cCMV infection, we needed data on the number of symptomatic and asymptomatic patients and the associated hearing loss. Concerning the different characteristics of cCMV-related hearing loss, we used the studies with the most complete information on that specific parameter. An additional goal was to determine the relationship between primary and nonprimary (reactivation or reinfection) infection and hearing loss.

Retrospective Approach

A method for retrospective diagnosis of cCMV was introduced in 1994 by Shibata et al.[53] They detected CMV DNA by means of PCR on neonatal dried blood spots (DBS). Since then several studies tested and adapted this method, with sensitivity ranging from 71% to 100% and specificities of 99% to 100%.[54] A recent study found much lower sensitivities, near 34%, when DBS were used as screening test.[55] However, it is the only way to detect a cCMV infection retrospectively. Detection of CMV DNA can vary depending on the method of DNA extraction from the cards, the amplification method, and the part of the CMV genome being detected.[56–58] It may also be influenced by the time and conditions in which the cards have been stored. Cross-contamination of adjacent stored cards has been reported.[54,59–61]

To understand the importance of cCMV as a cause of childhood hearing loss, we reviewed studies that conducted retrospective testing in a group of hearing-impaired children. Requirements were testing by real-time PCR for quantitative analysis of CMV DNA on DBS or on dried umbilical cords. A distinction was made between studies that excluded other risk factors for hearing loss and those that did not.

Statistical Analysis

We performed a meta-analysis by using a random effects model of DerSimonian and Laird to calculate estimated proportions. R version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria) was used to make calculations. For each inquiry a confidence interval (CI) was calculated and a forest plot was developed. I^2 is a measure of heterogeneity; it indicates the percentage of variance attributable to study heterogeneity rather than chance. The P value reflects the significance of the heterogeneity. The study was conducted in accordance with the instructions of the PRISMA statement for reporting systematic reviews and of the Meta-analysis of Observational Studies in Epidemiology group for reporting meta-analyses of observational studies.[48,62]

RESULTS

Quantitative Approach

Ten studies were selected according to the aforementioned protocol. An overview of the studies is shown in the Supplemental Information. We found an overall prevalence of cCMV infection of 0.58%. The proportions for symptomatic and asymptomatic infected children were 9.8% and 90.2%, respectively. Hearing loss occurred in 32.8% of symptomatic cases, compared with 9.9% of asymptomatic children. The overall rate of hearing loss in cCMV infection was 12.6%. The overall rate of hearing loss by cCMV infection in the population was estimated to be 0.5 in 1000 children. Table 1 includes an overview of the estimated proportions.

Qualitative Approach

Fourteen longitudinal cohort studies of children with cCMV infection that focused on hearing were included (Supplemental Information). In those studies, symptomatic children were overrepresented, so we stratified the results according to symptomatic or asymptomatic cCMV infection. In symptomatic cCMV infection hearing loss was bilateral in 71.2% and unilateral in 28.8% of cases. The majority of hearing loss was severe to profound, with 65.1% of bilateral hearing loss severe to profound, necessitating hearing amplification and rehabilitation. Of all symptomatic children with hearing loss, 18.1% had a delayed onset. Approximately 1 in 6 symptomatic children with hearing loss exhibited progressive hearing loss, and 1 in 5 symptomatic children with hearing loss experienced fluctuations. In the asymptomatic group, hearing loss was unilateral in 57%. The majority of hearing loss was also severe to profound, but the percentage of children with bilateral severe to profound hearing loss was less than in the symptomatic group. However, in 42.6% of the hearing-impaired asymptomatic children, hearing loss necessitated hearing amplification and rehabilitation. Of all asymptomatic children with hearing loss, 9% had a delayed onset. Approximately 1 in 5 asymptomatic children with hearing loss exhibited progressive hearing loss, and 1 in 4 asymptomatic children with hearing loss experienced fluctuations.

To evaluate the impact of maternal seroimmunity on hearing status, we selected 3 additional studies that reported the amount of hearing loss in relation to type of infection (primary or nonprimary). Hearing loss occurred in 12.1% of the primary infections and in 11.8% of the nonprimary infections. A summary of the qualitative approach is found in Tables 2 and 3.

Retrospective Approach

Thirteen studies were selected for a retrospective approach (Supplemental

TABLE 1 Results of the Quantitative Approach[3,8,23,27,40,51,63–66]

	Estimated Proportion, %	95% CI	I^2, %	*P* of Heterogeneity
Prevalence of cCMV in population	0.58	0.41–0.79	94.3	<.0001
Proportion of symptomatic cCMV	9.8	5.8–14.6	70	.0004
Proportion of asymptomatic cCMV	90.2	85.4–94.2	70	.0004
Proportion of symptomatic cCMV with hearing loss	32.8	23.2–43.2	0	.6423
Proportion of asymptomatic cCMV with hearing loss	9.9	6.3–14.2	46.9	.0495
Proportion of cCMV with hearing loss	12.6	9.4–16.3	26.7	.198
Prevalence of hearing loss by cCMV in population	0.05	0.03–0.09	79.6	<.0001

Information). In the first analysis, all selected retrospective studies were included. In the next 2 analyses the distinction was made between studies that excluded children with other risk factors for hearing loss (eg, known hereditary and environmental causes) and studies that did not. In the group of hearing-impaired children the prevalence of cCMV-related hearing loss was ∼8% (Table 4). In the group of hearing-impaired children with hearing loss from unknown origin where known risk factors for hearing loss were excluded, the prevalence of hearing loss by cCMV was ∼20%.

Quality of Studies

The majority of studies included in the quantitative and qualitative approach had a prospective study design. The number of hearing evaluations in studies used in the quantitative approach was low in comparison to studies in the qualitative approach. Also, the follow-up was longer in the studies included in the qualitative approach. Methods of outcome measurement seemed not to differ greatly between the studies. Only a few studies reported other risk factors for hearing loss.

DISCUSSION

This systematic review estimates the prevalence and nature of the hearing loss attributable to cCMV infection, based on a meta-analysis of a number of selected articles. We found an overall prevalence of cCMV infection of 0.58% in industrialized countries. This is consistent with the 0.64% found in a previous meta-analysis by Kenneson and Cannon.[12] Globally significant differences in epidemiology exist between and within countries. In developing nations with highly seropositive populations, prevalence ranges between 1% and 6%.[86] This correlation is explained by the fact that cCMV birth prevalence increases with maternal seroprevalence. A high seroprevalence means that there are more pregnant women at risk for reactivation or reinfection next to a higher prevalence of risk behavior and a higher rate of exposure to CMV. The increased rate of nonprimary infections leads to a higher birth prevalence on population level, despite the lower risk of vertical transmission.[12,30] The risk of symptomatic infection and permanent sequelae is higher among infants whose mothers experienced a primary infection, but disabilities have also been observed as a result of nonprimary infection.[27,87,88] Percentages of newborns with symptomatic disease or long-term sequelae after nonprimary infection vary between 1% and 10%.[28,29,89] Data are currently insufficient to estimate the exact proportion of cCMV-disabled children attributable to nonprimary infection.[88]

The overall incidence of hearing loss in cCMV is 12.6%. One in 3 symptomatic children will experience loss, in comparison with 1 in 10 asymptomatic children. Extrapolation of these results to the population level shows that of every 10 000 children born each year, 5 will have cCMV-related hearing loss. In combination with birth rate statistics in Europe, this means that each year 2600 live-born children will experience immediate or delayed hearing impairment caused by cCMV. In the United States, the number is 1975 children per year. The results in the quantitative approach all have a strikingly high heterogeneity, which in most of the cases was significant. So despite our strict selection criteria, the results should be interpreted with caution. The majority of symptomatic children had bilateral hearing loss. In the asymptomatic group unilateral losses predominated. Presumably, a large number of unilateral hearing losses, often diagnosed at school age, are attributable to a missed asymptomatic cCMV infection. The challenge is to confirm the diagnosis

TABLE 2 Nature of Hearing Loss Stratified by Symptomatic or Asymptomatic Infection[8,24,25,27–29,34,40,67–72]

Hearing Loss Characteristics	Symptomatic at Birth		Asymptomatic at Birth	
	Estimated Proportion, %	95% CI, I^2, *P* of Heterogeneity	Estimated Proportion, %	95% CI, I^2, *P* of Heterogeneity
Bilateral hearing loss	71.2	64.2–77.8, 0%, .8944	43.1	28.2–58.6, 39.8%, .1024
Unilateral hearing loss	28.8	22.2–35.9, 0%, .8944	56.9	41.4–71.8, 39.8%, .1024
Severe to profound hearing loss	76.8	70.1–83, 0%, .5044	77.7	59.6–91.6, 52.9%, .038
Bilateral severe to profound hearing loss	65.1	54.2–75.2, 0%, .4937	42.6	20.2–66.7, 49%, .0673
Delayed hearing loss	18.1	5.9–36.2, 65.4%, .0051	9	0.8–24.5, 64.8%, .0058
Progressive hearing loss	17.7	3.5–39.4, 80.5%, <.0001	20.3	5.3–41.8, 73.1%, .0002
Fluctuating hearing loss	21.5	9.3–37, 55.6%, .0272	24	2.1–59.6, 86.3%, <.0001

TABLE 3 Hearing Loss According to Type of Infection[24,25,27–29,40,71,72]

Type of Infection	Estimated Proportion, %	95% CI	I^2, %	*P* of Heterogeneity
Hearing loss in case of primary infection	12.1	8.6–16	18.8	.2814
Hearing loss in case of nonprimary infection	11.8	7.5–16.8	21.7	.2568

TABLE 4 Results of the Retrospective Approach

	Estimated Proportion, %	95% CI	I^2, %	*P* of Heterogeneity
Hearing loss by cCMV among hearing impaired[73–85]	10.4	8–13	54.1	.0103
Exclusion of other risk factors for hearing loss[73–76]	19.8	14.6–25.7	0	.5601
No exclusion of other risk factors for hearing loss[77–83]	8.2	6.5–10	0	.7938

retrospectively by PCR on DBS. In both groups, 3 in 4 children with hearing loss had a severe to profound hearing loss in ≥1 ear. In the symptomatic group 65% had a disabling bilateral severe to profound hearing loss with the need for hearing amplification and rehabilitation. In the asymptomatic group, 42.6% of hearing-impaired children had bilateral severe to profound hearing loss.

The hearing loss caused by cCMV infection has an exclusively sensorineural character. Its pathogenesis is poorly understood. Most studies describe injuries to endolymphatic structures and the stria vascularis that may cause potassium imbalance and subsequent degeneration of the sensory structures.[90,91] Some authors attribute hearing loss to the cytopathic effect of the virus itself and the host immune response on inner ear structures.[92–96] Regarding a possible delayed onset of hearing loss, percentages in the literature range from 0% to 50%.[3,24,27,66,67] We calculated ∼18% in the symptomatic group and ∼9% in the asymptomatic group, but in both groups there was significant heterogeneity between studies. This was also the case for progression and fluctuation of hearing loss. Part of the heterogeneity in delayed onset probably results from the fact that the first studies of cCMV and hearing loss date from the period before the implementation of universal neonatal hearing screening (UNHS), so that the onset of hearing loss could not be determined exactly. Furthermore, in this population middle ear problems and testing difficulties are important confounders, despite the fact that we tried to control for these confounding factors when selecting articles. The mechanisms behind delayed onset, progression, and fluctuation have not been elucidated. Like other herpesviruses, CMV establishes latency after primary infection. It is hypothesized that viral reactivation and localized host inflammatory responses to reactivation might play a role.[92–96]

Because of the high heterogeneity and low *P* values, the exact percentages for delayed onset, progression, and fluctuation are hard to define. It is important to inform the parents that hearing loss in cCMV can be delayed in onset and might progress and fluctuate over varying time frames. It is also important to realize that UNHS is not an absolute safeguard. This along with the unstable nature of the hearing loss makes longitudinal audiologic follow-up of children with cCMV infection mandatory. Delayed-onset hearing loss usually occurs before 6 years of age, mainly in the first year after birth, but hearing loss at older ages is reported occasionally.[3,24,65,67,69,97,98] Most authors suggest follow-up until the age of 6 years.[3,49,99,100] The risk of hearing loss does not vary between primary and nonprimary infections. Nonprimary infections usually result in an asymptomatic infection. The incidence of hearing loss in the nonprimary group therefore is comparable to the incidence of hearing loss in the asymptomatic group.

In our meta-analysis, we found a high I^2 for each parameter of hearing loss we investigated, despite strict selection criteria for the inclusion of articles. The high rate for I^2 indicates that most of the variability across studies results from heterogeneity rather than chance. Using strict eligibility criteria for studies selected, we tried to obtain high study quality and low heterogeneity, but some limitations exist. Baseline measurements were not always provided, and time points for collecting outcomes and method of measuring outcomes differed between studies. Most striking was the variability in defining symptomatic cCMV, the main indicator of permanent disabilities. A clear definition is crucial if we want to analyze and compare the results of different studies. The global study quality of selected studies was deemed to be moderate to good. With this systematic selection, the most appropriate articles to represent hearing outcomes in cCMV infection were included.

Regarding the importance of cCMV-related hearing loss in the total population of children with SNHL, we calculated that 1 in 10 hearing-impaired children has cCMV-related hearing loss. When known risk factors or causes of hearing loss are excluded, cCMV is the cause of hearing loss in 1 out of 5 children. Quantitative PCR assays have not been standardized across laboratories, which makes comparison of data from different studies difficult. When relying on a DBS test, we also have to consider that viral DNA levels are lower in peripheral neonatal blood than in urine or saliva.[98,101,102] It is possible that viremia had not yet occurred at the time of sampling.[103] Moreover, as mentioned earlier, length of storage of the DBS might decrease the apparent viral load.[104] These factors might lead to

underestimation of the role of cCMV. Therefore, this retrospective approach suggests an important etiological role for cCMV in hearing loss in childhood.

We did not focus on risk factors for hearing loss in our systematic review. Much research has already been done on that subject, but it remains controversial. Symptomatic infection; disseminated disease, especially with petechiae and intrauterine growth retardation; and a high viral load at birth seem to be associated with hearing loss.[75,105–107] Identification of risk factors might be helpful for a more directed and rigorous follow-up of infants at risk for hearing loss. Furthermore, it might decrease the number of dropouts in longitudinal follow-up of asymptomatic infants. Accurate prospective longitudinal studies would also help reveal the full spectrum of cCMV disease and identify such risk factors.

The absence of specific medical interventions for seronegative mothers and uncertainty about fetal prognosis has discouraged routine maternal antibody screening. To date, universal systematic screening of newborns for cCMV has not been implemented. Recent screening techniques such as PCR on urine, saliva, or blood are potentially simple, low-cost methods that could be used in future newborn screening programs.[50,55,108] In our center an ongoing prospective study is comparing sensitivity and specificity between PCR on DBS and urine culture. At present urine or saliva culture, with or without PCR, remains the gold standard. A systematic screening together with UNHS could identify the most suitable candidates for antiviral therapy. Currently, antiviral treatment with ganciclovir or valganciclovir is recommended only for symptomatic newborns with severe symptomatic focal organ disease or central nervous system involvement.[109–112] The remainder could be enrolled in a longitudinal follow-up program to detect delayed-onset or progressive hearing loss and other developmental delays. Early detection of hearing loss leads to early intervention and better patient outcomes.[113,114]

Prevention strategies, such as CMV vaccination or passive immunization with hyperimmune globulin, are currently subjected to clinical trials but are not yet in clinical use. Preliminary results are promising, but currently there are insufficient data to support the use of prenatal interventions.[115–117] Preconceptional seroimmunity provides only partial protection against newborn disease and adverse outcomes. Infected infants born to seroimmune mothers are not completely protected from SNHL, but their hearing loss is often milder and less frequently bilateral.[4,25,28,29] Increasing awareness of cCMV infection and implementing behavioral measures such as frequent hand-washing after exposure to young children's body fluids and avoiding intimate contact with young children for all prospective mothers remain the most important preventive strategies.

CONCLUSIONS

This systematic review confirms the important role of cCMV in childhood SNHL. However, because of the lack of systematic screening for cCMV in newborns and the characteristics of the disease, underestimation of its role in hearing loss is likely. Despite the threefold lower prevalence of hearing loss in asymptomatic cCMV, the numerous asymptomatic cases mean that this group is an important component of the group of hearing-impaired children. There is no pathognomonic configuration of hearing loss caused by cCMV. Rather, it is characterized by its unstable nature, with progression and fluctuations. Delayed-onset hearing loss is not uncommon. Long-term audiological follow-up for $\geq$6 years is strongly recommended. Systematic screening could identify the most suitable candidates for therapy, and the remainder could be enrolled in a longitudinal follow-up program to detect delayed-onset hearing loss.

Until a CMV vaccine becomes available, behavioral and educational interventions are the most effective strategy to prevent maternal CMV infection.[118–120] The high incidence and the devastating morbidity associated with cCMV emphasize the importance of preventive measures and of clinical research on prenatal and postnatal interventions. There is still a lot of work to do, but with this systematic review we hope to increase awareness of the cCMV disease burden.

REFERENCES

1. Medearis DN Jr. Viral infections during pregnancy and abnormal human development. *Am J Obstet Gynecol*. 1964;90 (suppl):1140–1148
2. Grosse SD, Ross DS, Dollard SC. Congenital cytomegalovirus (CMV) infection as a cause of permanent bilateral hearing loss: a quantitative assessment. *J Clin Virol*. 2008;41(2): 57–62
3. Fowler KB, Dahle AJ, Boppana SB, Pass RF. Newborn hearing screening: will children with hearing loss caused by congenital cytomegalovirus infection be missed? *J Pediatr*. 1999;135(1):60–64
4. Dollard SC, Grosse SD, Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. *Rev Med Virol*. 2007;17(5):355–363
5. Nance WE, Lim BG, Dodson KM. Importance of congenital cytomegalovirus infections as a cause for pre-lingual hearing loss. *J Clin Virol*. 2006;35(2):221–225
6. Morton CC, Nance WE. Newborn hearing screening—a silent revolution. *N Engl J Med*. 2006;354(20):2151–2164

7. Declau F, Boudewyns A, Van den Ende J, Peeters A, van den Heyning P. Etiologic and audiologic evaluations after universal neonatal hearing screening: analysis of 170 referred neonates. *Pediatrics*. 2008; 121(6):1119–1126
8. Saigal S, Lunyk O, Larke RP, Chernesky MA. The outcome in children with congenital cytomegalovirus infection. A longitudinal follow-up study. *Am J Dis Child*. 1982;136 (10):896–901
9. Stagno S, Pass RF, Dworsky ME, Alford CA Jr. Maternal cytomegalovirus infection and perinatal transmission. *Clin Obstet Gynecol*. 1982;25(3):563–576
10. Demmler GJ. Infectious Diseases Society of America and Centers for Disease Control. Summary of a workshop on surveillance for congenital cytomegalovirus disease. *Rev Infect Dis*. 1991;13(2):315–329
11. Hagay ZJ, Biran G, Ornoy A, Reece EA. Congenital cytomegalovirus infection: a long-standing problem still seeking a solution. *Am J Obstet Gynecol*. 1996;174(1 pt 1): 241–245
12. Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. *Rev Med Virol*. 2007;17(4):253–276
13. Ludwig A, Hengel H. Epidemiological impact and disease burden of congenital cytomegalovirus infection in Europe. *Euro Surveill*. 2009;14(9):26–32
14. Dollard SC, Schleiss MR, Grosse SD. Public health and laboratory considerations regarding newborn screening for congenital cytomegalovirus. *J Inherit Metab Dis*. 2010;33(suppl 2):S249–S254
15. Tookey PA, Ades AE, Peckham CS. Cytomegalovirus prevalence in pregnant women: the influence of parity. *Arch Dis Child*. 1992;67 (7 spec no):779–783
16. Mustakangas P, Sarna S, Ammälä P, Muttilainen M, Koskela P, Koskiniemi M. Human cytomegalovirus seroprevalence in three socioeconomically different urban areas during the first trimester: a population-based cohort study. *Int J Epidemiol*. 2000;29 (3):587–591
17. Gaytant MA, Galama JM, Semmekrot BA, et al. The incidence of congenital cytomegalovirus infections in The Netherlands. *J Med Virol*. 2005;76(1):71–75
18. Stagno S. Cytomegalovirus infection: a pediatrician's perspective. *Curr Probl Pediatr*. 1986;16(11):629–667
19. Cannon MJ, Schmid DS, Hyde TB. Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection. *Rev Med Virol*. 2010;20(4):202–213
20. Gaytant MA, Steegers EA, Semmekrot BA, Merkus HM, Galama JM. Congenital cytomegalovirus infection: review of the epidemiology and outcome. *Obstet Gynecol Surv*. 2002;57(4):245–256
21. Cannon MJ, Hyde TB, Schmid DS. Review of cytomegalovirus shedding in bodily fluids and relevance to congenital cytomegalovirus infection. *Rev Med Virol*. 2011;21(4):240–255
22. Harris S, Ahlfors K, Ivarsson S, Lernmark B, Svanberg L. Congenital cytomegalovirus infection and sensorineural hearing loss. *Ear Hear*. 1984;5(6):352–355
23. Yow MD, Williamson DW, Leeds LJ, et al. Epidemiologic characteristics of cytomegalovirus infection in mothers and their infants. *Am J Obstet Gynecol*. 1988; 158(5):1189–1195
24. Williamson WD, Demmler GJ, Percy AK, Catlin FI. Progressive hearing loss in infants with asymptomatic congenital cytomegalovirus infection. *Pediatrics*. 1992; 90(6):862–866
25. Fowler KB, Stagno S, Pass RF, Britt WJ, Boll TJ, Alford CA. The outcome of congenital cytomegalovirus infection in relation to maternal antibody status. *N Engl J Med*. 1992;326(10):663–667
26. Casteels A, Naessens A, Gordts F, De Catte L, Bougatef A, Foulon W. Neonatal screening for congenital cytomegalovirus infections. *J Perinat Med*. 1999;27(2):116–121
27. Ahlfors K, Ivarsson SA, Harris S. Report on a long-term study of maternal and congenital cytomegalovirus infection in Sweden. Review of prospective studies available in the literature. *Scand J Infect Dis*. 1999;31(5): 443–457
28. Ross SA, Fowler KB, Ashrith G, et al. Hearing loss in children with congenital cytomegalovirus infection born to mothers with preexisting immunity. *J Pediatr*. 2006; 148(3):332–336
29. Yamamoto AY, Mussi-Pinhata MM, Isaac ML, et al. Congenital cytomegalovirus infection as a cause of sensorineural hearing loss in a highly immune population. *Pediatr Infect Dis J*. 2011;30(12):1043–1046
30. de Vries JJ, van Zwet EW, Dekker FW, Kroes AC, Verkerk PH, Vossen AC. The apparent paradox of maternal seropositivity as a risk factor for congenital cytomegalovirus infection: a population-based prediction model. *Rev Med Virol*. 2013;23(4): 241–249
31. Picone O, Vauloup-Fellous C, Cordier AG, et al. A series of 238 cytomegalovirus primary infections during pregnancy: description and outcome. *Prenat Diagn*. 2013;33(8):751–758
32. Bodéus M, Kabamba-Mukadi B, Zech F, Hubinont C, Bernard P, Goubau P. Human cytomegalovirus in utero transmission: follow-up of 524 maternal seroconversions. *J Clin Virol*. 2010;47(2):201–202
33. Pass RF, Stagno S, Myers GJ, Alford CA. Outcome of symptomatic congenital cytomegalovirus infection: results of long-term longitudinal follow-up. *Pediatrics*. 1980;66(5):758–762
34. Kylat RI, Kelly EN, Ford-Jones EL. Clinical findings and adverse outcome in neonates with symptomatic congenital cytomegalovirus (SCCMV) infection. *Eur J Pediatr*. 2006;165(11):773–778
35. Boppana SB, Pass RF, Britt WJ, Stagno S, Alford CA. Symptomatic congenital cytomegalovirus infection: neonatal morbidity and mortality. *Pediatr Infect Dis J*. 1992;11 (2):93–99
36. Ross SA, Boppana SB. Congenital cytomegalovirus infection: outcome and diagnosis. *Semin Pediatr Infect Dis*. 2005;16(1):44–49
37. Pass RF. Congenital cytomegalovirus infection and hearing loss. *Herpes*. 2005;12 (2):50–55
38. Fowler KB, Boppana SB. Congenital cytomegalovirus (CMV) infection and hearing deficit. *J Clin Virol*. 2006;35(2):226–231
39. Yinon Y, Farine D, Yudin MH. Screening, diagnosis, and management of cytomegalovirus infection in pregnancy. *Obstet Gynecol Surv*. 2010;65(11):736–743
40. Preece PM, Pearl KN, Peckham CS. Congenital cytomegalovirus infection. *Arch Dis Child*. 1984;59(12):1120–1126
41. Arvin AM, Fast P, Myers M, Plotkin S, Rabinovich R; National Vaccine Advisory Committee. Vaccine development to prevent cytomegalovirus disease: report from the National Vaccine Advisory Committee. *Clin Infect Dis*. 2004;39(2): 233–239
42. Sculerati N. Analysis of a cohort of children with sensory hearing loss using the SCALE systematic nomenclature. *Laryngoscope*. 2000;110(5 pt 1):787–798
43. Bonfils P, François M, Aidan D, et al. Deafness in the neonatal period: basis for screening [in French]. *Arch Pediatr*. 1995;2 (7):685–691
44. Das VK. Aetiology of bilateral sensorineural hearing impairment in children: a 10 year study. *Arch Dis Child*. 1996;74(1):8–12
45. Ohlms LA, Chen AY, Stewart MG, Franklin DJ. Establishing the etiology of childhood hearing loss. *Otolaryngol Head Neck Surg*. 1999;120(2):159–163
46. Hicks T, Fowler K, Richardson M, Dahle A, Adams L, Pass R. Congenital cytomegalovirus infection and neonatal auditory screening. *J Pediatr*. 1993;123(5):779–782

47. Barbi M, Binda S, Caroppo S, Ambrosetti U, Corbetta C, Sergi P. A wider role for congenital cytomegalovirus infection in sensorineural hearing loss. *Pediatr Infect Dis J.* 2003;22(1):39–42
48. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ.* 2009;339(1): b2535
49. Kadambari S, Williams EJ, Luck S, Griffiths PD, Sharland M. Evidence based management guidelines for the detection and treatment of congenital CMV. *Early Hum Dev.* 2011;87(11):723–728
50. Balcarek KB, Warren W, Smith RJ, Lyon MD, Pass RF. Neonatal screening for congenital cytomegalovirus infection by detection of virus in saliva. *J Infect Dis.* 1993; 167(6):1433–1436
51. Melish ME, Hanshaw JB. Congenital cytomegalovirus infection. Developmental progress of infants detected by routine screening. *Am J Dis Child.* 1973;126(2):190–194
52. Stagno S, Pass RF, Reynolds DW, Moore MA, Nahmias AJ, Alford CA. Comparative study of diagnostic procedures for congenital cytomegalovirus infection. *Pediatrics.* 1980;65(2):251–257
53. Shibata M, Takano H, Hironaka T, Hirai K. Detection of human cytomegalovirus DNA in dried newborn blood filter paper. *J Virol Methods.* 1994;46(2):279–285
54. Barbi M, Binda S, Caroppo S. Diagnosis of congenital CMV infection via dried blood spots. *Rev Med Virol.* 2006;16(6):385–392
55. Boppana SB, Ross SA, Novak Z, et al; National Institute on Deafness and Other Communication Disorders CMV and Hearing Multicenter Screening (CHIMES) Study. Dried blood spot real-time polymerase chain reaction assays to screen newborns for congenital cytomegalovirus infection. *JAMA.* 2010;303(14):1375–1382
56. Barbi M, MacKay WG, Binda S, van Loon AM. External quality assessment of cytomegalovirus DNA detection on dried blood spots. *BMC Microbiol.* 2008;8:2
57. Soetens O, Vauloup-Fellous C, Foulon I, et al. Evaluation of different cytomegalovirus (CMV) DNA PCR protocols for analysis of dried blood spots from consecutive cases of neonates with congenital CMV infections. *J Clin Microbiol.* 2008;46(3): 943–946
58. Barbi M, Binda S, Primache V, Luraschi C, Corbetta C. Diagnosis of congenital cytomegalovirus infection by detection of viral DNA in dried blood spots. *Clin Diagn Virol.* 1996;6(1):27–32
59. Johansson PJ, Jönsson M, Ahlfors K, Ivarsson SA, Svanberg L, Guthenberg C. Retrospective diagnostics of congenital cytomegalovirus infection performed by polymerase chain reaction in blood stored on filter paper. *Scand J Infect Dis.* 1997;29(5): 465–468
60. Atkinson C, Walter S, Sharland M, et al. Use of stored dried blood spots for retrospective diagnosis of congenital CMV. *J Med Virol.* 2009;81(8):1394–1398
61. Scanga L, Chaing S, Powell C, et al. Diagnosis of human congenital cytomegalovirus infection by amplification of viral DNA from dried blood spots on perinatal cards. *J Mol Diagn.* 2006;8(2):240–245
62. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. *JAMA.* 2000; 283(15):2008–2012
63. Barbi M, Binda S, Primache V, Clerici D; NEOCMV Group. Congenital cytomegalovirus infection in a northern Italian region. *Eur J Epidemiol.* 1998;14(8):791–796
64. Mussi-Pinhata MM, Yamamoto AY, Moura Brito RM, et al. Birth prevalence and natural history of congenital cytomegalovirus infection in a highly seroimmune population. *Clin Infect Dis.* 2009;49(4):522–528
65. Numazaki K, Fujikawa T. Chronological changes of incidence and prognosis of children with asymptomatic congenital cytomegalovirus infection in Sapporo, Japan. *BMC Infect Dis.* 2004;4:22
66. Foulon I, Naessens A, Foulon W, Casteels A, Gordts F. A 10-year prospective study of sensorineural hearing loss in children with congenital cytomegalovirus infection. *J Pediatr.* 2008;153(1):84–88
67. Dahle AJ, Fowler KB, Wright JD, Boppana SB, Britt WJ, Pass RF. Longitudinal investigation of hearing disorders in children with congenital cytomegalovirus. *J Am Acad Audiol.* 2000;11(5):283–290
68. Madden C, Wiley S, Schleiss M, et al. Audiometric, clinical and educational outcomes in a pediatric symptomatic congenital cytomegalovirus (CMV) population with sensorineural hearing loss. *Int J Pediatr Otorhinolaryngol.* 2005;69(9): 1191–1198
69. Foulon I, Naessens A, Faron G, Foulon W, Jansen AC, Gordts F. Hearing thresholds in children with a congenital CMV infection: a prospective study. *Int J Pediatr Otorhinolaryngol.* 2012;76(5):712–717
70. Royackers L, Rector E, Verhaert N, Desloovere C. Long-term audiological follow-up of children with congenital cytomegalovirus. *B-ENT.* 2013;9(suppl 21): 57–64
71. Capretti MG, Lanari M, Tani G, et al. Role of cerebral ultrasound and magnetic resonance imaging in newborns with congenital cytomegalovirus infection. *Brain Dev.* 2014;36(3):203–211
72. Foulon I, Naessens A, Foulon W, Casteels A, Gordts F. Hearing loss in children with congenital cytomegalovirus infection in relation to the maternal trimester in which the maternal primary infection occurred. *Pediatrics.* 2008;122(6). Available at: www.pediatrics.org/cgi/content/full/122/6/e1123
73. Barbi M, Binda S, Caroppo S, et al. Multicity Italian study of congenital cytomegalovirus infection. *Pediatr Infect Dis J.* 2006; 25(2):156–159
74. Ogawa H, Suzutani T, Baba Y, et al. Etiology of severe sensorineural hearing loss in children: independent impact of congenital cytomegalovirus infection and GJB2 mutations. *J Infect Dis.* 2007;195(6):782–788
75. Walter S, Atkinson C, Sharland M, et al. Congenital cytomegalovirus: association between dried blood spot viral load and hearing loss. *Arch Dis Child Fetal Neonatal Ed.* 2008;93(4):F280–F285
76. Karltorp E, Hellström S, Lewensohn-Fuchs I, Carlsson-Hansén E, Carlsson PI, Engman ML. Congenital cytomegalovirus infection: a common cause of hearing loss of unknown aetiology. *Acta Paediatr.* 2012;101 (8):e357–e362
77. Stehel EK, Shoup AG, Owen KE, et al. Newborn hearing screening and detection of congenital cytomegalovirus infection. *Pediatrics.* 2008;121(5):970–975
78. Boudewyns A, Declau F, Smets K, et al. Cytomegalovirus DNA detection in Guthrie cards: role in the diagnostic work-up of childhood hearing loss. *Otol Neurotol.* 2009;30(7):943–949
79. Korver AMH, de Vries JJC, Konings S, et al; DECIBEL collaborative study group. DECIBEL study: congenital cytomegalovirus infection in young children with permanent bilateral hearing impairment in the Netherlands. *J Clin Virol.* 2009;46 (suppl 4):S27–S31
80. Tagawa M, Tanaka H, Moriuchi M, Moriuchi H. Retrospective diagnosis of congenital cytomegalovirus infection at a school for the deaf by using preserved dried umbilical cord. *J Pediatr.* 2009;155 (5):749–751
81. Kimani JW, Buchman CA, Booker JK, et al. Sensorineural hearing loss in a pediatric

population: association of congenital cytomegalovirus infection with intracranial abnormalities. *Arch Otolaryngol Head Neck Surg*. 2010;136(10):999–1004

82. Misono S, Sie KC, Weiss NS, et al. Congenital cytomegalovirus infection in pediatric hearing loss. *Arch Otolaryngol Head Neck Surg*. 2011;137(1):47–53
83. Avettand-Fenoël V, Marlin S, Vauloup-Fellous C, et al. Congenital cytomegalovirus is the second most frequent cause of bilateral hearing loss in young French children. *J Pediatr*. 2013;162(3):593–599
84. Furutate S, Iwasaki S, Nishio SY, Moteki H, Usami S. Clinical profile of hearing loss in children with congenital cytomegalovirus (CMV) infection: CMV DNA diagnosis using preserved umbilical cord. *Acta Otolaryngol*. 2011;131(9):976–982
85. Teek R, Kruustük K, Žordania R, et al. Hearing impairment in Estonia: an algorithm to investigate genetic causes in pediatric patients. *Adv Med Sci*. 2013;58(2):419–428
86. Lanzieri TM, Dollard SC, Bialek SR, Grosse SD. Systematic review of the birth prevalence of congenital cytomegalovirus infection in developing countries. *Int J Infect Dis*. 2014;22:44–48
87. Rutter D, Griffiths P, Trompeter RS. Cytomegalic inclusion disease after recurrent maternal infection. *Lancet*. 1985;2(8465):1182
88. Boppana SB, Fowler KB, Britt WJ, Stagno S, Pass RF. Symptomatic congenital cytomegalovirus infection in infants born to mothers with preexisting immunity to cytomegalovirus. *Pediatrics*. 1999;104(1 pt 1):55–60
89. Daniel Y, Gull I, Peyser MR, Lessing JB. Congenital cytomegalovirus infection. *Eur J Obstet Gynecol Reprod Biol*. 1995;63(1):7–16
90. Teissier N, Delezoide AL, Mas AE, et al. Inner ear lesions in congenital cytomegalovirus infection of human fetuses. *Acta Neuropathol*. 2011;122(6):763–774
91. Gabrielli L, Bonasoni MP, Santini D, et al. Human fetal inner ear involvement in congenital cytomegalovirus infection. *Acta Neuropathol Commun*. 2013;1(1):63
92. Stagno S, Reynolds DW, Amos CS, et al. Auditory and visual defects resulting from symptomatic and subclinical congenital cytomegaloviral and toxoplasma infections. *Pediatrics*. 1977;59(5):669–678
93. Keithley EM, Woolf NK, Harris JP. Development of morphological and physiological changes in the cochlea induced by cytomegalovirus. *Laryngoscope*. 1989;99(4):409–414
94. Strauss M. Human cytomegalovirus labyrinthitis. *Am J Otolaryngol*. 1990;11(5):292–298
95. Fowler KB, McCollister FP, Dahle AJ, Boppana S, Britt WJ, Pass RF. Progressive and fluctuating sensorineural hearing loss in children with asymptomatic congenital cytomegalovirus infection. *J Pediatr*. 1997;130(4):624–630
96. Noyola DE, Demmler GJ, Williamson WD, et al; Congenital CMV Longitudinal Study Group. Cytomegalovirus urinary excretion and long term outcome in children with congenital cytomegalovirus infection. *Pediatr Infect Dis J*. 2000;19(6):505–510
97. Royackers L, Christian D, Frans D, Ermelinde R. Hearing status in children with congenital cytomegalovirus: up-to-6-years audiological follow-up. *Int J Pediatr Otorhinolaryngol*. 2011;75(3):376–382
98. Rosenthal LS, Fowler KB, Boppana SB, et al. Cytomegalovirus shedding and delayed sensorineural hearing loss: results from longitudinal follow-up of children with congenital infection. *Pediatr Infect Dis J*. 2009;28(6):515–520
99. Fowler KB. Congenital cytomegalovirus infection: audiologic outcome. *Clin Infect Dis*. 2013;57(suppl 4):S182–S184
100. Lombardi G, Garofoli F, Stronati M. Congenital cytomegalovirus infection: treatment, sequelae and follow-up. *J Matern Fetal Neonatal Med*. 2010;23(suppl 3):45–48
101. Halwachs-Baumann G, Genser B, Pailer S, et al. Human cytomegalovirus load in various body fluids of congenitally infected newborns. *J Clin Virol*. 2002;25(suppl 3):S81–S87
102. Inoue N, Koyano S. Evaluation of screening tests for congenital cytomegalovirus infection. *Pediatr Infect Dis J*. 2008;27(2):182–184
103. Bradford RD, Cloud G, Lakeman AD, et al; National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Detection of cytomegalovirus (CMV) DNA by polymerase chain reaction is associated with hearing loss in newborns with symptomatic congenital CMV infection involving the central nervous system. *J Infect Dis*. 2005;191(2):227–233
104. DePasquale JM, Freeman K, Amin MM, et al. Efficient linking of birth certificate and newborn screening databases for laboratory investigation of congenital cytomegalovirus infection and preterm birth: Florida, 2008. *Matern Child Health J*. 2012;16(2):486–494
105. Ross SA, Novak Z, Fowler KB, Arora N, Britt WJ, Boppana SB. Cytomegalovirus blood viral load and hearing loss in young children with congenital infection. *Pediatr Infect Dis J*. 2009;28(7):588–592
106. Rivera LB, Boppana SB, Fowler KB, Britt WJ, Stagno S, Pass RF. Predictors of hearing loss in children with symptomatic congenital cytomegalovirus infection. *Pediatrics*. 2002;110(4):762–767
107. Lanari M, Lazzarotto T, Venturi V, et al. Neonatal cytomegalovirus blood load and risk of sequelae in symptomatic and asymptomatic congenitally infected newborns. *Pediatrics*. 2006;117(1). Available at: www.pediatrics.org/cgi/content/full/117/1/e76
108. de Vries JJ, Vossen AC, Kroes AC, van der Zeijst BA. Implementing neonatal screening for congenital cytomegalovirus: addressing the deafness of policy makers. *Rev Med Virol*. 2011;21(1):54–61
109. Kimberlin DW, Lin CY, Sánchez PJ, et al; National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. *J Pediatr*. 2003;143(1):16–25
110. Smets K, De Coen K, Dhooge I, et al. Selecting neonates with congenital cytomegalovirus infection for ganciclovir therapy. *Eur J Pediatr*. 2006;165(12):885–890
111. Amir J, Wolf DG, Levy I. Treatment of symptomatic congenital cytomegalovirus infection with intravenous ganciclovir followed by long-term oral valganciclovir. *Eur J Pediatr*. 2010;169(9):1061–1067
112. Stronati M, Lombardi G, Garofoli F, Villani P, Regazzi M. Pharmacokinetics, pharmacodynamics and clinical use of valganciclovir in newborns with symptomatic congenital cytomegalovirus infection. *Curr Drug Metab*. 2013;14(2):208–215
113. Robinshaw HM. Early intervention for hearing impairment: differences in the timing of communicative and linguistic development. *Br J Audiol*. 1995;29(6):315–334
114. Yoshinaga-Itano C. Early intervention after universal neonatal hearing screening: impact on outcomes. *Ment Retard Dev Disabil Res Rev*. 2003;9(4):252–266
115. Nigro G, Adler SP, La Torre R, Best AM; Congenital Cytomegalovirus Collaborating Group. Passive immunization during pregnancy for congenital cytomegalovirus infection. *N Engl J Med*. 2005;353(13):1350–1362
116. McCarthy FP, Giles ML, Rowlands S, Purcell KJ, Jones CA. Antenatal interventions for

preventing the transmission of cytomegalovirus (CMV) from the mother to fetus during pregnancy and adverse outcomes in the congenitally infected infant. *Cochrane Database Syst Rev.* 2011;(3):CD008371

117. Revello MG, Lazzarotto T, Guerra B, et al; CHIP Study Group. A randomized trial of hyperimmune globulin to prevent congenital cytomegalovirus. *N Engl J Med.* 2014;370(14):1316–1326
118. Adler SP, Finney JW, Manganello AM, Best AM. Prevention of child-to-mother transmission of cytomegalovirus by changing behaviors: a randomized controlled trial. *Pediatr Infect Dis J.* 1996;15(3):240–246
119. Vauloup-Fellous C, Picone O, Cordier AG, et al. Does hygiene counseling have an impact on the rate of CMV primary infection during pregnancy? Results of a 3-year prospective study in a French hospital. *J Clin Virol.* 2009;46(suppl 4):S49–S53
120. Bate SL, Cannon MJ. A social marketing approach to building a behavioral intervention for congenital cytomegalovirus. *Health Promot Pract.* 2011;12(3):349–360

HIDE AND SEEK: *When the kids were little, we used to play hide and seek all the time. There were innumerable hiding places around the house and yard, and we always had a great time. In the oceans, hide and seek has a different and much more serious context. Fish are hiding from other fish; if found, they are often eaten. Fish in coastal waters try to avoid this by using camouflage, blending into sand, rocks, and plants, or hiding among coral and kelp. However, in the middle of the ocean, there are no places to hide. Fish in these areas (particularly small fish) have to hide in plain sight.*

As reported in The New York Times *(Science: August 19, 2014), some fish living in the middle of the ocean have evolved clever ways to go unseen. Their bodies have a density and refraction index that is so similar to their watery environment that light actually passes through them, making them almost invisible. One problem with this transparency is that there is no protection from the sun, which can not only burn the external structures but internal organs as well. Secretions – similar to suntan lotions – protect them from the sun, but then they are no longer invisible to predators that can detect ultraviolet light.*

Terrestrial animals, of course, are unlikely to ever become transparent because they are so much denser than air and have a significantly different refraction index. As for me, I have no reason to become invisible. I want my family to be able to find me when I am home and I don't believe there are predators in my neighborhood that are trying to dine on me.

Noted by WVR, MD

Hearing Loss and Congenital CMV Infection: A Systematic Review

Julie Goderis, Els De Leenheer, Koenraad Smets, Helen Van Hoecke, Annelies Keymeulen and Ingeborg Dhooge

Pediatrics 2014;134;972; originally published online October 27, 2014;
DOI: 10.1542/peds.2014-1173

Hearing Loss and Congenital CMV Infection: A Systematic Review

J. Goderis

Nederlandse samenvatting

Congenitale CMV (cCMV) infectie is de meest voorkomende congenitale infectie en is de belangrijkste oorzaak van niet-erfelijk neurosensorieel gehoorverlies in de ontwikkelde landen bij jonge kinderen. Wereldwijd worden 0.2-2.5% van alle neonaten geboren met een cCMV infectie, in geïndustrialiseerde landen is er een gemiddelde prevalentie van 0.64-0.7%. Verspreiding van CMV gebeurt door contact met geïnfecteerd lichaamsvocht. Kinderen tussen 1 en 2 jaar zijn de belangrijkste besmettingsbron voor zwangere vrouwen. De kans op verticale transmissie bij een CMV infectie van de zwangere vrouw is 32% voor een primo-infectie en 1.4% voor een niet-primaire infectie door reactivatie van een latent virus of reinfectie met een nieuwe streng.

Het doel van deze review was om de prevalentie van cCMV in kaart te brengen, de eigenschappen van het gehoorverlies door cCMV infectie te definiëren en om retrograad het belang na te gaan van cCMV-geassocieerd gehoorverlies bij slechthorende kinderen. We baseerden ons hiervoor op de literatuur van de afgelopen 50 jaar. Er werd een systematisch literatuur onderzoek verricht volgens de PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. In totaal werden 101 artikels in detail gelezen en 37 relevante studies werden weerhouden voor meta-analyse. Alle artikels werden verondersteld een eenduidige definitie van cCMV infectie te hebben en een uniforme manier van diagnose.

De geselecteerde artikels werden vervolgens opgedeeld volgens drie verschillende benaderingen. Via de Kwantitatieve Analyse werd beoogd om de prevalentie van cCMV-geassocieerd gehoorverlies te bepalen op populatieniveau. Daarvoor werden studies geselecteerd die vertrokken van een universele screening van pasgeborenen voor een cCMV infectie gedurende een gegeven periode.

Het doel van de Kwalitatieve Analyse was om specifieke karakteristieken van cCMV geassocieerd gehoorverlies in kaart te brengen. Hiervoor werden studies geselecteerd met longitudinale audiologische follow-up bij kinderen gediagnosticeerd via universele screening van pasgeborenen en kinderen gediagnosticeerd door gekende

seroconversie bij de moeder tijdens de zwangerschap of suggestieve klinische symptomen bij geboorte, om de aantallen met kwalitatieve audiologische follow-up te verhogen. Door niet alleen met studies te werken die vertrekken van uit een universele screening van pasgeborenen voor cCMV, is er een overrepresentatie van symptomatische kinderen. Om dit te counteren werden de karakteristieken van het gehoorverlies apart geanalyseerd voor symptomatische en asymptomatische kinderen. Een bijkomend doel was om het verschil na te gaan in gehoorverlies bij een primaire en non-primaire infectie.

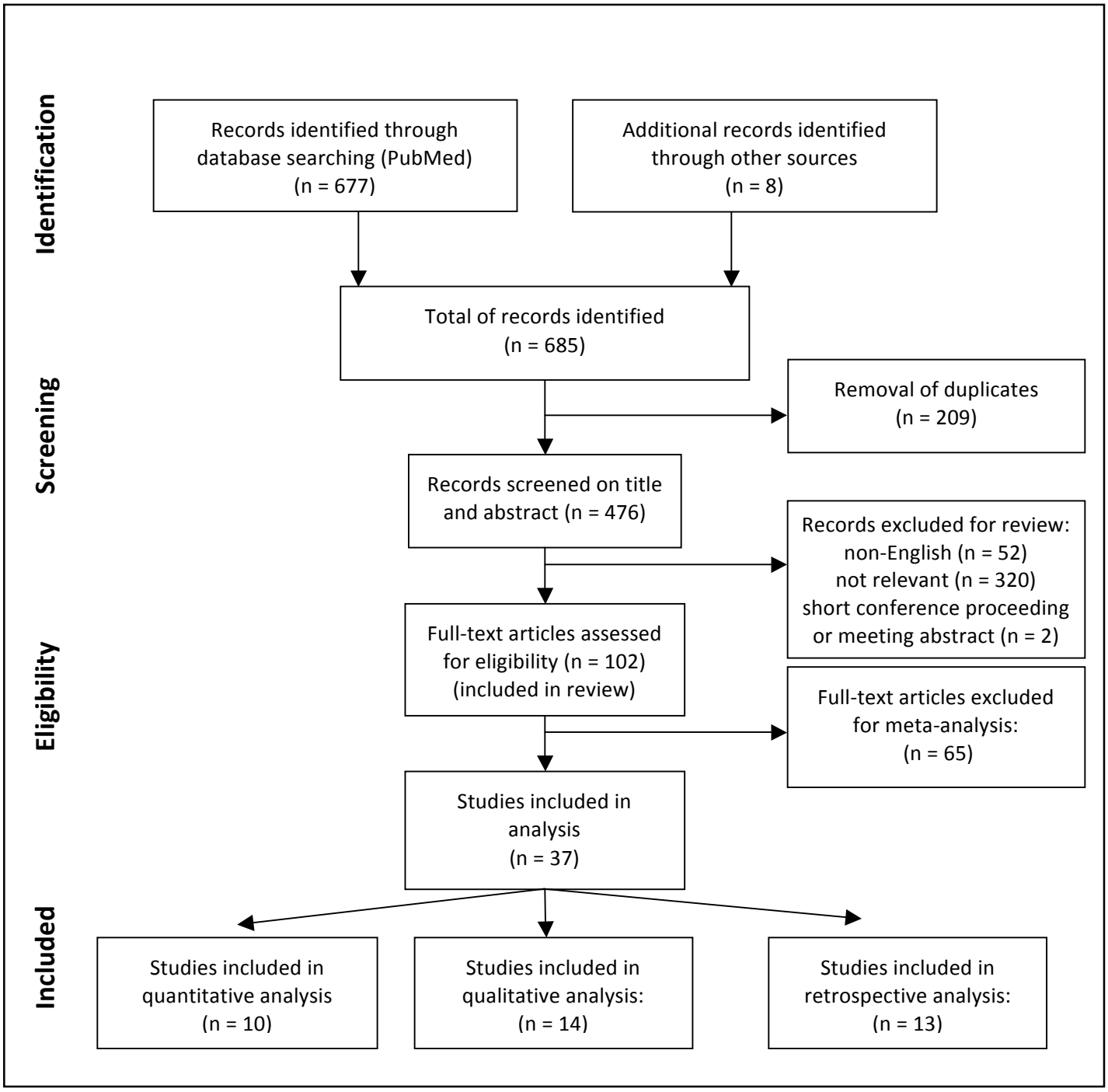
Om het belang na te gaan van cCMV infectie bij slechthorende kinderen, werden in de Retrospectieve Benadering studies geselecteerd die op een retrospectieve manier cCMV diagnosticeerden aan de hand van PCR voor CMV-DNA op Guthriekaartjes of op gedroogde navelstrengen.

Uit de Kwantitatieve Analyse bleek een algemene prevalentie van 0.58% van cCMV infectie onder alle gescreende pasgeborenen. Onder de kinderen met cCMV infectie waren er 9.8% symptomatisch, de overige 90.2% waren asymptomatisch. Gehoorverlies werd bij 32.8% van de symptomatische kinderen en bij 9.9% van de asymptomatische kinderen vastgesteld. In het algemeen kwam gehoorverlies voor bij 12.6% van de kinderen met een cCMV infectie. De incidentie van gehoorverlies door cCMV infectie in de populatie werd geschat op 0.5 op 1000 kinderen.

De Kwalitatieve Analyse toonde aan dat gehoorverlies in de symptomatische groep voornamelijk bilateraal was, namelijk in 71.2% van de gevallen. De meerderheid van symptomatische kinderen met gehoorverlies had een ernstig tot zeer ernstig gehoorverlies. Daarenboven had 65.1% een bilateraal ernstig tot zeer ernstig gehoorverlies met noodzaak aan gehoorversterking en revalidatie. Van alle symptomatische kinderen met gehoorverlies was er bij 18.1% een delayed-onset van het gehoorverlies. In de asymptomatische groep was het gehoorverlies unilateraal in 56.9%. De meerderheid was eveneens een ernstig tot zeer ernstig gehoorverlies maar het percentage kinderen met een bilateraal ernstig tot zeer ernstig gehoorverlies was minder dan de symptomatische groep, namelijk 42.6%. In geval van gehoorverlies in de asymptomatische groep, was er bij 9% een gehoorverlies met delayed-onset. De impact van sero-immuniteit op het gehoor werd eveneens nagekeken. Gehoorverlies trad op in 12.1% van de primaire infecties en in 11.8% van de non primaire infecties.

Uit de Retrospectieve Benadering bleek dat in een algemene groep met slechthorende kinderen er een prevalentie was van cCMV infectie van circa 8%, in een groep slechthorende kinderen met gehoorverlies van ongekende origine (met exclusie van andere risicofactoren voor gehoorverlies) was er een prevalentie van cCMV infectie van circa 20%.

Deze systematische review bevestigt de belangrijke rol van cCMV infectie in gehoorverlies bij kinderen. Ondanks dat het risico op gehoorverlies in de asymptomatische groep ongeveer 3 keer lager ligt dan in de symptomatische groep, draagt ook deze groep sterk bij tot gehoorverlies bij kinderen gezien de grote aantallen van asymptomatische kinderen. Er is geen pathognomonische configuratie van het gehoorverlies door cCMV infectie. Het wordt eerder gekarakteriseerd door zijn instabiele natuur, onderhevig aan fluctuaties, progressies en verbeteringen. Ook gehoorverlies met een delayed-onset is niet zeldzaam. Daarom adviseren we opvolging op lange termijn gedurende de eerste 6 levensjaar op zijn minst. Met een systematische screening van pasgeborenen voor cCMV infectie zouden we de mogelijkheid hebben de meest geschikte kandidaten te identificeren voor therapie en voor longitudinale follow-up. De hoge incidentie en de uitgesproken morbiditeit geassocieerd aan cCMV infectie benadrukken het belang van preventieve maatregelen en het klinisch wetenschappelijk onderzoek naar prenatale en postnatale interventies.


Identification
Records identified through database searching (PubMed) (n = 677)
Additional records identified through other sources (n = 8)
Total of records identified (n = 685)
Screening
Removal of duplicates (n = 209)
Records screened on title and abstract (n = 476)
Records excluded for review: non-English (n = 52) not relevant (n = 320) short conference proceeding or meeting abstract (n = 2)
Eligibility
Full-text articles assessed for eligibility (n = 102) (included in review)
Full-text articles excluded for meta-analysis: (n = 65)
Studies included in analysis (n = 37)
Included
Studies included in quantitative analysis (n = 10)
Studies included in qualitative analysis: (n = 14)
Studies included in retrospective analysis: (n = 13)

Hearing loss and congenital CMV infection:

a systematic review

Supplemental File 1

Julie Goderis[1], MD, Els De Leenheer[1], MD, PhD, Koenraad Smets[2], MD, PhD, Helen Van Hoecke[1], MD, PhD, Annelies Keymeulen[2], MD, Ingeborg Dhooge[1], MD, PhD

Affiliations: University Hospital Ghent, [1] Department of Otorhinolaryngology, [2] Neonatal Intensive Care Unit

Address corresponcence to: Julie Goderis, Department of Otorhinolaryngology, University Hospital Ghent, De Pintelaan 185, 9000 Ghent, Belgium, [julie.goderis@ugent.be]

Quantitative Approach

Study	Location, Time	Screening Method	Number of screened infants
Melish et al. 1973[51]	Rochester, New York 1968-1970	Urine culture	1 963
Saigal et al. 1982[8]	Ontario, Canada 1973-1976	Urine culture	15 212
Preece et al. 1984[40]	London, United Kingdom 1980-1983	Saliva and urine culture	14 200
Yow et al. 1988[23]	Houston, Texas 1981-1986	Urine culture	3 899
Barbi et al. 1998[63]	Milan, Italy 1994-1995	Saliva and urine culture	1 268
Ahlfors et al. 1999[27]	Malmö, Sweden 1977-1986	Urine culture	16 474
Fowler et al. 1999[3]	Birmingham, Alabama 1980-1996	Urine and saliva culture	40 000
Numazaki et al. 2004[65]	Sapporo, Japan 1977-2002	Urine culture	11 938
Mussi-Pinhata et al. 2009[64]	Sao Paulo, Brazil 2003-2007	Urine and saliva culture	8 047
Foulon et al. 2008[66]	Brussels, Belgium 1996-2006	Urine culture	14 021

Qualitative Approach

Study	Location, Time	Number of infants with longitudinal follow-up	Mean age of follow-up (months)
Saigal et al. 1982[8]	Ontario, Canada 1973-1976	41	43
Preece et al. 1984[40]	London, United Kingdom 1980-1983	47	36
Williamson et al. 1992[24]	Houston, Texas 1983-1989	59	n.a.
Ahlfors et al. 1999[27]	Malmö, Sweden 1977-1986	60	60
Dahle et al. 2000[67]	Birmingham, Alabama 1966-1999	860	84
Madden et al. 2005[68]	Cincinnati, Ohio (retrospective)	21	97

Kylat et al. 2006[34]	Toronto, Canada 1987-2000	42	51
Yamamoto et al. 2011[29]	Sao Paulo, Brazil 2003-2009	85	56
Foulon et al. 2012[69]	Brussels, Belgium 1995-2011	68	45
Royackers et al. 2013[70]	Leuven, Belgium 2003-2009	98	65
Capretti et al. 2013[71]	Bologna, Italy 2003-2010	40	36
Fowler et al. 1992[25]*	Birmingham, Alabama 1972-1990	189	54
Ross et al. 2006[28]*	Birmingham, Alabama 1980-2000	300	n.a.
Foulon et al. 2008[72]*	Brussels, Belgium 1996-2006	60	33

Retrospective Approach

Study	Location	Inclusion criteria	Number of subjects	PCR method	Exclusion of risk factors for HL
Barbi et al. 2006[73]	Milan, Italy	> 40dB loss in better ear	48	Nested PCR in triplicate on DBS	Yes
Ogawa et al. 2007[74]	Fukushima, Japan	Severe SNHL	67	Real time qPCR, on dried umbilical cord	Yes
Walter et al. 2007[75]	London, England	SNHL of unknown origin ≥ 20dB (PTA) en ≥ 30dB (ABR)	35	Real time qPCR in triplicate on DBS	Yes
Karltorp et al. 2012[76]	Stockholm, Sweden	Any SNHL from unknown origin (non syndromal, no family history)	45	IgG in blood, if positive nested PCR on DBS	Yes
Stehel et al. 2008[77]	Dallas, Texas	Confirmed SNHL after refer on UNHS	256	Urine culture	No
Boudewyns et al. 2009[78]	Antwerp, Belgium	Refer on UNHS Delayed HL	41 55	Real time PCR in triplicate on DBS	No
Korver et al. 2009[79]	Leiden, The Netherlands	Bilateral SNHL	179	Real Time qPCR in triplicate on DBS	No
Tagawa et al. 2009[80]	Nagasaki, Japan	Bilateral severe to profound SNHL	26	Real Time qPCR in triplicate on dried umbilical cord	No
Kimani et al. 2010[81]	Chapel Hill, North Carolina	Confirmed SNHL congenital or later onset	109	Real Time qPCR in duplicate on DBS	No
Misono et al. 2011[82]	Minnesota, Minneapolis	> 4y, SNHL > 25dB	222	Real time qPCR in triplicate on DBS	No
Avettand-Fenoël et al. 2013[83]	Paris, France	<3y, bilateral SNHL	100	Real time qPCR in 2 different labs on DBS	No
Furutate et al. 2011[84]	Matsumoto, Japan	Uni- or bilateral SNHL	134	Real time qPCR on dried umbilical cords	Partial
Teek et al. 2013[85]	Tallin, Estonia	Early onset uni- or bilateral SNHL, confirmed after UNHS	85	Real Time qPCR on DBS	Partial

Table 1. Studies comprised in meta-analysis. n.a. not available, * Only included in Qualitative approach for analysis of correlation between type of infection and hearing loss.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4 - 6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6 - 9
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6 (Fig 1)
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6 - 9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6 - 9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	N/A
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9 – 11, Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Supplemental file 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplemental file 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10 - 12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10 - 12
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12 - 15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16 - 17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097