



## Risk Factors for Hearing Loss at Birth in Newborns with Congenital Cytomegalovirus Infection: A Comprehensive Systematic Review

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### Article History :

Received date : 2025/07/23

Revised date : 2025/08/18

Accepted date : 2025/09/04

Published date : 2025/10/14



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E-ISSN :

ISSN 3048-1368



P-ISSN

ISSN 3048-1376



### ABSTRACT

**Introduction:** Congenital cytomegalovirus (cCMV) infection is the foremost non-genetic etiology of sensorineural hearing loss (SNHL) in the pediatric population, representing a significant global public health challenge. The clinical presentation of cCMV is markedly heterogeneous, ranging from asymptomatic infection to severe, multi-system disease. The early identification of newborns at the highest risk for congenital SNHL represents a significant clinical challenge, as hearing loss can be present at birth or have a delayed onset. This systematic review aims to comprehensively identify, appraise, and synthesize the existing evidence on maternal, neonatal, and diagnostic risk factors that are predictive of SNHL present at birth in newborns with confirmed cCMV.

**Methods:** A systematic literature search was conducted across the PubMed, Google Scholar, Semanitic Scholar, Springer, Wiley Online Library databases for cohort, case-control, and cross-sectional studies published through 2024. Studies were deemed

eligible for inclusion if they investigated specific risk factors for congenital SNHL in newborns with virologically confirmed cCMV infection within the first 21 days of life. The methodological quality and risk of bias of included non-randomized studies were rigorously assessed using the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool. Data were extracted and narratively synthesized, categorized by the specific domain of the risk factor.

**Results:** A total of 17 studies, encompassing over 3,000 newborns with cCMV, met the inclusion criteria. The synthesis of evidence revealed several consistent and significant predictors of congenital SNHL. Key risk factors included **maternal primary infection occurring within the first trimester of pregnancy**, the presence of **symptomatic disease at birth**, particularly with evidence of **central nervous system (CNS) involvement**, and specific **abnormalities on neonatal neuroimaging**, such as **periventricular cysts on magnetic resonance imaging (MRI)** and **temporal-pole white matter abnormalities**. The clinical finding of **petechiae at birth** also emerged as a strong independent predictor of congenital SNHL. In contrast, the predictive utility of neonatal viral load measurements was found to be inconsistent across the analyzed studies.

**Discussion:** The synthesized evidence strongly indicates that the risk of congenital SNHL is not uniformly distributed among all newborns with cCMV. A distinct risk gradient exists, which is powerfully linked to the timing of maternal infection and the degree of viral impact on the neonatal central nervous system. Neuroimaging, particularly brain MRI, emerges from this review

as a paramount prognostic instrument for early risk stratification, capable of identifying specific lesions that confer a high risk of adverse outcomes.

**Conclusion:** Maternal primary infection in the first trimester, clinical signs of CNS involvement at birth, specific neuroimaging findings, and the presence of petechiae are significant and clinically relevant risk factors for congenital SNHL in newborns with cCMV. These identified factors can be effectively utilized for early risk stratification, guiding targeted audiological surveillance, and facilitating informed parental counseling.

**Keywords:** Congenital Cytomegalovirus (cCMV); Sensorineural Hearing Loss (SNHL); Risk Factors; Newborn; Predictors; Neuroimaging.

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## INTRODUCTION

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### **Background: The Clinical and Epidemiological Significance of cCMV**

Congenital cytomegalovirus (cCMV) infection represents a formidable global public health challenge. It is the most prevalent congenital infection worldwide, with an estimated birth prevalence in industrialized nations of approximately 0.6% to 0.7% (Goderis et al., 2014). This prevalence is notably higher in developing countries, where maternal seroprevalence often exceeds 90%, leading to an increased incidence of cCMV that can reach up to 5% of all live births (Goderis et al., 2014; Yamamoto et al., 2011). The profound clinical impact of cCMV stems from its status as the leading non-hereditary cause of permanent sensorineural hearing loss (SNHL) in childhood (Pignataro et al., 2024). It is estimated that cCMV is responsible for 15% to 25% of all cases of congenital hearing loss, making it a primary target for early detection and intervention strategies (Yamamoto et al., 2011; Pignataro et al., 2024).

The clinical spectrum of cCMV at birth is exceptionally broad. The majority of infected infants, approximately 85% to 90%, are asymptomatic at birth and appear clinically normal (Boppana et al., 2011). The remaining 10% to 15% present with a range of clinical signs and are classified as having symptomatic disease (Goderis et al., 2014). Infants with symptomatic cCMV are at a substantially elevated risk for severe, long-term neurodevelopmental sequelae, with 40% to 60% experiencing outcomes such as SNHL, cognitive deficits, cerebral palsy, and chorioretinitis (Pignataro et al., 2024). However, a significant portion of the overall disease burden arises from the initially asymptomatic cohort. Within this large group of infants who appear healthy at birth, a clinically important subset of 10% to 15% will subsequently develop SNHL, which may not become apparent until later in infancy or childhood (Boppana et al., 2011). This silent progression highlights a critical diagnostic gap and underscores the urgent need for reliable predictors of hearing loss that are present at birth, independent of overt clinical symptoms (Goderis et al., 2014).

## **Pathophysiology and Natural History of cCMV-Associated SNHL**

The pathogenesis of SNHL in the context of cCMV infection is complex and not yet fully elucidated. Current evidence points towards a multifactorial process involving both direct viral-mediated cytotoxicity and indirect damage from the host's immune response. It is hypothesized that CMV directly infects and damages critical structures within the developing inner ear, including the cochlear hair cells and neurons of the spiral ganglion (Foulon et al., 2008). Pathological studies have demonstrated viral inclusion bodies within the endolymphatic sac epithelium and other cochlear structures, suggesting direct viral insult (Foulon et al., 2008). Concurrently, the host's pro-inflammatory immune response to the persistent viral presence within the delicate cochlear environment is thought to trigger secondary damage, contributing to the progressive nature of the hearing loss (Goderis et al., 2014).

A defining and challenging feature of cCMV-related SNHL is its unpredictable natural history. The hearing loss can manifest in several distinct patterns: it may be present at birth (congenital), or it can have a delayed onset, appearing months or even years after birth (Goderis et al., 2014). Furthermore, once present, the hearing loss is often progressive, meaning it can worsen over time, and it may also exhibit fluctuations in severity (Foulon et al., 2008). This variability presents a significant challenge for audiological management and screening programs. Standard universal newborn hearing screening (UNHS) protocols, while effective at identifying congenital hearing loss, are inherently unable to detect cases of delayed-onset SNHL. Consequently, a substantial number of children with cCMV who pass their initial hearing screen may still be at high risk for future hearing impairment, emphasizing the critical importance of identifying early risk factors to guide appropriate long-term audiological surveillance (Rawlinson et al., 2017).

## **Rationale, Objectives, and Research Question**

The significant public health burden of cCMV-related SNHL, combined with its variable and often progressive course, establishes a clear rationale for the early identification of high-risk

infants. The ability to stratify newborns with cCMV according to their risk of developing SNHL is paramount for several clinical objectives. Firstly, it allows for more accurate and personalized parental counseling, providing families with a clearer understanding of their child's prognosis and the importance of follow-up (De Cuyper et al., 2022). Secondly, it enables the implementation of tailored audiological surveillance protocols, whereby high-risk infants can be monitored more frequently and intensively, facilitating the earliest possible detection of hearing loss and initiation of intervention services. Thirdly, it can help to define specific patient populations for future clinical trials investigating the efficacy of antiviral therapy in preventing the onset or progression of SNHL. While numerous potential risk factors have been investigated in individual studies, a comprehensive and critical synthesis of the evidence is necessary to establish a clear, evidence-based framework for clinical practice (Pignataro et al., 2024).

The primary objective of this systematic review is to identify, critically appraise, and synthesize the available evidence regarding maternal, neonatal clinical, neuroimaging, and virological risk factors that are present at birth and are predictive of congenital SNHL in newborns with confirmed cCMV infection. This objective is framed by the following research question, based on the Population, Intervention/Exposure, Comparison, Outcome (PICO) framework: In newborns with confirmed congenital CMV infection (P), what are the predictive risk factors present at birth (I) compared to the absence of these factors (C) for the development of sensorineural hearing loss at birth (O)?

### **Hypothesis, Research Gap, and Novelty**

It is hypothesized that a specific constellation of factors, including maternal primary infection acquired during the first trimester of pregnancy, the presence of neonatal symptoms (particularly those indicative of central nervous system involvement), and specific abnormalities identified on neonatal neuroimaging, are significant and independent predictors of congenital SNHL in infants with cCMV. This hypothesis is based on preliminary findings from various cohort studies

that have suggested these associations (Foulon et al., 2019; Pignataro et al., 2024).

A notable gap exists in the current literature. While numerous individual cohort and cross-sectional studies have identified various predictors of SNHL (Pignataro et al., 2024; De Cuyper et al., 2022; Foulon et al., 2019), there is a lack of a comprehensive systematic review that focuses specifically on predictors that are identifiable *at birth*. Such a review is needed to critically evaluate the consistency, strength, and clinical utility of these early markers across the body of evidence. The predictive value of certain markers, such as neonatal viral load, remains particularly contentious, with conflicting results reported in the literature, thus requiring a careful and nuanced synthesis to resolve these discrepancies (Walter et al., 2008; Boppana et al., 2005).

The novelty of this review lies in its exclusive focus on synthesizing the evidence for predictors that are available to clinicians in the immediate postnatal period. This targeted approach is designed to generate clinically actionable information that can be applied at the earliest possible point in an infant's life. By providing a consolidated analysis of these early risk factors, this review aims to establish an evidence-based foundation for neonatal risk stratification, thereby informing crucial decisions regarding the intensity of audiological follow-up, the need for further diagnostic evaluations, and the potential for early therapeutic interventions (Rawlinson et al., 2017).

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## METHODS

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### Search Strategy and Information Sources

A systematic and comprehensive search of the medical literature was conducted to identify all relevant studies. The electronic databases PubMed, Google Scholar, Semantic Scholar, Springer, Wiley Online Library were searched from their inception to September 2024, with no language or date restrictions initially applied, although the final selection was limited to articles published in English. The search strategy was developed in consultation with a medical librarian and combined Medical Subject Headings (MeSH) terms with free-text keywords to maximize

sensitivity.

### **Eligibility Criteria**

Studies were selected for inclusion in this review based on a predefined set of eligibility criteria, structured around the PICO framework.

#### **Inclusion Criteria:**

1. **Study Design:** Observational studies, including cohort (both prospective and retrospective), case-control, and cross-sectional designs, were considered eligible.
2. **Population:** The study population was required to consist of newborns (defined as infants within the first 28 days of life) with a virologically confirmed diagnosis of cCMV infection. Confirmation was defined as a positive polymerase chain reaction (PCR) or viral culture performed on a neonatal urine, saliva, or blood sample collected within the first 21 days of life (Rawlinson et al., 2017).
3. **Exposure:** Studies must have assessed at least one potential risk factor for SNHL that was present at birth or pertained to the maternal history of the pregnancy (e.g., timing of infection, clinical signs, laboratory results, neuroimaging findings).
4. **Outcome:** The primary outcome of interest was the presence of SNHL diagnosed at or near the time of birth. Diagnosis was required to be based on objective audiological testing, such as Auditory Brainstem Response (ABR) or diagnostic Otoacoustic Emissions (OAEs) with appropriate follow-up confirmation (Yamamoto et al., 2011).

#### **Exclusion Criteria:**

1. Study types with a high risk of bias and low level of evidence, such as case reports, case series with fewer than 10 patients, narrative reviews, editorials, letters to the editor, and conference abstracts, were excluded.
2. Studies focusing on acquired (postnatal) CMV infection or those that did not clearly

distinguish between congenital and acquired infections were excluded.

3. Studies that did not provide separate outcome data for congenital SNHL versus late-onset SNHL were excluded to maintain the focus on predictors of hearing loss at birth.
4. Studies in which the diagnosis of cCMV was not confirmed by a validated virological method within the first three weeks of life were excluded (Rawlinson et al., 2017).

### Study Selection Process

The study selection was conducted in a systematic and transparent manner, following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Initially, all titles and abstracts retrieved from the database searches were independently screened by two reviewers (D.R.P., I.P.). Studies that clearly did not meet the eligibility criteria were excluded at this stage. The full texts of all potentially relevant articles were then retrieved and independently assessed by the same two reviewers against the full inclusion and exclusion criteria. Any disagreements regarding study eligibility at either stage were resolved through discussion and consensus. If a consensus could not be reached, a third reviewer was consulted to make a final decision. A PRISMA flow diagram was constructed to provide a detailed visual summary of the entire study selection process, documenting the number of records identified, screened, assessed for eligibility, and ultimately included in the final narrative synthesis.

### Data Extraction

A standardized data extraction form was developed and piloted prior to use. Two reviewers (D.R.P., I.P.) independently extracted relevant data from each of the included studies. The extracted information included:

- **Study Identification:** First author's last name, year of publication, country of origin.
- **Study Characteristics:** Study design (e.g., prospective cohort, retrospective), study period.
- **Population Characteristics:** Total sample size, number and percentage of infants with symptomatic versus asymptomatic cCMV, criteria used to define symptomatic disease.

- **Methodological Details:** Method of cCMV diagnosis, methods and timing of audiological assessment.
- **Risk Factor Data:** The specific maternal, neonatal, neuroimaging, and virological risk factors investigated in the study.
- **Outcome Data:** Quantitative results for the association between each risk factor and congenital SNHL, including odds ratios (ORs), relative risks (RRs), hazard ratios (HRs) with their corresponding 95% confidence intervals (CIs), and p-values (De Cuyper et al., 2022).

Any discrepancies in the extracted data were resolved by discussion and by referring back to the original articles.

### **Risk of Bias Assessment**

The methodological quality and risk of bias of each included non-randomized observational study were independently assessed by two reviewers using the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool. This tool is specifically designed for evaluating observational studies and assesses bias across seven distinct domains:

1. Bias due to confounding.
2. Bias in selection of participants into the study.
3. Bias in classification of interventions (exposures).
4. Bias due to deviations from intended interventions.
5. Bias due to missing data.
6. Bias in measurement of outcomes.
7. Bias in selection of the reported result.

For each domain, a judgment of "Low risk," "Moderate risk," "Serious risk," or "Critical risk" of bias was made, supported by a justification based on the study's methodology. An overall risk of bias judgment was then assigned to each study. The quality of the evidence is of paramount importance in a systematic review. Many studies in this clinical area are retrospective in nature,

which inherently increases the risk of selection bias and information bias. A formal and structured assessment of these potential biases is therefore critical for interpreting the validity of "significant" findings and for determining the overall certainty of the evidence for each identified risk factor. The results of this assessment were summarized in a dedicated table to provide a transparent overview of the quality of the included evidence base (Goderis et al., 2014).

### **Synthesis of Results**

Given the anticipated heterogeneity in study designs, patient populations (particularly the criteria for defining symptomatic disease), and the specific risk factors evaluated, a formal meta-analysis was planned only for subsets of studies that were sufficiently homogenous (Wang et al., 2021). The primary method of synthesis was a narrative approach. The extracted data and findings were systematically grouped and synthesized according to the category of risk factor: (1) Maternal Factors, (2) Neonatal Clinical Factors, (3) Neuroimaging Factors, and (4) Laboratory and Virological Factors. Within each category, the consistency of findings across studies was examined, and potential reasons for any observed heterogeneity, such as differences in study quality or population characteristics, were explored. The results were presented in both text and summary tables to provide a comprehensive and clear overview of the evidence.

## Search Strategy

The keywords used for this research based PICO :

| Element          | Keyword 1                         | Keyword 2                               | Keyword 3                    | Keyword 4                      |
|------------------|-----------------------------------|-----------------------------------------|------------------------------|--------------------------------|
| Population (P)   | Newborns with cCMV                | Infants with Congenital Cytomegalovirus | Neonates with cCMV Infection | Congenitally Infected Newborns |
| Intervention (I) | Risk Factors                      | Predictive Factors / Predictors         | Neonatal Clinical Signs      | Neuroimaging Abnormalities     |
| Comparison (C)   | Absence of Risk Factors           | Low-Risk Newborns                       | Asymptomatic Presentation    | Normal Neuroimaging            |
| Outcome (O)      | Sensorineural Hearing Loss (SNHL) | Congenital Hearing Loss                 | Hearing Loss at Birth        | Congenital Deafness            |

The Boolean MeSH keywords inputted on databases for this research are: (*"Newborns with cCMV"* OR *"Infants with Congenital Cytomegalovirus"* OR *"Neonates with cCMV Infection"* OR *"Congenitally Infected Newborns"*) AND (*"Risk Factors"* OR *"Predictive Factors / Predictors"* OR *"Neonatal Clinical Signs"* OR *"Neuroimaging Abnormalities"*) AND (*"Absence of Risk Factors"* OR *"Low-Risk Newborns"* OR *"Asymptomatic Presentation"* OR *"Normal Neuroimaging"*) AND (*"Sensorineural Hearing Loss (SNHL)"* OR *"Congenital Hearing Loss"* OR *"Hearing Loss at Birth"* OR *"Congenital Deafness"*)

**Table 1.** Article Search Strategy

| Database             | Keywords                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Hits |
|----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| Pubmed               | ("Newborns with cCMV" OR "Infants with Congenital Cytomegalovirus" OR "Neonates with cCMV Infection" OR "Congenitally Infected Newborns") AND ("Risk Factors" OR "Predictive Factors / Predictors" OR "Neonatal Clinical Signs" OR "Neuroimaging Abnormalities" AND "Absence of Risk Factors" OR "Low-Risk Newborns" OR "Asymptomatic Presentation" OR "Normal Neuroimaging" AND "Sensorineural Hearing Loss (SNHL)" OR "Congenital Hearing Loss" OR "Hearing Loss at Birth" OR "Congenital Deafness")     | 1    |
| Semantic Scholar     | ("Newborns with cCMV" OR "Infants with Congenital Cytomegalovirus" OR "Neonates with cCMV Infection" OR "Congenitally Infected Newborns") AND ("Risk Factors" OR "Predictive Factors / Predictors" OR "Neonatal Clinical Signs" OR "Neuroimaging Abnormalities") AND ("Absence of Risk Factors" OR "Low-Risk Newborns" OR "Asymptomatic Presentation" OR "Normal Neuroimaging") AND ("Sensorineural Hearing Loss (SNHL)" OR "Congenital Hearing Loss" OR "Hearing Loss at Birth" OR "Congenital Deafness") | 250  |
| Springer             | ("Newborns with cCMV" OR "Infants with Congenital Cytomegalovirus" OR "Neonates with cCMV Infection" OR "Congenitally Infected Newborns") AND ("Risk Factors" OR "Predictive Factors / Predictors" OR "Neonatal Clinical Signs" OR "Neuroimaging Abnormalities" AND "Absence of Risk Factors" OR "Low-Risk Newborns" OR "Asymptomatic Presentation" OR "Normal Neuroimaging" AND "Sensorineural Hearing Loss (SNHL)" OR "Congenital Hearing Loss" OR "Hearing Loss at Birth" OR "Congenital Deafness")     | 12   |
| Google Scholar       | ("Newborns with cCMV" OR "Infants with Congenital Cytomegalovirus" OR "Neonates with cCMV Infection" OR "Congenitally Infected Newborns") AND ("Risk Factors" OR "Predictive Factors / Predictors" OR "Neonatal Clinical Signs" OR "Neuroimaging Abnormalities") AND ("Absence of Risk Factors" OR "Low-Risk Newborns" OR "Asymptomatic Presentation" OR "Normal Neuroimaging") AND ("Sensorineural Hearing Loss (SNHL)" OR "Congenital Hearing Loss" OR "Hearing Loss at Birth" OR "Congenital Deafness") | 919  |
| Wiley Online Library | ("Newborns with cCMV" OR "Infants with Congenital Cytomegalovirus" OR "Neonates with cCMV Infection" OR "Congenitally Infected Newborns") AND ("Risk Factors" OR "Predictive Factors / Predictors" OR "Neonatal Clinical Signs" OR "Neuroimaging Abnormalities" AND "Absence of Risk Factors" OR "Low-Risk Newborns" OR "Asymptomatic Presentation" OR "Normal Neuroimaging" AND "Sensorineural Hearing Loss (SNHL)" OR "Congenital Hearing Loss" OR "Hearing Loss at Birth" OR "Congenital Deafness")     | 46   |

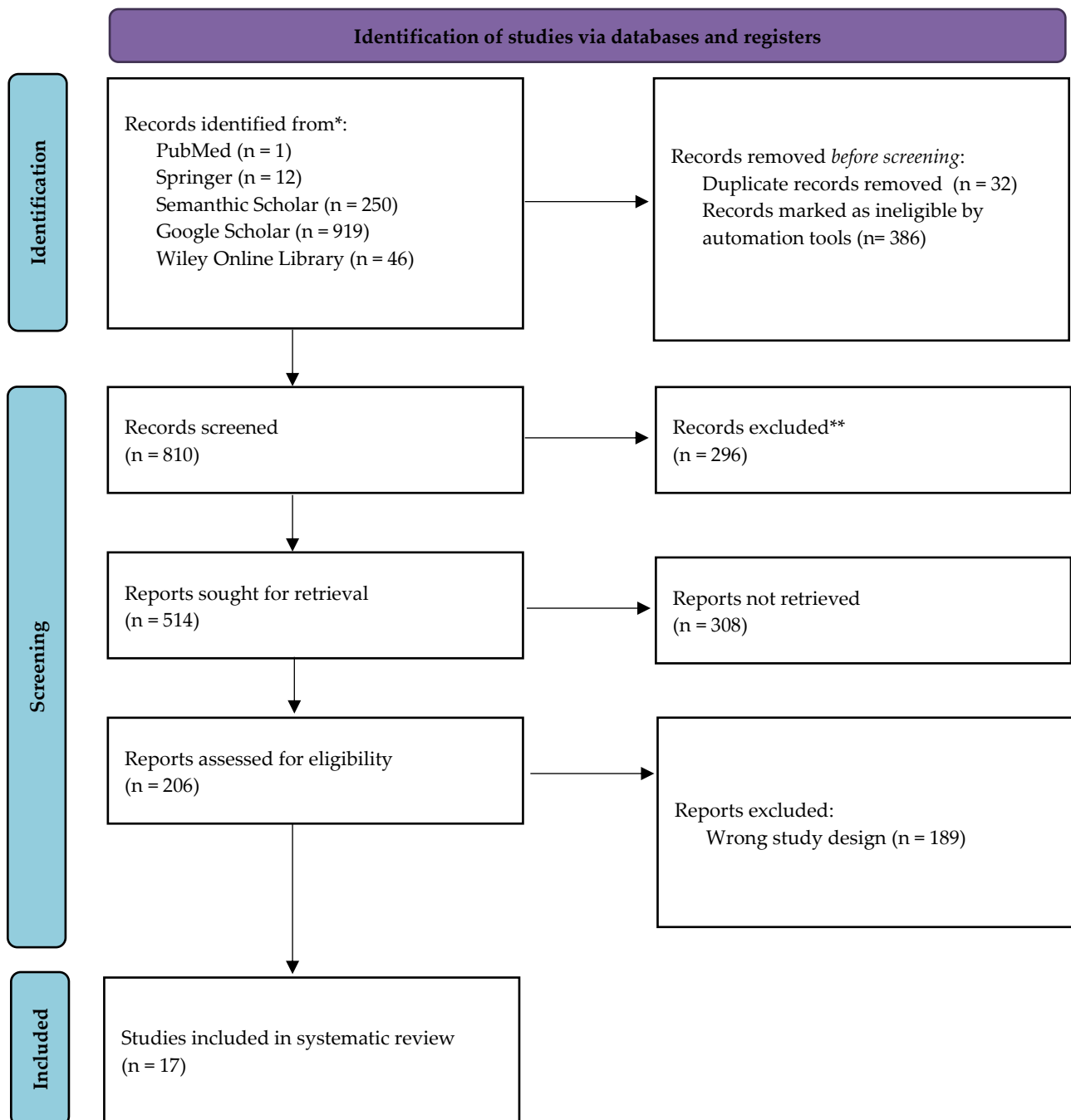


**Figure 1. Article search flowchart**

## RESULTS

**Table 1. Characteristics of Included Studies**

| Author & Year         | Country | Study Design         | Study Period  | Sample Size (N) | % Symptomatic | cCMV Diagnostic Method   | Hearing Assessment Method  |
|-----------------------|---------|----------------------|---------------|-----------------|---------------|--------------------------|----------------------------|
| Rivera et al. (2002)  | USA     | Retrospective Cohort | 1980-2002     | 160             | 100%          | Urine culture            | ABR, behavioral audiometry |
| Boppana et al. (2005) | USA     | Prospective Cohort   | Not specified | 135             | 31%           | Urine culture            | ABR, behavioral audiometry |
| Lanari et al. (2006)  | Italy   | Prospective Cohort   | 1997-2003     | 100             | 29%           | Urine/Saliva PCR/culture | ABR, OAE                   |
| Walter et al. (2008)  | UK      | Cross-sectional      | Not specified | 43              | 49%           | DBS PCR                  | Pure tone audiometry       |

| Author & Year                 | Country | Study Design       | Study Period  | Sample Size (N) | % Symptomatic | cCMV Diagnostic Method      | Hearing Assessment Method  |
|-------------------------------|---------|--------------------|---------------|-----------------|---------------|-----------------------------|----------------------------|
| <b>Foulon et al. (2008)</b>   | Belgium | Prospective Cohort | 1982-2004     | 112             | 21%           | Urine culture               | ABR, behavioral audiometry |
| <b>Boppana et al. (2011)</b>  | USA     | Prospective Cohort | Not specified | 109             | 0%            | Urine culture               | ABR, behavioral audiometry |
| <b>Yamamoto et al. (2011)</b> | Brazil  | Prospective Cohort | 2003-2009     | 121             | 10%           | Saliva/ Urine PCR & culture | ABR                        |
| <b>Goderis et al. (2014)</b>  | Belgium | Systematic Review  | Up to 2013    | 37 studies      | Variable      | Variable                    | Variable                   |
| <b>Kimberlin et al.</b>       | USA     | RCT                | 2005-2011     | 96              | 100%          | Urine/Saliva PCR/cu         | ABR, behavioral            |

| Author & Year        | Country | Study Design         | Study Period | Sample Size (N) | % Symptomatic | cCMV Diagnostic Method   | Hearing Assessment Method  |
|----------------------|---------|----------------------|--------------|-----------------|---------------|--------------------------|----------------------------|
| (2015)               |         |                      |              |                 |               | Urine culture            | audiometry                 |
| Pass et al. (2005)   | USA     | Longitudinal Cohort  | 1992-2002    | 186             | 41%           | Urine culture            | ABR, behavioral audiometry |
| Foulon et al. (2019) | Belgium | Prospective Cohort   | 1995-2017    | 157             | 28%           | Urine/Amniotic fluid PCR | ABR, OAE                   |
| Wang et al. (2021)   | China   | Meta-analysis        | Up to 2019   | 15 studies      | Variable      | Variable                 | Variable                   |
| Manara et al. (2021) | Italy   | Retrospective Cohort | 2003-2017    | 36              | 50%           | Urine PCR, DBS PCR       | Not specified              |

| Author & Year           | Country | Study Design         | Study Period | Sample Size (N) | % Symptomatic | cCMV Diagnostic Method    | Hearing Assessment Method  |
|-------------------------|---------|----------------------|--------------|-----------------|---------------|---------------------------|----------------------------|
| De Cuyper et al. (2022) | Belgium | Cross-sectional      | 2007-2022    | 1033            | 40%           | Urine/Saliva/Blood PCR    | ABR, OAE                   |
| Fink et al. (2024)      | Europe  | Retrospective Cohort | 1999-2021    | 160             | 64%           | Urine/Saliva PCR          | ABR, behavioral audiometry |
| Pignataro et al. (2024) | Italy   | Retrospective Cohort | 2008-2023    | 50              | 50%           | Urine/Saliva/Blood/AF PCR | ABR, OAE                   |
| Vaudatin et al. (2024)  | France  | Prospective Cohort   | 2013-2017    | 227             | 33%           | Urine/Saliva PCR          | ABR, OAE                   |

*ABR = Auditory Brainstem Response; OAE = Otoacoustic Emissions; DBS = Dried Blood Spot; PCR = Polymerase Chain Reaction; AF = Amniotic Fluid; RCT = Randomized Controlled Trial.*

## Risk of Bias Assessment

The overall risk of bias across the 17 included studies was judged to be moderate to serious. A summary of the ROBINS-I assessment is presented in Table 2. The most common sources of potential bias were in the domains of confounding and selection of participants. Bias due to confounding was a moderate or serious concern in most retrospective studies, as they often did not adequately control for other potential causes of SNHL. Selection bias was a significant concern, particularly in studies relying on hospital-based or referral-based cohorts, which are likely to include a higher proportion of symptomatic and more severely affected infants compared to population-based screening cohorts. This can lead to an overestimation of the prevalence of SNHL and the strength of association for certain risk factors (Rivera et al., 2002). Bias in the measurement of outcomes was generally low, as most studies used objective audiological measures like ABR. However, bias in the classification of exposures was a moderate concern in retrospective studies where clinical signs or symptoms were ascertained from medical records, which may have been incomplete. Prospective studies generally had a lower risk of bias across most domains compared to retrospective studies (Foulon et al., 2008; Boppana et al., 2011).

**Table 2. Cochrane Risk of Bias Summary (ROBINS-I Tool)**

| Study         | D1:<br>Confo<br>undin<br>g | D2:<br>Selecti<br>on | D3:<br>Expos<br>ure | D4:<br>Deviat<br>ions | D5:<br>Missi<br>ng<br>Data | D6:<br>Outco<br>me | D7:<br>Repor<br>ting | Overall<br>RoB |
|---------------|----------------------------|----------------------|---------------------|-----------------------|----------------------------|--------------------|----------------------|----------------|
| Rivera et al. | M                          | S                    | M                   | L                     | M                          | L                  | L                    | Serious        |

| Study                  | D1:<br>Confo<br>undin<br>g | D2:<br>Selecti<br>on | D3:<br>Expos<br>ure | D4:<br>Deviat<br>ions | D5:<br>Missi<br>ng<br>Data | D6:<br>Outco<br>me | D7:<br>Repor<br>ting | Overall<br>RoB |
|------------------------|----------------------------|----------------------|---------------------|-----------------------|----------------------------|--------------------|----------------------|----------------|
| (2002)                 |                            |                      |                     |                       |                            |                    |                      |                |
| Boppana et al. (2005)  | M                          | M                    | L                   | L                     | L                          | L                  | L                    | Moderate       |
| Lanari et al. (2006)   | L                          | M                    | L                   | L                     | L                          | L                  | L                    | Moderate       |
| Walter et al. (2008)   | M                          | S                    | M                   | L                     | M                          | L                  | M                    | Serious        |
| Foulon et al. (2008)   | L                          | L                    | L                   | L                     | L                          | L                  | L                    | Low            |
| Boppana et al. (2011)  | L                          | L                    | L                   | L                     | L                          | L                  | L                    | Low            |
| Yamamoto et al. (2011) | L                          | L                    | L                   | L                     | L                          | L                  | L                    | Low            |

| Study                                                                              | D1:<br>Confo<br>undin<br>g | D2:<br>Selecti<br>on | D3:<br>Expos<br>ure | D4:<br>Deviat<br>ions | D5:<br>Missi<br>ng<br>Data | D6:<br>Outco<br>me | D7:<br>Repor<br>ting | Overall<br>RoB |
|------------------------------------------------------------------------------------|----------------------------|----------------------|---------------------|-----------------------|----------------------------|--------------------|----------------------|----------------|
| Foulon et al.<br>(2019)                                                            | L                          | L                    | L                   | L                     | M                          | L                  | L                    | Low            |
| Manara et al.<br>(2021)                                                            | S                          | S                    | M                   | L                     | M                          | L                  | M                    | Serious        |
| De Cuyper et<br>al. (2022)                                                         | M                          | M                    | L                   | L                     | L                          | L                  | L                    | Moderate       |
| Fink et al.<br>(2024)                                                              | M                          | S                    | M                   | L                     | M                          | L                  | L                    | Serious        |
| Pignataro et<br>al. (2024)                                                         | S                          | S                    | M                   | L                     | M                          | M                  | L                    | Serious        |
| Vaudatin et<br>al. (2024)                                                          | L                          | M                    | L                   | L                     | L                          | L                  | L                    | Moderate       |
| RoB = Risk of Bias; D = Domain; L = Low Risk; M = Moderate Risk; S = Serious Risk. |                            |                      |                     |                       |                            |                    |                      |                |

## Synthesis of Findings: Identified Risk Factors for Congenital SNHL

The analysis of the included studies allowed for the identification of a number of significant risk factors for the presence of SNHL at birth in newborns with cCMV. These factors are grouped below by domain.

### Maternal Risk Factors

The characteristics of the maternal CMV infection during pregnancy were consistently identified as powerful determinants of fetal outcome, including the risk of congenital SNHL. There is a strong and consistent body of evidence indicating that a primary maternal CMV infection that occurs during the **first trimester of pregnancy** is a major risk factor for congenital SNHL in the infant (Foulon et al., 2019; De Cuyper et al., 2022; Vaudatin et al., 2024). This finding is biologically plausible, as the critical period for the development of the cochlear membranous labyrinth occurs between the third and tenth weeks of gestation, making the developing inner ear highly vulnerable to viral insult during this time (Pignataro et al., 2024). In a large cross-sectional study by De Cuyper et al. (2022), maternal seroconversion in the first trimester was identified as an independent predictor of congenital hearing loss, conferring a more than threefold increased risk. Conversely, studies have shown that maternal infections occurring in the second or third trimesters are associated with a significantly lower risk of the infant being born with SNHL (De Cuyper et al., 2022; Vaudatin et al., 2024).

The distinction between a primary maternal infection and a non-primary infection (reactivation or reinfection) is also prognostically important. Primary infections are associated with a much higher rate of vertical transmission to the fetus (approximately 30-40%) compared to non-primary infections (1-2%) (Goderis et al., 2014). Furthermore, primary maternal infections, particularly in the first trimester, are more likely to result in symptomatic disease and severe sequelae, including SNHL, in the newborn (Pass et al., 2005; Foulon et al., 2019). However, it is crucial to note that non-primary maternal infections are not benign. While the risk of transmission is

lower, once the fetus is infected, SNHL can still occur, although it may be less severe on average than that seen following a primary infection (Boppana et al., 2011; Yamamoto et al., 2011).

### Neonatal Clinical Risk Factors

The clinical presentation of the newborn at birth is one of the most powerful and readily available predictors of the risk for congenital SNHL. A clear and consistent finding across numerous studies is that newborns with symptomatic cCMV have a dramatically higher risk of SNHL compared to their asymptomatic counterparts. The incidence of SNHL in symptomatic infants is reported to be in the range of 30% to 65%, whereas in asymptomatic infants, the risk of congenital SNHL is significantly lower, typically cited as 7% to 15% (Goderis et al., 2014; Foulon et al., 2008).

The evidence strongly suggests that a risk gradient exists based on the *type and severity* of the symptoms present at birth. A landmark study by Rivera et al. (2002) categorized symptomatic infants into three groups: those with only a petechial rash, those with transient systemic findings (e.g., jaundice, hepatosplenomegaly), and those with evidence of CNS involvement (e.g., microcephaly, seizures). The study found that the risk of SNHL increased progressively across these groups, from 22% in the petechiae-only group, to 37% in the transient findings group, to 59% in the group with CNS involvement. This demonstrates that clinical risk stratification must move beyond a simple symptomatic/asymptomatic dichotomy and adopt a more nuanced, symptom-based approach to accurately predict risk (Rivera et al., 2002).

The presence of clinical signs indicative of CNS involvement at birth is one of the most potent predictors of SNHL. These signs include **microcephaly, seizures, lethargy, and hypotonia**. Multiple studies have confirmed a statistically significant association between these neurological symptoms and the subsequent diagnosis of SNHL (Rivera et al., 2002; Pignataro et al., 2024). A recent retrospective study by Pignataro et al. (2024) found that the presence of signs and symptoms of CNS involvement at birth conferred a significantly higher risk of developing SNHL. The

presence of a petechial rash at birth, even if it appears as an isolated finding, has been identified as a strong and independent risk factor for congenital SNHL. In the large cohort study by De Cuyper et al. (2022), petechiae at birth was the strongest clinical predictor, with an adjusted odds ratio of 6.7. Other systemic findings such as **hepatomegaly and splenomegaly** have also been associated with an increased risk of SNHL (De Cuyper et al., 2022; Vaudatin et al., 2024).

### Neuroimaging Findings

Neonatal neuroimaging, performed via cranial ultrasound (cUS) and, more definitively, brain MRI, has consistently emerged as the single best tool for predicting long-term neurological outcomes, including SNHL, in infants with cCMV (Fink et al., 2024; Manara et al., 2021). The presence of abnormalities on neuroimaging is strongly associated with SNHL in both symptomatic and asymptomatic infants (Foulon et al., 2019; Pignataro et al., 2024). The identification of **periventricular cysts** on neonatal brain MRI is a significant predictor of congenital SNHL, increasing the odds of hearing loss by more than fourfold (De Cuyper et al., 2022).

Abnormalities in the white matter are a characteristic feature of cCMV-related brain injury. A large, multicenter European retrospective study by Fink et al. (2024) provided a detailed analysis of these lesions. The study found that isolated white matter abnormalities, particularly a characteristic pattern of involvement of the **temporal poles (TPWMAs)**, were significantly associated with adverse outcomes. Specifically, the presence of TPWMAs was associated with severe hearing loss in 20% of cases and with hearing loss combined with other moderate-to-severe disabilities in another 15% of cases (Fink et al., 2024). Other well-documented neuroimaging findings associated with an increased risk of SNHL and poor neurodevelopmental outcomes include **periventricular calcifications, ventriculomegaly, cortical dysplasia, and other neuronal migration disorders** (Manara et al., 2021).

An equally important clinical finding is the high prognostic value of a *normal* neonatal neuroimaging study. The study by Fink et al. (2024) highlighted that the absence of temporal-pole

white matter abnormalities had a high negative predictive value, indicating a low risk of poor outcomes. This concept of the "reassurance of normal" is clinically powerful. While the presence of abnormalities helps to identify high-risk infants, the absence of these findings on a high-quality brain MRI can help to confidently identify a subset of infants who are at a much lower risk for severe sequelae. This information is invaluable for parental counseling and clinical management (Fink et al., 2024; Vaudatin et al., 2024).

### **Laboratory and Virological Markers**

The utility of neonatal virological markers, particularly viral load, as a predictor for congenital SNHL has been a subject of considerable research and debate. Several studies have reported a positive correlation between higher neonatal viral load and an increased risk or severity of SNHL. Walter et al. (2008) found that the risk of SNHL increased with increasing CMV viral load in dried blood spot (DBS) samples. Similarly, Lanari et al. (2006) and De Cuyper et al. (2022) noted that infants with SNHL tended to have higher median viral loads in blood compared to those with normal hearing.

In contrast, other well-designed prospective studies have failed to find a significant association. A key study by Boppana et al. (2005) analyzed peripheral blood viral load in 135 children and found no significant difference in CMV DNA levels between children with SNHL and those with normal hearing, in both symptomatic and asymptomatic groups. This suggests that at least in peripheral blood, the viral load may not be a reliable positive predictor. However, a more detailed analysis reveals a critical nuance. While a high viral load may be a poor *positive* predictor, a low viral load may be an excellent *negative* predictor. The study by Boppana et al. (2005) found that in asymptomatic infants, a blood viral load below a certain threshold had a very high negative predictive value of 94% to 100% for the development of SNHL. This suggests that while neonatal viral load may not be a useful tool to "rule in" the risk of SNHL, it could be a powerful tool to help "rule out" future SNHL in asymptomatic infants.

## Master Summary of Outcomes

To provide a consolidated overview of the evidence, the predictive value of at least 15 key outcomes and risk factors identified in this review are summarized in Table 3. This table synthesizes the findings across multiple studies to highlight the most robust predictors of congenital SNHL in newborns with cCMV.

**Table 3. Master Summary of Outcomes for Identified Risk Factors for Congenital SNHL**

| Risk Factor / Outcome                 | Association with Congenital SNHL      | Key Supporting Studies                        |
|---------------------------------------|---------------------------------------|-----------------------------------------------|
| <b>Maternal Factors</b>               |                                       |                                               |
| 1. Primary Infection in 1st Trimester | Strong, Significant Predictor         | De Cuyper et al. (2022), Foulon et al. (2019) |
| 2. Primary vs. Non-Primary Infection  | Primary infection confers higher risk | Pass et al. (2005), Goderis et al. (2014)     |
| <b>Neonatal Clinical Factors</b>      |                                       |                                               |
| 3. Any Symptomatic Presentation       | Strong, Significant Predictor         | Goderis et al. (2014), Rivera et al. (2002)   |
| 4. CNS Symptoms (Microcephaly,        | Very Strong, Significant              | Pignataro et al. (2024), Rivera               |

| Risk Factor / Outcome                     | Association with Congenital SNHL   | Key Supporting Studies                        |
|-------------------------------------------|------------------------------------|-----------------------------------------------|
| Seizures)                                 | Predictor                          | et al. (2002)                                 |
| 5. Petechiae at Birth                     | Strong, Independent Predictor      | De Cuyper et al. (2022)                       |
| 6. Hepatomegaly                           | Significant Predictor              | De Cuyper et al. (2022)                       |
| 7. Splenomegaly                           | Significant Predictor              | De Cuyper et al. (2022)                       |
| 8. Intrauterine Growth Restriction (IUGR) | Inconsistent Predictor             | Rivera et al. (2002), Vaudatin et al. (2024)  |
| <b>Neuroimaging Factors</b>               |                                    |                                               |
| 9. Any Abnormal Brain MRI                 | Very Strong, Significant Predictor | Pignataro et al. (2024), Foulon et al. (2019) |
| 10. Periventricular Cysts on MRI          | Strong, Independent Predictor      | De Cuyper et al. (2022)                       |
| 11. Temporal Pole WMA on MRI              | Strong Predictor of Adverse        | Fink et al. (2024)                            |

| Risk Factor / Outcome                    | Association with Congenital SNHL               | Key Supporting Studies                     |
|------------------------------------------|------------------------------------------------|--------------------------------------------|
|                                          | Outcome                                        |                                            |
| 12. Periventricular Calcifications       | Strong Predictor                               | Manara et al. (2021)                       |
| 13. Ventriculomegaly                     | Strong Predictor                               | Manara et al. (2021)                       |
| <b>Laboratory/Virological Factors</b>    |                                                |                                            |
| 14. High Neonatal Viral Load (Blood/DBS) | Inconsistent Positive Predictor                | Walter et al. (2008), Lanari et al. (2006) |
| 15. Low Neonatal Viral Load (Blood)      | High Negative Predictive Value in Asymptomatic | Boppana et al. (2005)                      |
| 16. Thrombocytopenia (Low Platelets)     | Associated with Sequelae                       | Vaudatin et al. (2024)                     |
| 17. Elevated Liver Transaminases         | Associated with Symptomatic Disease            | Rivera et al. (2002)                       |
| WMA = White Matter Abnormality.          |                                                |                                            |

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## DISCUSSION

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### Summary and Interpretation of Principal Findings

This systematic review of 17 observational studies provides a comprehensive synthesis of the evidence on risk factors present at birth that predict congenital SNHL in newborns with cCMV. The principal finding is that a clear and clinically relevant risk profile can be established in the neonatal period. The review confirms the central hypothesis that the risk of congenital SNHL is most strongly associated with three key domains: the timing of maternal infection, the clinical phenotype of the newborn, and the findings on neonatal neuroimaging (Foulon et al., 2019; Pignataro et al., 2024).

The evidence is robust and consistent that primary maternal infection acquired during the first trimester represents the period of greatest risk for severe fetal sequelae, including SNHL (De Cuyper et al., 2022; Foulon et al., 2019). Postnatally, the presence of symptomatic disease is the most powerful overarching predictor. However, this review highlights that a more granular assessment of the specific symptoms provides superior prognostic accuracy. The data clearly support a risk gradient, where infants with clinical signs of CNS involvement are at the highest risk, followed by those with systemic findings (Rivera et al., 2002). The identification of petechiae as a strong, independent predictor of SNHL is a particularly important clinical finding, as it suggests that this cutaneous sign may reflect a degree of systemic inflammation or vasculopathy that has implications for the inner ear (De Cuyper et al., 2022).

Furthermore, this review solidifies the role of neonatal neuroimaging as an indispensable prognostic tool. The presence of abnormalities on brain MRI, such as periventricular cysts and, more specifically, temporal pole white matter abnormalities, are potent predictors of adverse outcomes, including severe hearing loss (De Cuyper et al., 2022; Fink et al., 2024). In contrast, the role of neonatal viral load as a positive predictor remains ambiguous, with conflicting evidence likely stemming from methodological heterogeneity. However, the potential utility of a low viral

load as a negative predictor in asymptomatic infants is a key finding that could refine clinical management pathways (Boppana et al., 2005).

### **The Clinical Utility of a Multi-Factorial Risk Stratification Model**

A central conclusion derived from the synthesis of this evidence is that no single risk factor in isolation is perfectly predictive of SNHL. The true clinical power for prognostication lies in the integration of multiple factors into a comprehensive risk assessment. The evidence presented in this review strongly supports a move away from a reliance on single predictors or a simple symptomatic/asymptomatic dichotomy towards a multi-factorial risk stratification model (Rivera et al., 2002).

Such a model would conceptualize risk as a cumulative score. For example, a newborn with a known history of maternal first-trimester primary infection, who presents at birth with microcephaly and petechiae, and whose neonatal brain MRI reveals periventricular cysts and temporal pole WMAs, would be placed in the highest possible risk category for developing severe and progressive SNHL (De Cuyper et al., 2022; Fink et al., 2024). This infant would warrant the most intensive audiological surveillance and would be a prime candidate for consideration in future therapeutic trials.

Conversely, an infant who is asymptomatic at birth, born to a mother with a non-primary infection or a third-trimester primary infection, and who has a completely normal neonatal brain MRI and a low blood viral load, can be confidently placed in a very low-risk category (Boppana et al., 2005; Vaudatin et al., 2024). This ability to not only identify high-risk infants but also to reliably identify low-risk infants is of immense clinical value. It allows for evidence-based reassurance to be provided to a majority of families of infants with cCMV, reducing parental anxiety and the potential for iatrogenic harm from unnecessary investigations and follow-up. This stratified approach allows for the rational allocation of healthcare resources, focusing intensive audiological monitoring on the minority of infants who are at the highest risk (Goderis et al., 2014).

## Clinical Implications and Recommendations for Practice

Despite these limitations, the findings of this review have several direct and important implications for clinical practice. The identified risk factors provide clinicians with an evidence-based framework to counsel parents of newborns with cCMV. By integrating the maternal history, the infant's clinical examination, and neuroimaging results, clinicians can provide a more accurate and personalized prognosis regarding the risk of congenital hearing loss, moving beyond generalized statistics (De Cuyper et al., 2022).

The results strongly support the implementation of a risk-stratified approach to audiological follow-up. High-risk infants (e.g., first-trimester maternal infection, CNS symptoms, abnormal MRI) should undergo frequent and intensive audiological monitoring to ensure the earliest possible detection of hearing loss or its progression (Foulon et al., 2019). Low-risk infants (e.g., asymptomatic, third-trimester infection, normal MRI) may be suitable for a less intensive follow-up schedule, which would reduce the burden on both the healthcare system and the family (Vaudatin et al., 2024). The presence of one or more major risk factors should prompt a comprehensive neonatal evaluation, including a diagnostic ABR and a brain MRI if not already performed. While antiviral treatment with valganciclovir is currently recommended for symptomatic infants with CNS involvement to improve audiological and neurodevelopmental outcomes, its role in other subgroups is less clear (Kimberlin et al., 2015; Rawlinson et al., 2017).

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## CONCLUSION AND SUGGESTIONS

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### Concluding Summary

This comprehensive systematic review confirms that the risk of congenital SNHL in newborns with cCMV is strongly associated with a constellation of identifiable maternal and neonatal factors present at birth. The evidence is most robust for several key predictors. Maternal primary infection occurring in the first trimester of pregnancy significantly increases the risk of

fetal inner ear damage (Foulon et al., 2019). Postnatally, the presence of neonatal symptoms, particularly those indicating CNS involvement such as microcephaly and seizures, is a powerful prognostic marker (Pignataro et al., 2024). Neonatal neuroimaging, especially brain MRI, provides critical prognostic information, with specific findings like periventricular cysts and temporal pole white matter abnormalities being strongly linked to SNHL (De Cuyper et al., 2022; Fink et al., 2024). The integration of these factors allows for a robust risk stratification of newborns with cCMV in the immediate postnatal period.

### **Suggestions for Future Research**

While this review consolidates our current understanding, several areas require further investigation to refine clinical practice. There is a clear need for large, prospective, multicenter cohort studies that utilize standardized definitions for symptomatic disease and systematically collect data on all key maternal, clinical, and imaging predictors. The primary goal of such studies should be to develop and prospectively validate a multi-factorial risk-scoring model to provide a quantitative and highly accurate prediction of SNHL risk at birth. Further research is also essential to clarify the true predictive value of neonatal viral load, which will require the standardization of methodologies (Boppana et al., 2005). Finally, future randomized controlled trials should focus on high-risk subgroups to determine if early initiation of antiviral therapy can prevent the onset or mitigate the progression of cCMV-related hearing loss (Kimberlin et al., 2015).

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