Cochlear implant performance in children deafened by congenital cytomegalovirus—A systematic review

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Background: Congenital cytomegalovirus (cCMV) infection is a major cause of sensorineural hearing loss in children.

Objective of review: The objective of this systematic review was to compare performance in paediatric cochlear implant users with SNHL caused by cCMV compared to non-cCMV implantees.

Type of review: Systematic review

Search strategy: PubMed, EMBASE and the Cochrane databases were searched from inception up to 15 May 2017 for children, cochlear implant, performance and their synonyms.

Evaluation methods: Titles, abstracts and full texts were screened for eligibility. Directness of evidence and risk of bias were assessed. From the included studies, study characteristics and outcome data (speech perception, speech production, receptive language and auditory performance of cCMV groups and non-cCMV groups) were extracted.

Results: A total of 5280 unique articles were screened of which 28 were eligible for critical appraisal. After critical appraisal, 12 studies remained for data extraction. Seven of 12 studies showed worse performance after cochlear implantation in cCMV children compared to non-cCMV children. Worse performance in cCMV children was attributed to cCMV-related comorbidities in six of these studies. Available data on asymptomatic cCMV children compared to non-cCMV children did not reveal an unfavourable effect on cochlear implant performance.

Conclusions: The available evidence reveals that cCMV children often have worse cochlear implant performance compared to non-cCMV children, which can be attributed to cCMV related comorbidities. We urge physicians to take into account the cCMV related comorbidities in the counselling of paediatric CI users deafened by cCMV.
1 | INTRODUCTION

Congenital infection with cytomegalovirus (cCMV) is common in Western countries such as the Netherlands, with a birth prevalence of 0.53%. A meta-analysis of the worldwide literature revealed an overall birth prevalence of 0.64%. An infant may acquire cCMV when its mother encounters or reencounters the virus during pregnancy, which is transmitted through bodily fluids. Approximately 10%-15% of infants infected congenitally have clinical evidence of the disease (are symptomatic) at birth. Symptomatic infants present with symptoms such as intrauterine growth retardation, low birth weight, prematurity and hepatosplenomegaly. Contrarily, the majority of infected infants is asymptomatic at birth. In approximately 7%-25%, asymptomatic infants develop symptoms of the infection later in life.

The most common postnatal symptom of cCMV infection is sensorineural hearing loss (SNHL), presenting in 15%-65% of infected children. Additional symptoms or comorbidities associated with cCMV are visual impairment, cognitive and motor deficits which can result in neurodevelopmental delay and balance problems. In addition, these children are prone to neurodevelopmental dysfunction such as intellectual disability, autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD) and pervasive developmental disorder (PDD).

The SNHL is often progressive in the first 4 years of life for both asymptomatic and symptomatic CMV infected children. When it advances to severe to profound SNHL, cochlear implantation may be considered. Considering the comorbidities associated with cCMV, the question arises whether cCMV children are able to achieve the same performance level with a cochlear implant (CI) compared to non-cCMV children with a CI. A growing number of studies have investigated the performance of cCMV children after cochlear implantation on various speech perception, speech production, receptive language and auditory performance outcomes. A systematic review by Shin et al. reviewed the literature up to 2011 mainly focusing on the effect of antiviral medication on cCMV related SNHL and secondarily the effect of cochlear implantation on cCMV-related SNHL. As for the results on cochlear implantation, they found contradictory results in a combination of case-control studies and case series: some studies reported equal performance in cCMV children compared to non-cCMV children, often 1 year after implantation. Other studies found lower levels of CI performance in cCMV children compared to non-cCMV children. The effect of cCMV-related comorbidities on CI performance was not investigated specifically. This can be a major interest to analyse additionally. The primary aim of this systematic review was to evaluate CI performance in children deafened by cCMV compared to non-cCMV children. Our secondary aim was to investigate the effect of cCMV-related comorbidities on CI performance in cCMV children.

2 | METHODS

2.1 | Ethical considerations

No ethical considerations were made as this is a review of existing literature.

2.2 | Search and selection

A systematic literature search in PubMed, Embase and the Cochrane library was conducted from database inception up to the 15th of May 2017. Search terms were limited to the terms: “children,” “cochlear implant” and “performance” with all relevant synonyms (see Table S1). To avoid a too narrow search, we did not search on terms corresponding to “CMV.” Duplicates were removed. Titles and abstracts were independently screened by sets of two investigators each (E.H., F.v.H., J.M.L.H., S.F.v.d.H., J.V.) using predetermined inclusion and exclusion criteria. Studies were included when they examined speech perception, speech production, receptive language and auditory performance in children with SNHL due to cCMV infection after cochlear implantation. Exclusion criteria were adult patients and/or single-sided deafness. Commentaries, systematic reviews, non-English/Dutch studies and non-human studies were excluded. Unpublished studies were not excluded.

Eligible full-text articles were retrieved, and authors were emailed if a full text was unavailable. Full texts of eligible studies were independently screened by sets of two investigators each (E.H., F.v.H., J.M.L.H., S.F.v.d.H., J.V.). Differences in opinion were settled by discussion and consensus. Cross-referencing through Scopus was performed after full-text screening to identify titles not found with our initial search. The PRISMA and MOOSE statements were used as a guideline for set-up and writing of this systematic review.

2.3 | Study assessment

Eligible articles were independently assessed by two authors for directness of evidence (DoE), data extractability and risk of bias (RoB) using predefined criteria (see Table 1). DoE was scored by evaluating the population, intervention and outcome. In addition,
| Study (year)         | Study design | N cCMV | N non-cCMV | Patients | Therapy | Outcome | Data extractable | Selection bias | Standardisation of outcome | Blinding | Missing data | Time post-implant |
|---------------------|--------------|--------|------------|----------|---------|---------|------------------|----------------|--------------------------|----------|---------------|--------------------|
| Ramirez (2004)      | RCS          | 16     | 131        | ●        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ●                  |
| Ciobba (2009)       | RCS          | 16     | 7          | ●        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ●                  |
| Iwasaki (2009)      | PCS          | 2      | 5          | ●        | ●       | ●       | ●                | ●              | ●                        | ○        | ○            | ●                  |
| Yoshida (2009)      | RCS          | 4      | 17         | ●        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ●                  |
| Philips (2010)      | RCS          | 8      | 8          | ●        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ●                  |
| Malik (2011)        | RCS          | 14     | 45         | ●        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ●                  |
| Black (2012)        | RCS          | 2      | 23         | ●        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ●                  |
| Matsui (2012)       | RCS          | 5      | 7          | ●        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ●                  |
| Yamazaki (2012)     | RCS          | 9      | 14         | ●        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ●                  |
| Philips (2014)      | RCS          | 12     | 12         | ●        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ●                  |
| Karlrtor (2014)     | RCS          | 26     | 13         | ●        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ●                  |
| Ferreira (2015)     | RCS          | 11     | 61         | ●        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ●                  |
| Buyin (2013)        | RCS          | 1      | 7          | ●        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ●                  |
| Ramirez (2011)      | RCS          | 1      | 24         | ○        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ●                  |
| Pyman (2000)        | CS           | 7      | 68         | ●        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ●                  |
| Hiraumi (2010)      | RCS          | 3      | 13         | ○        | ●       | ●       | ●                | ●              | ●                        | ○        | ○            | ○                  |
| Lee (2009)          | CS           | 13     | 0          | ○        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ○                  |
| Geal-Dor (2013)     | CS           | ?      | 195        | ○        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ●                  |
| Gray (2003)         | CS           | 1      | 0          | ○        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ●                  |
| Beer (2012)         | RCS          | 1      | 22         | ○        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ●                  |
| Bille (2013)        | CS           | 2      | 31         | ○        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ●                  |
| Fryauf (1997)       | CS           | 1      | 33         | ○        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ●                  |
| Ogawa (2009)        | CS           | 4      | 0          | ○        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ●                  |
| Berrettini (2008)   | CS           | 2      | 21         | ○        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ●                  |
| Birman (2013)       | CS           | 5      | 83         | ○        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ●                  |
| Viccario (2012)     | CS           | 6      | 0          | ○        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ●                  |
| Percy-Smith (2012)  | CS           | 2      | 81         | ○        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ●                  |
| Laccourreye (2015)  | CS           | 15     | 0          | ○        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ●                  |
| Lyutenks (2016)     | CS           | 23     | 0          | ○        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ●                  |
| Hoey (2017)         | CS           | 11     | 0          | ○        | ●       | ●       | ●                | ●              | ●                        | ○        | ●            | ●                  |

Patients: ●, Paediatric patients with congenital CMV associated bilateral hearing loss vs non-congenital CMV bilateral hearing loss; ○, Non-comparative studies.

Therapy: ●, Cochlear implantation before the age of 18 years; ○, other therapy.

Outcome: ●, Speech perception, speech production, receptive language or auditory performance; ○, other outcome.

Data extractability: ●, Data extractable; ○, data not extractable.

Selection bias: ●, No selection bias; ○, selective inclusion of non-missing data in retrospective cohort; ?; Susceptible to bias.

Standardisation of outcome: ●, Predefined externally validated test; ○, No predefined externally validated test.

Blinding: ●, Blinding personnel; ○, No blinding.

Missing data: ●, <10% of missing data; ○, 10%-20% missing data; >20% missing data; ?, not reported.

Time post-implant: ●, Equal for all patients; ○, Varies between patients.

RCS, retrospective cohort study; PCS, prospective cohort study; CS, (retrospective) case series.
studies were scored satisfactory when data from the cCMV population was extractable and unsatisfactory when it was not.

RoB was scored on selection bias, standardisation of outcome, blinding, missing data and follow-up. Selection of population was scored satisfactory when there was no selection bias, moderate when authors selectively included non-missing data and unsatisfactory when sample selection was deemed susceptible to bias. We scored whether a test was externally validated (standardisation of outcome). Missing data were subdivided into less than 10%, between 10% and 20%, more than 20% or not reported. Finally, follow-up was scored satisfactory when measurements were performed at set times and unsatisfactory when follow-up was unequal between patients. Adhering to the Grade system for assessing RoB, no studies were excluded based on RoB. A sensitivity analysis was performed removing studies with a moderate or high RoB. Therefore, studies were excluded based on DoE and data extractability only.

2.4 | Data extraction

Study characteristics, such as study population, non-cCMV group, age at implantation, presence of cCMV-related comorbidities, follow-up period, outcome measures and scores, including statistical comparison (test and P-value), were extracted from selected articles independently by sets of two investigators each (V.K, E.H., F.v.H., J.M.L.H., S.v.d.H., J.V.). Meta-analyses of repeatedly reported outcomes were performed for the cCMV group compared to non-cCMV groups.

To answer our second research question, scores of asymptomatic cCMV children versus symptomatic cCMV children and asymptomatic cCMV children versus non-cCMV children were extracted and compared by the reviewers. Between-group analyses were performed using the Mann-Whitney U test for non-parametric numeric data and Fisher’s exact test for non-parametric ordinal data in SPSS, and a P-value of <.05 was deemed significant.

3 | RESULTS

3.1 | Search strategy and study selection

As shown in Figure 1, our search identified 5280 unique articles. After screening titles and abstracts in inclusion and exclusion criteria, 288 articles were left for full-text screening. Cross-reference screening did not yield additional articles. Corresponding authors were contacted when full texts were not available, which resulted in one additional full text. Consequently, 30 articles were eligible for critical appraisal.

3.2 | Assessing quality of studies

The critical appraisal of the 30 studies is presented in Table 1. One study was a prospective cohort study, all other studies were retrospective studies. Twenty-three studies included children with cCMV-related hearing loss as well as children with other causes of hearing loss. Eleven studies directly
compared a cCMV-group to a non-cCMV-group. 5,13,18-22,24-27 The non-cCMV group included children with various causes of SNHL in five studies, 13,18-20,22,23,28-31,33,35-37,39,40, and children with hereditary SNHL due to connexine 26 (Cx26) mutation in six studies. 5,21-24 In one study, a comparison could be distracted, yet no statistical analysis. 23 In seven studies, 32-34,38,41,43-45 no comparison with a non-cCMV-group was made.

Except for one patient in one study, 21 all patients were <18 years old at time of implantation. In ten studies, all patients were measured at the same time post-implant 5,18-19,24,25,28,30,37,40,43 in eighteen studies the time post-implant varied 13,20,22,23,26,27,29,31-33,35,36,38,39,41,42,44,45, and in two studies time post-implant was unclear. Blinding was not performed in any of the studies, as no randomised controlled trials included. Three studies were assessed as susceptible to selection bias 25,27,41, three 18,37,43 were assessed as selective inclusion of non-missing data in a retrospective cohort, all other 24 were assessed as having no selection bias 5,13,19-24,26,28-36,38,40,42,44,45.

Finally, 12 studies 5,13,18-27 were included in this review because all criteria for DoE were met and data were extractable.

3.3 | Data extraction

Primarily, we provided a descriptive table of study results from the study population and comparison group. Meta-analyses of repeatedly reported outcomes (SIR, CAP) were attempted but not reported due to insufficient reporting within the original studies. Computing a forest plot was attempted but failed due to the lack of reporting of measures of uncertainty in the cCMV group and/or control group and great variation in follow-up. Contacting corresponding authors for additional data yielded no response, which made it impossible to gain a sensible result. Secondarily, when available, scores of asymptomatic cCMV children versus symptomatic cCMV children and asymptomatic cCMV children versus asymptomatic non-cCMV children were extracted, displayed in tables and compared by the reviewers.

3.4 | Study characteristics

The characteristics of the 12 studies selected after critical appraisal are presented in Table 2. Sample size in these studies varied from 2 cCMV vs 5 non-cCMV 19 to 16 cCMV vs 131 non-cCMV. 18 Children were divided into two groups based on SNHL with or without comorbidities, respectively: symptomatic and asymptomatic cCMV children. The majority of studies included a combination of symptomatic and asymptomatic cCMV children versus a non-cCMV group. Four studies did not report the presence of comorbidities in the non-cCMV group. 18,21,22,25 As can be seen in Table 2, one study included only asymptomatic cCMV children and a non-cCMV group without comorbidities. 19 The following outcome measurements were described: auditory performance was tested in six studies 21-25,27, speech perception in four studies 5,13,18,20, speech production in nine studies 5,18-21,24-27, receptive language in three studies 22,24,26 and language-social developmental quotients in one study. 13 A list of abbreviations and explanation of outcome measures can be found in Table S2.

3.5 | Prognostic value of cCMV on CI performance and role of cCMV-related comorbidities

3.5.1 | Primary comparison: cCMV vs non-cCMV

As shown in Table 3, seven of twelve studies 5,13,18,20,22,23,27 showed worse outcome in cCMV children (symptomatic and/or asymptomatic) compared to non-cCMV groups on various speech and language outcomes. Six studies 5,13,18,20,22,27 explored cCMV-related comorbidities; in Malik et al. 22 a lower auditory performance was attributed to central nervous system damage and associated cognitive impairment in 11 of 14 cCMV children. In Ciobra et al. 5, a slower progression of speech perception and speech production in the cCMV group compared to a Cx26 group was attributed to concomitant cognitive impairment in the cCMV children. In Yamazaki et al. 13 lower language and social development and word discrimination skills in the cCMV group were contributed to the high(er) rate of comorbidities in this group. A sub-analysis on 2 cCMV children with PDD revealed significantly worse word discrimination than the non-cCMV group. In addition, two of four mentally retarded cCMV children revealed significantly worse word discrimination than in the non-cCMV group. In the study by Ramirez and Nikolopoulos, 18 worse speech perception in the cCMV group compared to the non-cCMV group was attributed to ASD in 3 of 16 cCMV children and additional behavioural or language development difficulties in the majority of the cCMV children. In Ferreira et al. 27 a developmental auditory delay in the cCMV group compared to the non-cCMV group was attributed to cognitive deficits in 7 of 11 cCMV children. In Yoshida et al. 20 worse speech production in a cCMV group compared to a non-cCMV group was ascribed to prematurity and motor delay in 3 of 4 cCMV children. In the study that did not perform a statistical analysis, 2 cCMV children scored the lowest category (4) on the Categories of Auditory Performance Index compared to scores between 1 and 4 in the non-cCMV group. 23 Both cCMV children showed poor compliance and suffered from recurrent otitis media but not from cCMV-related comorbidities.

On the other hand, in five 19,21,22,25,26 of twelve studies, no significant difference was seen in speech and language development between the cCMV group and the non-cCMV group: in Iwasaki et al. 19 no comorbidities were present in the cCMV group or in the non-cCMV group. In Philips et al. (2010) 21 and (2014), 25 cCMV children had comorbidities, while this was not reported in the non-cCMV group. In Karlorp et al. 26 and Matsui et al. 24 both the children from the cCMV group and the non-cCMV group had comorbidities and outcomes were comparable, although no statistical analyses were performed in Matsui et al.

A sensitivity analysis was performed removing three studies 23,26,27 with moderate RoB, leaving 5 of 9 studies with
| Study                          | Sample size | Age at implantation mean (range) | Comorbidities | Non-cCMV group matched for | Time post-implant range or mean (years) |
|-------------------------------|-------------|----------------------------------|---------------|----------------------------|----------------------------------------|
| Ramirez & Nikolopoulos (2004) | 16 131      | 46.8 49.2                        | 3 ASD NR      | Not matched                | 1-5                                    |
| Ciorba et al. (2009)          | 14 (4a) 7b  | 53.7 (6-196.5) 50.1 (27-89)      | 6 cognitive impairment, 10 motor impairment, 3 seizures, 3 visual impairment | 0 Age and pre-implant linguistic category | 0.5-5                                  |
| Iwasaki et al. (2009)         | 2 5         | 34 (29-39) 28.8 (22.8-34.8)      | 0             | Not matched                | 3.0                                    |
| Yoshida et al. (2009)         | 4 17        | 31.2 (24-39.6) 31.2 (21.6-43.2)  | 2 premature jaundice, 1 behavior difficulties, 3 slight motor delay | 0 Not matched | 3.0-4.3                                |
| Philips et al. (2010)         | 8 (5a) 8b   | 34.5 (6-161) NR                 | 1 microcephaly, 2 motor impairment, 2 epilepsy | NR | Age of implantation, experience with their CI and chronological age 0-6.4 |
| Malik et al. (2011)           | 14a 45      | 45.1 (23-99) NR                  | 13 learning difficulties/cognitive impairment | NR | Corrected for baseline, age, gender 1-11.5 |
| Black et al. (2012)           | 2a 23       | 25 (25-25) 9-92                 | 0             | Not matched                | 1.5-2                                  |
| Matsui et al. (2012)          | 5a 7b       | 39.2 (25-70) 36.6 (25-47)       | 2 intellectual disability 2 intellectual disability 1 ASD | Not matched | 4-5                                    |
| Yamazaki et al. (2012)        | 11a 14      | 37.5 (15-64) 28.2               | 1 ADHD, 2 PDD, 6 intellectual disability | 0 Not matched | 0.8-4.7                                |
| Karltorp et al. (2014)        | 26 13b      | 25.2 (4.8-57.6) 19.2 (7.2-66)   | 4 ASD, 2 ADHD, 2 cerebral palsy, 5 cognitive impairment, 5 motor impairment | 2 cognitive impairment, 1 motor impairment | Not matched | 5.7                                    |
| Philips et al. (2014)         | 12 12b      | 34.8 (15-82) 9 (7-12)           | 6 motor impairment, 5 MRI brain abnormalities NR | Matched for age & unilateral or bilateral implantation 3 y 11 m (9 m-7 y 9 m) vs 4 y 6 m (5 m-8 y 10 m) | 5.7                                    |
| Ferreira et al. (2015)        | 11 (2a) 61  | 47.7 (15-144) NR                | 5 motor impairmentataxia, 2 seizures/epilepsy, 7 MRI brain abnormalities | Matched on age of implantation <2 y: 1.48 2-3 y: 5.75 >3 y: 5.13 | 5.7                                    |

ADHD, attention deficit hyperactivity disorder; ASD, autistic spectrum disorder; NR, not reported; PDD, pervasive developmental disorder.

Reported asymptomatic cCMV children.

These non-cCMV children all have the genetic mutation Cx26.
TABLE 3 Overall results: performance after cochlear implantation in children with cCMV infection compared to a non-cCMV group

| Test                                    | NcCMV: non-cCMV | Time post-implant months | cCMV group | Non-cCMV group | Descriptives | P value and statistical test |
|-----------------------------------------|------------------|--------------------------|------------|----------------|--------------|-----------------------------|
| Speech perception                       |                  |                          |            |                |              |                             |
| Enjoji scale20                           | 4:17             | <12                      | 11.2       | 17.7           | Mean         | NS                          |
|                                         |                  | >12                      | 30.6       | 30.6           |               |                             |
| Hearing threshold (2½-4 kHz)13           | 11:14            | 31 (10-56)               | 35.2 dB    | 34.2 dB        | Mean         | NS                          |
|                                         |                  |                          |            |                | Mann Whitney U|                             |
| Hearing threshold (2½-6 kHz)27           | 11:61            | 3 m -12 y 3 m           | 32.0 dB (26.2-37.0) | 35.0 dB (32.8-37.2) | Mean (95% CI) | NS two-sample Kolmogorov-Smirnov test and Kruskal-Wallis test |
| Hearing threshold24b                     | 5:7              | Not reported             | 36.5 dB (30-41.2) | 37.5 dB (30-42.5) | Mean (range) | Not performed               |
| Closed-set infant words13               | 9:14             | 11-56                    | 76% (32)   | 91%            | Mean (SD)    | Not performed               |
| Open-set monosyllabic words13           | 9:14             | 11-56                    | 58% (33)   | 87%            | Mean (SD)    | Not performed               |
| IMCSS A18                                | 16:131           | 12                       | 6 (20)     | 27             | Mean (SD) vs mean | 0.04 Paired t-test or Wilcoxon S-R test of patients' last evaluation |
|                                         | 12:131           | 36                       | 68 (43)    | 80             |              |                             |
|                                         | 5:131            | 48                       | 92 (19)    | 85             |              |                             |
|                                         | 3:131            | 60                       | 93 (12)    | 93             |              |                             |
| IMCSS B18                                | 16:131           | 12                       | 0 (0)      | 1              | Mean (SD) vs mean | NS Paired t-test or Wilcoxon S-R test of patients' last evaluation |
|                                         | 12:131           | 36                       | 45 (48)    | 36             |              |                             |
|                                         | 5:131            | 48                       | 76 (43)    | 57             |              |                             |
|                                         | 3:131            | 60                       | 65 (57)    | 65             |              |                             |
| Geers&Moog5                             | 12:7             | 6                        | 2.3 (1.1)  | 2.1 (0.9)      | Mean (SD)    | <0.05d Permutation tests pre-post |
|                                         | 11:7             | 12                       | 3.6 (1.6)  | 4.0 (1.2)      |              |                             |
|                                         | 4:2              | 24                       | 4.0 (1.2)  | 5.0 (0.0)      |              |                             |
|                                         | 6:3              | 36                       | 4.5 (1.0)  | 5.3 (0.6)      |              |                             |
|                                         | 3:6              | 60                       | 5.7 (0.6)  | 5.8 (0.4)      |              |                             |
| Speech production                       |                  |                          |            |                |              |                             |
| SIR21                                   | 8:8              | 1-77                     | 2.0 (1.2)  | 2.8 (1.9)      | Mean (SD)    | NS                          |
| SIR18                                   | 16:131           | 12                       | 1.4 (0.7)  | 1.65           | Mean (SD) vs mean | NS Paired t-test or Wilcoxon S-R test of patients' last evaluation |
|                                         | 12:131           | 36                       | 2.5 (1.1)  | 2.64           |              |                             |
|                                         | 5:131            | 48                       | 2.8 (1.1)  | 3.00           |              |                             |
|                                         | 3:131            | 60                       | 3.0 (2.0)  | 3.20           |              |                             |
| SIR27                                   |                  | Implanted                |            |                | Mean (95% CI) | NS two-sample Kolmogorov-Smirnov test and Kruskal-Wallis test |
|                                         | 4:7              | <2 y                     | 3 (0-6)    | 4 (3-6)        |              |                             |
|                                         | 3:33             | 2-3 y                    | 2 (0-22)   | 5 (5-5)        |              |                             |
|                                         | 4:21             | >3 y                     | 4 (4-4)    | 4 (4-4)        |              |                             |
| SIR26                                   | 20:8             | >12                      | 3.5 (1.7)  | 4 (1.3)        | Mean (SD)    | NS Unpaired T-test          |
| SIR25                                   | 12:12            | 12                       | 3.0        | 4.0            | Median       | NS Wilcoxon Signed Rank test |
|                                         | 24               | 5.0                      | 5.0        |                |              |                             |
|                                         | 36               | 5.5                      | 5.0        |                |              |                             |
|                                         | 48               | 5.0                      | 5.0        |                |              |                             |
|                                         | 60               | 5.5                      | 5.5        |                |              |                             |

(Continues)
| Test                          | NcCMV: non-cCMV | Time post-implant months | cCMV group | Non-cCMV group | Descriptives | P value and statistical test |
|------------------------------|-----------------|--------------------------|------------|----------------|-------------|-----------------------------|
| MUSS<sup>27</sup>            | Implant         |                          |            |                | Mean (95% CI) | NS                          |
| 4:7                          | <2 y            | 33 (20-47)               | 37 (33-41) |                |             | two-sample Kolmogorov-Smirnov & Kruskal-Wallis |
| 3:33                         | 2-3 y           | 37 (10-62)               | 39 (38-40) |                |             |                            |
| 4:21                         | >3 y            | 36 (21-50)               | 35 (26-41) |                |             |                            |
| MUSS<sup>34</sup>            |                 |                          |            |                | Mean (SD)    | Not performed               |
| 5:7                          | 12              | 17 (5)<sup>f</sup>       | 11 (9)<sup>f</sup> |          |             |                            |
| 24                           |                 | 23 (6)                   | 17 (9)     |                |             |                            |
| 36                           |                 | 25 (7)                   | 20 (9)     |                |             |                            |
| 48                           |                 | 30 (5)                   | 28 (10)    |                |             |                            |
| Enjoji scale<sup>20</sup>    | 4:17            | <12                      | 5.7        | 11.3           | Mean         | 0.037                       |
|                              |                 | >12                      | 21.2       | 20.4           | NS           |                            |
| Nottingham classification<sup>5</sup> | 12:7            | 6                        | 1.7 (0.6)  | 2.0 (0.6)      | Mean (SD)    | <0.05<sup>d</sup> Permutation tests pre-post |
|                              |                 | 11:7                     | 12         | 2.0 (0.6)      |              |                            |
|                              |                 | 4:2                      | 24         | 2.3 (0.5)      |              |                            |
|                              |                 | 6:3                      | 36         | 2.2 (0.4)      |              |                            |
|                              |                 | 3:6                      | 60         | 2.7 (0.6)      |              |                            |
| Bates classification<sup>5</sup> | 12:7            | 6                        | 2.8 (1.2)  | 3.7 (1.0)      | Mean (SD)    | <0.05<sup>d</sup> Permutation tests pre-post |
|                              |                 | 11:7                     | 12         | 3.3 (1.3)      |              |                            |
|                              |                 | 4:2                      | 24         | 3.8 (1.0)      |              |                            |
|                              |                 | 6:3                      | 36         | 3.8 (1.2)      |              |                            |
|                              |                 | 3:6                      | 60         | 5.0 (1.0)      |              |                            |
| VCEG<sup>27</sup>            | Implant         |                          |            |                | Mean (95% CI) | NS                          |
| 4:7                          | <2 y            | 4 (4-4)                  | 4 (4-4)    |                |             | two-sample Kolmogorov-Smirnov & Kruskal-Wallis |
| 3:33                         | 2-3 y           | 4 (4-4)                  | 4 (4-4)    |                |             |                            |
| 4:21                         | >3 y            | 4 (4-4)                  | 4 (4-4)    |                |             |                            |
| Speech production            |                 |                          |            |                | Level        | Not performed               |
| S-S method<sup>24</sup>      |                 | Age: 54-90               | 80%: normal| 86%: normal    |              |                            |
|                              |                 |                          | 20%: low (MR<sup>+</sup>) | 14%: low (MR<sup>+</sup>) |          |                            |
| PPVT<sup>26</sup>            | 26:13           | >12                      | 106 (54)   | 82 (54)        | Mean (SD)    | NS                          |
|                              |                 |                          |            |                |              | Unpaired T-test            |
| Auditory performance         |                 |                          |            |                | Median       | NS                          |
| CAP<sup>21</sup>             |                 | 12                       | 2.0        | 4.0            | Mean (SD)    | NS                          |
|                              |                 | 24                       | 3.0        | 3.0            |              | Wilcoxon Signed Rank test  |
|                              |                 | 36                       | 4.5        | 4.0            |              |                            |
|                              |                 | 48                       | 4.0        | 4.0            |              |                            |
|                              |                 | 60                       | 4.0        | 5.0            |              |                            |

(Continues)
significantly worse performance in cCMV children compared to a control group and 4 of 9 studies with equal results.

In sum, the majority of studies found worse outcomes in the cCMV children compared to non-cCMV children, which was attributed by most authors to be related to cCMV comorbidities.

### 3.5.2 Secondary comparison 1: Asymptomatic cCMV vs non-cCMV

To test the aforementioned hypothesis, we tried to exclude the effect of comorbidities from the comparison by extracting data of children with solely asymptomatic cCMV versus a non-cCMV group which was possible in four studies (Table 4). None of the non-cCMV children had reported disabilities themselves apart from SNHL. From Ciorba et al., we extracted the results of 4 asymptomatic cCMV children and 7 Cx26 children which revealed no significant differences in speech perception and production skills.\(^5\) Iwasaki et al.\(^19\) found no differences between 2 asymptomatic cCMV children and 5 non-cCMV children. From Yamazaki et al.,\(^13\) we extracted the data of 2 asymptomatic cCMV children (without psycho-neurological symptoms) versus 14 non-cCMV children which revealed equal speech perception. In Philips (2010) et al.,\(^21\) speech perception and speech production was equal in 5 asymptomatic cCMV children compared to 8 Cx26 children. In sum, none of the four studies comparing asymptomatic cCMV children with non-cCMV children found worse outcomes in the cCMV children.

### TABLE 3 (Continued)

| Test                  | NcCMV: non-cCMV | Time post-implant months | cCMV group | Non-cCMV group | Descriptives | P value and statistical test |
|-----------------------|-----------------|--------------------------|------------|----------------|--------------|-------------------------------|
| **CAP\(^{27}\)**      |                 | Implanted                |            |                | Mean (95% CI) | NS                            |
| 11:61                 | 4:7             | <2 y                     | 26 (0-55)  | 8 (6-9)        |              | 0.049 two-sample Kolmogorov-Smirnov test & Kruskal-Wallis |
|                       | 3:33            | 2-3 y                    | 5 (0-24)   | 8 (8-8)        |              |                               |
|                       | 4:21            | >3 y                     | 9 (9-9)    | 6 (5-7)        |              |                               |
| **CAPI\(^{23}\)**     | 2:23            | 18-24                    | 3.0 (0.0)^g| 2.2 (0.8)^g    | Mean (SD)    | Not performed                 |
| **MAIS\(^{27}\)**     |                 | Implanted                |            |                | Mean (95% CI) | NS                            |
|                       | 4:7             | <2 y                     | 36 (22-48) | 40 (40-40)     |              |                               |
|                       | 3:33            | 2-3 y                    | 38 (18-57) | 40 (40-40)     |              |                               |
|                       | 4:21            | >3 y                     | 39 (37-41) | 39 (38-40)     |              |                               |
| **IT-MAIS\(^{59}\)**  | 2:5             | 3                        | 9.0 (7.1)  | 15 (12-18)     | Mean (SD or range) | NS                          |
|                       | 6               |                          | 16 (5.7)   | 18 (16-20)     |              |                               |
|                       | 12              |                          | 21 (8.5)   | 24 (23-26)     |              |                               |
|                       | 18              |                          | 25 (7.8)   | 27 (26-28)     |              |                               |
|                       | 24              |                          | 27 (7.1)   | 28 (27-29)     |              |                               |
|                       | 30              |                          | 34 (3.5)   | 29 (28-33)     |              |                               |
|                       | 36              |                          | 37 (2.1)   | 34 (33-37)     |              |                               |
| **IT-MAIS\(^{20}\)**  | 4:17            |                          | 32.8 (9.2) | Not measured   | Mean (SD)    | Not applicable                |
| **IT-MAIS\(^{24}\)**  | 5:7             | 12                       | 20 (9)^f   | 15 (12)^f      | Mean (SD)    | Not performed                 |
|                       | 24              |                          | 29 (5)     | 27 (11)        |              |                               |
|                       | 36              |                          | 31 (5)     | 30 (10)        |              |                               |
|                       | 48              |                          | 37 (2)     | 33 (5)         |              |                               |
| Language Social       | 9:14            | 11-56                    | 64% (21)^c | 97% (9.1)^c    | Mean (SD)    | <0.05^ Mann Whitney U         |
| DQ in K test\(^{13}\) |                 |                          |            |                |              |                               |
| MSLDS\(^{22}\)        | 24              |                          | 5.4 (3.2)  | 8.1 (1.9)      | Mean (SD)    | <0.001 Covariance test        |

\(^{a}\)Calculated by reviewers, provided that chance level was set at 16.5%.

\(^{b}\)Frequencies not reported.

\(^{c}\)Derived from figure.

\(^{d}\)Difference between increase of scores before and after cochlear implantation.

\(^{e}\): 85-116, average or above; 2: 80-84, mild delay; 3: 70-80, moderate delay; 4: >69, severely delayed.

\(^{f}\): excellent (7-8); 2: good (5-6); 3: average (3-4); 4: poor (0-2); NS = not significant; DQ: Developmental Quotients; ID: intellectual disability; For description of speech and language tests, see Table S2.

Bold p-values: significant difference between groups.
3.5.3 Secondary comparison 2: Asymptomatic vs symptomatic cCMV

Data of asymptomatic cCMV children versus symptomatic cCMV children were extracted from three studies to elucidate the effect of comorbidities in the performance of cCMV implantees (Table 5). From Ciorba et al.,\(^5\) significantly lower speech perception in the symptomatic cCMV children compared to the asymptomatic children was seen after 6 months. In Yamazaki et al.,\(^13\) the symptomatic cCMV children with ADHD, MR, and PDD showed significantly worse language and social skills than the asymptomatic cCMV children. In Phillips (2010) et al.,\(^21\) higher speech intelligibility ratings were noted in the asymptomatic group, yet not significant most likely due to the limited sample size (3 vs 5). In sum, in two of three studies comparing asymptomatic cCMV children with symptomatic cCMV children found significantly worse outcomes in the symptomatic group.

3.6 Prognostic value of cCMV on CI performance and role of time post-implant

Follow-up ranged from 3 to 77 months. The six studies\(^5,13,18,20,22,27\) that showed a significant difference between the cCMV and non-cCMV group reported this difference at a single test\(^13,18,20,27\) and most of them at a short follow-up (less than 2 years\(^5,13,20,22\)). Two studies\(^18,20\) reported a significantly worse performance in the cCMV children at multiple test moments: in Yoshida et al.,\(^20\) a significant difference between a cCMV group and a non-cCMV group before 12-month follow-up was noted, while after more than 12 months, no significant differences were noted. In the analysis of the study by Ramirez and Nikolopoulos\(^18\), follow-up varied between 1 and 5 years in the cCMV group (4 cases at 1 year, 7 cases at 3 years, 2 cases at 4 years and 3 cases at 5 years). A worse performance than the non-cCMV group at the final follow-up year was seen in 38% of cases (\(P = .04\)). Studies reporting no significant differences between cCMV children and non-cCMV groups all had a follow-up of more than 2 years.\(^19,21,24-26\)

4 | DISCUSSION

4.1 Summary of main findings

The aim of this systematic review was to evaluate the prognostic value of cCMV infection as a cause of SNHL on CI performance in cCMV children. In addition, we evaluated the effect of cCMV-related comorbidities on CI performance in cCMV children. Six of seven

| Test (type)                      | N cCMV: non-cCMV | Follow-up months | Asymptomatic cCMV group | non-cCMV group | Descriptives | P value |
|---------------------------------|------------------|------------------|-------------------------|----------------|--------------|---------|
| Geers&Moog (SPr)\(^5\)         | 3:7              | 6                | 3.7 (0.6)               | 2.1 (0.9)      | Mean (SD)    | NS      |
|                                 | 3:7              | 12               | 5.3 (0.6)               | 4.0 (1.2)      | NS           |         |
|                                 | 2:3              | 36               | 5.0 (1.4)               | 5.3 (0.6)      | NS           |         |
| Nottingham classification (SPr)\(^5\)   | 3:7              | 6                | 2.3 (0.6)               | 2.0 (0.6)      | Mean (SD)    | NS      |
|                                 | 3:7              | 12               | 2.7 (0.6)               | 2.6 (0.5)      | NS           |         |
|                                 | 2:3              | 36               | 2.5 (0.7)               | 3.0 (0.0)      | NS           |         |
| Bates classification (SPr)\(^5\)  | 3:7              | 6                | 4.0 (1.7)               | 3.7 (1.0)      | Mean (SD)    | NS      |
|                                 | 3:7              | 12               | 4.7 (1.5)               | 4.4 (0.8)      | NS           |         |
|                                 | 2:3              | 36               | 4.5 (2.1)               | 5.3 (0.6)      | NS           |         |
| IT-MAIS (SPr)\(^19\)           | 2:5              | 3                | 9                       | NR             | NS           |         |
|                                 | 2:5              | 6                | 16                      |                | NS           |         |
|                                 | 2:5              | 12               | 21                      |                | NS           |         |
|                                 | 2:5              | 18               | 24.5                    |                | NS           |         |
|                                 | 2:5              | 24               | 27                      |                | NS           |         |
|                                 | 2:5              | 30               | 33.5                    |                | NS           |         |
|                                 | 2:5              | 36               | 36.5                    |                | NS           |         |

NR, not reported; NS, not significant; SPr, speech production; SP, speech perception; AP, auditory performance; cCMV, congenital cytomegalovirus.

aDerived from figure.
studies that reported worse outcomes after cochlear implantation in cCMV children attributed the inferior results to such comorbidities. Of the five studies who found equal results in cCMV children compared to a non-cCMV group, one study solely included asymptomatic cCMV children and two studies showed inferior results in the cCMV group, yet insignificant due to the small sample sizes. A fourth study with symptomatic children in both the cCMV and the non-cCMV group saw worse CI performance in children with developmental delays from both groups.

The hypothesis that cCMV-related comorbidities can contribute to lower CI performance in cCMV affected children compared to non-cCMV was evaluated in our secondary analyses. The comparison between asymptomatic cCMV children and non-cCMV children without additional disabilities did not reveal unfavourable results in the cCMV group. This finding eliminates an exclusive unfavourable effect of the virus infection itself on CI performance. Furthermore, the comparison between symptomatic and asymptomatic cCMV children did show favourable results in the asymptomatic cCMV group on some outcome measures. This finding suggests that the comorbidities associated with cCMV are predictive of lower speech and language outcomes rather than the virus infection itself. Albeit, it is worth mentioning that data were gathered only from studies where individual results could be deducted, meaning data were not used when authors did not present them individually.

An evident pattern between the severity of comorbidities and the outcome in cCMV children after cochlear implantation could not be extracted from the studies in this review. An attempt was made, yet several characteristics of the studies included in this review made this analysis impossible. The studies that did not find a significant difference between cCMV and non-cCMV children, reported a variety of comorbidities in the cCMV group such as motor impairment, behavioural difficulties, as well as cognitive impairment. The non-cCMV groups in these studies had either no disabilities, no reported disabilities or the same amount of comorbidities as the cCMV children. As a result we were not able to recognise a pattern between the severity of comorbidities and speech and language development.

The majority of the studies that found lower performance in the cCMV group did so within 2 years after implantation. Lower performance mostly disappeared after a longer follow-up. This indicates that CI performance in cCMV children may be delayed but can progress to the level of other children after 2 years. This finding emphasises the benefit of counselling patients and their parents during the first years of speech and language development and explaining that cCMV children may take longer to achieve similar results as non-cCMV children but that they are able to achieve a similar level of speech and language development in approximately 2 years.

### 4.2 Comparison with literature

The finding of a lower CI performance score in cCMV implantees compared to other aetiologies is in agreement with the systematic review performed in 2011. In their subanalysis on outcome of surgical therapy for CMV-related SNHL, the authors state that children with congenital CMV will advance more slowly than those with other causes of SNHL. However, no analysis was performed to explore the role of associated comorbidities. The current study adds knowledge to the latter question.

| Test (type)                      | N cCMV: non-cCMV | Follow-up months | Symptomatic cCMV group | Asymptomatic cCMV group | Descriptives | P value |
|---------------------------------|------------------|-----------------|------------------------|-------------------------|--------------|---------|
| Geers & Moog (SP)               | 9:3              | 6               | 1.9 (0.8)              | 3.7 (0.6)               | Mean (SD)    | .036    |
|                                 | 8:3              | 12              | 3.0 (1.4)              | 5.3 (0.6)               | NS           |
|                                 | 4:2              | 36              | 4.3 (1.0)              | 5.0 (1.4)               | NS           |
| Nottingham classification (SPr) | 9:3              | 6               | 1.4 (0.5)              | 2.3 (0.6)               | Mean (SD)    | NS      |
|                                 | 8:3              | 12              | 1.8 (0.5)              | 2.7 (0.6)               | NS           |
|                                 | 4:2              | 36              | 2.0 (0.0)              | 2.5 (0.7)               | NS           |
| Bates classification (SPr)      | 9:3              | 6               | 2.3 (0.7)              | 4.0 (1.7)               | Mean (SD)    | NS      |
|                                 | 8:3              | 12              | 2.8 (0.9)              | 4.7 (1.5)               | NS           |
|                                 | 4:2              | 36              | 3.5 (0.6)              | 4.5 (2.1)               | NS           |
| Closed-set infant words (SP)    | 2:7              | 31 (10-56)      | 71% (36)               | 93% (3.5)               | Mean (SD)    | NS      |
| Open-set monosyllabic words (SP) | 2:7           | 31 (10-56)      | 49% (33)               | 88% (3.5)               | Mean (SD)    | NS      |
| Language Social DQ in K test (AP)| 2:7              | 31 (10-56)      | 57% (20)               | 85% (1.4)*              | Mean (SD)    | .040    |
| CAP (AP)                        | 3:5              | 1-77            | 3.3 (2.1)              | 3.4 (2.6)               | Mean (SD)    | NS      |
| SIR (Spr)                       | 3:5              | 1-77            | 1.0 (0.0)              | 2.6 (1.1)               | Mean (SD)    | NS      |

*Derived from figure. NS, not significant; SPr, speech production; SP, speech perception; AP, auditory performance; cCMV, congenital cytomegalovirus. Bold p-values: significant difference between groups.
Methodologically, the current review differs from the previous.\textsuperscript{9} The emphasis on the effect of cCMV and related comorbidities on speech and language development after cochlear implantation resulted in a broad search up to 2017 without the use of automated implosions through the databases described earlier. Our search strategy resulted in twelve comparative studies that were deemed valid for data extraction, of which only four were included in the earlier review. All seven articles in that review were included in the original search results of this review, indicating no articles were missed with this extensive search. All but one of the articles included in the previous review were included for critical appraisal in ours except for one case report.\textsuperscript{46} Certainly, this systematic review also has its limitations. A limitation of this review is that a meta-analysis could not be performed, due to previously mentioned reasons.

5 Conclusion

This systematic review shows that children deafened by cCMV are associated with impaired CI performance compared to non-cCMV implantees. In the majority of studies, the cCMV group reached lower levels of CI performance, especially in the first years post-implant. Inferior CI performance in cCMV children was attributed to comorbidities in the majority of studies and confirmed by additional statistical comparisons by the reviewers. Therefore, we urge clinicians to take into account the negative effects of comorbidities associated with cCMV-related deafness during the counselling of cCMV implantees. Regardless of the above mentioned, all studies revealed that children with CMV related SNHL benefit from cochlear implantation.

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Conflict of Interest

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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