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## Three years of Vestibular Infant Screening in Infants with Sensorineural Hearing Loss

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50

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53

54 **Data sharing statement:** Deidentified individual participant data will not be made available.

55

56 **Abbreviations:** UNHSP: Universal Newborn Hearing Screening Program; ABR: auditory  
57 brainstem responses; CI: cochlear implant; VIS: Vestibular Infant Screening; cVEMP:  
58 cervical Vestibular Evoked Myogenic Potentials; SCM: sternocleidomastoid muscle; cCMV:  
59 congenital cytomegalovirus; *Cx26*: *Connexin 26*; DFNB: autosomal recessive deafness;  
60 TORCHES: toxoplasmosis, other infections such as syphilis, varicella-zoster, parvovirus B19,  
61 rubella, cytomegalovirus, and herpes; GEE: Generalized Estimating Equations; OR: Odds  
62 ratios; 95% CI: 95% confidence intervals.

63

#### 64 **Article Summary**

65 This pioneer study reports the results of the first large-scale vestibular screening for hearing-  
66 impaired infants, including important risk factors for abnormal screening results.

67

#### 68 **What's Known on This Subject**

69 Hearing-impaired children are at risk for vestibular deficits due to the close anatomical and  
70 embryological relationship between the auditory and vestibular systems. Although vestibular  
71 deficits can affect the child's development, pediatric vestibular assessment is not routinely  
72 implemented in clinical practice.

73

#### 74 **What This Study Adds**

75 The Vestibular Infants Screening – Flanders project was a pioneer to implement a vestibular  
76 screening for all hearing-impaired infants in Flanders (Belgium). This large-scale study  
77 reports results after three years of vestibular screening and identifies risk factors for abnormal  
78 screening results.

79 **Contributors' Statement Page**

80 Drs. Martens collected data, coordinated data collection, carried out data analyses, drafted the  
81 initial manuscript, and revised the manuscript.

82 Prof. Dhooge conceptualized and designed the study, collected data, critically reviewed and  
83 revised the manuscript, and supervised the Vestibular Infants Screening – Flanders project.

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90 Prof. Deggouj collected data and critically reviewed and revised the manuscript.

91 Prof. Maes conceptualized and designed the study, collected data, contributed to interpretation  
92 of data analyses, critically reviewed and revised the manuscript, and supervised the Vestibular  
93 Infants Screening – Flanders project.

94 All authors approved the final manuscript as submitted and agree to be accountable for all  
95 aspects of the work.

96 **Abstract**

97

98 **Objectives**

99 Although vestibular deficits are more prevalent in hearing-impaired children and can affect  
100 their development on many levels, pediatric vestibular assessment is still uncommon in  
101 clinical practice. Since early detection may allow for timely intervention, this pioneer project  
102 has implemented a basic vestibular screening test for each six-month-old hearing-impaired  
103 infant in Flanders (Belgium). This study aims to report the vestibular screening results over a  
104 period of three years and to define the most important risk factors for abnormal vestibular  
105 screening results.

106

107 **Methods**

108 Cervical Vestibular Evoked Myogenic Potentials with bone-conduction were used as  
109 vestibular screening tool in all reference centers affiliated to the Universal Newborn Hearing  
110 Screening Program in Flanders. From June 2018 until June 2021, 254 infants (mean age: 7.4  
111 months, standard deviation: 2.4 months) with sensorineural hearing loss were included.

112

113 **Results**

114 Overall, abnormal vestibular screening results were found in 13.8% (35/254) of the infants.  
115 The most important group at risk for abnormal vestibular screening results were infants with  
116 unilateral or bilateral severe to profound sensorineural hearing loss (20.8%, 32/154) ( $p <$   
117  $0.001$ , Odds Ratio = 9.16). Moreover, abnormal vestibular screening results were more  
118 prevalent in infants with hearing loss caused by meningitis (66.7%, 2/3), syndromes (28.6%,  
119 8/28), congenital cytomegalovirus infection (20.0%, 8/40), and cochleovestibular anomalies  
120 (19.2%, 5/26).

121

122 **Conclusions**

123 The vestibular screening results in infants with sensorineural hearing loss indicate the highest  
124 risk for vestibular deficits in severe to profound hearing loss, and certain underlying etiologies  
125 of hearing loss such as meningitis, syndromes, congenital cytomegalovirus and  
126 cochleovestibular anomalies.

## INTRODUCTION

127

128 In 1993, the National Institutes of Health published a consensus statement recommending early  
129 identification of hearing impairment in infants.<sup>1</sup> Subsequently, the Joint Committee on Infant  
130 Hearing initiated a Universal Newborn Hearing Screening Program (UNHSP), which allowed  
131 early detection (i.e. within the first two months of life) and intervention (i.e. before the age of  
132 three months) of infants with permanent hearing loss in order to maximize their linguistic  
133 competences, communicative skills and literacy development.<sup>2,3</sup> In 1998, Flanders was a  
134 pioneer to implement this UNHSP by means of automated auditory brainstem responses  
135 (AABR), which was organized by the infant welfare agency of the Flemish government 'Child  
136 and Family'. This UNHSP has already proven its benefits, since an increasing number of  
137 children and adolescents with hearing aids or cochlear implants (CI) are enrolled in  
138 mainstream education.<sup>4</sup> Therefore, UNHSP can prevent hearing-impaired children to fall  
139 behind their hearing peers in language, cognition, and social-emotional development, which  
140 may improve the child's educational level and professional career in adulthood.<sup>5</sup>

141

142 The close anatomical and embryological relationship between the auditory and vestibular end  
143 organs suggests that the underlying etiology of hearing loss may also affect vestibular  
144 function.<sup>6,7</sup> Accordingly, a higher occurrence of vestibular deficits in children with  
145 sensorineural hearing loss in comparison with normal-hearing children was found in literature.<sup>8</sup>  
146 Similar to hearing loss, vestibular deficits can affect the child's development on many levels.  
147 Whereas a severe vestibular deficit can result in a reduced balance control and a delayed  
148 acquisition of gross motor milestones (e.g. head control, independent sitting and walking) in  
149 young children,<sup>6,9-17</sup> this can also affect fine motor, writing, reading and learning skills, as well  
150 as cognitive and socio-emotional development at a later age.<sup>15,18-24</sup> Nevertheless, a universal

151 vestibular infant screening program does not exist and pediatric vestibular assessment in  
152 clinical practice often remains limited to specific groups such as CI-candidates or older  
153 children with vestibular complaints. In June 2018, twenty years after the start of the Flemish  
154 UNHSP, Flanders was the first region worldwide to implement a vestibular screening for all  
155 six-month-old infants with confirmed permanent hearing loss.<sup>25,26</sup> The Vestibular Infant  
156 Screening (VIS) - Flanders project selected cervical Vestibular Evoked Myogenic Potentials  
157 (cVEMP) as vestibular screening tool, because it is a child-friendly, brief and objective  
158 examination.<sup>27,28</sup> Moreover, it is feasible to introduce this test on a large scale since ABR  
159 devices generally also contain cVEMP modules. Several studies have also shown that the  
160 results of the cVEMP, which mainly assesses saccular function,<sup>29-31</sup> strongly correlate with the  
161 child's motor performance.<sup>9,11,13</sup> Similar to UNHSP, early vestibular screening will enable  
162 early detection of vestibular deficits, which can lead to prompt referral for motor assessment  
163 and therapy if needed. However, it still remains to be proven that early detection of vestibular  
164 deficits results in better functional outcomes.

165

166 The purpose of this paper is to report the results after three years of vestibular screening in  
167 Flanders, and to identify the most important risk factors for abnormal vestibular screening  
168 results in infants with sensorineural hearing loss.

## METHODS

169

### 170 **Participants**

171 The vestibular screening was offered to all Flemish infants with permanent hearing loss  
172 around the age of 6 months in one of the 25 reference centers involved in the UNHSP. As the  
173 preliminary VIS-Flanders study showed normal screening results in infants with permanent  
174 conductive hearing loss, only infants with sensorineural hearing loss were included.<sup>26</sup> This  
175 multicenter cross-sectional study was approved by the leading Ethical Committee of the  
176 Ghent University Hospital and the ethical committees of all participating centers (Belgian  
177 registration number: B670201835971, ClinicalTrials.gov registration number:  
178 NCT05061069). In accordance with the ethical standards of the Helsinki Declaration, written  
179 informed consents of parents were obtained.

180

### 181 **Vestibular screening procedure**

182 The vestibular screening protocol and its addition to the existing Flemish neonatal hearing  
183 screening protocol are reported by Martens et al. (2019, 2020).<sup>25,26</sup> The cVEMP test was  
184 performed with the commercial Neuro-Audio equipment (Neurosoft, version 2010, Ivanovo,  
185 Russia). Bone-conducted stimuli (RadioEar B71W, Middelfart, Denmark) (59 dB nHL, 129  
186 dB FL) were presented at the ipsilateral mastoid. More details about the applied stimulus  
187 parameters, software algorithm, recording parameters, electrode configuration, and test setup  
188 can be consulted in Martens et al. (2020).<sup>26</sup> Electromyographic background activity was  
189 automatically quantified by the software (i.e. accepted range of mean rectified voltage: 80 –  
190 250  $\mu$ V) and displayed on a screen<sup>26</sup>. At least two trials were recorded on each side to check  
191 waveform reproducibility. The averaged rectified interpeak amplitude was calculated from the  
192 two trials with equivalent sternocleidomastoid muscle (SCM) tension (i.e. averaged



193 electromyographic differences  $\leq 30 \mu\text{V}$ ). Only final screening results were used for further  
194 analyses. More specifically, if the child needed a retest (i.e. within 3 months after the first  
195 screening, thus before the age of 10 months, prior to possible CI-surgery) in order to confirm  
196 the first screening results (e.g. in case of inconclusive results, see Martens et al. (2020)), only  
197 the second screening results were included.<sup>26</sup> Results were considered as normal if two  
198 reproducible biphasic P1-N1 waveforms were recorded with an averaged rectified interpeak  
199 amplitude  $\geq 1.3$  (i.e. based on normative data of the Ghent University Hospital in 34 control  
200 subjects (mean age = 7.6 months; SD = 1.5 months)).<sup>26</sup> Abnormal screening results included  
201 inconclusive responses (i.e. insufficient SCM tension) during the retest, absent responses (i.e.  
202 no reproducible waveforms), and decreased responses (i.e. reproducible waveforms with an  
203 averaged rectified interpeak amplitude  $< 1.3$ ). Since presence and amplitude of cVEMP  
204 responses strongly correlate with the child's motor performance,<sup>9,11</sup> these criteria are  
205 clinically relevant to decide if referral for motor assessment is needed.

206

### 207 **Possible predisposing factors for abnormal vestibular screening results**

208 All centers collected results of transient evoked or distortion product otoacoustic emissions,  
209 high frequency tympanometry (1000 Hz), and click-evoked ABR. These results were used to  
210 determine possible predisposing factors for abnormal vestibular screening results (i.e. further  
211 described as 'risk factors'). The International Bureau of Audiophonology criteria were taken  
212 into account to categorize the degree of hearing loss.<sup>32</sup> Onset of hearing loss was grouped as  
213 congenital (i.e. abnormal hearing screening after birth) or early-onset (i.e. normal hearing  
214 screening after birth, but permanent hearing loss detected before 10 months of age as a  
215 cVEMP retest is advised before this age). Additionally, risk factors related to hearing loss  
216 etiology included congenital cytomegalovirus (cCMV)-status, results of *Connexin 26* (*Cx26*

217 *or GJB2*, autosomal recessive deafness type 1 (DFNB1)) mutation analysis, and the presence  
218 of perinatal factors that are associated with an increased risk for hearing loss. Infants with  
219 sensorineural hearing loss were standardly tested for cCMV within three weeks after birth by  
220 performing virus isolation or polymerase chain reaction (PCR) in urine or saliva, or after this  
221 period with PCR on neonatal dried blot spots (i.e. Guthrie card). cCMV definitions were  
222 applied as described in the European Consensus Statement of 2017<sup>33</sup>. Perinatal factors were  
223 considered as present in case of prematurity (i.e. gestational age < 36 weeks), low birth  
224 weight (i.e. birth weight < 2500g),<sup>34</sup> or hospitalization longer than 5 days at neonatal intensive  
225 care unit. Other perinatal factors such as hyperbilirubinemia and ototoxic medications were  
226 not included as not provided by all centers. All aforementioned risk factors (including *Cx26*-  
227 and cCMV-status) were standardly known at the age of screening, whereas more advanced  
228 etiological work-up (such as imaging and genetic testing by means of next generation  
229 sequencing technology) was not always allowed by the parents, or available at the moment of  
230 screening. Therefore, underlying etiology of hearing loss was reported descriptively to  
231 estimate the most important groups at risk for abnormal screening results. Etiological work-up  
232 results were classified as genetic non-syndromic, genetic syndromic, TORCHES (i.e.  
233 toxoplasmosis, other infections such as syphilis, varicella-zoster, parvovirus B19, rubella,  
234 cytomegalovirus, and herpes) infections, meningitis, cochleovestibular anomalies (i.e.  
235 cochleovestibular nerve aplasia or inner ear malformations confirmed by magnetic resonance  
236 imaging or computed tomography that could not be classified into one of the first four  
237 categories), or an unknown etiology.

238

### 239 **Statistical analysis**

240 Statistical analysis was completed with SPSS software (IBM, version 27.0, Armonk, NY). On

241 subject level, abnormal screening results indicated abnormal responses in at least one ear, and  
242 the degree of hearing loss was categorized according to the worst ear in case of bilateral  
243 hearing loss. The two-tailed Fisher's Exact test was used to evaluate the association between  
244 screening results and possible predisposing factors. On ear level, data were analyzed more in-  
245 depth by means of Generalized Estimating Equations (GEE), which takes the clustered data  
246 structure (i.e. two ears within one child) into account and provides a robust estimator of the  
247 covariance matrix. Results of etiological work-up of hearing loss were not included as a  
248 predictor in order to avoid multicollinearity, and because the underlying etiology was not  
249 known in all infants. Included predictors were on ear level (i.e. degree and onset of hearing  
250 loss) or on subject level (i.e. gender, laterality of hearing loss, cCMV-status, Cx26-status, and  
251 presence of perinatal factors). Odds ratios (OR) with 95% confidence intervals (CI) were  
252 reported. The significance level (i.e. two-tailed) was set at  $p < 0.01$  to correct for multiple  
253 testing.

## RESULTS

254

### 255 **Subjects**

256 Overall, 301 hearing-impaired infants were screened of which 47 infants were excluded (Fig  
257 1). All twenty-two excluded infants with permanent conductive hearing loss showed normal  
258 vestibular screening results. In total, 254 infants (i.e. 125 boys, 129 girls) with sensorineural  
259 hearing loss were included (i.e. 508 ears). The mean age during the final screening test was  
260 7.4 months (standard deviation = 2.4 months). Table 1 displays the distribution of hearing loss  
261 characteristics and etiology. The majority showed unilateral or bilateral severe to profound  
262 hearing loss (60.6%, 154/254). Six infants had normal hearing at birth but developed early-  
263 onset hearing loss (2.4%, 6/254), in three children it was due to meningitis, and in three  
264 children it was caused by cCMV (symptomatic: n = 1; asymptomatic: n = 2). Genetic (i.e.  
265 non-syndromic and syndromic) hearing loss was found in 29.9% (76/254) of the infants,  
266 whereas 17.0% (43/254) had acquired hearing loss (i.e. TORCHES and meningitis). The  
267 majority of TORCHES infections was caused by cCMV (97.5%, 39/40). DFNB1 (*Cx26*) was  
268 the leading cause for genetic non-syndromic hearing loss (66.7%, 32/48), followed by  
269 DFNB3 (*MYO15A*) (6.3%, 3/48), DFNB16 (*STRC*) (6.3%, 3/48), and DFNB12 (*CDH23*)  
270 (4.1%, 2/48). The most common syndromic causes were Waardenburg syndrome (10.7%,  
271 3/28), CHARGE syndrome (7.1%, 2/28), Usher type 1 syndrome (7.1%, 2/28), Usher type 2  
272 syndrome (7.1%, 2/28), Down syndrome (7.1%, 2/28), and Pendred syndrome (7.1%, 2/28).

273

### 274 **Vestibular screening results**

275 On subject level, abnormal results were found in 13.8% of the infants (35/254) (Appendix 1).  
276 Unilateral abnormal results were found in 8.3% (21/254), whereas bilateral abnormal results  
277 were seen in 5.5% (14/254). The latter group contained six infants with bilateral inconclusive

278 results, in which a bilateral vestibular deficit was confirmed in five infants during vestibular  
279 follow-up at a later age (Table 2). Abnormal results were found significantly more often in  
280 infants with unilateral or bilateral severe to profound hearing loss (20.8%, 32/154) compared  
281 to unilateral or bilateral mild-moderate hearing loss (3.0%, 3/100) ( $p < 0.001$ ) (Fig 2).  
282 Moreover, abnormal results were more frequently noticed in early-onset hearing loss (i.e. only  
283 caused by meningitis and cCMV) (50.0%, 3/6) compared to congenital hearing loss (12.9%,  
284 32/248) ( $p = 0.036$ ) (Fig 2). cCMV-positive infants more often showed abnormal results  
285 (20.5%, 8/39) compared to infants without cCMV (12.6%, 27/215) ( $p = 0.207$ ) (Fig 3). No  
286 major differences in screening results were noticed between infants with and without perinatal  
287 factors ( $p = 0.840$ ) (Fig 3). In *Cx26*-infants, abnormal results were less common (3.1%, 1/32)  
288 compared to infants without *Cx26* (15.3%, 34/222) ( $p = 0.095$ ) (Fig 3). cCMV detection was  
289 negative on the Guthrie card of the only *Cx26*-infant with abnormal results. In respect to  
290 advanced etiological work-up, most abnormal results were found if the hearing loss was  
291 caused by meningitis (66.7%, 2/3), followed by syndromic hearing loss (i.e. especially Usher  
292 type 1 and CHARGE syndrome) (28.6%, 8/28), hearing loss caused by TORCHES infections  
293 (i.e. only in cases with cCMV) (20.0%, 8/40), and cochleovestibular anomalies (19.2%, 5/26)  
294 (Fig 4).

295

### 296 **Multivariable model predicting abnormal screening results**

297 On ear level, abnormal vestibular screening results were found in 9.6% (49/508) of the ears  
298 (Table 3). More in-depth analysis on ear level by means of GEE-modeling demonstrated that  
299 the odds ratios of an abnormal result were only significant for the degree of hearing loss  
300 (Table 4). More specifically, the odds of an abnormal result were about 9 times higher ( $p <$   
301  $0.001$ , OR = 9.16, 95% CI = [2.75 – 30.58]) for ears with severe to profound hearing loss

302 compared to the ears with normal hearing, for equal values on the other risk factors. No  
303 significantly increased risk ( $p = 0.76$ , OR = 0.83, 95% CI = [0.25 – 2.80]) was found between  
304 ears with mild-moderate hearing loss and normal hearing. In one of the three normal hearing  
305 ears with abnormal results, the vestibular screening was normal for the contralateral hearing-  
306 impaired ear (i.e. cCMV-positive). Moreover, the odds ratio of an abnormal result was almost  
307 13 times higher but on the border of statistical significance ( $p = 0.01$ , 95% CI = [1.80 –  
308 89.92]) for the confined group of ears with early-onset hearing loss (i.e. solely caused by  
309 cCMV and meningitis) in comparison with congenital hearing loss, for equal values on the  
310 other risk factors.

## DISCUSSION

311

312 This pioneer study aimed to map the occurrence of and to identify the most important risk  
313 factors for abnormal vestibular screening results in a large group of infants with congenital or  
314 early-onset sensorineural hearing loss. The cVEMP was selected as vestibular screening tool  
315 as saccular function is essential for the development of head control and gross motor  
316 milestones in young children.<sup>9</sup> Abnormal cVEMP results were found in 14% of all included  
317 infants, and in 21% of infants with severe to profound hearing loss, whereas higher  
318 percentages of abnormal cVEMP results (i.e. between 17% and 91%) were reported in  
319 literature.<sup>6,10,16,35-45</sup> However, various test protocols and cut-off criteria have been used to  
320 evaluate cVEMP abnormality in literature, resulting in a wide range of cVEMP  
321 abnormalities.<sup>8,25</sup> Additionally, previous studies mainly focused on older children with severe  
322 to profound sensorineural hearing loss, and were mostly conducted in specialized CI centers,  
323 therefore dealing with a population of children more at risk for vestibular deficits. Since  
324 hearing losses with various degrees and etiologies were included in the present study, the  
325 results are more representative for the whole group of infants who fail the neonatal hearing  
326 screening. As only the cVEMP was used to screen the vestibular function, which only  
327 assesses one part of the vestibular system, ongoing longitudinal vestibular research at the  
328 Ghent University Hospital will map the sensitivity of the vestibular screening to evaluate the  
329 overall vestibular function in hearing-impaired infants.

330

331 The current study showed that infants with severe to profound sensorineural hearing loss are  
332 the most important group at risk for abnormal cVEMP results, thereby confirming the  
333 preliminary VIS-Flanders results.<sup>26</sup> Consistent with these findings, Maes et al. (2014) reported  
334 significantly higher cVEMP abnormality rates in children with profound hearing loss

335 compared to those with non-profound hearing loss.<sup>43</sup> Also the systematic review of Verbecque  
336 et al. (2017) concluded that pediatric vestibular loss was reported more frequently with  
337 increasing degrees of hearing loss as the auditory and vestibular end organs are closely  
338 related.<sup>8</sup> Screening results did not differ significantly according to the laterality of hearing  
339 loss, which is supported by previous studies that described vestibular deficits in unilaterally  
340 hearing-impaired children.<sup>44,46</sup> In early-onset hearing loss, screening results seemed to be  
341 more abnormal compared to congenital hearing loss. However, only six infants with early-  
342 onset hearing loss could be included in the current study since infants were screened at an  
343 early age. In all infants with early-onset hearing loss, the underlying etiology was meningitis  
344 or cCMV, which are two etiologies repeatedly associated with a high risk for vestibular  
345 deficits in literature.<sup>42,47-52</sup> Besides cCMV and meningitis, abnormal screening results were  
346 noticed more often in infants with syndromic hearing loss, such as Usher type 1 and  
347 CHARGE syndrome, and cochleovestibular anomalies, which is in agreement with findings  
348 of previous studies and the recent review of Hazen et al. (2020).<sup>42,53-57</sup> No significant odds  
349 ratio for abnormal screening results was found in the group of cCMV-positive infants,  
350 because the group without cCMV also consisted of infants at risk for vestibular deficits, such  
351 as infants with meningitis, syndromic hearing loss and cochleovestibular anomalies.  
352 Furthermore, infants with genetic non-syndromic hearing loss were only at risk for abnormal  
353 vestibular screening results if the hearing loss was severe to profound (Appendix 1). Similar  
354 to the current findings, only a few pediatric cases with genetic non-syndromic hearing loss  
355 and concurrent severe vestibular deficits have been described in literature.<sup>10,38,42</sup> However, a  
356 major limitation of the current study was that advanced etiological work-up was not  
357 performed in all included infants, resulting in a large group of infants with an unknown  
358 underlying etiology of hearing loss. Nevertheless, only a minority of the latter group showed



359 abnormal screening results, which were mostly found in infants with severe to profound  
360 hearing loss (Appendix 1). Finally, abnormal screening results occurred approximately  
361 equally in hearing-impaired infants with and without perinatal factors. In line with the results  
362 of Zagólski et al. (2006), abnormal cVEMP results of hearing-impaired infants with perinatal  
363 factors were mainly found in case of severe to profound hearing loss (Appendix 1).<sup>58</sup> Thus, it  
364 seems that perinatal factors measured in this study are only relevant in the light of  
365 predisposing the infant to hearing loss, as it is the degree of hearing loss that determines the  
366 risk for vestibular deficits.

## CONCLUSION

367

368 This is the first study to report results after three years of vestibular screening in a group of  
369 infants with congenital or early-onset sensorineural hearing loss. Based on the current results,  
370 the authors highly recommend early vestibular screening for all infants with unilateral or  
371 bilateral severe to profound sensorineural hearing loss, and additionally for hearing-impaired  
372 infants with meningitis, syndromes, cCMV, and cochleovestibular anomalies. Hereby,  
373 vestibular deficits can be detected at a young age, which enables early referral for motor  
374 assessment and rehabilitation if needed. Future research should map the sensitivity of the  
375 cVEMP as vestibular screening tool in order to fine-tune this vestibular screening protocol.

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**Figure 1.** Number of screened infants, excluded infants and included study population.

**Figure 2.** Vestibular screening results according to characteristics of hearing loss (n = 254 infants).

**Figure 3.** Vestibular screening results according to etiology of hearing loss as standardly known at the age of screening (n = 254 infants).

Abbreviations: cCMV = congenital cytomegalovirus; DFNB = autosomal recessive deafness; *Cx26* = *Connexin 26*.

**Figure 4.** Vestibular screening results according to advanced etiological work-up of hearing loss (n = 254 infants).

Abbreviations: TORCHES = Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus, and Herpes infections.

**Table 1.** Characteristics and etiology of hearing loss (n = 254 infants).

**Table 2.** Characteristics of infants with inconclusive results during the first and second vestibular screening test (n = 6 infants).

**Table 3.** Vestibular screening results according to gender, characteristics and etiology of hearing loss (n = 508 ears).

**Table 4.** Multivariable model predicting abnormal screening results (n = 508 ears).

**Appendix 1.** Overview of all infants with abnormal screening results (n = 35 infants).



**Number of screened infants in Flanders (June 2018 – June 2021)**

Total: n = 301



**Excluded infants**

Parents refused informed consent: n = 9

Bilateral normal hearing during audiological follow-up: n = 9

Parents declined retest in case of initial inconclusive results: n = 6

Delayed-onset hearing loss after ten months of age: n = 1

Permanent conductive hearing loss due to external auditory canal atresia: n = 22

Total: n = 47

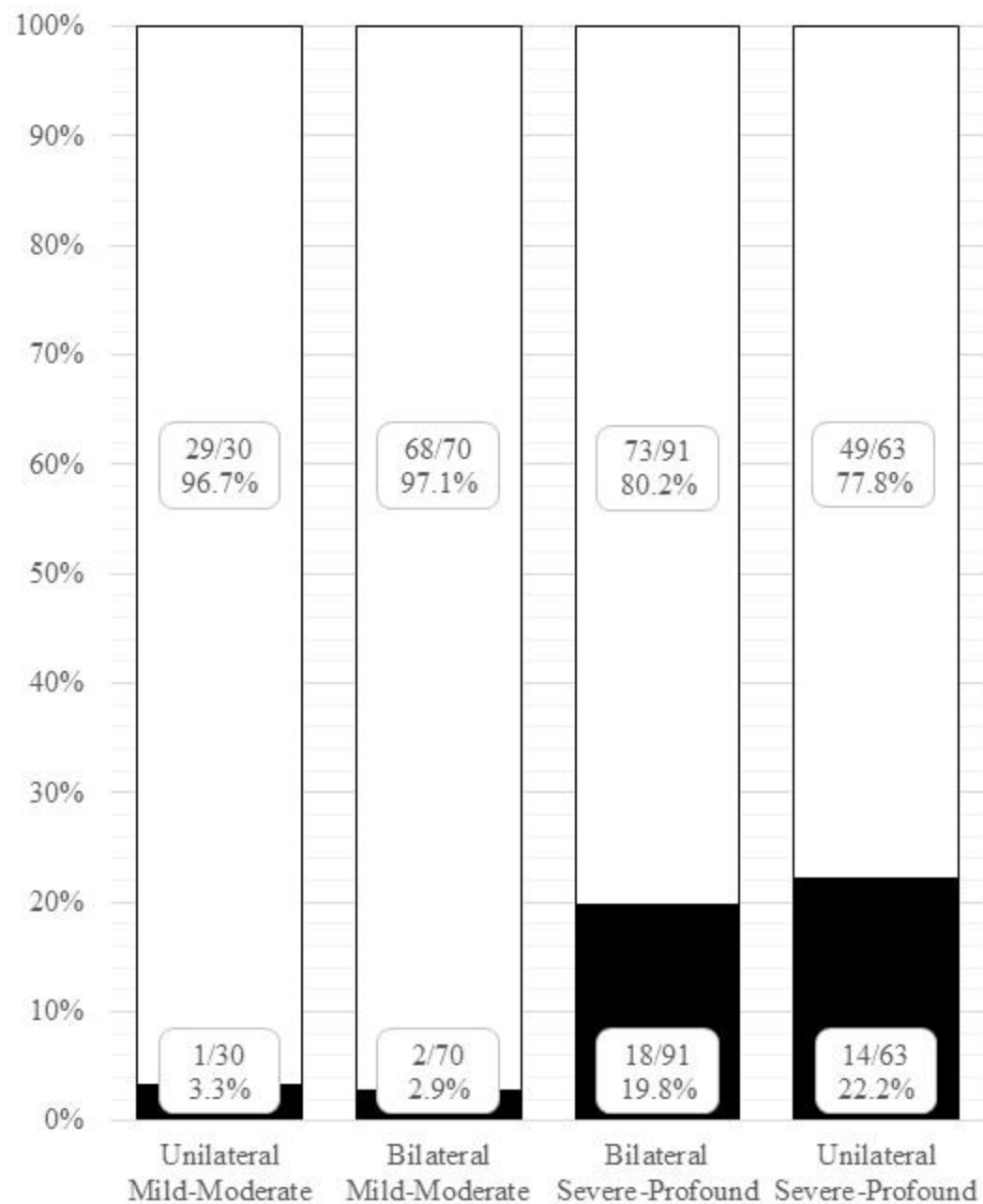


**Included study population**

Total: n = 254

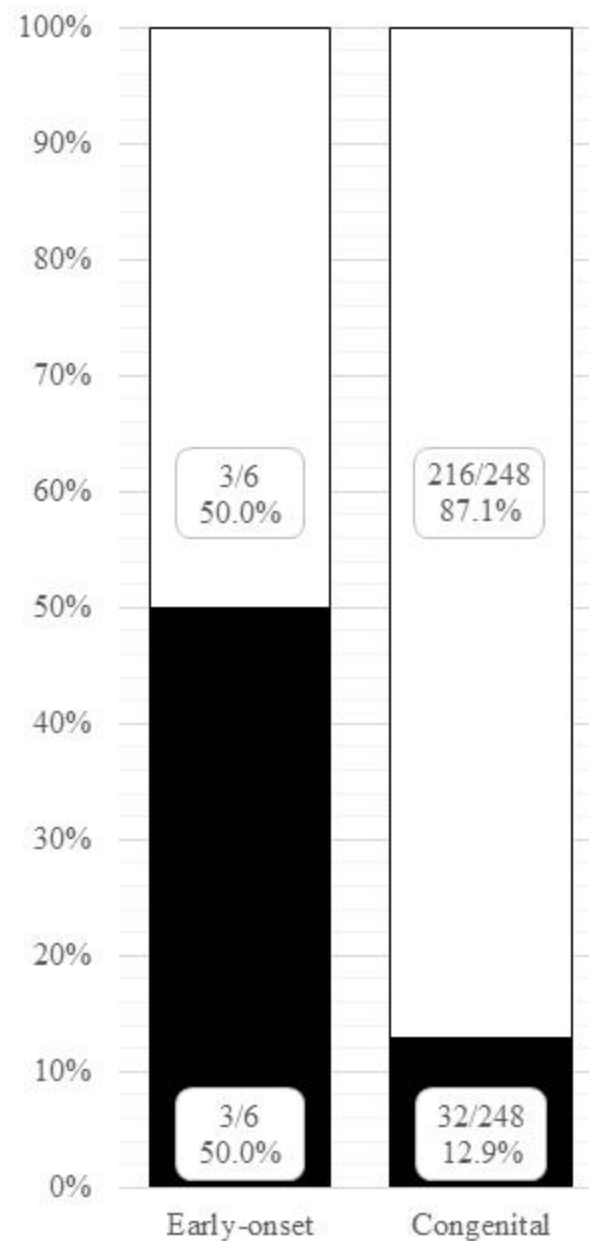
Degree and laterality of hearing loss

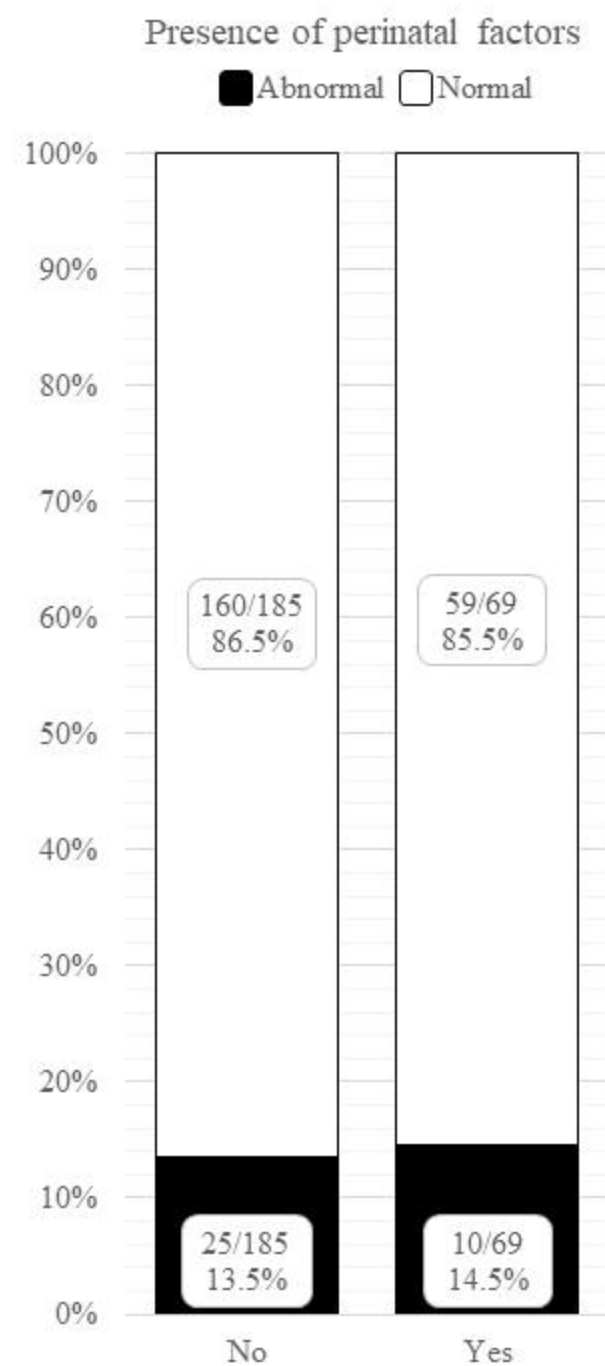
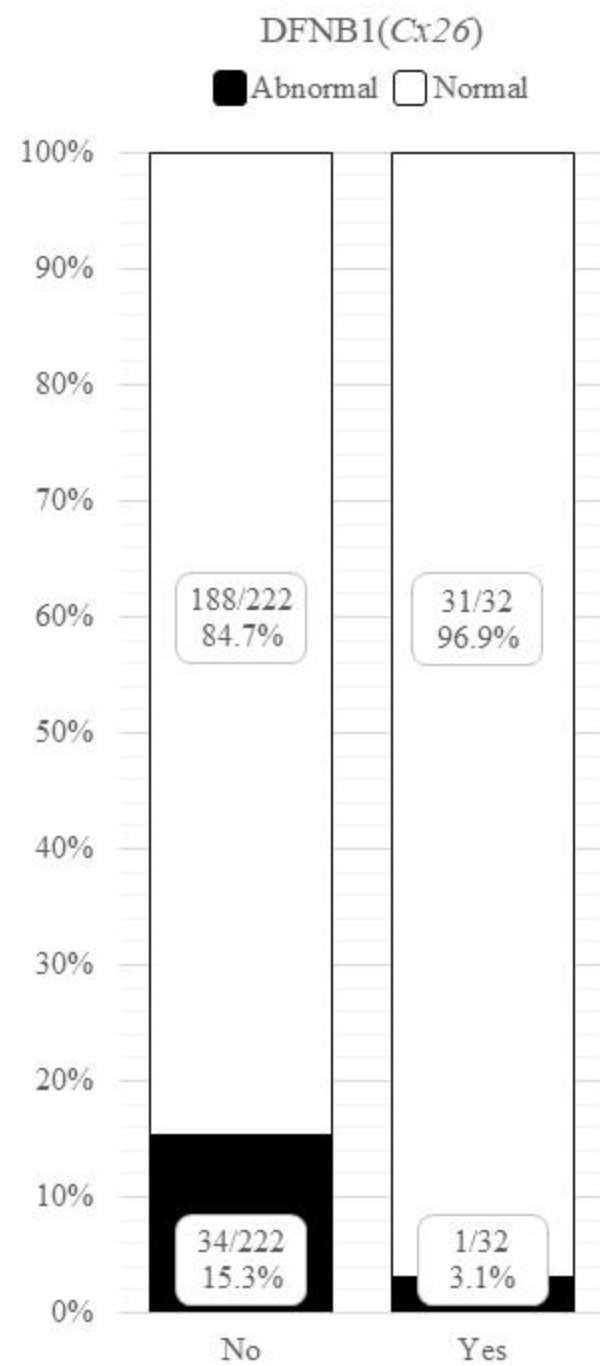
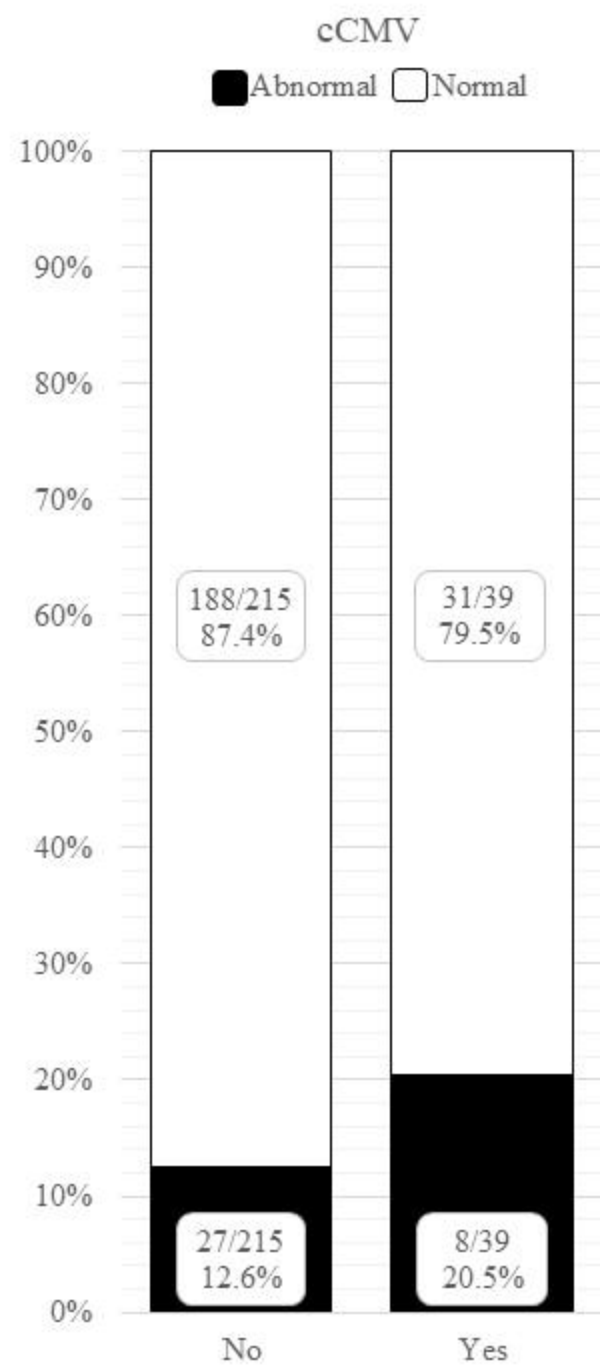
■ Abnormal □ Normal



Onset of hearing loss

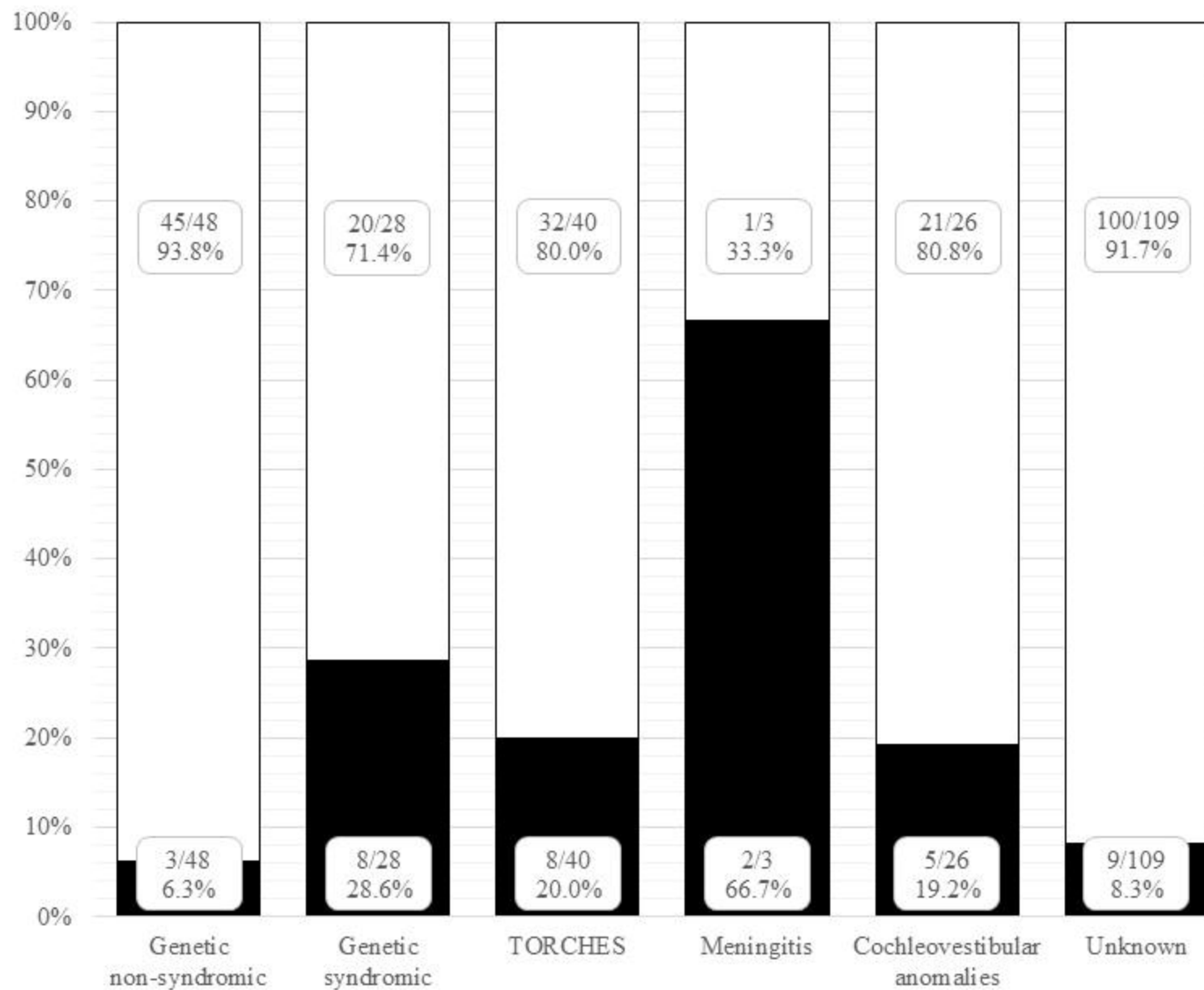
■ Abnormal □ Normal





### Etiology of hearing loss

■ Abnormal    □ Normal



## TABLES

**TABLE 1 Characteristics and etiology of hearing loss (n = 254 infants)**

Characteristics of hearing loss			
Degree and laterality	Unilateral Mild-Moderate	11.8%	(30/254)
	Bilateral Mild-Moderate	27.6%	(70/254)
	Unilateral Severe-Profound	24.8%	(63/254)
	Bilateral Severe-Profound	35.8%	(91/254)
Onset	Congenital	97.6%	(248/254)
	Early-onset	2.4%	(6/254)
Etiology of hearing loss			
cCMV <sup>1</sup>	No	84.6%	(215/254)
	Yes	15.4%	(39/254)
DFNB1( <i>Cx26</i> ) <sup>1</sup>	No	87.4%	(222/254)
	Yes	12.6%	(32/254)
Presence of perinatal factors <sup>1</sup>	No	72.8%	(185/254)
	Yes	27.2%	(69/254)
Advanced etiological work-up results	Genetic non-syndromic	18.9%	(48/254)
	Genetic syndromic	11.0%	(28/254)
	TORCHES	15.8%	(40/254)
	Meningitis	1.2%	(3/254)
	Cochleovestibular anomalies	10.2%	(26/254)
	Unknown (cCMV- and <i>Cx26</i> -negative)	42.9%	(109/254)

<sup>1</sup>Standardly known at the age of screening.

Abbreviations: cCMV = congenital cytomegalovirus; DFNB = autosomal recessive deafness; *Cx26* = *Connexin 26*; TORCHES = Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus, and Herpes infections.

**TABLE 2 Characteristics of infants with inconclusive results during the first and second vestibular screening test (n = 6 infants)**

	Hearing loss characteristics	Underlying etiology of hearing loss	Vestibular deficit confirmed at later age
1.	Bilateral severe-profound congenital sensorineural	Genetic syndromic (CHARGE syndrome)	Yes
2.	Bilateral severe-profound congenital sensorineural	Genetic non-syndromic (DFNB35)	Yes
3.	Bilateral severe-profound congenital sensorineural	Genetic syndromic (Usher syndrome type 1)	Yes
4.	Bilateral severe-profound congenital sensorineural	TORCHES (cCMV)	Yes
5.	Bilateral severe-profound congenital sensorineural	TORCHES (cCMV)	Yes
6.	Bilateral severe-profound congenital sensorineural	Unknown	No <sup>1</sup>

<sup>1</sup>Parents declined vestibular follow-up as the child had epileptic attacks and motor therapy was already initiated due to severe motor retardation.

Abbreviations: DFNB = autosomal recessive deafness; TORCHES = Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus, and Herpes infections; cCMV = congenital cytomegalovirus.

**TABLE 3 Vestibular screening results according to gender, characteristics and etiology of hearing loss (n = 508 ears)**

		Vestibular screening results			
		Abnormal		Normal	
Gender	Female	10.1%	(26/258)	89.9%	(232/258)
	Male	9.2%	(23/250)	90.8%	(227/250)
Degree of hearing loss	Normal	3.2%	(3/93)	96.8%	(90/93)
	Mild-Moderate	2.1%	(4/191)	97.9%	(187/191)
	Severe-Profound	18.8%	(42/224)	81.2%	(182/224)
Onset of hearing loss	Congenital	9.1%	(45/496)	90.9%	(451/496)
	Early-onset	33.3%	(4/12)	66.7%	(8/12)
Laterality of hearing loss	Unilateral	9.1%	(17/186)	90.9%	(169/186)
	Bilateral	9.9%	(32/322)	90.1%	(290/322)
cCMV <sup>1</sup>	No	8.8%	(38/430)	91.2%	(392/430)
	Yes	14.1%	(11/78)	85.9%	(67/78)
DFNB1( <i>Cx26</i> ) <sup>1</sup>	No	10.6%	(47/444)	89.4%	(397/444)
	Yes	3.1%	(2/64)	96.9%	(62/64)
Presence of perinatal factors <sup>1</sup>	No	9.2%	(34/370)	90.8%	(336/370)
	Yes	10.9%	(15/138)	89.1%	(123/138)

<sup>1</sup>Standardly known at the age of screening.

Abbreviations: cCMV = congenital cytomegalovirus; DFNB = autosomal recessive deafness; *Cx26* = *Connexin 26*.

**TABLE 4 Multivariable model predicting abnormal screening results (n = 508 ears)**

		OR	95% CI	<i>p</i> -value
Gender	Female*			
	Male	0.80	[0.36 - 1.74]	0.56
Degree of hearing loss	Normal*			
	Mild-Moderate	0.83	[0.25 - 2.80]	0.76
	Severe-Profound	<b>9.16</b>	<b>[2.75 - 30.58]</b>	<b>&lt; 0.001</b>
Onset of hearing loss	Congenital*			
	Early-onset	12.70	[1.80 - 89.92]	0.01
Laterality of hearing loss	Unilateral*			
	Bilateral	1.180	[0.51 - 2.69]	0.70
cCMV	No*			
	Yes	0.78	[0.27 - 2.27]	0.65
DFNB1( <i>Cx26</i> )	No*			
	Yes	0.17	[0.02 - 1.42]	0.10
Presence of perinatal factors	No*			
	Yes	1.18	[0.51 - 2.70]	0.70

\*Reference group.

Abbreviations: OR = Odds Ratio; 95% CI = 95% Confidence Interval for OR; cCMV = congenital cytomegalovirus; DFNB = autosomal recessive deafness; *Cx26* = *Connexin 26*.



**Appendix 1a Overview of all infants with abnormal screening results (n = 35 infants)**

Final screening result	Degree and laterality of hearing loss	Onset of hearing loss	Underlying etiology of hearing loss	Presence of perinatal factors
Bilateral absent	Bilateral severe-profound	Congenital	Genetic syndromic (CHARGE syndrome)	No
Bilateral absent	Bilateral severe-profound	Congenital	Genetic syndromic (Johanson-Blizzard syndrome)	Yes
Bilateral absent	Bilateral severe-profound	Congenital	Genetic syndromic (Usher syndrome type 1)	Yes
Bilateral absent	Bilateral severe-profound	Congenital	Genetic non-syndromic (DFNB1 (Cx26))	No
Bilateral absent (left) decreased (right)	Unilateral severe-profound (right)	Congenital	TORCHES (cCMV)	No
Bilateral absent (left) decreased (right)	Unilateral mild-moderate (left)	Early-onset	Meningitis	Yes
Bilateral decreased	Bilateral severe-profound	Congenital	Genetic non-syndromic (DFNB3)	No
Bilateral decreased	Bilateral severe-profound	Congenital	Unknown	No
Bilateral inconclusive	Bilateral severe-profound	Congenital	Genetic syndromic (CHARGE syndrome)	No
Bilateral inconclusive	Bilateral severe-profound	Congenital	Genetic non-syndromic (DFNB35)	No
Bilateral inconclusive	Bilateral severe-profound	Congenital	Genetic syndromic (Usher syndrome type 1)	No
Bilateral inconclusive	Bilateral severe-profound	Congenital	TORCHES (cCMV)	No

Abbreviations: DFNB = autosomal recessive deafness; *Cx26* = *Connexin 26*; TORCHES = Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus, and Herpes infections; cCMV = congenital cytomegalovirus.

**Appendix 1b Overview of all infants with abnormal screening results (n = 35 infants)**

Final screening result	Degree and laterality of hearing loss	Onset of hearing loss	Underlying etiology of hearing loss	Presence of perinatal factors
Bilateral inconclusive	Bilateral severe-profound	Congenital	TORCHES (cCMV)	Yes
Bilateral inconclusive	Bilateral severe-profound	Congenital	Unknown	Yes
Unilateral absent (right)	Unilateral severe-profound (right)	Congenital	Genetic syndromic (Duane retraction syndrome)	No
Unilateral absent (left)	Unilateral severe-profound (left)	Early-onset	TORCHES (cCMV)	No
Unilateral absent (right)	Bilateral severe-profound	Congenital	TORCHES (cCMV)	No
Unilateral absent (right)	Unilateral severe-profound (right)	Congenital	TORCHES (cCMV)	No
Unilateral absent (left)	Unilateral severe-profound (left)	Congenital	Cochleovestibular anomalies (left)	Yes
Unilateral absent (left)	Bilateral severe-profound (left) mild-moderate (right)	Congenital	Bilateral cochleovestibular anomalies	Yes
Unilateral absent (right)	Unilateral severe-profound (right)	Congenital	Cochleovestibular anomalies (right)	No
Unilateral absent (left)	Unilateral severe-profound (left)	Congenital	Unknown	No
Unilateral absent (right)	Unilateral severe-profound (right)	Congenital	Unknown	Yes
Unilateral absent (right)	Unilateral severe-profound (right)	Congenital	Unknown	No

Abbreviations: DFNB = autosomal recessive deafness; *Cx26* = *Connexin 26*; TORCHES = Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus, and Herpes infections; cCMV = congenital cytomegalovirus.

**Appendix 1c Overview of all infants with abnormal screening results (n = 35 infants)**

Final screening result	Degree and laterality of hearing loss	Onset of hearing loss	Underlying etiology of hearing loss	Presence of perinatal factors
Unilateral decreased (right)	Bilateral severe-profound (right) mild-moderate (left)	Congenital	Genetic syndromic (Feingold syndrome type 2)	Yes
Unilateral decreased (right)	Bilateral severe-profound (right) mild-moderate (left)	Congenital	Genetic syndromic (Down syndrome)	No
Unilateral decreased (left)	Unilateral severe-profound (left)	Congenital	TORCHES (cCMV)	No
Unilateral decreased (left)	Unilateral severe-profound (right)	Congenital	TORCHES (cCMV)	No
Unilateral decreased (right)	Bilateral severe-profound (left) mild-moderate (right)	Early-onset	Meningitis	No
Unilateral decreased (right)	Bilateral severe-profound	Congenital	Bilateral cochleovestibular anomalies	No
Unilateral decreased (right)	Unilateral severe-profound (right)	Congenital	Cochleovestibular anomalies (right)	No
Unilateral decreased (right)	Unilateral severe-profound (right)	Congenital	Unknown	No
Unilateral decreased (left)	Unilateral severe-profound (left)	Congenital	Unknown	Yes
Unilateral decreased (right)	Bilateral mild-moderate	Congenital	Unknown	No
Unilateral decreased (left)	Bilateral mild-moderate	Congenital	Unknown	No

Abbreviations: DFNB = autosomal recessive deafness; *Cx26* = *Connexin 26*; TORCHES = Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus, and Herpes infections; cCMV = congenital cytomegalovirus.