**Cytomegalovirus - a risk factor for childhood hearing loss: a systematic review**


**Authors**

Bénédicte Vos[1,2,3], Dorie Noll[1,2], JoAnne Whittingham[2], Marie Pigeon[4], Marlene Bagatto[5], Elizabeth Fitzpatrick[1,2*]

**Affiliations**

[1] Faculty of Health Sciences, University of Ottawa, 451 Smyth Road, Ottawa, Ontario K1H 8M5, Canada.
[2] CHEO Research Institute, 401 Smyth Road, Ottawa, Ontario K1H 8L1, Canada.
[3] School of Public Health, Université libre de Bruxelles (ULB), Route de Lennik 808 CP 598, 1070 Brussels, Belgium.
[4] CHEO Audiology Department, 401 Smyth Road, Ottawa, Ontario K1H 8L1, Canada.
[5] School of Communication Sciences and Disorders and the National Centre for Audiology, Western University, 1201 Western Road, London, Ontario N6G 1H1, Canada.

**All correspondence should be addressed to**

Elizabeth Fitzpatrick:
Faculty of Health Sciences, University of Ottawa, 451 Smyth Road, Ottawa, Ontario K1H 8M5, Canada
+1 613-562-5800 ext. 4545
elizabeth.fitzpatrick@uottawa.ca



**Conflicts of interest and source of funding**

Funding from the Ministry of Children, Community and Social Services to Western University (M. Bagatto) for its work in support of the Ontario Infant Hearing Program. There are no conflicts of interest, financial, or otherwise.

# Cytomegalovirus - a risk factor for childhood hearing loss: a systematic review


## Abstract

**Context**: Permanent hearing loss is an important public health issue in children with consequences for language, social, and academic functioning. Early hearing detection, intervention, and monitoring are important in mitigating the impact of permanent childhood hearing loss. Congenital cytomegalovirus (CMV) infection is a leading cause of hearing loss.

**Objective**: To synthesize the evidence on the association between CMV infection and permanent childhood hearing loss.

**Design**: We performed a systematic review and examined scientific literature from the following databases: MEDLINE, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R), Embase, and CINAHL. The primary outcome was permanent bilateral or unilateral hearing loss with congenital onset or onset during childhood (birth to 18 years). The secondary outcome was progressive hearing loss. We included studies reporting data on CMV infection. Randomized controlled trials, quasi-experimental studies, nonrandomized comparative non-comparative studies, and case series were considered. Data were extracted and the quality of individual studies was assessed with the Qualitative Assessment Tool for Quantitative Studies (McMaster University). The quality and strength of the evidence were graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE). A narrative synthesis was completed.

**Results**: Sixty-five articles were included in the review. Prevalence of hearing loss at birth was over 33% among symptomatic CMV-infected newborns, and less than 15% in asymptomatic infections. This difference in prevalence was maintained during childhood with more than 40% prevalence reported for symptomatic and less than 30% for asymptomatic CMV. Late-onset and

progressive hearing loss appear to be characteristic of congenital CMV infections. Definitions of hearing loss, degree of loss and reporting of laterality varied across studies. All degrees and both bilateral and unilateral loss were reported, regardless of symptomatic and asymptomatic status at birth and no conclusions about the characteristics of hearing loss could be drawn. Various patterns of hearing loss were reported including stable, progressive, and fluctuating, and improvement in hearing (sometimes to normal hearing) was documented. These changes were reported in children with symptomatic/asymptomatic congenital CMV infection, presenting with congenital/early onset/late-onset hearing loss and in children treated and untreated with antiviral medication.

**Conclusions**: Symptomatic and asymptomatic congenital CMV infection should be considered a risk factor for hearing loss at birth and during childhood, and for progressive hearing loss. Therefore, CMV should be included as a risk factor in screening and surveillance programs and be taken into account in clinical follow-up of children with hearing loss.

**Keywords**

Hearing loss, Congenital hearing loss, Late-onset hearing loss, Acquired hearing loss, Progressive hearing loss, Cytomegalovirus, Surveillance, Newborn, Children

## Introduction

Permanent bilateral hearing loss is one of the most prevalent disabilities at birth, affecting at least one to three per 1000 newborns (Butcher et al., 2019; Fortnum et al., 2001; Kaye et al., 2006; Wood et al., 2015). Population-based neonatal hearing screening has been implemented worldwide to improve early detection of permanent childhood hearing loss (PCHL) (Ching et al., 2017; Wood et al., 2015) and is the standard of practice in early hearing detection and intervention (EHDI) programs. The prevalence of PCHL increases during childhood, occurring after infancy (late-onset PCHL) in up to 25-50% of children with hearing loss (Fortnum et al., 2001; Watkin & Baldwin, 2011; Weichbold et al., 2006). Consequently, targeted surveillance programs have become an essential component of EHDI programs. Almost half of children with PCHL experience deterioration in hearing (Barreira-Nielsen et al., 2016; Dahl et al., 2013), therefore, monitoring hearing is important for timely intervention.

An understanding of congenital and childhood risk factors is critical for public health intervention and may help determine optimal screening procedures and identify children at risk for late-onset PCHL (Wood et al., 2013). In most EHDI programs, surveillance protocols have been implemented using risk factors for PCHL established by the Joint Committee on Infant Hearing (The Joint Committee on Infant Hearing, 2007), sometimes adapted to the local context (Thangavelu et al., 2019; Vos et al., 2014; Wroblewska-Seniuk et al., 2005). This list, published more than ten years ago and recently updated (The Joint Committee on Infant Hearing, 2019), triggers a referral to a surveillance program.

Although there is good evidence that some risk factors are associated with hearing loss (Dumanch et al., 2017), investigators have questioned the utility of other risk factors included in screening or surveillance programs because of the low yield of late-onset PCHL (Wood et al., 2013) and changes in standards of care (Beswick et al., 2012; Beswick et al., 2013; Lü et al., 2011; O'Connor et al., 2013). Surveillance programs are costly for both the health system and parents (The Joint Committee on Infant Hearing, 2019); therefore, updating knowledge on risk factors for PCHL is warranted.

Our research aimed to synthesize evidence on risk factors related to neonatal, early and late-onset PCHL, as well as progressive PCHL. We investigated risk factors that have an immediate or delayed effect on hearing. Our ultimate goal is to inform surveillance protocols within EHDI programs worldwide. In this paper, we present the results of our systematic review related to one risk factor: cytomegalovirus (CMV) infection.

As a leading risk indicator for PCHL, congenital CMV (cCMV) infection has received increasing attention. An estimated 0.6 to 0.7 percent of newborns are infected congenitally with CMV, making it an important cause of neurodevelopmental disabilities in children, including sensorineural hearing loss (SNHL) (Dahle et al., 2000; Davis et al., 2017). Approximately 10% of infants with cCMV present with symptoms at birth (Fowler & Boppana, 2018), and clinical and societal costs are substantial due to long-term impairments (Retzler et al., 2019). cCMV is recognized as the most frequent cause of nongenetic hearing loss, which may be present at birth or have onset later in childhood (Fowler & Boppana, 2018; Goderis et al., 2014; Lanzieri et

al., 2017). Antiviral long-term treatment of cCMV has shown positive effects, improving or preventing deterioration in hearing (Fowler & Boppana, 2018) and treatment for infected neonates is recommended (Rawlinson et al., 2017). However, deterioration in hearing has also been reported in children treated with antiviral medication (McCrary et al., 2019).

The purpose of this report is to synthesize the evidence on the association between CMV infection (including congenital symptomatic/asymptomatic or postnatal infection in children) and PCHL to inform public health programs.

## Materials and methods

The protocol for our systematic review on risk factors associated with PCHL was developed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) and was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42018104121) and published (Vos et al., 2019). The risk factors captured in the systematic review were categorized into five subtopics: CMV infection, meningitis infection, cancer treatment, newborn/childhood conditions and treatment, and genetic conditions including syndromes and malformations. This report provides the results related to the CMV subtopic.

### Eligibility criteria

Eligibility criteria for the review are summarized in Table 1 and described in more detail below.

*Design.* Randomized controlled trials, quasi-experimental studies, nonrandomized comparative studies (cohort, case-control), nonrandomized studies without control groups (e.g., cohort, cross-sectional), and case series were included. Case reports (less than five cases) and non-primary studies were excluded.

*Population.* Studies on children (<18 years) with bilateral or unilateral PCHL were included. We included studies combining children and young adults (<22 years), or if results were presented for children separately.

*Intervention (Exposure).* We considered all types of CMV infection, without restriction on the timing of infection (prenatal [any trimester] or postnatal) or on symptoms (symptomatic and asymptomatic).

*Outcome.* The primary outcome was bilateral or unilateral PCHL, including SNHL or "structural" conductive hearing loss (lasting at least six months) (Ontario Ministry of Children and Youth Services Ontario Infant Hearing Program, 2017). Onset of PCHL was categorized into two groups: i) congenital/early onset – PCHL at birth or diagnosed <3 months; ii) late-onset – onset of PCHL after three months of age (The Joint Committee on Infant Hearing, 2007), based on normal hearing screen or audiologic assessment. The secondary outcome was progressive PCHL as defined by the authors.

126 *Timing*. We included birth cohorts from 1985 or when studies were not based on birth cohorts,
127 we included those with hearing assessments performed ≥1985 to ensure relatively recent
128 testing methods.
129
130 *Duplicate results and overlapping studies.* For studies with a series of reports on the same
131 cohort, we included only the most recent or most relevant report for our review question.
132
133 **Search method**
134 We searched MEDLINE, including Epub Ahead of Print, In-Process & Other Non-Indexed
135 Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 to July 30 2018), Embase (1946 to
136 July 30 2018) using the Ovid interface, and CINAHL (from inception on July 23, 2018) (search
137 strategy available in Supplemental appendix). We considered papers published in English since
138 1990.
139
140 **Study selection and management**
141 The study selection was managed using Covidence systematic review software
142 (http://www.covidence.org) and involved two stages: i) title and abstract screening, and ii)
143 eligibility assessment of all potentially relevant full text articles (all articles tagged as “yes” or
144 “maybe” during the previous stage). Screening was carried out by three researchers (BV, EF, DN)
145 with expertise in pediatric hearing loss and public health. During the second stage, we re-
146 reviewed all potentially relevant articles giving specific attention to the audiologic criteria
147 inclusion. Two independent reviewers performed the first two stages. Conflicts were discussed

or resolved by a third reviewer. Bias was minimized during the processes based on the application of objective inclusion/exclusion criteria.

**Data extraction, quality assessment**

Relevant data were extracted for each study (e.g., study characteristics, study design, study and control group information, results). We extracted details on hearing loss including laterality, type, severity, and changes in hearing thresholds as well as any information related to antiviral treatment. Each study was assigned to only one of five specified subtopics to avoid duplication. One researcher extracted and entered all data into an excel spreadsheet and a second reviewer verified the extraction. Discussions took place throughout the process.

The risk of bias was assessed by one researcher and verified by a second, using the Qualitative Assessment Tool for Quantitative Studies (Effective Public Health Practice Project, https://merst.ca/ephpp/). This tool, developed at McMaster University, provides an overall methodological rating (weak, moderate, or strong) based on an appraisal of eight domains: selection bias, study design, confounders, blinding, data collection methods, withdrawals and dropouts, intervention integrity, and analysis.

**Evidence synthesis**

A summary table can be found in Supplemental appendix. Meta-analysis was not possible due to heterogeneity in study designs, definitions of cases and exposure, and variability in studies. A narrative synthesis of the evidence was conducted (Siddaway et al., 2019). First, articles

analyzing the prevalence of PCHL in children with CMV were synthesized; we subdivided them based on the timing of infection: congenital, postnatal or unspecified. For congenital infection, we presented prevalence of PCHL during the neonatal period and childhood separately and according to the health status at birth: symptomatic, asymptomatic, combined (symptomatic/asymptomatic presented conjointly) or unspecified infection. Some studies provided data for more than one subgroup in our summary table (e.g. data on symptomatic and asymptomatic cCMV in a single paper). Second, we presented the articles analyzing the proportion of CMV infection in children with PCHL, whether infection was known to be congenital or not. Characteristics of PCHL, late-onset PCHL and change in hearing over time were summarized, along with results from studies about the effects of treatment on hearing.

**Grading strength of evidence**

The quality and strength of the overall body of evidence were assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool (http://www.gradeworkinggroup.org) (Guyatt et al., 2008; Mercuri et al., 2018). The evidence was rated for the primary and secondary outcomes across the five domains in GRADE (risk of bias, consistency, directness, precision, and publication bias). We rated the evidence from high (very confident that the outcome is related to the risk factor) to very low (little confidence in the outcome/risk factor association) to guide the strength of the recommendations; consensus was reached by the research team.

## Results

**Selection of the relevant articles**

A total of 5234 documents were identified for the full systematic review after removal of 27 duplicates. Figure 1 shows the selection process: 654 articles related to various risk factors were included in the full review; 65 reported CMV infection and are the focus of this report.

**Study characteristics**

All studies were observational studies except two controlled clinical trials (Supplemental appendix). Using the McMaster tool, one study was assessed as strong (Kimberlin et al., 2015), four as moderate (Alarcon et al., 2013; Bilavsky et al., 2015; Kimberlin et al., 2003; Pasternak et al., 2018), and 60 as weak. Most studies were published ≥2010 (n=47), 17 from 2000-2009 and one <2000. The majority were conducted in Europe (n=30). Forty-seven studies included cohorts of children with CMV who were assessed for PCHL (with/without control group), and the remaining 18 were based on children with PCHL who were subsequently assessed for CMV.

**Assessment of CMV infection**

CMV identification was based on urine, saliva or blood samples from children assessed by: i) DNA extraction and PCR amplification, ii) culture or shell-vial culture, or iii) detection of specific CMV IgM or viral antigen (in blood). cCMV was confirmed either by i) initial screening followed by testing to confirm CMV positive screens or ii) by direct referral to a diagnostic test. The screening was a clinical examination of the newborn (to identify symptomatic CMV) or a biological screening test.

Symptomatic cCMV, although not consistently defined, was defined in most studies as presentation of at least one of the following: petechiae, hepatomegaly, splenomegaly, microcephaly, SNHL, chorioretinitis, thrombocytopenia, laboratory evidence of hepatitis or cholestasis, or intracranial calcifications.

**Prevalence of PCHL**

*Neonatal*. Prevalence of PCHL varied widely depending on symptomatic versus asymptomatic cCMV (Table 2). In symptomatic cCMV newborns, prevalence ranged from 33% to 70% across studies (n=9). In asymptomatic cCMV, PCHL was markedly less frequent, ranging from 0-15% (n=5). In studies that combined symptomatic/asymptomatic cCMV (n=15), prevalence ranged from 0%-66.6%. In two studies that did not specify whether cCMV was symptomatic or asymptomatic, prevalence ranged from 14.6%-16.3%. In several studies, PCHL at birth was one of the symptoms required for classification of symptomatic CMV, which may explain the higher prevalence of PCHL in symptomatic cCMV newborns compared to asymptomatic cCMV. Two studies included a control group without CMV (Kasztelewicz et al., 2017; Korndewal et al., 2017) and only one reported on prevalence in the control group, who showed no PCHL at birth (Korndewal et al., 2017).

*Childhood*. PCHL was more prevalent in cases of symptomatic cCMV than in asymptomatic cCMV regardless of age at assessment. This was consistent with findings for neonatal onset PCHL. The length of follow-up after birth or age at hearing assessment during childhood varied across studies between six months and 18 years. Table 3 provides details on prevalence

according to age at assessment. In all but one study, the prevalence of PCHL for symptomatic cCMV was at least 40%; the prevalence was <30% for asymptomatic cCMV (except in one study). In four studies with unspecified symptomatic status at birth, prevalence of PCHL ranged from 0% to >25% (one study, cCMV infection but negative amniocentesis). Of the four studies including a control group without CMV, controls showed no PCHL during childhood in 2 studies, (Korndewal et al., 2017; Lanari et al., 2006), one study did not report results in controls (Kasztelewicz et al., 2017), and a fourth study reported 2% PCHL in a control group of very low birth weight newborns, which is another risk indicator for PCHL (Turner et al., 2014).

Three small studies (<60 children in the largest study) addressed postnatal CMV infection via breastmilk (Gunkel et al., 2018; Jim et al., 2015; Vollmer et al., 2004). They reported no PCHL (up to five years of age). In one study, onset of CMV-infection (congenital or postnatal) was unknown (Yadav et al., 2010).

**CMV infection in children with PCHL**

A subset of 18 articles analyzed the proportion of CMV-infected children with PCHL (Table 4). Study groups were diverse ranging from newborns to adolescents, recruited in hospitals (e.g., through audiology clinics), or from schools for the deaf. cCMV infection was reported in approximately 10% of all children with PCHL and in 15% of children with profound SNHL. Two studies reported higher prevalence of PCHL (21% and 30%) (Park et al., 2014; Sugiura et al., 2004) than the others: this may be explained by the samples which were limited to children with unknown etiology or only to children with cochlear implants. In three retrospective studies,

timing of infection (congenital/postnatal, before/after PCHL) could not be ascertained, therefore the proportion of CMV-related PCHL is not reliable (Devdariani et al., 2011; Noorbakhsh et al., 2017; Samileh et al., 2008).

**Characteristics of PCHL**

PCHL was defined in most publications, with details on severity and laterality. Hearing threshold cut-points differed across studies, affecting prevalence estimates (e.g., cut-points between 20-35 dB HL for mild hearing loss).

Characteristics of PCHL were reported in 33 prospective studies (Table 5). To avoid selection bias, the 18 retrospective studies on CMV infection in children with known PCHL were not included in this analysis because selection criteria such as setting /context may bias the characteristics of PCHL (e. g. recruitment occurred in schools for the deaf with primarily profound hearing loss or cochlear implant users). Severity and laterality of PCHL was usually presented by child and less frequently by individual ears. Studies reported both bilateral and unilateral PCHL (except two with unilateral and two with bilateral PCHL only) and all degrees of loss. It was not possible to draw conclusions about specific patterns of loss or about symptomatic versus asymptomatic cCMV; symptomatic cCMV did not seem to be associated with more severe degrees of PCHL.

**Late-onset PCHL**

In 27 studies investigating late-onset PCHL, 20 studies documented PCHL and four no PCHL in cCMV-infected children; three studies on children with PCHL who had cCMV also reported late-onset (Table 6). In several studies, the number of children with normal hearing at birth who received follow-up was unclear.

Of the four studies that reported no late-onset PCHL, three focused on symptomatic cCMV and followed 4-8 children (all or some treated) with normal hearing at birth for at least one year (del Rosal et al., 2012; Lombardi et al., 2009; Michaels et al., 2003). The fourth study reported no late-onset PCHL at 6-month follow-up among 27 children symptomatic/asymptomatic cCMV with normal hearing at birth (Kasztelewicz et al., 2017).

In 20 studies, late-onset PCHL occurred in children in all cCMV subgroups (symptomatic, asymptomatic and unspecified) (Table 6). Onset of PCHL was reported up to 5-6 years of age in studies with long-term follow-up (Forner et al., 2015; Foulon et al., 2012; Korndewal et al., 2017). The number of children with normal hearing at birth who received follow-up was not systematically reported and frequently only the number with late-onset PCHL was reported. In children with normal hearing at birth, up to 25% of children developed PCHL in two studies (one symptomatic, one asymptomatic cCMV) (Forner et al., 2015; Goderis et al., 2016). Some children with normal hearing in one or both ears at birth developed late-onset PCHL ranging from mild to profound degree (unilateral or bilateral) (Bilavsky et al., 2016; Goderis et al., 2016; Iwasaki et al., 2007).

In three retrospective studies with small samples (n <15), late-onset PCHL was reported in 20%-50% of the CMV-related children with hearing loss.

**Changes in hearing (childhood)**

*Definition of changes in hearing.* Studies applied two different criteria to define change in hearing: i) a change of ≥10 dB in the auditory threshold, and/or ii) a change in degree of hearing loss category. Some authors provided frequency-specific information related to change in hearing.

A total of 26 studies examined changes in hearing and reported various patterns: stable, deterioration (progressive PCHL), fluctuations and improvement (sometimes to normal hearing) (Amir et al., 2016; Bilavsky et al., 2016; Bilavsky et al., 2015; Boudewyns et al., 2009; Capretti et al., 2014; del Rosal et al., 2012; Engman et al., 2008; Foulon et al., 2012; Furutate et al., 2011; Goderis et al., 2016; Iwasaki et al., 2007; Kimberlin et al., 2015; Kimberlin et al., 2003; Korver et al., 2009; Leruez-Ville et al., 2016; Lombardi et al., 2009; Michaels et al., 2003; Misono et al., 2011; Park et al., 2014; Pasternak et al., 2018; Ross et al., 2017; Ross et al., 2009; Royackers et al., 2013; Tagawa et al., 2009; Verbeeck et al., 2008). Changes were reported in symptomatic/asymptomatic cCMV in congenital/early onset/late-onset PCHL and in children treated and untreated (Foulon et al., 2012; Goderis et al., 2016; Iwasaki et al., 2007; Misono et al., 2011; Royackers et al., 2013; Verbeeck et al., 2008). According to Foulon et al., symptomatic children were more likely to have PCHL (p=0.045) and less likely to show improvement (p=0.057), but deteriorations and fluctuations in PCHL were equally frequent in children with

symptomatic and asymptomatic cCMV (Foulon et al., 2012). According to Royackers et al. (2013), the first change (deterioration or improvement) in hearing appeared after one year of age in treated children. In one retrospective study that examined the association between progressive PCHL and various etiologies and risk factors (e.g., CMV, low birthweight, genetic), progressive loss appeared to be two times more common among children with CMV-related PCHL (Misono et al., 2011).

**Effects of antiviral treatment**

Eight studies examined the effects of antiviral treatment in cCMV children (Table 7). Kimberlin et al. (2003) showed a lower percentage of symptomatic children with worsening of hearing between baseline and ≥1-year follow-up with 6-week treatment compared to no treatment, and Lackner et al. (2009) reported cases of late-onset PCHL only in asymptomatic untreated children with long-term follow-up (four to ten years). In symptomatic cCMV children, hearing was more likely to remain normal or improve at 12 and 24 months with longer treatment (6-week versus 6-month) (Kimberlin et al., 2015). Consequently, at 1-year follow-up, treatment seems to have a positive effect on some children, improving or reducing the progression of PCHL, when compared either to no treatment or shorter duration of treatment and these effects seem to be maintained at 2-year follow-up (Kimberlin et al., 2015; Kimberlin et al., 2003; Lackner et al., 2009).

In the five studies with no control group, four studies of children with symptomatic cCMV with antiviral treatment (n=5 to 12) showed improvement in hearing in 25%-50% of cases, no late-

onset PCHL was reported (del Rosal et al., 2012; Lombardi et al., 2009; Michaels et al., 2003; Pasternak et al., 2018), and hearing did not deteriorate in better ear analysis (del Rosal et al., 2012; Pasternak et al., 2018) (Table 7). In the fifth study, symptomatic newborns of mothers were treated during pregnancy, and while PCHL was reported in the neonatal period, no late-onset PCHL was observed (Leruez-Ville et al., 2016).

**Summary of the body of evidence**

Table 8 summarizes the overall level of the body of evidence related to our main outcomes:

- Neonatal (congenital/early) PCHL,
- Childhood PCHL and late-onset PCHL,
- Change in hearing.

The three outcomes are specifically synthesized according to symptomatic/asymptomatic status at birth; postnatally acquired CMV was also analyzed for the last two outcomes.

*Neonatal.* All studies were observational with the exception of two controlled clinical trials, and therefore, the level of evidence is low. Independent of symptomatic status, the body of evidence showed that cCMV seems to be related to PCHL at birth or early in life. Studies of the clinical history of infection have shown resultant damage to the brain and hearing pathway. A gradient is observed according to symptomatic status: prevalence of PCHL at birth or early in life was higher in symptomatic than in asymptomatic cCMV. Studies of the prevalence of PCHL in asymptomatic cCMV showed mixed results, with some reporting no PCHL and some a much higher prevalence of PCHL compared to the general population of newborns without risk factors

for hearing loss, (e.g., reported in universal hearing screening studies); studies reporting asymptomatic cCMV did not include a control group.

*Childhood PCHL and late-onset PCHL.* In symptomatic and asymptomatic newborns without antiviral treatment, the body of evidence shows a higher prevalence of PCHL during childhood than in the general population without risk factors. Late-onset PCHL was also reported in some studies, with high proportions in children with normal hearing at birth. The level of evidence is rated as low. Consistent with other reports, postnatally acquired CMV showed no relationship with PCHL during childhood. Therefore, level of evidence related to the relationship between postnatal CMV and PCHL was rated as very low.

The effects of antiviral treatment on children with cCMV was not studied in randomized clinical trials. Based on two controlled clinical trials, there seems to be a positive effect on hearing, but it should be confirmed in further studies with appropriate design and control group. At this stage, limited data preclude strong conclusions and consequently, the level of evidence is rated as low.

*Change in hearing.* Despite the 26 studies reporting changes in hearing, it is difficult to draw conclusions, because of the variation in study groups (symptomatic/asymptomatic) and in the multiple outcomes reported (stable/improvement/deterioration of hearing). Instability in hearing thresholds is characteristic of cCMV-related PCHL: improvement or deterioration

appears to occur in both symptomatic and asymptomatic cCMV, neonatal PCHL and late-onset PCHL, and in treated and untreated children.

## Discussion

This review is part of a broader research project on risk factors related to PCHL. This report synthesized evidence specifically on CMV related to PCHL at birth and during childhood, as well as progressive PCHL.

Our study identified a high prevalence of congenital or early-onset (<3 months of age) PCHL in infants with cCMV, ranging from 0% to 71.4%. Notably, important differences are reported in prevalence according to symptomatic (33.7% to 71.4%) and asymptomatic (0.0% to 14.9%) cCMV. These results are consistent with other literature reviews (Fletcher et al., 2018; Goderis et al., 2014; Riga et al., 2018). However, we were not able to identify an association between degree of loss or laterality of PCHL and the symptomatic status of CMV at birth. Other reviews have reported that symptomatic children were more likely to present with bilateral PCHL and severe to profound loss (Goderis et al., 2014; Riga et al., 2018), but based on our review, there is no conclusive evidence to support this finding. A key difference between our review and these two reviews lies in the length of follow-up: we did not include any restriction while these two reviews included studies with either a follow-up of at least two years or at least two audiological assessments during follow-up. This may lead to overrepresentation of children who require the most frequent audiological services, indicating a more severe degree of hearing loss. Consistent

409 with other reports, no association with PCHL was found in newborns with postnatally acquired
410 CMV (via breastmilk).
411
412 Consistent with other reviews, we found late-onset PCHL to be an important characteristic of
413 cCMV-infected children (Fletcher et al., 2018; Goderis et al., 2014). Late-onset PCHL was
414 reported for newborns with symptomatic or asymptomatic cCMV at birth. In universal CMV
415 screening programs, all cases of cCMV infection (symptomatic/asymptomatic) are targeted and
416 early identified, whether PCHL is present or not, and affected children are enrolled in hearing
417 surveillance programs. In the absence of cCMV screening, children who present with “severe”
418 symptoms will be investigated after suspicion of CMV infection and children with asymptomatic
419 cCMV may not be identified. cCMV testing weeks or months after birth using neonatal dried
420 blood spot screening is challenging to ascertain and the prevalence of late-onset PCHL in
421 asymptomatic children may be underestimated, due to unknown cCMV infection status.
422 Concerns have been raised about the use of the dried blood spot for identifying infants with
423 CMV-associated hearing loss and is not recommended by some researchers (Rawlinson et al.,
424 2017; Ross et al., 2017). Estimating the prevalence of late-onset hearing loss is further
425 complicated by the fact that children present with late-onset PCHL at various times after the
426 infection. Various length of follow-up across studies, and short follow-up periods may also
427 contribute to an underestimation of late-onset PCHL in cCMV-infected children.
428
429 We also sought to document information related to changes in hearing loss over time
430 (improvement or deterioration). Although studies suggest this is an important challenge in

clinical management, change in hearing does not seem to occur more frequently in symptomatic or asymptomatic children. Our findings are consistent with other reviews that reported progressive and fluctuating PCHL as important characteristics of cCMV-related PCHL (Fletcher et al., 2018; Goderis et al., 2014). Our review did not find evidence that any particular characteristics (symptomatic/asymptomatic, neonatal or late-onset PCHL) were associated with progressive PCHL.

This review did not focus on the effects of antiviral treatment in cCMV infection, but our findings highlight its critical role. The effects of antiviral treatment seem globally positive; it was mostly studied in symptomatic children (with PCHL) and appeared to show better outcomes in hearing for treatment or with longer (six months) treatment. However, since treatment effects was not the central research question and our search was not conducted to capture all studies on antiviral treatment, we cannot confidently draw any conclusions. Further studies focusing on antiviral treatment in cCMV-infected newborns should be performed, including both symptomatic and asymptomatic (with PCHL) children, to assess the effect on the trajectory of hearing. Because antiviral treatment may act as a confounding factor between cCMV and the evolution of hearing, rating the body of evidence may be biased, especially regarding symptomatic children who are more frequently treated. It reflects the complex nature of cCMV infection; while it is typically associated with late-onset PCHL or deterioration in hearing, antiviral treatment may reverse the effects on hearing.

Based on our results, all cases of cCMV infections should be early-identified and hearing for all children with CMV-related PCHL should be monitored, because improvement or deterioration may occur. This will enable adjustments in rehabilitation in a timely manner. Based on this review, we strongly recommend recognizing cCMV infection as a risk indicator for PCHL and that its presence trigger surveillance programs to detect late-onset PCHL as well as close audiologic monitoring of children with CMV-related PCHL to ensure early detection of change in hearing. Given the limited evidence reported here on the benefits of antiviral treatment, we do not currently recommend different surveillance protocols based on treatment or no treatment.

*Quality of studies*

As expected, due to our research question, most reports were observational studies, and only a few included a control group. The majority were cohort studies (with various lengths of follow-up and study designs), that recruited children with cCMV and assessed the onset of PCHL. Almost one-third (21/65) of reports were based on children with known PCHL with subsequent investigation of cCMV as a possible cause of PCHL. Methodological rating of individual studies (using the McMaster tool) was low in 92.3% of studies (60 of 65). Consequently, the overall body of evidence on CMV infection was rated as (very) low.

*Elements influencing the assessment of the body of evidence*

Definition and degree of targeted PCHL were not standardized across studies. However, we strictly applied the inclusion criteria for permanent PCHL, as targeted by EHDI programs (Ontario Ministry of Children and Youth Services Ontario Infant Hearing Program, 2017; The

Joint Committee on Infant Hearing, 2019). Exposure included all CMV infections confirmed in newborns (not only in mothers during pregnancy or a maternal seroconversion), through tests performed on saliva, urine or blood in newborns. Type of tests and criteria to determine symptomatic infection varied across studies. An outcome of normal hearing was based on clinical practice from hearing screening programs and accepted as a normal hearing screen (when performed) without an extensive audiological assessment. This variety of definitions in exposure and outcome precluded a meta-analysis.

Some studies reported a possible differential effect of cCMV on hearing according to infection attributes: primary versus non-primary maternal infection, timing of infection during pregnancy, results of amniocentesis or cerebrospinal fluid. One limitation of our review is that our inclusion criteria did not include these specific characteristics and therefore subgroup analyses were not possible. Consequently, types of cCMV infection were not standardized across the studies, resulting in a heterogenous population. This heterogeneity reflects clinical practice, as usually no information other than the CMV infection is available for hearing assessments in public health programs. We therefore adopted a pragmatic approach because our goal was to inform public health programs (based on large populations) and not to provide guidance for an individual clinical approach.

As noted, overall, study designs were rated as low quality. This is partly due to lack of use of statistical tools and tests: precision of the results, and lack of representative samples. Most studies showed an increased prevalence in cases of cCMV infection, while some reported no

cases of PCHL (in asymptomatic cCMV children). Small sample sizes may also explain the inconsistent results of prevalence of PCHL across studies. In addition, small sample sizes in most studies may explain the very low prevalence of PCHL (and the absence of reported cases in some studies), particularly for a low-incidence disorder in the control group of children without risk factors (Butcher et al., 2019; Kaye et al., 2006; Wood et al., 2015). Therefore, larger samples or multi-center studies are required to ensure valid results. All of these issues contribute to the low level of quality evidence.

*Review limitations*

Due to the large number of studies identified through our search, limitations of this review are that we restricted it to articles in English and we did not contact study authors to clarify results or inclusion criteria (Morrison et al., 2012). We also limited our review to the citations retrieved through our search of databases and did not review the references from the articles included in our review. Studies were excluded if they did not clearly mention that PCHL was targeted or that conductive hearing loss was not documented, potentially leading to missing some pertinent information. In addition, our criteria may have led to the exclusion of some studies on progressive hearing loss because study groups having both CMV and hearing loss were excluded. Our literature search was carried out in July 2018. We re-examined the databases to ensure that we did not miss any relevant articles with different results since data extraction. Articles on cCMV have been published but their findings were not contradictory with our report or did not bring new evidence and therefore no adjustments were made in our findings.

## Conclusion

cCMV is a relevant risk factor to include in screening programs at birth and in surveillance programs during childhood, regardless of symptomatic or asymptomatic infection status at birth. Children with cCMV related hearing loss should also be enrolled in follow-up programs to rapidly identify any evolution of their hearing over time, and consequently adapt their audiological interventions.


## Acknowledgement

The authors would like to acknowledge the contribution of Dr. Margaret Sampson, Manager at Library Services, CHEO, Ottawa, for her assistance in developing the search strategy and for conducting the literature searches in the databases. They also would like to acknowledge the huge work done by Eunjung Na in retrieving the full-text articles.


BV, DN, MP, MB, and EF conceived the protocol. BV, DN, JW and EF performed screening and extracted data. BV drafted the manuscript. DN, JW, MP, MB and EF critically reviewed the manuscript. All authors read and approved the final manuscript.

## Abbreviations

CMV: Cytomegalovirus; cCMV: congenital cytomegalovirus; EHDI: Early hearing detection and intervention; PCHL: permanent childhood hearing loss; PRISMA-P: Preferred Reporting Items for Systematic review and Meta-Analysis Protocols; SNHL: sensorineural hearing loss

## References


Alarcon, A., Martinez-Biarge, M., Cabañas, F., Hernanz, A., Quero, J., & Garcia-Alix, A. (2013). Clinical, biochemical, and neuroimaging findings predict long-term neurodevelopmental outcome in symptomatic congenital cytomegalovirus infection. J Pediatr, 163(3), 828-834.e821. https://doi.org/10.1016/j.jpeds.2013.03.014

Amir, J., Atias, J., Linder, N., & Pardo, J. (2016). Follow-up of infants with congenital cytomegalovirus and normal fetal imaging. Arch Dis Child Fetal Neonatal Ed, 101(5), F428-432. https://doi.org/10.1136/archdischild-2015-308357

Avettand-Fenoël, V., Marlin, S., Vauloup-Fellous, C., Loundon, N., François, M., Couloigner, V., Rouillon, I., Drouin-Garraud, V., Laccourreye, L., Denoyelle, F., Guilleminot, T., Grabar, S., & Leruez-Ville, M. (2013). Congenital cytomegalovirus is the second most frequent cause of bilateral hearing loss in young French children. J Pediatr, 162(3), 593-599. https://doi.org/10.1016/j.jpeds.2012.08.009

Barbi, M., Binda, S., Caroppo, S., Ambrosetti, U., Corbetta, C., & Sergi, P. (2003). A wider role for congenital cytomegalovirus infection in sensorineural hearing loss. Pediatr Infect Dis J, 22(1), 39-42. https://doi.org/10.1097/00006454-200301000-00012

Barkai, G., Ari-Even Roth, D., Barzilai, A., Tepperberg-Oikawa, M., Mendelson, E., Hildesheimer, M., & Kuint, J. (2014). Universal neonatal cytomegalovirus screening using saliva - report of clinical experience. J Clin Virol, 60(4), 361-366. https://doi.org/10.1016/j.jcv.2014.04.024

Barreira-Nielsen, C., Fitzpatrick, E., Hashem, S., Whittingham, J., Barrowman, N., & Aglipay, M. (2016). Progressive Hearing Loss in Early Childhood. Ear Hear, 37(5), e311-321. https://doi.org/10.1097/aud.0000000000000325

Beswick, R., Driscoll, C., Kei, J., & Glennon, S. (2012). Targeted surveillance for postnatal hearing loss: a program evaluation. Int J Pediatr Otorhinolaryngol, 76(7), 1046-1056. https://doi.org/10.1016/j.ijporl.2012.04.004

Beswick, R., Driscoll, C., Kei, J., Khan, A., & Glennon, S. (2013). Which risk factors predict postnatal hearing loss in children? J Am Acad Audiol, 24(3), 205-213. https://doi.org/10.3766/jaaa.24.3.6

Bilavsky, E., Pardo, J., Attias, J., Levy, I., Magny, J. F., Ville, Y., Leruez-Ville, M., & Amir, J. (2016). Clinical Implications for Children Born With Congenital Cytomegalovirus Infection Following a Negative Amniocentesis. Clin Infect Dis, 63(1), 33-38. https://doi.org/10.1093/cid/ciw237

Bilavsky, E., Schwarz, M., Pardo, J., Attias, J., Levy, I., Haimi-Cohen, Y., & Amir, J. (2015). Lenticulostriated vasculopathy is a high-risk marker for hearing loss in congenital cytomegalovirus infections. Acta Paediatr, 104(9), e388-394. https://doi.org/10.1111/apa.13053

Boudewyns, A., Declau, F., Smets, K., Ursi, D., Eyskens, F., Van den Ende, J., & Van de Heyning, P. (2009). Cytomegalovirus DNA detection in Guthrie cards: role in the diagnostic work-up of childhood hearing loss. Otol Neurotol, 30(7), 943-949. https://doi.org/10.1097/MAO.0b013e3181b76b22

Butcher, E., Dezateux, C., Cortina-Borja, M., & Knowles, R. L. (2019). Prevalence of permanent childhood hearing loss detected at the universal newborn hearing screen: Systematic review and meta-analysis. PLoS One, 14(7), e0219600. https://doi.org/10.1371/journal.pone.0219600

Cannie, M. M., Devlieger, R., Leyder, M., Claus, F., Leus, A., De Catte, L., Cossey, V., Foulon, I., Van der Valk, E., Foulon, W., Cos, T., Bernaert, A., Oyen, R., & Jani, J. C. (2016). Congenital cytomegalovirus infection: contribution and best timing of prenatal MR imaging. Eur Radiol, 26(10), 3760-3769. https://doi.org/10.1007/s00330-015-4187-0

582 Capretti, M. G., Lanari, M., Tani, G., Ancora, G., Sciutti, R., Marsico, C., Lazzarotto, T., Gabrielli, L., Guerra,
583 B., Corvaglia, L., & Faldella, G. (2014). Role of cerebral ultrasound and magnetic resonance imaging
584 in newborns with congenital cytomegalovirus infection. Brain Dev, 36(3), 203-211.
585 https://doi.org/10.1016/j.braindev.2013.04.001

586 Ching, T. Y. C., Dillon, H., Button, L., Seeto, M., Van Buynder, P., Marnane, V., Cupples, L., & Leigh, G.
587 (2017). Age at Intervention for Permanent Hearing Loss and 5-Year Language Outcomes.
588 Pediatrics, 140(3). https://doi.org/10.1542/peds.2016-4274

589 Courtmans, I., Mancilla, V., Ligny, C., Le Bon, S. D., Naessens, A., & Foulon, I. (2015). Incidence of
590 congenital CMV in children at a hearing rehabilitation center. B-ent, 11(4), 303-308.

591 Dahl, H. H., Ching, T. Y., Hutchison, W., Hou, S., Seeto, M., & Sjahalam-King, J. (2013). Etiology and
592 audiological outcomes at 3 years for 364 children in Australia. PLoS One, 8(3), e59624.
593 https://doi.org/10.1371/journal.pone.0059624

594 Dahle, A. J., Fowler, K. B., Wright, J. D., Boppana, S. B., Britt, W. J., & Pass, R. F. (2000). Longitudinal
595 investigation of hearing disorders in children with congenital cytomegalovirus. J Am Acad Audiol,
596 11(5), 283-290.

597 Dar, L., Namdeo, D., Kumar, P., Thakar, A., Kant, S., Rai, S., Singh, P. K., Kabra, M., Fowler, K. B., &
598 Boppana, S. B. (2017). Congenital Cytomegalovirus Infection and Permanent Hearing Loss in Rural
599 North Indian Children. Pediatr Infect Dis J, 36(7), 670-673.
600 https://doi.org/10.1097/inf.0000000000001527

601 Davis, N. L., King, C. C., & Kourtis, A. P. (2017). Cytomegalovirus infection in pregnancy. Birth Defects Res,
602 109(5), 336-346. https://doi.org/10.1002/bdra.23601

603 de Vries, J. J., Vesseur, A., Rotteveel, L. J., Korver, A. M., Rusman, L. G., Wessels, E., Kroes, A. C., Mylanus,
604 E. A., Oudesluys-Murphy, A. M., Frijns, J. H., & Vossen, A. C. (2013). Cytomegalovirus DNA
605 detection in dried blood spots and perilymphatic fluids from pediatric and adult cochlear implant
606 recipients with prelingual deafness. J Clin Virol, 56(2), 113-117.
607 https://doi.org/10.1016/j.jcv.2012.10.008

608 del Rosal, T., Baquero-Artigao, F., Blázquez, D., Noguera-Julian, A., Moreno-Pérez, D., Reyes, A., & Vilas, J.
609 (2012). Treatment of symptomatic congenital cytomegalovirus infection beyond the neonatal
610 period. J Clin Virol, 55(1), 72-74. https://doi.org/10.1016/j.jcv.2012.06.001

611 Devdariani, T., Gogberashvili, K., Manjavidze, N., & Kamkamidze, G. (2011). Association between the
612 cytomegalovirus seroprevalence and hearing loss in early childhood. Georgian Med News(195), 61-
613 65.

614 Dumanch, K. A., Holte, L., O'Hollearn, T., Walker, E., Clark, J., & Oleson, J. (2017). High risk factors
615 associated with early childhood hearing loss: a 3-year review. Am J Audiol, 26(2), 129-142.
616 https://doi.org/10.1044/2017_aja-16-0116

617 Duryea, E. L., Sánchez, P. J., Sheffield, J. S., Jackson, G. L., Wendel, G. D., McElwee, B. S., Boney, L. F.,
618 Mallory, M. M., Owen, K. E., & Stehel, E. K. (2010). Maternal human immunodeficiency virus
619 infection and congenital transmission of cytomegalovirus. Pediatr Infect Dis J, 29(10), 915-918.
620 https://doi.org/10.1097/INF.0b013e3181e0ce05

621 Engman, M. L., Malm, G., Engstrom, L., Petersson, K., Karltorp, E., Tear Fahnehjelm, K., Uhlen, I.,
622 Guthenberg, C., & Lewensohn-Fuchs, I. (2008). Congenital CMV infection: prevalence in newborns
623 and the impact on hearing deficit. Scand J Infect Dis, 40(11-12), 935-942.
624 https://doi.org/10.1080/00365540802308431

625 Fletcher, K. T., Horrell, E. M. W., Ayugi, J., Irungu, C., Muthoka, M., Creel, L. M., Lester, C., & Bush, M. L.
626 (2018). The Natural History and Rehabilitative Outcomes of Hearing Loss in Congenital
627 Cytomegalovirus: a Systematic Review. Otol Neurotol, 39(7), 854-864.
628 https://doi.org/10.1097/mao.0000000000001861

629 Forner, G., Abate, D., Mengoli, C., Palù, G., & Gussetti, N. (2015). High Cytomegalovirus (CMV) DNAemia
630 Predicts CMV Sequelae in Asymptomatic Congenitally Infected Newborns Born to Women With
631 Primary Infection During Pregnancy. J Infect Dis, 212(1), 67-71.
632 https://doi.org/10.1093/infdis/jiu627

633 Fortnum, H. M., Summerfield, A. Q., Marshall, D. H., Davis, A. C., & Bamford, J. M. (2001). Prevalence of
634 permanent childhood hearing impairment in the United Kingdom and implications for universal
635 neonatal hearing screening: questionnaire based ascertainment study. BMJ, 323(7312), 536-540.
636 https://doi.org/10.1136/bmj.323.7312.536

637 Foulon, I., Naessens, A., Faron, G., Foulon, W., Jansen, A. C., & Gordts, F. (2012). Hearing thresholds in
638 children with a congenital CMV infection: a prospective study. Int J Pediatr Otorhinolaryngol,
639 76(5), 712-717. https://doi.org/10.1016/j.ijporl.2012.02.026

640 Foulon, I., Vleurinck, L., Kerkhofs, K., & Gordts, F. (2015). Hearing configuration in children with cCMV
641 infection and proposal of a flow chart for hearing evaluation. Int J Audiol, 54(10), 714-719.
642 https://doi.org/10.3109/14992027.2015.1046506

643 Fowler, K. B., & Boppana, S. B. (2018). Congenital cytomegalovirus infection. Semin Perinatol, 42(3), 149-
644 154. https://doi.org/10.1053/j.semperi.2018.02.002

645 Fowler, K. B., McCollister, F. P., Sabo, D. L., Shoup, A. G., Owen, K. E., Woodruff, J. L., Cox, E., Mohamed,
646 L. S., Choo, D. I., & Boppana, S. B. (2017). A targeted approach for congenital cytomegalovirus

screening within newborn hearing screening. Pediatrics, 139(2). https://doi.org/10.1542/peds.2016-2128

Furutate, S., Iwasaki, S., Nishio, S. Y., Moteki, H., & Usami, S. (2011). Clinical profile of hearing loss in children with congenital cytomegalovirus (CMV) infection: CMV DNA diagnosis using preserved umbilical cord. Acta Otolaryngol, 131(9), 976-982. https://doi.org/10.3109/00016489.2011.583268

Giannattasio, A., Di Costanzo, P., De Matteis, A., Milite, P., De Martino, D., Bucci, L., Augurio, M. R., Bravaccio, C., Ferrara, T., Capasso, L., & Raimondi, F. (2017). Outcomes of congenital cytomegalovirus disease following maternal primary and non-primary infection. J Clin Virol, 96, 32-36. https://doi.org/10.1016/j.jcv.2017.09.006

Goderis, J., De Leenheer, E., Smets, K., Van Hoecke, H., Keymeulen, A., & Dhooge, I. (2014). Hearing loss and congenital CMV infection: a systematic review. Pediatrics, 134(5), 972-982. https://doi.org/10.1542/peds.2014-1173

Goderis, J., Keymeulen, A., Smets, K., Van Hoecke, H., De Leenheer, E., Boudewyns, A., Desloovere, C., Kuhweide, R., Muylle, M., Royackers, L., Schatteman, I., & Dhooge, I. (2016). Hearing in children with congenital cytomegalovirus infection: results of a longitudinal study. J Pediatr, 172, 110-115.e112. https://doi.org/10.1016/j.jpeds.2016.01.024

Goycochea-Valdivia, W. A., Baquero-Artigao, F., Del Rosal, T., Frick, M. A., Rojo, P., Echeverría, M. J., Noguera-Julian, A., Bringué, X., Saavedra-Lozano, J., Vives-Oñós, I., Moliner, E., Cilleruelo, M. J., Cuadrado, I., Colino, E., Castells, L., Tagarro, A., Vilas, J., Soler-Palacin, P., & Blázquez-Gamero, D. (2017). Cytomegalovirus DNA detection by polymerase chain reaction in cerebrospinal fluid of infants with congenital infection: associations with clinical evaluation at birth and implications for follow-up. Clin Infect Dis, 64(10), 1335-1342. https://doi.org/10.1093/cid/cix105

669 Gunkel, J., de Vries, L. S., Jongmans, M., Koopman-Esseboom, C., van Haastert, I. C., Eijsermans, M. C. J.,
670 van Stam, C., van Zanten, B. G. A., Wolfs, T. F. W., & Nijman, J. (2018). Outcome of preterm infants
671 with postnatal cytomegalovirus infection. Pediatrics, 141(2). https://doi.org/10.1542/peds.2017-
672 0635

673 Guyatt, G. H., Oxman, A. D., Kunz, R., Vist, G. E., Falck-Ytter, Y., & Schünemann, H. J. (2008). What is
674 "quality of evidence" and why is it important to clinicians? BMJ, 336(7651), 995-998.
675 https://doi.org/10.1136/bmj.39490.551019.BE

676 Hicks, T., Fowler, K., Richardson, M., Dahle, A., Adams, L., & Pass, R. (1993). Congenital cytomegalovirus
677 infection and neonatal auditory screening. J Pediatr, 123(5), 779-782.
678 https://doi.org/10.1016/s0022-3476(05)80859-5

679 Iwasaki, S., Yamashita, M., Maeda, M., Misawa, K., & Mineta, H. (2007). Audiological outcome of infants
680 with congenital cytomegalovirus infection in a prospective study. Audiol Neurootol, 12(1), 31-36.
681 https://doi.org/10.1159/000096156

682 Jim, W. T., Chiu, N. C., Ho, C. S., Shu, C. H., Chang, J. H., Hung, H. Y., Kao, H. A., Chang, H. Y., Peng, C. C.,
683 Yui, B. H., & Chuu, C. P. (2015). Outcome of preterm infants with postnatal cytomegalovirus
684 infection via breast milk: a two-year prospective follow-up Study. Medicine (Baltimore), 94(43),
685 e1835. https://doi.org/10.1097/md.0000000000001835

686 Karimian, P., Yaghini, O., Nasr Azadani, H., Mohammadizadeh, M., Arabzadeh, S. A., Adibi, A., & Rahimi,
687 H. (2016). Prevalence, characteristics, and one-year follow-up of congenital cytomegalovirus
688 infection in Isfahan City, Iran. Interdiscip Perspect Infect Dis, 2016, 7812106.
689 https://doi.org/10.1155/2016/7812106

690 Kasztelewicz, B., Czech-Kowalska, J., Lipka, B., Milewska-Bobula, B., Borszewska-Kornacka, M. K.,
691 Romańska, J., & Dzierżanowska-Fangrat, K. (2017). Cytokine gene polymorphism associations with
692 congenital cytomegalovirus infection and sensorineural hearing loss. Eur J Clin Microbiol Infect Dis,
693 36(10), 1811-1818. https://doi.org/10.1007/s10096-017-2996-6

694 Kaye, C. I., Accurso, F., La Franchi, S., Lane, P. A., Northrup, H., Pang, S., & Schaefer, G. B. (2006).
695 Introduction to the newborn screening fact sheets. Pediatrics, 118(3), 1304-1312.
696 https://doi.org/10.1542/peds.2006-1782

697 Kimani, J. W., Buchman, C. A., Booker, J. K., Huang, B. Y., Castillo, M., Powell, C. M., & Weck, K. E. (2010).
698 Sensorineural hearing loss in a pediatric population: association of congenital cytomegalovirus
699 infection with intracranial abnormalities. Arch Otolaryngol Head Neck Surg, 136(10), 999-1004.
700 https://doi.org/10.1001/archoto.2010.156

701 Kimberlin, D. W., Jester, P. M., Sánchez, P. J., Ahmed, A., Arav-Boger, R., Michaels, M. G., Ashouri, N.,
702 Englund, J. A., Estrada, B., Jacobs, R. F., Romero, J. R., Sood, S. K., Whitworth, M. S., Abzug, M. J.,
703 Caserta, M. T., Fowler, S., Lujan-Zilbermann, J., Storch, G. A., DeBiasi, R. L., Han, J. Y., et. al. (2015).
704 Valganciclovir for symptomatic congenital cytomegalovirus disease. N Engl J Med, 372(10), 933-
705 943. https://doi.org/10.1056/NEJMoa1404599

706 Kimberlin, D. W., Lin, C. Y., Sánchez, P. J., Demmler, G. J., Dankner, W., Shelton, M., Jacobs, R. F., Vaudry,
707 W., Pass, R. F., Kiell, J. M., Soong, S. J., & Whitley, R. J. (2003). Effect of ganciclovir therapy on
708 hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system:
709 a randomized, controlled trial. J Pediatr, 143(1), 16-25. https://doi.org/10.1016/s0022-
710 3476(03)00192-6

711 Korndewal, M. J., Oudesluys-Murphy, A. M., Kroes, A. C. M., van der Sande, M. A. B., de Melker, H. E., &
712 Vossen, A. (2017). Long-term impairment attributable to congenital cytomegalovirus infection: a

retrospective cohort study. Dev Med Child Neurol, 59(12), 1261-1268. https://doi.org/10.1111/dmcn.13556

Korver, A. M., de Vries, J. J., Konings, S., de Jong, J. W., Dekker, F. W., Vossen, A. C., Frijns, J. H., & Oudesluys-Murphy, A. M. (2009). DECIBEL study: Congenital cytomegalovirus infection in young children with permanent bilateral hearing impairment in the Netherlands. J Clin Virol, 46 Suppl 4, S27-31. https://doi.org/10.1016/j.jcv.2009.09.007

Lackner, A., Acham, A., Alborno, T., Moser, M., Engele, H., Raggam, R. B., Halwachs-Baumann, G., Kapitan, M., & Walch, C. (2009). Effect on hearing of ganciclovir therapy for asymptomatic congenital cytomegalovirus infection: four to 10 year follow up. J Laryngol Otol, 123(4), 391-396. https://doi.org/10.1017/s0022215108003162

Lanari, M., Lazzarotto, T., Venturi, V., Papa, I., Gabrielli, L., Guerra, B., Landini, M. P., & Faldella, G. (2006). Neonatal cytomegalovirus blood load and risk of sequelae in symptomatic and asymptomatic congenitally infected newborns. Pediatrics, 117(1), e76-83. https://doi.org/10.1542/peds.2005-0629

Lanzieri, T. M., Chung, W., Flores, M., Blum, P., Caviness, A. C., Bialek, S. R., Grosse, S. D., Miller, J. A., & Demmler-Harrison, G. (2017). Hearing loss in children with asymptomatic congenital cytomegalovirus infection. Pediatrics, 139(3). https://doi.org/10.1542/peds.2016-2610

Leruez-Ville, M., Ghout, I., Bussières, L., Stirnemann, J., Magny, J. F., Couderc, S., Salomon, L. J., Guilleminot, T., Aegerter, P., Benoist, G., Winer, N., Picone, O., Jacquemard, F., & Ville, Y. (2016). In utero treatment of congenital cytomegalovirus infection with valacyclovir in a multicenter, open-label, phase II study. Am J Obstet Gynecol, 215(4), 462.e461-462.e410. https://doi.org/10.1016/j.ajog.2016.04.003

735 Leyder, M., Vorsselmans, A., Done, E., Van Berkel, K., Faron, G., Foulon, I., Naessens, A., Jansen, A.,
736 Foulon, W., & Gucciardo, L. (2016). Primary maternal cytomegalovirus infections: accuracy of fetal
737 ultrasound for predicting sequelae in offspring. Am J Obstet Gynecol, 215(5), 638.e631-638.e638.
738 https://doi.org/10.1016/j.ajog.2016.06.003

739 Lipitz, S., Yinon, Y., Malinger, G., Yagel, S., Levit, L., Hoffman, C., Rantzer, R., & Weisz, B. (2013). Risk of
740 cytomegalovirus-associated sequelae in relation to time of infection and findings on prenatal
741 imaging. Ultrasound Obstet Gynecol, 41(5), 508-514. https://doi.org/10.1002/uog.12377

742 Lombardi, G., Garofoli, F., Villani, P., Tizzoni, M., Angelini, M., Cusato, M., Bollani, L., De Silvestri, A.,
743 Regazzi, M., & Stronati, M. (2009). Oral valganciclovir treatment in newborns with symptomatic
744 congenital cytomegalovirus infection. Eur J Clin Microbiol Infect Dis, 28(12), 1465-1470.
745 https://doi.org/10.1007/s10096-009-0806-5

746 Lü, J., Huang, Z., Yang, T., Li, Y., Mei, L., Xiang, M., Chai, Y., Li, X., Li, L., Yao, G., Wang, Y., Shen, X., & Wu,
747 H. (2011). Screening for delayed-onset hearing loss in preschool children who previously passed
748 the newborn hearing screening. Int J Pediatr Otorhinolaryngol, 75(8), 1045-1049.
749 https://doi.org/10.1016/j.ijporl.2011.05.022

750 McCrary, H., Sheng, X., Greene, T., & Park, A. (2019). Long-term hearing outcomes of children with
751 symptomatic congenital CMV treated with valganciclovir. Int J Pediatr Otorhinolaryngol, 118, 124-
752 127. https://doi.org/10.1016/j.ijporl.2018.12.027

753 Mercuri, M., Baigrie, B., & Upshur, R. E. G. (2018). Going from evidence to recommendations: Can GRADE
754 get us there? J Eval Clin Pract, 24(5), 1232-1239. https://doi.org/10.1111/jep.12857

Michaels, M. G., Greenberg, D. P., Sabo, D. L., & Wald, E. R. (2003). Treatment of children with congenital cytomegalovirus infection with ganciclovir. Pediatr Infect Dis J, 22(6), 504-509. https://doi.org/10.1097/01.inf.0000069767.43169.2d

Misono, S., Sie, K. C., Weiss, N. S., Huang, M. L., Boeckh, M., Norton, S. J., & Yueh, B. (2011). Congenital cytomegalovirus infection in pediatric hearing loss. Arch Otolaryngol Head Neck Surg, 137(1), 47-53. https://doi.org/10.1001/archoto.2010.235

Morrison, A., Polisena, J., Husereau, D., Moulton, K., Clark, M., Fiander, M., Mierzwinski-Urban, M., Clifford, T., Hutton, B., & Rabb, D. (2012). The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. Int J Technol Assess Health Care, 28(2), 138-144. https://doi.org/10.1017/s0266462312000086

Nigro, G., Adler, S. P., Gatta, E., Mascaretti, G., Megaloikonomou, A., La Torre, R., & Necozione, S. (2012). Fetal hyperechogenic bowel may indicate congenital cytomegalovirus disease responsive to immunoglobulin therapy. J Matern Fetal Neonatal Med, 25(11), 2202-2205. https://doi.org/10.3109/14767058.2012.684111

Noorbakhsh, S., Farhadi, M., Haghighi, M., Movahedi, Z., Jomeh, H. E., & Ashouri, S. (2017). Searching the CMV infection (Ag65 in blood; and CMV-DNA (PCR in perilymphatic fluid) in children with cochlear implant surgery: a cross sectional study in Tehran, Iran. Curr Pediatr Res, 21(3), 395-399.

O'Connor, A., O'Sullivan, P. G., Behan, L., Norman, G., & Murphy, B. (2013). Initial results from the newborn hearing screening programme in Ireland. Ir J Med Sci, 182(4), 551-556. https://doi.org/10.1007/s11845-013-0924-z

Ogawa, H., Suzutani, T., Baba, Y., Koyano, S., Nozawa, N., Ishibashi, K., Fujieda, K., Inoue, N., & Omori, K. (2007). Etiology of severe sensorineural hearing loss in children: independent impact of congenital

cytomegalovirus infection and GJB2 mutations. J Infect Dis, 195(6), 782-788. https://doi.org/10.1086/511981

Ontario Ministry of Children and Youth Services Ontario Infant Hearing Program. (2017). Ontario Infant Hearing Program: a guidance document. .

Oosterom, N., Nijman, J., Gunkel, J., Wolfs, T. F., Groenendaal, F., Verboon-Maciolek, M. A., & de Vries, L. S. (2015). Neuro-imaging findings in infants with congenital cytomegalovirus infection: relation to trimester of infection. Neonatology, 107(4), 289-296. https://doi.org/10.1159/000375439

Park, A. H., Duval, M., McVicar, S., Bale, J. F., Hohler, N., & Carey, J. C. (2014). A diagnostic paradigm including cytomegalovirus testing for idiopathic pediatric sensorineural hearing loss. Laryngoscope, 124(11), 2624-2629. https://doi.org/10.1002/lary.24752

Pasternak, Y., Ziv, L., Attias, J., Amir, J., & Bilavsky, E. (2018). Valganciclovir Is Beneficial in Children with Congenital Cytomegalovirus and Isolated Hearing Loss. J Pediatr, 199, 166-170. https://doi.org/10.1016/j.jpeds.2018.02.028

Pati, S. K., Pinninti, S., Novak, Z., Chowdhury, N., Patro, R. K., Fowler, K., Ross, S., & Boppana, S. (2013). Genotypic diversity and mixed infection in newborn disease and hearing loss in congenital cytomegalovirus infection. Pediatr Infect Dis J, 32(10), 1050-1054. https://doi.org/10.1097/INF.0b013e31829bb0b9

Rawlinson, W. D., Boppana, S. B., Fowler, K. B., Kimberlin, D. W., Lazzarotto, T., Alain, S., Daly, K., Doutré, S., Gibson, L., Giles, M. L., Greenlee, J., Hamilton, S. T., Harrison, G. J., Hui, L., Jones, C. A., Palasanthiran, P., Schleiss, M. R., Shand, A. W., & van Zuylen, W. J. (2017). Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. Lancet Infect Dis, 17(6), e177-e188.

799 Rawlinson, W. D., Palasanthiran, P., Hall, B., Al Yazidi, L., Cannon, M. J., Cottier, C., van Zuylen, W. J., &
800 Wilkinson, M. (2018). Neonates with congenital Cytomegalovirus and hearing loss identified via
801 the universal newborn hearing screening program. J Clin Virol, 102, 110-115.
802 https://doi.org/10.1016/j.jcv.2018.03.006

803 Retzler, J., Hex, N., Bartlett, C., Webb, A., Wood, S., Star, C., Griffiths, P., & Jones, C. E. (2019). Economic
804 cost of congenital CMV in the UK. Arch Dis Child, 104(6), 559-563.
805 https://doi.org/10.1136/archdischild-2018-316010

806 Riga, M., Korres, G., Chouridis, P., Naxakis, S., & Danielides, V. (2018). Congenital cytomegalovirus
807 infection inducing non-congenital sensorineural hearing loss during childhood; a systematic
808 review. Int J Pediatr Otorhinolaryngol, 115, 156-164. https://doi.org/10.1016/j.ijporl.2018.10.005

809 Ross, S. A., Ahmed, A., Palmer, A. L., Michaels, M. G., Sánchez, P. J., Stewart, A., Bernstein, D. I., Feja, K.,
810 Fowler, K. B., & Boppana, S. B. (2017). Newborn dried blood spot polymerase chain reaction to
811 identify infants with congenital cytomegalovirus-associated sensorineural hearing loss. J Pediatr,
812 184, 57-61.e51. https://doi.org/10.1016/j.jpeds.2017.01.047

813 Ross, S. A., Novak, Z., Fowler, K. B., Arora, N., Britt, W. J., & Boppana, S. B. (2009). Cytomegalovirus blood
814 viral load and hearing loss in young children with congenital infection. Pediatr Infect Dis J, 28(7),
815 588-592. https://doi.org/10.1097/INF.0b013e3181979a27

816 Royackers, L., Rector, E., Verhaert, N., & Desloovere, C. (2013). Long-term audiological follow-up of
817 children with congenital cytomegalovirus. B-ent, Suppl 21, 57-64.

818 Samileh, N., Ahmad, S., Mohammad, F., Framarz, M., Azardokht, T., & Jomeht, E. (2008). Role of
819 cytomegalovirus in sensorineural hearing loss of children: a case-control study Tehran, Iran. Int J
820 Pediatr Otorhinolaryngol, 72(2), 203-208. https://doi.org/10.1016/j.ijporl.2007.10.009

Siddaway, A. P., Wood, A. M., & Hedges, L. V. (2019). How to Do a Systematic Review: A Best Practice Guide for Conducting and Reporting Narrative Reviews, Meta-Analyses, and Meta-Syntheses. Annu Rev Psychol, 70, 747-770. https://doi.org/10.1146/annurev-psych-010418-102803

Stehel, E. K., Shoup, A. G., Owen, K. E., Jackson, G. L., Sendelbach, D. M., Boney, L. F., & Sánchez, P. J. (2008). Newborn hearing screening and detection of congenital cytomegalovirus infection. Pediatrics, 121(5), 970-975. https://doi.org/10.1542/peds.2006-3441

Sugiura, S., Yoshikawa, T., Nishiyama, Y., Morishita, Y., Sato, E., Beppu, R., Hattori, T., & Nakashima, T. (2004). Detection of herpesvirus DNAs in perilymph obtained from patients with sensorineural hearing loss by real-time polymerase chain reaction. Laryngoscope, 114(12), 2235-2238. https://doi.org/10.1097/01.mlg.0000149466.80703.55

Tagawa, M., Tanaka, H., Moriuchi, M., & Moriuchi, H. (2009). Retrospective diagnosis of congenital cytomegalovirus infection at a school for the deaf by using preserved dried umbilical cord. J Pediatr, 155(5), 749-751. https://doi.org/10.1016/j.jpeds.2009.04.033

Thangavelu, K., Martakis, K., Fabian, S., Venkateswaran, M., Roth, B., Beutner, D., & Lang-Roth, R. (2019). Prevalence and risk factors for hearing loss in high-risk neonates in Germany. Acta Paediatr, 108(11), 1972-1977. https://doi.org/10.1111/apa.14837

The Joint Committee on Infant Hearing. (2007). Year 2007 position statement: Principles and guidelines for early hearing detection and intervention programs. Pediatrics, 120(4), 898-921. https://doi.org/10.1542/peds.2007-2333

The Joint Committee on Infant Hearing. (2019). Year 2019 position statement: Principles and guidelines for early hearing detection and intervention programs. The Journal of Early Hearing Detection and Intervention, 4(2), 1-44.

Turner, K. M., Lee, H. C., Boppana, S. B., Carlo, W. A., & Randolph, D. A. (2014). Incidence and impact of CMV infection in very low birth weight infants. Pediatrics, 133(3), e609-615. https://doi.org/10.1542/peds.2013-2217

Uematsu, M., Haginoya, K., Kikuchi, A., Hino-Fukuyo, N., Ishii, K., Shiihara, T., Kato, M., Kamei, A., & Kure, S. (2016). Asymptomatic congenital cytomegalovirus infection with neurological sequelae: A retrospective study using umbilical cord. Brain Dev, 38(9), 819-826. https://doi.org/10.1016/j.braindev.2016.03.006

Verbeeck, J., Van Kerschaver, E., Wollants, E., Beuselinck, K., Stappaerts, L., & Van Ranst, M. (2008). Detection of perinatal cytomegalovirus infection and sensorineural hearing loss in belgian infants by measurement of automated auditory brainstem response. J Clin Microbiol, 46(11), 3564-3568. https://doi.org/10.1128/jcm.00757-08

Vollmer, B., Seibold-Weiger, K., Schmitz-Salue, C., Hamprecht, K., Goelz, R., Krageloh-Mann, I., & Speer, C. P. (2004). Postnatally acquired cytomegalovirus infection via breast milk: effects on hearing and development in preterm infants. Pediatr Infect Dis J, 23(4), 322-327. https://doi.org/10.1097/00006454-200404000-00009

Vos, B., Lagasse, R., & Levêque, A. (2014). Main outcomes of a newborn hearing screening program in Belgium over six years. Int J Pediatr Otorhinolaryngol, 78(9), 1496-1502. https://doi.org/10.1016/j.ijporl.2014.06.019

Vos, B., Noll, D., Pigeon, M., Bagatto, M., & Fitzpatrick, E. M. (2019). Risk factors for hearing loss in children: a systematic literature review and meta-analysis protocol. Syst Rev, 8(1), 172. https://doi.org/10.1186/s13643-019-1073-x

Watkin, P. M., & Baldwin, M. (2011). Identifying deafness in early childhood: requirements after the newborn hearing screen. Arch Dis Child, 96(1), 62-66. https://doi.org/10.1136/adc.2010.185819

Weichbold, V., Nekahm-Heis, D., & Welzl-Mueller, K. (2006). Universal newborn hearing screening and postnatal hearing loss. Pediatrics, 117(4), e631-636. https://doi.org/10.1542/peds.2005-1455

Wood, S. A., Davis, A. C., & Sutton, G. J. (2013). Effectiveness of targeted surveillance to identify moderate to profound permanent childhood hearing impairment in babies with risk factors who pass newborn screening. Int J Audiol, 52(6), 394-399. https://doi.org/10.3109/14992027.2013.769067

Wood, S. A., Sutton, G. J., & Davis, A. C. (2015). Performance and characteristics of the Newborn Hearing Screening Programme in England: The first seven years. Int J Audiol, 54(6), 353-358. https://doi.org/10.3109/14992027.2014.989548

Wroblewska-Seniuk, K., Chojnacka, K., Pucher, B., Szczapa, J., Gadzinowski, J., & Grzegorowski, M. (2005). The results of newborn hearing screening by means of transient evoked otoacoustic emissions. Int J Pediatr Otorhinolaryngol, 69(10), 1351-1357. https://doi.org/10.1016/j.ijporl.2005.03.023

Yadav, S. S., Narula, G., Narayan, S., Biswas, S., & Gupta, G. (2010). Cytomegalovirus infection in six neonates. Indian Pediatr, 47(2), 174-175. https://doi.org/10.1007/s13312-010-0028-z

Yamamoto, A. Y., Mussi-Pinhata, M. M., Isaac Mde, L., Amaral, F. R., Carvalheiro, C. G., Aragon, D. C., Manfredi, A. K., Boppana, S. B., & Britt, W. J. (2011). Congenital cytomegalovirus infection as a cause of sensorineural hearing loss in a highly immune population. Pediatr Infect Dis J, 30(12), 1043-1046. https://doi.org/10.1097/INF.0b013e31822d9640

Figure 1: PRISMA flowchart

886

887 **Supplemental digit content**

888 Search strategy 1.pdf

889 Summary table (extracted data) 2.pdf

Figure 1: PRISMA flowchart

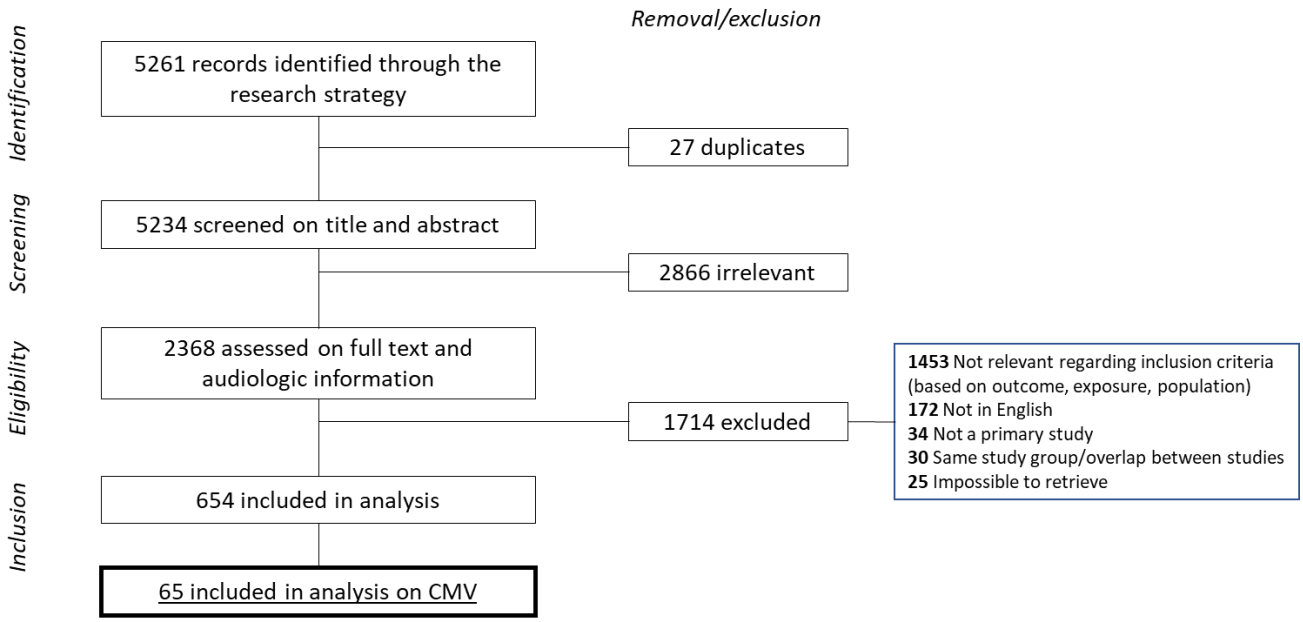

**Table 1: Eligibility criteria**

| | |
|---|---|
| Design | I: Randomized controlled trials, quasi-experimental studies, nonrandomized comparative or non-comparative studies, case series.<br>E: Case reports |
| Population | Children |
| Exposure | CMV infection |
| Outcome | Primary outcome: bilateral or unilateral PCHL (congenital or delayed onset)<br>Secondary outcome: progressive PCHL |
| Timing | ≥1985 (birth cohorts and hearing assessments) |

I: inclusion criteria; E: exclusion criteria; PCHL: permanent childhood hearing loss

**Table 2: Summarized prevalence of PCHL in newborns with cCMV (symptomatic, asymptomatic, combined or unspecified)**

| Symptomatic status at birth | Number of studies | Reported prevalence (range) | References |
|---|---|---|---|
| Symptomatic cCMV | 9 * | 33.7%-71.4% | Alarcon et al., 2013; Goderis et al., 2016; Kimberlin et al., 2003; Kimberlin et al., 2015; Leruez-Ville et al., 2016; Lombardi et al., 2009; Michaels et al., 2003; Ross et al., 2017; Royackers et al., 2013 |
| Asymptomatic cCMV | 5 * | 0.0%-14.9% | Engman et al., 2008; Goderis et al., 2016; Leruez-Ville et al., 2016; Ross et al., 2017; Royackers et al., 2013 |
| Combined (symptomatic and asymptomatic cCMV) | 15 * | 0.0%-66.6% | Barkai et al., 2014; Bilavsky et al., 2016; Dar et al., 2017; Duryea et al., 2010; Fowler et al., 2017; Goycochea-Valdivia et al., 2017; Karimian et al., 2016; Kasztelewicz et al., 2017; Korndewal et al., 2017; Leruez-Ville et al., 2016; Nigro et al., 2012; Pati et al., 2013; Ross et al., 2017; Royackers et al., 2013; Stehel et al., 2008 |
| Unspecified if symptomatic or asymptomatic cCMV | 2 | 14.6%-16.3% | Amir J. et al., 2016 ; Foulon I. et al., 2015 |

*Including 4 studies whose results were used in several subgroups: symptomatic, asymptomatic, combined symptomatic/asymptomatic

cCMV: congenital cytomegalovirus, PCHL: permanent childhood hearing loss

**Table 3: Summarized prevalence of PCHL in children (during childhood)**

| Age at assessment[$] | Number of studies | Range of prevalence | Contributing articles |
|---|---|---|---|
| **Symptomatic cCMV** | | | |
| ≤1 yr | 3 | 50%-85% | del Rosal T. et al., 2012 ; Iwasaki S. et al., 2007; Lombardi G. et al., 2009 |
| >1 yr | 9 | 7.7%-62.6% | Alarcon A. et al., 2013; Foulon I. et al., 2012; Giannattasio A. et al., 2017; Goderis J. et al., 2016; Korndewal M. J. et al., 2017 ; Lanari M. et al., 2006; Michaels M. G. et al., 2003; Ross S. et al., 2009; Yamamoto A. Y. et al., 2011 |
| **Asymptomatic cCMV** | | | |
| ≤1 yr | 2 | 0-25% | Iwasaki S. et al., 2007; Lackner A. et al., 2009 |
| >1 yr | 9 | 2.8%-18.6% | Engman M-L. et al., 2008; Foulon I. et al., 2012; Giannattasio A. et al., 2017; Goderis J. et al., 2016; Korndewal M. J. et al., 2017 ; Lackner A. et al., 2009; Lanari M. et al., 2006; Ross S. et al., 2009; Yamamoto A. Y. et al., 2011 |
| ≤1 and >1 yr | 3 | 0%-66.7% | Forner G. et al., 2015; Leruez-Ville M. et al., 2016; Uematsua M. et al., 2016 |
| **Combined (symptomatic/asymptomatic cCMV)** | | | |
| ≤1 yr | 3 | 27.7%-35.7% | Goycochea-Valdivia W-A. et al., 2017; Iwasaki S. et al., 2007*; Kasztelewicz B. et al., 2017 |
| >1 yr | 13 | 0%-83% | Bilavsky E. et al., 2016; Capretti M. G. et al., 2014; Foulon I. et al., 2012 *; Giannattasio A. et al., 2017*; Goderis J. et al., 2016*; Iwasaki S. et al., 2007*; Karimian P. et al., 2016; Korndewal M. J. et al., 2017; Lanari M. et al., 2006*; Ross S. et al., 2009*; Ross S. et al., 2017; Turner K. M. et al., 2014; Yamamoto A. Y. et al., 2011* |
| ≤1 and >1 yr; and NR) | 5 | 2.6%-25% | Barkai G. et al., 2014; Dar L. et al., 2017; Fowler K. B. et al., 2017 ; Hicks T. et al., 1993; Oosterom N. et al., 2015 |
| **Unspecified if symptomatic or asymptomatic cCMV** | | | |
| >1 yr | 2 | 14.9%-16% | Cannie M. M. et al., 2016 ; Foulon I. et al., 2015 |
| ≤1 and >1 yr; and NR) | 2 | 8.8%-25.7% | Leyder M. et al., 2016 ; Lipitz S. et al., 2013 |
| **Postnatal CMV** | | | |
| >1 yr | 3 | 0% | Gunkel J. et al., 2018; Jim W-T. et al., 2015; Vollmer B. et al., 2004 |
| **Unspecified time of CMV infection** | | | |
| >1 yr | 1 | 33.3% | Yadav S. S. et al., 2010 |

*: Results of the study extracted in several sections (symptomatic/asymptomatic/combined)

$: based on age (range) at follow-up or assessment (on mean and standard deviation if not available)

(c)CMV: (congenital) cytomegalovirus, PCHL: permanent childhood hearing loss, NR: not reported, yr: year

**Table 4: Proportion of CMV infection in children with PCHL**

| Author, year | Population | Proportion of CMV |
|---|---|---|
| Avettand-Fenoel V. et al., 2013 | 100 with B-HL, <3 yr | 8.0% (2.7-13.3) (8/100) CMV PCR+ on DBS; 13.7% (8/59) in profound B-HL |
| Barbi M. et al., 2003 | 130 with SNHL >40 dB HL in the best ear | In unidentified cause of HL: 10% (9/87) <2 mo, 34.2% (13/38) in 3 mo-4 yr. Excluding familial and syndromic etiology: 15.8% (9/57) <2 mo, 39.4% (13/33) in 3 mo-4 yr. |
| Boudewyns A. et al., 2009 | 41 with U- or B-SNHL of any severity after failed UNHS<br>Ctl: 55 with SNHL after passed NHS | 7.3% (3/41) with cCMV in congenital HL (after failed NHS) vs 7.3% (4/55) in non-congenital HL (after passing NHS) |
| Courtmans I. et al., 2015 | 75 with HL and DBS available | 10.6% (8/75) CMV DNA detected in DBS |
| de Vries J.J.C. et al., 2013 | 76 pediatric CI recipients (8 mo-8 yr) | 14% (10/70) CMV DNA+ on DBS |
| Devdariani T. et al., 2011 | 15 with HL<br>Ctl: 30 healthy matched on age | At 3-6yr: CMV IgG in 93.3% (14/15) with HL, 46.7% (14/30) ctl; CMV IgM in 6,7% (1/15) with HL, 0% (0/30) ctl (p=0.0029) |
| Furutate S. et al., 2011 | 134 with B- or U-SNHL | 8.7% (4/46) CMV DNA+ dried umbilical cord specimens in B-SNHL, 6.8% (8/88) CMV DNA positive in U-SNHL |
| Kimani J. W. et al., 2010 | 112 with HL (after NHS or later with age at onset 9-24 mo) | 10% (11/109) CMV DNA positive on DBS |
| Korver A.M.H. et al., 2009 | 179 with PCHL at age 3-5 yr, with DBS and hearing screening in 1st yr of life | 8% (14/179) (23% (9/39) of profound PCHL (>90 dB)) |
| Misono S. et al., 2011 | 222 with HL, >4 yr; 132 additional cases<br>Ctl: 222 (matching DOB, sex, race, hospital birth), with NH | 9.9% (22/222) cCMV in cases; 1.4% (3/222) in controls. Population attributable risk: 8.9%.<br>9.9% (35 cCMV/354) |
| Noorbakhsh S. et al., 2017 | 39 CI candidates | 43% (18/39) CMV-Ag65+, 26.7% (10/39) CMV-PCR+ in perilymphatic fluid |
| Ogawa H. et al., 2007 | 67 with severe SNHL<br>Ctl: 4 with typical sympt. cCMV at birth | 14.9% (10/67) |
| Park A. H. et al., 2014 | 83 with SNHL (<3 yr), no obvious etiology | 30% (25/83) with probable (n=9) or confirmed (n=16) CMV induced SNHL |
| Rawlinson W. D. et al., 2018 | 323 with confirmed HL after failed NHS and CMV testing after failed NHS | 5.9% (19/323) with cCMV (8 probable + 11 definite) |
| Samileh N. et al., 2008 | 95 with SNHL with unknown etiology<br>Ctl: 63 matched for age | 34.7% (33/95) CMV-IgM, 72.6% (69/95) CMV-IgG in cases; 3.5% (2/57) CMV-IgM, 94.7% (54/57) CMV-IgG in ctl (p<0.001) |
| Sugiura S. et al., 2004 | 14 with SNHL (CI recipients) | 21.4% (3/14) cCMV (2 sympt.) |
| Tagawa M. et al., 2009 | 26 with B-SNHL (profound/severe) without severe mental or physical handicap) from a school for the deaf | 12% (3/26) CMV-DNA detected on cord samples (asympt.) |
| Verbeeck J. et al., 2008 | 194 who failed first NHS (58 without confirmed HL, 146 with confirmed HL)<br>Ctl: 332 healthy newborns matched for cases | 1) cell culture: 10.3% (14/134) in HL, 6.9% (4/58) in NH after failed NHS, 3.3% (11/332) in ctl<br>2) quantitative PCR: 12.5% (17/134) in HL, 8.6% (5/58) in NH after failed NHS, 4.5% (15/332) in ctl.<br>OR: 8.1 (1.7-38.6) for CMV viral load ≥4.5 log copies/ml |

Asympt.: asymptomatic, B-: bilateral, cCMV: congenital cytomegalovirus, CMV: cytomegalovirus, ctl: control(s), dB: decibel, DNA: deoxyribonucleic acid, DBS: dried blood spots, HL: hearing loss, Ig: immunoglobulin, mo: month, NH: normal hearing, NHS: newborn hearing screening, PCHL: permanent childhood hearing loss, PCR: polymerase chain reaction, SNHL: sensorineural hearing loss, sympt.: symptomatic, U-: unilateral, yr: year

**Table 5: Characteristics of hearing loss (degree, laterality) in children with cCMV infection**

| Authors, year | Bilateral PCHL | Unilateral PCHL | Unspecified |
|---|---|---|---|
| **Symptomatic cCMV** | | | |
| del Rosal T. et al., 2012 | | | (ears) 7 mild, 3 mod., 8 sev.; at 12mo: 3 mild, 1 mod., 7 sev. |
| Foulon I. et al., 2012* | 4 | 1 | |
| Giannattasio A. et al., 2017 | | | 14 sev. |
| Goderis J. et al., 2016* | In 61% with PCHL: 28% | In 61% with PCHL: 33% | |
| Iwasaki S. et al., 2007* | | 1 prof. | |
| Kimberlin D. W. et al., 2003 | | | 10 mild, 1 mod., 6 sev. |
| Kimberlin D. W. et al., 2015 | | | 13 mild, 5 mod., 11 sev. |
| Korndewal M. J. et al., 2017* | 1 | 1 | |
| Lanari M. et al., 2006 | 3 sev. | 2 mild | 1 |
| Leruez-Ville M. et al., 2016 | 2 | 3 | |
| Lombardi G. et al., 2009 | | | 3 sev., 5 mod. |
| Michaels M. G. et al., 2003 | 1 mild/sev. | 2 mod., 2 sev.; 1 mild, 1 mod., 3 sev. at FU | |
| **Asymptomatic cCMV** | | | |
| Engman M-L. et al., 2008 | | 1 sev. | |
| Forner G. et al., 2015 | 4 sev. | 4 mod. | |
| Foulon I. et al., 2012* | 3 | 8 | |
| Goderis J. et al., 2016* | 4 mild, 1 mod., 1 prof. | 13 mild, 3 mod., 2 sev., 9 prof.; 15 at FU | |
| Iwasaki S. et al., 2007* | 1 prof. | 2 mild, 1 prof. | |
| Korndewal M. J. et al., 2017* | 1 | 2 | |
| Lackner A. et al., 2009 | 1 | 1 sev. | |
| Pasternak Y. et al., 2018 | 21 | 38 | |
| **Combined (symptomatic/asymptomatic cCMV)** | | | |
| Barkai G. et al., 2014 | | 1 mod. | 1 |
| Bilavsky E. et al., 2016 | 2 mild, 2 mod., 1 mod./sev., 1 sev. | 4 mild, 3 mod., 3 sev. | |
| Dar L. et al., 2017 | 2 prof. | | |
| Fowler K. B. et al., 2017 | 19 | 16 | |
| Hicks T. et al., 1993 | 2 mild, 1 mod., 6 prof. | 2 mod., 1 prof. | |
| Karimian P. et al., 2016 | 1 mild | | |
| Kasztelewicz B. et al., 2017 | 1 mild, 4 mod., 1 sev., 8 prof. | 1 mild, 2 mod., 5 prof. | |
| Nigro G. et al., 2012 | 1 | 1 | 2 |
| Oosterom N. et al., 2015 | 9 | | |
| Ross S. et al., 2009 | 5 | | 9 |
| Royackers L. et al., 2013 | 2 mild, 2 mod., 8 prof. | 1 mild, 5 mod., 3 sev., 7 prof. | |
| Stehel E. K. et al., 2008 | 2 mod., 1 sev., 3 prof. | 1 sev., 5 prof. | |
| Yamamoto A. Y. et al., 2011 | 1 mod., 4 prof. | 1 mod., 4 sev. | |
| **Unspecified if symptomatic or asymptomatic cCMV** | | | |
| Amir J. et al., 2016 | 2 sev. | 4 mild, 2 mod. | (ears) 13 mild, 9 mod., 3 sev. |
| Cannie M. M. et al., 2016 | 6 (including 3 sev.) | 12 (including 7 sev.) | |
| Foulon I. et al., 2015 | 5 mild to prof., 4 NR | 1 mild to prof., 8 NR | |
| Leyder M. et al., 2016 | 2 sev., 1 prof. | 1 mild, 5 sev. | |

*4 studies contributed to 2 subgroups (sympt and, asympt.)
cCMV: congenital cytomegalovirus, FU: follow-up; NR: no responses; mod.: moderate; PCHL: permanent childhood hearing loss; prof.: profound; sev.: severe

**Table 6: Late-onset PCHL in children**

| | Number of studies | Reported prevalence (range) | Contributing articles |
|---|---|---|---|
| **Symptomatic cCMV** | 5 | 0%-27.1% | del Rosal T. et al., 2012; Foulon I. et al., 2012*; Goderis J. et al., 2016* ; Lombardi G. et al., 2009; Michaels M. G. et al., 2003 |
| Cases reported but no denominator/prevalence in Korndewal M. J. et al., 2017*; Royackers L. et al., 2013* | | | |
| **Asymptomatic cCMV** | 5 | 0%-24.2% | Engman M-L. et al., 2008; Forner G. et al., 2015; Foulon I. et al., 2012*; Goderis J. et al., 2016*; Korndewal M. J. et al., 2017* |
| Cases reported but no denominator/prevalence in Iwasaki S. et al., 2007*; Lanari M. et al., 2006*; Royackers L. et al., 2013* | | | |
| **Combined (symptomatic/ asymptomatic cCMV)** | 10 | 0%-60% | Dar L. et al., 2017; Foulon I. et al., 2012*; Fowler K. B. et al., 2017; Goderis J. et al., 2016*; Karimian P. et al., 2016; Kasztelewicz B. et al., 2017; Korndewal M. J. et al., 2017*; Pati S. et al., 2013; Ross S. et al., 2009; Yamamoto A. Y. et al., 2011 |
| Cases reported but no denominator/prevalence in Barkai G. et al., 2014; Bilavsky E. et al., 2016; Goycochea-Valdivia W-A. et al., 2017; Iwasaki S. et al., 2007*; Lanari M. et al., 2006*; Royackers L. et al., 2013*; | | | |
| **Unspecified if symptomatic/ asymptomatic cCMV** | 1 | 1.5% | Foulon I. et al., 2015 |
| Cases reported but no denominator/prevalence in Amir J. et al., 2016; Leyder M. et al., 2016 | | | |
| **Late-onset PCHL among children with HL (retrospective studies)** | 3 | 20%-50% | Furutate S. et al., 2011; Korver A.M.H. et al., 2009; Tagawa M. et al., 2009 |

*: Results of the study extracted in several sections (symptomatic/asymptomatic/combined symptomatic and asymptomatic)
PCHL: permanent childhood hearing loss

**Table 7: Effects of treatment on hearing in cCMV children or infected fetuses**

| Author, year | Design | Population | Effects of treatment (based on the objective of the study) on HL (prevalence, evolution) | Treatment |
|---|---|---|---|---|
| **With control group** | | | | |
| Kimberlin D. W. et al., 2003 | Controlled clinical trial | 25 cCMV, with baseline/6-mo FU assessments and 6 wk treatment (sympt.)<br>Ctl: 17 cCMV, with baseline/6-mo FU assessments and untreated (sympt.) | 1. Improvement btw baseline and 6mo: 24% (6/25) in treated vs 29% (5/17) untreated (22% (11/49 ears) vs 17% (6/36 ears)); btw baseline and ≥1yr: 17% (4/24) vs 0% (0/19) (25% (12/48 ears) vs 0% (0/36 ears)).<br>2. NH at baseline and FU, btw baseline and 6mo: 60% (15/25) treated vs 29% (5/17) untreated (47% (23/49 ears) vs 22% (8/36 ears)); btw baseline and ≥1yr: 33% (8/24) vs 26% (5/19) (23% (11/48 ears) vs 22% (8/36 ears)).<br>3. Same degree of HL btw baseline and 6mo: 16% (4/25) treated vs 0% (0/17) untreated (31% (15/49 ears) vs 19% (7/36 ears); btw baseline and ≥1yr: 29% (7/24) vs 5% (1/19) (31% (15/48 ears) vs 17% (6/36 ears)).<br>84% (21/25) GCV recipients improved hearing/maintained NH btw baseline and 6mo vs 59% (10/17) ctl (p=0.06).<br>4. Worsening btw baseline and 6mo: 0% (0/25) treated vs 41% (7/17) untreated (0% (0/49 ears) vs 42% (15/36 ears)) (p<0.01); btw baseline and ≥1yr: 21% (5/24) vs 68% (13/19) (21% (10/48 ears) vs 61% (22/36 ears) (p<0.01). Significantly fewer GCV-treated patients had hearing deterioration at ≥1yr vs ctl (in best-ear analysis (adjusted p<0.01) and total ear analysis (adjusted p=0.03))<br>*Characteristics of HL: 10 mild (19 ears), 1 moderate (6 ears), 6 severe (19 ears) at baseline* | Randomly allocated: GCV (6 mg/kg IV every 12 hours for 6 wk) or no treatment. |
| Kimberlin D. W. et al., 2015 | Controlled clinical trial | 47 cCMV with 6mo-treatment (sympt.)<br>Ctl: 49 cCMV with 6wk-treatment (sympt.) | Btw baseline and 6mo FU, 6mo vs 6wk treatment: 4.7% (2/43) vs 7.0% (3/43) improved hearing, 65.1% (28/43) vs 53.5% (23/43) had NH (baseline and FU), 18.6% (8/43) vs 32.6 (14/43) kept same level of HI, 11.6% (5/43) vs 7.0% (3/43) worsened; aOR: 1.75 (0.69-4.43), p=0.24.<br>Btw baseline and 12mo FU, 6mo vs 6wk treatment: 4.9% (2/41) vs 5.0% (2/40) improved hearing, 73.2% (30/41) vs 57.5% (23/40) had NH (baseline and FU), 14.6% (6/41) vs 25.0% (10/40) kept same level of HI, 7.3% (3/41) vs 12.5% (5/40) worsened; aOR: 2.81 (0.99-7.99), p=0.05.<br>Btw baseline and 24mo FU, 6mo vs 6wk treatment: 5.4% (2/37) vs 6.5% (2/31) improved hearing, 81.1% (30/37) vs 64.5% (20/31) had NH (baseline and FU), 5.4% (2/37) vs 22.6% (7/31) kept same level of HI, 8.1% (3/37) vs 6.5% (2/31) worsened; aOR: 3.28 (0.91-11.9), p=0.07.<br>Significance is reached when all ears are considered: total-ear hearing more likely to be improved or to remain normal at 12mo in the 6-mo group than in the 6-wk group (73% vs. 57%, p=0.01). Benefit in total-ear hearing maintained at 24mo (77% vs. 64%, p=0.04).<br>Logistic regression (outcome: improved or protected in best ear or total ear): statistically significant results for 12mo analysis (best ear and total ears) and for 24mo analysis (best ear and total ears) --> 12mo analysis: best ear: aOR: 2.81 (0.99-7.99, p=0.05) and total ears: aOR: 3.04 (1.26-7.35, p=0.01); 24mo analysis: best ear: 3.28 (0.91-11.9, p=0.07), total ears: 2.61 (1.05-6.43, p=0.04)<br>*Characteristics of HL: 13 mild 13, 5 moderate, 11 severe at baseline* | V-GCV in all participants (16 mg/kg orally twice daily) for 6wk. Then, randomization in 1:1 ratio: continued V-GCV or placebo for 4.5mo. |
| Lackner A. et al., 2009 | Cohort prospective | 12 treated (asympt.)<br>Ctl: 11 untreated (asympt.) | Hearing loss in 0% (0/12) treated vs (0/11) untreated, during 1st yr and at 1yr;<br>0% (0/10) treated vs 25% (2/8) untreated (NS), at 4-10y FU (mean age (yr): 8.1 (4.2-11.2))<br>*Characteristics of HL: 1 B-SNHL (high-frequency), 1 U-SNHL (severe)* | Randomly allocated: IV GCV (within first 10 days of life + 10 mg GCV/kg for 21 days), or no therapy |
| **No control group** | | | | |
| del Rosal T. et al., 2012 | Retrospective | 13 sympt. cCMV and CNS involvement<br>No ctl group. | 85% (11/13) had elevated thresholds on BAER at CMV diagnosis; 50% (6/12) at 12 mo.<br>0% (0/8 NH ears at baseline), at 12mo FU<br>Improvement in 7/18 baseline-affected ears (3 mild, 3 moderate, 1 severe); no deterioration in remaining ears<br>*Characteristics of HL: 18/26 ears with HL at baseline: 7 mild, 3 moderate, 8 severe at baseline; 11 ears at 12 mo: 3 mild, 1 moderate, 7 severe* | V-GCV oral solution at 32mg/kg/day; some also received IV GCV prior to V-GCV (12 mg/kg/day). Treatment started after neonatal period. |

| | | | | |
|---|---|---|---|---|
| Leruez-Ville M. et al., 2016 | Cohort prospective | 40 infected fetuses (mothers treated during pregnancy)<br>No ctl group. | 12.5% (5/40, all in sympt. [5/7]), at birth<br>0% (0/33 asympt.) at med. FU (mo): 12 (4-36)<br>No LO HL.<br>*Characteristics of HL: 2 B-HL, 3 U-HL* | Oral V-GCV in pregnant women (2 g., 4 times a day). Medication continued until delivery or 24 treatment wk. |
| Lombardi G. et al., 2009 | Cohort prospective | 13 cCMV (sympt.)<br>No ctl group. | 61.5% (8/13), at baseline<br>61.5% (8/13) at 6-mo assessment.<br>Evolution at 6-mo FU: 6/8 with SNHL did not change, 2 improved scoring from 2 to 1 (mild, the lowest degree of impairment).<br>No LO HL.<br>*Characteristics of HL: 3 with severe score (highest reported level), 5 with moderate score at baseline* | Oral V-GCV of 90 mg/ml. 15 mg/kg of V-GCV syrup for 6wk and dose adjusted for weight gain during the 6wk treatment. |
| Michaels M. G. et al., 2003 | Retrospective | 9 sympt. cCMV and CNS involvement and/or HL (treated)<br>No ctl group. | At birth: 55.5% (5/9) before therapy starting at median age of 10 days (3 days-11mo). During childhood: 55.5% (5/9), median FU (yr): 2 (1-7).<br>0/5: progression of HL during 1-7yr FU; improvement in 2 (1 ear in each child: from mild to NH and from moderate to mild)<br>LO HL: 0% (0/4 NH at start of treatment) at 1-4yr FU<br>*Characteristics of HL: 1 B-HL (mild/severe), 4 U-HL (2 moderate, 2 severe) (before treatment); 5 U-HL (1 mild, 1 moderate, 3 severe) at FU* | <1yr of age with sympt. cCMV infection and CNS involvement, HL or both were offered treatment with IV GCV followed by oral GCV. |
| Pasternak Y. et al., 2018 | Retrospective | 59 with SNHL at birth and treated for cCMV <12wk of life and FU ≥1yr (asympt., except SNHL)<br>No ctl group. | 68.8% (55/80) affected ears at baseline improved, 2.5% (2/80) deteriorated, 28.8% (23/80) same level of HL.<br>96.3% (53/55) improved ears returned to NH with no deterioration in ears unaffected at baseline. Best ear evaluation: 21 with B-HL --> 16 (76.1%) improved (15/16 regaining NH); 0 deteriorated.<br>*Characteristics of HL: 21 B-SNHL, 38 U-SNHL* | (1) IV GCV 5 mg/kg/day for 6wk followed by oral V-GCV 17 mg/kg/dose twice a day for 6wk and then 1 daily dose until completion of 12mo of treatment; or (2) oral V-GCV 17 mg/kg/dose twice a day for 12wk, then 1 daily dose until completion of 12mo of treatment. |

aOR: adjusted odds ratio, Asympt.: asymptomatic, B-: bilateral, btw: between, cCMV: congenital cytomegalovirus, CMV: cytomegalovirus, CNS: central nervous system, ctl: control(s), FU: follow-up, GCV: ganciclovir, HL: hearing loss, IV: intravenous, LO HL: late-onset hearing loss, mo: month, NH: normal hearing, SNHL: sensorineural hearing loss, sympt.: symptomatic, U-: unilateral, V-GCV: Valganciclovir, vs: versus, wk: week, yr: year
In parenthesis: range of the descriptive data

**Table 8: Level of evidence according to each outcome**

| Outcome | Population | Level of evidence |
|---|---|---|
| Neonatal hearing loss | In symptomatic cCMV newborns | Low |
| | In asymptomatic cCMV newborns | Very low |
| | In cCMV newborns (symptomatic/asymptomatic) | Very low |
| PCHL (during childhood*, including late-onset) | In symptomatic | Low |
| | In asymptomatic | Low |
| | Globally | Low |
| | Postnatally | Very low |
| Progressive hearing loss | In symptomatic | Very low |
| | In asymptomatic | Very low |
| | Globally | Very low |
| | Postnatally | NA |

* effects of antiviral treatment not assessed

cCMV: congenital cytomegalovirus, NA: not applicable due to absence of subjects with hearing loss in reported studies, PCHL: permanent childhood hearing loss