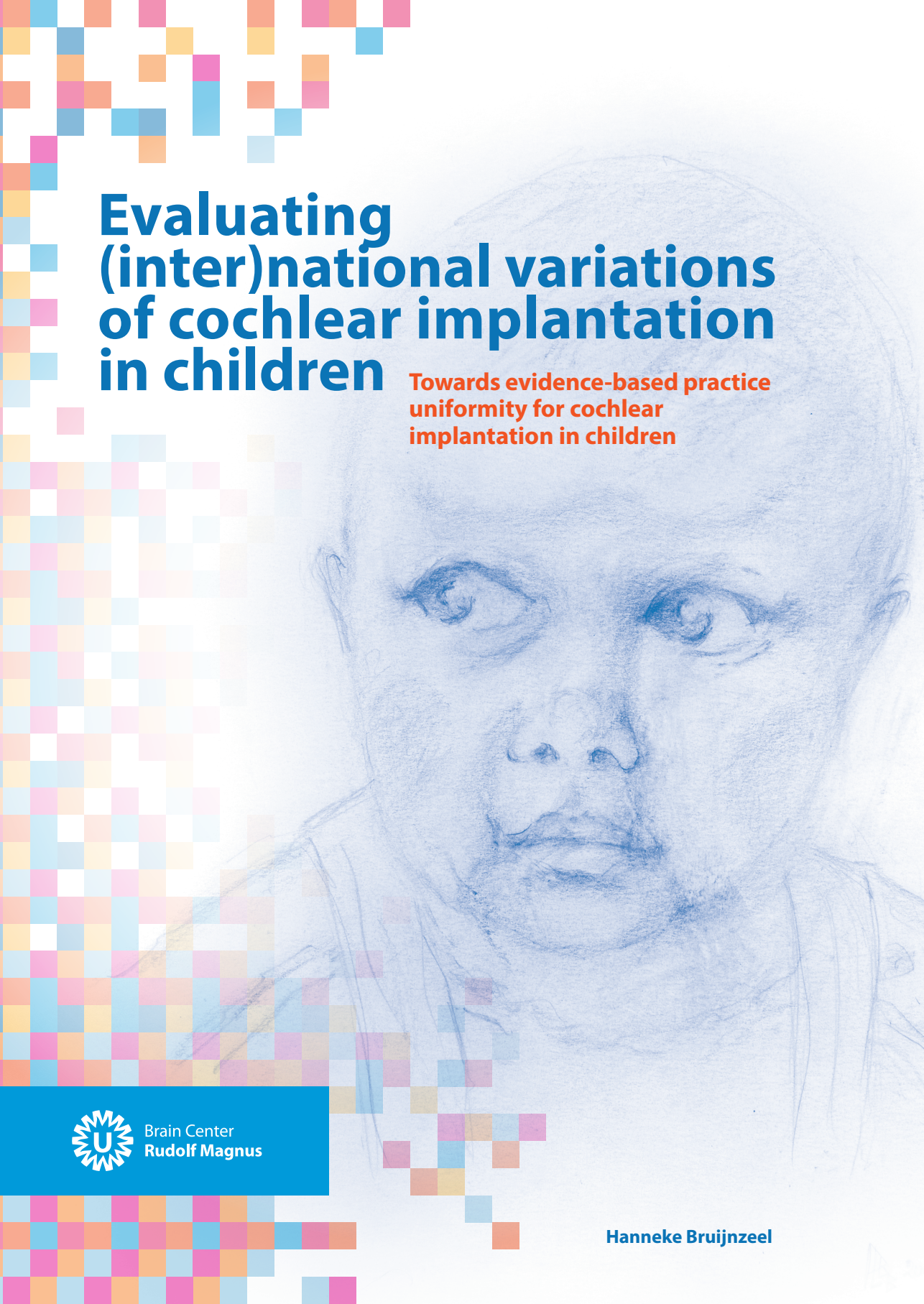
Evaluating (inter)national variations of cochlear implantation in children

Towards evidence-based practice uniformity for cochlear implantation in children



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Evalueren van (inter)nationale variatie van cochleaire implantatie bij kinderen
Streven naar evidence-based practice uniformiteit voor cochleaire implantatie bij kinderen
(met een samenvatting in het Nederlands)

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Hanneke Bruijnzeel

geboren op 10 augustus 1987
te Vianen

Promotor
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Copromotor
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Waarom?
Wie een waarom heeft waarvoor hij kan leven,
kan bijna elke hoe verdragen.

Friedrich Nietzsche

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GENERAL INTRODUCTION AND THESIS OUTLINE

The recommended age and audiological eligibility criteria for cochlear implantation in children vary between both national cochlear implant guidelines and guidelines provided by cochlear implant manufacturers[1]. Despite recommendations to start prompt hearing rehabilitation following hearing loss identification, timely implantation of cochlear implant candidates remains a worldwide issue, even in developed countries[2]. Therefore, the aim of this thesis is to formulate evidence-based practice guidelines for cochlear implantation in children, regarding: the recommended age at surgery, the cut-off hearing loss level serving as cochlear implant indication criterion and the advised surgical and anesthetic perioperative techniques. Furthermore, we aim to provide support to prevent future delays for cochlear implant candidates, by first, quantifying current European cochlear implantation delays and secondly, suggest to improve parental awareness by education (telemedicine).

This introduction provides an overview of the cochlear implant candidate selection process by focusing on the size of the paediatric population that can qualify for a cochlear implant and the identification of cochlear implant candidates through neonatal hearing screening programs (Figure 1). Specific issues such as the maturation of the auditory system, speech and language acquisition during childhood and its importance for cochlear implantation are addressed. Finally, current differences between both national cochlear implantation guidelines and guidelines provided by cochlear implant manufacturers are underlined (Figure 1, Table 1).

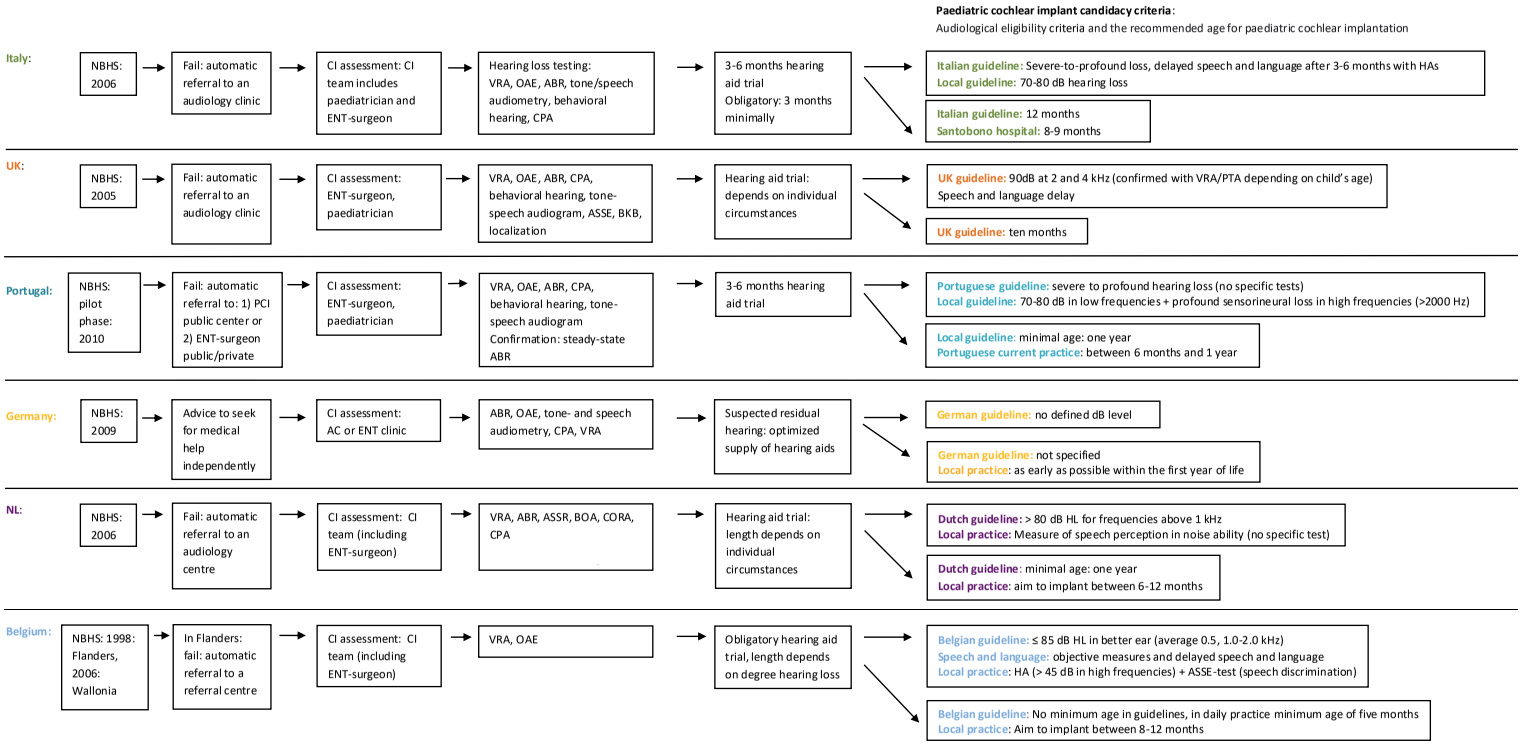
1. Paediatric hearing loss prevalence

The World Health Organization (WHO) estimates that 360 million people worldwide suffer from hearing loss of which thirty-three million (9%) individuals are children[3]. The highest paediatric hearing loss prevalence is reported in South Asia (2.4%), Pacific Asia (2.0%) and Sub-Saharan Africa (1.9%)[3]. In developed countries, paediatric hearing loss prevalence rates are considerably lower: in 2012, 0.8 million children suffered from hearing loss in high-income countries in Western Europe and North America, which entails 0.5% of the entire paediatric population with hearing loss[4]. In 2016, the WHO has started a hearing loss awareness campaign ('Act Now, Here's How!') to both increase hearing loss prevention and stimulate early hearing loss identification and treatment worldwide[5].

The WHO classifies hearing loss into five categories, ranging between no hearing loss (category 0: ≤ 25 decibel (dB) in the better ear) to profound hearing loss (category 4: ≥ 81 dB in the better ear)[4]. In Western Europe and North America, severe (category 3; [61 - 80 dB] in the better ear) to profound hearing loss is estimated to occur in 0.943 to 1.182 per 1000 new-borns[6-9]. Ninety-six percent of these infants are born to two hearing parents[10]; therefore, the majority of these infants will have little to no initial linguistic experience (i.e. speech, sign)[11].

Aforementioned hearing loss prevalence rates could be underestimated due to either: failure to identify children with hearing loss at initial new-born hearing screening (NBHS) or absence of (nationwide) NBHS implementation. For example, Fortnum *et al.* described that paediatric hearing loss was identified in 1.07 per 1000 children aged below three years, in 1.33 to 1.44 per 1000 children between five to ten years of age and increased to 2.05 per 1000 children when the paediatric cohort reached 16 years[12-13].

Figure 1. Summary of the variation regarding the paediatric cochlear implant candidate selection process between six European countries.



Legend: ABR = auditory brainstem response; AC = Auditory Center; ASSE = auditory sound speech evaluation; ASSR = auditory steady-state response; BOA = behavioural observation audiometry; BKB = Bamford-Kowal-Bench; CI = cochlear implant; CORA = conditioned orientation reflex audiometry; CPA = conditioned play audiometry; dB = decibel; ENT = ear, nose and throat; HA = hearing aid; HL = hearing loss; kHz = kilohertz; NBHS = new-born hearing screening; NL = the Netherlands; OAE = otoacoustic emmisions; PCI = paediatric cochlear implantation; PTA = pure tone audiometry; UK = United Kingdom; VRA = visual reinforcement audiometry. * This selection entails NBHS identified infants with prelingual hearing loss. In all six countries, an MRI/CT-scan of the temporal bone will be performed following hearing loss confirmation to evaluate the patency of the cochlea, identify congenital malformations, and assess the cochlear nerve anatomy. Furthermore, in all selected countries, profound hearing loss following from meningitis is an exception to the guideline. As soon as possible, CI implantation will occur to avoid performing surgery after ossification of the cochlea.

Table 1. Paediatric CI FDA guidelines reported by various CI manufacturers (patients < 18 years old)[1].

Cochlear implant – Audiometric indication	CI Manufacturers				
	Advanced Bionics		Cochlear® (Nucleus Freedom)	MED-EL GmbH (Pulsar, Sonata, Concert)	
Year of guideline approval	**2003**	**2016**	**2009**	**2005**	**2018**
Preoperative Hearing aid (HA) duration	12 - 23 months: 3 months HA 2 - 17 years: 6 months HA	12 - 23 months: 3 months HA 2 - 17 years: 6 months HA *waived in case X-rays indicate ossification	12 - 23 months: 3 months HA 2 - 17 years: 6 months HA	n.r.	A minimum of three months
Audiological HA criterion	Little/no benefit appropriately fitted HA	-	Little/no benefit appropriately fitted HA	Lack of auditory progress with hearing aid use of 3 to 6 months	Little/no benefit appropriately fitted HA
Definition of: younger children	**Age range**: [12 – 47 months]	**Age range**: [12 – 47 months]	**Age range**: [12 – 23 months]	**Age range**: [12 months – 17 years]	n.r.
	Hearing loss degree: profound bilateral SNHL (> 90 dB HL)	Severe-to-profound bilateral sensorineural deafness or severe-to-profound unilateral hearing loss	**Hearing loss degree**: profound bilateral SNHL (> 90 dB HL)	**Hearing loss degree**: profound bilateral SNHL (> 90 dB HL)	Severe-to-profound bilateral sensorineural deafness or severe-to-profound unilateral hearing loss
	Auditory progress: failure to reach age-appropriate auditory milestones (e.g. IT-MAIS) or < 20% correct on open-set word-recognition test (e.g. MLNT) at 70 dB SPL	**Auditory progress**: failure to reach age-appropriate auditory milestones (e.g. IT-MAIS) or < 20% correct on open-set word-recognition test (e.g. MLNT) at 70 dB SPL	**Auditory progress**: despite 3 to 6 months intensive aural habilitation: lack of auditory progress (e.g. MAIS)	**Auditory progress**: despite 3 to 6 months intensive aural habilitation: lack of auditory progress	n.r.
Definition of: older children	**Age range**: > 48 months	**Age range**: > 48 months	**Age range**: > 24 months	**Age range**: able to participate in speech recognition testing	
	Hearing loss degree: profound bilateral SNHL (> 90 dB HL)	Severe-to-profound bilateral sensorineural deafness or severe-to-profound unilateral hearing loss	**Hearing loss degree**: severe to profound SNHL (> 70 dB HL)	**Hearing loss degree**: profound bilateral SNHL (> 90 dB HL)	
	Auditory progress: < 12% on difficult open-set word recognition (e.g. PB-K) or < 30% on an open-set sentence test (e.g. HINT-C) using recorded materials at 70 dB SPL	**Auditory progress**: < 12% on difficult open-set word recognition (e.g. PB-K) or < 30% on an open-set sentence test (e.g. HINT-C) using recorded materials at 70 dB SPL	**Auditory progress**: ≤ 30% correct word recognition (MLNT or LNT)	**Auditory progress**: < 20% correct for MLNT or LNT depending on cognitive ability and linguistic skills	

Legend: CI = cochlear implant; dB = decibel; Ear, Nose and Throat; FDA = Food and Drug Administration; HA = hearing aid; HL = hearing level; HINT-C = hearing in noise test for children; IT-MAIS = Infant-Toddler Meaningful Auditory Integration Scale; LNT = Lexical Neighbourhood Tests; MAIS = Meaningful Auditory Integration Scale; MLNT = Multisyllabic Lexical Neighbourhood Test; NBHS = new-born hearing screening; n.r = not reported; PB-K = Phonetically Balanced Kindergarten; SNHL = Sensorineural hearing loss; SPL = sound pressure level.

2. Identification of infants presenting with hearing loss: NBHS implementation

The widespread implementation of NBHS programs in Western Europe and North America, developed in the early 1990s, led to earlier identification and timely rehabilitation for children presenting with hearing loss[14]. Timely recognition and rehabilitation of NBHS-identified hearing loss is essential to prevent negative consequences for the speech and language development of the child, and the cognitive and social development of children subjected to auditory deprivation. We will elaborate on the current Dutch NBHS practice, and will additionally elaborate on current trends found in the Dutch population further on in this thesis (**Chapter 1.2**, **Chapter 3.2** and **Chapter 3.3**).

Dutch NBHS was implemented in 2006 (Figure 1). This screening aims to identify infants with permanent unilateral or bilateral hearing loss of at least 40 decibel (dB) at frequencies ranging between 1000 and 4000 Hertz (Hz)[15]. This hearing loss level is in accordance with the highest three WHO grades of hearing loss (category 2; moderate (41 - 60 dB) to category 4; (> 81 dB))[4]. Although auditory brainstem response (ABR) is the current gold standard for paediatric hearing loss screening, regular Dutch NBHS entails click-evoked otoacoustic emissions (EOAEs) screening during the first week following birth[15]. Although this NBHS is not obligatory, currently around 98% of Dutch new-borns are screened. Most infants pass initial EOAE screening (around 95% of the NBHS screened infants); in case of a screening refer, a second EOAE screening is scheduled. In the Netherlands, ABR is only used for NBHS purposes in new-borns who do not pass the second EOAE screening or in preterm born infants who are admitted to a Neonatal Intensive Care Unit (NICU) (as reliable testing can only be performed from the age of 28 weeks) and is repeated at the full term date[15]. At birth, ABR thresholds are around 30 dB hearing level (HL) and reach adult level between the age of three to five years. Accurate hearing loss identification is essential for preterm born infants, since they show abnormal brainstem maturation, which could affect later auditory development[16]. This is reflected in the prevalence of congenital bilateral hearing loss of infants admitted at the NICU (1.7%), which is almost 25 times higher than in infants delivered at full term[15]. Furthermore, auditory neuropathy spectrum disorder (ANSD) can be identified using ABR, which will not be identified by standard Dutch NBHS using EOAEs.

Although, Lammers *et al*. showed that through Dutch NBHS implementation, infants with profound sensorineural hearing loss (SNHL) were recognized earlier after birth[17], Korver revealed that around 35% [range: 26 - 44%] of the children with profound SNHL are still not identified at Dutch NBHS[18]. This could be explained by, for example, late hearing loss recognition, either due to immigration (e.g., a lack of NBHS in the country of birth and too old to undergo NBHS in the Netherlands) or progressive hearing loss (e.g., no hearing loss detection or fail at initial screening, however, hearing loss deterioration leading to development of severe to profound SNHL). For example, Fitzpatrick *et al.* marked that more than half of their population was not eligible for a cochlear implant (CI) assessed by audiological criteria at initial diagnosis and only became a CI candidate when their hearing thresholds deteriorated[19].

3. Paediatric hearing rehabilitation: the '1 - 3 - 6 guidelines'

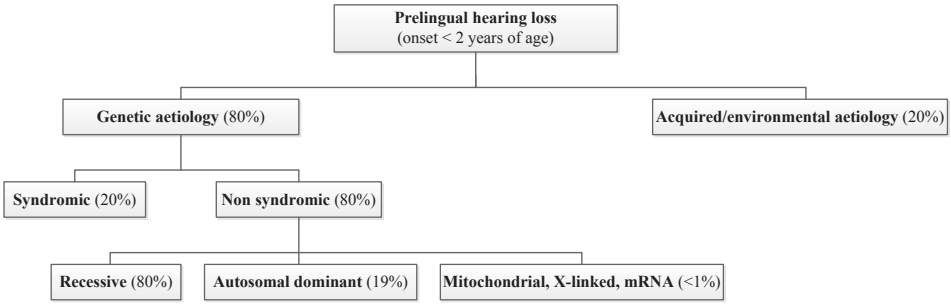
The Joint Committee on Infant Hearing (JCIH) aims for implementation of the '1 - 3 - 6 plan'[20]. This plan aims to increase the proportion of new-borns being screened for hearing loss by the age of one month, having had diagnostic audiology evaluation by three months of age and being enrolled in an early (hearing aid) intervention program by six months of age[20]. Implementation of this '1 - 3 - 6 plan' varies between European countries. Figure 1 summarizes timing of audiological intervention for paediatric CI candidates in several countries within Europe (*data gathered during this thesis*).

This selection process does not only vary on a national basis, but also between institutions within Southern European countries like Italy and Portugal. In the Netherlands, children presenting with severe to profound hearing loss are offered conventional hearing aids (HAs) for at least a trial period during three months, before the age of three months, in accordance with the '1 - 3 - 6 plan' (Figure 1)[15,21]. Furthermore, following parental agreement, diagnostic investigations are initiated between the age of three and six months[21]. A multidisciplinary team (containing otologists, audiologists, paediatricians and clinical geneticist) will perform dual modality imaging (CT scan and/or MRI scan) and additional etiological testing on specific indication[21]. Identified etiologies during these investigations can entail a combination or either conductive hearing loss (originating from the external or middle ear) or SNHL (originating from the inner ear). This latter form of hearing loss can result from a wide variety of hearing loss aetiologies, which are mostly congenital (50%), followed by acquired (25%) (e.g., meningitis) and 25% of unknown origin[15]. Congenital hearing loss can be either hereditary or acquired (multifactorial or due to viral syndromes, e.g., CMV)[15,22].

In 2005, Topsakal *et al.* already expected that thereafter, more than 50% of the hearing loss aetiologies could be explained by a genetic cause, whereas currently around 80% of the hearing loss cases are of genetic origin[22,23]. Hereditary hearing loss is most often nonsyndromic (80%) and can have different types of inheritance patterns; the majority is of recessive origin (80%) and most frequently, a mutation in the GJB6 gene (encoding for the Connexine 26 protein) is identified (Figure 2)[23]. Since the genetic aetiology of hearing loss can be revealed through genetic testing, many centers have screening programs benefitting from improved and faster gene panel screening strategies. Identification of the genetic defect causing hearing loss reveals the pathophysiology allowing clinicians to counsel for hearing loss progression, its inheritance risk and results can provide essential information to confirm the medical diagnosis of the child[22].

In addition to the '1 - 3 - 6 plan', which targets timely audiological intervention in children[20], it is essential to define which modality of hearing rehabilitation should be opted to ensure maximum exposure to auditory information. Hearing aids (HAs) can provide rehabilitation in patients presenting with conductive or moderate SNHL, however they could provide too little benefit for children with severe to profound SNHL. When HAs cannot facilitate age-appropriate speech and language development, the paediatric population with severe to profound hearing loss could qualify for cochlear implantation (Figure 1). The majority of SNHL aetiologies, when due to intracochlear deficits in the auditory pathway, can be treated successfully with CIs. The sooner this initial auditory deprivation is resolved in infants, the

Figure 2. Overview of the aetiology of hereditary hearing loss.



Legend: mRNA = messenger RiboNucleic Acid.

smaller the delay in speech and language development[24] and the higher the change of restoring the age-appropriate speech and language development of the implanted child. Therefore, not only implementation of the '1 - 3 - 6 plan', but also timely cochlear implantation seems to be essential to prevent speech and language delays for children presenting with severe to profound hearing loss. In line with this finding, Ching *et al.*[25] have showed that for children using CIs at three years of age, the age at CI switch-on was significantly associated with better age-appropriate spoken language outcomes, whereas the effect of the age of initial HA fitting was only weak.

4. Maturation of the auditory system and speech and language acquisition

Both inner ear and auditory development start in the first weeks following gestation. Between the eighth and the eleventh week following gestation, the cochlea, a bony, snail-shaped structure, reached its full two and a half turns[26-29]. The cochlea entails three structures (the scala vestibuli, media and tympani) of which the scala media contains the sensory receptors that facilitate hearing: the organ of Corti with inner and outer hair cells[28].

Cochlear function starts around the twentieth week of gestation[30-31] and cochlear development is completed by the end of the second trimester[29]. Around the twenty-seventh week of gestation, the first auropalpebral reflexes and Brainstem Evoked Responses Audiometry (BERA) can be measured[29,32-35]. The third trimester is essential for the maturation of the auditory system (e.g., cochlear nerve myelination): in line with cochlear growth, the brainstem and auditory pathway will further develop[29]. Since preterm infants are born during this third trimester, their myelination can be affected by the early exposure to an extra-uterine environment which can delay overall neural auditory maturation[16]. During this third trimester, the fetus shows its first responses to internal noise, which are either rhythmic (e.g., heartbeat, breathing, speech patterns) or non-rhythmic (e.g., swallowing, isolated speech noise)[15]. Reactions resulting from this noise exposure result in fetal heartbeat changes and changes in motoric reactions. Infant recognition of the mother's voice results from this first intrauterine noise exposure[15]. Following delivery, the central part of the auditory system will additionally

evolve. The maturation of the neural auditory system occurs in a peripheral to central way: in the direction from the nervus cochlearis to the cortex. During hearing development, both the number of neurons as their specificity increases. This neuronal development of the auditory system entails myelination, axonal sprouting, axonal diameter increase, development of central dendritic contacts and central synapses and integration with the visual system. This axonal myelination and maturation slowly progresses up to the age of six years[26,29,36].

During this critical period of cortical neuroplasticity, a sensitive period in which speech and language develop, auditory stimulation and perception must occur to organize neural auditory connections. Merely through receiving auditory input (activation of central nerves by auditory signals received from the peripheral auditory system), maturation of the auditory system occurs. If no auditory development is established, deprivation of the auditory system commences. Between the age of six and 28 months, auditory input has the most significant impact. Specific reorganization of the child's brain is required when access to sound only occurs after 24 months of age and the child needs to unlearn visual pathways to initiate auditory pathway development[37]. In this type of situation, phonology learning starts after critical windows have passed and, therefore, speech and language development is most likely severely affected by the lack of early auditory stimulation[38].

Whether delayed auditory input affects specific speech and language domains relatively more than others and whether language development occurs in a uniform manner across different language domains is unclear and currently still studied[24]. Werker and Hensch suggest that several overlapping critical periods for different aspects of phonological development exist during the first year of life[38]. Each of these critical windows has cascading effects on the next, therefore, children who develop one skill later, will develop the next speech skill later in line with the delay of the previous skill[11,38]. When single-sided deafness occurs during early childhood, auditory pathways form toward the hearing ear and the deafened ear is centrally underrepresented, which is also called an 'aural preference syndrome'[39]. Although frequently underestimated, delayed auditory rehabilitation for the deafened ear results in slow rates of hearing development, therefore, early stimulation by auditory prosthesis is also essential to restore auditory function in children presenting with single-sided deafness[39]. Neuroplasticity of the cortex probably exists till the age of 42 months[40]. Parallel with maturation of the neural system, speech and language will further develop until the age of six years.

5. Cochlear implantation

Currently, CIs are the most effective neural prostheses in medicine regarding functional restoration of a sensory organ[41]. The number of CI users worldwide is significantly higher than users of any other type of neural function restoration prostheses[41]. Cochlear implants are surgically implanted prosthetic devices that electrically stimulate the cochlear nerve to provide hearing sensation (Figure 3). A CI contains an external part (the speech processor), which is worn behind the ear and an internal part that is surgically placed subcutaneously (the receiver) and within the cochlea (the electrode array). The external part entails a transmitting coil and a speech processor that contains a microphone. This microphone captures sound waves, which

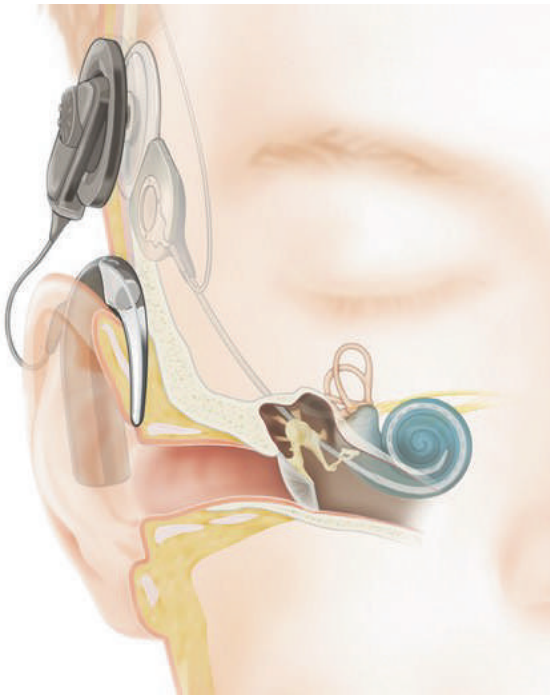


Figure 3. Schematic model of a multichannel cochlear implant.
Courtesy of Cochlear Ltd

are converted to digital signals by the speech processor. This digital signal is led to the transmitter coil, which transmits these signals through the skin to the subcutaneous receiver. When these signals are presented to the receiver, these signals are converted into electrical energy that is transferred to the multichannel electrode array within the cochlea (Figure 3). Subsequently, the spiral ganglion cells of the auditory nerve are exposed to this electrical energy, which results in depolarization of these cells and therewith restores initial sound perception. This electrical energy is encoded in such a way that different electrodes are stimulated by different frequencies[29]. Since different pitches can be perceived, the tonotopical organization of the cochlea is (partly) restored through cochlear implantation[29].

In 1972, the Food and Drug Administration (FDA) approved cochlear implantation in postlingually deafened adults presenting with SNHL using the House 3M single intra-cochlear electrode system[42]. In the Netherlands, in 1985, the first adult CI candidate was implanted in the UMC Utrecht, using the same system[43]. Although this device only contained one electrode in its array, patients were able to accurately perceive sounds[29]. Thereafter, implant arrays with multiple electrodes were developed and auditory and speech performance with CIs has significantly improved[29,43].

In 1986, paediatric clinical trials with the Nucleus 22 CI began and in 1990, the FDA approved cochlear implantation in children between two and 17 years of age[1]. In 1994, the first child was implanted in the UMC Utrecht and, between 1993 and 1996, in total 20 children were implanted in a research project together with the RadboudUMC in Nijmegen[43].

Since the early 1990s, the paediatric candidacy criteria have been significantly expanded due to both: 1) its proven efficacy in implanted children and 2) increased technical availability of CIs[14].

In 1990, the FDA approved cochlear implantation for children who were over 24 months old. During the late 1990s, this recommended age was lowered to 18 months and, in 2000, even to over 12 months of age[14]. Although paediatric cochlear implantation is recommended from one year of age, infants less than 12 months old have been previously implanted[44]. Currently, the lower age criterion remains 12 months; therefore, during the last 18 years, the age criterion has not been adjusted[14]. There is still no widely accepted lower age limit for paediatric cochlear implantation[45], therefore, in **Chapter 1.1**, current literature is summarized to formulate a (lower limit of the) recommended paediatric implantation age.

6. International variation in paediatric CI candidacy criteria

Currently, FDA guidelines regarding paediatric CI indication criteria vary both with age and between the three main CI manufacturers (Table 1)[1]. Remarkably, audiometric criteria for children are significantly more restrictive than for adult patients, although during the early years of life, auditory rehabilitation is essential to not miss the critical window of cortical plasticity[1]. Aforementioned criteria indicate the manufacturer warranty limits and provide surgical guidelines for the treating otologist, however, do not necessarily reflect success of cochlear implantation.

Furthermore, not only variation exists between CI manufacturers, but is also present regarding audiological eligibility and the recommended age for implantation between national CI guidelines (Figure 1). For example, there is international variation regarding the pure-tone average (PTA) cut-off thresholds (in decibel (dB) hearing loss) at which rehabilitation with a CI is recommend in children and the frequencies at which its audiometry should be performed: in the United States, a CI treatment is recommended at 3-frequency PTA thresholds of ≥ 90 dB hearing loss[46], in the United Kingdom (UK) at ≥ 90 dB hearing loss measured at 2 and 4 kHz frequencies[47], whereas in Belgium the CI indication criterion is ≥ 85 dB[48] (Figure 1). This international variation could be explained by both the difficulty to define cut-off thresholds (in dB hearing loss) at which CI treatment is superior to HAs in terms of, for example, age-appropriate speech and language development progression[49], and the lack of a international recommended paediatric implantation age[45]. Furthermore, local political and economical differences also greatly determine the number of CIs that insurance companies can reimburse for children. Figure 1 marks the international variation between several European national CI guidelines[50] and includes institutional information regarding local implant criteria (*gathered during this thesis*), which are not always aligned with national CI recommendations.

In the Netherlands and Belgium, studies have estimated that between 80 to 95% of the children diagnosed with profound SNHL actually received a CI[51-52]. Although these countries with implemented NBHS have the intention to start prompt hearing rehabilitation, implantation delays are still present[2]. **Chapter 4.1** of this thesis will assess whether there is a gap between aforementioned guidelines and current European paediatric CI practice.

7. Aims and scope of this thesis

Substantial evidence shows that cochlear implantation is the preferred treatment for infants presenting with severe to profound hearing loss[53-55]. However, the sensitive period of neurolinguistic development varies between speech and language domains[54], and therefore, determining the ideal timing for cochlear implantation based on these time frames remains difficult and has not yet been strictly defined[45]. Furthermore, differences between CI manufacturers' (included in FDA guidelines) and national CI guidelines exist regarding paediatric cochlear implant candidacy eligibility criteria. Therefore, through evidence-based strategies this thesis aims to define: 1) the recommended age to perform cochlear implantation based on speech and language development data, 2) the hearing loss level that should serve as indication for surgery and 3) the surgical and anesthesia techniques that should be used during this procedure. Prelingual hearing loss will be defined as hearing loss with its onset before the acquisition of spoken language skills (< two years of age)[56]. Furthermore, the final part of this thesis evaluates whether paediatric cochlear implantation in European countries is performed according to our formulated evidence-based recommendations.

8. Outline of this thesis

This thesis presents five main sections in relation to the discussed aims:

- Since better insight is needed to define the ideal age at which CI surgery should be performed in infants, the first part of this thesis defines the recommended age for paediatric CI surgery based on speech and language development data. In **Chapter 1.1**, the current literature was reviewed to define the recommended age for surgery based on long-term speech and language outcomes. In addition, in **Chapter 1.2**, a retrospective evaluation was performed assessing the variation in five-year speech perception outcomes between children from different age-at-implantation groups implanted at the Wilhelmina Children's Hospital, UMC Utrecht.
- There seems to be no general international consensus at what audiological threshold, or which level of hearing impairment, cochlear implantation in children should be performed. Therefore, in the second part of this thesis, we have summarized available evidence from the literature to more accurately define the audiological candidacy criteria (e.g., cut-off thresholds in decibel hearing loss) for children presenting with prelingual hearing loss (**Chapter 2.1**).
- In the third part of this thesis, an investigation was performed to assess which surgical and anesthesia techniques are preferable during surgery to warrant a safe procedure with the lowest likelihood of adverse events. As otologists currently tend to perform day-case CI surgery, it is essential to define which surgical and anesthetic techniques lead to the lowest adverse event occurrence and can possibly help in shortening hospital admission for operated children. Therefore, in both **Chapter 3.1** and **Chapter 3.2**, we assessed the adverse events of the SupraMeatal Approach (SMA)[57] compared to the golden standard the Mastoidectomy with Posterior Tympanotomy Approach (MPTA)[58]. In **Chapter 3.1**, we have summarized the current literature regarding CI surgery outcomes between

aforementioned surgical techniques performed in both children and adults. To further define the surgical safety for paediatric CI candidates, we have retrospectively compared surgical adverse event rates between children operated by the MPTA or the SMA in **Chapter 3.2**. Understanding the anesthesia-related risks associated with paediatric cochlear implantation can provide crucial information to define the optimal age for cochlear implantation. Therefore, we aimed to identify which type of anesthetic maintenance medication administration resulted in the lowest rate of anesthesia-related and surgical adverse events during and following paediatric cochlear implantation in **Chapter 3.3**.

- In the fourth part of this thesis, we have evaluated whether paediatric cochlear implantation in several European countries is performed according to our formulated evidence-based recommendations. **Chapter 4.1** represents a descriptive review assessing whether timely paediatric cochlear implantation is performed throughout eight European countries.
- The final chapter elaborates on the effect of paediatric cochlear implantation on the quality of life (QoL) of implanted children. In **Chapter 5.1**, we have assessed the consistency of postoperative QoL report between children and their parents. Definition of the age at which QoL is most consistent could provide guidance in accurate interpretation of these QoL scores during the rehabilitation period of cochlear implantation in children.
- The main conclusions of this thesis are discussed in the final part of this thesis **(Summary of main results** and **general discussion)**. In this chapter, we outline both the clinical implications of our studies, as well as the possible future directions of our investigations.

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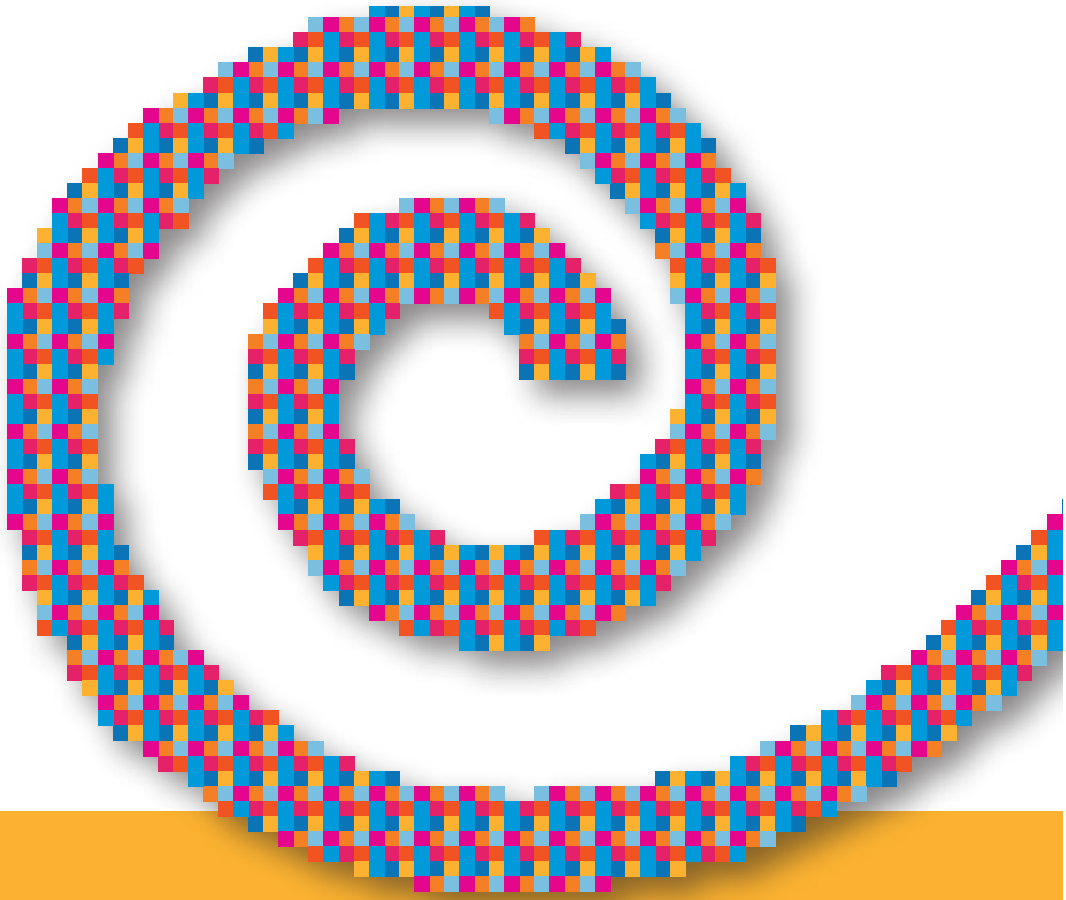
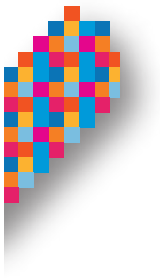


PART I

Definition of the ideal age for cochlear implantation in children based on speech and language developmental data



Chapter 1.1

A systematic review to define the speech and language benefit of early (< 12 months) paediatric cochlear implantation

Audiology & Neurotology 2016;21(2):113–126.

Hanneke Bruijnzeel, Fuat Ziylan, Inge Stegeman, Vedat Topsakal, Wilko Grolman

ABSTRACT

Objective

This review aimed to evaluate the additional benefit of cochlear implantation in children before 12 months of age considering improved speech and language development and auditory performance.

Materials and Methods

We conducted a search in the PubMed, Embase and CINAHL databases and included studies comparing groups with different age at implantation and assessing speech perception and speech production, receptive language and/or auditory performance. We included studies with a high directness of evidence (DoE).

Results

We retrieved 3360 articles. Ten studies with a high DoE were included. In addition, four articles with medium DoE were discussed. Six studies compared infants implanted before 12 months with children implanted between 12 and 24 months. Follow-up ranged from six months to nine years.

Cochlear implantation before two years of age is beneficial according to one speech perception score (regarding combined Phonetically Balanced Kindergarten combined with Consonant Nucleus Consonant scores), but not on Glendonald Auditory Screening Procedure scores. Implantation before 12 months of age resulted in better speech production (Diagnostic Evaluation of Articulation and Phonology and Infant-Toddler Meaningful Auditory Integration Scale), auditory performance (Categories of Auditory Performance-II score) and two out of the five receptive language scores (Preschool Language Scale combined with Oral and Written Language Skills and Peabody Picture Vocabulary Test).

Conclusions

The current best evidence lacks level 1 evidence studies and consists mainly of cohort studies with a moderate to high risk of bias. Included studies showed consistent evidence that cochlear implantation should be performed early in life, but evidence is inconsistent on all speech and language outcome measures regarding the additional benefit of implantation before the age of 12 months. Long-term follow-up studies are necessary to provide insight on additional benefits of early cochlear implantation in children.

INTRODUCTION

Through the introduction of universal NBHS, infants with profound SNHL are recognized earlier after birth. This has led to earlier cochlear implantation[1]. In 1990, the FDA approved paediatric cochlear implantation from the age of two years[2], whereas currently the FDA has approved the use of CIs in children from 12 months of age onwards[3].

Neuroplastic and neurolinguistic dynamics are the main reasons to opt for early cochlear implantation, mainly to gain optimal benefit from implantation during the critical period of cortex neuroplasticity: a sensitive period in which speech and language are developed. In this critical period, auditory experience must occur to organize the neural connections in the brain. Human central auditory pathways are thought to be maximally plastic for a period of 3.5 years[4,5]. Cochlear implantation outside this sensitive language period might result in the development of different and delayed patterns of speech and language. Because the period of neurolinguistic development is flexible and varies between children, determining the optimal timing for cochlear implantation based on these time frames remains difficult and has not yet been strictly defined[6].

The "earlier the better" trend[7] in cochlear implantation originated mainly from results and assumptions from both physiological studies and extrapolation of data of studies including children using HAs. Children fitted with HAs within the first two months of life were found to have significantly better language development than children aided between three and 12 months[8], which suggested an indication to start implanting children earlier to accomplish optimal language development and minimize the period of auditory deprivation.

Some surgeons suggest that cochlear implantation should be performed before one year of age, or even before six months of age[9]. Despite the fact that early implantation is considered to be a predictor of good language and speech development, there is conflicting and incomplete evidence regarding the benefits of implantation before 12 months and particularly before six months of age[7,10]. An underlying reason for this conflicting evidence could be that early implantation (< nine months of age) leads to the loss of the ability to discern: the accurate determination of hearing abilities, hearing aid benefit[10] and co-existing cognitive and behavioural anomalies, which could all affect the performance and outcome following cochlear implantation.

We aim to identify the existing evidence demonstrating the additional speech and language development benefit of cochlear implantation performed within the first year of life, compared to implantation after 12 months of age.

MATERIALS AND METHODS

Literature selection - Search strategy

To systematically identify all relevant studies regarding the influence of age at cochlear implantation, we performed a literature search in the following three databases: 1) PubMed,

2) Embase and 3) Cumulative Index to Nursing and Allied Health Literature (CINAHL) on April 24, 2014. Since search results can change over time, monthly search updates were checked for additional article inclusions. We included studies focusing on speech and language performance differences after cochlear implantation by comparing groups of children implanted at different ages. We developed a search strategy by establishing a matrix of synonyms to cover all possible outcome measures of speech perception, speech production and language development after cochlear implantation (Appendix - Compared speech and language outcome measures). Authors can be contacted to receive the review protocol. The search term 'age' (or related synonyms as 'below one year') was not included in the search strategy, because age was the principle prognostic factor in the current review.

Study selection

Two authors (H.B., I.S.) performed independent systematic title and abstract screening based on predefined selection criteria (Figure 1). Studies that included a performance comparison between different age-at-implantation groups were included. Subsequently, the same authors screened the full text of the selected articles for eligibility. As 1999 was the year of FDA approval of implantation before the age of two years[2], we included studies published after this date to increase the likelihood to retrieve analysis on the study population of interest. Because it could take a significant amount of time before the benefits of early cochlear implantation can be demonstrated[11], we aimed to include studies with a minimal follow-up of five years. If several studies were retrieved that analysed the same study cohort, the study with the largest sample size was included. Disagreement between authors was solved by discussion. No language restrictions were applied.

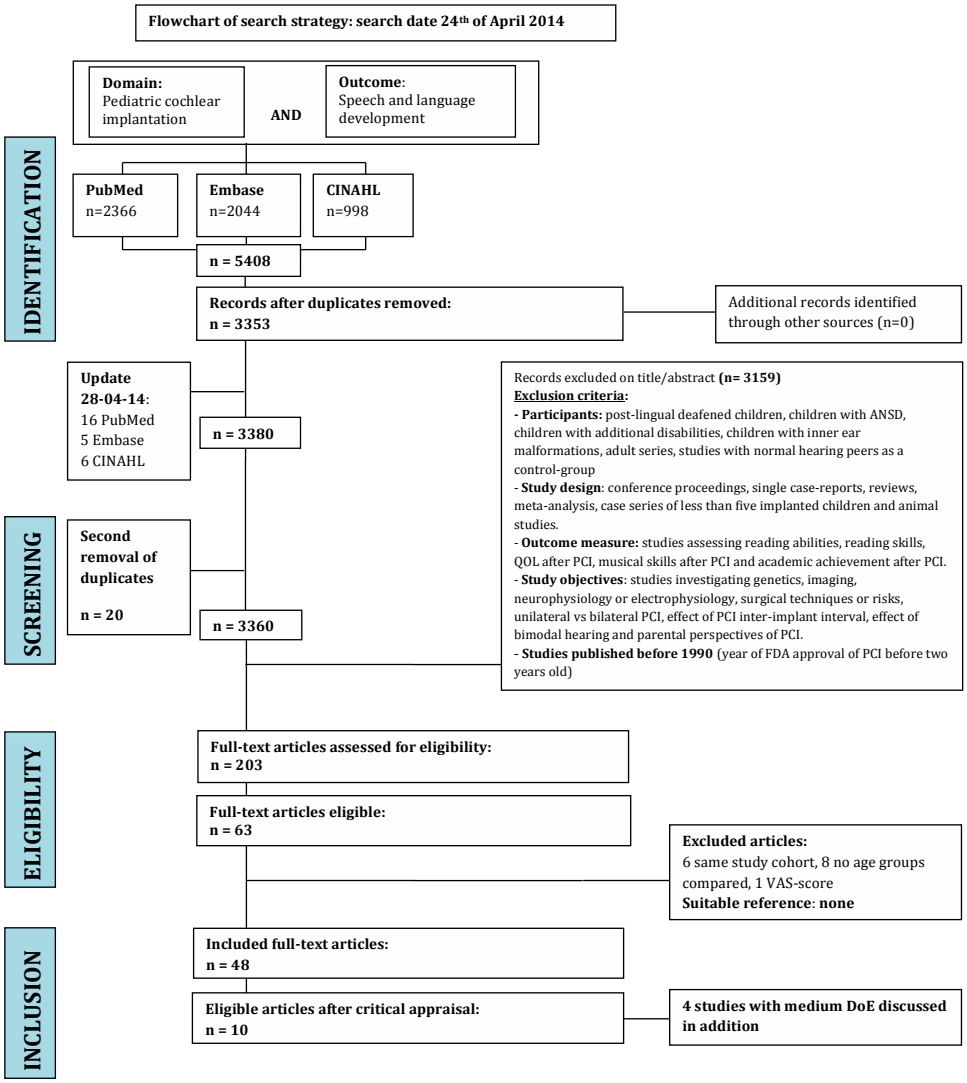
Quality or Risk of bias Assessment

Two authors (H.B., F.Z.) independently assessed the methodological quality of included studies. This assessment was performed using a constructed critical appraisal of a topic (CAT) tool assessing 11 directness of evidence (DoE) domains and five risk of bias (RoB) domains (Table 1). Both main domains (DoE or RoB) were validated per complete domain and rated as having a low (L), moderate (M) or high (H) DoE or RoB. We selected studies with a high DoE, since both: 1) long-term follow-up is important and 2) speech and language development should be assessed on various language domains. Consensus on quality assessment was reached by discussion between the authors. Publication bias could affect cochlear implantation results. To prevent selective reporting of identified evidence, we aimed to present results on all speech and language outcome assessments that were performed in each independent study.

Data extraction and analysis

The same authors (H.B., F.Z.) collected the following information from studies: author, publication year, study design and sample size (Table 1). The first reviewer (H.B.) independently collected additional information of the included studies regarding: age group comparisons, the applied speech and language outcome measures and timing of the follow-up visits. Original

Figure 1. Flowchart demonstrating the selection of studies assessing the influence of age at cochlear implantation in children on postoperative speech and language performance.



Legend: ANSD = Auditory neuropathy spectrum disorder; CINAHL = Cumulative Index to Nursing and Allied Health Literature DoE = directness of evidence; FDA = Food and Drug Administration; PCI = paediatric cochlear implantation; QoL = quality of life; VAS = visual analogue scale.

results on postoperative speech and language performance from the selected studies are presented in the Tables and classified according to reported age-at-implantation groups. Data were extracted from original articles by magnifying the Figure size to 500%. This paper was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement[12].

In case of homogeneity of: age group comparisons, applied outcome measures, the type of applied statistical analysis and elected follow-up visits, we aimed to combine results of studies in a meta-analysis. When consistency measure I^2 was below 50%, we performed statistical pooling of the data using Review Manager (RevMan, version 5.3; Department of Informatics and Knowledge Management, The Nordic Cochrane Centre, Copenhagen, Denmark).

RESULTS

Search results

We retrieved 3360 articles by performing a search on April 24, 2014. After title and abstract screening, 203 articles were assessed for eligibility in full text by two authors (H.B., I.S.). Sixty-three articles were selected for inclusion (Figure 1). We screened reference lists of selected articles, which did not result in inclusion of additional articles. Figure 1 shows that 15 articles were excluded after full text assessment. Reasons for exclusion were: the use of similar patient cohorts (n = six studies), no direct comparison of various age-at-implantation groups (n = eight studies) and one study that assessed child's health using Visual Analogue Scale (VAS) scores instead of assessing speech and language outcomes (Figure 1). Three included studies were not written in English: two German articles and one Turkish article. Both reviewers screened the German articles and both a Turkish Ear, Nose and Throat (ENT) surgeon (V.T.) and Turkish student (F.Z.) from our department reviewed the Turkish article.

Risk of bias assessment

Ten articles contained a high DoE and were, therefore, included in the current review. The RoB of included studies ranged from low (L) to high (H) (Table 1). Half of the included studies were retrospective case series (RCS) and the other five studies were prospective case series (PCS) (Table 1 – marked in white). All included studies represented level 2 evidence (Grade B). Twenty-six selected studies showed a medium DoE. In addition to the aforementioned articles, we decided to discuss results of studies with a medium DoE (> score above five) and a medium RoB. Four studies were additionally included due to this decision (Table 1, italicized – marked in light grey).

Twelve out of the 14 studies clearly defined baseline characteristics. The exact age at implantation of all implanted individuals was provided in five studies. Eight studies provided the mean age at implantation and the age range of each age-at-implantation group. The remaining study provided the mean age at implantation in months, but did not define the exact age range of each age group. Only 11 included studies defined the aetiology of the hearing loss of their included patients. One study clarified whether the cause of deafness was (un)known, but did not define exact etiologies[13]. Although five studies did not define whether patients were unilaterally or bilaterally implanted, nine studies did mention how many implants were used in each individual patient (Table 1).

Table 1. Critical appraisal of studies reporting differences in speech and language outcomes between older and younger implanted children.

				Directness of evidence (DoE)															Risk of Bias (RoB)	
				Domain				Outcome							Treatment					
Study	**Publication year**	**Study design**	**Sample size**	**Aetiology**	**Unilateral,bilateral or sequential**	**Baseline Characteristics**	**Determinant**	**Auditory performance**	**Speech perception**	**Speech production**	**Receptive language**	**Follow-up**	**DoE (total)**	**Loss to Follow-up**	**Surgical procedure**	**CI brand**	**Standardization of outcome**	**Missing data**	**RoB (total)**
Coletti	2012	PCS	45	●	●	●	◑	●	○	●	●	◑	H	●	●	●	●	●	L
Dunn	2014	RCS	83	○	●	●	●	○	●	○	●	●	H	◑	○	●	●	●	L
Holman	2013	RCS	34	●	●	●	●	○	○	●	●	○	H	◑	●	●	○	◑	M
Leigh	2013	RCS	120	○	●	●	◑	○	●	●	●	◑	H	◑	○	○	●	◑	M
Lesinski-Schiedat	2005	RCS	116	●	●	◑	◑	○	●	●	○	◑	H	◑	○	●	○	◑	M
Suh	2009	PCS	86	●	●	●	○	●	○	●	●	○	H	○	●	●	○	○	M
Uziel	2007	PCS	82	●	●	●	●	○	●	●	●	●	H	●	○	●	○	◑	M
Niparko	2010	PCS/CSA	188	●	●	●	◑	○	●	●	●	◑	H	●	○	○	○	◑	H
Artières	2009	RLS	74	●	○	◑	◑	○	●	●	●	◑	H	○	○	●	○	○	H
Baumgartner	2002	PCS	33	●	○	●	●	○	●	●	○	◑	H	○	○	●	○	○	H
Anderson	2004	RCS	37	●	○	●	◑	○	●	●	○	◑	M	◑	○	●	○	◑	M
Manrique	2004	PCS	182	◑	○	●	◑	○	●	○	●	●	M	○	●	●	●	○	M
Schauwers	2004	PCS	10	●	○	●	●	●	○	●	○	○	M	●	○	●	○	●	M
Zwolan	2004	RCS	295	●	●	●	◑	○	●	○	○	◑	M	◑	○	●	○	●	M
Brackett	1998	PCS	33	●	○	◑	○	○	●	●	●	◑	M	○	○	○	○	◑	H
Houston	2010	RCS	15	●	○	◑	●	○	○	●	●	◑	M	◑	○	○	○	◑	H
Akin	2012	RCS	37	○	●	●	○	●	○	●	○	◑	M	●	●	●	●	●	L
Boons	2012	RMC	288	●	●	●	○	○	○	○	●	◑	M	◑	○	◑	●	◑	M
Connor	2006	RCS	100	●	○	◑	◑	○	○	●	●	◑	M	○	○	●	●	○	M
Tomblin	2005	PCS	29	●	●	●	○	○	○	○	●	○	M	◑	○	●	●	●	L
El Hakim	2001	RCS	37	●	○	●	○	○	○	○	●	◑	M	○	○	●	●	◑	M
Fulcher	2012	PCS/RCS	94	○	○	●	◑	○	○	○	●	◑	M	◑	○	●	●	◑	M
Geers	2004	PCS	133	◑	○	○	○	○	●	●	○	◑	M	●	○	●	○	●	M
Gupta	2012	PCS	30	●	○	○	○	●	○	●	○	○	M	●	○	●	○	●	M
James	2008	PCS	19	●	○	●	●	○	○	○	●	◑	M	●	○	●	○	●	M
Laszig	2009	RCS	156	●	○	○	◑	○	●	○	○	●	M	●	○	○	○	●	M
Lonka	2011	RCS	123	○	○	◑	○	●	○	●	●	○	M	●	○	◑	○	●	M
Moog	1999	PCS	22	○	○	○	●	○	●	●	●	○	M	●	○	●	○	●	M
Nicholas	2013	PCS	69	○	●	◑	◑	○	○	○	●	◑	M	●	○	○	○	●	M
Szagun	2012	PCS	25	○	◑	◑	○	○	○	●	●	◑	M	●	○	◑	○	●	M
Nicholas	2007	PCS	76	○	○	○	●	○	○	●	●	○	M	●	○	◑	○	●	M
Holt	2008	PCS	96	○	○	●	●	○	○	○	●	◑	M	○	○	○	○	◑	H
Iwasaki	2012	PCS	190	○	●	○	●	○	○	●	●	○	M	○	○	○	○	○	H
Low	2008	RCS	58	○	○	●	◑	○	○	●	●	○	M	○	○	●	○	○	H
Rinaldi	2013	PCS	22	○	○	◑	○	○	○	○	●	○	M	●	○	○	○	●	H
Tait	2007	PCS	92	◑	○	●	○	○	●	○	○	○	M	○	○	●	○	○	H
Wang	2007	PCS	29	○	○	●	◑	○	●	●	●	◑	M	○	○	●	○	○	H
Tajudeen	2010	RCS	117	○	●	◑	○	○	●	○	○	◑	M	◑	○	○	○	◑	H
Hassanzadeh	2002	PCS	119	◑	○	○	○	○	●	○	○	◑	L	●	○	●	●	●	L
Govaerts	2002	RLS/CSA	48/70	○	○	○	◑	●	○	○	○	○	L	◑	○	●	○	●	M

see next page for the continuation of Table 1 >>

Table 1. *Continued*

				Directness of evidence (DoE)															Risk of Bias (RoB)
				Domain				Outcome						Treatment					
Study	Publication year	Study design	Sample size	Aetiology	Unilateral,bilateral or sequential	Baseline Characteristics	Determinant	Auditory performance	Speech perception	Speech production	Receptive language	Follow-up	DoE (total)	Loss to Follow-up	Surgical procedure	CI brand	Standardization of outcome	Missing data	RoB (total)
Hammes	2002	RCS	47	○	○	○	○	○	●	○	●	○	L	◑	○	◑	●	◑	M
Loundon	2000	RCS	40	◑	○	○	○	○	●	●	○	○	L	●	○	◑	○	●	M
McConkey Robbins	2004	PCS	107	○	○	◑	◑	○	○	●	○	○	L	◑	○	●	○	◑	M
Papsin	2000	RCS	66	○	○	○	○	○	●	○	○	◑	L	◑	○	●	○	◑	M
Gibson	2000	RCS	92	○	○	○	○	○	●	●	○	○	L	○	○	●	○	○	H
May-Mederake	2012	RCS	28	○	○	○	○	○	○	●	○	○	L	◑	○	○	○	●	H
Miyamoto	2008	RCS	91	○	○	○	○	○	○	○	●	○	L	◑	○	○	○	◑	H
Chen	2010	RCS	259	○	○	○	○	○	○	●	○	○	L	○	○	○	●	○	H

Legend: CSA = cross-sectional analysis; H = high; L = low, M = moderate; PCS = prospective case series; RCS = retrospective case series; RCT = randomized controlled trial; RLS = retrospective longitudinal analysis; RMC = retrospective multicentre study.
Legend Directness of Evidence (DoE): Domain: Aetiology of deafness provided: yes: ●; part of the children: ◑; or no: ○. Unilateral, bilateral or sequential implantation described: yes: ●; part of the children: ◑; or no: ○. Baseline characteristics: complete : ●; incomplete/distribution not reported: ◑; no baseline characteristics reported: ○. Determinant: Age at CI described: yes: ●; no exact age given: only number of children in specific ag-at-implantation groups defined (age range + mean): ◑; or age at implantation of part of included children provided/no age-range and mean provided: ○. Outcome: Study reports on: Auditory performance: yes: ●; or no: ○, Speech perception: yes: ●; or no: ○Speech production: yes: ●; or no: ○, Receptive language: yes: ●; or no: ○. Follow-up. Duration of follow-up (for all tested individuals): > 5 years: ●; 2-5 years: ◑; < 2 years: ○, not reported: ○. Overall Directness of Evidence: Low (L): < 3 points; Moderate (M): = 3 - 5 points; High (H): > 5 points.
Legend Risk of Bias (RoB): Loss to follow-up: Loss to follow-up: ≤ 20%: ●; > 20%: ◑; not reported: ○. Standardization of treatment: Surgical procedure according to protocol: yes: ●; or no: ○. CI manufacturer described: yes: ●; brands defined, but not specified per patient/in actual numbers: ◑; or no: ○. Standardization of outcome: Data acquisition after specific follow-up time and according to protocol: ●; no standardized data acquisition: ○. Missing data: No missing data: ●; missing data mentioned/quantified in study and method of handling described: ●; missing data mentioned in study, method of handling not described: ◑; missing data not reported: ○. Overall Risk of Bias: High (H): < 2 points; Moderate (M): = 2 - 3 points; Low (L): 4 - 5 points.

Six of the included studies tested children on three speech and language outcomes: four studies on speech production, speech perception and receptive language and two studies on auditory performance, speech production and receptive language. Although we aimed to include studies with a minimal follow-up of five years, only three of the selected studies had a follow-up that was longer than five years. Eight studies had a follow-up between two and five years and, in three studies, the follow-up was shorter than two years. In four studies, the loss to follow-up was less than 20% and in six studies above 20%; the remaining three studies did not report loss to follow-up. The applied surgical procedure was described in four studies. The type of cochlear device was described in 12 out of the 14 studies. In only four studies, outcome measurements were performed according to a defined protocol. Four studies defined the method of handling of missing data. Five studies mentioned the amount of missing data, however, did not describe how these missing values were accounted for in their analysis.

Table 2. Studies reporting on speech perception outcome measures: CNC, PB-K and GASP, classified according to age at cochlear implantation and follow-up time of included children.

Authors	Directness of Evidence (DoE)	no. = 6-12 months	no. = 13-18 months	no. = 19-24 months	no. = 25-30 months	no. = 31-36 months	no. = 37-40 months	no. = 41-48 months	no. > 48 months	Outcome measure	Age at evaluation	FU 12 months	FU 18 months	FU 24 months	FU 36 months	FU 48 months	FU 60 months	FU 72 months	Scores
Leigh *et al.* [2013]	H	27	68		0					CNC	IE > 2 yrs.								After two yrs. of IE: results neither showed a significant difference between groups nor a significant correlation between CNC word or phoneme scores and age at implantation
Dunn *et al.* [2014]	H	28			39				0	CNC + PB-K	CNC: 6-8 yrs. PB-K: 4-5 yrs.						x	x	At five yrs. of age: the younger implanted group had higher scores than older implanted group (p < .001); the gap between the two groups was not significant at seven yrs.
Uziel *et al.* [2007]	H	41							41	PB-K	IE: 5 and 10 yrs.								IE five yrs.: < four yrs.: 73% vs. > four yrs.: 57%. IE ten yrs: < four yrs.: 81% vs. > four yrs.: 60% (ANOVA: p < .001). Univariate analysis: < four yrs.: 67.4% above median vs. > four yrs.: 18% above median (p < .001)
Lesinski-Schiedat *et al.* [2005]	H	27	89		0					GASP		x	x	x					The development of speech understanding showed better results at FU > 24 months in the group who received a cochlear implant < 12 months (n.s.)
Zwolan *et al.* [2004]	M	59				236				GASP-S + GASP-W		x		x	x				One-year FU: mean score of group 4 > score of group 1 (n = 59; p = .01) and group 2 (n = 85; p = .004); Mean score group 5 > group 1 (p = .02) and group 2 (p = .01). 24- and 36-month FU: mean score of group 1 was better than those of the 4 other groups (n.s.)

Legend: ANOVA = Analysis of variance; CNC = Consonant-Nucleus-Consonant; FU = Follow-up; GASP = Glendonald Auditory Screening Procedure; GASP-W/GASP-S = GASP for words/sentences; H = High; IE = implant experience; M = Medium; no. = number of children; n.s. = non-significant; PB-K = Phonetically Balanced Kindergarten (test); vs. = versus; yrs. = years.

Study characteristics

The age range of included children in the studies varied widely (Table 2 to Table 5). We identified six studies with a high DoE that compared children implanted under the age of one year with children implanted between 12 and 24 months of age. Inclusion of these studies resulted in the identification of 125 children implanted before the age of one year (Table 2 to Table 5). The outcome assessment in these studies ranged from preoperative measurements (n = five studies) to nine years of implant experience (IE; Table 2 to Table 5).

Data analysis

The study results of included studies are presented in Tables 2 to 5, subdivided by the four categories of speech and language development: receptive language, speech perception, speech production and auditory performance. Studies are enumerated by similarly applied outcome measures to quantify speech and language development. Due to the heterogeneity of groups regarding age at cochlear implantation, outcome measures, applied statistical analysis and elected follow-up moments, we did not perform statistical pooling of the data (Tables 2 to 5).

Speech perception outcomes

Speech perception of included studies was measured on: Consonant-Nucleus-Consonant (CNC), Phonetically Balanced Kindergarten (PB-K) and Glendonald Auditory Screening Procedure (GASP) scores (Table 2).

Leigh *et al.*[7] did not identify significant differences when comparing CNC word or phoneme scores between groups implanted between six to 12 months and 13 to 24 months at two years of IE. However, Dunn *et al.*[14] showed that younger implanted children (< 24 months) did perform superior than older implanted children on combined CNC and PB-K-scores measured at five years of age ($p < .001$). Scores of the two groups remained significantly different ($p < .05$) at eight, nine, ten and 12 years of age. Uziel *et al.*[15] tested children on PB-K scores at five and ten year follow-up visits and showed that speech perception skills continued to grow after five years of IE: no performance plateau was reached in the assessed children. The authors detected a positive effect for implantation age under the age of four years ($p < .00001$). Uziel *et al.*[15] showed higher speech perception scores than the modelled values at 60 months of Dunn *et al.*[14]: 55% at seven years of age (< two years) and 48% at eight years of age (two - four years). Both studies testing children on GASP-scores[16-17] found that older implanted children (implanted after 12 months and 36 months respectively) performed better at 12-month follow-up. However, at 24 months of follow-up, the youngest implanted children (< 12 months)[16] (and implantation between one and three years)[17] outperformed the older implanted children in both studies (non-significant) (Table 2).

Speech production outcomes

Speech production was assessed using the Diagnostic Evaluation of Articulation and Phonology (DEAP), Speech Intelligibility Rate (SIR) and Infant-Toddler Meaningful Auditory Integration Scale (IT-MAIS) scores (Table 3). Children are currently implanted in their pre-lexical period;

Table 3. Studies reporting on speech production outcome measures: DEAP, SIR, (IT-) MAIS and LittlEARS®-scores, classified according to age at cochlear implantation and follow-up time of the included children.

Authors	Directness of Evidence (DoE)	no. = 6-12 months	no. = 13-18 months	no. = 19-24 months	no. = 25-30 months	no. = 31-36 months	no. = 37-48 months	no. > 48 months	Outcome measure	Age at evaluation	Preoperative	FU 3 months	FU 6 months	FU 12 months	FU 18 months	FU 24 months	FU 48 months	FU 60 months	Scores
Leigh *et al.* [2013]	H	16	16		0				DEAP	IE > 2 yrs.									IE two yrs.: group 1: DEAP 93% and group 2: DEAP 85% ($p = .033$); both groups performed poorer than their hearing peers ($p = .002$, $p = .001$); mean speech production score was correlated with age at CI ($p = .014$)
Artières *et al.* [2009]	H	32			15		14	13	SIR	4, 5, 6, 7 or 8 yrs.							x	x	No significant differences between the performance of groups 1 and 2 and between groups 2 and 3 at four yrs. of age; median SIR for group 3 was significantly lower than for group 1 (no *p*-value provided)
Uziel *et al.* [2007]	H	41						41	SIR	IE 10 yrs.									IE ten yrs.: < four yrs.: mean SIR 4.3 vs. > four yrs.: mean SIR 3.4 (ANOVA: $p < .0005$) IE > ten yrs.: children implanted < four yrs. demonstrated 65% (vs.12% > four yrs.) SIR greater than the median ($p < .001$)
Holman *et al.* [2013]	H	17	17		0				IT-MAIS or LittlEARS®		x	x	x	x					All patients made significant gains after CI; children implanted < 12 months or younger reached age-appropriate speech and language skills by 24 months of age vs. 41 months for the older paediatric control group ($p < .05$).
Lesinski-Schiedat *et al.* [2005]	H	27	89		0				MAIS		x	x	x	x	x	x			Three-months FU: good response to noise in 75% of the early implanted group vs. 69% of the later implanted group; identification of noise in 59% of the early implanted group vs. 48% of the later implanted group (n.s.) 18-months FU: good response to noise in 97% of the earlier implanted group (n.s.). 24-months FU: identification of noise in 97% of the early implanted group vs 87% of the later implanted group

Legend: ANOVA = analysis of variance; CI = cochlear implantation; DEAP = diagnostic evaluation of articulation and phonology; FU = Follow-up; IE = implant experience; H = high; IT-MAIS = infant-toddler meaningful auditory integration scale; NH = normal hearing; no. = number of children; n.s. = non-significant; SIR = Speech Intelligibility Rate (test); vs. = versus; yrs. = years.

therefore, a major landmark in their development becomes the onset of babbling[18]. Normally, babbling occurs between six and ten months of age[19-20].

Schauwers *et al.*[18] tested the onset of the postoperative babbling spurt and results showed that the earlier the child was implanted, the more consistent their results were with the development of their normal hearing (NH) peers. In line with this finding, Leigh *et al.*[13] showed a significant effect ($p < .05$) for early implanted children (< 12 months), compared to later implanted children at two years IE on DEAP-scores. Both tested groups performed poorer than their NH peers ($p = .002$ and $p = .001$ respectively) (Table 3).

Two included studies[15, 21] compared groups implanted before and after 48 months on SIR-scores; however, follow-up moments were different (Table 3). Artières *et al.*[21] assessed young children (< two years), who reached ceiling scores from six years of age onwards, and could not confirm significant differences between groups. Uziel *et al.*[15] showed that after ten years of IE, the mean SIR score of the group of children implanted before four years was significantly higher than in children implanted after four years of age ($p < .0005$).

Two studies compared IT-MAIS scores of children at the same follow-up visits: at three, six and 12 months[16, 22]. Studies compared similar age groups, but one study[22] combined IT-MAIS with Little Ears questionnaire scores, whereas only MAIS-scores were applied in the study of Lesinski-Schiedat *et al.*[16]. Holman *et al.*[22] found over 60% of correct scores of their youngest implanted children at 12-months follow-up. Similarly, Lesinski-Schiedat *et al.*[16] found over 70% correct answers at several subsets of the MAIS-scores on their youngest group of implanted patients (< 12 months) at one year follow-up. In both studies, at 21 months of age[22] and at 24 months of follow-up[16], scores of both age groups varied between 80 and 100% correct scores, without significant differences between the assessed age-at-implantation groups.

Receptive language outcome measures

Receptive language was measured on Oral and Written Language Skills (OWLS), Clinical Evaluation of Language Fundamentals (CELF), Preschool Language Scale (PLS), Peabody Picture Vocabulary Test (PPVT) and Reynell Developmental Language Scale (RDLS) scores (Table 4).

Holman *et al.*[22] assessed PLS-4 and OWLS scores and concluded that children implanted before 12 months of age reached speech and language skills by 24 months of age compared to 41 months for the group implanted between 12 and 24 months of age ($p < .05$). Niparko *et al.*[23] confirmed significantly higher rates of both comprehension and expression of language (RDLS-scores) in children implanted before 18 months of age compared with children who underwent implantation between 18 and 36 months of age, and especially compared to children implanted after 36 months of age. Manrique *et al.*[13] applied similar RDLS scores and showed that children implanted before 36 months of age had a delay of two years compared to NH peers, whereas older implanted children (> 36 months) deviated more than four years from their NH peers. A comparison on CELF-3-scores[14] indicated that at seven years of age, the younger-implanted group (< two years) achieved scores that were on average 12 points higher than the later implanted group ($p = .01$).

Table 4. Studies reporting on receptive language outcome measures: PLS (-3, -4), OWLS, CELF-3, K-PVT, PPVT (-3, -4, -R), RDLS (-3), CELF-3 and MB-CDI scores, classified according to age at cochlear implantation and follow-up time of the included children.

Authors	Directness of Evidence (DoE)	no. = 0-6 months	no. = 7-12 months	no. = 13-18 months	no. = 19-24 months	no. = 25-30 months	no. = 31-36 months	no. = 36-40 months	no. = 41-48 months	no. > 48 months	Outcome measure	Age at evaluation	Pre-op measurement	FU 3 months	FU 6 months	FU 12 months	FU 24 months	FU 36 months	FU 48 months	FU 60 months	Scores
Holman *et al.* [2013]	H	17		17		0					PLS-4 + OWLS		x			x	x	x			Children implanted < 12 months tended to demonstrate significantly ($p < .05$) better receptive language abilities than children implanted between 13 and 24 months
Niparko *et al.* [2010]	H	72		64		52					RDLS		x					x			Higher rates of RDLS comprehension and expression language scales in children implanted < 18 months vs. children implanted between 18 and 36 months and > 36 months of age ($p < .05$)
Dunn *et al.* [2014]	H	13		26		0					CELF-3	7,8 and 9 yrs.									At seven yrs. of age, the youngest implanted group achieved scores that were 12 points higher than the older implanted group ($p = .01$) By ten and up to 11 yrs. of age, there was no significant difference between both groups
Artières *et al.* [2009]	H	32				15	14	13 (4-5 yrs.)			PPVT-R (French)								x	x	Four and five yrs. FU: significant ($p < .05$) difference between groups 1 (implanted < two yrs.) and 2 (implanted between two and three yrs.); receptive language levels for group 1 reached a normal lexical level by four yrs. of age
Coletti *et al.* [2012]	H	12 (2-6 months)	9	11	13	0					PPVT-R						x	x	x		The youngest group achieved better results than groups implanted > 12 months 24-months FU: < 6 months vs. > 12 months: $p < .001$ 36-months FU: < 6 months vs. > 12 months: $p < .05$ 48-months FU: < 6 months vs. > 12 months: $p < .001$ No significant difference regarding PPVT-R scores between age groups 1 and 2
Leigh *et al.* [2013]	H	0	21	40		0					PPVT-3 + PPVT-4							x			36-months FU: group 1 achieved higher receptive vocabulary standard scores than group 2 ($p = .033$) PPVT standard score had a significant correlation with age at CI ($p < .001$)
Manrique *et al.* [2004]	M	94						88 (4-14 yrs)			PPVT + RDLS (Spanish)		x			x	x	x	x		PPVT: children implanted between 0 and three yrs. followed an almost normal acquisition of their vocabulary, whereas older implanted children had a deviation of almost three yrs. from the baseline; RDLS-scores: children implanted < 36 months showed a delay of two yrs. vs. NH peers, older implanted children deviated > four yrs
Suh *et al.* [2009]	H	22				23	19	22 (4-6 yrs.)			K-PVT			x	x	x	x	x			The K-PVT percentile score improvement was significantly ($p = .037$) higher for the younger implanted group; this group also showed a more rapid improvement ($p = .004$) Children implanted < two yrs. caught up with their NH peers after 2-3 yrs. of IE; children implanted > three yrs. only achieved a score at the 20th percentile of their NH peers
Uziel *et al.* [2007]	H	41								41	PPVT-R	IE 10 yrs.									Ten yrs. FU: children implanted < four yrs.: PPVT-R 2.8 vs. PPVT-R: 2.3 of children implanted > four yrs. ($p < .05$)

Legend: CELF = clinical evaluation of language fundamentals; FU = Follow-Up; IE = implant experience; K-PVT = Korean Peabody Picture Vocabulary Test; NH = Normal Hearing; no. = number of children; OWLS = Oral and Written Language Skills; PLS = Preschool Language Scale; PPVT (-R) = Peabody Picture Vocabulary Test (Revised); vs = versus; yrs. = years.

Table 5. Studies reporting on auditory performance outcome measures (CAP-scores) classified according to age at cochlear implantation and follow-up time of the included children.

Authors	Directness of Evidence (DoE)	no. = 0-6 months	no. = 7-12 months	no. = 13-18 months	no. = 19-24 months	no. = 25-30 months	no. = 31-36 months	no. = 37-48 months	no. > 48 months	Outcome measure	Pre-op measurement	FU 3 months	FU 6 months	FU 12 months	FU 18 months	FU 24 months	FU 36 months	FU 48 months	Scores
Coletti *et al.* [2012]	H	12	9	11	13	0				CAP-II								x	48-months FU: cohort implanted < six months reached higher scores than all other implanted groups ($p < .001$); this youngest group showed no significant difference from the NH group
Schauwers *et al.* [2004]	M	0	10			0				CAP				x	x				Children implanted in their first year showed a normal CAP development as early as three months after implantation, whereas children implanted in their 2nd year needed up to 12 months to reach an age-appropriate CAP level; children who received their implant at approximately 18 months of age lag a bit behind their NH peers, whereas those receiving their implant in their first year of life follow the normal line (n.s.)
Suh *et al.* [2009]	H	22				23	19	22		CAP imp	x	x	x	x		x	x		The CAP improvement was not significantly different among groups; the youngest age group did show a more rapid improvement (a steeper inclination) than the other groups ($p = .002$)

Legend: CAP = Categories of Auditory Performance; FU = Follow-Up; H = high; imp = improvement; M = medium; NH = Normal Hearing; no. = number of children; n.s. = non-significant.

Coletti *et al.*[24] used the PPVT-Revised (PPVT-R) to assess receptive language measures, and their results showed that the youngest group (implanted between two and six months of age) significantly outperformed children implanted after one year of age ($p < .001$), an effect that remained significant till 48 months follow-up. A performance comparison[24] between children implanted before six months (n = 12) and between six and 12 months of age (n = 9) failed to show a significant difference at any follow-up visit. Artières *et al.*[21] compared PPVT-R scores of children implanted before and after two years of age, and found a statistically significant difference between groups evaluated at one year (n = 32), two years (n = 15; $p < .05$) and at four and five years postoperatively (Table 4). Uziel *et al.*[15] showed that children implanted before four years of age outperformed children implanted after four years at ten-year follow-up on PPVT-R scores ($p < .05$).

The PPVT-3 and the PPVT-4 are highly correlated[25]. Leigh et *al.*[7] compared both PPVT scores between different age-at-implantation groups (< one year vs. > one year) at 36 months follow-up. The authors found that younger implanted children achieved higher receptive vocabulary scores compared with older implanted children ($p = .033$).

Suh *et al.*[26] showed that patients who were implanted before 24 months of age caught up with the NH population after two to three years follow-up (Korean PPVT scores). However, children implanted after three years of age only caught up with the 20th percentile of NH children's scores after two, and even after three years follow-up. Therefore, Suh *et al.*[26] concluded that two years of age seems to be the critical time point for cochlear implantation in children.

Auditory performance

In the included studies, auditory performance was assessed using Categories of Auditory Performance (CAP) scores only (Table 5).

At four-year follow-up, Coletti *et al.*[24] found their youngest implanted group (implanted between two and six months) to outperform their later implanted peers on the second version of the CAP (CAP-II) score ($p < .001$). Their results indicated that using the CAP-II score is needed to show performance differences between children implanted before two years of age[24]. No significant difference was seen when their youngest implanted group was compared to NH peers. Schauwers *et al.*[18] evaluated children at the 12-month follow-up and found that 80% of the children implanted between six and 18 months achieved a CAP score between 5 and 6. The authors concluded that children who undergo cochlear implantation at approximately 18 months of age lag a bit behind their NH peers, whereas those receiving their implant in their first year of life follow the normal line (non-significant). Suh *et al.*[26] found their youngest cohort to show a more rapid CAP improvement than their older implanted peers. However, this CAP improvement rate was not significantly different between age-at-implantation groups.

DISCUSSION

Our review shows consistent evidence for the benefit of early cochlear implantation in children, but literature remains indistinct on defining the additional speech and language benefits of cochlear implantation before 12 months of age. The number of available studies was substantial. Ten of the 14 discussed studies showed to contain of high DoE, however, RoB ranged from low to moderate. The best available evidence is based on independent subjective outcome measures and indicates that implantation before two years of age is beneficial when considering speech perception (on combined PB-K and CNC but not on GASP scores)[14,16,27]. Implantation before 12 months resulted in better speech production (DEAP and IT-MAIS)[27-28], auditory performance (CAP-II score)[24] and two out of the five receptive language scores (combined PLS and OLWS and PPVT scores)[22,24,27]. One study showed that implantation before six months resulted in superior four year auditory performance (CAP-II)[24]. Although the latter study of Coletti *et al.*[24] showed safe and effective results, the majority of ENT surgeons will refrain from this elective surgery before 12 months of age[3]. The exception for performing cochlear implantation in early infancy remains the occurrence of deafness following meningitis[3]. However, in Europe, a trend to implant children before their first year of life is emerging.

Due to concerns regarding unreliable preoperative auditory assessment, underdeveloped anatomy, lack of FDA approval[3] and a possibly increased risk for anaesthetic complications, cochlear implantation has not been performed widely in the population under one year[22]. However, increasing evidence shows that cochlear implantation can be performed without increased risk of anaesthetic and surgical complications in this population. Four included studies reported on complication rates in children[13, 16, 22, 24] of which three studies[16,22,24] included children operated before 12 months of age. These studies did not report any significant difference in anaesthetic or surgical complications between early (< 12 months) and later (> 12 months) implanted children. Coletti *et al.*[24] did report that young children (two – six months) experienced a significant ($p < .05$) higher heart rate; however, this reflected an age-appropriate heart rate for these young children.

We found variation in the recommended age children should be implanted to be able to close gaps in speech and language delays compared to NH peers. The recommended age for cochlear implantation varied from six to 24 months[23,29]. Coene *et al.*[30] stated that implantation before 16 months of age will prevent speech and language delays; however, this small study sample lacked a comparison of age-at-implantation groups. Svirsky *et al.*[31] used developmental trajectory analysis and showed that implantation before the age of two years resulted in significant speech and language advantages. The identified variation in recommended implantation age might be the consequence of the inconsistent, incomplete en conflicting evidence that was identified from the current literature.

To monitor the initial positive 'age at CI effect', adequate longitudinal analysis is essential to account for confounding effects. For example, Dunn *et al.*[14] showed initial significant differences at the seven-year follow-up among age-at-implantation groups, but no differences were found at the ten and 11-year follow-up (Table 4). The initial speech and language growth

rate could be higher in early implanted children due to auditory stimulation during the sensitive developmental period[32]. Alternatively, this group has the advantage of: earlier diagnosis, earlier hearing aid intervention, more time to learn to listen with the implant ('starting early') and earlier education intervention. Therefore, the lower performance level in older implanted children could be a consequence of their lower level of device experience[10,33]. Tajudeen *et al.*[32] underlined this in their analysis by showing that younger implanted children outperformed older implanted children, however, when implanted children were compared at similar follow-up postoperatively, there was almost a complete overlap in scores. Therefore, studies that compare children at similar follow-up postoperatively are essential. The Childhood Development after Cochlear Implantation (CDaCI) study[28] is one of the few retrieved prospective, longitudinal studies assessing auditory and language benefits obviating these limitations.

An earlier review marked the limited and low quality evidence regarding age-at-implantation effects on speech and language performance following cochlear implantation in children[6]. We confirm the lack of level 1 evidence but provide additional evidence from more recent studies[7,14,22,24] comparing children implanted before one year of age with children implanted between 12 and 24 months on longer follow-up (> 48 months). In addition to the review of Vlastarakos *et al.*[6], we assessed receptive language and auditory performance outcome measures.

Due to the recent trend of earlier cochlear implantation in children, the majority of the children have not yet reached an age in which objective measures can be applied. Furthermore, elected subjective measures might be too grammatically complex (e.g., GASP scores) for these young children[16-17]. Another consequence of the aforementioned trend is that a limited number of children are implanted early and current study samples might be too small to show significant differences between different age-at-implantation groups[10,16]. Therefore, there is a need for age-normed test standards for both meaningful comparisons of these young implanted children with NH peers and comparisons of study results with respect to age at cochlear implantation. A recent survey[34] proved the lack of consistency in the preoperative and postoperative selection of speech perception measures across paediatric CI centres. The need for uniform protocols to assess children preoperatively and the development of a working group to establish a standard paediatric postoperative test battery (similar to the adult Minimum Speech Test Battery (MSTB)) was underlined[34]. In addition, variability in CI fitting protocols exist: in a worldwide survey[35], the large variability on all aspects of the CI fitting process and the small role that objective measures play in this process was marked.

Some limitations of this review should be mentioned. First, we refrained from including non-comparative studies of children implanted before one year of age, because the number of comparative studies provided sufficient direct evidence to address our review query. The fact that positive study outcomes might be more likely to be reported (reporting bias) could have influenced our conclusions. In addition, various confounders are known to affect performance following cochlear implantation[17,36], such as the communication mode (speech only or speech/sign combined) and the intelligence and participation and support of the child's family during

the rehabilitation[26]. Therefore, there is a need for additional multivariate analysis in studies to accurately assess the effect of age at cochlear implantation. The majority of studies consisted of retrospective designs with inconsistent or incomplete language measures and lacked multivariate analysis. Therefore, we applied critical appraisal to select the literature that most adequately corrected for these confounders and was transparent regarding data collection. Third, since language is complex behaviour consisting of multiple sensitive periods of various speech and language skills[37], it is difficult to assess language as one exact outcome measure. By assessing multiple speech and language outcome measures (Tables 2 to 5) we aimed to assess language as complete and accurately as possible.

CONCLUSION

In conclusion, our systematic review provides consistent evidence for early cochlear implantation in children; however, the literature remains indistinct about the additional benefit of implantation before 12 months of age. The current best evidence showed that early implanted children (< 12 months of age) score better speech production (DEAP and IT-MAIS-scores), auditory performance (CAP-II score) and (on two out of the five) receptive language scores (combined PLS-4 and OWLS and PPVT scores) compared to their later implanted peers (> 12 months). This evidence consists of cohort studies with a moderate to high RoB; therefore, protocols for standardized preoperative and postoperative evaluations and CI fitting procedures should be developed to allow: consistent comparison of speech and language outcomes between various age-at-implantation groups and to gather additional high-level evidence for timely implantation for children with profound hearing loss.

APPENDIX

Compared speech and language outcome measures

Outcome measure	Applicable age	Test content
Speech perception		
CNC-scores	> 3 years*	A 500 monosyllabic word test, to assess open-set word recognition. [Peterson 1962] *no minimal age known; but most likely after the age of three years
PBK	5 – 7 years	A monosyllable open-set test to assess spoken word recognition (50 phonetically balanced words). [Dunn *et al.* 2014]
WIPI	> 4 years	A 25 item, 6-choice monosyllable closed-set discrimination task where a child must identify a phonetically similar word, represented by one of the six pictures. [Fryauf-Bertschy *et al.* 1997]
GASP	> 5 years	An open-set test which measures the ability to understand simple sentences. [Erber 1982]
Speech production		
DEAP	3 – 83 months	Test designed to identify the presence of a delay in articulation or phonology. [Dodd *et al.* 2002]
SIR	> 1 year	Used to rank spontaneous speech production into five hierarchic scales. [Cox 1989]
IT-MAIS	Birth – 36 months	A structured parental-reported scale designed to assess the child's spontaneous responses to sound in its everyday environment. It assesses 1) vocalization behavior, 2) alerting to sounds, 3) deriving meaning from sound. Scores can be converted to normal-hearing age equivalents. [Zimmerman-Phillips 2000]
MAIS	No limit	Evaluates observable auditory behavior in everyday situations. [Robbins *et al.* 1991]
LittlEARS®	Until hearing age of 24 months	A parental questionnaire to assess the auditory development of their child. Normative data are available. [Tsiakpini *et al.* 2004]
Receptive language		
OWLS	3 – 21 years > 5 years [written]	Individual administered language test that assess receptive and expressive language. [Carrow-Woolfolk 1996]
CELF®	5 – 21 years	An individually administered language test that assess receptive and expressive language. It can determine whether a language disorder is present. Norm-reference scores available. [Semel *et al.* 2003] CELF-3 and CELF-4 yielding correlation (correlation coefficient: 0.37- 0.79) [Dunn 1997]
PLS	Birth – 83 months	A standardized test of auditory comprehension and expressive communication for infants and toddlers. Age-equivalent scores can be calculated. [Zimmerman 2002]
PPVT	> 30 months	Provides information to compare receptive and expressive vocabulary skills. Age/grade equivalents and normal curve equivalents are provided [Dunn 1997] PPVT-3 and PPVT-4 strongly correlated (correlation coefficient = 0.84) [Dunn 1997]
PPVT-R	> 30 months	Receptive language level relative to that of normally hearing peers. [Dunn 1997]
K-PVT	> 30 months	Korean version of the PPVT [Kim *et al.* 1995]
RDLS	1 – 6 years	A norm referenced test to assess the language abilities. It contains two scales: 1) verbal comprehension and 2) expressive language. [Edwards *et al.* 1997]
MB-CDI	8-18 months (gestures) 16-30 months (sentences) > 30 months (phrases)	Parental questionnaire to identify various words that their child either says or signs. Norms for hearing children between 18 and 36 months of age are available. [Fenson *et al.* 2006]
Auditory performance		
CAP	infancy-adulthood	CAP scores reflect a profile of the developing child and can be used to monitor auditory progress of the child. CAP-ceiling level is reached when a score of 7 is accomplished. [Archbold *et al.* 1995] CAP-II assesses two additional new scales: CAP-8 and CAP-9. [Ear Foundation 2009]

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Chapter 1.2

Incorporating ceiling effects during analysis of speech perception data from a paediatric cochlear implant cohort

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ABSTRACT

Objective

To compare speech perception between children with a different age at cochlear implantation.

Design

We evaluated speech perception by comparing Consonant-Vowel-Consonant (Auditory) (CVC(A)) scores at five-year follow-up of children implanted between 1997 and 2010. The proportion of children from each age-at-implantation group reaching the 95%CI of CVC(A) ceiling scores (> 95%) was calculated to identify speech perception differences masked by ceiling effects.

Study Sample

54 children implanted between eight and 36 months of age.

Results

Although ceiling effects occurred, a CVC(A) score difference between age-at-implantation groups was confirmed (H (4) = 30.36; p <.001). Outperformance of early (< 18 months) compared to later implanted children was demonstrated (p <.001). A larger proportion of children implanted before 13 months compared to children implanted between 13 and 18 months reached ceiling scores. Logistic regression confirmed that age at implantation predicted whether a child reached a ceiling score.

Conclusions

Ceiling effects can mask thorough delineation of speech perception. However, this study showed long-term speech perception outperformance of early implanted children (< 18 months) either including or not accounting for ceiling effects during analysis. Development of long-term assessment tools not affected by ceiling effects is essential to maintain adequate assessment of young implanted infants.

INTRODUCTION

Cochlear implants (CIs) are beneficial in providing hearing, speech and language rehabilitation to children presenting with profound hearing loss[1]. The timing of cochlear implantation is essential for prompt rehabilitation in developing age appropriate hearing and in turn, other skills[2]. Early cochlear implantation has shown promising outcomes. The current literature indicates that infants who receive a CI before 12 months of age outperform children receiving CIs after this age on a variety of language outcome measures[2-13]. However, in order to reach consensus within the medical community, both Vlastarakos *et al.*[13] and Dettman *et al.*[7] highlight the need to define the optimal age for cochlear implantation in children. Several factors could explain why this optimal age for cochlear implantation is not explicitly defined. The absence of objective paediatric speech and language outcome measures without the occurrence of ceiling effects is known to be one of these underlying factors[13].

Following cochlear implantation in children, regular postoperative follow-up is necessary to closely monitor speech and language development. Since there is no clear guideline for universal postoperative assessment of children using CIs, a wide variety of speech and language outcome measures are currently used[14]. Some of these tests could provide data that are hindered by ceiling effects, as they are not able to adequately monitor the rapid speech and language improvement following cochlear implantation in children[15]. Ceiling effects occur when the majority of tested patients reach the maximum or near maximum test score[15]. Helms *et al.*[15] identified that speech perception ceiling effects occurred already one month following CI device activation in 51% of their adult CI population. Similarly, Massa and Ruckenstein[16] reported postoperative plateau scores between six months and three years following implantation in adult CI users. Since ceiling effects limit measuring the maximum performance of CI users, current postoperative tests could not accurately reflect the speech and language performance of CI patients. Therefore, application of these scores can potentially bias the interpretation of the postoperative test results[15]. To prevent this bias from affecting speech and language outcome scores and to accurately depict the competence of the CI user, the difficulty of testing should increase when a CI user reaches a ceiling score on a less complex test[17].

The occurrence of ceiling effects could be more pronounced in the paediatric CI population compared to adult CI users due to the use of categorical outcome measures and advances in CI technologies. First, current categorical outcome measures used in children have a limited number of test categories. For example, in SIR and CAP scores, paediatric CI users can rapidly achieve the highest category[18-19]. For this reason, two additional category levels have been added in the CAP assessment (CAP - 8 and CAP – 9; CAP - II score) (NEAP© [Nottingham Early Assessment Package]; The Ear Foundation, Nottingham, UK, 2009). Colletti *et al.*[20] showed that younger patients (implanted between two and six months) significantly (p <.001) outperformed later implanted children on CAP - II scores at four-year follow-up. Results indicated that CAP - II scores greatly aided in identifying important differences between children implanted before two years of age[20]. Secondly, several authors demonstrated that young adult patients (mean age of 44.1 years [19.2 - 67.3] and between 26 and 39 years respectively) who used newer CI technologies achieved plateau scores sooner[21-22]. This effect could be even more pronounced in children using newer CI technologies.

Vlastarakos *et al.*[13] suggested that using assessment tools with possible ceiling effects limits accurate identification of implant success for early implanted children. To assess whether the influence of age at implantation on long-term speech perception was not masked by ceiling effects, we compared two speech perception analyses: a data assessment between paediatric CI cohorts grouped according to age at implantation and groups divided by the proportion of children reaching a ceiling Consonant-Vowel-Consonant (Auditory) (CVC(A)) score. By comparing aforementioned analyses, we attempted to clarify whether ceiling effects masked performance differences initiated by a different age at implantation. Furthermore, the ceiling effect analysis allowed us to assess speech perception performance differences between the youngest age-at-implantation groups (implanted before 13 months and between 13 and 18 months): an analysis that could not have been performed by comparing raw scores only since all children performed at the highest (ceiling) CVC(A) range.

METHODS

Study Design – Participants

We conducted a retrospective review of children implanted before 36 months of age between 1997 and 2010 at our institution (UMC Utrecht). All included patients presented with prelingual hearing loss; defined as hearing loss that occurred before the acquisition of spoken language skills (before two years of age)[23]. All CI candidates used preoperative hearing aids for a minimum of six weeks. Cochlear implant indication was established following standardized multidisciplinary assessment. Five surgeons performed cochlear implantation through the Suprameatal (SMA) or Mastoidectomy with Posterior Tympanotomy Approach (MPTA)[24-27]. Patients receiving unilateral or bilateral implants were included (Table 1).
Two authors conducted a retrospective review of institutional digitalised outpatient reports. Outcome measures included baseline demographic and hearing characteristics, surgical details and postoperative speech perception scores. In line with previous studies, children with a significant cognitive delay were excluded from our analysis[7]. Reporting was conducted according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines[28]. Local ethical committee provided approval for this study (protocol number: METC 14-486/C).

Variables

Speech and language therapists from a certified CI revalidation team performed speech perception assessment by administering CVC(A) wordlists during postoperative follow-up[29-30]. This stimulus-repetition task is based on presenting recorded, open-set meaningful monosyllabic words (CVCs) in a quiet room at a level of 65 dBs sound pressure level (SPL) without providing visual cues. The participant should correctly repeat the aforementioned meaningful CVC(A) words. Bosman *et al.*[29] and Bosman & Smoorenburg *et al.*[30] developed 60 different CVC(A) wordlists, of which 15 can be applied in the paediatric population. Each

of these 15 CVC(A) lists contains 11 words, which contain a total of 33 phonemes. During the speech perception assessment in this study, the speech and language therapist performed an assessment using two randomly selected and different CVC(A) wordlists. The speech and language therapist calculated the percentage of correctly repeated CVC(A) words from the total of 22 presented words (containing a total of 66 phonemes). Examples of CVC(A) phonemes are: lip, bus, pop, men, net and big. The speech perception of included children was evaluated for five years after their initial CI surgery. In our institution, paediatric CI users are evaluated every three months during the first year after implantation and on an annual basis thereafter. During each postoperative evaluation, different CVC(A)-word lists are selected. The five-year postoperative data were selected in this study to minimalize the influence of relative maturation effects[31].

To demonstrate CI performance differences between patients and to account for ceiling effects, Helms *et al.*[15] used the 95% confidence interval around maximum speech perception scores. In line with this approach, we allocated CVC(A) scores above 95% correct phonemes as ceiling scores. Secondly, to evaluate whether particular age groups demonstrated significant speech perception differences, patients were divided into five different age-at-implantation groups based on six-months intervals (Table 1). This approach was in line with various other studies evaluating age-at-implantation effects in paediatric CI populations[7,11,32-33]. We evaluated the number of children per age-at-implantation group attaining the ceiling score (> 95% correct CVC(A) phonemes). Then, we compared the number of children between age-at-implantation groups reaching this CVC(A) ceiling score. We defined a between group performance difference as a significant difference between the 95% confidence interval of the number of ceiling scoring children between age-at-implantation groups.

Statistical analysis

Statistical analysis was performed using SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). During analysis of baseline characteristics (Table 1) and correlations between variables (Table 3), we deemed statistical tests significant at a value of $p = .05$. We applied Bonferroni-correction ($p = .005$) when multiple between age-at-implantation group comparisons were performed (Table 2). Shapiro-Wilk test was used to confirm non-normal data distribution. To examine whether age at implantation affected speech perception we used implantation age both as a continuous (CVC(A) raw score comparisons between age-at-implantation groups) and a categorized variable (CVC(A) ceiling score comparisons between age-at-implantation groups).

Baseline characteristics

Univariate relations between variables and confounders were studied using Spearman correlation (e.g., age at implantation and bilateral implantation). Relations between dichotomous variables were studied using Fisher exact test (e.g., prematurity and bilateral implantation). The Pierson Chi-square test was elected for comparisons between multiple unpaired groups on discrete outcomes (e.g., age-at-implantation groups and aetiology of hearing loss).

CVC(A) scores

1. CVC(A) raw score comparisons between age-at-implantation groups

As CVC(A)-scores were not normally distributed, we elected two statistical tests to study between group differences. First, the Kruskal-Wallis test was used to determine whether significant differences in speech perception scores (CVC(A) values) existed between all age-at-implantation groups. Secondly, Mann-Whitney U tests were used to perform comparison between sets of two specific age-at-implantation groups.

2. CVC(A) ceiling score comparisons between age-at-implantation groups

Fisher exact tests were used to perform age-at-implantation group comparisons to assess whether a greater proportion of children from a specific age-at-implantation group reached a ceiling CVC(A) score.

3. Logistic regression

Since we subdivided our data into binary outcome measures (reaching or not reaching a CVC(A) ceiling score), we used logistic regression to study which variables influenced the probability to reach the ceiling CVC(A) score. This analysis included variables that are reported in the literature to affect CI speech perception performance: gender, level of hearing loss (measured by Auditory Brainstem Response (ABR)), hearing loss aetiology, comorbidities, prematurity, CI device type, surgical implantation technique and unilateral or bilateral implantation.

RESULTS

Between 1997 and 2014, 122 children were implanted before 36 months of age at the UMC Utrecht. Ninety patients completed five-year CVC(A) score follow-up and were selected for this study. We included 54 out of the 90 selected children. Thirty-six patients were excluded due to: CI-induced facial nerve excitation (n = 1), Dutch not as primary language (n = 9), post-lingual hearing loss (n = 2) and incomplete speech perception follow-up scores (n = 24). Incomplete speech perception follow-up occurred due to: migration (n = 5), immigration (n = 5) or the inability to fulfill CVC(A) assessment due to cognitive delay (n = 14).

Statistical analysis - Baseline characteristics

Table 1 shows baseline characteristics of the included children. Children were grouped according to their age at implantation. Median age at implantation of the 54 included patients was 22.92 months [range: 8.52 - 34.08 months]. Median hearing loss at indication was 100.0 decibel (dB) [range: 90 - 110 dB]. The youngest age-at-implantation group showed significantly less hearing loss compared to older implanted children (p = .005). The MED-EL CI device was only used in the two youngest age-at-implantation groups (p = .012). The number of unilateral and bilateral implanted patients per age-at-implantation groups significantly differed

at five-year follow-up (p = .018). Nine patients presented with comorbidities not intervening with speech perception testing (Usher/Beckwith Wiedemann syndrome (n = 4), diabetes mellitus (DM) type I (n = 1), motoric developmental disorders (n = 2), asthma (n = 1) and antibody synthesis defect (n = 1)) (data not presented in Table 1).

CVC(A) scores

1. CVC(A) raw score comparisons between age-at-implantation groups

The median CVC(A) score at five-year follow-up was 92.00% [range: 57 - 100 %]. Shapiro-Wilk testing showed that data were not normally distributed: most children scored the highest possible CVC(A) scores (CVC(A) ceiling scores). Although ceiling scores occurred, a Kruskal-Wallis test confirmed a significant CVC(A) score difference between age-at-implantation groups (H (4) = 30.36; p < .001) (Table 1). Mann-Whitney U tests between age-at-implantation groups showed that the youngest age-at-implantation group (implanted before 13 months) outperformed children implanted after 18 months (Table 2). No statistical speech performance difference was found between age-at-implantation groups 1 (implanted before 13 months) and 2 (implanted between 13 and 18 months) (*data not shown in Table 2*).

More recently implanted children (implanted after 2006) significantly outperformed earlier implanted children (*data not presented*). Within the paediatric cohort that was implanted after 2006, age at cochlear implantation still significantly (p < .001) affected the level of the CVC(A) score.

Since the number of unilateral and bilateral implanted patients per age-at-implantation group significantly differed at five-year follow-up, children using an unilateral CI were separately analysed. After Bonferroni correction, all of the aforementioned CVC(A) raw score comparisons remained significant, except for the comparison between age-at-implantation groups 1 and 3 (using a Mann-Whitney U test). Although between group comparisons of CVC(A) raw scores did not differ between separate analysis of unilaterally or bilaterally implanted children, within age-at-implantation groups 2 and 4 significant CVC(A) score differences were identified in favour of bilaterally implanted children (U = 28.00, z = 2.42, p = .017, r = 0.73; U = 28.00, z = 2.23, p =.028, r = 0.62).

2. CVC(A) ceiling score comparisons between age-at-implantation groups

Between age-at-implantation group analysis using Fisher exact test demonstrated performance differences between groups 1 and 4 (p < .001), groups 1 and 5 (p < .001) and groups 2 and 4 (p < .001) after Bonferroni correction (Figure 1).

Logistic regression

Binominal logistic regression showed that a larger proportion of young implanted children (< 18 months) reached CVC(A) ceiling levels ($\chi^2(1) = 11.77$; p < .05) compared to older (> 18 months of age) implanted children. Table 3 shows correlations among various variables that are reported in the literature to affect speech perception performance following cochlear implantation.

Table 1. Baseline characteristics of included patients arranged by age-at-implantation group.

Implantation age group	**1**	**2**	**3**	**4**	**5**	**total no.**	***p*-value**	**Test**
Age at CI surgery [range in months]	6 - 12	13 - 18	19 - 24	25 - 30	31 - 36	54		
Age at CI surgery (median in months)	11	13	23	26	32	54		
No. of implanted children	9	11	11	13	10	54		
Gender (female : male)	3 : 6	6 : 5	6 : 5	7 : 6	4 : 6	26 : 28	ns	Fisher's exact
Year of birth [range in years]	2002 - 2009	2001 - 2009	1999 - 2008	1995 - 2006	1996 - 2001	54	**.006***	Pearson Chi-square
Year of CI surgery [range in years]	2003 - 2010	2002 - 2010	2001 - 2010	1997 - 2008	1999 - 2004	54	ns	Pearson Chi-square
ABR hearing loss pre CI (median in dBHL)	90	100	100	100	110	54	**.012***	Independent samples median
ABR hearing loss pre CI [range in dBHL]	90 - 100	90 - 110	90 - 105	95 - 110	90 - 110	54	**.005***	Kruskal-Wallis
Age at FU 5 years after CI (median in months)	71	74	85	90	95	54	**< .001***	Independent samples median
Age at FU 5 years after CI [range in months]	64 - 76	69 - 77	81 - 92	83 - 97	93 - 97	54	**< .001***	Kruskal-Wallis
Aetiology							ns	Pearson Chi-square
Unknown (non syndromic)	6	4	7	7	8	32		
Connexine 26		1				1		
Syndromic (Beckwith Wiedemann, Waardenburg, Usher)	0	2	2	1	1	6		
Meningitis	3	4	1	5	1	14		
CMV infection			1			1		
Disabilities								
Comorbidity	1		1	3	4	9	ns	Fisher's exact
Prematurity		1	1	2	1	5	ns	Fisher's exact
CI surgical techniques							ns	Pearson Chi-square
MPTA	7	9	10	13	10	49		
SMA	2	1	1			4		
Unknown		1				1		
CI device							**.012***	Pearson Chi-square
Cochlear®	6	9	11	13	10	49		
MED-EL	3	2				5		
Unilateral : bilateral	5 : 4	5 : 6	10 : 1	10 : 3	10 : 0	40 : 14	**.018***	Fisher's exact
Time gap 1st CI - 2nd CI [range in months]	0 - 20	0 - 47	51	0 - 32			ns	Kruskal-Wallis
Outcomes								
CVC(A)-score (median in %)	100	97	89	89	75,5	92	**<.001***	Kruskal-Wallis
CVC(A)-score [range in %]	95 - 100	88 - 100	77 - 100	70 - 95	57 - 94	57 - 100		

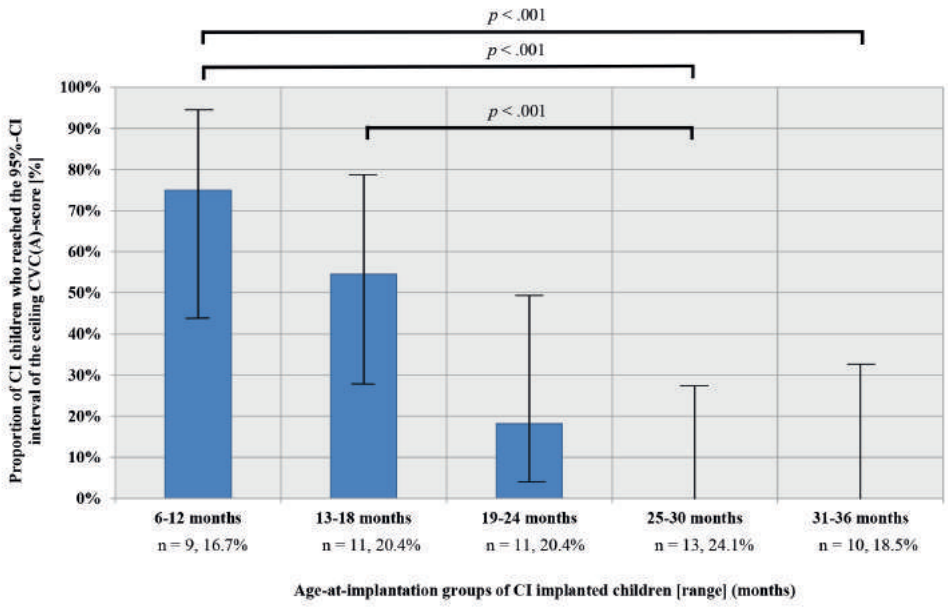
Legend: ABR = Auditory Brainstem Response; CI = Cochlear Implant; CMV = CytoMegaloVirus; CVC(A) = Consonant-Vowel-Consonant (Auditory); dBHL = decibel hearing loss; FU = follow-up; MPTA = Mastoidectomy with Posterior Tympanotomy Approach; no. = number; ns = not significant; SMA = SupraMeatal Approach. * = significant at the $p = .05$ level.

Table 2. Mann-Whitney U tests between raw CVC(A) scores from different age-at-implantation groups.

	U	z	p	r
Group comparisons (using Mann-Whitney U tests)				
Group 1 (6 - 12 months) vs. Group 3 (19 - 24 months)	9.50	-3.09	**.001***	.69
Group 1 (6 - 12 months) vs. Group 4 (25 - 30 months)	1.00	-3.88	**< .001***	.83
Group 1 (6 - 12 months) vs. Group 5 (31 - 36 months)	0.00	-3.71	**< .001***	.85
Group 2 (13 - 18 months) vs. Group 5 (31 - 36 months)	5.00	-3.54	**< .001***	.77
Group 3 (19 - 24 months) vs. Group 5 (31 - 36 months)	14.00	-2.90	**.003***	0.63

Legend: CVC = Consonant-Vowel-Consonant, * = significant at the $p = .005$ level.

Figure 1. Proportion of children (n = 54) from each age-at-implantation group reaching the CVC(A) ceiling score at five-year follow-up.



Legend: CI = Cochlear Implant; CVC = Consonant-Vowel-Consonant; N = number. Error bars represents the 95% confidence interval.

Results marked in bold show a strong correlation ($p < .01$). We included the variables that significantly correlated to age at CI surgery into our logistic regression: hearing loss level at CI indication, comorbidities, the CI device type and unilateral or bilateral implantation. This logistic regression analysis showed that age at implantation was the only significant predictor for reaching a five-year CVC(A) ceiling score (Table 4). Logistic regression did not confirm a bilateral CI use advantage (over unilateral CI use) in reaching a CVC(A) ceiling score (> 95% CVC) at five-year follow-up (Table 4).

Table 3. Report of Spearman's rho correlation among variables.

		CVC score 5 years FU [%]	Ceiling	Age at CI surgery	ABR hearing loss	Aetiology	Comorbidity	Prematurity	CI device	CI technique	Unilateral vs. Bilateral CI at 5 years FU
N		54	54	54	54	54	54	54	54	54	54
Ceiling CVC(A)-score	ρ	**.78****									
	p (2-tailed)	**<.001**									
Age at CI surgery	ρ	**-.77****	**-.64****								
	p (2-tailed)	**<.001**	**<.001**								
ABR hearing loss	ρ	**-.47****	-.28*	**.45****							
	p (2-tailed)	**<.001**	.038	**.001**							
Aetiology	ρ	.22	.069	-.14	-.26						
	p (2-tailed)	.11	.62	.30	.059						
Comorbidity	ρ	-.058	-.055	**.35****	.14	.10					
	p (2-tailed)	.68	.69	**.009**	.33	.46					
Prematurity	ρ	.12	.087	.13	.058	.28*	**.37****				
	p (2-tailed)	.37	.53	.37	.68	.044	**.006**				
CI device	ρ	**.68****	**.62****	**-.68****	-.24	.14	-.21	.023			
	p (2-tailed)	**<.001**	**<.001**	**<.001**	.087	.33	.14	.87			
CI technique	ρ	.22	.31*	-.20	-.17	.15	.25	.16	.24		
	p (2-tailed)	.11	.023	.15	.23	.27	.068	.26	.084		
Unilateral vs. Bilateral CI at 5 years FU	ρ	**.56****	**.48****	**-.42****	-.17	.22	-.038	-.19	**.53****	.18	
	p (2-tailed)	**<.001**	**<.001**	**.002**	.23	.11	.79	.17	**<.001**	.19	
Age at FU 5 years after CI	ρ	**-.76****	**-.65****	**.93****	.31*	-.049	.33*	.11	**-.75****	-.25	**-.50****
	p (2-tailed)	**< .001**	**< .001**	**< .001**	.024	.72	.014	.42	**< .001**	.067	**< .001**

Legend: ** = correlation is significant at the *p* = .01 level (two-tailed), * = correlation is significant at the *p* = .05 level (two-tailed). ABR = auditory brainstem response; CI = cochlear implant; CVC = consonant-vowel-consonant; FU = follow-up.

DISCUSSION

In this study, we evaluated paediatric age-at-implantation effects on postoperative speech perception. Analyses on raw CVC(A) scores showed that the two youngest age-at-implantation groups (implanted between six - 18 months of age) outperformed older implanted children (implanted between 18 - 36 months of age) at five-year follow-up. After accounting for ceiling effects, a larger proportion of young implanted children (< 18 months of age) reached CVC(A) ceiling levels compared to older (> 18 months of age) implanted children.

Since we demonstrated benefits of early implantation in both analyses (raw CVC(A) score analysis and while accounting for CVC(A) ceiling effects), we can derive that ceiling effects can be successfully measured and its effect on speech perception outcomes can be weighed.

Table 4. Report of results of binominal logistic regression analysis. In this model age at implantation is the only significant predictor for reaching the five-year CVC(A) ceiling score (p = .021).

	β	Stand. error	Wald	df	*p*	Exp(β)
Age at CI surgery	-3.25	1.41	5.33	1	**.021***	.039
CI device	.65	.35	3.39	1	.066	1.91
Unilateral vs. Bilateral CI at five-year FU	1.31	1.06	1.54	1	.21	3.72
Comorbidity	2.02	1.83	1.22	1	.27	7.57
ABR hearing loss	-.062	.085	.53	1	.46	.94
(Constant)	4.90	7.75	.40	1	.53	134.13

Legend: ABR = auditory brainstem response; CI = cochlear implant; FU = follow-up. * = significant at the p = .05 level.

However, current speech perception evaluation tools, such as the CVC(A) score, have their limitations and, thus, prevented further in-depth (statistical) comparison between the two youngest implanted groups. By comparing the proportion of children reaching the 95%CI CVC(A) ceiling score between age-at-implantation groups, we were able to show that a relatively larger proportion of earlier implanted children (< 13 months of age) reached CVC(A) ceiling scores compared to those implanted between 13 and 18 months. This comparison not being statistically significant could be due to either ceiling effects, the limited number of children per group or a diminishing age-at-implantation effect during long-term follow-up[34].

In this study, earlier age at implantation was related to a higher long-term speech perception score. However, current studies report different time points to reach optimal speech perception benefit after cochlear implantation. Houston *et al.*[35] assessed speech perception using two closed-set word recognition tests (Grammatical Analysis of Elicited Language - Pre-Sentence Level (GAEL-P) and the Paediatric Speech Intelligibility Test (PSI)) and an open-set word recognition test (LNT). Authors showed that speech perception outcomes of children implanted before 13 months were largely similar to those implanted between 16 and 23 months of age[35]. In line with this finding, Dettman *et al.*[7] reported that their three youngest age-at-implantation groups (all implanted before 24 months of age) outperformed older implanted children on the following speech perception outcome measures: open-set monosyllabic word (OSW) recognition (including CVC words) and open-set sentence recognition (using Bench-Kowal-Bamford (BKB) sentences). Dettman *et al.*[7] suggested that children develop speech perception skills if they have access to CIs before and after 12 months and emphasized that children should receive CIs before 24 months of age. Similarly, we were unable to show statistical long-term performance differences between children implanted before 13 months and those implanted between 13 and 18 months of age. However, our ceiling effect analysis did demonstrate that a relatively larger proportion of children implanted before 13 months reached a CVC(A) ceiling score. Although Dettman *et al.*[7] 's study retrospectively assessed children implanted in a similar time frame as our cohort; they used different outcome measures evaluated over a shorter follow-up that limits additional comparison between Dettman *et al.*[7]'s and our results.

Colletti *et al.*[20] concluded that earlier implantation (< six months of age) is essential for adequate speech and language development. The authors based their conclusions on a combination of speech perception, receptive language development, receptive vocabulary and speech production scores. However, CI indication and year of surgery data were not provided[20]. The latter could have affected outcomes of the youngest implanted patients similar to our results, in which patients implanted after 2006 outperformed patients implanted before this period. This could be explained by age at implantation being significantly correlated to the year of CI surgery in our study. Since the year at CI surgery correlated with the age at cochlear implantation, we further investigated this correlation. To assess whether a positive age-at-implantation effect could still be shown in the most recent (> 2006) implanted children, we performed a sub-analysis including these patients and only age at implantation remained to significantly ($p < .001$) affect the level of the CVC(A) score.

Boons *et al.*[34] demonstrated that the first CI fitting effect disappeared after three-year follow-up. This finding justifies electing the five-year follow-up moment in this study to prevent measuring first fitting or maturation effects due to different duration of CI use. Although authors have warned that age-at-implantation effects could decrease during long-term follow-up, our regression models did not show a reduced age-at-implantation effect over time[34]; our findings confirmed age-at-implantation effects in a young paediatric population using data measured at five-year follow-up. However, a relative decrease in age-at-implantation effects during long-term follow-up[34] could explain why we were not able to show a significant difference between the proportion of children reaching ceiling CVC(A) scores of the youngest two age-at-implantation groups.

Niparko *et al.*[36] showed that bilateral implantation did not result in significant improvement of verbal language development, while Boons *et al.*[34] demonstrated improved language test scores in bilaterally implanted children. In the current study, bilateral implantation significantly correlated with age at implantation and year of CI surgery. More recently implanted children were implanted at a younger age and more frequently bilateral due to application of newer guidelines and reimbursement rates; e.g., in the Netherlands, bilateral cochlear implantation is only reimbursed since September 2013, which could explain why 85.7% of our included bilateral patients were implanted after 2006. Therefore, age at implantation, the year of CI surgery and receiving bilateral implants could affect the CVC(A) ceiling score at 5-year follow-up. However, logistic regression confirmed that only the age at implantation significantly affected reaching CVC(A) ceiling scores at five-year follow-up.

Although logistic regression and between group analysis did not demonstrate that bilateral implantation affected reaching CVC(A) ceiling scores, within group analysis did show a relative benefit of being bilaterally implanted in age-at-implantation groups 2 (implanted between 13 and 18 months) and 4 (25 - 30 months). Table 1 shows that this effect could not be explained by a difference in age at bilateral implantation. Most likely, this effect was only retrieved within these groups because unilaterally and bilaterally implanted patients were equally distributed while in other age-at-implantation groups numbers of bilaterally implanted children were too small to detect a relative benefit.

Limitations

Most CI studies assess a combination of several auditory, speech perception and production and language outcomes[7,20]. Therefore, evaluation of a single speech perception test score might not allow recommendations regarding an optimal age at paediatric cochlear implantation. In our centre, CVC(A) scores are part of a larger postoperative test battery, including for example CAP and SIR scores[18-19]. These outcome measures on other language domains were performed on fewer children and therefore, lacked statistical power to be included in the current study. Secondly, the fact that data were collected retrospectively led to the inability to correct for several variables in our regression analysis that could have affected speech perception. Szagun and Stumper[37] marked that the child's home language environment significantly contributed to the child's opportunities to derive benefit from early cochlear implantation. Beside the aforementioned variable, we were also not able to account for: age at hearing aid fitting and family factors (e.g., maternal education and relative socio-economic advantage).

Thirdly, our youngest cohort had significantly less hearing loss at CI indication (90 dB [range: 90 – 100]) than older age-at-implantation groups. Since these younger children had relatively better thresholds, they probably had greater stimulation of their auditory system before implantation compared to children presenting with worse thresholds (older implanted children). However, children from both groups showed no auditory benefit from an obligatory preoperative six-week hearing aid trial. Aforementioned auditory benefit was defined by observing reactions to sound, parental assessment (e.g., LittlEARS[38]) and measuring aided thresholds. Furthermore, a recent study comparing long-term outcomes of children using conventional hearing aids or wearing CIs showed that 90 dB is already a hearing loss margin at which a CI is more beneficial regarding speech and language development compared to using hearing aids[39].

FUTURE STUDIES

Since young implanted children (< 19 months of age) all scored CVC(A) ceiling scores, current follow-up methods did not enable us to assess long-term speech perception outcomes between the youngest two age-at-implantation groups. We only showed relative differences between proportions of children reaching a ceiling CVC(A) value, whereas actual significant differences between groups could exist. These could be elucidated by newly developed tests that are not affected by ceiling effects. In addition, a wide variation of CI follow-up tests is currently used to evaluate performance, which makes comparison of outcomes between CI studies difficult[14]. Both findings indicate that there is a major need for development of additional and universal assessment methods to monitor paediatric age-at-implantation impact on speech and language performance without ceiling effects masking performance differences[40]. Colletti *et al.*[20] showed that application of the CAP - II score could be essential to identify performance differences between children implanted before 24 months of age. However, since no normed scores are available, the CAP-II could be most useful in combination with other outcomes measures

(test-battery setting). An example of a language test that could be used independently and could be less prone to be affected by ceiling effects is the digits-in-noise (DIN) test, a newly developed Dutch speech recognition test[41].

Furthermore, there is a need for large, prospective, multi-centre clinical studies that consistently assess long-term outcome measures in a standardized prospective protocolled manner to elucidate the benefits of early cochlear implantation (< 12 months of age). These outcomes could eventually shift current FDA guidelines to permit a lower implantation age than 12 months[7]. An example of such a prospective, long-term follow-up study is the Longitudinal Outcomes of Children with Hearing Impairment study (LOCHI) study[3,42]. Findings from this study regarding children using CIs showed that earlier age at activation of the first CI was associated with better language scores[43]. Furthermore, results showed clear evidence that earlier age at intervention was associated with better outcomes at five years of age[43].

CONCLUSION

Ceiling effects can mask thorough delineation of speech performance following cochlear implantation in children. However, we did show improved speech perception of the youngest age-at-implantation cohorts compared to older implanted children (after 18 months) at five-year follow-up. In addition, a larger, however not significantly different, proportion of earlier implanted children (before 13 months) reached speech perception ceiling scores (> 95% CVC(A)) compared to the proportion of children who was implanted between 13 and 18 months. Age at implantation was the only significant predictor in reaching a CVC(A) ceiling score at five-year follow-up. To assess speech perception differences initiated by different age at implantation in future studies, it is essential to develop and use alternative assessment methods without ceiling effects masking postoperative performance.

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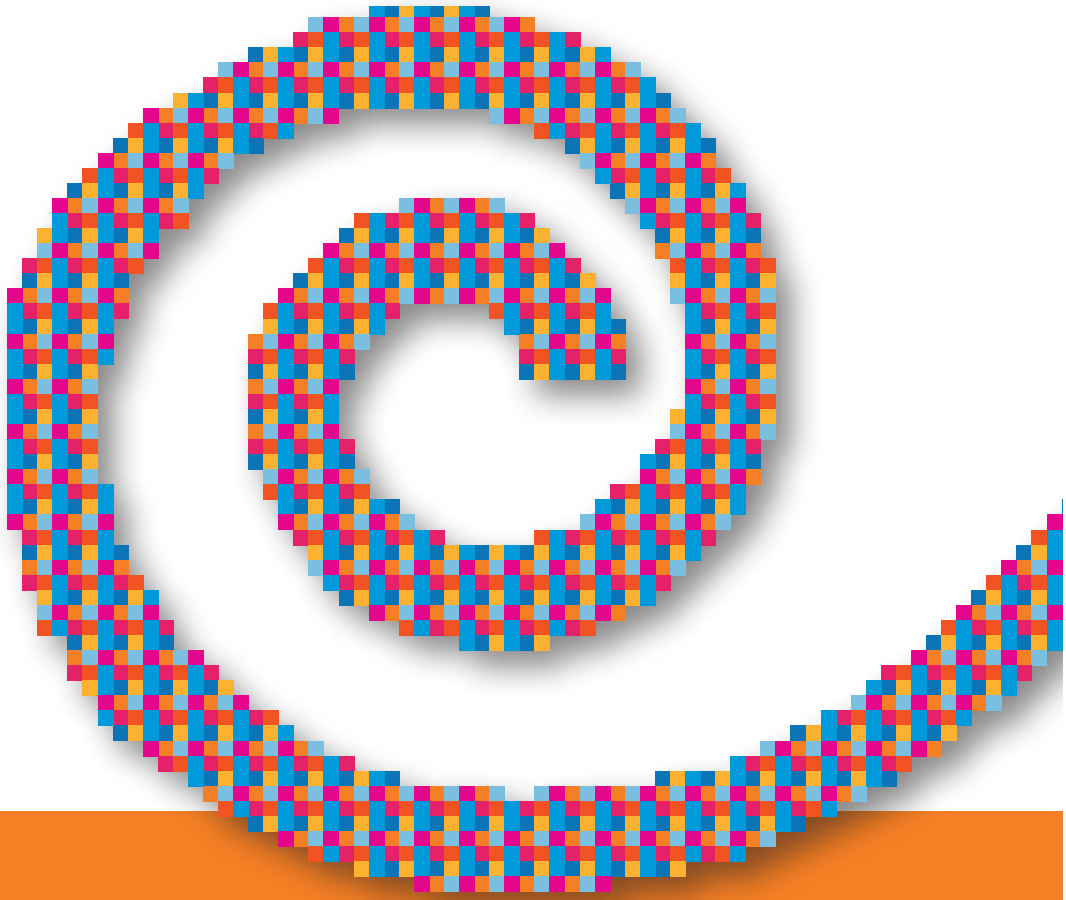
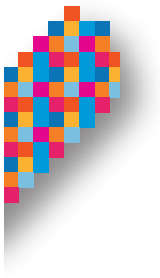
SUPPLEMENTARY MATERIALS

Categories of Auditory Performance (CAP)-II (Version 1.0 (12 Nov 2009), part of the National Paediatric Bilateral Audit, retrieved from: *http://www.bilateralcochlearimplants.co.uk/wp-content/uploads/2012/05/CAP2.pdf*, Accessed on 25-06-2015.



PART II

Definition of audiological candidacy criteria for cochlear implantation in children



Chapter 2.1

Identification of pure-tone audiologic thresholds for paediatric cochlear implant candidacy: a systematic review

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ABSTRACT

Importance

Although current guidelines recommend cochlear implantation only for children with profound hearing impairment (HI) (> 90 decibel (dB) hearing level (HL)), studies show that children with severe hearing impairment (> 70-90 dB HL) could also benefit from cochlear implantation.

Objective

To perform a systematic review to identify audiologic thresholds (in dB HL) that could serve as an audiologic candidacy criterion for paediatric cochlear implantation using four domains of speech and language development as independent outcome measures (speech production, speech perception, receptive language and auditory performance).

Evidence review

PubMed and Embase databases were searched up to June 28, 2017, to identify studies comparing speech and language development between children who were profoundly deaf using CIs and children with severe HI using hearing aids (HAs), because no studies are available directly comparing children with severe HI in both groups. If CI users with profound HI score better on speech and language tests than those with severe HI who use HAs, this outcome could support adjusting cochlear implantation candidacy criteria (e.g., lowering audiologic thresholds). Literature search, screening and article selection were performed using a predefined strategy. Four authors in two pairs executed article screening; consensus on article inclusion was reached by discussion between these four authors. This study is reported according to the PRISMA statement.

Findings

Title and abstract screening of 2822 articles resulted in selection of 130 articles for full-text review. Twenty-one studies were selected for critical appraisal, resulting in selection of ten articles for data extraction. Two studies formulated audiologic thresholds (in dB HLs) at which children could qualify for cochlear implantation: 1) at 4-frequency PTA thresholds of 80 dB HL or greater based on speech perception and auditory performance subtests and 2) at PTA thresholds of 88 and 96 dB HL based on a speech perception subtest. In eight out of 18 outcome measures, children with profound HI using CIs performed similar to children with severe HI using HAs. Better performance of CI users was shown on a picture-naming test and speech perception in noise test. Owing to large heterogeneity in study population and selected tests, it was not possible to conduct a meta-analysis.

Conclusions and relevance

Studies indicate that lower audiologic thresholds (≥ 80 dB HL) than are advised in current national and manufacturer guidelines would be appropriate as audiological candidacy criteria for paediatric cochlear implantation.

INTRODUCTION

Substantial evidence[1-3] shows that cochlear implantation is the preferred treatment for children presenting with profound hearing impairment (HI) (> 90 decibel (dB) hearing level (HL))[4]. Owing to the clinical success of cochlear implantation in both the speech and language development (SLD) and audiological rehabilitation of these children, there is discussion questioning whether children with severe HI [> 70 – 90 dB HL][4] could also benefit from cochlear implantation. Children presenting with severe or profound HI are fitted with conventional HAs for a trial period of at least three months in accordance with manufacturer guidelines[5]. If insufficient age-appropriate SLD progression occurs after the HA trial period, only the paediatric population with profound, but not severe, HI qualifies for cochlear implantation. Therefore, a consensus statement of the British Cochlear Implant Group[6] reports that paediatric cochlear implantation is appropriate in a broader range of patients than only for those who are eligible according to both National Institute for Health and Clinical Excellence (NICE)[3] and manufacturer guidelines[5]. Similarly, Lovett *et al.*[7] noted that children presenting with less profound forms of HI could benefit from CI treatment. Furthermore, Carlson *et al.*[5] already recommended that current paediatric implant candidacy criteria should be expanded.

Variation regarding audiological candidacy eligibility for cochlear implantation in children exists between manufacturer and national cochlear implantation guidelines owing to the influence of local formal legislation and reimbursement criteria. Furthermore, these differences could be explained by the difficulty to define audiologic thresholds (in dB HLs) at which cochlear implantation is superior to HAs in terms of, for example, age-appropriate SLD progression[8]. In the United States, paediatric cochlear implantation criteria vary with age and amongst each of the three CI manufacturers[5,9]. The audiologic thresholds for cochlear implantation are greater than 90 dB HL (3-frequency PTA thresholds) for children between ages 12 and 23 months and greater than 70 dB HL (Cochlear®) or greater than 90 dB HL (Advanced Bionics or MED-EL) for children older than two years (and based on scores on age-appropriate speech recognition tests)[9]. In the UK, the audiologic thresholds are ≥ 90 dB HL at frequencies of 2 and 4 kHz for all age groups[3], whereas in Belgium, the audiologic thresholds are ≥ 85 dB HL for all eligible children[10].

Although the '1 – 3 - 6 plan'[11] (e.g., screen children for hearing loss by one month of age, have a diagnostic audiologic evaluation done by three months of age, and enrol in appropriate early intervention services by six months of age) assists in establishing timely audiological intervention in children, it is essential to define which modality of hearing rehabilitation (based on audiological candidacy criteria) these children should receive to prevent auditory deprivation and ensure maximum exposure to auditory information during the sensitive period. This exposure to auditory information during the sensitive period results in SLD; therefore, we used four SLD domains (speech production (SPr), speech perception (Spe), receptive language (RL) and auditory performance (AP)) to verify the modality of hearing rehabilitation that children with severe HI should receive. Because children with severe HI could possibly benefit

from cochlear implantation[2,6,7], we performed a systematic review to identify audiologic thresholds (in dB HL) as an audiological candidacy criterion for cochlear implantation in these children. These thresholds could contribute to expanding the indication field for hearing rehabilitation using CIs and reduce ambiguity between national and manufacturer cochlear implantation guidelines.

METHODS

Search strategy

A systematic literature search was performed in collaboration with an academic librarian in the PubMed and Embase databases on May 15, 2016, and updated on June 28, 2017. Initial literature searches revealed a lack of studies directly comparing children presenting with severe HI using either CIs or HAs (mean PTA thresholds ranging between 70 and 90 dB HL). Therefore, we identified studies comparing CI users with profound HI (> 90 dB HL) to HA users with severe HI [> 70 - 90 dB HL] as the best available evidence in the current literature to answer our research question. Search terms included synonyms of children, CIs, HAs and SLD. The search syntax is provided in the Appendix. This study is reported according to PRISMA guidelines[12]. Authors can be contacted in order to receive the review protocol.

Study selection

Two independent pairs of authors (J.L.d.K. with B.M.D.V. and M.J.B.v.d.V. and L.W.M.v.K.) performed title and abstract screening. Each pair independently screened 50% of the selected articles (inclusion and exclusion criteria are provided in the Appendix). The same four authors performed subsequent full-text screening (Figure 1). Consensus on article inclusion was reached by discussion between the four authors. No language restrictions or restrictions by year of publication were applied. Studies including children with additional (cognitive) disabilities were excluded. Cross-reference check was performed to include additional relevant studies.

Critical appraisal

Aforementioned four authors performed critical appraisal of selected studies regarding 17 CAT dimensions in different pairs used in article selection (J.L.d.K. with M.J.B.v.d.V. and B.M.D.V. with L.W.M.v.K) (Table 1). A straightforward grading system was used: each CAT item was rated satisfactory (●), partly satisfactory (◖) or unsatisfactory (○) (Table 1). Consensus on critical appraisal was reached by discussion. After critical appraisal, articles were selected based on three selection criteria: domain (unaided PTA thresholds in the HA group [> 70 - 90 dB HL]), device experience duration, and report of complete baseline characteristics. To accurately compare SLD outcomes between the CI and HA groups, these three factors were required to be reported for inclusion in the review because these factors can affect SLD and should be accounted for during analysis. First, articles that fully met domain criteria in our CAT were

selected. In addition, articles that reported device experience and those with complete baseline characteristics were included. To elucidate whether study populations possibly overlapped when several articles from the same author were included, the authors of those publications were contacted. Table 1 demonstrates that when no contact with these authors could be established, the article with a highest CAT domain score was included.

Data extraction

The following data were extracted from each eligible article: the number of patients, the study design, SLD outcome measures, and results. The results were extracted and presented separately according to four SLD domains: SPr, SPe, RL and AP. Pooling of data was considered in case of homogeneity between studies regarding both study population and selected SLD tests and subtests.

RESULTS

Retrieving studies

Figure 1 shows the articles that were retrieved based on the search. The initial search of May 15, 2016, was updated on June 28, 2017, resulting in a total of 2822 articles. The update resulted in inclusion of one additional study[13] directly comparing children using CIs or HAs in which both groups had mean PTA thresholds in the range of severe HI. After exclusion of 2692 articles based on title and abstract screening, 130 articles were selected for full-text screening. Figure 1 shows that 21 articles were considered eligible for inclusion in this review. Cross-reference checking revealed no additional relevant articles.

Assessing studies

Table 1 reports the relevance and validity assessment of the 21 selected studies[7,14-32]. Relevance assessment showed that two of the 21 studies[26-27] (10 %) included HA users with severe HI. In the remaining 19 studies, the HA users had mean PTA thresholds in the range of severe HI (PTA thresholds ranged between 50 and 110 dB HL). All selected studies assessed SPr or SPe: 11 studies[13,15,17,19,20,22,26-30] assessed SPr and 11 studies[7,14,16,18,21-25,31,32] assessed SPe. In addition, five studies[15,20,22,23,32] evaluated RL and three studies[7,14,20] examined AP. One study[22] reported on three SLD domains, and three studies[7,14,22] reported on two SLD outcome measures. All included studies lacked blinding, randomization and standardization of determinants (Table 1).

Data extraction

Based on the domain selection criterion, three studies[13,26,27] were selected for data extraction. In addition, 11 of the remaining 18 studies[7,14-18,22,28-31] were selected based on either device experience and/or complete baseline characteristics. This resulted in the inclusion of 14 of the 21 (67%) initially selected studies (Figure 1). These 14 articles included four articles from

Table 1. Critical Appraisal of a Topic (CAT) Table

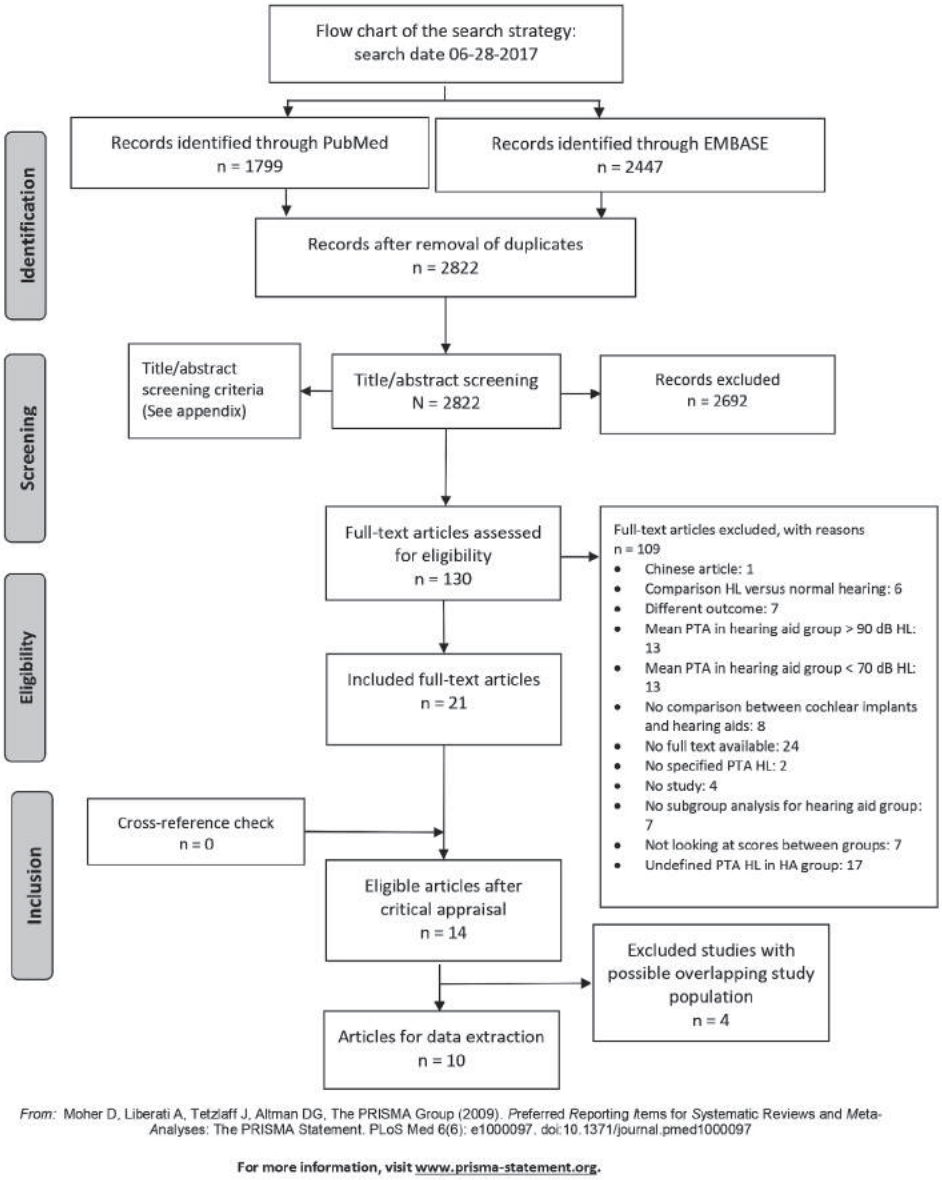
	Relevance						Validity										
Study of publication	**Domain**	**Determinant**	**Outcome:Speech production (SPr)**	**Outcome:Speech perception (SPe)**	**Outcome: Receptive language (RL)**	**Outcome: Auditory performance (AP)**	**Device (CI) experience**	**Baseline characteristics**	**Randomization**	**Blinding**	**Standardization determinant**	**Standardization outcome**	**Missing data**	**Confounding described**	**Confounding adjusted**	**Confounding by indication**	**Analysis**
Rezaei 2017 [13,a]	○	●	●	○	○	○	●	●	○	○	○	●	●	○	○	○	●
Baudonck 2010 [26,b]	●	●	●	○	○	○	●	●	○	◖	○	●	●	○	○	○	●
Most 2007 [27,c]	●	●	●	○	○	○	●	●	○	○	○	●	●	●	○	○	◖
Lovett 2015 [7]	○	●	○	●	○	●	●	●	○	○	○	●	◖	●	●	○	●
Looi 2011 [14]	○	●	○	●	○	●	●	●	○	○	○	●	●	◖	○	○	◖
Skoruppa 2014 [15]	○	●	●	○	●	○	●	●	○	○	○	●	●	◖	○	○	◖
Baudonck 2010 [28,b]	○	●	●	○	○	○	●	●	○	◖	○	●	◖	○	○	○	◖
Baudonck 2015 [29,b]	○	●	●	○	○	○	●	●	○	◖	○	●	○	◖	○	○	◖
Yang 2012 [16]	○	●	○	●	○	○	●	●	○	○	○	●	●	○	○	○	◖
Baudonck 2011 [30,b]	○	●	●	○	○	○	●	●	○	○	○	●	○	◖	○	○	◖
Most 2009 [31,c]	○	●	○	●	○	○	●	●	○	○	○	●	○	○	○	○	◖
Meister 2015 [17]	○	●	●	○	○	○	◖	●	○	○	○	●	●	●	○	○	●
Blamey 2001 [22]	○	●	●	●	●	○	◖	●	○	○	◖	●	●	◖	○	○	●
Davidson 2006 [18]	○	●	○	●	○	○	◖	●	○	○	○	●	●	◖	○	○	●
Blamey 2002 [23]	○	●	○	●	●	○	○	●	○	○	◖	●	●	◖	○	○	●
Leigh 2011 [24,d]	○	●	○	●	○	○	○	●	○	○	○	◖	◖	◖	◖	○	◖
Hammer 2015 [19]	○	●	●	○	○	○	○	●	○	○	○	●	○	○	○	○	◖
Leigh 2016 [25,d]	○	●	○	●	○	○	○	◖	○	○	○	◖	●	◖	○	○	●
Johnson 2010 [20]	○	●	●	○	●	●	○	◖	○	○	○	◖	●	◖	○	○	◖
James 2005 [21]	○	●	○	●	○	○	○	◖	○	○	○	◖	●	○	○	○	◖
Eisenberg 2004 [32]	○	●	○	●	●	○	○	○	○	○	○	●	○	◖	○	○	○

Legend:
[a]: only study in which CI users had mean PTA thresholds in the range of severe HI (88.70 dB HL)
[b]: Articles of Baudonck *et al*. possibly assessed an overlapping study population
[c]: Articles of Most *et al*. possibly assessed an overlapping study population
[d]: Articles of Leigh *et al*. possibly assessed an overlapping study population.
Bold: articles in bold were selected for data extraction.

Domain: ● range of PTA thresholds in HA group [>70-90 dB HL]; ○ range of PTA thresholds in HA group (< 70 dB HL) or (> 90 dB HL), mean 71-90 dB HL.
Determinant: ● comparison between CIs and HAs; ○ no comparison.
Outcome: ● assesed; ○ not assesed.
Device (CI) experience: ● > 1 year; ◖ mean > 1 year; ○ < 1 year or not reported.
Baseline characteristics: ● in both groups; ◖ in one group; ○ not reported.
Randomization: ● yes; ○ no.
Blinding: ● double blind ◖ single blind; ○ no blinding.
Standardization determinant: ● standardized protocol for both groups; ◖ standardized protocol for one group; ○ no or failed standardized protocol.
Standardization outcome: ● standardized test protocol; ◖ imperfect test protocol; ○ no or failed protocol.
Missing data: ○ ≤ 10% in al outcome measurements; ◖ > 10 % in one of the outcome measurements; ○ > 10% in more than one outcome measurements or not reported.
Confouding described: ● in methods; ◖ not consequently persued; ○ not reported.
Confounding adjusted: ● yes; ◖ imperfect; ○ no.
Confounding by indication: ● no; ○ yes. *Analysis*: ● results are reducible and reproducibility; ◖ roughly described; ○ not described.

Baudonck *et al.*[26,28-30] and two from Most *et al.*[27,31]. These authors were contacted; however, no data were provided to inform on possible patient cohort overlap between selected studies. To prevent reporting bias, we included the study with the highest CAT domain score for data extraction[26,27]. This process resulted in selection of ten studies[10,6-40,14,31,19] for data extraction (Figure 1).

Figure 1. Flow chart demonstrating the selection of included studies.



Legend: dB = decibel; HL = hearing level; PTA = pure-tone average.

Data presentation

Extracted data from the ten included studies reported according to SLD domain are included in Tables 2 to 5.

Sample sizes contained CI users with profound HI (> 90 dB HL) and HA users with severe HI [mean unaided PTA thresholds of > 70 - 90 dB HL]. Four potential factors can influence the outcome of CI and HA treatment and concomitant SLD: the age at implantation[33], device experience duration, the CI device type and the type of HA processing strategies.

Most included studies[7,13-15,18,22,26,27] reported device experience duration and the CI device type; the latter two factors were described in only four studies[18,22,26,27]. None of the included studies standardized the type of hearing device for children presenting with severe HI, and only one study[22] standardized the type of CI. Because the findings as noted in Tables 2 to 5 indicate large heterogeneity regarding both study population (e.g., HI level, duration of device use) and selected SLD tests and subtests, we were unable to accurately pool the results of included studies and perform a meta-analysis.

SLD domain 1: Speech production (SPr)

Five included studies[13,15,17,22,26] assessed SPr using five different validated tests (Table 2)[22,34-37]. Four studies[13,15,17,22] reported no SPr performance differences between CI or HA users. Although the CI group scored significantly better on four of the 15 subtests ($p < .05$), Baudonck *et al.*[26] reported no SPr difference between the CI and HA groups on 11 of their 15 SLD subtests (73%). None of the studies found better SPr results for the HA group.

SLD domain 2: Speech perception (SPe)

Six studies[7,14,16,18,22,27] reported SPe results measured with seven different SLD tests[14,16,27,38-42] (Table 3). Three studies[14,22,27] did not report significant SPe differences between CI and HA users. However, one of these studies[27] did also observe a significantly better SPe performance for the HA group regarding two out of the four suprasegmental features.

Contrarily, three studies[7,16,18] reported better outcomes for CI compared with HA users. Yang *et al.*[16] reported a significant better performance for CI users on both SNRs (0 and 10 dB), while assessing SPe in noise (SPIN) at different signal to noise ratios (SNRs).

In addition, CI users can be expected to score significantly better than HA users on the LNT[41] at PTA thresholds of 88 and 96 dB HL at a speech perception level of 50 dB[18]. Ultimately, we identified a study[7] that defined audiologic thresholds at which bilateral CIs (biCIs) users outperformed HA users: 4-frequency PTA thresholds of 79 dB HL were associated with an odds of 4:1 of performing better with CIs than with HAs on the Chear Auditory Perception Test (CAPT[42]).

SLD domain 3: Receptive language (RL)

Two studies[15,22] assessed RL. Table 4 reports that studies conducted three different validated tests for RL[43-45] assessment and found no significant difference between CI and HA users.

Table 2. Results on Speech Production (Spr) Tests.

Study	N	dB HL HA mean ± SD (range)	MAI y;m ± SD (range)	DE y;m ± SD (range)	Tests (reference)	Results CI	HA	*p*-value	Conclusion
Baudonck 2010 [26]	44 (61)	83 (72-90)	4;2 (0;8-10;11)	> 1	***Picture naming test*** [34]				
					Phonetic (errors)				
					Omissions/consonants produced	2%	4%	=.026	
					Omissions/consanants in error	10%	15%	=.040	
					5 other subtests	NR	NR	>.05	
									CI > HA 4/15 subtests
					Phonological (errors)				CI ~ HA 11/15 subtests
					Stopping	0%	5%	=.01	
					5 other subtests	NR	NR	>.05	
					Other (errors)				
					Substitution s/ʃ	5%	9%	=.01	
					1 other subtest	1%	4%	=.08	
Blamey 2001 [22]	87 (87)	78 ± 17 (40-103)	3.5 ± 1.5 (1.2-8.2)	4.2 ± 2.0 (.9-9.2)	***Overall intelligibility* (correct produced)** [22]				
					Unintelligible words	5.8% (6.7%)	2.7% (4.6%)	>.05	CI ~ HA
					Phonetically correct words	39.4% (13.6%)	40.5% (14.9%)	>.05	CI ~ HA
					Monophthongs	81.3% (9.1%)	83.3% (10.6%)	>.05	CI ~ HA
					Diphthongs	74.6% (13.1%)	72% (15.6%)	>.05	CI ~ HA
					Consonants	68.7% (10.5%)	69% (10.5%)	>.05	CI ~ HA
Meister 2015 [17]	52 (100)	> 60-80	1;11 ± 1	2;2 ± 1;2	*FAPCI score list* [35]	77 ± 26	74 ± 24	>.05	CI ~ HA
Rezaei 2017 [13,a]	30 (45)	88.33	NR	6;9	*Speech intelligibility* [36]	72.31 ± 23.42	68.94 ± 17.57	=.901	CI ~ HA
Skoruppa 2014 [15]	27 (48)	71 ± 11 (50-91)	3;1	4;8 ± 1;1 (3;3-5;9)	*DEAP* [37]	No mean score provided		>.05	CI ~ HA

Legend: [a] the only study in which the CI users had a mean PTA thresholds in the range of severe HI (88.70 dB HL); CI: children with cochlear implants; dB: decibel; DE: device (CI) experience; DEAP: Diagnostic Evaluation of Articulation and Phonology; FAPCI: Functioning after Paediatric Cochlear Implantation; HA: children with hearing aids; HL: hearing level; m: months; MAI: mean age at implantation; N: sample size; ns: not significant; NR; not reported; SD: standard deviation; y: years.

Table 3. Results on Speech Perception (Spe) tests.

Study	N	dB HL HA mean ± SD (range)	MAI y;m ± SD (range)	DE y;m ± SD (range)	Tests (reference)	Results CI	HA	*p*-value	Conclusion
Blamey 2001 [22]	87 (87)	78 ± 17 (40-103)	3.5 ± 1.5 (1.2-8.2)	4.2 ± 2.0 (.9-9.2)	***CNC*** [38]	No mean score provided		>.05	CI ~ HA
					BKB [39]	No mean score provided		>.05	CI ~ HA
Looi 2011 [14]	17 (38)	75 ± 11 (55-85)	5.3 ± 2.2 (3.2-8.7)	7;10 ± 2;10 (2;4-11;2)	***CNC*** [38]				
					words (% correct)	71.87 ± 14.79	65.39 ± 11.54	>.05	CI ~ HA
					phonemes (% correct)	87.33 ± 7.95	82.34 ± 7.13	>.05	CI ~ HA
					HINT **(sentences % correct)** [40]				
					S0	92.97 ± 11.56	96.64 ± 4.64	>.05	CI ~ HA
					S0N0	88.12 ± 13.50	93.39 ± 5.68	>.05	CI ~ HA
					S0CI	84.87 ± 15.77	91.22 ± 6.70	>.05	CI ~ HA
					S0NHA	90.12 ± 11.05	92.25 ± 8.53	>.05	CI ~ HA
Davidson 2006 [18]	52 (52)	79.4 ± 9.9 (60-98)	5.0 ± 3.0 (1.6-13.4)	3.6 ± 1.3 (1.3-6)	***LNT*** [41]				
					% correct at 50 dB SPL	at 68.5 - 85 dB HL CI ~ HA			CI > HA at 88-96 dB HL
						at 88 - 96 dB HL CI > HA		<.05	CI > HA at 97-113 dB HL
					% correct at 70 dB SPL	at 82.1 - 90.5 dB HL CI ~ HA			
						at 97 - 113 dB HL CI > HA		<.05	
Lovett 2015 [7]	71 (71)	70.1 ± 16.6	1;10 ± 0;9.5	3;6 ± 0;11	***CAPT*** [42]				
					4-frequency PTA	Odds 4:1 CI > HA at 79 dB HL			Bilateral CI implantation
					3-frequency PTA	Odds 4:1 CI > HA at 78 dB HL			from 80dB
					2-frequency PTA	Odds 4:1 CI > HA at 83 dB HL			
Most 2007 [27]	20 (30)	77 ± 4.96	7;11 ± 3.14 (3;6-12;4)	4;2 ± 2;4 (1;0-8;0)	***% correct response*** [27]				
					word pattern	97.05 ± 4.35	99.11 ± 1.42	>.05	CI ~ HA
					word emphasis	72.92 ± 15.8	88.33 ± 11.49	>.05	CI ~ HA
					syllable stress	20.83 ± 27.56	73.33 ± 14.59	<.05	CI < HA
					intonation	42.5 ± 27.55	89.99 ± 14.98	<.05	CI < HA
Yang 2012 [16]	34 (34)	84.58 ± 11.85	3.91 ± 2.69	9;5 ± 1;5	***SPIN % correct*** [16]				
					SNR 10 dB	49.44 ±13.90	33.33 ± 14.73	<.05	CI > HA
					SNR 0 dB	31.95 ±15.72	19.52 ± 6.67	<.05	CI > HA

Legend: BKB: Bench-Kowal-Bamford; CAPT = Chear Auditory Perception Test; CI: children with cochlear implants; CNC: Consonant-Nucleus-Consonant; dB: decibel; DE: device (CI) experience; HA: children with hearing aids; HINT: hearing in noise test; HL: hearing level; m: months; LNT: Lexical Neighbourhood Test; MAI: mean age at implantation; N: sample size; ns: not significant; PTA: pure-tone average; SD: standard deviation; SNR: signal-to-noise ratio; SPIN: Mandarin Speech Perception in Noise; y: years.

Table 4. Results on Receptive Language (RL) tests.

Study	N	dB HL HA mean ± SD (range)	MAI y;m ± SD (range)	DE y;m ± SD (range)	Tests (reference)	Results			
						CI	HA	*p*-value	Conclusion
Blamey 2001 [22]	87 (87)	78 ± 17 (40-103)	3.5 ± 1.5 (1.2-8.2)	4.2 ± 2.0 (.9-9.2)	***PPVT*** [43]	0.63	0.65	ns	CI ~ HA
					CELF [44]	0.56	0.59	>.05	CI ~ HA
Skoruppa 2014 [15]	27 (48)	71 ± 11(50-91)	3;1	4;8 ± 1;1(3;3-5;9)	***BPVS*** [45]	No mean score provided		ns	CI ~ HA
						No mean score provided			

Legend: BPVS: British Picture Vocabulary Scale; CELF: Clinical Evaluation of Language Fundamentals; CI: children with cochlear implants; dB: decibel; DE: device (CI) experience; HA: children with hearing aids; HL: hearing level; m: months; MAI: mean age at implantation; N: sample size; ns: not significant; PPVT: Peabody Picture Vocabulary Test; SD: standard deviation; y: years.

Table 5. Results on Auditory performance (AP) tests.

Study	N	dB HL HA mean ± SD (range)	MAI y;m ± SD (range)	DE y;m ± SD (range)	Tests (reference)	Results			
						CI	HA	*p*-value	Conclusion
Looi 2011 [14]	17 (38)	75 ± 11(55-85)	5.3 ± 2.2 (3.2 – 8.7)	7;10 ± 2;10 (2;4-11;2)	**PRT subtest** [47]				
					1 octave	83.30%	95.42%	<.05	CI < HA
					½ octave	77.60%	88.54%	<.05	CI < HA
					¼ octave	67.45%	79.11%	>.05	CI ~ HA
Lovett 2015 [7]	71 (71)	70.1 ± 16.6	1;10 ± 0;9.5	3;6 ± 0;11	**TDT** [46]				
					4-frequency PTA				
					noise	Odds 4:1 CI > HA at 86 dB HL			BiCI implantation from 80dB
					babble	Odds 4:1 CI > HA at 76 dB HL			
					3-frequency PTA				
					noise	Odds 4:1 CI > HA at 86 dB HL			
					babble	Odds 4:1 CI > HA at 75 dB HL			
					2-frequency PTA				
					noise	Odds 4:1 CI > HA at 92 dB HL			
					babble	Odds 4:1 CI > HA at 80 dB HL			

Legend: BiCi: bilateral cochlear implants; CI: children with cochlear implants; dB: decibel; DE: device (CI) experience; HA: children with hearing ads; HL: hearing level; m: months; MAI: mean at of implantation; N; sample size; ns: not significant; PRT: pitch ranking task; PTA: pure-tone average; SD: standard deviation; TDT: toy discrimination test; y: years.

SLD domain 4: Auditory performance (AP)

Two studies[7,14] compared AP between CI and HA users (Table 5). One of these studies[7] aimed to define a HI level associated with better AP comparing CI to HA treatment; 4-frequency PTA thresholds of 76 and 86 dB HL were associated with an odds of 4:1 of performing better with a CI than with HAs on the Toy Discrimination Test (TDT[46]), in noise and regarding babbling, respectively[7]. The other retrieved study[14] used pitch-ranking tests[47] to compare AP between CI and HA users. The HA group performed significantly better when pitch differences of 1 or ½ octave were used[14].

DISCUSSION

Summary of main results

This systematic review found lower audiologic thresholds for cochlear implantation in children than are advised in current guidelines: children with 4-frequency PTA thresholds of ≥ 80 dB HL could qualify for cochlear implantation based on SPe and AP subtests and CI users scored significantly better than HA users based on SPe subtests at PTA thresholds of 88 and 96 dB HL. Outperformance of CI users was shown on a SPr test (picture naming test)[26] and a SPe test (SPIN)[16]; HA users performed superiorly on a SPe test (percentage correct)[27] and an AP test (pitch ranking task)[14].

Several children with profound HI treated with CIs performed similar to those presenting with severe HI who were using HAs. However, the latter finding was documented for only 44% of the reported tests. This result could indicate that children with severe HI using HAs could perform superiorly (audiologically) using CIs instead of HAs. Aforementioned thresholds are lower than those currently recommended by national and manufacturer cochlear implantation guidelines (e.g., American 3-frequency PTA thresholds of ≥ 90 dB HL[9], British thresholds of ≥ 90 dB HL at frequencies of 2 and 4 kHz[3], and Belgian thresholds of ≥ 85 dB HL[10]).

Consistent with our findings regarding most SLD outcomes, no SPr difference between CI and HA users was found in the study of Rezaei *et al.*[13], which was the only identified investigation directly comparing children using CIs or HAs in which both groups had mean PTA thresholds ranging between 70 and 90 dB HL. Although included studies were inconsistent in the applied preoperative and postoperative tests to assess SLD, which is a common problem across paediatric CI studies[48], our results suggest that children with severe HI could benefit from CIs in reaching more optimal SLD than using HAs alone.

Comparison with other reviews

Although the study of Leigh *et al.*[25] was excluded because the authors did not report device experience duration, the study showed results to consider while we evaluated our data. The study reported that children with PTA thresholds of 60 dB HL have a 75% chance, and patients with PTA thresholds of 82 dB HL have a 95% chance, of benefit with CI treatment over using conventional bilateral HAs[24]. The audiologic thresholds reported by Lovett *et al.*[7],

Davidson[18] and Leigh *et al.*[25] all fall into the range of severe HI. Hence, these thresholds could suggest that some children with severe HI could benefit from CI treatment.
Bittencourt *et al.*[2] reported that CI treatment is beneficial compared to treatment with conventional HAs for children with severe to profound HI. The authors[2] based their conclusions on SPe and developmental data. Our study compared four SLD domains between both groups and specified results based on severe HI. Furthermore, only two out of the 12 studies selected by Bittencourt *et al.*[2], were relevant for inclusion in our review[26,31]. Therefore, our paediatric cochlear implantation candidacy analyses could be more precise, and thus, more easily used for implementation in national and manufacturer cochlear implantation guidelines.

Overall completeness and applicability of evidence

Because this study identified lower audiologic thresholds for cochlear implantation in children than are advised in current national and manufacturer guidelines, children with severe HI who are currently treated with HAs could potentially reach more optimal SLD when CIs are used. This conclusion is further supported by results from a non-comparative and retrospective study[5] in which children treated with CIs, who had less severe HI than specified in current CI guidelines, also had significant SLD improvement after cochlear implantation. Furthermore, Lovett *et al.*[7] stated that children should be CI candidates if their 2-frequency PTA thresholds are ≥ 85 dB HL or their 4-frequency PTA thresholds are ≥ 80 dB HL. However, paediatric cochlear implantation criteria are not merely based on audiological candidacy criteria (the severity of HI), but also entail factors as cognitive ability, intelligence, comorbidities, parental motivation, social situation, anatomy of the cochlea and the benefit the child obtains from HAs[3]. Therefore, the results of this review do not support standardized CI surgery in children presenting with severe HI, but summarize available evidence to more accurately define the lower audiological candidacy criteria (audiologic thresholds) for paediatric CI candidacy that currently vary between both national and manufacturer paediatric cochlear implantation guidelines. Additional studies, such as a systematic review of children who received CIs based on expanded candidacy criteria (HI ranging between 70 and 90 dB HL), could provide additional evidence to further support adjustment of audiological candidacy criteria. The first step in reaching superior guideline alignment could be to select the same number of frequencies at which the HL is defined, because 2-, 3- and 4-frequency PTA levels[3,9] are currently used in guidelines. Second, the audiologic thresholds provided as audiological candidacy criteria for paediatric cochlear implantation resulting from this literature review could attribute to expanding the indication field for hearing rehabilitation using CIs and assist in better international alignment between national and manufacturer guidelines.

Limitations

Speech and language development consists of multiple sensitive periods of various speech and language skills[49]; therefore, it is difficult to assess this complex behaviour as one outcome measure. By assessing four different SLD outcome measures, we aimed to assess language development as completely and accurately as possible.

Studies comparing SLD outcomes of CI users with profound HI with those of HA users with severe HI could be affected by confounding by indication because the CI group presented with a relative higher level of HI. Hence, HA users with severe HI could benefit from their residual hearing. However, the CI users with profound HI were stimulated with CIs instead of HAs, resulting in relatively superior auditory stimulation, possibly leading to relatively superior SLD progression. A search update led to inclusion of a study that lacked this type of bias; this study directly compared children using CIs or HAs in which both groups had mean PTA thresholds in the range of severe HI. However, only one out of the four SLD domains of interest was reported as an outcome measure in this study, therefore, the initially included studies were essential to completely answer our research query. Finally, owing to large heterogeneity in study population and selected tests, we were unable to conduct a meta-analysis.

CONCLUSION

Studies indicate potential benefit for lowering audiologic threshold criteria for paediatric cochlear implantation (≥ 80 dB HL) compared with current manufacturer guidelines: children with 4-frequency PTA thresholds of ≥ 80 dB HL could qualify for cochlear implantation based on SPe and AP subtests, and CI users scored significantly better than HA users based on SPe subtests at PTA thresholds of 88 and 96 dB HL. Considering four selected SLD domains (SPr, SPe, RL, and AP), children with profound HI treated with CIs performed similarly to children presenting with severe HI using HAs on only 44% of the reported tests, which could indicate that HA users with severe HI could perform better with CIs.

Overall results indicate that the SLD of children presenting with severe HI could benefit from cochlear implantation; therefore, our results could contribute to expanding the indication field for hearing rehabilitation using CIs and reducing ambiguity between national and manufacturer cochlear implantation guidelines.

APPENDIX

Search syntax

Pubmed

((((child*[Title/Abstract]) OR infant*[Title/Abstract]) OR toddler*[Title/Abstract]) OR infant[MeSH Terms]) OR child[MeSH Terms])))) AND (((((((cochlear implant*[Title/Abstract]) OR Cochlear prosth*[Title/Abstract]) OR Cochlear implants[MeSH Terms]) OR Cochlear implantation[MeSH Terms])) AND (((((((((Hearing aid*[Title/Abstract]) OR Ear mold*[Title/Abstract]) OR Ear mould*[Title/Abstract]) OR Earmould*[Title/Abstract]) OR Earmold*[Title/Abstract]) OR Hearing device*[Title/Abstract]) OR Deaf aid*[Title/Abstract]) OR Listening device*[Title/Abstract]) OR Hearing Aids[MeSH Terms])))) AND ((((((language[Title/Abstract]) OR speech[Title/Abstract]) OR Semantic Pragmatic Disorder[Title/Abstract]) OR verbal[Title/Abstract]) OR Language Development Disorders[MeSH Terms]))

Embase

(child*:ab,ti OR toddler*:ab,ti OR infant*:ab,ti OR 'child'/exp OR 'infant'/exp) AND (cochlear:ab,ti AND (implant*:ab,ti OR prosth*:ab,ti) OR 'cochlear implantation'/exp OR 'cochlea prosthesis'/exp) AND (hearing:ab,ti AND aid*:ab,ti OR (ear:ab,ti AND mold*:ab,ti) OR (ear:ab,ti AND mould*:ab,ti) OR earmold*:ab,ti OR earmould*:ab,ti OR (hearing:ab,ti AND device*:ab,ti) OR (aid*:ab,ti AND deaf:ab,ti) OR (device*:ab,ti AND listening) OR 'hearing aid'/exp) AND (language:ab,ti OR speech:ab,ti OR 'semantic pragmatic disorder':ab,ti OR verbal:ab,ti OR 'developmental language disorder'/exp)

Inclusion criteria

Screening criteria title / abstract

Inclusion

- Children
- Studies comparing cochlear implants and hearing aids
- Cochlear implant group with profound hearing loss [> 90 dB]
- Hearing aid group with severe hearing loss [> 70-90 dB]
- Include study if the level of hearing loss in the hearing aid group is not specified

Exclusion

- Diagnostic, prognostic, etiological studies
- Animal studies
- Adults
- No comparison between cochlear implant and hearing aids
- (Systematic) review, meta-analysis
- Letter to the editor
- Conference proceedings
- Case series (less than five patients in cochlear implant of hearing aid group)
- Full-text not available
- Language other than: English, Dutch, German, Polish or Portuguese

Screening criteria full text

Inclusion

Hearing aid (sub)group analysis with severe hearing loss [> 70-90 dB]

Exclusion

- In the hearing aid group, all children have profound hearing loss
- In the hearing group the level of hearing loss is not defined
- In the hearing aid group, no separate analysis was performed for children with severe hearing loss

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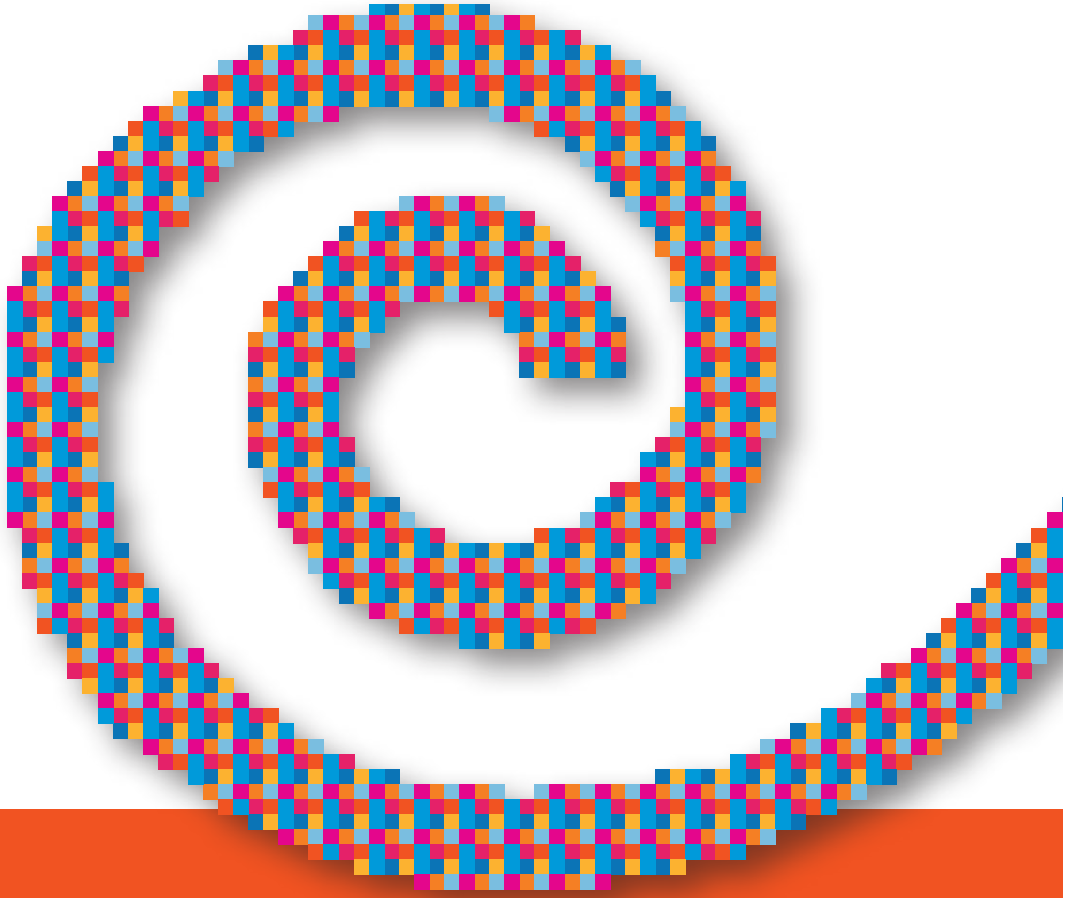
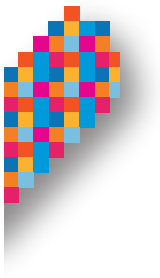


PART III

Definition of the surgical and anesthetic strategy for cochlear implantation in children



Chapter 3.1

Systematic review on surgical outcomes and hearing preservation for cochlear implantation in children and adults

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Hanneke Bruijnzeel, Kaspar Draaisma, Roderick W.J. van Grootel, Inge Stegeman, Vedat Topsakal, Wilko Grolman

ABSTRACT

Objective

The Mastoidectomy with Facial Recess Approach (MFRA) is considered the reference standard for cochlear implantation. The SupraMeatal Approach (SMA) was developed more recently and does not require mastoidectomy, which could influence postoperative outcomes. We aim to identify the optimal operative approach for cochlear implantation based on postoperative complications and hearing preservation in children and adults.

Data sources

PubMed, Embase, Scopus and Google Scholar.

Review Methods

Studies comparing the MFRA and the SMA in children and adults were eligible for inclusion. Original reports with moderate relevance and validity were included. Relevance and validity were assessed using a self-modified critical appraisal tool. This review was reported in accordance with PRISMA guidelines.

Results

We retrieved 294 citations. Only retrospective, non-randomized studies were identified (Level 3 evidence). Six articles were selected for full-text inclusion and four articles were selected for data extraction. No article found a significant difference between the MFRA and the SMA with respect to postoperative complications in children and adults. One study found a significantly ($p < .023$) higher paediatric MFRA mastoiditis rate; however, meta-analysis did not indicate an overall effect. Hearing preservation was reported only in adults and outcomes between techniques did not differ.

Conclusion

No evidence was noted for lower complication rates or improved hearing preservation between the MFRA and the SMA for cochlear implantation in children and adults. Paediatric data were available for children implanted above the age of 24 months only. Level 1 evidence is needed to resolve the uncertainty regarding differences in postoperative outcomes between the MFRA and the SMA in paediatric and adult patients.

INTRODUCTION

The reference surgical approach for cochlear implantation is the Mastoidectomy with Facial Recess Approach (MFRA)[1-3]. This approach requires a mastoidectomy and uses the facial recess for CI electrode passage from the mastoidectomy to the middle ear[4]. Because of narrow middle ear access and need for surgical precision[4], numerous other approaches without mastoidectomy have been explored[5-12], such as the SupraMeatal Approach (SMA), developed in 1999[12]. Through suprameatal tunnel formation, the mastoid remains largely intact in the SMA. In an attempt to surgically open the middle ear, eardrum manipulations and/or drilling near the incus can result in conductive hearing loss. Postelmans *et al.*[13] explained that the SMA could induce conductive hearing loss due to incus damage or implanted array contact. In contrast, incus injury can be avoided in the MFRA.

Nonetheless, while incus contact can be prevented, MFRA mastoid removal could potentially damage the facial nerve or chorda tympani[14-17]. However, both complications are rarely reported (between 0.1 - 1.1%) and in cases where patients are affected, the majority of them completely recover[18]. Facial nerve damage is even less frequently reported regarding the SMA[11,13]. However, the chorda tympani could be at risk when opening the tympanomeatal flap to attain middle ear access for cochleostomy[9,12].

Different approaches to access the cochlea can be elected in either surgical approach. A cochleostomy or round window (RW) approach could affect residual hearing maintenance. Although Postelmans *et al.*[13] suggested that the SMA provides better CI electrode exposure due to direct middle ear access, the endaural approach of the SMA can compromise clear visualization of the intra-cochlear structures and therefore, hinder the application of soft surgery techniques[19]. This collection of techniques first described by Lehnhardt[19] contains a small cochleostomy and considerate electrode insertion that can establish residual hearing preservation (HP) during cochlear implantation.

Due to an intact mastoid, postoperative infections could be more likely to occur following the SMA. Especially in children with underdeveloped anatomy, inadequate fluid drainage and acute otitis media (AOM) can develop. Tange *et al.*[20] compared mastoids of 79 patients operated by the SMA on preoperative and postoperative CT scans. Although the mastoid cavity did not show any sign of mucosal reaction in 96% of patients, in one child (11% of the included children) opacification of the middle ear and the entire mastoid was observed six months postoperatively[20].

Shin *et al.*[21] reported on the likelihood of developing postoperative AOM following cochlear implantation in children with and without a history of otitis media (OM). The MFRA was used in all included studies (n = 6) in this literature review. Although children with preoperative OM or ventilation tubes showed a trend toward relatively more postoperative AOM than patients without preoperative OM or ventilation tubes, OM prone children tended to develop less AOM following the MFRA[21]. The authors[21] concluded that MFRA could be performed in preoperatively treated OM children, expecting that postoperative AOM-related complication occurrence could decrease. Due to aforementioned benefits and risks of both surgical

approaches, we aim to review the literature to identify studies comparing surgical outcomes of both techniques. Specifically, we assess superiority regarding postoperative complications and HP specified for children and adults.

METHODS

Retrieving studies

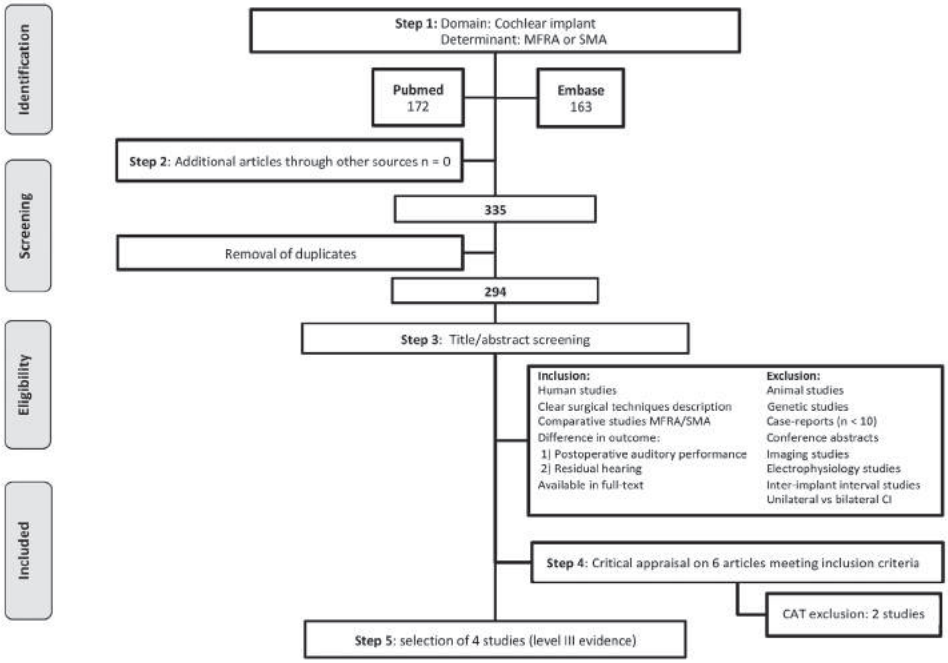
A search strategy was composed containing CI synonyms and synonymous words for both surgical techniques (Appendix). PubMed and Embase databases were used to identify studies comparing surgical outcomes (1975 to December 14, 2014). Google Scholar and Scopus were used for cross-reference checking to retrieve studies not identified by the initial search. No language restrictions were applied. This systematic review was reported in accordance with PRISMA guidelines[22].

Two reviewers (K.D., R.G.) independently screened titles and abstracts of retrieved citations according to predefined inclusion and exclusion criteria (Figure 1). Migirov *et al.*[23] showed that the paediatric cochlear implantation and postoperative infection formation interval was on average 9.37 months (SD: 7.05). Therefore, a minimal follow-up of ten months was deemed essential to include studies in the current review. Consensus between reviewers was reached by discussion. No review protocol was used. Review methodology is depicted in a five-phase diagram (Figure 1).

Assessing studies

Three authors (H.B., K.D., R.G.) performed independent critical appraisal of articles meeting inclusion criteria. They performed critical appraisal by the model proposed by Reisch *et al.*[24]. These criteria are designed to evaluate therapeutic studies and facilitate recommendation for patient management in any area of medicine[24]. Critical appraisal consisted of 11 separate dimensions assessing relevance and validity. Relevance describes the manner of comparison between surgical techniques and validity assesses if studies accurately measured proposed comparison variables. Validity assessment clarifies publication bias and selective reporting in studies. Each dimension was dichotomously scored indicated by a clear (yes) or unclear (no) report of that specific dimension. Relevance consisted of four dimensions (1 - 4) and validity of six dimensions (5 - 11) (Table 1A and Table 1B). Relevance dimensions consisted of 17 sections (maximum, 16 points). The reviewers considered 0 - 5 points as low, 5 - 10 points as medium and 10 - 16 points as high relevance (Table 1A). Validity assessment consisted of 20 dimensions (maximum, 19 points). Studies with 0 - 6 points were regarded as having low validity; 6 - 12 medium validity; and 12 - 19 points, high validity. When an item was not reported, the dimension was rated unspecified (U). Disagreements between authors (H.B., K.D., R.G.) reached consensus by discussion. Studies with low relevance and/or low validity were excluded for additional analysis.

Figure 1. Inclusion and exclusion criteria to select studies reporting on the difference in outcome between the mastoidectomy with facial recess approach (MFRA) and the suprameatal approach (SMA).



Legend: CAT = critically appraised topic; CI = Cochlear Implant; MFRA = mastoidectomy with facial recess approach; SMA = suprameatal approach.

Data extraction

Three reviewers (H.B., K.D., R.G.) independently extracted the following information from included articles: number of patients, study design, patient characteristics, selected outcome measures, follow-up and results. Raw data from original articles were extracted. The authors performed heterogeneity assessment to evaluate whether data could be pooled in a meta-analysis. Comprehensive Meta-analysis (version 2.2.046, Biostat. Englewood, New Yersey) was used to perform heterogeneity analysis and pool study results when I^2 was < 50%[25].

RESULTS

Retrieving studies

Literature search yielded 294 articles from which six were considered eligible for data extraction (Figure 1). Cross-reference checking did not result in the identification of additional articles. One author[13,26] was contacted to obtain additional information regarding included paediatric patients.

Assessing studies

1. Relevance

All articles eligible for data extraction were of moderate relevance (Table 1A). Five studies[13,16,23,26,27] had a retrospective (R) design and the remaining design was unspecified (U). Therefore, no study selected subjects prior to treatment (Table 1A: 2). In addition, none of the studies reported whether an a priori power calculation was performed or consecutive patients were enrolled (Table 1: 3A). A minimal set of baseline characteristics was described in most studies: one study[26] failed to mention the age of included subjects, only four studies[4,16,23,27] specified sex (Table 1A: 4A.3) and deafness aetiology was provided in two studies[13,16]. Residual hearing level was assessed in only one study[26] (Table 1A: 4A.7).

2. Validity

Four studies[13,23,26,27] contained moderate (M) validity and two studies[4,16] low (L) validity (Table 1B). Description of provided care and outcome measurement was poor in the majority of studies: only two studies[23,26] used standardized evaluation methods (Table 1B: 9C), and two studies did not clarify whether all patients received similar care[4,26] (Table 1B: 7A). Five studies[13,16,23,26,27] reported follow-up and two studies[4,16] did not report whether follow-up was consistent (Table 1B: 8B). None of the studies defined loss to follow-up; however, one study[26] did describe patient characteristics of lost to follow-up patients (Table 1B: 8D). The four studies carrying a moderate (M) relevance and a moderate (M) validity were eligible for inclusion in this review (Figure 1). All included studies consisted of Level 3 evidence[28]. All studies[13,23,26,27] clearly identified, used and interpreted reported tests to draw conclusions supported by their data analysis (Table 1B - 10B, 10D, 11B).

3. Data Extraction

Migirov *et al.*[23,27] conducted two studies reporting on postoperative complications in paediatric patients (AOM, secretory OM (SOM) and mastoiditis). Similar patients cohorts were assessed in both studies[23,27]. Patients operated by the SMA were sampled more recently (1999 - 2003) in the study[23] reporting on AOM and mastoiditis compared to the SOM study (1999 - 2001)[27]. Postelmans *et al.*[13] compared postoperative complications in children and adults and reported adult residual hearing six months postoperatively[26]. Extracted data from aforementioned studies originated from the same patient cohort although retrospective sampling of one study[26] was more recent (2010 vs. 2008) (Table 2). Since different complications (AOM, SOM) and postoperative outcomes (complications, residual hearing) were assessed, we decided to include all four studies. The results were discussed according to analyzed outcome measures: postoperative complications, HP and surgery time (Table 2).

4. Complications in children

Three studies[13,23,27] reported on postoperative complications in children. All included studies[13,23,27] registered complications of children over one year postoperatively (Table 2).
Migirov *et al.*[23,27] assessed postoperative SOM and AOM occurrence in 142 and 234 children, respectively. The authors[23] did not identify a significant postoperative SOM difference between

Table 1A. Critical Appraisal of a Topic (CAT) based on relevance of studies reporting on the difference in outcome between the MFRA and the SMA.

Relevance						
Included studies for Critical Appraisal of a Topic (CAT)	**Migirov *et al.* (2006) ORL68(3)**	**Migirov *et al.* (2006) IJPORL**	**Postelmans *et al.* (2009)**	**Postelmans *et al.* (2014)**	**Migirov *et al.* (2006) ORL 68(4)**	**Zernotti *et al.* (2012)**
1. Purpose of study						
A Statement of purpose given	●	●	●	●	●	●
B Outcome variables clearly defined	●	●	●	●	●	●
C Sources of support for study specified	○	○	●	●	○	○
D Magnitude of difference in outcome to be identified described	●	●	●	○	○	○
2. Experimental design						
Selection of subjects: planned prior to treatment	○	○	○	○	○	○
Prospectively (P), retrospectively (R), according to outcome (ATO), unspecified (U)	R	R	R	R	R	U
3. Sample size determination						
A Sample size determined by: predetermined number of subjects (a priori power calculation), sequential experimental design *or* independent committee (any other: score = 0)	○	○	○	○	○	○
B Total number of subjects specified	●	●	●	●	●	●
4. Description and suitability of subjects						
A Entry criteria:						
1. Age of subjects given	●	●	●	○	○	○
2. Type of cochlear implant given	○	○	●	●	○	○
3. Gender of subjects given	●	●	○	○	●	●
4. Socioeconomic status given	○	○	○	○	○	○
5. Comorbidities given	○	○	○	○	○	○
6. Aetiology of deafness given	○	○	●	○	●	○
7. Residual hearing of subjects given	○	○	○	●	○	○
B Eligible subjects who refused to participate are adequately described	U	U	U	U	U	U
C Subjects for this study are suitable for posed research question	●	●	●	●	●	●
Overall relevance	M	M	M	M	M	M

children operated by the MFRA and the SMA. No retrospective stratification was applied for the significantly different male:female ratio between groups (MFRA 1.2:1.0 vs. SMA 3.8:1.03 (p =.006))[23]. Follow-up time was 60.5 months (SD: 27.1) for children operated by the MFRA and 36.2 months (SD: 8.0) for children operated by the SMA[23]. In an additional report[27], no significant difference in postoperative AOM between the MFRA and SMA children was described. SMA patients were significantly younger (p =.0017) and no stratification was applied. Postoperative follow-up time was at least 18 months in both groups.

Postelmans *et al.*[13] studied complications arising in 64 children: 45 children operated by the MFRA and 19 children operated by the SMA. Two children operated by the MFRA developed complications: one child suffered from a mastoiditis, and another patient had a traumatic CI luxation.

Table 1B. Critical Appraisal of a Topic (CAT) based on validity of studies reporting on the difference in outcome between the MFRA and the SMA.

Included studies for Critical Appraisal of a Topic (CAT)	Migirov *et al.* (2006) ORL68(3)	Migirov *et al.* (2006) IJPORL	Postelmans *et al.* (2009)	Postelmans *et al.* (2014)	Migirov *et al.* (2006) ORL 68(4)	Zernotti *et al.* (2012)
Validity						
5. Randomization and stratification						
A Randomization claimed and documented	○	○	○	○	○	○
B Use of either prognostic stratification prior to study entry or retrospective stratification during data analysis	○	○	●	○	○	○
6. Usage of comparison groups						
Historical (Hi) *or* subjects selected for availability (A) *or* no comparison group included (N)	Hi	Hi	Hi	A	Hi	A
7. Procedures for treatment						
A Subjects in different groups appear to receive same care	●	●	●	○	●	○
B Surgical technique clearly described	●	●	●	●	●	●
C Informed consent obtained	U	U	U	U	U	U
8. Follow-up						
A Follow-up time is given	●	●	●	●	●	○
B Follow-up is consistent	●	●	●	●	○	U
C Loss-to-follow up is described	○	○	○	○	○	○
D Description of all dropped subjects is given	○	○	○	●	○	○
E Blinding (of observer of outcome)	U	U	U	U	U	U
9. Evaluation of subjects and treatment/management						
A Complication registration is standardized and consistent	○	○	○	NA	○	○
B Evaluation methods are adequately described	●	○	●	●	○	○
C Standardized methods are used for evaluations (e.g. consistent method to measure auditory function)	●	○	○	●	○	○
10. Data analysis						
A All comparisons involve same number of subjects or any discrepancy is explained	●	●	●	●	●	●
B Descriptive measures (mean, range, standard deviation, proportion, etc.) identified for all important variables	●	●	○	●	○	○
C Statistical tests used for comparisons involving important variables	●	●	●	●	●	○
D Reported tests appear to be clearly identified *and* appropriately used *and* appropriately interpreted	●	●	●	●	○	○
11. Recommendations/conclusions						
A Authors provide a clear recommendation/conclusion	●	●	●	●	●	●
B Recommendations/conclusions are supported by data analysis	●	●	●	●	○	○
Overall validity	M	M	M	M	L	L

Legend: A = availability; ATO = according to outcome; H = high; Hi = historical; IJPORL = International Journal of Pediatric Otorhinolaryngology; L = low; M= moderate; MFRA = Mastoidectomy with Facial Recess Approach; NA = not applicable; N = no comparison; P = prospectively; ORL = Journal of Oto-Rhino-Laryngology – Head & Neck surgery; R = retrospectively; SMA = SupraMeatal Approach; U = unspecified; ● = yes, ○ = no.

Table 2. Results of studies reporting on postoperative outcome differences between two different surgical techniques for cochlear implantation surgery: the MFRA and the SMA.

Authors (Year)	Evidence Level (study design)	Year inclusion	No. of operated ears			Age at implantation (years (SD))		Statistics	Outcome Measures	Follow-up (months [range])	Results		
	1 - 4		SMA	MFRA	Total	SMA	MFRA				Complications		*p*-value
Migirov (2006) IJPORL	3 (RCS)	1993 - 1999 MFRA 1999 - 2003 SMA	118	116	234	3.08 (± 1.42)*	1,75 (± 1.0)*	Chi-square, Fisher's exact Test.	Postoperative AOM and mastoiditis incidence.	18.0 [18.0 - 24.0]	pre. AOM MFRA: 29 pre. AOM SMA: 38	post. AOM MFRA: 7 post. AOM SMA: 12	$p = .59$
											no pre. AOM MFRA no pre. AOM SMA	post. AOM MFRA: 13 post. AOM SMA: 15	$p = .65$
											mastoiditis SMA: 0	mastoiditis MFRA: 11	$p = .023$*
Migirov (2006) ORL 68 (3)	3 (RCS)	1993 - 1999 MFRA 1999 - 2001 SMA	48	94	142	3.02 (± 0.67)	5.04 (± 2.26)	Chi-square, Fisher's exact Test.	Preoperative and postoperative SOM comparison.	24.0	pre. SOM MFRA: 30 pre. SOM SMA: 16	post. SOM MFRA: 7 post. SOM SMA: 3	$p = .86$
Postelmans (2009)	3 (RCS)	2000 - 2008 MFRA: Maastricht SMA: Amsterdam	107	214	315	39.6* (19 children)	45.3* (45 children)	*T* test, Chi-square test, Logistic regression.	Perioperative and postoperative complication rate.	MFRA: 33.6 [3.0 - 87.0]* SMA: 25.7 [3.0 - 59.0]*	SMA major: 4 SMA minor: 25	MFRA major: 14 MFRA minor: 48 MFRA child: 1 mastoiditis	$p = .295$ $p = .884$
											Higher age at implantation was associated with more minor complications in SMA and MFRA patients.		$p = .001$*
									Surgery duration		SMA: 111.7 min.	MFRA: 132.2 min.	$p = .0005$*
Postelmans (2014)	3 (RCS)	2000 - 2010 MFRA: Maastricht SMA: Amsterdam	84	143	227			Unpaired t test, Chi-square test.	Complete or partial (> 10 dB) residual hearing preservation.	6.0	SMA complete: 8 SMA partial: 10 SMA total: 21.4%	MFRA complete: 19 MFRA partial: 12 MFRA total: 21.7%	$p = .96$

Legend: AOM = acute otitis media; dB = decibel; EMA = endomeatal approach; FR = facial recess; IJPORL = International Journal of Pediatric Otorhinolaryngology; min. = minutes; MFRA = Mastoidectomy with Facial Recess Approach; no. = number of patients; ORL = Journal of Oto-Rhino- Laryngology – Head & Neck surgery; pre = preoperative; post. = postoperative; RCS = retrospective case series, SD = standard deviation; SOM = secretory otitis media; SMA = Suprameatal approach. °Categories for level of evidence: 1 = RCTs; 2 = nonrandomized concurrent cohort studies; 3 = nonrandomized cohort studies using historical controls; 4a = prospective case series without controls and 4b = retrospective case series without controls. *statistically significant ($p < .05$).

Complications in children operated by the SMA included two wound infections leading to CI explantation and one CI device failure. The authors reported that the two wound infections were caused by hematoma-induced device contamination and a suture-related skin reaction[13]. Progressive speech recognition deterioration indicated possible CI device failure in the latter patient, which was confirmed by CI integrity measurement after CI explantation[13]. The aforementioned three children operated by the SMA were reimplanted successfully after initial CI explantation[13].

Ages of the two wound infection patients were not specified, nor an average age at implantation was provided of both children operated by the MFRA and the SMA[13]. Therefore, the authors were contacted, and they provided the following information: children operated by the SMA had a mean age at implantation of 2.43 years (SD: 1.41), and the CI device failure occurred in a three-year-old male child operated by the SMA. Ages of the two CI explantation patients, operated by the SMA, and paediatric age-at-implantation data regarding the children implanted by the MFRA were not available.

Two studies[13,23] reported on the number of mastoiditis cases in children who received a CI. One study[23] showed significantly (p = .023) more mastoiditis in children operated by the MFRA, and the remaining study[13] reported one case of mastoiditis in a child operated by the MFRA (Table 2). Because SMA study populations had similar characteristics (age at implantation and complication follow-up time), mastoiditis complication results were pooled in a meta-analysis. The overall effect was not significant (p = .69; I^2 = 47.10%; Figure 2). Therefore, pooled study results[13,23] indicated that mastoiditis did not occur significantly more often in children operated by the MFRA.

5. Complications in adults

Postelmans *et al.*[13] was the only author reporting on long-term (> one year) complications in adult patients. Follow-up length was significantly (p =.001) longer for patients operated by the MFRA (33.6 months, range: 3.0 - 87.0) than for patients operated by the SMA (25.7 months, range: 3.0 - 59.0)[13]. The authors reported two intermittent facial nerve paralyses in 166 adult patients operated by the MFRA (1.2%).

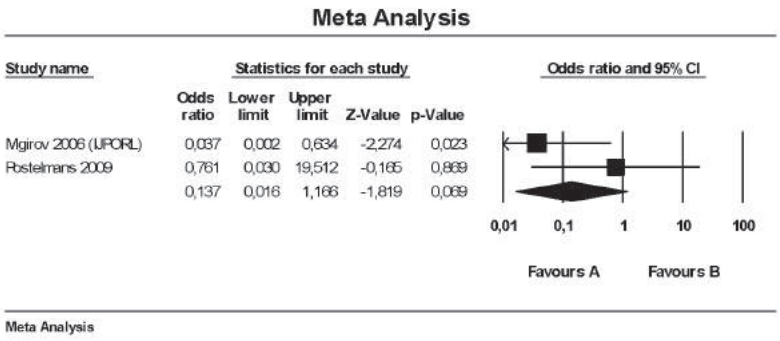
In adult patients operated by the SMA, one incorrect electrode placement was reported in a 55-year-old patient[29]. In addition, two SMA wound infections leading to CI explantation were described[13]. The ages of aforementioned affected patients remained unspecified[13]. Overall analysis of minor and major complications did not show significant differences between adult patients operated by the MFRA and the SMA[13].

Age at cochlear implantation was significantly (p =.015) lower in patients operated by the SMA[13] and higher age at surgery was related to significantly (p =.001) more minor postoperative complications in both adult patient groups[13].

6. Hearing preservation (HP)

Postelmans *et al.*[26] compared difference in residual HP between approaches in adult CI users six months postoperatively. All patients had measurable preoperative hearing thresholds at 250, 500 and 1000 Hz on the baseline audiogram. Authors reported no significant difference in partial or in complete residual HP[26].

Figure 2. Meta-analysis of results of studies reporting on mastoiditis in children operated by the MFRA.



Legend: 95%CI = 95% confidence interval; IJPORL = International Journal of Paediatric Otolaryngology; MFRA = Mastoidectomy with Facial Recess Approach.

7. Surgery time

Mean SMA surgery time (111.7 minutes) was significantly (p <.0005) shorter than MFRA operative time (132.2 minutes) in children and adults[13]. Surgery time was not reported in the studies of Migirov *et al.*[23,27].

DISCUSSION

We aimed to define which surgical approach for cochlear implantation is preferable based on postoperative complications and HP in children and adults. Three paediatric studies[13,23,27] reporting on two cohorts did not identify complication differences (SOM, AOM and mastoiditis) between children operated by the MFRA and the SMA. Similarly, in adults, no statistical difference between surgical outcomes was described[13]. Furthermore, the authors did not report significant difference in partial nor complete residual HP six months postoperatively[26]. Therefore, the included literature did not identify a favourable surgical approach for cochlear implantation.

Both the small numbers of articles reporting on this subject and the fact that all studies contained Level 3 evidence[28] (e.g., small nonrandomized, retrospective, intervention studies subject to type II error) could explain why differences in outcomes between surgical approaches could not be identified. Therefore, Level 1 evidence studies (e.g., Randomized Controlled Trials (RCTs)) are required to underline different outcomes.

Second, the fact that similar patient cohorts were assessed in study pairs could have influenced outcomes. In addition, included studies could not have been fully representative for all valid studies undertaken (e.g., publication bias). Xu *et al.*[30] reached similar conclusions, although only one of our selected studies[13] was included in their analysis and two of their selected studies[4,16] did not pass our critical appraisal. In line with this review, Xu *et al.*[30] were not able to prove different outcomes between surgical techniques in their meta-analysis. In addition

to Xu *et al.*[30], outcomes for paediatric and adult patients were assessed separately and paediatric mastoiditis data were pooled independently in this literature review. Secondly, Xu *et al.*[30] did not refer to HP outcomes, whereas a study[26] providing insight in adult HP outcomes was included in the current review. Third, this study underlines the need for accurate critical appraisal to assess the lack of transparent data report and select relevant and unbiased studies. Ultimately, in this study review results were reported according to guidelines[22].

Complications in children

Two paediatric studies[23,27] reported no significant difference on the number of postoperative SOM[23] and AOM[27] cases between children operated by the MFRA and the SMA. An additional study[13] reported one mastoiditis case of a child operated by the MFRA. Although Migirov *et al.*[27] showed that significantly (p = .023) more mastoiditis occurred postoperatively in children operated by the MFRA, meta-analysis indicated that mastoiditis did not occur significantly more in children following cochlear implantation by the MFRA (Figure 2). Shin *et al.*[21] reported mastoiditis occurrence in 0 to 3.3% of their included children. This concords with the 0.5% mastoiditis prevalence reported by Postelmans *et al.*[13]. However, Migirov *et al.*[27] reported that 11 children (9.5% of the MFRA children; 4.7% of all CI surgeries) in their cohort suffered from mastoiditis. Two patients (18.2%) even suffered from a second postoperative mastoiditis[27]. The 11 children who presented with mastoiditis were implanted at an average age of 41 months and presented with mastoiditis on average 10.9 months postoperatively[27]. Of these 11 patients, seven (63.6%) did not suffer from preoperative AOM. Therefore, the selection of the surgical technique was not based on preoperative AOM presentation.

Postelmans *et al.*[13] did not describe whether the child presenting with mastoiditis suffered from preoperative AOM, nor did they define the age at which mastoiditis occurred. The authors[13] included fewer children operated by the MFRA (n = 45) compared with Migirov *et al.*[27] (n = 116) and did not define age at implantation of included children operated by the MFRA. Therefore, included children by Postelmans *et al.*[13] could have been older at the time of cochlear implantation than the children included by Migirov *et al.*[27], resulting in a lower likelihood of developing mastoiditis during follow-up. Alternatively, the CI surgeries of Migirov *et al.*[27], were performed earlier (between 1993 and 1999) than those by Postelmans *et al.*[13] (between 2000 and 2008). Therefore, the lower occurrence of postoperative mastoiditis in the study of Postelmans *et al.*[13] could have resulted from increased experience with CI surgery and improved CI care over time.

Although we hypothesized that more complications could occur following the SMA performed in children, the included studies did not report a significantly higher complication rate. Included children[23] had a mean age at implantation of 46.9 months (SD: 22.6). Therefore, these data are most applicable to older implanted children (> 24 months) and cannot be generalized to younger implanted patients (< 24 months). Since included children in the present review[23] could have surpassed the age of being prone to develop infections (e.g., OM, AOM, SOM and mastoiditis), complications between performing the MFRA and the SMA

at a younger age at implantation could differ. In particular, since the peak incidence of AOM and mastoiditis occurs between six and 12 months[31,32]; a period that corresponds to the age at which paediatric cochlear implantation is currently performed[33,34]. Yin *et al.*[35] performed cochlear implantation by the SMA in children of the younger age group (45 children; including three children under one year) and did not report any postoperative complications in their youngest patients. However, four patients had vestibular complaints and their age remained undefined[35]. Therefore, future studies are required to elucidate whether both the MFRA and the SMA can be performed safely in young (< one year) children.

Complications in adults

One study[13] reported on long-term (> one year) complications in adults. No significant complication differences between the MFRA and the SMA were found[13]. Vaca *et al.*[36] compared another mastoid-sparing approach (the Trans-attical Approach (TA)) with MFRA outcomes in children and adults. In line with results from Postelmans *et al.*[26], no significant differences in complication ratios were reported[36]. Two studies[4,16] excluded from the current review also investigated postoperative complications in adults. Similar to Postelmans *et al.*[13], Zernotti *et al.*[4] did not report significant complication differences between patients operated by the MPTA and the SMA between 1 and 80 years old. Contrarily, Migirov *et al.*[16] suggested that the SMA was associated with fewer major complications due to six facial nerve paralyses in 166 MFRA patients (3.6%). However, facial nerve injury is a rare cochlear implantation complication and has been reported to occur only in 1.7 to 2.0%[14,15,37,38] of all CI surgeries. More recently, even lower rates of immediate onset (0.1%) and delayed onset (1.1%) facial nerve paresis were reported[18]. Similarly, Postelmans *et al.*[13] reported two intermittent facial nerve paralyses in 166 adult patients operated by the MFRA (1.2%). Both Postelmans *et al.*[13] and Migirov *et al.*[16] suggested that MFRA nerve injuries occurred due to heat generation by the posterior tympanotomy drilling. Migirov *et al.*[16] reported that three out of the six facial nerve paralysis (50%) occurred in the first 20 operated CI patients at their institution. Therefore, exclusion of the first 20 CI cases results in a 1.8% complication rate (three out of 163 patients)[16], which concords with previously reported facial nerve paralysis incidences[14,15,18,37,38]. Hence, authors[16] should not suggest that SMA was associated with less major complications; both CI techniques might be related with similar minor and major adult complication rates.

No significant difference in minor complications between patients operated by the MFRA and the SMA was identified by Postelmans *et al.*[13]. Similarly, Migirov *et al.*[16] did not report any significant difference in complications between their paediatric (n = 234) and adult (n = 83) patients operated by the MFRA and the SMA, except for mastoiditis being reported only in children and vestibular problems that were significantly (p <. 0001) more often reported in adult compared to paediatric patients[16]. The latter resulted most presumably from adults being more capable to self-report disequilibrium than children[16].

Postelmans *et al.*[13] did report significantly (p = .001) more minor complications in older versus younger CI patients. Children (n = 64) and adults (n = 251) were both included in the studied cohort, and no age definition of older patients suffering from more complications was provided.

Patients operated by the SMA had a mean age of 39.6 years and were significantly younger (p = .001) than patients operated by the MFRA[13]. Although an adjustment for age was applied during logistic regression, later age at implantation showed to be associated with more minor complications. Since paediatric and adult CI patients were both included in the cohort studied by Postelmans *et al.*[13], one cannot distinguish whether the effect that more minor complications occurred in older patients resulted from the age of the adult population only. In addition, not all minor complications defined by Cohen *et al.*[14,15] were classified by Postelmans *et al.*[13]. For example, no wound dehiscence or infection ratios were specified as minor complications. In case these complications would have been reported, similar minor complication ratios between younger and older implanted patients, in line with results from Migirov *et al.*[16], could have been reported.

Hearing Preservation (HP)

One included study[26] reported that neither one of the CI techniques resulted in significant differences in partial or complete HP[26]. Since HP outcomes of adult patients operated by the MFRA and the SMA were assessed in only one patient cohort[26], outcomes should not be generalized to the entire CI population.

In contrast to aforementioned findings, Santa Maria *et al.*[39] confirmed that the MFRA led to significantly (p < .01) lower unsuccessful HP rates than the SMA application. However, the authors could not confirm higher rates of complete HP (p = .05) in patients operated by the MFRA. Although the MFRA showed improved HP results at 12-month follow-up, the authors[39] suggested the MFRA to be less favourable after 12 months. These findings could explain why results from both studies[26,39] differ, thereby indicating the need for HP studies investigating long-term (> two years) HP outcomes between these two surgical techniques. Contrarily to Postelmans *et al.*[26], Santa Maria *et al.*[39] refrained from comparing HP outcomes of patients operated by the MFRA and the SMA in one patient cohort (e.g., included results in their meta-analysis were retrieved from individual MPTA and SMA studies). Comparing HP outcomes in the same study with similar audiological assessment is essential for future HP studies.

Surgery time

Surgery time was reported only by Postelmans *et al.*[13] and authors confirmed significantly (p <.0005) shorter SMA surgery time. Reduced SMA surgery time is expected, because SMA does not require a complete mastoidectomy. Majdani *et al.*[40] reported a mean MFRA surgical time of 171 minutes. Contrarily, Kronenberg *et al.*[11] reported a SMA surgical time of 60 minutes. In addition, Vaca *et al.*[36] confirmed that the non-mastoidectomy procedure (TA) was significantly (p < .001) shorter than the MFRA: TA took on average 124 minutes (range: 85 – 240), compared to 161 minutes (no range provided) in the MFRA. However, the aforementioned surgical time differences are unlikely to affect patient outcomes following CI surgery.

Postelmans *et al.*[13] reported that MFRA time was reduced from approximately 300 to 120 minutes in four years. Contrarily, SMA time did not show a similar declining curve[13]. Since MPTA time eventually corresponded to that of the SMA group, the authors suggested MFRA surgery time reduction reflected a surgical learning curve[13]. Second, not all studies reported whether a CI implant bed was constructed, which could explain assessed operation duration differences.

Limitations

A modified, non-validated CAT tool was applied as based on the critical appraisal model of Reisch *et al.*[24], which could therefore render its applicability to test the quality of included evidence. However, we believe that our critical appraisal provided a thorough relevance and validity evaluation, as it was carried out by three independent authors (H.B., K.D., R.G.) and evaluated a large number of study aspects (n = 11).

Since included studies did not report statistical power or false-negative results, sample sizes of included studies (Table 2) could have been too small to ensure that a non-significant result was not subject to a Type II error. Der Simonian *et al.*[41] described that when neither statistical power, nor a false-negative result is provided in a study, the reader can assume that the study was too small to detect important differences. This implicates that (significant) complication differences between techniques could have been reported if initial sample sizes would have been larger. The fact that included studies could have been subject to type II error is due to the quality of selected reports and independent of the quality of the current review. This underlines the need for future studies using large sample sizes. We calculated the necessary sample size for future studies using paediatric complication ratios reported in studies of Postelmans *et al.*[13] and Migirov *et al.*[27]. Nquery software (version 7.0; Statistical Solutions Ltd., Cork, Ireland) was used to perform sample size calculations. To show significant differences between CI techniques between 999 and 1358 CI children are required to ensure 90% power at an alpha of 0.05.

The current literature does not provide insight into which of the two CI techniques leads to the most optimal surgical outcome in children and adults. Clinical recommendations cannot be solely based on results of the four included studies in the current review. Due to the fact there is no clear consensus on superiority on either one of the surgical techniques from the literature, additional research is essential to define which approach should be elected for both the paediatric and adult population with SNHL.

CONCLUSION

Our review did not reveal favourable results regarding postoperative complications in children and adults and adult HP between the MFRA and the SMA for cochlear implantation. Current research only reports on children implanted after the age of 24 months and adult CI patients. Because there is no consensus on optimal outcome of either one of the surgical techniques, there is a need for Level 1 evidence (e.g., RCTs) to delineate the favourable surgical approach in young (< 24 months) and adult CI candidates.

APPENDIX

Search query of the literature search performed on December 14, 2014.

PubMed

((((cochlea*[tiab] OR cochlea[MeSH]) AND (implant*[tiab] OR devic*[tiab] OR prosth*[tiab])) OR "Cochlear Implants"[Mesh] OR "Cochlear Implantation"[Mesh]) AND (posterior tympanotomy[tiab] OR posterior approach[tiab] OR posterior technique[tiab] OR facial recess[tiab] OR MPTA[tiab])) OR ((((cochlea*[tiab] OR cochlea[MeSH]) AND (implant*[tiab] OR devic*[tiab] OR prosth*[tiab])) OR "Cochlear Implants"[Mesh] OR "Cochlear Implantation"[Mesh]) AND (suprameatal approach[tiab] OR suprameatal technique[tiab] OR alternative techniq*[tiab] OR SMA[tiab]))

Embase

((((cochlea*:ab,ti OR 'cochlea'/exp) AND (implant*:ab,ti OR devic*:ab,ti OR prosth*:ab,ti OR 'implant'/exp OR 'prosthesis'/exp)) AND [embase]/lim) AND ('posterior tympanotomy'/exp OR 'posterior approach'/exp OR 'posterior technique'/exp OR 'facial recess'/exp OR MPTA:ab,ti AND [embase]/lim))

AND ((((cochlea*:ab,ti OR 'cochlea'/exp) AND (implant*:ab,ti OR devic*:ab,ti OR prosth*:ab,ti OR 'implant'/exp OR 'prosthesis'/exp)) AND [embase]/lim) AND ('suprameatal approach'/exp OR 'suprameatal technique'/exp OR 'alternative technique'/exp OR 'SMA'/exp))

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Chapter 3.2

Retrospective complication rate comparison between surgical techniques in paediatric cochlear implantation

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ABSTRACT

Objective

To compare paediatric complication occurrence between the Mastoidectomy with Posterior Tympanotomy (MPTA) and the SupraMeatal Approach (SMA) for cochlear implantation.

Design

Retrospective cohort study.

Setting

Children receiving a cochlear implant before five years of age between 1996 and 2014 in our tertiary centre.

Participants

A total of 144 patients receiving a cochlear implant (121 by MPTA and 23 by SMA) operated on 165 ears (129 and 39 respectively).

Main outcome measures

The severity (minor or major) using Cohen and Hoffman criteria and time of occurrence of complications (intraoperative, early postoperative or late postoperative) were identified. Intraoperative surgical challenges were correlated to complication occurrence.

Results

The mean age at implantation was 2.13 ± 1.14 years old. Patients operated by the SMA (1.27 ± 0.69 years old) were significantly ($p < .001$) younger than those receiving a cochlear implant by MPTA (2.40 ± 1.12). Most complications were minor (MPTA: 64.0%; SMA: 73.1%) and occurred early postoperatively (MPTA: 61.5%; SMA: 76.9%). More overall complications occurred in SMA compared to MPTA cases (61.5% versus 20.6%; $p < .001$). Younger SMA cohort patients (6 - 12 and 18 – 24 months; $p < .008$ and $p = .016$) most often developed these complications. When looking at specific complications, more infectious complications occurred in patients receiving a cochlear implant through the SMA ($p < .05$). Logistic regression showed that the surgical technique and not the age a implantation was responsible for the documented complications. No relationship between complications and intraoperative difficulties was identified.

Conclusion

In our institution, cochlear implantation in young patients through the SMA resulted in significantly more (infectious) complications than those operated through the MPTA. Outcomes from our institution recommend using the MPTA when opting for a cochlear implant surgical technique in young children who are more prone to develop infectious complications.

INTRODUCTION

For children with severe to profound SNHL not benefiting from hearing aids, cochlear implantation is the proposed solution for the rehabilitation of hearing[1]. Cochlear implantation allows children to perceive environmental sounds through electrical cochlear nerve stimulation and not delay their speech developmental process[2].

Currently, the Mastoidectomy with Posterior Tympanotomy Approach (MPTA) is considered the reference surgical technique for cochlear implantation[3-7]. However, the more recently developed SupraMeatal Approach (SMA) bypasses the mastoid cavity by drilling a suprameatal tunnel[8] thus minimalizing facial nerve damage risks. Migirov *et al.*[9] reported a facial nerve injury incidence of 3.6% in MPTA patients (1/116 children and 5/50 adults), while no SMA patients presented with facial nerve damage. Nonetheless, it is important to note that SMA is performed less frequently than MPTA, most likely because it can present with surgical challenges requiring additional training.

A meta-analysis by Xu *et al.*[10] revealed no difference in postoperative complication rates between patients operated by the SMA and MPTA. However, included children receiving a CI were older than two years old[9] or ages in studies were not defined[3,5]. As AOM and mastoiditis are known to have higher occurrence rates in children between six and 12 months[11,12], older included children (> two years)[9] could be less susceptible in developing postoperative complications. In the Netherlands, the recommended age for cochlear implantation is below 12 months of age. This recommend age has gradually declined throughout recent years; thus, it is not surprising that postoperative infectious complications are increasingly common in young implanted children[13].

A study by Luntz *et al.*[14] in otitis media (OM) prone children showed that OM prevalence declined after cochlear implantation by the MPTA. Preoperative OM control (through ventilating tubes), lower OM incidence in older children and the added benefit of mastoidectomy could have influenced their results[14]. Although OM primarily involves the middle ear, the disease is known to extend into the mastoid[15]. In particular, in chronic OM (COM), middle ear mucosa can be hyperplastic, irreversibly diseased and affecting the mastoid[15]. Thus, mastoid removal during CI surgery by the MPTA could prevent these infectious postoperative complications. Complications deriving from CI surgery could have devastating consequences ultimately leading to device explantation[15]. Therefore, it is important to elect the CI surgical technique that could result in fewer complications.

The present retrospective study aims to compare complication incidences arising from CI surgery by the SMA and MPTA in children implanted at our institution.

METHODS

Study design

A retrospective cohort study was conducted after receiving approval from the local ethical commission (Institutional Review Board of the UMC Utrecht) (METC protocol 14-486/C).

Medical records were used to identify children receiving a CI in the UMC Utrecht between 1996 and 2014. This represents 20.4%[16] of the paediatric patients who received a CI in the Netherlands. Two independent reviewers (F.Z., H.B.) conducted the medical records review. Children were excluded in case of: CI revision surgery, CI device failure occurring more than one year postoperatively, follow-up shorter than one year after CI activation and missing information in patients charts. Outcomes retrieved from remaining patients included: ages at implantation, data on baseline characteristics, implant type, surgical technique and occurrence of intraoperative difficulties and complications. Children were divided into groups based on age at implantation. This report is written according to STROBE guidelines[17].

Complication Assessment

Documented complications were assessed according to the Cohen and Hoffman classification[18] (Table 1). A complication was considered minor if resolution occurred spontaneous or after medication administration[18]. Major complications required hospitalisation or additional surgery. Cochlear implant device failure (> one year) was not considered a complication deriving from the surgical approach. Complications were classified according to their time of occurrence; intraoperatively, early postoperatively (< three months) or late postoperatively (> three months). Intraoperative difficulties were recorded to evaluate whether a relation between intraoperative challenges and complication occurrence existed. These difficulties were classified as infectious-prone or infectious difficulties (e.g., thickened mucosa, middle ear glue), anatomical difficulties (e.g., small mastoid) and electrode insertion problems (e.g., cochlea ossification). Infectious-prone or infectious difficulties were subdivided into infectious-prone or infectious mucosal changes (1A) and intraoperative infectious tissue bleeding (1B). Bleeding resulting from removal of the inflamed mucosa was stratified according to Boezaart's classification[19].

Statistical Methods

SPSS software (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) was used and a *p*-value below .05 was considered significant. χ^2- and Kruskal-Wallis tests were applied to assess complication differences between and within age-at-implantation groups. A logistic regression differentiated between age at implantation and surgical technique effects.

RESULTS

There were 160 children (186 ears) receiving CIs at our institution (Table 2). During statistical analysis, four children implanted by other surgical techniques were excluded. This included one child (two ears) operated by the endaural approach and three children (six ears) operated through the endaural approach combined with the SMA. An additional five children (six ears) were excluded due to incomplete medical charts. Seven children operated by the MPTA were

Table 1. Method of CI complication classification deducted from Hoffman and Cohen criteria[18].

Major complications	Minor complications
Flap infection or flap necrosis	Dehiscence of incision
CI extrusion	SOM without AB
Migration of the receiver coils	Facial nerve stimulation
Improper or incorrect electrode placement	Vertigo
Device failure (< one year)	Postoperative pain
Facial nerve paralysis	Facial edema
Meningitis	Seroma
CSF leak	Hematoma (treated with punction or AB)
Foreign body reaction	Delayed wound healing (> one week)
Cholesteatoma	Tinnitus
Perilymfatic fistula	Taste disturbances
Implant migration	Eardrum defect
Wound dehiscence	Postoperative petechiae
AOM, treated with hospital admission	AOM, treated with AB
Mastoiditis, treated with AB	
Mastoiditis, treated with hospital admission	

Legend: AB = antibiotics; AOM = acute otitis media; CI = cochlear implant; CSF = cerebrospinal fluid; SOM = serous otitis media.

Table 2. An overview of the performed surgical technique (MPTA, SMA and other surgical techniques) per age-at-implantation group of the complete paediatric CI cohort (160 children operated on 186 ears).

Age at implantation (range in months)	MPTA (n (group %))	SMA (n (group %))	Other surgical techniques (n)	Total (n)	Mean age (years) (SD)
6 - 12	13 (40.6%)	18 (56.3%)	2	33	0.81 (0.14)
12 - 18	17 (50%)	9 (26.5%)	8	34	1.14 (0.12)
18 - 24	22 (73.3%)	8 (26.7%)	0	30	1.80 (0.15)
24 - 30	24 (88.9%)	2 (7.4%)	1	27	2.20 (0.12)
30 - 36	23 (95.8%)	1 (4.2%)	0	24	2.74 (0.14)
36 - 48	19 (86.4%)	0 (0%)	3	22	3.49 (0.28)
48 - 60	15 (93.8%)	1 (6.3%)	0	16	4.52 (0.21)
Total (n)	133 (100%)	39 (100%)	14	186	2.27 (1.14)

Legend: CI = cochlear implant; MPTA= mastoidectomy with posterior tympanotomy approach; n = number of operated ears; SD = standard deviation; SMA= suprameatal approach.

excluded due to CI device failure (> one year). These patients were implanted after the age of one year (mean: 2.6 years). Two CI failures occurred due to trauma (car crash and head trauma), while other causes were not reported. Twelve children (operated on ten ears) underwent revision surgery. Outcomes from initial CI surgeries were included for statistical analysis.

Aforementioned excluded 16 children (21 ears) are represented in Table 2 and Table 3 to provide insight in their age at implantation and hearing loss aetiology. The majority of patients had hearing loss of unknown aetiology (Table 3).

Outcome from 144 children (165 ears) was included for statistical analysis. One hundred and

Table 3. Aetiology of sensorineural hearing loss in the different groups according to the applied operation technique (SMA or MPTA). The seven cases of CI device failure after one year are included in this Table.

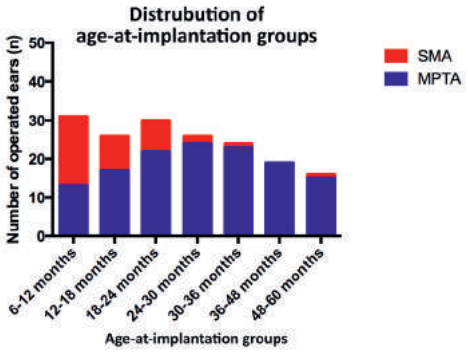
Type of aetiology	Operation technique (n)		Total (n)
	MPTA (n (MPTA %))	SMA (n (SMA%))	
Congenital/unknown	82 (61.7%)	20 (51.3%)	102
Meningitis	33 (24.8%)	8 (20.5%)	41
Connexin 26 mutation	0 (0%)	5 (12.8%)	5
Syndromic/neuro-cognitive	8 (6.0%)	2 (5.1%)	10
CMV infection	7 (5.3%)	2 (5.1%)	9
Labor complication (e.g., hypoxia)	2 (1.5%)	0 (0%)	2
Prematurity	1 (0.8%)	2 (5.1%)	3
Total	133 (100%)	39 (100%)	172 (=100%)

Legend: CI = cochlear implant; CMV = Cytomegalovirus; MPTA= Mastoidectomy with Posterior Tympanotomy Approach; n = number of operated ears; SMA= SupraMeatal Approach.

21 included patients (133 ears) received their CI through the MPTA and 23 patients (39 ears) through the SMA (Table 3). Both SMA and MPTA were performed according to previously described surgical techniques[6,8]. The selection of surgical approach was based on the patients' anatomical features and the surgeon's experience and opinion. All children received intraoperative Augmentin® and one week postoperative oral Augmentin®. No intraoperative or postoperative corticosteroids were administered. Mean age at implantation was 2.13 ± 1.14 years. Patients operated by the SMA were significantly (p <.001) younger (1.27 ± 0.69 years) than patients operated by the MPTA (2.40 ± 1.12 years). No children were implanted before the age of six months. Figure 1 shows the distribution of children operated by both techniques among various age-at-implantation groups. More children were implanted with a Cochlear® device (113 MPTA; 22 SMA) compared to MED-EL (eight MPTA; one SMA). SMA follow-up time (2.27 years) was significantly (p <.001) shorter than MPTA follow-up time (12.27 years). Five surgeons performed the CI surgeries, however, no surgeons performed both surgical techniques. To statistically compare an approximate equal number of children in each age-at-implantation group, patients of the sixth and seventh age groups were combined.
Fifty-one operated ears (30.9%) suffered from a minor or major complication: 26 SMA (66.6%) and 25 MPTA ears (19.8%) (p <.0001) (Figure 2A).
Most complications occurred early postoperatively (overall: 69.2%, MPTA: 61.5%; SMA: 76.9%) and were of minor severity (overall: 68.6%, MPTA: 64.0%; SMA: 73.1%). More SMA than MPTA operated ears suffered from infectious complications (p < .05) (Figure 2B).

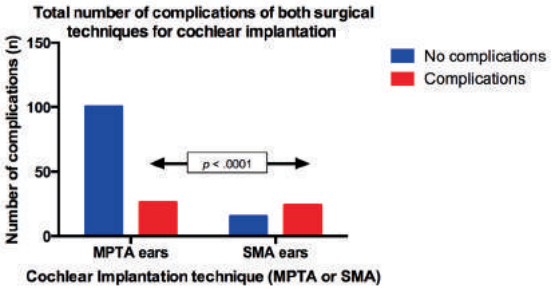
Acute otitis media (AOM) treated with AB was the most common reported minor complication (Table 4A). Significantly (p <.05) more minor infectious complications occurred in SMA (20.5%) compared to MPTA patients (5.6%). Sixteen ears were reported having major complications: nine MPTA and seven SMA (Table 4B). Acute otitis media (AOM) treated during hospital admission was the most frequently documented complication (Table 4B).
Two children operated by the MPTA (1.7%) and one by the SMA (4.4%) suffered from mastoiditis (mean age at implantation: two years). More infectious-related major complications

Figure 1. Distribution of SMA and MPTA children among various age-at-implantation groups.



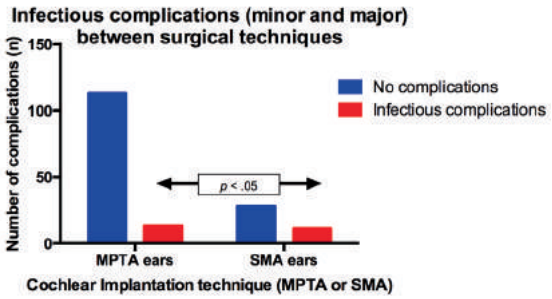
Legend: n = number; MPTA = Mastoidectomy with Posterior Tympanotomy Approach; SMA = SupraMeatal Approach.

Figure 2a. Number of total (minor and major) complications between MPTA and SMA operated ears.



Legend: n = number; MPTA = Mastoidectomy with Posterior Tympanotomy Approach; SMA = SupraMeatal Approach.

Figure 2b. Number of total (minor and major) infectious complications between MPTA and SMA operated ears.



Legend: n = number; MPTA = Mastoidectomy with Posterior Tympanotomy Approach; SMA = SupraMeatal Approach.

Table 4A. Results of minor complications occurring in the SMA and MPTA operated ears (*n*) (infectious minor complications are marked in **bold**).

Minor complication type	Operation technique (n)		Total (n)
	MPTA (n (MPTA %))	SMA (n (SMA %))	Total (% of all included SMA and MPTA patients)
AOM treated with AB	**7 (5.6%)**	**7 (18.0%)**	14
SOM without AB	**0 (0%)**	**1 (2.6%)**	1
Dehiscence of incisions	1 (0.8%)	2 (5.1%)	3
Hematoma	4 (3.2%)	3 (7.7%)	7
Eardrum defect	0 (0.0%)	1 (2.6 %)	1
Facial oedema	3 (2.4%)	2 (5.1%)	5
Postoperative pain	1 (5.9%)	2 (5.1%)	2
Postoperative petechiae	0 (0.0%)	1 (2.6%)	1
Total	**126 (100%)**	**39 (100%)**	**35 (21.2%)**

Legend: AB = antibiotics; AOM = Acute Otitis Media; MPTA= Mastoidectomy with Posterior Tympanotomy Approach; n = number of operated ears; SMA= SupraMeatal Approach; SOM = serous otitis media.

Table 4B. Results of major complications occurring in the SMA and MPTA operated ears (n) (infectious major complications are marked in **bold**).

Major complication type	Operation technique (n)		
	MPTA (n) (% of MPTA ears)	SMA (n) (% of SMA ears)	Total (% of all included SMA and MPTA patients)
AOM, treated with hospital admission	**4 (3.2%)**	**2 (5.1%)**	6
Mastoiditis, treated with hospital admission	**1 (0.8%)**	**0 (0.0%)**	1
Mastoiditis, followed by CI extrusion	**1 (0.8%)**	**1 (2.6%)**	2
Extrusion	2 (1.6%)	1 (2.6%)	3
Postoperative hospital admission	0 (0.0%)	3 (7.7%)	3
CSF leak	1 (0.8%)	0 (0.0%)	1
Total	**126 (100%)**	**39 (100%)**	**16 (9.7%)**

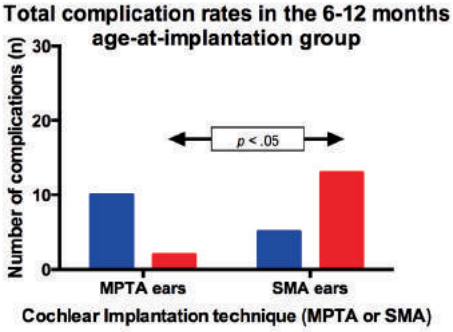
Legend: AOM = Acute Otitis Media; CI = cochlear implant; CSF = cerebrospinal fluid; MPTA= Mastoidectomy with Posterior Tympanotomy Approach; n = number of operated ears; SMA= SupraMeatal Approach.

emerged in children operated by the SMA (7.7%) than the MPTA (4.8%) (Table 4B). Complications occurred significantly more often following surgery by the SMA in the first (6 - 12 months) (Figure 3A) and third (18 - 24 months) (Figure 3B) age-at-implantation groups. Logistic regression showed that the surgical technique and not the age at implantation caused this effect ($\chi^2(3) = 26.90$, $p < .05$). The surgical technique effect to provoke complications was similar for every age-at-implantation group. The performing surgeon did not affect complication occurrence.

No statistical difference in complication rates between unilateral and bilaterally implanted children was identified. Neither the CI implantation side nor the first or second implant showed to have a significant influence on complication occurrence in sequentially implanted patients.

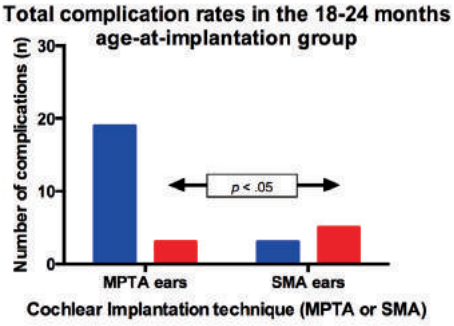
Intraoperative difficulties were encountered in 65 children (74 ears): in 13 SMA (33.3%) and 61 MPTA (50.4%) operated ears. No significant relationship between intraoperative difficulties

Figure 3A. Number of total (minor and major) complications of children from the 6-12 months age-at-implantation group operated through the MPTA and SMA technique.



Legend: n = number; MPTA = Mastoidectomy with Posterior Tympanotomy Approach; SMA = SupraMeatal Approach.

Figure 3B. Number of total (minor and major) complications of children from the 18-24 months age-at-implantation group operated through the MPTA and SMA technique.



Legend: n = number; MPTA = Mastoidectomy with Posterior Tympanotomy Approach; SMA = SupraMeatal Approach.

and complication occurrence was revealed. Group 1 was subdivided into infectious (-prone) mucosal changes (Group 1A: 29 ears) and intraoperative bleeding (Group 1B: 9 ears). Group 1B was sub-classified according to Boezaart *et al.*[18]: 1 (1 ear), 2 (4 ears) and 3 (4 ears). χ^2-test showed that children with intraoperative confirmation of infectious mucosal changes did not suffer from more postoperative complications (p = .60). Anatomical difficulties were identified in twenty-one operated ears (Group 2). All Group 2 patients (mean age at implantation: 2.5 ± 1.37 years) were operated using the MPTA.

In 14 operated ears electrode insertion problems were documented (Group 3). Partial insertion occurred in 4.3% children operated by the SMA and 5.8% operated by the MPTA. No correlation between intraoperative difficulties and partial or complete CI electrode insertion was identified.

DISCUSSION

Key Findings

Complications between two cochlear implantation techniques (the MPTA and SMA) were compared in children. Most complications were of minor severity and occurred early postoperatively. Although SMA follow-up was shorter than MPTA, more SMA-related complications occurred comparing both surgical approaches (p <.001). In particular, significantly more infectious complications occurred in children operated by the SMA.

Young implanted children suffered from more complications than older implanted children. Therefore, the fact that patients, operated by the SMA, were significantly (p <.001) younger at implantation (1.27 ± 0.69 years) could explain why more patients operated by the SMA, suffered from complications. However, logistic regression confirmed that complications occurred significantly more often after the SMA than after the MPTA. This SMA effect to provoke complications was independent of the age at implantation and similar for every age-at-implantation group. In addition, analysis between techniques within every age-at-implantation group showed that SMA application in the first (6 - 12 months) and third (18 - 24 months) age-at-implantation groups resulted in significantly more complications than MPTA application. Both aforementioned and logistic regression findings indicated that although children operated by the SMA were younger and younger implanted patients suffered from more complications, the surgical technique effect and not the implantation age provoked complication occurrence.

Literature comparison

Not performing a mastoidectomy could result in higher SMA complication rates because the remaining mastoid serves as a postoperative infection source[14]. Mastoidectomy has been suggested as a serous otitis media (SOM) treatment for SOM-prone children[20,21]. (A)OM occurrence and mastoid hypo-air cellularity possibly correlate[14] and by enlarging the mastoid volume, mastoidectomy can improve middle ear ventilation and lower AOM/SOM-incidence[20]. In line with these findings, Zhang *et al.*[22] reported mastoidectomy improved Eustachian tube function and decreased SOM recurrence.

Alternatively, SMA and MPTA complication rate differences could be explained by other preoperative AOM or SOM susceptibility. Susceptibility could vary due to different age at implantation[11,12]. However, χ^2-square test analysis in the current study showed that children with intraoperative confirmation of infectious mucosal changes did not present with significantly more postoperative complications. Although our study encompassed a relatively younger patient cohort, postoperative AOM and SOM rates were not increased due to low(er) age at implantation and in line with results from previous studies. Migirov *et al.*[9] reported a 12% postoperative AOM rate in patients operated by the MPTA and 17.9% in patients operated by the SMA, which is comparable with the 23.1% documented in our children operated by ther SMA. Serous otitis media (SOM) incidence was relatively higher (30.4%) than AOM incidence (23.1%), however, still in line with reported numbers from the general and CI population (25% - 58%)[13,23,24].

Migirov *et al.*[13] reported no difference in preoperative and postoperative SOM between children operated by the MPTA and SMA. Although postoperative SOM (7.0%) was significantly lower than preoperative reported SOM (32.4%), authors[13] stated that mastoidectomy failed to show influence on SOM incidence. Migirov *et al.*[13] explained the incidence decrease by: 1) children getting older and 2) SOM incidence naturally declining by age. However, the average age at implantation was 3.97 years[13] and therefore not represents the most SOM-prone children[11,12]. Contrarily, Fayad *et al.*[15] did show a significant OM incidence decrease following cochlear implantation in a paediatric MPTA population with a OM history and without a history of bilateral myringotomy and tubes. Authors[15] studied a cohort implanted before the age of four years (mean age at implantation: 2.29 years). Therefore, studied children might need to be implanted young (< 2.5 years) to be able to show a significant mastoidectomy effect on postoperative infection rates. In our series, complication rates within age-at-implantation groups were studied. Therefore, the likelihood to develop AOM/SOM was similar within each group and surgical technique effects were evaluated without age-at-implantation effects affecting the statistical analysis.

In both surgical approaches, the identification of intraoperative difficulties (infectious(-prone) difficulties, anatomical difficulties and/or electrode insertion problems) did not affect complication occurrence, nor successful electrode insertion. Therefore, both surgical techniques provided the possibility for successful paediatric cochlear implantation during anatomically challenging surgeries. Migirov *et al.*[25] reported that disequilibrium and wound problems were the most common paediatric complications. Authors[9] described that adults suffered significantly more from disequilibrium than children (28.9 vs. 10.3%; p <.0001), which could be related to better adult recognition and expression of disequilibrium symptoms. Therefore, our studied patients could have been too young to self-report disequilibrium.

In 2006, NBHS was established in the Netherlands and therefore, congenital deafness was identified earlier in more recent implanted patients. The SMA was implemented during this period, which could explain why children operated by the SMA were implanted younger (p <.001) than children operated by the MPTA. In addition, later SMA implementation could explain why SMA patient follow-up time was shorter than MPTA (2.27 and 12.27 years, respectively). Migirov *et al.*[13] showed that the average interval between cochlear implantation and postoperative infection formation (e.g., SOM) was 9.37 ± 7.05 months. Therefore, our SMA patient follow-up was accounted to be of sufficient length to identify infectious complications.

Preoperative CT scans were not used to examine presence of middle ear fluid or middle ear opacification. Nonetheless, in patients who suffer from AOM, CT scan alterations are not likely to be found[15] and recognition of middle ear fluid would not have had any therapeutic consequences (e.g., affect the type of elected surgical technique).

Clinical applicability

There is still little evidence on surgical outcomes between the SMA and MPTA in children. Current literature evaluates older implanted children (age at implantation: > 2.5 years).

Contrarily, this study assessed a younger population (age at implantation: 2.13 ± 1.14 years) and suggests that young children are more susceptible to develop (infectious) complications when operated by the SMA. Therefore, to avoid infection occurrence in this population, the MPTA is recommended.

CONCLUSION

Cochlear implant surgery through the SMA resulted in more complications in children implanted before the age of five years in our institution, especially in the youngest age-at-implantation groups. This population is prone to develop middle ear infections; therefore, treatment strategies should be elected that minimise postoperative complication risk factors. As the MPTA resulted in the lowest postoperative complication rates, this surgical technique is recommended in the young paediatric population (< two years) to decrease the likelihood of developing early minor and major (infectious) complications postoperatively.

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Chapter 3.3

Assessment of anaesthetic and surgical adverse events during cochlear implantation in children

Submitted

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ABSTRACT

Objectives

Paediatric cochlear implantation is performed during infancy to prevent auditory deprivation during the sensitive period. However, multiple anaesthetic procedures are required during diagnostic workup and cochlear implantation, and previous research shows that infants are at higher risk for adverse events during anaesthesia. Therefore, we studied the clinical outcome and adverse events of cochlear implantation in relation to age to define the ideal age for surgery.

Methods

This retrospective study included all anaesthetic and surgical procedures performed between 2008 and 2015 in children who received a cochlear implant in a tertiary paediatric centre. Children were classified according to age at cochlear implantation. We compared anaesthetic and surgical adverse events between age-at-implantation (0 - 12 and 12 - 24 months) and anaesthetic maintenance technique groups (total intravenous anaesthesia and inhalation anaesthesia).

Results

Forty-six cochlear implantations were performed in 43 children requiring 105 anaesthetic procedures. Nineteen procedures (41.3%) were performed during infancy. The maintenance agent was sevoflurane (n = 22) or propofol (n = 24). None of the children encountered major anaesthetic adverse events, whereas minor adverse events occurred during 34 procedures. Those attributed to surgery occurred following six procedures. Neither the age at implantation or the anaesthetic maintenance agent was significantly related to adverse events.

Conclusion

Adverse events occur independent of the age at implantation, the number of anaesthetic preoperative procedures and the type of anaesthetic maintenance agent in ASA 1 or 2 classified children implanted before 24 months of age. Therefore, CI surgery can be performed safely in these children.

INTRODUCTION

Children with profound SNHL are provided with cochlear implants (CIs) when their speech and language development does not develop sufficiently following a hearing-aid trial. Exposure to auditory input during the first year of life is essential to prevent neural plasticity decline that could delay language development[1-6]. Since scheduling cochlear implantation during this critical period of cortex neuroplasticity is essential, most clinicians currently advocate implantation during infancy or early childhood[1-6].

From a surgical perspective, CI surgery is considered a safe procedure with low rates of surgical adverse events, which are irrespective of the age at implantation[7-9]. Previous studies report surgical adverse event rates ranging between 3.2[7] to 24.7%[8]; variation exists due to different definition of adverse events and application of different surgical techniques. Due to these low rates, consensus exists that cochlear implantation can be safely performed during infancy[7-8].

However, there is clear evidence from animal studies that exposure to anaesthesia during infancy could lead to an increased risk of poor neurodevelopmental outcome[10-11]. Besides this potential neurotoxicity, children suffer from relatively higher rates of anaesthetic adverse events compared to adults (4.6 and 1.2% respectively)[12], and even relatively more during infancy than childhood[13]. This is possibly explained by the infants' heart and lung function being more susceptible for cardiac and respiratory adverse events due to their smaller airway, altered drug metabolism, fragile fluid balance and relatively smaller blood volume[12]. Understanding these anaesthesia-related risks could provide crucial information to define the ideal age for cochlear implantation[8]. Furthermore, multiple anaesthetic procedures are required during diagnostic workup for cochlear implantation which could induce a (negative) cumulative effect during the anesthesia of the CI surgery (e.g., preoperative MRI scan).

Previous research showed that propofol can lower the amount of perioperative blood loss: through its hypotensive or vasodilatory actions it can alter the amount of bleeding and optimize the condition of the surgical field[14]. Therefore, some surgeons prefer propofol maintenance anaesthesia to sevoflurane[14]. Furthermore, propofol maintenance anaesthesia is associated with a lower risk of perioperative laryngospasm in children than sevoflurane[15]. Therefore, especially in children with frequent upper respiratory tract infections, the administered anaesthetic maintenance medication could affect clinical outcome.

Hence, we investigated anaesthetic and surgical adverse events in children undergoing cochlear implantation in relation to the age at surgery, in which we accounted for any cumulative effect of previous anaesthesia-related procedures. Additionally, we evaluated the effect of the anaesthetic maintenance technique (total intravenous anaesthesia (TIVA) versus inhalation anaesthesia) on the occurrence of anaesthetic and surgical adverse events.

MATERIALS AND METHODS

In this respective cohort study, all children were included who received a CI before the age of 24 months (within the sensitive period) in a tertiary hospital (Wilhelmina Children's Hospital,

Utrecht, The Netherlands) between January 2008 and July 2015. Electronic patient charts, anaesthetic records (Anaesthesia Information and Management System (AIMS)) and postoperative nursing reports were assessed for any potential adverse event and the clinical outcome. Bilateral simultaneous cochlear implantations were assessed as one anaesthetic procedure. Sequential and CI revision surgeries (< 24 months) were included as separate anaesthetic procedures. We subdivided included CI procedures into two groups: surgery performed < 12 months and between 12 and 24 months, in line with previous reports studying adverse events following paediatric CI surgery[7-9]. To account for any anaesthesia-related cumulative effect, we recorded all preoperative CI-related anaesthetic procedures.

Indication for cochlear implantation was decided upon a multidisciplinary meeting and based on the BERA result and the clinical outcome following an 12-week obligatory hearing aid trial. Aforementioned CI team includes audiologists, speech and language therapists, social workers and otologists[16]. The local ethical committee (UMCU Institutional Review Board) provided approval for this study (protocol number: METC 15-327/C), which is written in line with the STROBE guidelines[17].

Baseline characteristics

The following baseline characteristics were collected: age at birth (prematurity defined as birth < 37 weeks), gender, preoperative weight, hearing loss aetiology, comorbidities, number of preoperative anaesthetic procedures, age at implantation, CI side, recent respiratory tract infections (< two weeks preoperatively) and American Society of Anaesthesiologists (ASA) classification[18]. Extracted anaesthetic variables included: the anaesthetic induction and maintenance technique and perioperative administered medication. The following periods were recorded: surgery duration (first incision until skin closure; minutes), operating room (OR) time (general anaesthesia duration; minutes), Post-Anaesthesia Care Unit (PACU) time (admission until discharge; minutes) and time to discharge (PACU discharge until hospital discharge; days). Follow-up was defined as the period between hospital discharge and last recorded visit during data inclusion (years).

Anesthesia protocol

In accordance with WHO standards[19], all cochlear implantations started with a surgical briefing and time-out procedure. Based on parental preference, children received induction anaesthesia containing intravenous (IV) propofol or sevoflurane induction. Oro-tracheal intubation was performed following administration of sufentanyl (0.1 - 0.3 mg/kg) and muscle relaxation (atracurium 0.5 mg/kg). The paediatric-trained anaesthesiologist defined the type of maintenance anaesthesia (TIVA or sevoflurane inhalation) and intraoperative pain treatment (remifentanyl or sufentanyl). Peri-operatively lidocaine (xylocaïne 1% with adrenaline 1:80.000) was infiltrated retroauricularly by the surgeon. Postoperative analgesia included paracetamol (IV 15mg/kg/6 hr), combined with diclofenac in patients older than 6 months (IV 1 mg/kg/8hr), and morphine (IV 0.1mg/kg bolus and 0.25 mg/kg/24hr continuously) on indication by the attaining anaesthesiologist. Perioperative standard monitoring contained:

an electrocardiogram, pulse oximetry, non-invasive blood pressure, facial nerve monitoring and temperature measurement. All patients were positioned on a heating mattress (38˚C) and covered with a heating blanket (42˚C) to maintain the core temperature between 36.5 and 37.5˚C.

Adverse event classification

Anaesthetic adverse events were classified into: major (stroke, cardiac arrest, sepsis, re-intubation and death[7]) and minor adverse events (laryngospasm and/or bronchospasm, gastrointestinal (nausea, vomiting), fever (> 37.5˚C; present until third day postoperatively), excessive pain, skin reactions, facial oedema and nosebleeds). Furthermore, we collected information regarding the surgical technique (mastoidectomy with posterior tympanotomy approach[20], suprameatal[21] or endaural approach) and perioperative and postoperative major (meningitis or CI infection needing surgical intervention) and minor (skin erythema or infection, acute otitis media (AOM), vertigo, CI device failure needing re-intervention) surgical adverse events occurring within 30 days postoperatively.

Statistical Methods

Data were analysed using IBM SPSS statistics software package (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). We used χ^2-tests, Fisher's exact Test and Mann-Whitney U tests to assess differences between age-at-implantation groups regarding baseline characteristic and perioperative periods (reporting the interquartile range). Quantitative variables and adverse events were analysed using χ^2-tests. Forward logistic regression was used to evaluate the effect of age at surgery and maintenance anaesthesia on adverse event occurrence. Significance was set to a *p*-value of .05.

RESULTS

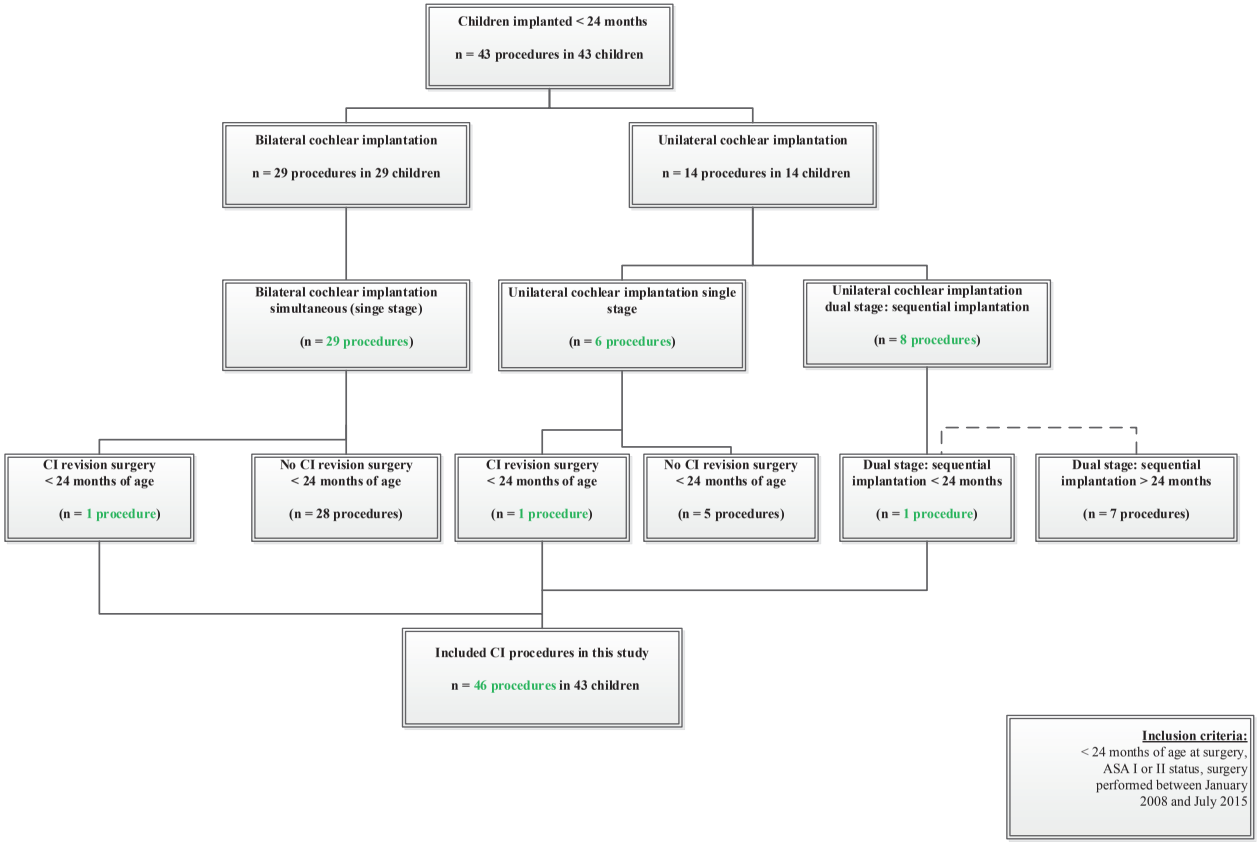
Fifty-nine preoperative anaesthesia procedures related to CI candidate assessment were performed. The number of these procedures per candidate varied significantly between age-at-implantation groups (Table 1). Furthermore, 46 anaesthetic procedures were included that contained cochlear implantation performed in 43 children (Figure 1:19 surgeries performed < 12 months and 27 between 12 and 24 months). Twenty-nine children (67.4%) received bilateral CIs and 14 children received an unilateral CI (Figure 1). Three additional procedures performed before 24 months were included: one sequential CI surgery in an already unilaterally implanted patient and two additional procedures of patients undergoing revision surgery. Aforementioned revision cases included one simultaneously implanted child who was explanted unilaterally due to infection and successfully reimplanted following antibiotic treatment, and, the other child was immediately reimplanted following explantation of an incomplete CI electrode placement due to cochlear ossification following meningitis (Figure 1).

Table 1. Baseline characteristics of included CI procedures (n = 46) performed in 43 children, arranged according to age-at-implantation group (n = 2).

Age-at-implantation group	CI < 12 mo.	CI 12 – 24 mo.	total (% of total)	*p*-value
No. of patients	18	27	45 (100%)	-
Total number of anaesthetic procedures related to cochlear implantation	34	71	105	-
Total number of anaesthetic procedures containing CI surgery	19	27	46 (100%)	-
Total number of preoperative anaesthetic procedures related to CI candidacy assessment	15	44		
Number of preoperative anaesthetic procedures related to CI assessment per individual cochlear implanted child [range]	1 [0-1]	1 [0-3]	n.a.	**.043**
Baseline characteristics				
Females (% of no. of children per age group)	7 (39%)	16 (59%)	23 (50%)	.115
Preoperative weight (kg in mean) (SD)	8.71 (1.43)	10.41 (1.77)		**.006**
Preoperative respiratory tract infection (% of no. of children per age group)	7 (39%)	7 (26%)	14 (31%)	.319
Year of birth [range]	2007 - 2014	2007 - 2014		n.a.
Age at surgery (median in yrs.) [Q1,Q3]	0.79 [0.68,0.94]	1.19 [1.04,1.67]	n.a.	**< .001**
ASA I : II (no. of children per age group)	14 : 4	18 : 9		.430
Prematurity	0	4	4 (9 %)	.108
Comorbidities (% of no. of children per age group)	4 (22%)	10 (37%)		.203
Duration of hospitalization + follow-up				
OR time (median in min.) [Q1,Q3]	267 [226,310]	257 [175,307]		1.00
PACU time (median in min.) [Q1,Q3]	64 [55,87]	60 [49,85]		1.00
Time to discharge (median in days) [Q1,Q3]	2.06 [1.83,2.97]	1.91 [1.73,2.01]		.549
Follow-up time (median in years) [Q1,Q3]	3.62 [1.05,4.87]	4.10 [2.31,5.40]		.549

Legend: ASA = American Society of Anaesthesiologists; CI = Cochlear Implant; IQR = interquartile range; kg = kilograms; min. = minutes; mo. = months; n.a. = not applicable; no. = number; OR = operating room; PACU = Post-Anaesthesia Care Unit; SD = standard deviation. Significant *p*-values are marked in bold.

Figure 1. Flowchart demonstrating included cochlear implant procedures in this study.



Legend: ASA = American Society of Anesthesiologists; CI = cochlear implant; n = number of procedures. Procedures marked in green represent the included CI procedures.

Baseline characteristics

Half of the studied population was female. Aetiology of hearing loss entailed: post-meningitis (n = 7), connexin 26 mutation (n = 3), CMV infection (n = 4), syndrome related (n = 5) and unknown aetiologies (n = 24). These aetiologies did not vary between age-at-implantation groups (p = .099) and did not significantly affect adverse event occurrence (anaesthetic adverse events p = .835; surgical p = .564).

Fourteen children (33%) suffered from comorbidities: epilepsy (n = 2), metabolic disorders (n = 2; antibody synthesis defect and hyperbilirubinemia), neurological pathology (n = 3; encephalopathy, cerebral infarction, psychomotor retardation) and various syndromes (n = 7; Waardenburg (n = 2), Usher, Emanuel, Jervell-Lange-Nielsen, Beckwith-Wiedemann, 7q11.23 duplication). Follow-up and duration of hospital stay did not significantly differ between age-at-implantation groups.

Anaesthetic technique

No significant differences existed between age at implantation groups regarding: ASA classification[18], the number of simultaneous or sequential implantations or applied surgical techniques (Table 1 and Table 2). However, sevoflurane was used significantly (p <.001) more often in the younger group (Table 2). Table 2 shows that both diclofenac and remifentanil were administered significantly more often in the oldest implanted group.

Anaesthetic adverse events

No major anaesthetic adverse events were documented. Most minor anaesthetic adverse events occurred during cochlear implantation, however, one child from the youngest and two children from the oldest group experienced laryngospasm during preoperative CI-related anaesthesia. These events did not affect adverse event occurrence. Fifty-five minor anaesthetic adverse events occurred during 34 anaesthetic procedures containing CI surgery (74%) performed in 32 children (Table 3). Most common minor anaesthetic adverse events were respiratory (n = 13) and gastro-intestinal (n = 17) (Table 3). During 17 of the 34 procedures more than one adverse event was registered (Table 3). Two patients suffered from an adverse event during both the initial and the second anaesthetic procedure (one reimplantation and one sequential implantation). No significant differences existed regarding anaesthetic adverse events between age-at-implantation groups (Table 3).

Surgical adverse events

Surgical adverse events occurred in six children implanted at a mean age of 12.6 months and most events were minor adverse events (n = 5) and related to infection (OM that needed antibiotic treatment (n = 3)) (Table 3).

Table 3 shows that one major surgical adverse event was documented: one patient was suspected of meningitis (2.3%). This latter child developed AOM and fever three days postoperatively.

Table 2. Surgical and anaesthetic techniques used during the included CI procedures (n = 46) performed in 43 children, arranged according to age-at-implantation group (n = 2).

Age-at-implantation group	**CI < 12 mo.**	**CI 12 - 24 mo.**	**total (% of total)**	***p*-value**
No. of patients	18	27	45 (100%)	-
No. of anaesthetic procedures containing CI surgery	19	27	46 (100%)	-
Unilateral vs. bilateral implantation				.173
Unilateral (L) : Unilateral (R)	0 : 5	7 : 5	17 (37%)	
Bilateral simultaneous	14	15	29 (63%)	
CI surgical techniques				.451
MPTA : SMA	6 : 11	9 : 14	46 (100%)	
Endaural	1	0	1 (2%)	
Combined	0	3	3 (7%)	
MPTA (revision) surgery	1	1	2 (4%)	
Anaesthetic techniques				
Sevoflurane : Propofol	15 (79%): 4 (21%)	7 (26%): 20 (74%)	46 (100%)	**< .001**
Sufentanyl (% procedures per group)	15 (79%)	16 (59%)	46 (100%)	.139
Remifentanyl (% procedures per group)	6 (32%)	21 (78%)	46 (100%)	**.002**
Morphine (% procedures per group)	17 (88%)	24 (89%)	41 (89%)	.667
Perfalgan® (% procedures per group)	18 (95%)	26 (96%)	44 (96%)	.661
Diclofenac (% procedures per group)	7 (37%)	21 (78%)	28 (61%)	**.006**
Perioperative administered muscle relaxers				
Atracurium : Mivacurium: none	12 : 0 : 7	19 : 2 : 6		.311
Perioperative administered antibiotics				
Augmentin® : Cefazoline	19 : 0	23 : 4		.108
Perioperative administered anti-emetics				.118
None (% procedures per group)	10 (53%)	12 (44%)	22 (48%)	
Ondansetron (% procedures per group)	3 (16%)	12 (44%)	15 (33%)	
Dexamethasone (% procedures per group)	5 (26%)	3 (11%)	8 (17%)	
Ondansetron + Dexamethasone (% procedures per group)	1 (5%)	0	1 (2%)	

Legend: CI = cochlear implant; L = left; MPTA = mastoidectomy with posterior tympanotomy approach; mo. = months; n.a. = not applicable; no. = number; R = right; SMA = suprameatal approach. Significant *p*-values are marked in bold.

Table 3. Report of anaesthetic and surgical adverse events occurring during the included CI procedures (n = 46) performed in 43 children, arranged according to age-at-implantation group (n = 2).

Age-at-implantation group	CI < 12 mo.	CI 12 - 24 mo.	total (% total no.)	*p*-value
No. of anaesthetic adverse events during 1 CI procedure				.470
0	6	6	12	-
1	5	13	18	-
2	5	6	11	-
3	3	2	5	
No. of anaesthetic procedures	**19**	**27**	**46** (100%)	-
Type of anaesthetic adverse events				
Respiratory event	5	8	13	.538
Gastrointestinal event	8	9	17	.382
Fever	1	3	4	.448
Excessive pain	1	1	2	.661
Skin reaction	1	1	2	.661
Facial oedema	4	6	10	.610
Nose bleedings	4	3	7	.303
Total number of anaesthetic adverse events	**24**	**31**	**55** (during 34 CI procedures (74%))	-
Type of surgical adverse events (< 30 days)				.662
Otitis media treated with AB	2	1	3 (6.5%)	-
Vertigo	1	1	2 (4.4%)	-
Meningitis*	0	1	1 (2.2%)	-
Surgical adverse events (total no.)	**3**	**3**	**6** (during 6 CI procedures (13%))	.484
Type of surgical adverse events (> 30 days)				
Otitis media treated with AB	2	2	4 (8.7%)	-
Skin infection treated with AB	0	2	2 (4.4%)	
CI failure needing intervention	1	1	2 (4.4%)	-
CI infection needing intervention*	2	1	3 (6.5%)	-
Surgical adverse events (total no.)	**5**	**6**	**11** (during 11 CI procedures (23.9%))	.508

Legend: AB = antibiotics; CI = Cochlear Implant; mo. = months; no. = number.
Respiratory anaesthetic adverse events included: bronchospasm, inspiratory stridor, and desaturation. Gastrointestinal anaesthetic adverse events included: nausea, vomiting, and diarrhoea. Major surgical adverse events are marked with an asterisk (*). Group totals are marked in bold.

Although cultures remained negative, a ten-day ceftriaxone and vancomycin empirical treatment was administered. The fever resolved and no long-term meningitis sequelae are present.
Surgical adverse events occurred on average after 11 days. Age at implantation did not affect its occurrence. During long-term follow-up (> 30 days), adverse events were continuously documented: eight minor and three major adverse events were retrieved (Table 3).
The mean age at implantation of long-term complications was 11.6 months (not significantly different from the age at which early adverse events occurred). Two hard failures (one software and one traumatic; mean: 2.3 years postoperatively) and three children undergoing explantation due to infection were identified (mean: 0.84 years postoperatively).
Children, who experienced several anaesthetic adverse events, did not suffer from significantly more surgical adverse events. Furthermore, forward logistic regression showed that none of

Table 4. Report of performed forward logistic regression analysis (n = 2).

Logistic regression regarding anaesthesia related adverse events				
	DF	**Wald statistic**	**Odds ratio (OR)**	***p*-value**
Variable (source)				
Preoperative weight	1	2.57	11.04	.109
Age at surgery	1	.026	.963	.872
No. of anaesthetic procedures related to CI surgery	1	.474	.562	.491
Maintenance agent	1	.623	1.802	.430
Diclofenac administration	1	1.205	.375	.272
Logistic regression regarding surgery related adverse events				
	DF	**Wald statistic**	**Odds ratio (OR)**	***p*-value**
Variable (source)				
Preoperative weight	1	2.09	1.150	.648
Age at surgery	1	.251	.505	.616
Maintenance agent	1	.022	.869	.881
Surgical technique	1	3.127	1.956	.077

Legend: CI = cochlear implant; DF = degrees of freedom; no. = number. Significant *p*-values are marked in bold.

the significant variables (preoperative weight, age at surgery, number of preoperative anaesthetic procedures related to CI assessment, anaesthetic maintenance technique and diclofenac administration) were significantly related to occurrence of anaesthetic or surgical adverse events (Table 4).

DISCUSSION

The present study including all anaesthetic procedures for cochlear implantation in children confirms that the age at implantation and anaesthetic maintenance agent (TIVA or volatile sevoflurane) did not affect clinical outcome in ASA 1 or 2 classified children implanted before 24 months of age. These results are in line with previous reports suggesting that cochlear implantation can be performed safely in infants[4,7-9,22-27]. From an anaesthetic perspective, previous research might advocate to perform elective surgery only in candidates over 12 months since the risk of anaesthetic adverse events is relatively high during infancy[13]. Infants have an increased risk of hypoxia and bradycardia during general anaesthesia, which is caused by their relative immature sympathetic response[28]. A minor respiratory adverse event, such as short-term hypoxia, can therefore lead to severe cardiovascular events[7]. Furthermore, a decreased functional residual lung capacity renders them even more susceptible to hypoxia[7]. Although adverse event occurrence is inversely related to the age at surgery, the benefit of early cochlear implantation[1-6] initiates performing cochlear implantation soon after birth to prevent speech and language developmental delay[29].

Four other studies[7-9,22] evaluated anaesthetic adverse events in relation to age-at-implantation groups. Concordant to our results, no significant differences between age-at-implantation groups were found[7-9,22]. Cohort sizes of included infants (implanted < 12 months) were comparable to our groups[7-9,22].

Several factors could explain why we did not observe a significant difference regarding adverse events between age-at-implantation groups. First, in line with Darlong *et al.*[8], only healthy infants (ASA 1 or 2) were included, whereas higher ASA status could affect adverse event occurrence. Secondly, small surgical incisions and minimal blood loss are common during CI surgery, which have minor impact on the cardiovascular system and are therefore unlikely to result in a major fluid or hematological imbalance[9]. Thirdly, Young[30] already underlined that CI surgery should be supervised by paediatric-trained anaesthesiologist and Keenan *et al.*[31] reported no cardiac adverse events when a paediatric-trained anaesthesiologist (instead of an all-round anaesthesiologist) supervised the surgery. Furthermore, Habre *et al.*[13] advised that before 36 months, children should be managed by paediatric-trained anaesthesiologist to reduce adverse event risk. Therefore, in line with our study, a paediatric-trained anaesthesiologist should administer anaesthetics in these children.

According to the results from our study, infants can be safely implanted receiving both types of anaesthetic maintenance medication. This is the first study assessing this relationship and also, accounting for administered preoperative anaesthetic procedures. Three other paediatric CI studies[8,9,22] reported the administered maintenance anaesthetic agent, however, did not relate its administration to adverse event occurrence nor accounted for the number of administered preoperative anaesthetic procedures. Both Holman *et al.*[22] and Darlong *et al.*[8] used volatile maintenance in all patients. Yeh *et al.*[9] used a combination of an inhalational agent (sevoflurane or isoflurane) with an opioid (fentanyl) (75.6%) or IV propofol (24.4%). The latter patients were older than ten years, but no relation between the age at implantation and propofol administration was observed[9], which is contrary to our results, since we found that children who received sevoflurane were significantly younger, because these children are less likely to cooperate with peripheral IV insertion[9].

Reported anaesthetic adverse event rates following cochlear implantation (< 18 years) vary between 0[4,7,9,22] to 8.4%[8]. Respiratory events are reported to occur more frequently during ENT surgery[32]. Similarly, respiratory incidents are the most frequently reported anaesthetic adverse events following cochlear implantation in children (4.7%[9]). These respiratory adverse events are more likely to occur due to the infants' additional physiological risk factors[13,22]: following general anaesthesia, more airway irritation occurs due to their immature and narrow trachea. For example, Yeh *et al.*[9] reported that laryngospasm could already result from inhalational induction in children. Furthermore, preoperative respiratory tract infections, frequently seen in children, can further provoke respiratory adverse events such as coughing, stridor and bronchospasm[33]. In line with this finding, Darlong *et al.*[8] identified an association between respiratory tract infections (occurring two - four weeks preoperatively) and intraoperative laryngospasm. Although, von Ungern-Sternberg *et al.*[15] specified that sevoflurane administration could lead to significantly more laryngospasm in children. Respiratory adverse events did not differ between groups in which different anaesthetic maintenance techniques were administered in the current study.

In line with O'Connell *et al.*[7], none of our patients suffered from major anaesthetic adverse events. However, during 34 anaesthetic procedures containing cochlear implantation, minor anaesthetic adverse events were reported, which is high compared to aforementioned results from previous studies (0[4,7,9,22] to 8.4%[8]). We analysed three different data sources; a stringent approach that could have resulted in identifying relatively more anaesthetic adverse events than previous studies. Furthermore, reported events could have been considered too minor to report by previous authors. For example, the level of nosebleeds was high (15.2%), most likely resulting from intraoperative nasal thermometer use.

Since postoperative pain levels are difficult to measure in children, establishing adequate postoperative analgesia is essential[8,34]. However, few studies report on postoperative pain relief requirements[34]. Birman *et al.*[34] reported that 31.2% of the children did not need analgesia following CI surgery and indicated analgesics use was distributed similarly among five age-at-implantation groups. In our cohort, diclofenac was administered significantly more in the older group. This relation can be explained two-fold: firstly, no diclofenac is administered in children below six months in our hospital according to our local protocol, and secondly, this group of children might have needed additional diclofenac because of the high rate of bilateral CI. Following bilateral surgery, children have no pain free side to lie on and are reported to need postoperative analgesics during a longer period[34].

Previous studies report surgical adverse event rates ranging between 3.2[7] and 24.7%[8]. Therefore, the 13% adverse event rate of this study is relatively high. A recent review reported a meningitis occurrence of 0.15% in CI patients (8/5234)[35], indicating that meningitis following CI surgery is rare. The child who was suspected of meningitis received empirical antibiotic treatment in accordance with studies suggesting aggressive AOM and mastoiditis treatment to reduce meningitis risk[36,37]. Our meningitis patient did not undergo a lumbar puncture to confirm diagnosis and could be preventively over-treated; excluding this case results in a 10% adverse event rate.

In this study, the type of maintenance anaesthesia depended on the preference of the paediatric-trained anaesthesiologist. Some surgeons prefer propofol maintenance since it could result in less bleeding, and therefore, provide a superior surgical field than sevoflurane[14]. Although TIVA could affect blood loss, we did not find any significant relation with its administration and lower rates of perioperative bleeding, nosebleed occurrence or adverse events.

The majority of implanted children stayed one night postoperatively (Table 1). O'Connell *et al.*[7] intend to discharge children directly from the PACU when no unexpected postoperative issues arise. Although minor anaesthetic adverse events do not lead to serious long-term complications, they can still result in less comfortable children and more anxious parents, especially if their child is not hospitalized[9]. Both the high minor anaesthetic adverse event rate (74%) and perioperative morphine administration resulting in more gastro-intestinal adverse events in the current study, seem to favour a 1-day hospitalization following cochlear implantation in children. However, implementation of adjusted anaesthetic protocols could lead to performing day-case surgery successfully.

CONCLUSION

Anaesthetic and surgical adverse events occur independent of: the number of anaesthetic preoperative procedures, the anaesthetic maintenance agent during surgery and the age at implantation in ASA 1 or 2 classified children implanted before 24 months of age. Therefore, adverse events are limited and CI surgery can be performed safely in these children using both anaesthetic maintenance medication types.

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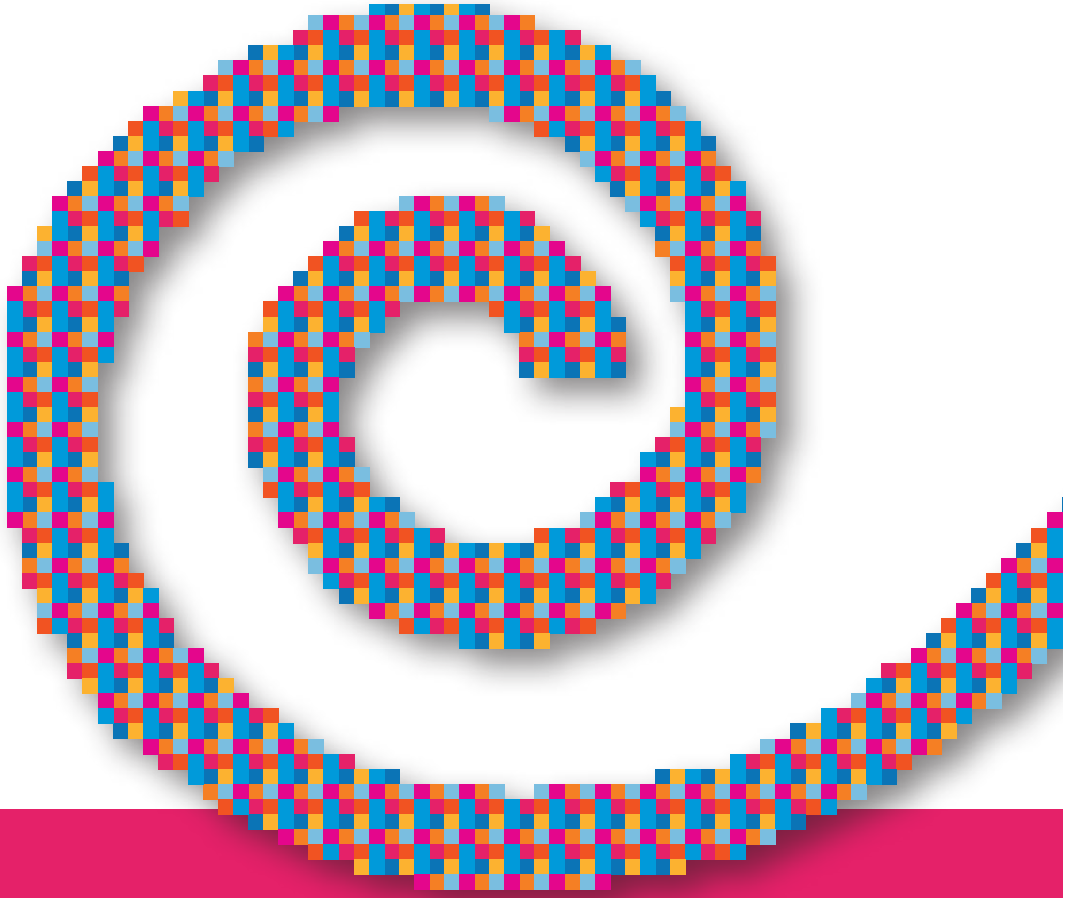
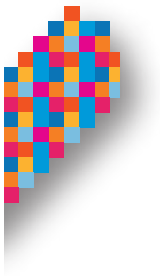


PART IV

Definition of delay regarding cochlear implantation in children in Europe



Chapter 4.1

Evaluation of timely paediatric cochlear implant care throughout Europe

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ABSTRACT

Objectives

International guidelines indicate that children with profound SNHL should receive a CI soon after diagnosis in order to optimize speech and language rehabilitation. Although prompt rehabilitation is encouraged by current guidelines, delays in cochlear implantation are still present. This study investigated whether European countries establish timely paediatric CI care based on epidemiological, commercial and clinical data.

Methods

An estimation of the number of paediatric CI candidates in European countries was performed and compared to epidemiological (Euro-CIU), commercial (Cochlear®) and clinical (institutional) age-at-implantation data. The ages at implantation of paediatric patients in eight countries (the Netherlands, Belgium, Germany, the United Kingdom, France, Turkey, Portugal and Italy) between 2005 and 2015 were evaluated.

Results

From 2010 onwards, over 30% of the paediatric CI candidates were implanted before 24 months. Northern European institutions implanted children on average around 12 months of age, whereas southern European institutions implanted children after 18 months. The Netherlands and Germany implanted earliest [between six - 11 months].

Discussion

Implemented new-born hearing screening programs and reimbursement rates of CIs vary greatly within Europe due to local, social, financial and political differences. However, internationally accepted recommendations are applicable to this heterogeneous European CI practice. Although consensus on early paediatric cochlear implantation exists, this study identified marked delays in European care.

Conclusion

Regardless of the great heterogeneity in European practice, reasons for latency should be identified on a national level and possibilities to prevent avoidable future implantation delays should be explored to provide national recommendations.

INTRODUCTION

The WHO estimates that 360 million people suffer from hearing loss worldwide[1]. Thirty-three million (9%) of these individuals are children[1]. The highest paediatric hearing loss prevalence is reported in South Asia (2.4%), Pacific Asia (2.0%) and Sub-Saharan Africa (1.9%)[1]. Paediatric hearing loss prevalence rates in developed countries are considerably lower: 0.8 million children (0.5% of the entire paediatric population with hearing loss) suffered from hearing loss in high-income countries in Western Europe and North America in 2012[2].

In Western Europe and North America, NBHS is used to identify hearing loss at birth, which is estimated to occur in 0.943 to 1.182 per 1000 new-borns[3-5]. However, this prevalence is underestimated because not all children with hearing loss are identified at initial NBHS. Others can be identified later on in life due to factors such as immigration or progressive hearing loss. Fortnum *et al.*[6-7] describes that paediatric hearing loss occurs in 1.07 per 1000 children aged three years or younger, in 1.33 to 1.44 per 1000 children between five and ten years of age and rates increase to 2.05 per 1000 children when the paediatric cohort reached 16 years.

When applying Fortnum's hearing loss prevalence rates[7] to European birth-rates, we could estimate that in 2014, the E-28 included between 4829 and 6053 new-borns suffering from hearing loss identified at NBHS, which could have increased to 10 497 children when this birth cohort reached 16 years[8-9]. Authors estimated that between 30 and 45% of these new-borns present with profound sensorineural hearing loss (SNHL) and can therefore benefit from cochlear implantation[10]. More specifically, Raine[11] estimated that 20% of the children diagnosed with severe hearing loss (70 - 90 decibel (dB)) suffer from a hearing loss of at least 85 dB, thereby qualifying for a cochlear implant (CI) in for example Belgium[12]. Davis *et al.*[13] reported that 37% of aforementioned potential CI candidates are missed at initial NBHS. In line with this report, Korver[14] revealed that around 35% [26 - 44%] of the children with profound SNHL were not identified at Dutch NBHS. Nonetheless, in the Netherlands and Belgium, studies have estimated that between 80 to 95% of the children diagnosed with profound SNHL received a CI[10,15]. In the United States, Sorkin[16] reported that only 50% of children who could potentially benefit from a CI actually received one compared to the 90% reported in the Flanders part of Belgium and the United Kingdom (UK). This could indicate that American paediatric CI candidates are a relatively underserved population[16-17].

International CI guidelines state that children with profound SNHL should receive a CI soon after diagnosis to shorten the period of auditory deprivation and to optimize speech and language rehabilitation using the optimal window of brain plasticity[12,18-19]. However, there is a great gap between aforementioned guidelines and current European paediatric CI practice due to differences in NBHS implementation and CI reimbursement rates. Although countries have the intention to start prompt hearing rehabilitation, implantation delays are still present[20].

To evaluate the implementation of aforementioned international recommendations and to examine whether European countries establish timely CI care for early childhood SNHL, epidemiological, commercial and clinical data from five institutions across Europe were investigated.

METHODS

To evaluate whether timely CI care for childhood SNHL is established, national numbers of paediatric CI candidates were estimated. We developed two tools that aid at estimating the proportion of paediatric CI candidates in each country using national epidemiological data. New-born hearing screening data were based on pre-established hearing loss levels for candidacy by either brainstem evoked response audiometry (BERA) (Belgium) or otoacoustic emissions (OAEs) (the Netherlands).

The second step in the evaluation of timely CI care for childhood SNHL is to assess the age at implantation. Cochlear® data were used to evaluate the development of mean ages of paediatric cochlear implant candidates in eight countries (The Netherlands, Germany, the UK, Portugal, Italy, Belgium, France and Turkey) between 2005 and 2015.

The third step in the evaluation of timely CI care for childhood SNHL is to assess whether national reported age-at-implantation numbers are in line with those at local institutions. Therefore, we collected data on paediatric CI surgeries performed between 2005 and 2015 from five collaborating European institutions: (UMC Utrecht (The Netherlands) and MMH Hannover (Germany)) and three paediatric hospitals (Birmingham Children's Hospital (UK), Santobono (Italy) and Dona Estefânia Hospital (Portugal)).

Step 1. Estimation of the number of paediatric CI candidates using Belgian and Dutch epidemiological data

1. Estimation of the number of paediatric CI candidates using Belgian epidemiological data

We identified the ratios of new-borns suffering from severe (70 - 90 dB) and profound (> 90 dB) hearing loss from previous investigations[21]. A hearing loss of at least 85 dB is a CI indication in Belgium[12]. Therefore, the number of potential paediatric CI candidates was estimated by combining 20% of children with severe hearing loss (85 - 90 dB) and all children with profound SNHL (> 90 dB) identified at NBHS. Belgian birth rates from 2012 and 2013 and incidences of new-borns with hearing loss identified at NBHS were used[21-23]. To include the population of non-identified children in our estimation, we added 50% of the children presenting with hearing loss not identified at NBHS (0.019% of the national birth rate)[4]. Only half of aforementioned population was included since 50% of these children are assumed to suffer from SNHL profound enough to qualify for a CI[14]. To assess the accuracy of our estimation, we compared the number of estimated CI candidates with the number of reported paediatric CI implantations in Belgium[24]. In Belgium, the number of re-implantations is not separately reported and was therefore not excluded from this comparison[24].

2. Estimation of the number of paediatric CI candidates using Dutch epidemiological data

To estimate the number of Dutch CI candidates identified at NBHS in 2012, 30 to 45% of new-borns that presented with profound SNHL[10] were selected from all new-borns that presented with hearing loss at NBHS[25]. In line with the Belgian estimation, 50% of the 0.019%[4] of the Dutch birth rate in 2012[26] was added to this initial number. To assess the

accuracy of our estimation, we compared the number of estimated CI candidates with national reports on performed CI surgeries in children[27]. Re-implantations were excluded from this analysis[27].

Step 2. Identification of the age at implantation of paediatric CI candidates using commercial data

The proportion of children implanted before the age of 12 and 24 months were compared between assessed countries. Statistical comparison between national implantation percentages from European countries was performed using independent t-tests from IBM SPSS Statistics were used (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). Statistical significance was set at $p = .05$.

Step 3. Identification of the age at implantation of paediatric CI candidates using institutional data from five leading paediatric CI centers

The mean age at implantation of the selected paediatric cohorts from included institutions was calculated, compared with other included European institutions and with national age-at-implantation numbers (Cochlear® data).

RESULTS

Step 1. Estimation of the number of paediatric CI candidates using Belgian and Dutch epidemiological data

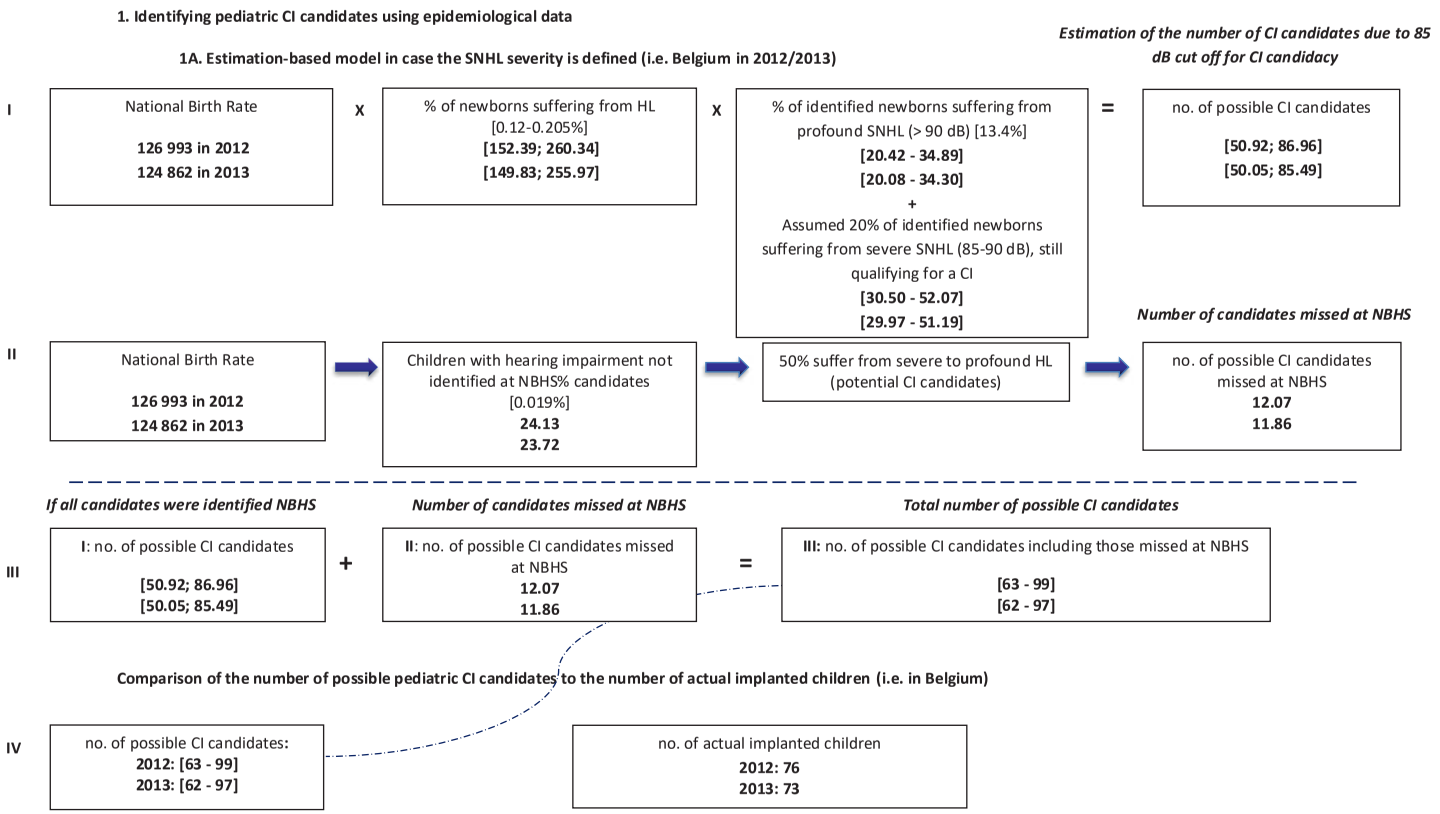
1. Estimation of the number of paediatric CI candidates using Belgian epidemiological data

Figure 1A shows the estimation of paediatric CI candidates using Belgian birth rates from 2012 and 2013[22-23]. In Belgium, between 152 and 260 children (2012) and between 150 and 256 children (2013) were estimated to present with hearing loss at NBHS (Figure 1A - I). Figure 1A – I shows that only part of these children are estimated to be possible paediatric CI candidates: between 51 and 87 (2012) and between 50 and 86 (2013). Application of the hearing loss missed at NBHS (0.019%) prevalence revealed that 24 children in both years were estimated to present with hearing loss not identified at NBHS (Figure 1A - II)[4]. Figure 1A – III indicates that between 63 and 99 (2012) and between 62 and 97 children (2013) were estimated to be Belgian paediatric CI candidates based on audiology criteria. The number of actual implanted Belgian children in 2012 (n = 75) and 2013 (n = 73) was in line with this estimation (Figure 1A - IV)[24].

2. Estimation of the number of paediatric CI candidates using Dutch epidemiological data

Since 119 children presented with hearing loss at NBHS, between 36 and 54 children (30 – 40%) were estimated to be paediatric CI candidates in 2012 (Figure 1B - I)[14, 25]. Figure 1B - II indicates that in 2012, approximately 17 additional paediatric CI candidates were missed at NBHS in 2012 (50% of 33 possible CI candidates)[14,26], which indicates that in total between

Step 1. Estimation of the number of paediatric CI candidates using Belgian and Dutch epidemiological data
Figure 1A. Identifying paediatric CI candidates using epidemiological data. (A) Estimation-based model in case the SNHL severity is defined (Belgium in 2012/2013)



Legend: CI = cochlear implant; dB = decibel; HL = hearing loss; NBHS = new-born hearing screening; no. = number; SNHL = sensorineural hearing loss.

52 and 70 children were estimated to be Dutch paediatric CI candidates based on audiology criteria in 2012 (Figure 1B - III). In this year, more implantations (n = 75)[27] were performed than our estimation suggested (between 52 and 70 children) (Figure 1B - IV).

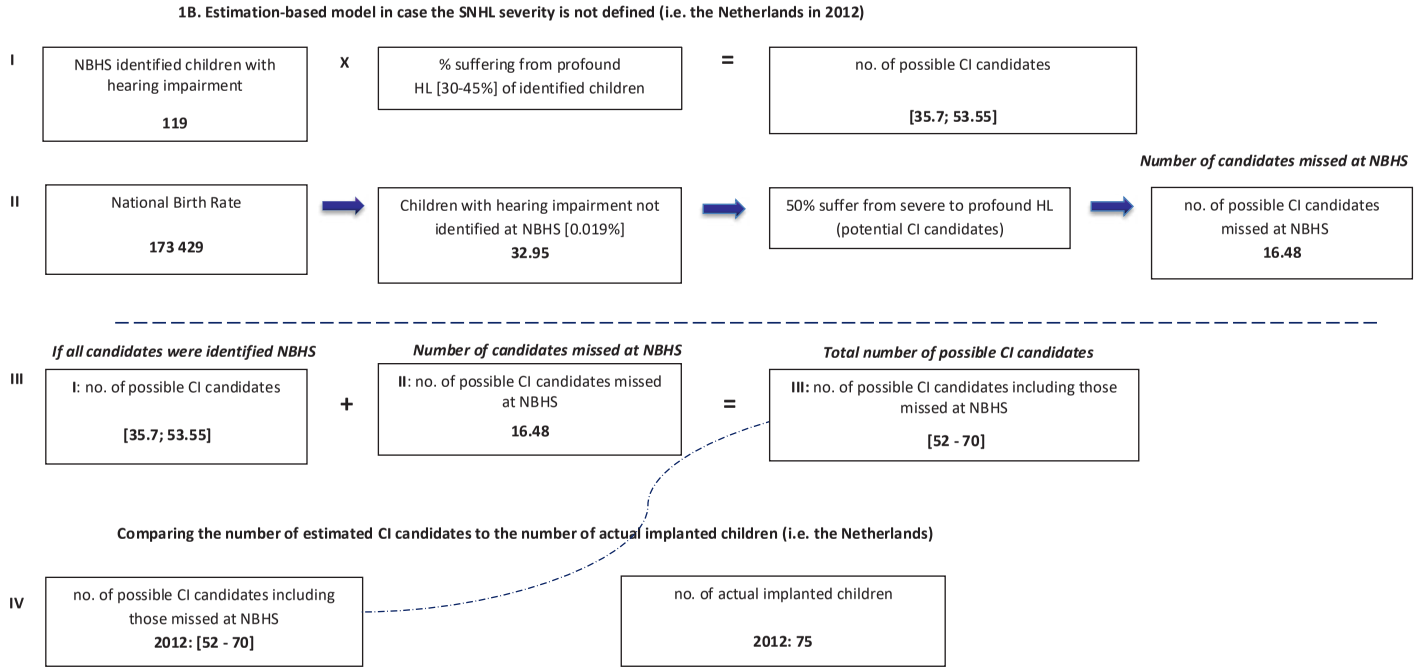
Step 2. Identification of the age at implantation of paediatric CI candidates using commercial data

Figure 2A demonstrates that, in 2015, assessed European countries implanted over 30% of their paediatric candidates before 24 months of age. Cochlear® implantation percentages of included countries were less variable in 2015 [32.07 - 51%] compared to those in 2005 [5.88 - 47.76%]. In addition, Figure 2B shows that, in 2015, a significant ($t(4) = 5.94$, $p = .004$) difference existed between the proportions of children implanted before the age of 12 months in northern ([18 – 28%] Netherlands, Belgium and Germany) compared to southern ([0 – 6%] France, Portugal and Turkey) European countries. Cochlear® age-at-implantation distributions demonstrate that, in 2014, the Netherlands and Germany implanted the largest proportion of paediatric patients before the age of 12 months (25 and 15% respectively) (Table 1). The other six assessed countries implanted the largest proportion of their cohort between 12 and 17 months (Table 1 - marked in **bold**). Portugal and Turkey implanted a relatively large proportion of their paediatric population around three years of age (19 and 17% respectively). Table 1 shows that a (second) age-at-implantation peak between three and four years was noticed in all studied countries [8 - 19%].

Step 3. Identification of the age at implantation of paediatric CI candidates using institutional data from five leading paediatric CI centers

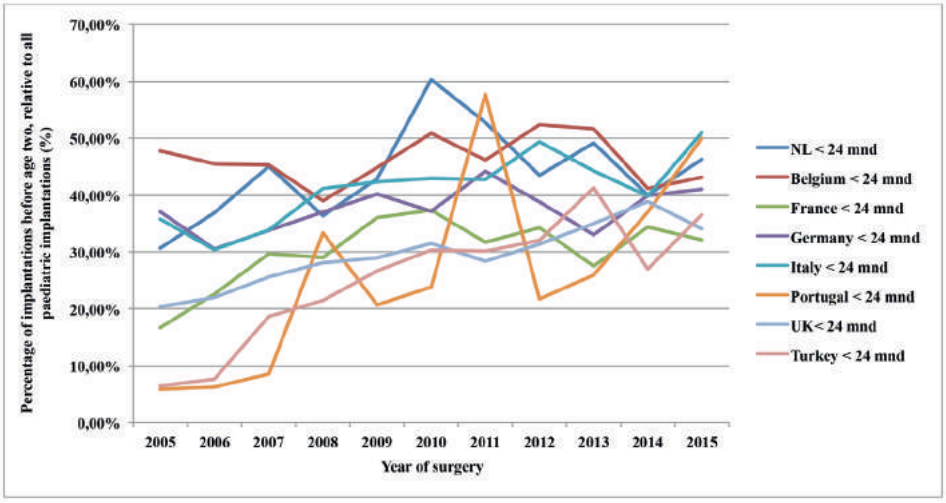
The selection of age-at-implantation data from five paediatric CI institutions resulted in the inclusion of 490 paediatric CI surgeries (the Netherlands; n = 102, Germany; n = 164, the UK; n = 93, Portugal; n = 49, Italy; n = 82) (Figure 3A). Children implanted before three years of age were pooled separately (n = 322) to investigate prelingual SNHL as a CI indication (Figure 3B). Both Figure 3A and Figure 3B show that northern European institutions implanted CI candidates earlier (around 12 months) than the selected southern European institutions (around 18 months) between 2010 and 2015.

Step 1. Estimation of the number of paediatric CI candidates using Belgian and Dutch epidemiological data
Figure 1B. Identifying paediatric CI candidates using epidemiological data. (B) Estimation-based model in case the SNHL severity is not defined (the Netherlands in 2012)



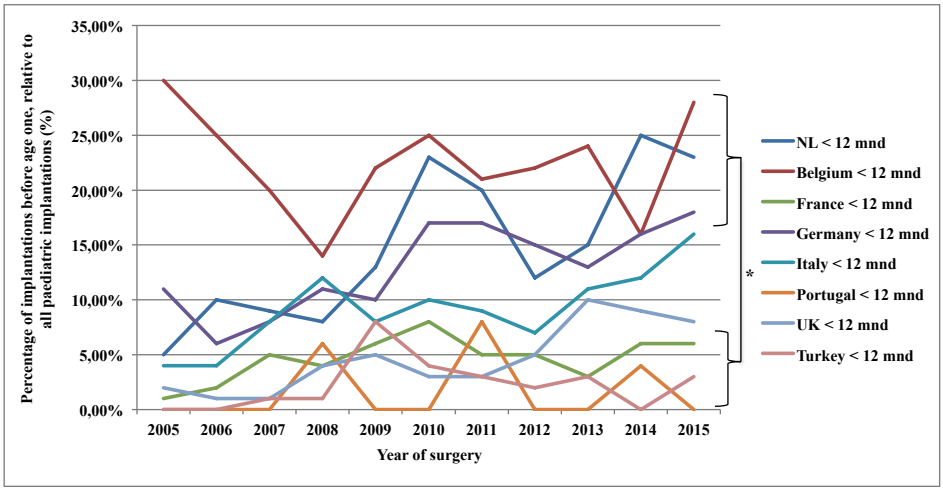
Legend: CI = cochlear implant; dB = decibel; HL = hearing loss; NBHS = new-born hearing screening; no. = number; SNHL = sensorineural hearing loss.

Step 2. Identification of the age at implantation of paediatric CI candidates using commercial data
Figure 2A. Comparison of the annual proportion of children implanted before the age of 24 months between eight European countries between 2005 and 2015



Legend: CI = Cochlear Implant; NL = the Netherlands; UK = United Kingdom.

Step 2. Identification of the age at implantation of paediatric CI candidates using commercial data
Figure 2B. Comparison of the annual proportion of children implanted before the age of 12 months between eight European countries between 2005 and 2015



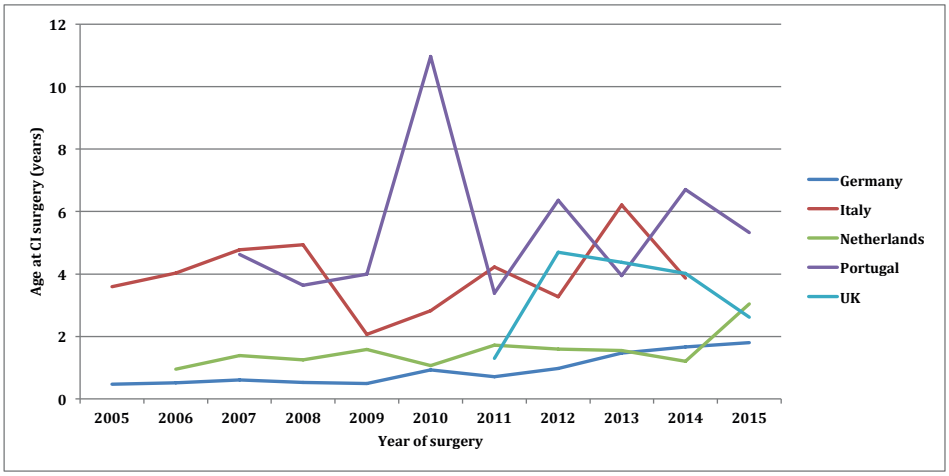
Legend: CI = Cochlear Implant; NL = the Netherlands; UK = United Kingdom. The astersisk marks the statistical difference between compared groups (t (4) = 5.94, p = .004).

Step 2. Identification of the age at implantation of paediatric CI candidates using commercial data
Table 1. Cochlear® data demonstrating the proportion of children in separate age-at-implantation groups in eight countries in 2014

Age-at-implantation cohorts	NL	Germany	The UK	Portugal	Italy	Belgium	France	Turkey
< 6 months	0%	1%	1%	0%	1%	0%	0%	0%
6 - 11 months	**25%**	**15%**	8%	4%	11%	16%	5%	0%
12 - 17 months	5%	14%	**15%**	**26%**	**19%**	**20%**	**17%**	**16%**
18 - 23 months	11%	10%	15%	7%	9%	6%	12%	10%
24 - 29 months	6%	8%	7%	7%	12%	8%	9%	13%
30 - 35 months	5%	5%	4%	11%	6%	2%	7%	10%
3 years	6%	6%	**8%**	**19%**	**10%**	4%	**11%**	**17%**
4 years	**12%**	**8%**	5%	4%	6%	**10%**	5%	8%

Legend: CI = cochlear implant; NL = the Netherlands; UK = United Kingdom.

Step 3. Identification of the age at implantation of paediatric CI candidates using institutional data from five leading paediatric CI centers
Figure 3A. Comparison of the mean age-at-implantation of all prelingual and postlingual children implanted at five European institutions (n = 490)



Legend: CI = Cochlear Implant; UK = United Kingdom.

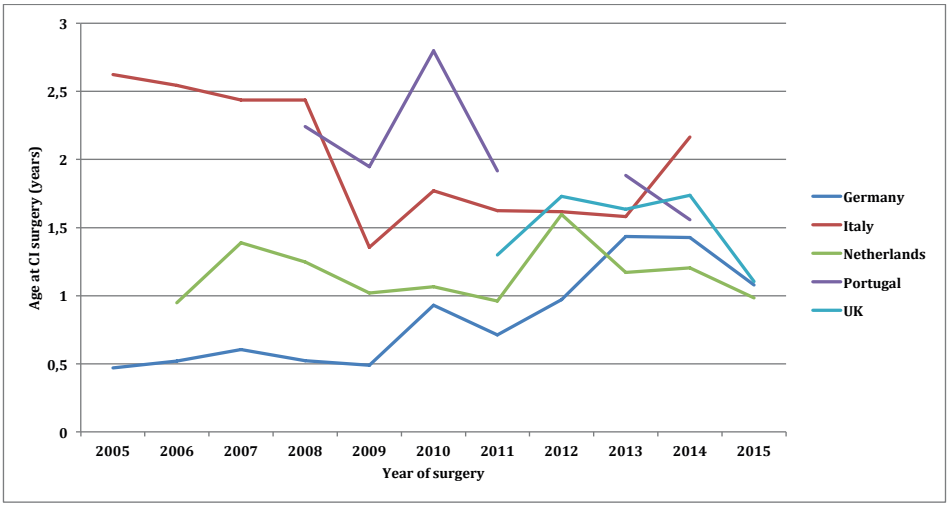
DISCUSSION

Key Findings – Interpretation

Infants presenting with profound SNHL should receive a CI soon after confirmation of candidacy to shorten the period of auditory deprivation[12,18-19]. To prevent delays, nationwide NBHS programs have been implemented to identify children with SNHL soon after birth and shorten the auditory deprivation period. Hence, benchmarks similar to the '1 - 3 - 6 Plan' have been developed[28]. This plan aims to increase the proportion of new-borns being screened for hearing loss by one month of age, having had diagnostic audiology evaluation by three

Step 3. Identification of the age at implantation of paediatric CI candidates using institutional data from five leading paediatric CI centers

Figure 3B. Comparison of the mean age-at-implantation of all prelingual children (< three years) implanted at five European institutions (n = 322)



Legend: CI = Cochlear Implant; UK = United Kingdom.

months of age and being enrolled in an early intervention program by six months of age[28]. Nonetheless, implantation delays are still present[20].

Bradham and Jones[17] suggested implantation delays still exist primarily due socioeconomic status differences, insufficient reimbursement rates, parental opposition, immigration and a shortage of qualified personnel to serve paediatric CI candidates.

We used a three-step model to evaluate whether the implementation of aforementioned international recommendations is accurately established in Europe. Our estimation of the national number of paediatric CI candidates can be used to study and predict trends of current paediatric CI practice by health care providers, public policy makers and epidemiologist and researchers, and ultimately, enlarge public awareness and improve access to CI care for children having profound hearing loss[17].

The provided estimation-based models are a prediction to anticipate on the national paediatric CI candidate numbers. These models entail country specific characteristics (e.g., the NBHS method, CI implantation criteria). Therefore, the models cannot be applied uniformly to other countries and should be adjusted based on specific country based implantation criteria. Although we found that more children were implanted before 12 months of age in northern European (Belgium, Germany and the Netherlands) compared to Mediterranean countries (Turkey, Portugal and France), the infant European CI population (< 12 months) is still underserved throughout Europe. Relative differences in providing early interventions for SNHL children between northern and southern European countries can be explained by both a lack of nationwide-implemented NBHS programs[29] and the novelty of this screening.

NBHS coverage differs between regions, cities and even institutions in countries such as Italy[30]. In several Portuguese hospitals, NBHS was in a pilot phase only in 2010 in an attempt to address paediatric hearing loss identification delays[31] compared to, for example, the Netherlands that provides more than 90% NBHS coverage since 2006[30]. Therefore, Lammers *et al.*[32] already acknowledged that a well-established NBHS is essential in providing timely intervention for paediatric CI candidates.

Belgian clinics implanted the largest proportion of children before the age of 18 months (36%). This could be the result of early Belgian NBHS implementation in 1998 that warranted early identification of children with SNHL. Nevertheless, in Belgium, only partial NBHS is, or was initially, implemented[30]. Although NBHS was implanted early in the Belgian Flanders region, in the Walloon region NBHS was only implemented in 2006[15,34].

This NBHS implementation in the Walloon region could explain the steep decline in age at implantation between 2005 and 2008. Similarly, in Germany no system is implemented which assures that children identified with SNHL are subsequently seen and examined by an audiologist or ENT-physician following NBHS[32]. Contrarily, Belgium national screening centres receive obligatory anonymous feedback whether a child failed or passed screening. A recent study from the United States emphasizes on the lack of parental awareness of the importance of these hearing screening tests that could be applicable to European countries[35]. Educating parents on the importance of children who do not pass screening could greatly improve follow-up and hence, prompt early intervention if indicated.

The Netherlands and Germany implanted the highest proportion of children between six and 11 months. In line with these commercial data, clinical data showed that both the Dutch and German institution implanted their CI candidates relatively younger compared to other institutions. Implementation of Dutch NBHS led to significantly earlier cochlear implantation at our institution[32]. In several German centres, a series of diagnostic procedures is performed during a short (three-day) inpatient hospital stay[36]. This prompt CI candidacy evaluation minimizes diagnostic delay and could explain why both commercial and clinical data show that Germany established timely intervention.

Since countries like Germany, where only a partial NBHS program is implemented[30], were still able to implant most paediatric candidates before 12 months of age, additional reasons could affect implantation latency. Duarte *et al.*[33] suggested that decreased Portuguese paediatric CI numbers between 2011 and 2012 resulted from the effect of the economic crisis on tax-financed health care systems. Cochlear® percentages from those years also showed an implantation decline, which could result from the economic crisis between 2010 and 2011. In addition to these financial issues[33], partial NBHS implementation[30], delays in informing audiology centres on the number of NBHS failures[32], acquired hearing loss after birth[37], family opposition or cultural delay[17, 32], limited parental education[35], immigration[38] or limited access to CI care[17] could have also affected paediatric cochlear implantation delays in all assessed countries. Aforementioned reasons could explain the second age-at-implantation peak we

retrieved: between eight and 19% of the children were implanted between three and four years in all evaluated countries. This trend could reflect children who are implanted later either due to patient (e.g., post-lingual SNHL, progressive SNHL, immigration, family opposition) or healthcare delay (e.g., lack of a tracking system[32] or delayed reimbursement approval).

Limitations

Acquired hearing loss, resulting from an external factor (e.g., meningitis, ototoxic drugs, trauma, neonatal hyperbilirubinemia) occurring after a normal NBHS test result can cause delayed SNHL identification and could result in delayed cochlear implantation[37]. The NBHS unidentified cohort of children with hearing loss could contain up to 20% of children who acquire hearing loss later in life primarily due to meningitis or progressive hearing loss[13]. We aimed to correct for this confounder by including a reported prevalence of children with hearing loss not identified at NBHS into our estimations[4]. Nonetheless, this confounder could have still affected our analysis and could have led to an underestimation of the final paediatric CI provision rate.

Contrarily to the Dutch estimation, the number of implanted children included CI re-implantations in Belgium. Exclusion of these cases was not possible and could have hindered the accuracy of our estimation. Moreover, this could have indicated that we overrated the paediatric CI provision rate in Belgium. Alternatively, the Belgian estimation could have provided a more accurate CI provision rate than the Dutch estimation, as the collection of Belgian data could be more accurate. Implantation numbers reported by the Belgian National Institute for Health and Disability Insurance (RIZIV) reflect actual preoperative reimbursements by insurance companies, whereas Dutch CI-ON numbers are retrospectively retrieved data provided via voluntary self-report of CI institutions. This could explain why the Belgian estimation more accurately reflected reported CI provision rates.

Another aspect that could have affected the accuracy of our estimated national CI provision rates is the inclusion of reported hearing loss prevalence estimations. These estimations vary on a national basis, shown by the difference in estimated paediatric hearing loss prevalence in Belgium and the Netherlands (30%[21] and between 30 - 45%[10] respectively). Furthermore, for the Netherlands this range was included, whereas for Belgium one reported value was selected which could have affected our estimation accuracy.

Fourthly, our calculations included data strictly from one CI manufacturer (Cochlear®). Therefore, our evaluations only represent a proportion of European paediatric cochlear implantation. However, the Cochlear® market share is reported to be relatively the highest of current main CI manufacturers (between 53%[39] and 62%[40]).

Ultimately, only one institution per country was assessed. Nonetheless, all selected institutions are top-3 national paediatric cochlear implantation centres and therefore, most likely represent national implantation trends.

CONCLUSION

European paediatric cochlear implantation trends over the past ten years revealed that early paediatric CI care (before < 24 months) is performed in Europe. To achieve timely care, NBHS programs and the '1 - 3 - 6 Plan' have been implemented. Although there is an increasing trend towards implanting children earlier, the infant CI population (< 12 months) is still a minority of the paediatric CI population, especially in southern Europe. In order to limit the duration of auditory deprivation, early auditory intervention for the infant population needs to be realized. Future studies investigating European reasons for paediatric cochlear implantation latency are recommended. These studies could define tailored national and European recommendations to ensure that European countries establish timely cochlear implantation care for early childhood SNHL in line with international recommendations.

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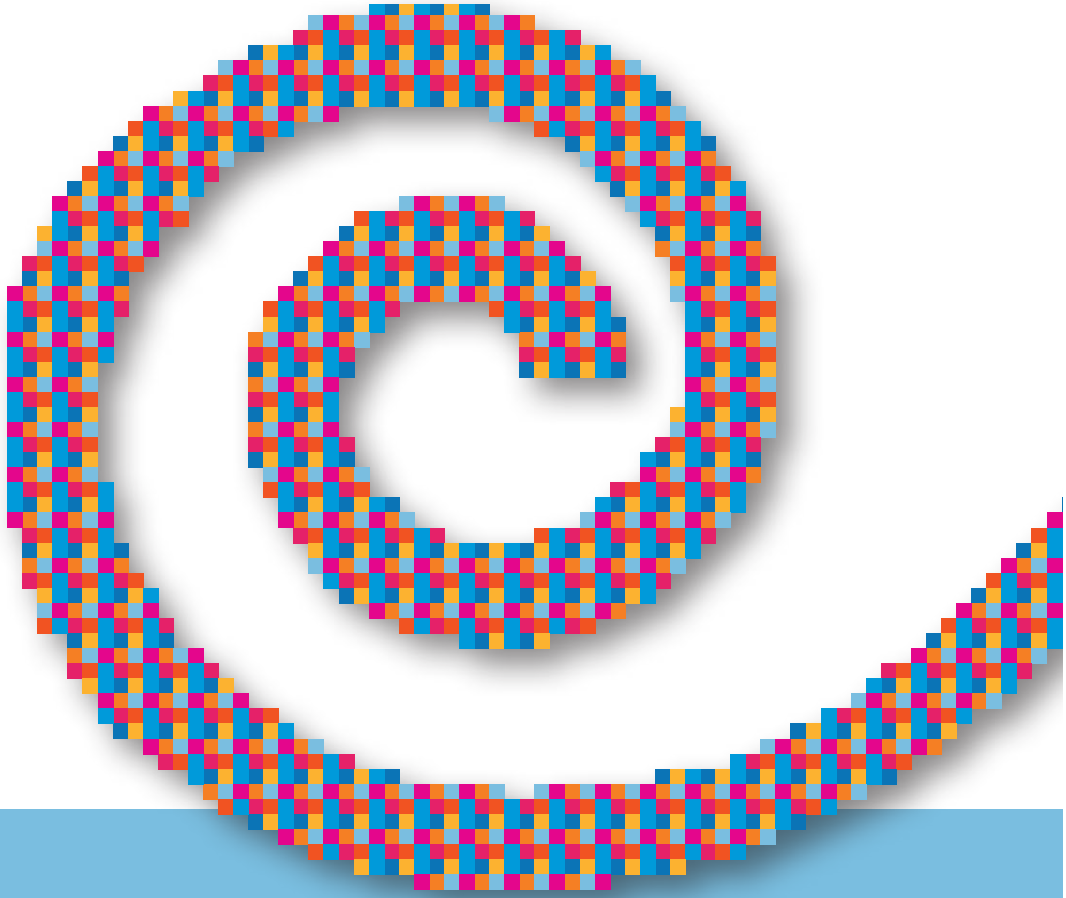
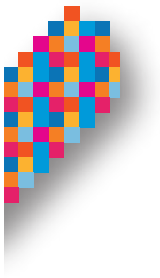


PART V

Definition of quality of life consistency between children and their parents following cochlear implantation



Chapter 5.1

Quality of life (QoL) evaluation of children using cochlear implants: consistency assessment between paediatric and parent proxy-QoL reports

Submitted

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ABSTRACT

Objectives

There is a great variability between paediatric and parent-reported proxy-Quality of Life (QoL) questionnaires. The objective of the present study was to define the age at which QoL is most consistent between paediatric and parent-reported questionnaires and to provide insight for reported QoL variability during postoperative cochlear implant follow-up.

Methods

Paediatric cochlear implant recipients who were implanted before 36 months of age and their parents were included in this cross-sectional study. We evaluated postoperative QoL using two questionnaires: The Paediatric Quality of Life Inventory (PedsQL) and the Glasgow Children Benefit Inventory (GCBI). To assess consistency between paediatric and parental QoL perception, PedsQL intra-class correlations (ICCs) were calculated.

Results

Forty-four questionnaires were returned (response rate: 55.6%). Children who were evaluated between eight to 12 years of age reported highest absolute total and subscale PedsQL scores. Highest consistency was found when: the PedsQL score was ≥ 60.00 (p = .0001); children were between eight to 12 years at evaluation (ICC: between 0.917 [95%CI: 0.676 - 0.981], and 0.972 [95%CI: 0.882 - 0.994]) and QoL was reported regarding physical health (ICC: 0.964, [95%CI: 0.849 - 0.992]).

Conclusions

It is well-known that cochlear implantation improves QoL in children. However, gathered QoL data could vary depending on whether these are reported by the patient or parent. This study highlights a highly reliable consistency (ICC > 0.8) between paediatric and parental QoL report when implanted children were assessed between eight and 12 years of age. Therefore, it is recommended that, for paediatric cochlear implant recipients, QoL status is evaluated during this postoperative period.

INTRODUCTION

There is a wealth of scientific evidence supporting that there is a striking inconsistency between self-report and parent-reported proxy Quality of Life (QoL) assessment scales[1]. This alarming variability can be explained by factors such as: the limitation of paediatric language skills (e.g., the ability to comprehend and complete a QoL questionnaire), the inability to reflect upon the inner state, family stress, shorter rehabilitation period, and lack of education and/or social support networks[2]. Despite this, some consider paediatric self-report scales as the most representative method to assess paediatric QoL[3,4]. Contrarily, other studies have demonstrated that parents could still be reliable reporters of their children's QoL[5–7]. To date, there is no consensus as to whether paediatric self-reports or QoL completed by the parent most accurately represents the QoL of the child.

Alongside auditory evaluations, long-term follow-up QoL assessments play an essential role in monitoring progress of children who received a cochlear implant (CI) during early infancy. Children with profound sensorineural hearing loss (> 90 decibels (dBs)) that significantly impede age-appropriate speech and language development, can be offered CIs[8]. Substantial evidence demonstrates that early cochlear implantation is crucial to facilitate optimal speech and language development in children[9–12]. Several studies evaluated the impact of CI surgery on QoL using questionnaires, either by parental assessment only[5,13–15] or by a combination of paediatric and parental QoL assessments[2,4,6,16]. In this study, the variability between paediatric and parent-reported QoL questionnaires is investigated for a cohort of paediatric CI recipients and their parents. Defining the age at which QoL is most consistent between both paediatric and parent-reported outcomes provides important insight on the validity of QoL reports during postoperative follow-up.

METHODS

Two researchers (M.H., H.B.) recruited children implanted with a CI and their parents at the University Medical Centre Utrecht (UMCU) to perform this cross-sectional study. This study was approved by our local ethical committee (METC 15-017/C) and reported according to STROBE guidelines[17]. Children who received a CI before 36 months of age at the UMCU between March 2000 and April 2014 were recruited. Included children were classified into five groups based on their age at implantation. We excluded non-users (children who did not use their CI for the past five years) and CI-users who could not complete questionnaires due to comorbidities (e.g., mental retardation, cognitive impairment or serious developmental disabilities).

The inclusion period entailed three months (March until May 2015). Patients and parents were recruited either via 1) an outpatient visit, 2) approach by phone or 3) approach by email (when they could not be reached by phone) (Figure 1). The physician, audiologist or speech and language therapist informed the families during their outpatient visit about the possibility

to participate in this study. Informed consent was obtained for all included patients and parents. If no outpatient visit was planned during the inclusion period, parents were approached by phone, or by email (Figure 1). Both a letter pertaining instructions and the questionnaires were provided in person or by email. Parents and children completed all questionnaires at home. To ensure optimal reporting parents were carefully instructed as followed: one parent completed the adult version of the Paediatric Quality of Life Inventory (PedsQL) questionnaire, while another adult supervised that the child completing the paediatric PedsQL questionnaire version, without influencing answers.

Questionnaires

Parents completed three questionnaires: a generic questionnaire (the adult version of the PedsQL)[3], a disease-specific questionnaire (Glasgow Children's Benefit Inventory (GCBI))[18], and a baseline characteristics form. The baseline characteristics form was used to collect information such as age at implantation, duration of CI use and unilateral or bilateral implantation. Included paediatric CI users only completed the paediatric version of the PedsQL questionnaire.

Generic Questionnaires (PedsQL analysis)

The PedsQL permitted comparison of QoL scores between children and their parents. The PedsQL (version 4.0) measures a child's current health-related QoL using 23 items on a five-point Likert scale [0 (never) and 4 (always)][3] and is divided into four domains. The inventory is designed to assess the child's physical (eight items), emotional (five items), social (five items) and school (five items) functioning. The scores are transformed into a 100-point scale; 0 representing the lowest QoL level and 100 representing maximal QoL. Paediatric CI users and their parents received questionnaires in concordance to the child's age at evaluation (four categories ranging between two and 18 years)[3]. Children who were under four years of age during inclusion did not report QoL; only a parent-proxy version for this age category was administered.

Disease-specific questionnaires (GCBI analysis)

The GCBI retrospectively assesses parental perspectives on paediatric QoL following any paediatric surgery[18]. The questionnaire comprises 24 items divided into four domains: an emotional (12 items), a physical health (seven items), a learning (12 items) and a vitality (ten items) domain[18]. Scores are transformed and reflect either a low [-100] or high [100] QoL level. Due to its retrospective design recall bias is inevitable. The GCBI score was used regardless of the age at implantation or age at evaluation of the child[18]. However, the GCBI could be affected by unilateral or bilateral cochlear implantation since bilateral implantation can provide superior sound localization and ability to understand speech in noise. Therefore, GCBI scores of unilaterally and bilaterally implanted children were evaluated separately.

Statistical analysis

Data analysis was performed using IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp. (Released 2012). The level of statistical significance was set at $p = .05$. Tests

were Bonferroni corrected when multiple between age-at-implantation groups comparisons were performed (p = .05/10 variables tested: p = .005). In line with previous studies, scores were excluded from our analysis when ≥ 50% questionnaire items remained unanswered[3]. We performed sensitivity analyses to evaluate whether including results from incomplete questionnaires or outliers (i.e. a total GCBI score below -25 or a total PedsQL score below 50) affected QoL results.

PedsQL scores were analysed according to both the age at evaluation of the assessed child and the age at implantation of the included children. The Friedman test was used to determine differences between paediatric and parental PedsQL scores. To compare current QoL scores between children and parents from two PedsQL age designed categories the Wilcoxon signed-rank test was applied. The Kruskall-Wallis test was used to compare total PedsQL and GCBI scores between age-at-implantation groups. To assess GCBI differences between age-at-implantation groups the Mann-Whitney U test was applied.

In addition, PedsQL scores were divided into categorical groups of 20.00 points to determine whether consistency existed between paediatric and parental QoL ratings. Categorized paediatric and parental scores were compared using χ^2-tests. Furthermore, intra-class correlation coefficients (ICCs) were calculated to assess agreement between paediatric and parental report on the PedsQL questionnaire.

RESULTS

Patient demographics

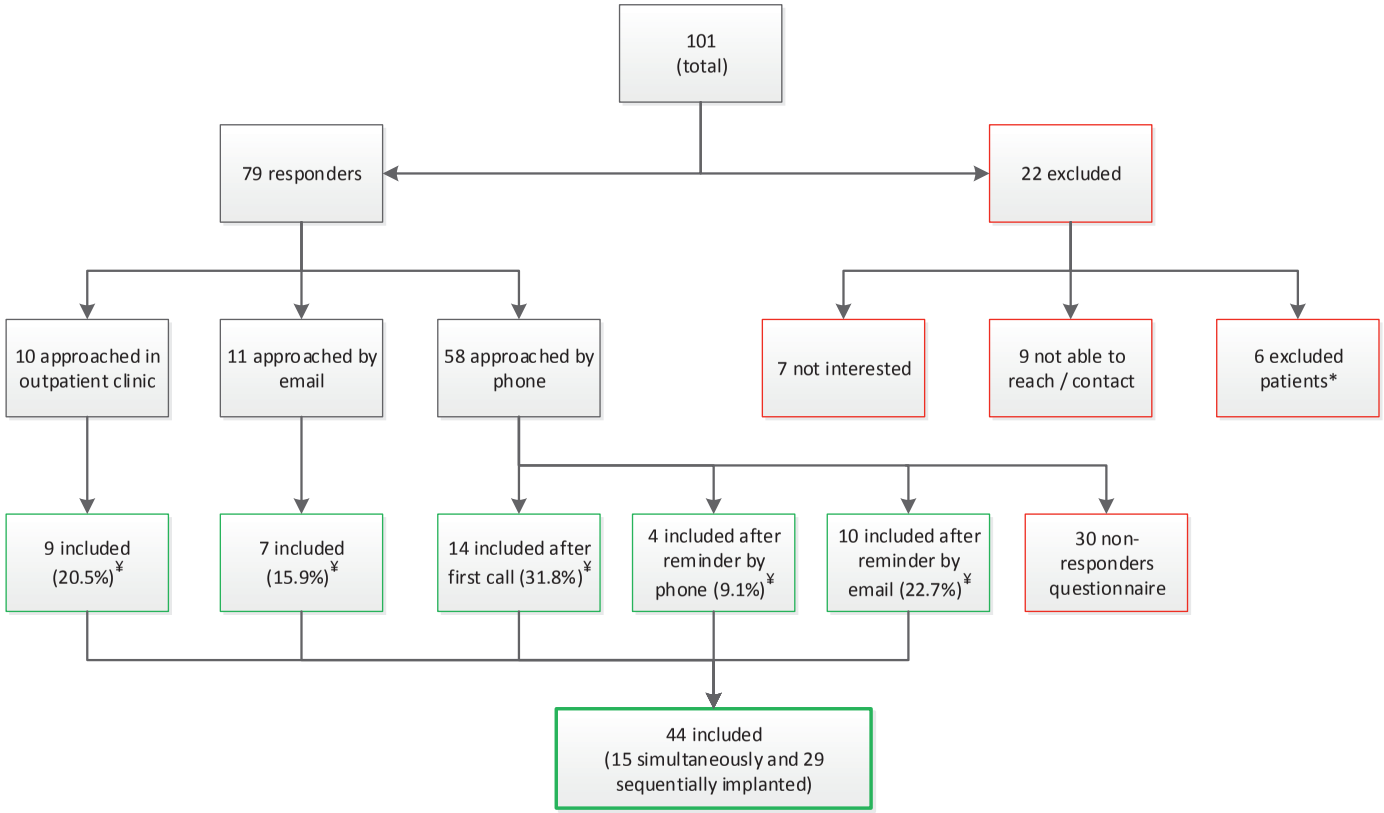
Figure 1 shows that 101 children were implanted before 36 months of age. Seventy-nine of the approached children and parents (78.2%) agreed to partake in this study. Twenty-one subjects did not receive questionnaires due to a lack of interest on participation, not being able to be contacted or exclusion from this study. Two subjects were excluded because they were considered non-users (communicated through sign language only) and four due to comorbidities (e.g., mental retardation and cognitive impairment). Forty-four of the 79 questionnaires were returned within the response time (response rate: 55.6%) (Figure 1). Email reminders were sent to 15 non-responders and 20 patients who could not be contacted by phone. However, none of these emails resulted in a questionnaire return (Figure 1).

Table 1 shows baseline characteristics of the 44 included children classified according to the age at implantation**.** The median age at implantation was 18.8 months [range: 8.04 -33.96]. Fifteen patients were implanted simultaneously, whereas 29 children were implanted sequentially. As a consequence of age at implantation group formulation, the age at evaluation and duration of CI use were statistically different between age-at-implantation groups (Table 1).

PedsQL analysis

Thirty-four children and 44 parents completed the PedsQL questionnaire. One child (age at evaluation: 13 to 18 years) was considered an outlier (mean score: 34.78) and one incomplete

Figure 1. Flowchart showing the selection of CI children



Legend: * two non CI users and four children were unable to fulfill the questionnaires due to comorbidities
¥ Percentage between brackets indicates the relative percentage compared to the total number of included patients

PedsQL questionnaire was returned (age at evaluation: five to seven years). PedsQL sensitivity analysis indicated that including both questionnaires did not significantly affect results, and therefore, these patients remained included in the PedsQL analysis.

Total paediatric and parental PedsQL scores did not significantly vary when arranged according to PedsQL designed age categories (Table 2A). Simultaneous implantation, duration of CI use and sign language did not affect paediatric and parental PedsQL scores. Parental education did not affect PedsQL reported by the parent (data not shown). Both the youngest (age at evaluation: five to seven years) and oldest evaluated children (age at evaluation: 13 to 18 years) reported relatively lower QoL than their parents. Contrarily, children evaluated between eight to 12 years reported higher current QoL scores compared to their parents (Table 2A). Only the social functioning subdomain scores were significantly higher in favour of children between eight to 12 years at evaluation (p = .016) (Table 2A).

Comparison of total PedsQL scores reported by children and their parents, arranged according to paediatric age at implantation, did not result in identification of significant differences (Table 2B).

Consistency of PedsQL analysis

Paediatric and parental-reported QoL measured by the PedsQL was most consistent when the PedsQL score was ≥ 60.00 (p = .0001) (Table 3). Table 4 shows that the level of the reported QoL agreement was high in all categories (ICC: 0.760 - 0.972). Most consistency between paediatric and parental-reported PedsQL scores existed regarding the physical health domain and when children were between eight to 12 years at evaluation (Table 4).

Table 1. Results regarding baseline characteristics of included CI patients presented per age-at-implantation group.

Age-at-implantation group (no.)	**6 - 12 mo. (9)**	**12 - 18 mo. (12)**	**18 - 24 mo. (10)**	**24 - 30 mo. (7)**	**30 - 36 mo. (6)**	***p*-value**
Current age (years (SD))	5.67 (3.06)	9.38 (4.17)	9.17 (4.63)	15.33 (5.75)	16.42 (1.46)	**.001**
Age at implantation (years (SD))	0.80 (0.08)	1.07 (0.10)	1.83 (0.16)	2.12 (0.11)	2.69 (0.14)	**.000**
Duration of use (years (SD))	4.92 (3.03)	8.29 (4.19)	7.21 (4.60)	13.25 (5.72)	13.63 (1.48)	**.015**
Sex Male:Female	6:3	5:7	4:5	4:4	4:2	.681
Aetiology						.891
Congenital	4	3	3	1	4	
CMV	2	0	2	0	0	
Prematurity	0	1	0	0	0	
Meningitis	0	5	2	3	1	
Connexin 26	0	0	1	0	0	
Waardenburg	0	0	0	1	1	
Other	2	2	2	0	0	
Sequential; simultaneous implantation	6; 3	9; 3	7; 3	3; 4	4; 2	.522
Sign language Yes; No	5; 4	6; 6	6; 3	5; 2	3; 3	.863
Comorbidities Yes; No	0; 9	3; 10	1; 9	0; 7	1; 5	.400

Legend: CI = Cochlear Implant; CMV = Cytomegalovirus; mo. = months; no. = number; SD = Standard Deviation. Significant *p*-values are marked in bold.

Table 2A. Results on current QoL scores measured by the paediatric and parental PedsQL questionnaire presented per age-at-evaluation group.

Current QoL									
	2 - 4 years		**5 - 7 years**		**8 - 12 years**		**13 - 18 years**		***p*-value***
Median score [range]	**Child (0)**	**Parent (8)**	**Child (7)**	**Parent (8)**	**Child (9)**	**Parent (9)**	**Child (18)**	**Parent (18)**	
PedsQl total score	-	82.14 [72.62-100]	71.74 [57.50-97.83]	81.52 [58.70-97.83]	87.39 [65.91-100]	85.87 [59.10-100]	78.80 [34.78-98.91]	79.35 [34.78-94.57]	0.095
PedsQl Physical	-	88.16 [71.05-100]	75.00 [57.14-100]	87.50 [46.88-100]	100.00 [76.86-100]	96.88 [64.29-100]	93.07 [40.63-100]	90.85 [40.63-100]	0.491
PedsQl Emotional	-	80.00 [55.00-100]	70.00 [59.00-100]	77.50 [50.00-100]	75.00 [55.00-100]	75.00 [50.00-100]	75.00 [25.00-100]	71.88 [25.00-100]	0.577
PedsQl Social	-	80.00 [70.00-100]	70.00 [60.00-100]	80.00 [60.00-100]	87.22 [70.00-100]	75.00 [60.00-100]	77.50 [10.00-100]	72.50 [10.00-100]	**0.016**
PedsQl School	-	91.67 [58.33-100]	80.00 [50.00-100]	75.00 [50.00-100]	77.00 [55.00-100]	80.00 [50.00-100]	72.50 [37.50-95.00]	72.50 [35.00-100]	0.695

Legend: Current QoL scores were classified according to the age at evaluation of the CI child. Abbreviations: CI = Cochlear implant; PedsQL = Paediatric Quality of Life Inventory; QoL = Quality of Life; *Friedman Rank test. Significant *p*-values are marked in bold.

Table 2B. Results on current QoL scores measured by the paediatric and parental PedsQL questionnaire presented per age-at-implantion group.

Age at cochlear implantation												
	6 - 12 mo.		**12 - 18 mo.**		**18 - 24 mo.**		**24 - 30 mo.**		**30 - 36 mo.**		***p*-value***	
	Child (6)	**Parents (9)**	**Child (10)**	**Parents (12)**	**Child (6)**	**Parents (10)**	**Child (6)**	**Parents (7)**	**Child (6)**	**Parents (6)**	**Child**	**Parents**
PedsQl Total score	80.43 [69.57-100]	80.43 [72.62-100]	77.72 [34.78-97.83]	80.65 [34.78-97.83]	88.04 [65.91-96.74]	86.38 [64.13-100]	85.33 [71.74-92.39]	78.57 [60.87-94.57]	73.37 [61.32-98.91]	82.71 [65.22-94.57]	.628	.337
Physical Functioning	100.00 [75.00-100]	100 [71.05-100]	85.94 [40.63-100]	84.38 [40.63-100]	95.31 [57.14-100,00]	94.53 [46.88-100]	95.31 [68.75-100]	91.07 [65.63-100]	82.81 [75.00-100]	93.75 [71.88-100]	.218	.146
Emotional Functioning	52.50 [45.00-100]	70.00 [50.00-100]	70.00 [25.00-100]	60.00 [25.00-100]	82.50 [65.00-100]	85.00 [55.00-100]	77.50 [70.00-100]	75.00 [50.00-100]	75.00 [60.00-100]	80.00 [60.00-100]	.229	.412
Social Functioning	80.00 [70.00-100]	75.00 [60.00-100]	80.00 [10.00-100]	75.00 [10.00-100]	87.50 [70.00-100]	90.00 [60.00-100]	75.00 [60.00-100]	70.00 [30.00-100]	80.00 [24.80-100]	72.50 [55.00-100]	.878	.640
School Functioning	82.50 [55.00-100]	75.00 [55.00-100]	72.50 [50.00-95.00]	75.00 [35.00-100]	77.50 [65.00-100]	84.17 [75.00-100]	77.50 [65.00-90.00]	80.00 [60.00-91.67]	65.00 [37.50-95.00]	65.00 [60.00-100.00]	.447	.373

Legend: Current QoL scores were classified according to the age at cochlear implantation of the child. Abbreviations: mo. = months; PedsQL = Paediatric Quality of Life Inventory; * Kruskall-Wallis test. Significant *p*-values are marked in bold.

Table 3. Conformity testing between paediatric and parental PedsQL scores.

		Mean score parents (binned scores)					
		0.00-20.00	**20.001-40.00**	**40.001-60.00**	**60.001-80.00**	**80.001+**	**Total**
Mean score children using CIs	0.00-20.00	0	0	0	0	0	0
	20.001-40.00	0	1	0	0	0	1
	40.001-60.00	0	0	1	0	0	1
	60.001-80.00	0	0	2	10	3	15
	80.001+	0	0	0	3	14	17
	Total	0	1	3	13	17	34

Legend: CI = cochlear implant; PedsQL = Paediatric Quality of Life Inventory.

Table 4. Intra-class correlation coefficient (ICC) between paediatric and parental scores of the PedsQL questionnaire.

	Intra-class Correlation Coefficient			
PedsQL (no.)	**Total sample** (33)	**5-7 years** (7)	**8-12 years** (9)	**13-18 years** (18)
Total score (95%CI)	.821* (.671 – .906)	.842** (.333 - .971)	.972* (.882 - .994)	.760* (.465 - .903)
Physical Health (95%CI)	.871* (.757 - .933)	.856** (.376 - .974)	.964* (.849 - .992)	.834* (.611 - .935)
Social Functioning (95%CI)	.867* (.750 - .931)	.901** (.534 - .982)	.917* (.676 - .981)	.839* (.620 - .936)

Legend: CI = cochlear implant; 95%CI = 95% confidence interval; no.= number; PedsQL = Paediatric Quality of Life Inventory. Statistically significant child / parent correlation *p <.0001, ** p < .01.

GCBI analysis

Forty-four parents completed the GCBI questionnaire. Mean time between CI surgery and questionnaire completion was 8.35 years (SD: 4.69). One incomplete questionnaire was returned, and one questionnaire response was defined as an outlier (mean score: -43.75). Both questionnaires were from children who were implanted between 12 to 18 months. Since GCBI sensitivity analyses did not show that excluding outliers significantly influenced results, all received questionnaires remained included in the GCBI analysis.

Table 5 shows median total GCBI scores and scores specified per GCBI subdomain; no statistically significant difference in total GCBI scores between age-at-implantation groups was found (Table 5). Simultaneous implantation, duration of CI use and parental education did not affect parental QoL report measured by GCBI.

DISCUSSION

There is a great variability between paediatric and parent-reported proxy-Quality of Life (QoL) questionnaires. The objective of the present study was to define the age at which QoL is most consistent between paediatric and parent-reported questionnaire and to provide insight for reported QoL variability during postoperative cochlear implant follow-up. The highest consistency between paediatric and parent proxy-QoL assessments was achieved when children were between eight to 12 years of age at evaluation when compared to reported outcomes by their patients. There was a significantly greater consistency when PedsQL scores were high (≥ 60.00) and when QoL was reported regarding physical health.

Table 5. Results on GCBI scores of 44 included CI patients classified according to age at implantation.

Median	Age at cochlear implantation						
	Total [range] (44)	**6 – 12 mo. (9)**	**12 – 18 mo. (12)**	**18 – 24 mo. (10)**	**24 – 30 mo. (7)**	**30 - 36 mo. (6)**	***p*-value***
Total GCBI	24.81 [-43.75-64.583]	14.58 [-4,17-50,00]	14.58 [-43,75-58,33]	16.67 [0,00-54,17]	37.50 [-2,08-64,58]	50.00 [6,25-5417]	.091
GCBI Emotion	24.81 [-62.50-70.83]	20.83 [-8,33-62,50]	14.58 [-62,50-70,83]	10.42 [-4,17-62,50]	41.67 [0,00-62,50]	47.92 [0,00-66,67]	.257
GCBI Physical health	9.90 [-35.71-50.00]	0.00 [-35,71-21,43]	10.71 [-35,71-28,57]	7.14 [-14,29-28,57]	21.43 [-7,14-50,00]	28.57 [7,14-50,00]	**.017**
GCBI Learning	35.61 [-41.67-83.33]	33.33 [-8,33-70,83]	25.00 [-41,67-83,33]	31.25 [-8,33-75,00]	50.00 [0,00-70,83]	56.25 [16,67-70,83]	.57
GCBI Vitality	26.59 [-55.00-75.00]	10.00 [0,00-50,00]	17.50 [-55,00-70,00]	12.50 [5,00-60,00]	50.00 [0,00-75,00]	45.00 [-5,00-60,00]	.239

Legend: CI = cochlear implant; GCBI = Glasgow Children Benefit Inventory; mo. = months, *Kruskall-Wallis test. Significant *p*-values are marked in bold.

In 2009, Engelen *et al.*[19] presented Dutch PedsQL normative data assessed in a cohort of healthy children with normal hearing. The PedsQL scores gathered in our study were only in line with the QoL scores of the children between eight to 12 years of age in the previous study (Engelen *et al.*[19]: 82.11 and our cohort 87.39). In our study, the five to seven years and the 13 to 18 years cohorts reported relatively lower PedsQL scores. Reasons for discrepancies amongst scores could be attributed to various factors. Relatively lower absolute scores from the five to seven years cohort could have resulted from the lack of ability to comprehend the QoL questionnaire and/or reflect upon their QoL. Relatively shorter rehabilitation period could have also affected QoL reports as the CI rehabilitation process hasn't yet reached a satisfactory improvement. Nonetheless, QoL outcomes reflecting on the paediatric patients could also be influenced by the parents. Parental factors such as family stress, lack of social support networks or inability to adequately assess various QoL components could have influenced the reported QoL scores[2]. Our results from the eight to 12 years group could indicate that these children experienced comparable QoL to healthy individuals of similar age living in the Netherlands. Thus, if a patient-reported QoL is poor, physicians and parents should evaluate the factors resulting in a low QoL report, especially in cases when the CI is accurately placed and functioning.

Eiser and Morse[20] concluded through a systematic review that: 1) an ICC of ≥ 0.80 marks highly reliable agreement between subjects, 2) agreement between parents and chronically sick children compared with parents and healthy children could be relatively higher and 3) the highest agreement between paediatric and parental QoL scores existed regarding physical QoL aspects (ICC 0.59). Similarly, a highly reliable agreement (ICC > 0.8) between parents and chronically disabled children (e.g., presenting with severe hearing loss) was observed in the current study. Alternatively, a high ICC can result from heterogeneity within a study sample[21,22]. Therefore, the high ICC could have resulted from high variance within our study sample. For example, heterogeneity could have resulted from variation in the duration of CI use or unsupervised questionnaire completion at home. Future consistency studies in children using CIs need to mark whether we were indeed able to confirm Eiser and Morse's conclusions[20].

Furthermore, Eiser and Morse[20] marked that specific QoL domains, such as physical QoL, could show relatively higher consistency between parent and paediatric reports than emotional or social domains. Similarly, Achenbach *et al.*[23] concluded that parents can more accurately reflect on the child's externalizing problems (e.g., aggression or rule-breaking) than assessing the child's internalizing problems (e.g., sadness or anxiety). This could explain why most consistency between paediatric and parent proxy-QoL report was found in the current study when QoL was reported regarding the physical health domain.

Cremeens *et al.*[1] assessed the effect of chronological age and domain type on the PedsQL consistency between paediatric and parental reports in healthy children. Cremeens *et al.*[1] identified highest consistency (ICC: 0.23) in the oldest evaluated children, who were between 7.5 to 8.5 years at evaluation. In our cohort, highest consistency (ICC: 0.972) existed when children were evaluated between eight to 12 years. Therefore, relatively older children in our cohort demonstrated highest consistency. Older children could have reflected more representatively on their QoL due to the child's normal, age-related, development and increasing independence[18], and consequently, these more representative scores could lead to superior consistency. Furthermore, Cremeens *et al.*[1] found statistically significant median differences between child and parent-reports on all PedsQL subscales. In our study, we only identified statistically significant differences regarding the social functioning subdomain. This variation could be explained by the fact that the study of Cremeens *et al.*[1] only assessed healthy children (compared to chronically handicapped children in our cohort).

During the last decade, the PedsQL was applied in eight studies and the GCBI questionnaire in 16 studies in the paediatric otorhinolaryngology literature[24]. Both questionnaires comprise a physical health domain, however, the PedsQL physical health subdomains' questions focus on the patient's ability to run or walk a certain distance[3], whereas the GCBI physical health subdomains' questions assess the importance to sleep at night, attend school and enjoy leisure activities[18]. The variation of included questions regarding this domain in both questionnaires could explain why we retrieved significant differences between reported GCBI physical health subdomain scores; however, were unable to demonstrate significant differences regarding the physical health subdomain scores of the PedsQL questionnaire.

The retrospective design of the GCBI questionnaire could have introduced bias. Firstly, introduction of selection bias, since only motivated parents could have been willing to participate. Kubba *et al.*[18] reported that parents completed the GCBI of children implanted between one to 15 years of age, which results in a comparable mean reporting time (7.18 years) to our study. A recommended time for the parents to retrospectively fill in the GCBI following the surgery has not been provided[18]. The period between initial surgery and completing questionnaires could result in relatively longer experienced disability time[25]. However, also longer time of CI experience for earlier implanted patients, which could have both affected QoL report[26]. We elected this questionnaire since its retrospective approach is more sensitive to change, and can be used in settings where gathering a considerable patient cohort can take several years[18].

Response rates are reported to be low in questionnaire studies (< 30%)[27]. However, our follow-up inclusion approach (containing reminder emails and calls) certainly enhanced the response rate of our study (55.6%). This approach led to inclusion of 14 additional children and parents.

CONCLUSION

It is well-known that cochlear implantation improves QoL in children. However, QoL data could vary depending on whether these are reported by the patient or parent. This study highlights a highly reliable consistency (ICC > 0.8) between paediatric and parental QoL report when implanted children were assessed between eight and 12 years of age. The highest agreement existed regarding physical QoL aspects. These findings can help interpret inconsistencies of QoL report between children and their parents during the rehabilitation period since this variation can already be explained by the age at QoL evaluation of the child.

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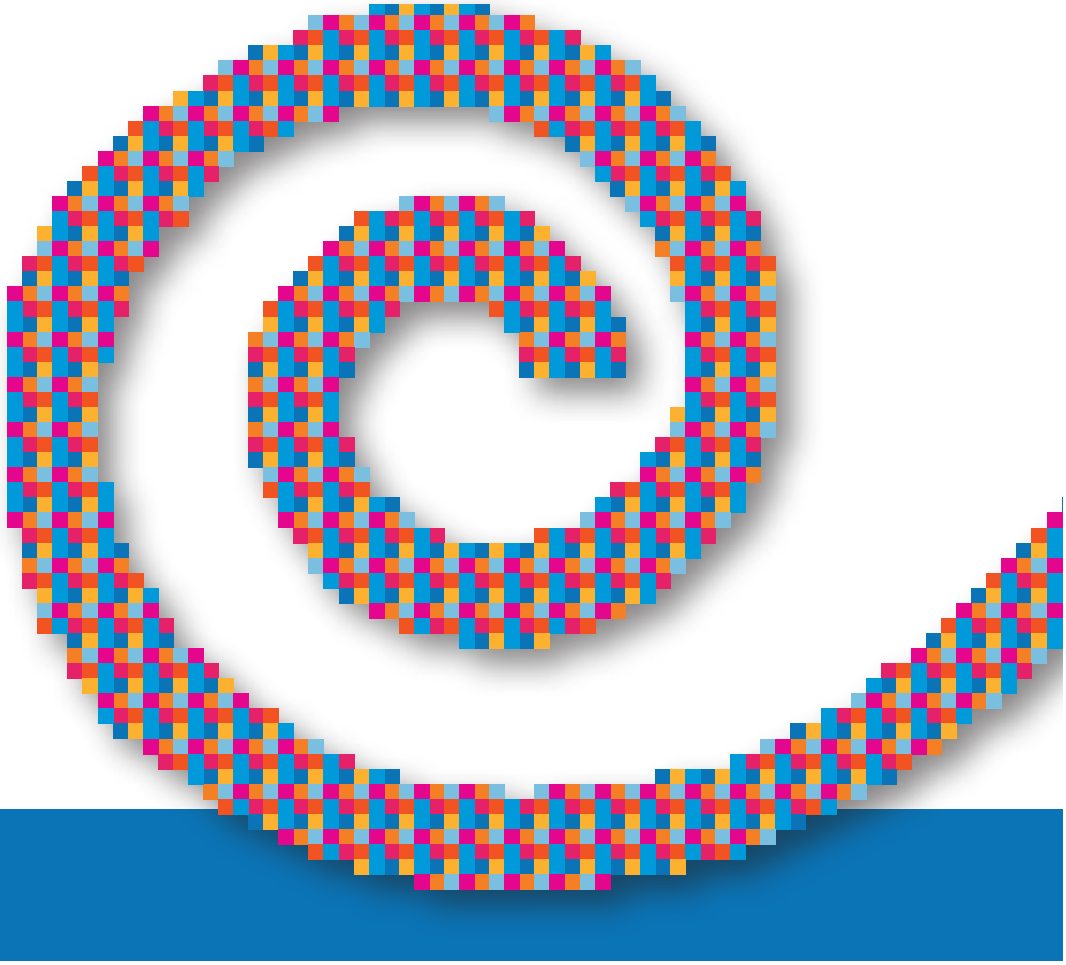
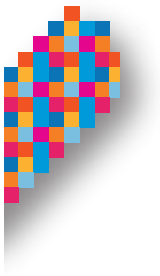


PART VI

Discussion and (Dutch) summary



Chapter 6.1

Summary of main results and general discussion

Overview

Although medical treatments should vary, variation from clinician-to-clinician is more difficult to defend than patient-to-patient variation, especially in children[1]. Since clinician-to-clinician variation is present in paediatric cochlear implantation, this thesis addressed several controversies and challenges regarding hearing restoration through cochlear implantation. Moreover, this thesis provides evidence-based practice guidelines to lower this clinician-to-clinician variation through five evaluations of factors affecting the clinical outcome of early treatment.

This thesis is subdivided in five parts, of which every individual part evaluates a factor, which can affect the outcome of paediatric cochlear implantation:

- **Part I**: Identification of the ideal age for cochlear implantation in children based on speech and language developmental data (**Chapter 1.1** and **Chapter 1.2**)
- **Part II**: Identification of the audiological candidacy criteria for cochlear implantation in children (**Chapter 2.1**)
- **Part III**: Identification of the surgical and anaesthetic strategy for cochlear implantation in children (**Chapter 3.1**, **Chapter 3.2** and **Chapter 3.3**)
- **Part IV**: Identification of delayed cochlear implantation in children in Europe (**Chapter 4.1**)
- **Part V**: Identification of quality of life (QoL) consistency between children and their parents following cochlear implantation (**Chapter 5.1**)

This chapter contains: a summarization of results per thesis part, a general discussion per thesis part and finally, a provision of limitations and future perspectives resulting from this thesis. This last section contains a discussion regarding the improvement of parental awareness through education (e.g., telemedicine).

Main results summarized per thesis part

Part I: Identification of the ideal age for cochlear implantation in children based on speech and language developmental data

Based on the findings of **Chapter 1.1** and **Chapter 1.2**, we recommend that a child presenting with prelingual hearing loss without severe comorbidities, undergoes cochlear implantation between 12 and 18 months of age based on four speech and language domains (speech perception and production, receptive language and auditory performance).

Chapter 1.1 clarified the reported benefits of early cochlear implantation retrieved in the literature, however, also demonstrated the conflicting evidence regarding the benefits of implantation before 12 months of age, and particularly before six months of age. This systematic review showed that:

- Cochlear implantation < 24 months of age is beneficial according to the development of speech perception: based on one speech perception score (the Phonetically Balanced Kindergarten (PB-K) combined with the Consonant-Nucleus-Consonant (CNC) score, but not regarding Glendonald Auditory Screening Procedure (GASP) scores).
- Cochlear implantation < 12 months of age is beneficial according to the development of speech production, auditory performance and receptive language scores: based on two

speech production scores (the Diagnostic Evaluation of Articulation and Phonology (DEAP) and the Infant-Toddler Meaningful Auditory Integration Scale (IT-MAIS) scores), one auditory performance score (the Categories of Auditory Performance II (CAP II) score) and two out of five receptive language scores (combined Preschool Language Scale (PLS) and Oral and Written Language Skills (OWLS) scores and the Peabody Picture Vocabulary Test (-Revised) (PPVT(-R)) score).
- Cochlear implantation < six months of age is beneficial according to development of auditory performance: based on one auditory performance score (CAP-II).

In **Chapter 1.2**, we showed superior long-term speech perception scores resulting from a relatively lower age at implantation (< 18 months of age) than were previously identified in the literature (**Chapter 1.1**: < 24 months of age). After accounting for ceiling effects, we found a significant Consonant-Vowel-Consonant (Auditory) (CVC(A)) score difference between age-at-implantation groups ($p < .001$): a larger proportion of young implanted children (< 18 months of age) reached CVC(A) ceiling scores compared to older (> 18 months of age) implanted children.

Part II: Identification of audiological candidacy criteria for cochlear implantation in children

Based on the findings of **Chapter 2.1**, we recommend that children presenting with prelingual hearing loss receive cochlear implants (CIs) when their audiological thresholds are ≥ 80 decibels (dBs)(2-frequency Pure Tone Average (PTA) thresholds of ≥ 85 dB hearing level (HL) or 4-frequency PTA thresholds ≥ 80 dB HL). This is a lower audiological threshold than is currently advised in both national guidelines and manufacturer recommendations.

In **Chapter 2.1**, we performed a systematic review to identify audiological candidacy criteria for cochlear implantation in children (e.g., audiological thresholds (dB HL)) to clarify current inconsistency regarding these criteria. Furthermore, Fitzpatrick *et al.*[2] reported that as soon as children meet these audiological candidacy criteria, no further delays in cochlear implantation should exist. Therefore, clear definition of audiological cochlear implantation criteria could prevent future CI delays for these children. This literature review concludes that:

- Children presenting with a 4-frequency PTA threshold of ≥ 80 dB HL qualify for cochlear implantation based on speech perception and auditory performance subtests.
- Cochlear implant users scored significantly better than hearing aid (HA) users based on a speech perception subtest at PTA thresholds of 88 and 96 dB HL.

Part III: Identification of the surgical and anaesthetic strategy for cochlear implantation in children

Chapter 3.2 showed that the Mastoidectomy with Posterior Tympanotomy Approach (MPTA)[3] should be selected as the surgical technique in children implanted < 24 months of age, who are more prone to develop infectious adverse events. In addition, **Chapter 3.3** showed that both intravenous propofol and sevoflurane inhalation could be safely administered as

anaesthesia maintenance techniques in American Society of Anaesthesiologists (ASA) 1 or ASA 2 classified children implanted < 24 months of age.

In **Chapter 3.1**, we queried whether the SupraMeatal Approach (SMA)[4] could be the preferable surgical technique in children. Currently, the MPTA[3] is considered the surgical reference technique for cochlear implantation. However, the SMA[4] does not require a mastoidectomy, which could influence both adverse event rates and the hearing preservation outcome. Performing a mastoidectomy can improve middle ear aeration and lower, for example, acute otitis media (AOM) incidence[5]. Hence, we hypothesized that performing a mastoidectomy (e.g., using the MPTA[3]) could have a protective effect and result in lower adverse event rates, and therefore, could be favoured over the application of the SMA[4]. Since the performed literature review in **Chapter 3.1** identified a similar outcome regarding adverse event rates between both surgical techniques, we could not confirm that the MPTA[3] should be favoured. Although one included study did find a significantly ($p < .023$) higher mastoiditis rate in children operated through the MPTA[3], the included meta-analysis in **Chapter 3.1** did not indicate an overall effect. Hearing preservation was not reported in included paediatric cases and hearing outcomes were not reported to differ between techniques in retrieved adult patients. Since included paediatric data in **Chapter 3.1** did not contain our population of interest (retrieved data only contained children implanted > 24 months of age), we performed a surgical technique outcome comparison in younger children in **Chapter 3.2**. Information regarding surgical technique preference during this period is essential since children are currently implanted during infancy. Furthermore, children implanted > 24 months of age have already surpassed the age of being most prone to develop postoperative infections (e.g., AOM and/or mastoiditis), since the peak incidence of these infections lays between six and 12 months of age[6-7].

Chapter 3.2 confirmed that not performing a cortical mastoidectomy (using the SMA[4]), resulted in significantly more infectious adverse events, and therewith, confirmed our initial hypothesis that using the MPTA[3] has a protective effect. Since we showed a significant 'mastoidectomy effect' on the postoperative infection rate in our evaluated children, we recommend the MPTA[3] for children implanted < 24 months of age.

Furthermore, **Chapter 3.3** marked that anaesthetic and surgical adverse events occurred independent of the age at implantation, the number of anaesthetic preoperative procedures and the type of anaesthetic maintenance agent in ASA 1 or 2 classified children implanted < 24 months of age. The motivation to query whether administration of different anaesthesia maintenance medication could lead to different adverse event rates during and after cochlear implantation was four-fold:

- Cochlear implantation is currently performed during infancy and infants are at higher risk for adverse events during anesthesia[8]. This higher risk results for example from frequent upper airway infections, which could induce the occurrence of perioperative laryngospasms and postoperative hypoxia.
- Multiple anaesthetic procedures are required during work-up for cochlear implantation (e.g., MRI/CT), which could have a cumulative effect on the clinical outcome of the implanted child.

- Propofol maintenance anaesthesia is associated with less perioperative blood loss due to its hypotensive and/or vasodilatory actions[9]. Therefore, propofol administration could result in a superior perioperative surgical field.
- Administration of volatile anaesthetics could contain potential risks for neonatal brain development: sevoflurane maintenance could induce long-term memory impairment[10].

Although propofol maintenance anaesthesia is associated with a lower risk of perioperative laryngospasm in children than sevoflurane[11], **Chapter 3.3** could not confirm that propofol maintenance medication was related with a lower aesthetical and/or surgical adverse event rate.

Part IV: Identification of delayed cochlear implantation in children in Europe

Chapter 4.1 identified remarkable delays regarding provision of current European CI care: from 2010 onwards, only over 30% of the European CI candidates were implanted < 24 months of age. Therefore, there is need for improvement, by means of: broader NBHS implementation, increase of parental awareness, superior adherence to implemented guidelines and improved alignment between international guidelines. We aimed to delineate aforementioned European delays since Leigh *et al.*[12] described that the majority of children in Australia still receive CIs > 24 months of age and Fitzpatrick *et al.*[13] confirmed that in Canada, NBHS identified candidates were (on average) only implanted 24 months following initial hearing loss confirmation. Lester *et al.*[14] reported that, in favourable health care systems like the United States, still 42% of their population did not receive a CI < 24 months of age, which is relatively more favourable than our European results.

Part V: Identification of quality of life (QoL) consistency between children and their parents following cochlear implantation

In **Chapter 5.1**, we confirmed a highly reliable agreement (ICC > 0.8) between reported QoL scores between chronically handicapped children (e.g., children presenting with profound hearing loss) and their parents, who reported the QoL of their children. Highest agreement existed regarding physical QoL aspects. Since highest consistency existed when children were between eight and 12 years of age at evaluation, we advise paediatric and parental QoL consistency assessment during this postoperative age period. Furthermore, we identified that paediatric or parental long-term QoL report was not affected by the initial age at cochlear implantation.

Data discussion per thesis part

Part I: Identification of the ideal age for cochlear implantation in children based on speech and language developmental data

Chapter 1.1 and **Chapter 1.2** indicate that the recommended implantation age, based on speech and developmental data, is speech and language domain dependent. Language is complex behaviour that contains multiple sensitive periods of various speech and language skills[15]. Therefore, catching up to age-appropriate hearing levels post-implantation could vary

per assessed speech and language domain. In other words, every speech and language domain could have different critical periods for development of that specific skill, which impedes definition of an overall recommended implantation age. Furthermore, although neuroplasticity diminishes with age (e.g., cortex neuroplasticity probably exists till the age of 42 months[16]), it never disappears[17], which could further complicate definition of a lower (overall) CI age based on (postoperative) speech and language outcomes.

Two years after our review (**Chapter 1.1)**, Dettman *et al.*[18] performed a similar study and reported comparable results: data supported CI provision < 24 months of age to optimize speech perception and < 12 months to facilitate speech production and enable language acquisition. Furthermore, the authors marked the same problem regarding this field: the great variation in administered clinical outcomes (e.g., speech and language tests) and study methodologies[18]. This variety underlines the need for uniform outcome measurement and large, prospective, multi-centre studies[18]. The first example of such a prospective, multicentre, long-term (> five-year) follow-up study to systematically assess early CI outcomes in children is the CDaCI study[19].

Ceiling effects could have prevented earlier speech perception studies to demonstrate superior speech perception scores when children were implanted < 18 months of age (finding from **Chapter 1.2**). Ceiling effects more frequently affect the paediatric CI population due to the need to apply categorical outcome measures (e.g., CAP scores). Basically, no other assessment tools are available to evaluate infants who have not yet acquired speech and language. Vlastarakos *et al.*[17] already suggested that using assessment tools with possible ceiling effects limits accurate identification of implant success for early implanted children. Since all our implanted children performed at the highest (ceiling) CVC(A) range, we used ceiling effect analysis which allowed us to identify speech perception performance differences between age-at-implantation groups. We demonstrated benefits of early implantation (< 18 months of age) resulting from both raw CVC(A) score analysis and ceiling effect analysis. Therefore, we concluded that ceiling effects can be successfully measured and their effect on speech perception can be weighed. A relatively larger proportion of earlier implanted children (< 13 months of age) reached CVC(A) ceiling scores compared to those implanted between 13 and 18 months of age. However, this proportion variation was not significantly different and it remains undetermined whether no between-group differences could be demonstrated due to:

- Ceiling effects masking thorough delineation of speech perception differences for the youngest ceiling-scoring children
- No presence of speech perception differences between the youngest groups and/or
- Type II-error affecting our analysis (underpowered study to assess this variance)

Future studies are essential to provide data to answer this question.

Part II: Identification of the audiological candidacy criteria for cochlear implantation in children

Setting candidacy criteria for cochlear implantation in children is challenging since:

- Discrepancy exists between CI candidate and postoperative assessments: the method of

candidacy assessment (e.g., defining the hearing loss severity by detecting pure tones) is inconsistent with assessing the aimed outcome of cochlear implantation: age-appropriate speech and language development (e.g., postoperative speech and language performance tests).

- Significant variation exists between postoperative outcomes of implanted children, which hinders accurate prediction of implant performance preoperatively[20-21].
- Preterm born infants could be pitfall candidates for cochlear implantation since they demonstrate improved hearing during follow-up due to delayed maturation of their immature auditory pathway[22].

Lovett *et al.*[21] used the actuarial method to avoid these challenges and found that an unaided 4-frequency PTA of ≤ 80 dB HL in both ears should serve as a CI criterion (this study was included in **Chapter 2.1**).

Furthermore, paediatric CI candidacy evaluation is a time consuming and complex process that requires an extensive multidisciplinary assessment[23]: early surgery can only be performed when a strict, case-to-case preoperative evaluation has advised surgery and the child fulfils all the recommended criteria[24]. Paediatric cochlear implantation criteria are not merely based on audiological candidacy criteria (e.g., the hearing loss severity), but also entail factors as cognitive ability, intelligence, comorbidities, parental motivation, social situation, anatomy of the cochlea and the benefit the child obtains from HAs. Therefore, **Chapter 2.1** only entails the audiological candidacy part of all aspects that a child presenting with hearing loss needs to fulfil to be a candidate for cochlear implantation. Although this chapter only entailed the audiological aspects of these criteria, we did find that current audiological thresholds (e.g., advised in both national guidelines and manufacturer recommendations) could be too conservative.

Part III: Identification of the surgical and anaesthetic strategy for cochlear implantation in children

Currently, there are no guidelines defining which surgical or anaesthesia techniques should be used during cochlear implantation in children. For example, in our clinic, anaesthesia selection is still based on the anaesthesiologists' preference. Since this thesis aimed to lower current clinician-to-clinician variation in paediatric cochlear implantation, we defined recommended surgical or anaesthesia techniques. **Chapter 3.2** revealed that the alternative surgical technique (the SMA[4]) did not meet the safety outcomes of the current golden standard: the MPTA[3]. Therefore, the latter strategy should be selected in children. Furthermore, **Chapter 3.3** addressed anaesthetist-to-anaesthetist variation in our clinic; however, this assessment did not result in definition of a superior anaesthesia strategy (sevoflurane inhalation or TIVA).

Based on **Chapter 3.3**'s results, we could recommend a 1-day hospitalization following cochlear implantation. However, implementation of adjusted anaesthetic protocols could lead to successfully performing day-case surgery. Due to similar high numbers of minor anaesthetic adverse events, the collaborating Birmingham Children's Hospital (BCH) established the anaesthetic protocol presented in Table 1. Application of this BCH protocol led to successfully

implementing day case paediatric CI surgery. If desired, implementation of this protocol could result in performing paediatric day case surgery in the near future in our centre.

Part IV: Identification of delayed cochlear implantation in children in Europe

Chapter 4.1 described a lower European percentage of children implanted before 24 months of age (only over 30%) than reported by Lester *et al*.[14] in the United States (42%). This relatively larger European underserved population could have resulted from:

- Incomplete data selection: data from only one CI manufacturer were included
- Incomplete data inclusion: data of only five international clinics were included
- Geographical variation: superior and more timely CI provision in the United States

Although these data might not completely represent current CI care, the selected study populations represent a certain care delay (in top clinical European centres) that marks the need for improving provision of timely CI care for children.

We assessed a subpopulation from the evaluated children in **Chapter 4.1** (n = 27) to further study latency reasons for paediatric cochlear implantation (e.g., implantation > 42 months) (*data not presented earlier in this thesis*). We retrieved the following latency reasons: 55% of the implantations were delayed due to system delays (e.g., no NBHS implementation, refugees not receiving NBHS in country of origin) and the remaining 45% due to medical delays (e.g., acquired hearing loss or comorbidities delaying CI assessment). Dettman *et al*.[18] also found that their late-to-implant group (implanted between 43 and 72 months) contained refugees and children with multiple medical issues. Since our identified latency reasons could be interrelated with unreported parental issues, we aim to further identify these latency reasons and document their interrelations in future studies of our (international) cohort.

Part V: Identification of quality of life (QoL) consistency between children and their parents following cochlear implantation

Quality of life self-report is difficult to assess in infants and no QoL reference data are available for children using CIs. Furthermore, it is questionable whether the physicians' and parental postoperative QoL impression of the implanted child is comparable with the actual QoL perception. Therefore, we studied QoL of implanted children and identified age ranges in which QoL is most consistent with parental impression of the child's QoL report (between eight and 12 years of age at QoL evaluation).

Eiser and Morse[25] concluded through a systematic review that:

- An ICC of ≥ 0.80 marks highly reliable agreement between subjects.
- Agreement between parents and chronically handicapped children (e.g., children presenting with hearing loss) could be relatively higher than agreement between parents and healthy children.
- Highest agreement between reported paediatric and parental QoL scores existed on physical QoL aspects (ICC 0.59).

Chapter 5.1's findings are in line with Eiser and Morse[25]'s conclusions, however, future consistency studies need to mark whether we indeed confirmed their conclusions or, alternatively, whether our findings resulted from heterogeneity of our study sample[26-27].

Table 1. Birmingham Children's Hospital (BCH) anaesthetic paediatric CI Protocol to establish day case surgery.

During surgery	
Maintenance anaesthesia	Total intravenous anaesthesia (TIVA) or volatile anaesthetic and remifentanil infusion
Maintenance analgesia	Administration of intravenous paracetamol (in addition: diclofenac by rectum or intravenous if the child is old enough) no perioperative opioids (e.g., avoidance of especially intravenous morphine)
Maintenance anti emetics	ondansetron and dexamethasone
Postoperatively	
Local analgesia	Retroauricular block containing bupivacaine
Oral analgesia	Oramorph, paracetamol, ibuprofen

(Provided via personal communication by Dr. Tzifa, ENT-surgeon, BCH, UK)

GENERAL DISCUSSION

This thesis provides evidence-based practice guidelines regarding cochlear implantation in children. The need to formulate an evidence-based practice guideline comprises:

- Increase in parental awareness regarding the need of timely implantation in children
- Establishment of appropriate CI candidate referrals for managing primary health care physicians and audiologists incorporating shifting and variable candidacy criteria[23]
- Improvement of patient safety (e.g., identical surgical and anaesthesia strategies)
- Alignment of discrepancies of national guidelines and manufacturer recommendations (leading to uniform European provision of CI care)

The systematically developed evidence-based practice recommendations in this thesis do not yet cover all considerations that should be included in a clinical practice guideline. Evidence was gathered to highlight surgical, anaesthetic and (part of the) candidacy considerations regarding cochlear implantation in children. Therewith, the first steps of formulation of an evidence-based practice guideline are established, however, should be further supplemented with circumstantial evidence (e.g., environmental factors like parental preferences). Especially since a guideline should contain a balance between scientific considerations and other considerations, such as: care organization (to prevent medical delays), patient or parental wishes (to prevent parental delays) and benefit for society (to prevent system delays)[28]. Inclusion of this circumstantial evidence could result in either: lowering current clinician-to-clinician variation, however, could also facilitate motivated deviation from an international uniform guideline due to variation in care organization (e.g., referral networks in current practice) between countries.

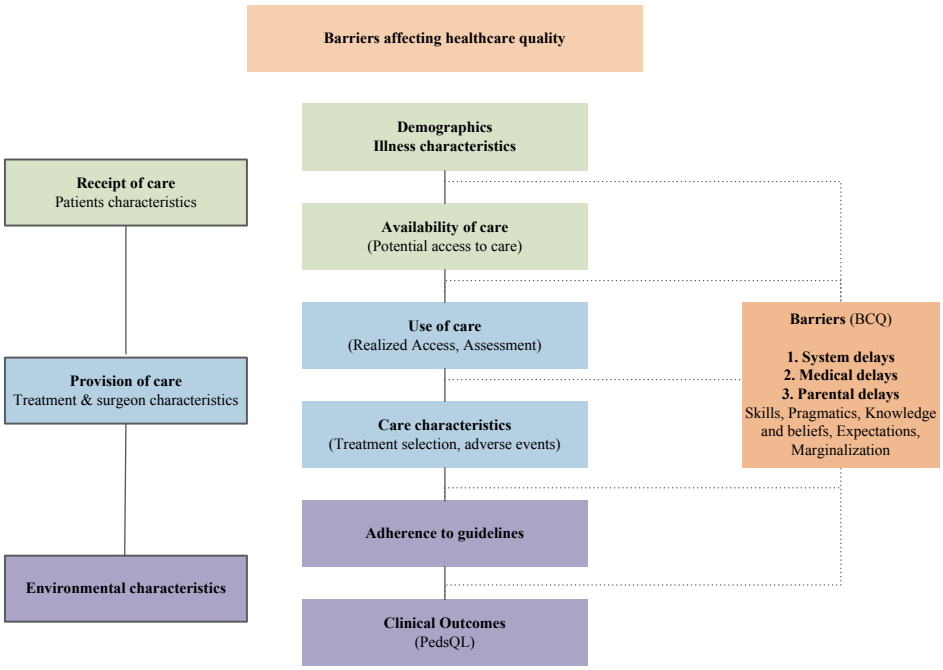
Prior to additional evidence-based guideline development, a downstream disparity evaluation should occur: including identification which children receive CIs and which do not, as well as the differences between their families and socio-economic background[23,29]. This evaluation enables understanding care discrepancies before children enter the CI candidate selection process[23]. Since latency reasons can significantly vary and are interrelated[14], this process of

identifying and defining the factors that impact whether a child becomes a CI candidate is difficult and complex[2]. For example, decision making regarding a child presenting with complex medical and/or developmental disabilities can be delayed due to several interrelated reasons: middle ear disease, dubiety regarding audiological test results (e.g., due to affected cognition and/or inconsistent test results) and absence due to comorbidity treatment[2].
Sorkin[30] specified seven barriers to explain low CI utilization in the United States: 1) low general CI awareness, 2) hearing loss referral networks that are unaware of candidacy criteria and CI outcomes, 3) political issues associated with deafness, 4) clinical and hospital financial issues, 5) need for widely accepted 'best clinical practices', 6) timely and comprehensive cost-effectiveness data and 7) the need for a dedicated organization focused on CIs. More pragmatically, Armstrong *et al.*[31] subdivided these barriers into three categories:

- System delays (e.g., uninsured status, delays in getting insurance approval for appointments, evaluations or hearing aids)
- Medical delays (e.g., complex medical comorbidities, neurocognitive issues that complicate CI candidacy assessment, doctors delay regarding candidacy)
- Parental delays (e.g., missed/delayed/non-compliance to appointments, misunderstanding the candidacy process, hesitations for surgery)

In line with Fitzpatrick *et al.*[13], Armstrong *et al.*[31] also marked that the delay of most patients was not dependent on just one reason, but could be explained by several (interrelated) reasons from the aforementioned categories, which hinders accurate latency reason identification.
Although many authors confirm in the literature that early implantation is essential, little research has been performed to identify why implantation in children is delayed. Table 2 provides an overview of several studies assessing latency reasons. Prior to developing a new CI guideline, similar reasons should be assessed within cohorts and solutions should be incorporated in this guideline to prevent that these delays will continue to affect paediatric CI care.
Figure 1 marks factors affecting the clinical outcome of cochlear implantation in children and therewith, marks the aspects that should still be assessed to enable clinical guideline formulation[32]. For example, environmental factors (Figure 1 - *left lower purple panel)*, which can affect care organization, have not been assessed in this thesis.
Figure 1 *(right panel)* marks that delay and barriers to early cochlear implantation can be identified using the 'Barriers to care questionnaire'(BCQ)[32-33]. Latency reasons should be identified using this questionnaire and classified according to Armstrong *et al.*[31]'s subdivisions. Furthermore, management plans within guidelines should be developed to prevent delay in auditory rehabilitation for groups at risk for delay.
Besides adjusting and defining candidacy criteria, there might also be a need to incorporate flexibility regarding the application of candidacy criteria into future guidelines. Hanvey *et al.*[42] demonstrated that often guideline guidance is interpreted as strict 'criteria' resulting in clinicians adhering to specific audiometric thresholds without accounting for the acceptable performance

Figure 1. Model to demonstrate factors that affect clinical outcome[32].



Legend: BCQ = Barriers to care questionnaire; PedsQL = Paediatric Quality of Life Inventory.

range on individual tests or a child's functional development. Since relatively more non-traditionally implanted children are demonstrating significant benefit from their surgery[43], not only the recommended hearing loss level (PTA thresholds) need to be lowered, but also, in specified situations, relaxation of (audiological) candidacy criteria could be considered[42].

Overall limitations

Our results could have been affected by low treatment prevalence[44]; the analyses in small sample sizes could have led to analysis imprecision and introduction of type II error. Since profound hearing loss occurs in only 0.943 to 1.182 per 1000 new-borns[45-48], only a minority of patients can qualify for cochlear implantation, which marks that this treatment is relatively rare. Therefore, only a small number of implanted children were included in our clinical studies (e.g., **Chapter 1.2**: inclusion of 54 implanted children). These small sample sizes could have impeded identification of statistically significant differences between implanted groups, although these were present (e.g., introduction of type II error). Hence, instead of the conclusion from **Chapter 3.3** that both sevoflurane inhalation and intravenous propofol can be safely used in children, there could be a therapy preference that was not identified due to our small sample size. Studies containing larger sample sizes are needed to evaluate whether this type-II error has affected our analysis.

Secondly, the methodological design of our studies could have introduced bias and affected the accuracy of our research findings[44]. We performed several retrospective studies, and in these studies, both the chance of missing data and the risk of bias is higher than in prospective or experimental studies[44]. Missing data in retrospective studies are common because data are not gathered for a research perspective, but are registered to monitor the patients' clinical outcome[49].

In our retrospective studies, we performed complete case analysis, executed no (additional) analysis on cases with missing data and therefore, could not define whether these data were missing at random or, more importantly, not at random. Therefore, our retrospective study design could have resulted in exclusion of essential data, which could have led to both introducing selection bias and could have resulted in a loss of statistical power[50-51]. A solution for including missing data is application of the multiple imputation technique[51]. Data imputation was considered in **Chapter 1.2**, however, in agreement with our audiology team, not considered since imputation does not necessarily lead to an accurate representation of the possible outcome of the evaluated child. Speech and language development outcome can vary and is affected by an indefinite number of covariates. For example, when data was missing, this was mostly of non-users or children with severe comorbidities, who generally underperform with CIs. Therefore, estimation of missing data using imputation could have led to overestimation of their speech and language performance with CIs. Furthermore, to formulate a uniform CI guideline, additional studies are needed that represent a higher level of evidence than included studies in this thesis. Especially since guidelines preferably contain high-level evidence (e.g., Level 1 or 2) to formulate an advice regarding a specific treatment. The evidence level of our studies was low: the methodological study design of included studies was retrospective (Level 3b) (**Chapter 1.2**, **Chapter 3.2**, **Chapter 3.3** and **Chapter 4.1**), summarizing the literature via a systematic review (Level 3a (**Chapter 1.1**, **Chapter 2.1** and **Chapter 3.1**), or gathering retrospective data in a prospective design (Level 4) (**Chapter 5.1**)[52].

Future developments: Telemedicine

Factors that induce latency to the CI candidacy process defined by Sorkin[30] (e.g., low CI awareness) can be improved and changed through telemedicine implementation[53]. Since (Appalachian) parents already reported their desire for closer guidance and expressed a strong interest in telemedicine[40], implementation of telemedicine can both prevent:

- Significant CI candidate selection delays
- Significant delays in postoperative follow-up appointments, programming and support

Both first categories of latency reasons defined by Armstrong *et al.*[31] (insurance problems and medical issues) require system reform to prevent further delays, however, the last category (parental barriers) could be potentially modifiable[14,33]. Furthermore, Table 2 marks that most reported latency reasons result from parental delay (marked in bold). Yang *et al.*[54] marked that potential future areas for improvement to maximize benefit of vulnerable parents are for example: 'getting enough help with paperwork' and 'knowing how to make the health care system work for you'. By creating a system in which families are educated and guided through

Table 2. Overview of studies reporting on latency reason assessment.

Risk factor for system, medical and/or parental delay	Latency reason	Article (reference)
Medical and **parental delay**	Delay in CI access: Affluence, disabilities involving learning or cognition	Fortnum *et al.*[34]
Medical and **parental delay**	Slow referrals for care, parental delays *Number of parents did not affect the analysis	Lester *et al.*[14]
Medical and **parental dela**y	Delay reasons for access to CI: Additional disabilities, lower hearing loss degree, less affluent families, not likely to use spoken language at home prior to CI referral, not taught using spoken language only at home, older children	Fortnum *et al.*[35]
Parental and system delay	Risk factor for delay: No NBHS, NBHS not identifying hearing loss, medicaid insurance alone, family physician is the primary care provider, audiologist/otologist as secondary care provider (in stead of an implant centre)	Lester *et al.*[14]
Parental and system delay	Delay in access to cochlear implantation: Rural: lack of local rehabilitation services/SL providers, increased costs/travel to access care, low SES, insurance status, low parental education (no awareness of rehabilitation importance)	Noblitt *et al.*[36]
Parental and system delay	Loss to FU after NBHS: Race (non-white), public insurance, smokers during pregnancy, residing in western, north-eastern, or south-eastern Massachusetts *Without early intervention services*: unilateral or mild or moderate degree of hearing loss, normal birth weight, or living in the south-eastern or Boston region	Liu *et al.*[37]
Parental and system delay	Predictors of CI rehabilitation outcomes: Low SES related disparities: internal factors of parental influence (e.g., parental self-efficacy, adherence, and habilitation carryover) and external factors (e.g., inadequate therapy and lack of available resources)	Kirkham *et al.*[38]
Parental and system delay	Delay in referral reasons: Marital status parents (single parent), children who were not managed by an ENT surgeon (otologist) *Insurance type did not hold in the multiple regression analysis (was confounded by marital status)	Wiley *et al.*[23]
Parental and system delay	Predictor of good CI outcome: NBHS presence, health insurance type	Lester *et al.*[14]
Parental and system delay	Risk factor for delay: No NBHS, NBHS not identifying hearing loss, medicaid insurance alone, family physician is the primary care provider, audiologist/otologist as secondary care provider (in stead of an implant centre)	Lester *et al.*[14]
Medical and system delay	Progressive hearing loss, other medical conditions (complex medical and/or developmental disabilities; eg ANSD, syndromes), other reasons (borderline hearing levels, immigration (no CI available in country of birth)	Fitzpatrick[13]
Parental delay	Disparity regarding postoperative follow-up: Lower socioeconomic background associated with: higher rates of postoperative complications, worse follow-up compliance, and lower rates of sequential bilateral implantation	Chang *et al.*[29]
Parental delay	NBHS non adherence: Low income, few prenatal care visits, minimal education, multiparous child	Cavalcanti *et al.*[39]
Parental delay	Delayed/missed appointments, reluctance for evaluations for surgery, having public insurance *According to CI team: delayed insurance approval, medical comorbidities	Armstrong *et al.*[31]
Parental delay	Barriers to NBHS (in rural areas): Education, distance, accessibility, and socioeconomic factors	Bush *et al.*[40]
Parental delay	Disparity within CI population: Race, higher median income	Stern *et al.*[41]

Legend: ANSD = auditory neuropathy spectrum disorder; CI = cochlear implant; ENT = Ear, Nose and Throat; FU = follow-up; NBHS = New-born Hearing Screening; SES = socioeconomic status; SL = Speech and Language

the complex CI candidate process, aforementioned delays caused by parental barriers could be prevented[31]. Although parents carry responsibility regarding the hearing rehabilitation of their child[36], parents from lower socioeconomic environments could lack communication skills to enable them to arrange accurate hearing rehabilitation for their child in a complex healthcare environment[38]. Easily interpretable information provided via telemedicine could assist them to handle this situation.

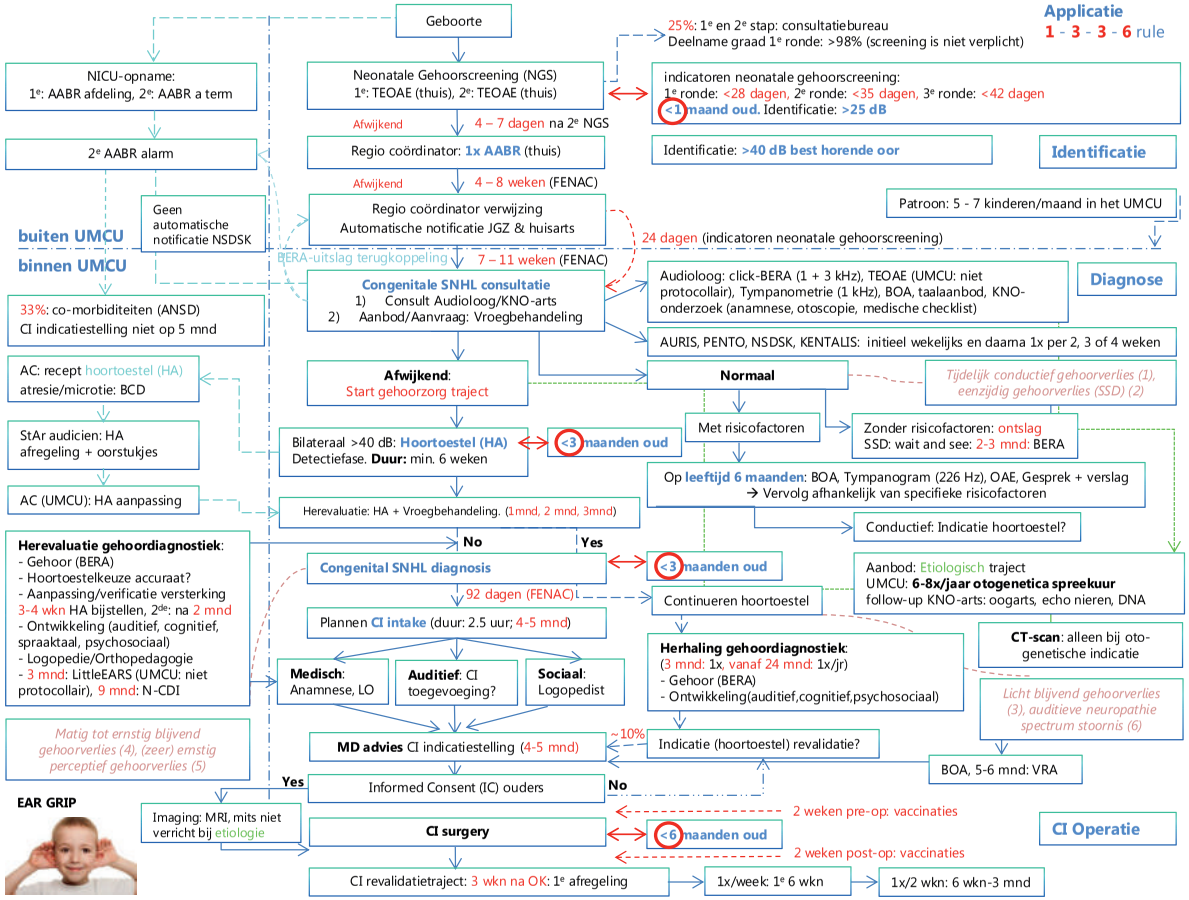
Telemedicine application could assist in providing a tracking system in which delays can be prevented. For example, non-compliant families with a history of missed hearing-aid evaluations and/or therapy appointments could contain potential CI candidates, who could get lost to follow-up and will not be referred for a candidacy evaluation[23]. However, identifying families at risk and chaperoning them via telemedicine could potentially prevent delay[31]. Moreover, specific aspects of the family environment[55] could affect variability in speech and language outcomes following CI: for example, children who have received CIs and live in a lower socioeconomic environment are less likely to derive full benefits from them[38]. Therefore, tracking them via telemedicine could facilitate more optimal follow-up and, more importantly, implantation benefit. Furthermore, since the number and diversity of CI recipients is currently increasing, provision of personalized post-implant rehabilitation services via telemedicine could more accurately meet the needs of this diverse and constantly changing population[23]. Especially since CI designs are used that include auto-feedback to enable comfortable fitting and in the near future, proxy-adjustment of fitting programs will be available, which could be easily facilitated and coordinated through telemedicine.

Definition of a structured timeline of the CI candidate selection process can assist parents in accurately understanding the candidate selection process[31]. Therefore, we clarified the possible care pathways that children presenting with hearing loss could follow in our clinic to provide parents insight in this selection process. Figure 2 represents the pathway to cochlear implantation in the UMC Utrecht and marks the complexity of CI candidate selection and access to this type of surgery (*data not presented earlier in this thesis*).

Based on Figure 2, we have designed an application for IPhone (Apple) and Android. Via this application, parents can interact with the CI team to ask questions and alternatively, the CI team can navigate parents through the diagnostic preoperative work-up[31].

Feasibility studies should follow to demonstrate whether implementation of this application results in reducing delays in both the CI candidate selection process and follow-up after cochlear implantation. Since this thesis clearly defines 'Here's How!' we should manage cochlear implantation in children, the readership should 'Act Now'! (WHO's hearing loss awareness campaign).

Figure 2. Figure demonstrating the (complexity of the) pathway to cochlear implantation in the UMCU.



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Chapter 6.2

Dutch summary (Nederlandse samenvatting)

Overzicht

Hoewel medische behandelvariatie kan voorkomen, is variatie van clinicus tot clinicus moeilijker te verdedigen dan variatie van patiënt tot patiënt, zeker wanneer het de behandeling van kinderen betreft[1]. Omdat er klinische variatie bestaat aangaande het faciliteren van cochleaire implantatie bij kinderen, heeft dit proefschrift enkele variaties van deze gehoorherstellende behandeling onderzocht. Middels evaluatie van vijf factoren die van invloed zijn op de behandeluitkomst, werden in dit proefschrift evidence-based richtlijnen opgesteld. Applicatie hiervan zal de eerder genoemde klinische variatie in de toekomst kunnen verminderen.

Dit proefschrift is ingedeeld in vijf delen. Ieder deel evalueert een factor die van invloed kan zijn op de behandeluitkomst na cochleaire implantatie bij kinderen:

- **Deel I**: Identificatie van de ideale leeftijd voor cochleaire implantatie bij kinderen op basis van spraak- en taalontwikkelingsgegevens (**Hoofdstuk 1.1** en **Hoofdstuk 1.2**)
- **Deel II**: Identificatie van de audiologische indicatiecriteria voor cochleaire implantatie bij kinderen (**Hoofdstuk 2.1**)
- **Deel III**: Identificatie van de chirurgische en anesthesiologische technieken die toegepast dienen te worden tijdens cochleaire implantatie bij kinderen (**Hoofdstuk 3.1**, **Hoofdstuk 3.2** en **Hoofdstuk 3.3**)
- **Deel IV**: Identificatie van Europese variatie in het tijdstip van effectueren van cochleaire implantatie bij kinderen (**Hoofdstuk 4.1**)
- **Deel V**: Identificatie van de consistentie van kwaliteit van leven (QoL) rapportage tussen kinderen en hun ouders na cochleaire implantatie (**Hoofdstuk 5.1**)

Deel I: Identificatie van de ideale leeftijd voor cochleaire implantatie bij kinderen op basis van spraak- en taalontwikkelingsgegevens

Op basis van de bevindingen van **Hoofdstuk 1.1** en **Hoofdstuk 1.2**, raden wij aan dat een kind met prelinguaal gehoorverlies, zonder ernstige co-morbiditeit, cochleaire implantatie ondergaat tussen de leeftijd van 12 en 18 maanden op basis van vier spraak- en taaldomeinen (spraakproductie en - perceptie, receptieve taalontwikkeling en auditieve prestaties). **Hoofdstuk 1.1** bevestigde de reeds bekende voordelen van vroege cochleaire implantatie, maar demonstreerde tevens het tegenstrijdige bewijs over de voordelen van implantatie vóór de leeftijd van 12 maanden, en in het bijzonder vóór de leeftijd van zes maanden. Dit systematische literatuuronderzoek liet het volgende zien:

- Cochleaire implantatie < 24 maanden oud is gunstig voor de ontwikkeling van spraakperceptie op basis van één spraakperceptiescore (de Phonetically Balanced Kindergarten (PB-K) gecombineerd met de Consonant-Nucleus-Consonant (CNC) score, maar niet aangaande Glendonald Auditory Screening Procedure (GASP) scores)
- Cochleaire implantatie < 12 maanden oud is gunstig voor de ontwikkeling van spraakproductie, auditieve prestaties en receptieve taalscores op basis van twee spraakproductiescores (de Diagnostic Evaluation of Articulation and Phonology (DEAP) en Infant-Toddler Meaningful Auditory Integration Scale (IT-MAIS) scores), één auditieve

prestatiescore (de Categories of Auditory Performance II (CAP II) score) en twee van de vijf receptieve taalontwikkelingsscores (de gecombineerde Preschool Language Scale (PLS)- en Oral and Written Language Skills (OWLS) score en Peabody Picture Vocabulary Test (-Revised) (PPVT-R) scores)
- Cochleaire implantatie < zes maanden oud is gunstig voor de ontwikkeling van auditieve prestaties op basis van één auditieve prestatiescore (CAP-II)

Hoofdstuk 1.2 toonde dat eerdere cochleaire implantatie (< 18 maanden oud), dan werd gerapporteerd in de literatuur (**Hoofdstuk 1.1**: < 24 maanden oud), leidt tot relatief superieure lange termijn spraakperceptiescores. De spraakperceptie werd beoordeeld middels het afnemen van lijsten met Consonant-Vowel-Consonant (CVC) woorden. Dit zijn woorden die zijn opgebouwd uit een medeklinker (consonant), klinker (vowel) en medeklinker en daadwerkelijk een betekenis hebben. Voorbeelden zijn: lip, bus of pop. Na correctie van plafondeffecten, vonden wij een significant CVC-scoreverschil (p <.001) tussen groepen van kinderen die op een verschillende leeftijden werden geïmplanteerd. Wij zagen dat kinderen die op jongere leeftijd (< 18 maanden oud) werden geïmplanteerd meer CVC plafondscores bereikten, dan kinderen die op latere leeftijd (> 18 maanden oud) werden geïmplanteerd.

Deel II: Identificatie van de audiologische indicatiecriteria voor cochleaire implantatie bij kinderen

Op basis van de bevindingen van **Hoofdstuk 2.1**, adviseren wij dat kinderen met prelinguaal gehoorverlies een cochleair implantaat (CI) verdienen indien hun audiologische gehoordrempels gelijk zijn aan of groter zijn dan 80 decibel (dB) (2-frequentie Pure Tone Average (PTA)-drempels van ≥ 85 dB hearing level (HL) of 4-frequentie PTA-drempels ≥ 80 dB HL). Dit is een lager audiologisch indicatiecriterium dan momenteel wordt aanbevolen in zowel nationale richtlijnen als adviezen van CI producenten.

In **Hoofdstuk 2.1** verrichtten wij een systematisch literatuuronderzoek, omdat er momenteel internationale variatie bestaat aangaande de audiologische indicatiecriteria voor cochleaire implantatie. Middels dit literatuuronderzoek hoopten wij uniforme audiologische indicatiecriteria voor cochleaire implantatie bij kinderen te kunnen definiëren. Fitzpatrick *et al*.[2] vermeldden dat, zodra kinderen aan audiologische indicatiecriteria voor cochleaire implantatie voldoen, er geen verdere vertraging van CI zorg meer bestaat. Daarom zou een uniforme definitie van audiologische cochleaire implantatiecriteria toekomstige CI-vertragingen voor kinderen kunnen voorkomen. In **Hoofdstuk 2.1** concludeerden wij het volgende:
- Kinderen met een 4-frequentie PTA-drempelwaarde van ≥ 80 dB HL dienen in aanmerking te komen voor cochleaire implantatie op basis van spraakperceptie en auditieve prestatiescores
- Kinderen met CI's scoren significant beter dan kinderen met hoortoestellen (HA) op basis van een spraakperceptie test bij PTA-drempels van 88 en 96 dB HL

Deel III: Identificatie van de chirurgische en anesthesiologische technieken die voor cochleaire implantatie bij kinderen dienen te worden toegepast

Op basis van de bevindingen van **Hoofdstuk 3.2**, raden wij aan dat de mastoïdectomie met posterieure tympanotomie benadering (MPTA)[3] wordt toegepast als chirurgische techniek voor cochleaire implantatie bij kinderen die < 24 maanden oud zijn, omdat zij gezien hun leeftijd meer kans hebben op infectieuze complicaties. Bovendien wordt in **Hoofdstuk 3.3** aangetoond dat beide anesthesie onderhoudstechnieken (intraveneuze propofol en sevofluraan narcosegas) veilig kunnen worden toegediend aan American Society of Anaesthesiologists (ASA) 1 en ASA 2 geclassificeerde kinderen die < 24 maanden oud worden geïmplanteerd.

In **Hoofdstuk 3.1** onderzochten wij welke chirurgische techniek voor cochleaire implantatie de voorkeur verdient bij kinderen. Momenteel wordt namelijk de MPTA[3] beschouwd als de chirurgische referentietechniek voor cochleaire implantatie. De suprameateale benadering (SMA)[4] vereist echter geen mastoïdectomie, welke van invloed zou kunnen zijn op het infectierisico en het behoud van restgehoor. Het uitvoeren van een mastoïdectomie kan de middenoorbeluchting verbeteren en hierdoor leiden tot een lagere incidentie van acute otitis media (AOM)[5]. Daarom veronderstelden wij dat juist het uitvoeren van een mastoïdectomie door het toepassen van de MPTA[3], een beschermend effect zou kunnen hebben en zou resulteren in minder complicaties. Dit zou het toepassen van deze techniek gunstiger maken ten opzichte van de SMA[4].

De uitgevoerde literatuurstudie in **Hoofdstuk 3.1** toonde echter een vergelijkbare klinische uitkomst aangaande complicaties tussen beide chirurgische technieken. Daarom konden wij niet bevestigen dat de MPTA[3] de voorkeur verdient. Hoewel een geïncludeerde studie uit **Hoofdstuk 3.1** wel een significant (p <.023) hogere mastoïditisratio vond bij kinderen die werden geopereerd middels de MPTA[3], sloot de meta-analyse uit **Hoofdstuk 3.1** een dergelijk effect uit. Gehoorbehoud werd niet gerapporteerd bij kinderen en de gehooruitkomst bij volwassen patiënten bleek tussen beide technieken niet te verschillen.

Omdat de geïncludeerde kinderen in **Hoofdstuk 3.1** allemaal > 24 maanden oud waren, vergeleken wij de klinische uitkomst van beide operatietechnieken in jongere kinderen in **Hoofdstuk 3.2**. Het bepalen van de meest optimale chirurgische techniek tijdens deze periode is essentieel, omdat kinderen momenteel bij voorkeur gedurende het eerste levensjaar worden geïmplanteerd. Daarnaast zijn kinderen die > 24 maanden oud zijn tijdens cochleaire implantatie minder vatbaar voor postoperatieve infecties (bijv. AOM en/of mastoïditis). De piekincidentie van deze postoperatieve infecties ligt namelijk tussen de leeftijd van zes en 12 maanden[6-7].

Hoofdstuk 3.2 bevestigde onze aanvankelijke hypothese dat het gebruik van de MPTA[3] een beschermend effect heeft: het niet uitvoeren van een corticale mastoïdectomie (middels de SMA[4]) resulteerde in significant meer infectieuze complicaties. Omdat wij in ons cohort een significant 'mastoïdectomie-effect' op de postoperatieve infectieratio hebben gevonden, raden wij dan ook aan dat de MPTA[3] wordt toegepast bij kinderen die < 24 maanden oud zijn als ze worden geïmplanteerd.

In **Hoofdstuk 3.3** vonden wij dat complicaties bij ASA 1 en ASA 2 geclassificeerde kinderen, die < 24 maanden oud waren toen ze werden geïmplanteerd, onafhankelijk optraden van de leeftijd tijdens implantatie, het aantal preoperatieve anesthesiologische procedures en het type onderhoudsanestheticum. De reden om te evalueren of toediening van verschillende typen onderhoudsanesthetica effect zouden kunnen hebben op de complicatieratio tijdens en na de cochleaire implantatie was vierledig:

- Cochleaire implantatie wordt momenteel uitgevoerd gedurende het eerste levensjaar en jonge kinderen lopen een groter risico op bijwerkingen tijdens een narcose[8]. Dit hogere risico kan bijvoorbeeld ontstaan door het frequenter optreden van bovenste luchtweginfecties bij jonge kinderen, waardoor perioperatieve laryngospasmen en postoperatieve hypoxie sneller kunnen worden geïnduceerd.
- Multipele preoperatieve anesthesiologische procedures zijn vereist om te evalueren of een kind een kandidaat is voor cochleaire implantatie (bijv. een MRI -scan). Dit zou een nadelig cumulatief effect kunnen hebben op de klinische uitkomst van de narcose gedurende de cochleaire implantatie.
- Propofol onderhoudsanesthesie gaat gepaard met minder perioperatief bloedverlies vanwege de hypotensieve en/of vaatverwijdende werking[9]. Daarom zou propofol toediening kunnen resulteren in een optimaler perioperatief chirurgisch werkveld.
- Toediening van een inhalatie anestheticum kan een nadelig effect hebben op de ontwikkeling van het neonatale brein: sevofluraan onderhoudsanesthesie kan leiden tot langdurige geheugenstoornissen[10].

Hoewel propofol onderhoudsanesthesie geassocieerd is met een lager risico op perioperatieve laryngospasmen bij kinderen dan sevofluraan[11], bevestigde **Hoofdstuk 3.3** niet dat propofol onderhoudsanesthesie resulteert in minder anesthesiologische en/of chirurgische complicaties.

Deel IV: Identificatie van Europese variatie in het tijdstip van effectueren van cochleaire implantatie bij kinderen

In **Hoofdstuk 4.**1 vonden wij opmerkelijke vertraging van het tijdig effectueren van cochleaire implantatie in Europa. Vanaf 2010 werd slechts circa 30% van de Europese CI-kandidaten geïmplanteerd < 24 maanden oud. Dit tijdsinterval kan worden ingekort door uitgebreidere implementatie van neonatale gehoorscreening, optimalere naleving van reeds geïmplementeerde richtlijnen, verbeterde afstemming tussen internationale richtlijnen en meer bewustwording bij ouders van de impact van het gehoorverlies voor hun kind.

Leigh *et al.*[12] beschreven dat de meerderheid van de Australische kinderen nog steeds cochleaire implantaten krijgt > 24 maanden oud en Fitzpatrick *et al.*[13] bevestigden dat in Canada (gemiddeld) pas geïmplanteerd wordt 24 maanden na de bevestiging van het gehoorverlies. Bovenstaande bevindingen motiveerden ons om de vertraging van Europese CI-zorg in kaart te brengen.

Lester *et al.*[14] rapporteerden dat in gunstige gezondheidszorgstelsels zoals de Verenigde Staten nog steeds 42% van de onderzochte populatie geen CI ontving < 24 maanden oud, hetgeen nog altijd relatief gunstiger is dan onze Europese bevindingen.

Deel V: Identificatie van de consistentie van kwaliteit van leven (QoL) rapportage tussen kinderen en hun ouders na cochleaire implantatie

In **Hoofdstuk 5.1** vonden wij dat de gerapporteerde QoL-scores significant (ICC > 0.8) overeenkwamen tussen kinderen met een ernstig gehoorverlies en die van hun ouders, die de QoL van hun kind rapporteerden. De grootste QoL-score overeenkomst (consistentie) werd gevonden voor scores die betrekking hebben op fysieke QoL-aspecten. Omdat de QoL-scores tussen ouders en kinderen die tussen de acht en 12 jaar oud waren tijdens de QoL-evaluatie het meest overeenkwamen, adviseren wij QoL consistentie bepaling tijdens deze postoperatieve leeftijd.

In de **Algemene discussie** vatten wij de resultaten van dit proefschrift samen en bediscussiëren wij de beperkingen van dit proefschrift. Samengevat onderstreept dit proefschrift het belang van tijdige en uniform verrichte cochleaire implantatie bij kinderen. Middels onze evidence-based adviezen hopen wij de huidige variatie van clinicus tot clinicus te verminderen. In de toekomst verwachten wij dat middels informatieverstrekking via telemedicine (bijv. het toepassen van mobiele applicaties), ouders de indicatiecriteria en de tijdlijn van het kandidaat-selectieproces beter begrijpen en dat hiermee zorgvertraging kan worden voorkomen.

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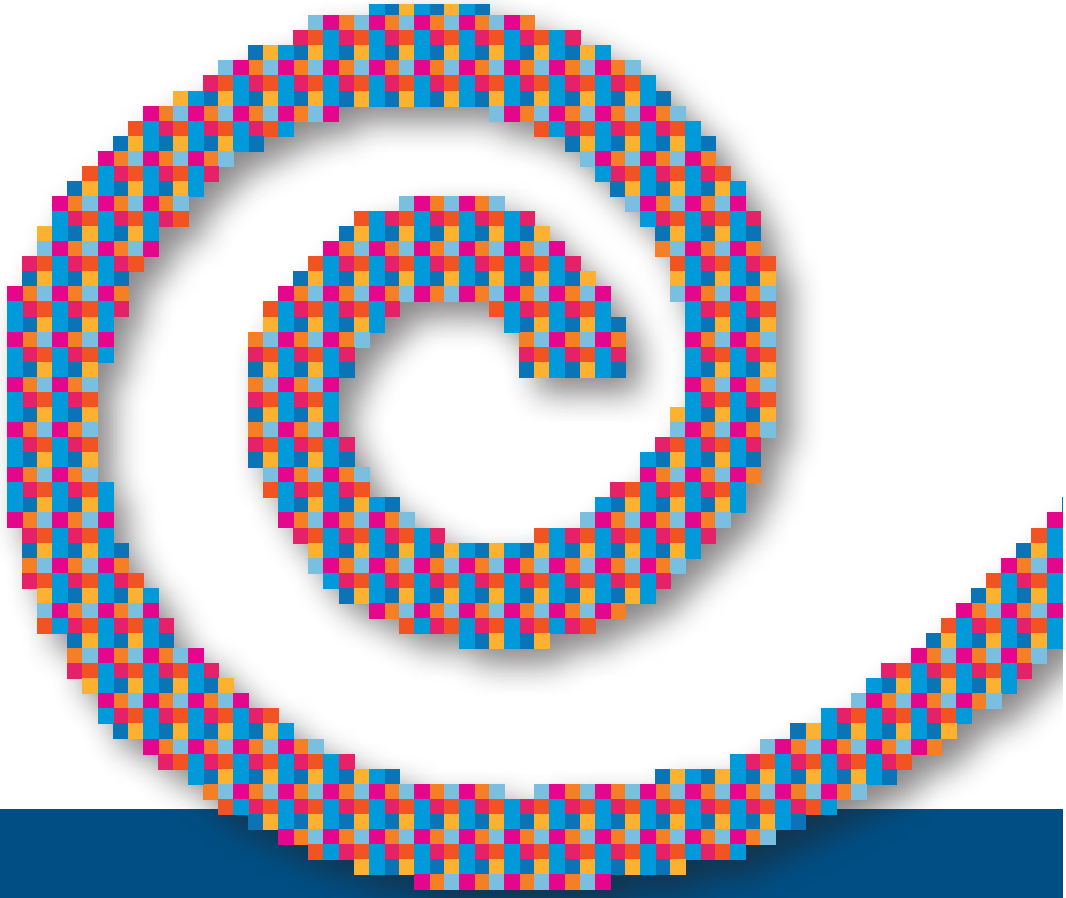


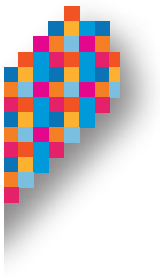
APPENDICES

List of abbreviations

Graduate School of Life Sciences Certificate

List of publications

Acknowledgements (Dankwoord)



LIST OF ABBREVIATIONS

AB	Antibiotics
ABR	Auditory Brainstem Response
AC	Auditory Centre
AIMS	Anesthesia Information and Management System
(A)OM	(Acute) Otitis Media
ANOVA	Analysis of Variance
ANSD	Auditory Neuropathy Spectrum Disorder
AP	Auditory Performance
ASA	American Society of Anesthesiologists
ASSE	Auditory Sound Speech Evaluation
ASSR	Auditory Steady-State Response
ATO	According to Outcome
BERA	Brainstem Evoked Responses Audiometry
BCH	Birmingham Children's Hospital (United Kingdom)
BCQ	Barriers to Care Questionnaire
BiCIs	Bilateral Cochlear Implants
BKB	Bamford-Kowal-Bench
BOA	Behavioural Observation Audiometry
CAP	Categories of Auditory Performance
CAPT	Chear Auditory Perception Test
CAT	Critically Appraised Topic/Critical Appraisal of a Topic
CDaCI	Childhood Development after Cochlear Implantation
CELF	Clinical Evaluation of Language Fundamentals
CI(s)	Cochlear Implant(s)
CI-ON	Cochleaire Implantatie Overleg Nederland (Dutch CI society)
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CMV	Cytomegalovirus
CNC/CVC(A)	Consonant-Nucleus-Consonant/Consonant-Vowel-Consonant (Auditory)
COM	Chronic Otitis Media
CORA	Conditioned Orientation Reflex Audiometry
CPA	Conditioned Play Audiometry
CSA	Cross-Sectional Analysis
CSF	CerebroSpinal Fluid
CT scan	Computed Tomography scan
95%CI	95%Confidence Interval
dB	decibel
DEAP	Diagnostic Evaluation of Articulation and Phonology
DF	Degrees of Freedom

DIN	Digits-In-Noise
DoE	Directness of Evidence
ENT	Ear, Nose and Throat
EMA	EndoMeatal Approach
FAPCI	Functioning after Paediatric Cochlear Implantation
FDA	Food and Drug Administration
FR	Facial Recess
FU	Follow-Up
GAEL-P	Grammatical Analysis of Elicited Language - Pre-Sentence Level
GASP	Glendonald Auditory Screening Procedure
GCBI	Glasgow Children Benefit Inventory
GJB6	Gap junction beta-6 protein
H	High
HA(s)	Hearing Aid(s)
HI	Hearing Impairment
HINT	Hearing in Noise Test
HL	Hearing Level
HP	Hearing Preservation
Hz	Hertz
ICC(s)	Intra-Class Correlation(s)
IE	Implant Experience
IJPORL	International Journal of Paediatric Otolaryngology
(IT-)MAIS	(Infant-Toddler) Meaningful Auditory Integration Scale
IQR	InterQuartile Range
JCIH	Joint Committee on Infant Hearing
Kg.	Kilograms
L	Low
LNT	Lexical Neighborhood Test
LOCHI	Longitudinal Outcomes of Children with Hearing Impairment study
M	Medium
MAI	Mean age at implantation
MB-CDI	MacArthur–Bates Communicative Development Inventories
MFRA	Mastoidectomy with Facial Recess Approach
min.	minutes
MLNT	Multisyllabic Lexical Neighborhood Test
MRI scan	Magnetic Resonance Imaging scan
MPTA	Mastoidectomy with Posterior Tympanotomy Approach
MSTB	Minimum Speech Test Battery
NBHS	New-born Hearing Screening
NH	Normal Hearing

NICE	National Institute for Health and Clinical Excellence
NICU	Neonatal Intensive Care Unit
NL	the Netherlands
no.	number
n.s.	not significant
OAE	OtoAcoustic Emmision
OR time	Operating Room time
ORL	Journal for Oto-Rhino-Laryngology, Head and Neck Surgery
OSW	Open-Set monosyllabic Word
OWLS	Oral and Written Language Skills
PACU	Post-Anaesthesia Care Unit
PBK	Phonetically Balanced Kindergarten
PCS	Prospective Case Series
PedsQL	Paediatric Quality of Life Inventory
PLS	Preschool Language Scale
PPVT(-R)	Peabody Picture Vocabulary Test (-Revised)
PRISMA	Preferred Reporting Items for Systematic Review and Meta-analysis
PSI	Paediatric Speech Intelligibility test
PTA	Pure Tone Average
QoL	Quality of Life
RCS	Retrospective Case Series
RCT	Randomized Controlled Trial
RDLS	Reynell Developmental Language Scale
RIZIV	Rijksinstituut voor ziekte- en invaliditeitsverzekering (Belgian National Institute for Health and Disability Insurance)
RoB	Risk of Bias
RL	Receptive Language
RLS	Retrospective Longitudinal Analysis
RMC	Retrospective Multicentre Study
RW	Round Window
SD	Standard Deviation
SES	Socio-Economic Status
SIR	Speech Intelligibility Rate
SLD	Speech and Language Development
SMA	SupraMeatal Approach
SOM	Secretory Otitis Media
SNHL	SensoriNeural Hearing Loss
SPe	Speech Perception
SPIN	SPe in noise
SNR	Signal to Noise Ratio
SPL	Sound Pressure Level
SPr	Speech Production

STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
TA	Trans-attical Approach
TIVA	Total IntraVenous Anesthesia
TDT	Toy Discrimination Test
UK	United Kingdom
UMC(U)	University Medical Centre (Utrecht)
VAS	Visual Analogue Scale
VRA	Visual Reinforcement Audiometry
vs.	versus
WHO	World Health Organization
WIPI	Word Intelligibility by Picture Identification
yrs.	years

GRADUATE SCHOOL OF LIFE SCIENCES

Name PhD candidate: H., Hanneke, Bruijnzeel
Date of birth: 10-08-1987 Place of birth: Vianen
PhD program: Clinical and Experimental Neuroscience Date thesis defense: 20-12-2018

Educational program

	# EC
Introduction course	0.5
General courses	
Workshop statistical course UMCU - BCRM	0.5
BROK-course	1.0
Statistics Course Graduate School of Neurosciences Amsterdam/Rotterdam	3.6
Systematic Review Course Cochrane	0.6
Workshop Time Management	0.5
Workshop Tutoring master students	0.5
Workshop Scientific Writing	0.5
Workshop What is important for a Scientific Career	0.5
Workshop Career Orientation	0.5
Theoretical / disciplinary courses	
Course Clinical Epidemiology - Elevate	1.5
Course Current Issues in Clinical Neuroscience: Epilepsy	1.5
Topics in Neurophilosophy	1.5
Academical Writing Course 2015	1.5
BCRM Summer School 2014	0.5
BCRM Summer School 2015	0.5
BCRM PhD day	0.5
BCRM Research day 2014	0.5
ONWAR PhD meeting - Woudschoten	1.0
Courses of other GS-LS PhD programmes and/or attended external courses or meetings	
Clinical training	6.0
Training abroad	1.5
Conferences & symposia	1.8
TOTAL NUMBER OF CREDITS (EC) =	**27.0 EC**

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CURRICULUM VITAE

Hanneke Bruijnzeel was born on the 10th of August in Vianen, the Netherlands. After 16 months, she emigrated with her family to Davos, Switzerland, where she spend the first four years of her life. As a fluently speaking Swiss-German toddler she returned to Utrecht, where she graduated at the Stedelijk Gymnasium in 2005. She took a gap year, in which she studied the Spanish language in Barcelona, Spain, and worked, in an orphanage in Buenos Aires, Argentina.

In 2006, she was decentrally selected to study Medicine at the University of Amsterdam and moved to our capital. During her studies, Hanneke went back to Davos to work in the Dutch Asthma Clinic. In 2010 she decided to do a laboratory research rotation in dr. S. Krasinksi's lab in Boston Children's Hospital, United States. On the streets of Cambridge, Massachusetts, she met André, who later became her husband. This meet-up made her decide to return to Boston to perform a clinical research rotation in MGH's Orthopedics department of dr. D. Ring.

In 2011, she returned to Amsterdam to start her clinical internships. During this period, she spent two months in her 'second hometown' Lisbon, Portugal, at the Hospital Dona Estefânia for an elective ENT clerkship under supervision of dra. L. Monteiro. After her graduation in the summer of 2013, she moved to Birmingham, United Kingdom, to work as ENT Senior House Officer in the Birmingham Children's Hospital under supervision of mr. M. Kuo.

In 2014, she returned to the Netherlands to start her PhD project, that led to this thesis, at the UMC Utrecht under the initial supervision of prof. dr. W. Grolman and dr. V. Topsakal and ultimately, supervised by prof. dr. R.J. Stokroos. For the purpose of her thesis work, she travelled to Portugal, Italy, Belgium, the UK and Germany to create a database from various pediatric cochlear implant centers to evaluate pediatric cochlear implantation across Europe.

In 2016, Hanneke has started her residency in Otorhinolaryngology and Head & Neck surgery at the UMC Utrecht. During her residency, she completed part of her training at the St. Antonius Hospital, Nieuwegein (supervision by dr. M.P. Copper), the Meander MC, Amersfoort (supervision: dr. J. van de Akker & prof. dr. H.F. Mahieu) and the Gelderse Vallei, Ede, (supervision by dr. M.H.J.M Majoor).

Brain Center
Rudolf Magnus

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