Early detection and screening for childhood deafness in the Philippines

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Introduction

Introduction

Early Detection and Screening for Childhood Deafness

Deafness is considered in a child when hearing loss is severe to profound (average thresholds >70-90 dB) such that linguistic information cannot be processed accordingly. Congenital hearing loss remains as one of the most common of congenital disorders in children affecting 1.5- 6.9 per 1000 live births (Parving 1999; Parving and Haunch 2001). In more than 50% of cases the cause is genetic mostly due to GJB2 or GJB6 mutations (Morton 1991; Cohen and Gorlin 1995; Norris et al. 2006) but may be lower from 19%-30% depending perhaps on the severity of hearing loss in the population studied (Chinetti et al. 2010; Roux et al. 2004; Cama et al. 2009). Of the genetically caused or hereditary hearing loss approximately 70% are classified to be non-syndromic while 30% syndromic with other associated clinical features (Morton 1991). The proportion of children with permanent significant hearing impairment present since the neonatal period is reportedly 80-90% (Davis et al. 1997; Kuhl and Williams 1992). Hearing loss before the development of speech and language is termed prelingual deafness. A number of studies describe an intricate link between hearing impairment and the sensory development of the infantile brain and neurosensory netwoks (Ruben and Schwartz 1999; Sininger, Doyle and Moore 1999; Stockard-Pope 2001; Hannon 2003). Late diagnoses of prelingual deafness result in deleterious effects that include psychosocial, educational and economic aspects both from an individual and societal viewpoint (Bess, Dodd Murphy and Parker 1998; Ruben 2000; Schroeder et al. 2006). Given these pervasive individual disadvantages and the significant economic burden to society efforts at early detection of hearing loss slowly gained importance. A greater emphasis on screening and identification of hearing impaired children evolved to mitigate the harmful consequences on language, speech and overall mental development. While Wilson and Junger (1968) laid out the 10 basic principles of screening that in a review of hearing screening in children was also adapted by Davis and co-workers (1997). Based on these principles, epidemiological studies at the local level are deemed necessary to determine the value of screening and for proper planning of service provision. The availability and accuracy of objective testing and proper intervention following the diagnosis need to be established. Likewise, cost and effectiveness of any hearing screening should be examined on a case type basis to maximize benefit. This cost-benefit of screening will have to be justified before public financing of this secondary prevention measure is made available more so in an era of stiffly competing health interventions that need financial support. This issue is especially

significant in developing countries where the incidence of hearing impairment especially among children have reportedly been higher but resources are limited.

Risk factors and Objective Screening

The Joint Committee on Infant Hearing in 1982 already recognized the problems related to delayed diagnosis of childhood deafness and recommended identification by the age of 3 to 6 months. It updated several times a list of high risk factors or high risk registry (HRR) for neonates and infants whereby identification of hearing loss would be of paramount importance (JCIH 1982; JCIH 2000; JCIH 2007). In 1993, along with the United States National Institutes of Health it published a consensus statement which emphasized the need for early detection of hearing loss by the use of objective testing like otoacoustic emission (OAE) testing and auditory brainstem response (ABR) testing (National Institute on Deafness and Other Communication Disorders Consensus Statement 1993). In 1995, the World Health Assembly in its resolution 48.9 exhorted countries to set up national plans for the prevention and early detection of hearing loss among children (WHO 1995). There was evidence that with risk screening alone about 42% of hearing impaired children will be likely missed such that objective testing for hearing loss must be universally applied (Wrightson 2007). On the other hand The Wessex Universal Neonatal Screening Trial Group (1998) diagnosed those with permanent childhood hearing loss who had risk factors such as stay in the NICU or low birth weight, infections in only about 8 % giving further support to the need for objective screening to be applied universally to all newborns.

OAE testing entails the introduction of clicks or tones in the ear canal while “cochlear echoes” detected by a sensitive microphone in turn would indicate good outer hair cell motility in hearing ears. The thresholds at which responses are detected are 30 dB for transient evoked OAE and 40 dB for distortion product OAE in which two tones are used. ABR testing looks at the electrophysiological responses elicited by transient acoustic stimuli such as tone bursts or clicks that are detected by surface electrodes placed on the forehead and near the ears. It looks at the integrity of the neural pathways from the ear to the brainstem with Wave I response coming from the distal eight nerve, Waves II to IV from the proximal end of the eight nerve to the caudal pons, the trapezoid body and the superior olivary complex while Wave V generally comes from the lateral lemniscus as it approaches the inferior colliculus, is the most robust of all waves such that the threshold of hearing is usually based on this particular wave (Hall JW III 2007). Automated ABR devices or AABR that ascertains the presence of a Wave V response at 35 dB HL have confirmed failure rates as low as 2% in a healthy baby

population and only 4% in intensive care nursery infant population (Stewart et al. 2000). AABR is more sensitive in detecting a hearing loss including those that may be missed by OAE such as auditory neuropathy or hair cell dys-synchrony (Rance G et al. 1999) which may affect up to 8.44% of profoundly deaf children (Foerst 2006; Ngo et al. 2006). Early intervention with early detection of hearing loss depends on objective OAE or AABR followed by diagnostic confirmation by ABR. Auditory Steady State Response (AASR) is a test that uses FM modulated stimuli in order to binaurally assess the auditory system and provides frequency specific information valuable for the estimation of auditory thresholds particularly those with severe to profound hearing loss (Stapells et al. 1984; Rance G and Rickards F 2002).

Developed countries variably adopted different newborn hearing screening protocols for carrying out this early identification of hearing loss. In the United Kingdom the mandatory screening by health visitor distraction test of all babies at eight months eventually gave way to universal newborn hearing for the early detection of hearing loss within three months of birth and early intervention by the age of six months (Davis et al. 1997). While the first screening could be carried out while the baby was still in the hospital a second screening utilizing either an otoacoustic emission test or automated auditory brainstem response test within three months have become the norm. A second failed screening result with either OAE and AABR was followed by a diagnostic ABR. Before universal newborn hearing screening (UNHS) was instituted the median age of identifying hearing loss in children varied from 10.4 months to 43.2 months in the U.S, and some European countries in the early 1990's (Harrison, Roush and Wallace 2003; Marttila and Karikoski 1996; Parving 1999; Watkin, Baldwin and McEnery 1991) but now stands at 3 months in most of the developed world with UNHS programmes. This is in contrast to the experience in developing countries where parental suspicion prompted by a child's inappropriate response usually constitutes the reason for consultation at a mean age of about 22 months (Mukari Vandort, Ahmad, Saim and Mohamed 1999; Olusanya, Luxon and Wirz 2006). Last year, 97.4% of babies born in the U.S. have been screened which was a significant increase from the 46.5% reported in 1999. About 1.6% did not pass the final or most recent examination. Of those who did not pass the initial screen a diagnosis of whether there was hearing loss or not could be obtained in 68.4% before 3 months of age. Of those with hearing loss a quarter weighed less than 2500 grams with the same proportion having one or more other developmental disabilities (Center for Disease Control and Prevention 2012).

Hearing aids can be fitted between 3 to 6 months in most instances. Early intervention at around six months were found to correlate well with better reading compr ehension and speech and language development (Yoshinaga-Itano et al. 1998). There may well be other factors than early fitting of hearing aids or even cochlear implantation such as the auditory verbal training, audiological support and commitment of the parents and the family, presence of other disabilities as well as the ultimate choice of mode of communication that would greatly impact on outcomes. Some studies have reported a correlation between the presence of GJB2 mutation and outcome following cochlear implantation suggesting that genetic screening services would be clinically valuable. Though this is now carried out in some developed countries more studies will be needed to ascertain that such mutations are consistently responsible for the majority of congenital hearing loss and that this genetic screening will be clinically valuable in predicting outcomes and further aid genetic counseling.

Challenges of Hearing Screening in a Developing Country like the Philippines

Of the 6.5 billion people in the world about 5.3 billion live in developing countries. Population growth rates continue to rise in some of these countries in Asia, Africa and Latin America. The World Health Organization (WHO) estimated that two thirds of those with severe to profound hearing loss live in developing countries (Kumar 2001). Classification of countries whether developed or developing depends on several indices (GNI), gross national income per capita (lower income group cut off at $3255); Human Development Index (HDI) of 0.8 or GINI Index ideally at 0 with equal income distribution). In 2010, The Philippines' HDI at 0.64 ranked 112th among 187 countries surveyed putting it at medium development category, a GDP per capita of $3600 (Lower middle income economy <$3855) with expenditures for health pegged at 1.3% of GDP versus the 5% recommendation of the WHO (UNDP 2012).

In the Philippines, the path towards an efficient and systematic universal screening for newborns and early detection of hearing loss in infants therefore remains to be a daunting task. Despite the fact that structured educational programmes in audiology have been instituted in two universities since 1999, most of the graduates get employment in other countries with better salaries and professional growth opportunities. An established programme on speech pathology previously offered in the national university (University of the Philippines) continues to lose its graduates to foreign employment (Cheng, Olea and Marzan 2002). It recently was joined by a private university (University of Santo Tomas) in offering a bachelor's

degree in speech and language pathology and it is hoped that there will be more who will decide to stay to augment the number of trained speech therapists. Notable also are the geographic (the Philippines is an archipelago of 7000 islands), economic, infrastructure problems (audiologic equipment not readily available in most hospitals) with less than 24 hospitals within Manila having OAE or ABR equipment (CONHSCA 2006). Universal newborn hearing screening protocols from developed countries needed to be investigated with respect to local adaptability. In fact, though few tertiary hospitals offered targeted OAE testing since 1996 none of the government hospitals could offer this given the lack of equipment and trained personnel. The usual protocols in developed countries needed modification given that the number of births in hospitals comprise only 40% with more home deliveries. This is especially challenging in a country like the Philippines with a population of 95 million and where the population grows at 1.87% whilst infant mortality rate is 18.75 per 100 live births (Philippines Fact Sheet 2012).

Scope and Objectives of this Thesis

As discussed earlier there was first the need to establish baseline epidemiologic data regarding the risk of neonatal hearing loss in a national tertiary academic referral center such as the Philippine General Hospital as there were no published epidemiologic data in the country on the prevalence of hearing loss among newborns with or without risk factors (Quintos et al. 2003; Chiong et al. 2004). Clearly the neonatal intensive care unit of a hospital where the sickest babies maybe found provided a good starting point at which the percentage of babies with risk of hearing loss could be established is the subject for discussion in **Chapter 2.** The associated risk factors for failing the evoked otoacoustic emission testing was investigated. Male gender and low birth weight emerged as significantly associated with a fail result which was found in up to 29% of NICU babies. Etiologic basis for profound deafness was noted in those undergoing cochlear implantation with 32% with maternal rubella and other infections (labyrinthitis, meningitis, chronic otitis media and ototoxicity comprising about 50% of the causes to be preventable (Chiong et al. 2012b). This is consistent with the report by Alberti (1996). This highlights the importance of primary prevention of hearing loss with good prenatal and perinatal care, increased public awareness and maternal education. While such preventative programs are limited the significance of secondary prevention such as hearing screening is heightened.

Otoacoustic emissions (OAE) tests employed in two stages in most of the centers could be adopted as specificity and sensitivity compared well to the diagnostic

ABR. Children were brought to our diagnostic unit at a much later age over 12 months of age in the majority of cases (Llanes and Chiong 2004) as discussed in **Chapter 3**.

Two other related studies published from our center investigated 1) the value of ASSR and showed that 85% of very young children with flat or absent ABR responses had residual thresholds noted in frequencies 500Hz, 1kHz, 2kHz and 4kHz (Tan et al. 2009) and 2) the validity of a human voice "BAAH" reflexive test and its accuracy in detecting a hearing loss compared to OAE among infants aged 6 months and below (Garcia et al. 2012). While the former allowed more precise hearing aid fitting and objective choice of which ear to amplify (limited funds preclude bilateral hearing aids), the latter gives an alternative method that can be carried out in the communities for newborn and infants by trained community health workers.)

That hearing loss in infants results in significant delays in development is well accepted. In **Chapter 4** not only do we establish the prevalence of profound bilateral hearing loss at 1.38 per 1000 in a population based study but we also discuss evidence regarding the effects of even a mild or unilateral hearing loss on overall mental development using the Griffith's scale that is used by developmental pediatricians in evaluating young children over a period of two years from birth. That mild or unilateral permanent hearing loss can also lead to difficulties with language, psychosocial and educational development is further supported by the findings in this study (Chiong et al. 2007).

Other Risk Factors: Auditory Effects of Maternal Exposure to Pesticides

Most developing countries rely on agriculture as the main fuel for the economy and potentially hazardous chemicals are used not only to combat pests but also to increase crop yields, for control of vector borne diseases and parasites among livestock. That low level and long term exposure to pesticides can cause diverse health effects is well known (WHO/UNEP 1990). In the rural areas of developing countries insecticides comprise the greatest proportion of pesticides because of their cheaper cost (Araki, Yokoyama and Murata 1997). Both peripheral and central nervous system damage from organophosphates and pyrethroid products were noted especially among workers with a 7.58 relative risk of central auditory dysfunction measured through duration and pitch pattern sequencing tests (Teixeira and Brandao 1998; Teixeira, Augusto and Morata 2002). However, fetal outcomes of maternal exposure to these toxic products are less known.

The substrate with which such pesticides have been commonly measured in adults include serum, blood, urine but the incidence and levels of exposure

among dyads of mother and child in an agricultural community in the Philippines proved that meconium was most sensitive in detecting fetal exposure to environmental pesticides (Ostrea et al. 2008; Ostrea et al. 2009). In **Chapter 5** we describe in a similar cohort of children the possible effects of maternal exposure to environmental toxins to the auditory system by correlating the presence of different pesticides on matrices such as maternal or infant hair, umbilical cord blood and meconium and hearing loss. ABR thresholds and latencies were measured in both the exposed and non-exposed groups in order to look at possible neurotoxic or auditory effects of these known toxic products (Chiong et al. 2012a).

Cost Benefit Analysis of Universal newborn hearing Screening in the Philippines

Schroeder (2006) reported that there are increased costs for health and social services and education in hearing impaired children compared to their hearing peers. Nonetheless, early detection and intervention have been reportedly cost beneficial in the long term from a societal point of view (Porter, Neely and Gorga 2009) but likely affected by the selection criteria used in the UNHS programme. The United States Preventive Services Task Force (USPSTF) recommended screening for hearing loss in all newborns given that early identification and early intervention showed benefits irregardless of the degree of hearing loss (Kennedy 2006; Appuzo and Yoshinaga-Itano 1995; Moeller 2000). When diagnosed after the age of six months there was correlation between the language abilities and the degree of hearing loss but not when diagnosed before the age of six months (Yoshinaga-Itano 2003). Keren and co-workers (2002) modeled similar language benefits for a hypothetical cohort of 80,000 infants and demonstrated the cost-effectiveness of UNHS. In a public hospital in Brazil, the annual cost of the universal newborn hearing screening programme was US$ 26,940.47 with about 11,466 screened over three years and 11 children diagnosed with hearing loss or a prevalence of 0.96:1000 (Bevilacqua et al. 2010).

In a study by Neumann (2006) in Germany the cost for a child with severe hearing loss amounted to Euros 13,438; 8241 Euros for risk screening only and 4760 Euros without systematic screening. However the cost of education, speech training will tend to reverse the conclusion as education within the first 16 years of life with hearing loss would have amounted to 125,778 Euros in UNHS, 140,605 Euros for risk screening and 155,944 Euros without screening.

Given the cost of screening it seems pragmatic to relegate developing countries to the use of the HRR and screen only high risk newborns and infants. However,

Olunsaya highlighted the fact that this appeal of targeted screening in resource limited regions such as the Sub-Saharan Africa and Southeast Asia (to which the Philippines belong) entails diverse operational constraints that could significantly reduce its cost effectiveness. The baseline prevalence (risk) of hearing loss will likely affect the estimated economic burden in a universal strategy as shown by Burke et al. (2012) as illustrated when comparing India with the U.K. in his study that utilized a decision tree approach. In **chapter 6** we describe the cost benefit of a universal newborn hearing screening programme in the Philippines (Chiong and Santos-Cortez 2012) that utilized the data from earlier studies in chapters 3 and 4 regarding the prevalence rate and accuracy of OAE vis a vis the ABR. Incidentally, all these studies provided the evidence base that helped push for a law that mandates UNHS to be enacted in 2009 as Republic Act 9709 otherwise known as the Universal Newborn Hearing Screening, Prevention, Early Detection and Intervention Act (Appendix 1) signed by former President Gloria Macapagal-Arroyo. The year 2010 saw the implementing rules and regulations approved by the Department of Health (Appendix 2) and the final manual of operations expected to be approved by the first quarter of 2013. The legislative mandate is expected to push UNHS in the communities where they are most needed.

Aside from newborn hearing screening done to detect early the presence of congenital hearing loss some countries have introduced genetic screening as a way by which hearing loss might be detected early and looking at its etiologic basis. **Chapter 7** describes the first attempt at looking at the genetic cause of congenital profound hearing loss among Filipinos. Genotypic-phenotypic correlation was done for two subjects found to have GJB2 mutations. No correlation with cochlear implant performance could be proven in this study however as the rate of GJB2 mutation was noted at 3.3% only).

In summary, in the last ten years we did studies to look at the epidemiology of hearing loss, the age at identification, the risk factors involved, how both objective testing either by OAE, ABR or ASSR, and if other alternative behavioural testing could be utilized for the early detection and screening of childhood deafness. Maternal exposure to environmental toxic products and its possible effects on the auditory system was likewise investigated. Finally a cost benefit analysis of universal newborn hearing screening in the Philippines could be undertaken based on data culled from the studies at hand. This thesis further exemplifies a developing country perspective on how research evidence can be used to translate to a national policy and legislation to address an important health issue with an intervention that takes into consideration the problems encountered in a resource limited setting.

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Chapter 2

Neonatal Hearing Screening in a Neonatal Intensive Care Unit Using Distortion-product Otoacoustic Emissions

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Abstract

Objective:
To determine pass and refer rates, and identify risk factors relating to refer responses, in neonates screened using distortion-product otoacoustic emissions (DPOAEs).

Material and Methods:
A total of 435 neonates admitted to the neonatal intensive care unit (NICU) of the Philippine General Hospital between May and October 2000 were screened using DPOAEs within 48 h of admission.

Results:
The male:female ratio in the sample was 1.05. In total, 56% of neonates were born preterm, the mean birthweight was 2428.39±710.39 g and 8.9% weighed <1500 g. In total, 47.9% were delivered by Caesarian section and 44.9% were delivered vaginally. Almost 14% of neonates had 1-min Apgar scores of <6, and 4% had 5-min Apgar scores of <7. Approximately 95% of neonates had a poor perinatal history. Using pediatric aging it was noted that 46% of these neonates were born preterm, and 30.4% were small for gestational age. At least one neonatal disease was found in 42% of neonates, whilst 95.7% had to be given medication. The bilateral refer rate was 29.1%. Two-by-two analysis of risk factors for hearing loss and DPOAE measurements showed that only male sex seemed to have a significant association with a refer response. Neonates weighing <1500 g at birth showed a marginally significant association with a refer response (p = 0.07). All other neonates showed no crude association with DPOAE measurements.

Conclusion:
These preliminary data show that a high proportion of NICU patients may have poor outer hair cell function, and thus poor hearing. In order to develop an effective neonatal hearing screening program, further studies of prevalence and risk factors should be pursued in the same setting. *Key words*: *distortion product otoacoustic emissions*, *neonatal hearing screening*, *risk factors*.

Introduction

In recent decades a great deal of effort has been expended in the development of hearing screening programs. Early identification of deaf children at the neonatal stage would result in early treatment and rehabilitation, and prevent language, developmental and social problems.[1] The prevalence of bilateral hearing impairment does not vary much, as reported in various studies: (i) 2.18/1,000 births per year[1]; (ii) 1.2/1,000 births per year over the period 1983-1988[2]; and (iii) 1 2/1000 well babies and 4-5% of neonates with one or more audiologic risk factors[3], as summarized in the Joint Committee on Infant Hearing (JCIH) Position Statement in 1993[4]. Early diagnosis of hearing loss has been made possible by means of auditory brainstem responses (ABRs) and otoacoustic emission testing. Universal neonatal hearing screening has been proposed and instituted in developed countries, in which even a single case of permanent hearing loss is a cause for concern. In spite of increased costs [screening of each infant may cost US$ 17-26[4], US$ 19.88[5] or US$ 24.48[2], and the cost of identifying 1 case of sensorineural hearing loss may range from US$ 22,114[4] to US$ 56,045[2] or US$ 5,000-$ 17,750[4], consensus statements supporting the need for universal neonatal hearing screening have been proposed by the different specialties and committees.[4,6-8]

In most developing countries, such as the Philippines, both the government and the general population lack an awareness of the importance of preventing bilateral permanent hearing loss. The prioritization and allocation of resources for hearing prevention programs, if any exist, are lacking. Active case identification through hearing screening programs cannot be pursued if most patients with hearing loss are diagnosed at a later age, when treatment and rehabilitation may no longer be of value. Among local medical specialists, however, there has been much concern about the possible effects on the quality of life of neglected cases of bilateral permanent hearing loss. There is a need to conduct local studies on the epidemiology of hearing loss and the validity of different hearing screening equipment in our setting, in order to be able to design an available, appropriate and affordable hearing screening program.

For the last 10 years, diagnostic ABR testing has been employed to screen babies for hearing loss on a referral basis in our Otorhinolaryngology department. Active ABR screening of babies in the neonatal intensive care unit (NICU) may not be feasible because it is time consuming and expensive. In contrast, otoacoustic emissions testing, which is less time consuming, automated and has great promise as a mass screening tool among neonates, has yet to be introduced in

our country. This preliminary study aims to determine the pass and refer rates for distortion product otoacoustic emissions (DPOAEs) testing among neonates in the NICU and the factors associated with refer responses.

Material and methods

All neonates admitted to the NICU between May and October 2000 were subjected to DPOAE testing using the Welch Allyn® AudioPath EOAE Screener 29230, after obtaining maternal consent. A trained research assistant monitored all admissions using the NICU logbook. Before each test, the screener performed a calibration test. The background noise was measured and if there was a 10 dB difference detected in response to two tonal stimulations, the machine automatically showed a ‘‘pass’’ response. Otherwise, a ‘‘refer’’ response was shown. ‘‘Fail’’ responses necessitated checking for vernix or obstruction in the canal, or inappropriate probe fitting. The hearing test was repeated 24 h later once the vernix or cerumen in the canal had been cleared. Determinations were done in the afternoon to minimize noise. Appropriate ear probe tips were used to fit the ears of the subjects. The following variables were determined: pass and refer rates for DPOAE; birthweight; gestational age; sex; maternal factors; perinatal factors; method of delivery; Apgar scores at 1 and 5 min; pediatric aging; medication; and history of rubella, syphilis, TORCH (toxoplasmosis, other, rubella, cytomegalovirus and herpes), mumps and chickenpox. Data from the hearing screening and the patient’s charts were retrieved using a data abstraction sheet. The data gathered were encoded, processed and analyzed using EPI-INFO software, version 6.05.

Results

A total of 435 neonates were screened in the NICU during the study period (Table 1). Seven had incomplete data and were excluded from the analysis. There were approximately equal numbers of boys and girls (male:female ratio 1.05). In total, 56% of neonates were born preterm, the mean birthweight was 2428.39$\pm$710.39 g and 8.9% weighed <1500 g. In total, 47.9% were delivered by Caesarian section and 44.9% were delivered vaginally. Almost 14% of neonates had 1-min Apgar scores of <6, and 4% had 5-min Apgar scores of <7. Approximately 95% of neonates had a poor perinatal history. Using pediatric aging it was noted that 46% of these neonates were born preterm, and 30.4% were small for gestational age.

At least one neonatal disease was found in 42% of neonates, whilst 95.7% had to be given medication (antibiotics in almost all cases). Maternal diseases that may cause hearing loss in neonates included rubella (*n* = 9; 2.1%), TORCH (*n* = 2; 0.5%), syphilis (*n* = 1; 0.2%) and trauma (*n* = 1; 0.2%).

Table 1: Risk factors for hearing loss among neonates

Neonatal risk factor	*N (%)*
Gestational age ≤37 weeks	178/406 (43.8)
Birthweight <1500 g	39/428 (8.9)
Caesarian section	199/421 (47.1)
Apgar score at 1 min in range 1-5	58/360 (13.9)
Apgar score at 5 min in range 1-6	17/401 (4.1)
Poor perinatal history (at least one of hypotonia, jaundice, poor lacrimation, cyanosis, birth trauma, cord coil, meconium staining)	346/365 (94.8)
Small for gestational age	111/369 (30.1)
Presence of neonatal disease	133/347 (38.3)
Medication administered	289/302 (95.7)
Maternal age <33 years	86/155 (55.5)

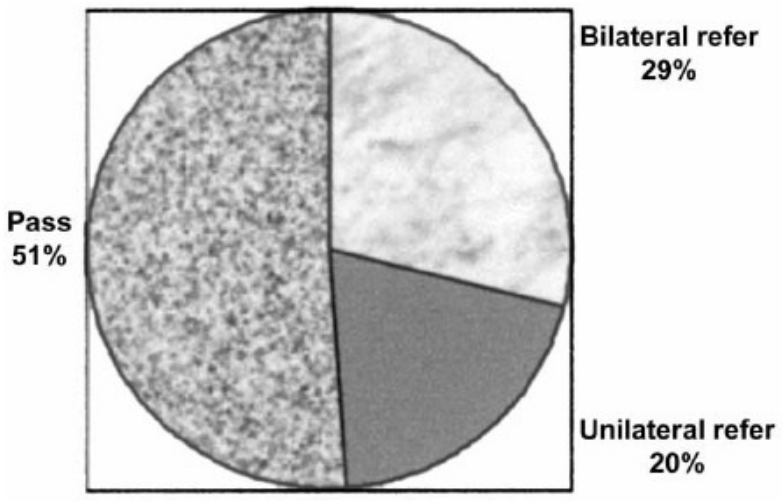

Figure 1: Distribution of results of DPOAE measurements among neonates

DPOAE measurements showed that the bilateral refer rate (which connotes permanent congenital hearing impairment) was ≈29%, and the overall refer rate, which includes unilateral refer responses in either ear, was ≈49.2% (Figure 1).
Two-by-two analysis of risk factors for hearing loss and DPOAE measurements showed that only male sex seemed to have a significant association with a refer response (Table 2). Neonates weighing <1500 g at birth showed a marginally

significant association with a refer response (p = 0.07). All other neonates showed no statistically significant association with DPOAE measurements.

Table 2: Association of DPOAE pass and refer responses with risk factors among neonates

Risk factor	Refer; *n*(%)	Pass; *n*(%)	*p*	Odds ratio (95% CI)
Male gender	121 (55.3)	98 (44.7)	0.012	1.63 (1.09-2.45)
Gestational age ≤37 weeks	79 (44.4)	99 (55.6)	0.165	0.76 (0.50-1.15)
Apgar score at 1 min in range 1-5	25 (43.1)	33 (56.9)	0.31	0.75 (0.41-1.36)
Apgar score at 5 min in range 1-6	7 (41.2)	10 (58.8)	0.495	0.71 (0.24-2.09)
Birthweight <1500 g	24 (63.2)	14 (36.8)	0.073	1.86 (0.89-3.94)
Poor perinatal history	203 (49.8)	205 (50.2)	0.514	1.36 (0.49-3.83)
Caesarian section/forceps	113 (48.9)	118 (51.1)	0.825	0.96 (0.64-1.44)
Small/large for gestational age	61 (49.2)	63 (50.8)	0.35	1.23 (0.77-1.95)
Presence of neonatal diseases	67 (46.2)	78 (53.8)	0.352	0.88 (0.56-1.38)
Medication administered	131 (45.3)	158 (54.7)	0.25	0.52 (0.14-1.82)
Maternal age <33 years	131 (45.3)	158 (54.7)	0.25	0.52 (0.14-1.82)
Presence of bleeding episodes	12 (44.4)	15 (55.6)	0.56	0.79 (0.33-1.87)
Pre-eclampsia	29 (49.2)	30 (50.8)	0.94	0.98 (0.54-1.79)
Presence of maternal diseases	41 (41.2)	44 (51.8)	0.41	0.75 (0.36-1.57)

Discussion

A high percentage of bilateral refer responses was found among neonates in this study; this is comparable to the result found in a parallel study conducted locally (unpublished work), but higher than those reported in other studies: 6.67%[14], 10%[9] and 5/1000.[10] This may be due to very high-risk neonates being admitted to the NICU or increased false-positives resulting from the performance of DPOAE testing in the nursery setting, with a relatively high level of background noise. Almost 95% of NICU patients had a poor neonatal history, with half having one or more risk factors associated with hearing loss. Babies admitted to our NICU may be more seriously ill compared to those in studies conducted in developed countries (family history of hearing impairment, 6.6%; perinatal infection, 3.8%; birthweight <1500 g, 1.2%.[9]). False-positive values reported from OAE testing include 3.5%[5], 6.63%[10], 16.2%[11] and 11-35%[12]. These cases may be mislabeled ‘‘refer’’ and cause undue anxiety to the parents, even though this worry may be unsubstantiated.[13] Parents should be told that a refer response only means that their child is scheduled for OAE retesting and ABR screening.

Risk factors that were studied but not found to be significantly associated with a refer response included those used in the JCIH registry. This may be due to two reasons: (i) only a certain proportion of high-risk babies will have hearing loss,

even with the presence of risk factors; and (ii) the inadequate sample size in this study, considering the relatively low prevalence of hearing loss, even among high-risk neonates. Further studies utilizing a larger sample and multivariate techniques need to be done in order to determine a model of predictors that can predict hearing loss among neonates with a refer response. It is necessary to determine the validity of hearing screening tests such as DPOAE. Significant barriers to the performance of ABR testing in a large sample are that it is time consuming, difficult to do and requires sedation of the subject[12]; however, it is necessary for comparison with DPOAE results. In a local study (unpublished work), involving 100 infants with bilateral refer responses from DPOAE testing, 12 were submitted for re-screening, 9 of whom (75%) converted to ‘‘pass’’. Preliminary results on referral data from January to July 2002 at our Ear Unit show good concordance between DPOAE and diagnostic ABR.

Only male gender was significantly associated with a refer response, in accordance with the finding of a significant sex effect at 4 kHz, where the mean amplitude of DPOAEs was higher in female than male babies.[13] Low birthweight, poor perinatal history and being small for gestational age had odd ratios above the null (>1), consistent with other findings, but were not found to be statistically significant. The aim of universal neonatal hearing screening is to identify neonatal hearing loss before the age of 3 months, so that rehabilitation can be performed before the age of 6 months.[7] This is ideal in our setting, considering the costs that may be incurred. However, because of the inherent poor follow-up of patients in our hospital, this may not be feasible at this time. Initially, in lieu of retesting of OAE failures, the presence of a constellation of validated risk factor predictors can be used to determine whether babies should be subjected to diagnostic ABR screening. Proper follow-up of patients should be ensured, as loss to follow-up is the primary reason for failure to confirm hearing loss and institute rehabilitation before children reach the age of 1 year.[14]

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Chapter 3

Evoked Otoacoustic Emissions and Auditory Brainstem Responses: Concordance in Hearing Screening Among High-risk Children

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Abstract

Objective:
Evoked otoacoustic emissions (OAEs) and diagnostic auditory brainstem responses (ABRs) were determined in 379 high-risk children referred for hearing screening.

Material and Methods:
This was a retrospective, cross-sectional study. The records of 379 children referred for hearing screening between January 2002 and March 2003 at the Ear Unit of the Philippine General Hospital were evaluated.

Results:
Of the 379 children, 53.6% were male and 46.4% were female and the mean age was 41±47 months. The age distribution was as follows: ≤ 12 months, 32.2%; 12-24 months, 52.2%; and > 24 months, 11%. Out of 229 right and 232 left ears, 111 (48.5%) and 112 (48.3%) had ‘‘pass’’ responses and 113 (49.3%) and 116 (50.5%) had ‘‘refer’’ responses, respectively. Five right and four left ears had ‘‘noise’’ responses. Out of 266 right and 209 left ears, the ABR results showed 72 (27.1%) and 30 (14.4%) with normal auditory pathways and 194 (72.9%) and 179 (85.6%) with abnormal auditory pathways, respectively. Of the 131 children whose parents gave their consent for concomitant OAE and ABR testing, agreements were observed between the two tests in terms of classifying the results as normal or abnormal of 78.9% ($_K$ = 0.51; p = 0.00) in right and 78.6% ($_K$ = 0.51; p = 0.00) in left ears. When the children were classified as either ‘‘with hearing loss - bilateral abnormal ABRs’’ or ‘‘at least one normal ABR’’, there was an observed agreement of 81% ($_K$=0.6; p=0.00). OAEs had a sensitivity of 76.9% (95% CI 66.7-84.8%) and a specificity of 90% (95% CI 75.4-96.7%).

Conclusion:
There is good concordance between OAE and ABR results among high-risk children referred for hearing screening. Key words: auditory brainstem response, evoked otoacoustic emissions, hearing screening, sensitivity, specificity.

Introduction

With heightened awareness of the importance of preventing hearing loss at an earlier age, universal neonatal hearing screening has been advocated by many institutions worldwide. This would enable health professionals to identify cases of hearing loss earlier and therefore institute treatment and rehabilitation for patients identified as having hearing loss before irreversible consequences could ensue. Since 2000, our institution has used otoacoustic emissions (OAEs) and auditory brainstem responses (ABRs) to evaluate the hearing status of high-risk children.[1] At present, universal hearing screening is still not practicable given the difficulties of establishing a program, which requires logistic and financial resources. Thus, hearing screening of high-risk children is the responsibility of the Ear Unit, which receives referrals for hearing evaluation from pediatricians and other otorhino-laryngologists both within and outside the hospital.

Evoked OAEs and ABRs each have advantages and disadvantages in hearing screening, and the following parameters should be considered: (i) the ease of testing and obtaining results; (ii) cost; and (iii) technician dependence. In terms of reliability for screening, the diagnostic ABR remains the preferred test, with OAE testing as the initial investigation, as evident in most universal hearing screening protocols.[2,3] Thus, a ‘‘refer’’ response from OAE testing will be followed by an ABR test for confirmation, considering that false-positive and -negative responses may occur with OAE testing.

In our setting, where patients often want to optimize their spending, a single, reliable, accessible, non-invasive and valid hearing test is usually desired to minimize the inconvenience and discomfort to patients, and in particular children. Determining the concordance between OAE and ABR testing, and identifying cases where non-agreement occurred, might be helpful in planning a more efficient flow of patients and may assist in identifying patients who are likely to have or to develop hearing loss with minimum cost. We aimed to determine the concordance between OAE testing and ABRs for assessing the hearing status of children referred for hearing evaluation at a tertiary institution.

Material and methods

The records of all patients referred to the Ear Unit for hearing screening between January 2002 and March 2003 were reviewed, where hearing status was assessed using both OAEs and ABRs. For every patient referred for hearing

evaluation, both OAE and ABR testing were usually performed, after obtaining consent from the parents and/or guardian. Otherwise, only the procedure (either OAE or ABR) requested by the referring otorhinolaryngologist was performed.
All procedures were performed at the Ear Unit, which provides a quiet and conducive area for testing. OAE testing was done as previously reported[1], and ABR testing was done using the Pilot ABR Evostar 2/1 machine, after allowing the patient to sleep. Either diphenhydramine hydrochloride or chloral hydrate was used to sedate irritable or younger patients.Data were extracted from the request form, and included sex, age, diagnosis, OAE results and ABR readings. The results were analyzed using EPI-INFO 6.05 and SPSS (Version 9.05) software.

Results

A total of 229 right and 232 left ears were subjected to OAE testing, while 266 right and 209 left ears underwent ABR testing. The majority of the referrals were for speech delay, suspected hearing loss or global developmental delay/autism/ mental retardation, etc. (Table 1). Of the 379 children, 53.6% were male and 46.4% were female and the mean age was 41$\pm$ 47 months. The age distribution was as follows: $\leq$12 months, 32.2%; 12-24 months, 52.2%; and > 24 months, 11%. Out of 229 right and 232 left ears, 111 (48.5%) and 112 (48.3%) had ‘‘pass’’ responses and 113 (49.3%) and 116 (50.5%) had ‘‘refer’’ responses, respectively.

Table 1: Distribution of diagnoses of patients referred for hearing screening

Diagnosis	n (%)
Speech delay	79 (30.27)
Suspected hearing loss	66 (25.29)
Global developmental delay/	42 (16.09)
mental retardation/autism/	
attention deficit hyperactive disorder	
Congenital rubella syndrome	15 (5.75)
Prematurity	10 (3.83)
Down’s syndrome	10 (3.83)
Cerebral palsy	10 (3.83)
Ear malformation/microtia	9 (3.45)
Post-meningitic hydrocephalus	5 (1.92)
Meningitis	3 (1.15)
Others	12 (4.58)
Total	261 (100.0)

Five right and four left ears had ‘‘noise’’ responses. Out of 266 right and 209 left ears, the ABR results showed 72 (27.1%) and 30 (14.4%) with normal auditory pathways and 194 (72.9%) and 179 (85.6%) with abnormal auditory pathways, respectively. Figure 1 shows the distribution of ABR results (normal, mild, moderate, severe and profound hearing loss) and the number of ‘pass’ and ‘refer’ responses per category.

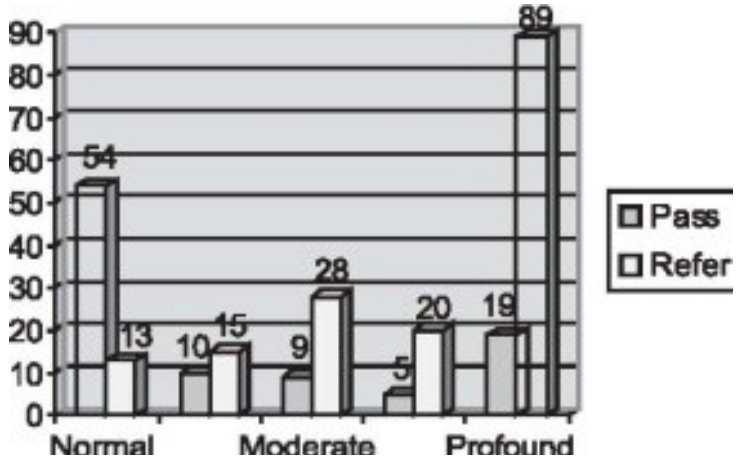

Figure 1: Distribution of ABR results

Of the 262 (*n*=131 children) ears subjected to both OAE and ABR testing, 152 (58.02%) were referred with an abnormal ABR, and 54 (20.6% passed the OAE test and had a normal ABR, with a sensitivity (defined as the ability of the test to identify patients with hearing loss) of 77.9% (95% CI 71.3-83.4%) and a specificity (defined as the ability of the test to identify patients without hearing loss) of 80.6% (95% CI 68.8-88.9%) (Table 2). In our setting, a patient with a ‘‘refer’’ response has a 92.1% (95% CI 86.6-95.6%) chance of having abnormal ABRs, while a patient with a ‘‘pass’’ response has a 55.7% (95% CI 45.2-65.6%) chance of having normal ABRs. In total, 43/262 ears (16.4%) had a ‘‘pass’’ OAE response and abnormal ABRs, representing false-positive results, while 13/262 ears (4.96%) gave false-negative results.

Table 2: Summary of sensitivity, specificity and predictive values of OAEs with ABR. Values given in parentheses are 95% CIs

OAE	Sensitivity	Specificity	PPV	NPV	k
Right ear	77.6% (67.8-85.1)	81.8% (63.9-92.4)	92.7% (84.2-97)	55.1% (40.3-69.1)	0.51
Left ear	78.4% (68.6-85.8)	79.4% (61.6-90.7)	91.6% (82.9-96.3)	56.3% (41.3-70.2)	0.51
Both ears	77.9% (71.3-83.4)	80.6% (68.8-88.9)	92.1% (86.6-95.6)	55.7% (45.2-65.6)	0.51

PPV=positive predictive value; NPV=negative predictive value.

Of the 131 children whose parents gave their consent for concomitant OAE and ABR testing, agreements were observed between the two tests in terms of classifying the results as normal or abnormal of 78.9% ($_k$=0.51; *p*=0.00) in right and 78.6% ($_k$= 0.51; *p*=0.00) in left ears, with an overall agreement of 79% ($_k$=0.51; *p*=0.00) for both ears. When the children were classified as either ‘‘with hearing loss* bilateral abnormal ABRs’’ or ‘‘at least one normal ABR’’, there was an observed agreement of 81% ($_k$=0.6; *p*=0.00). OAEs had a sensitivity of 76.9% (95% CI 66.7-84.8%) and a specificity of 90% (95% CI 75.4-96.7%). In total, 70/131 children (53.4%) had a bilateral ‘‘refer’’ response together with an abnormal ABR (Table 3). Of these 70 patients, 10 used hearing aids and 39 had undergone speech therapy. Twenty of these (mean age 3.8 years) had baseline language assessment, 17 of whom (85%) were found to have delayed language development.

Table 3: OAEs and ABRs for the 131 children whose parents gave consent for OAE and ABR testing. Values shown represent numbers of patients, with percentages in parentheses

	ABR		
OAE	With hearing loss	Without hearing loss	Total
Refer	70 (53.4)	4(3.1)	74 (56.5)
Pass	21 (16)	36 (27.5)	57 (43.5)
Total	91 (69.5)	40 (30.5)	131 (100)

Observed agreement0.81; agreement due to chance= 0.53; k=0.6, p0.00; sensitivity=76.9% (95% CI 66.7-84.8%); specificity=90% (95% CI 75.4-96.7%); positive predictive value=94.6% (95% CI 86-98.3%); negative predictive value=63.2% (95% CI 49.3-75.2%).

Discussion

In a setting in which there are various limitations in establishing an effective and affordable hearing program, the adoption of a universal hearing screening program has proven to be difficult, especially given the inherent problem of inadequate follow-up for most of our patients. Because of the high prevalence of bilateral hearing loss among babies with risk factors of ≈29%[1], it is imperative to determine the value of OAE testing, in comparison with ABR, for screening during the last 10 years. This may be valuable in planning an effective screening program for neonates and infants that may be applicable to most institutions nationwide.

The majority of patients referred were aged 1- 2 years, and most presented with speech delay or hearing loss. This group of patients may represent cases where risk factors for hearing loss are unknown, indicating that there is still much work to be done to identify risk factors that may give clues as to the cause of hearing loss,

as well as predicting that a child may develop hearing loss. Congenital rubella and prematurity reflect the standard of prenatal care, and still pose risks to children. Ideally, in a given situation, hearing loss should be identified early enough in order to treat and prevent sequelae of speech delay. Thus, in many countries, identification of hearing loss is being advocated at the age of 6 months, to ensure early treatment and rehabilitation.[2,3] In our type of population, without the benefit of universal hearing screening, the use of OAE testing alone, considering the difficulties inherent in recording an ABR, may be justified, with certain limitations.

There seemed to be no difference between the right and left ears in terms of the parameters determined, and there was also no difference when both ears were analyzed together. Sensitivity and specificity were ≈77.9% and ≈80.6%, respectively.

In this study, the concordance between OAEs and ABRs seems to be adequate for our purposes, and in determining validity of OAE as a screening tool against ABR, the performance of OAE (sensitivity, 77.9%; specificity, 80.6%) may be acceptable as a screening tool among children referred for suspicion of hearing loss, although it is worse compared to most previous studies.[4] With the kind of population we serve, the likelihood that a patient with a ‘‘refer’’ response will have hearing loss (positive predictive value) is 92.1%. In contrast, the likelihood that a patient with a ‘‘pass’’ response will not have hearing loss (negative predictive value) is 55.7%. These data suggest that for most patients with risk factors for developing hearing loss referred to our unit, a ‘‘refer’’ response may be reliable enough to warrant early intervention, with repeat testing using behavioral audiometry (visual reinforcement audiometry) being performed at an appropriate age. However, caution must be exercised in advising parents and/or guardians when the response registers as ‘‘pass’’, as the false positive rate is ≈16%. This may lead to children who really have hearing loss and need further testing being missed. This may be due to the limitations of the screening test or, if associated with an abnormal ABR, may indicate possible auditory neuropathy. In previous studies[4], false-negative rates ranged between 5% and 13%. In recent reports[5-7], patients with normal OAE results but abnormal ABRs were considered to have a condition called auditory neuropathy or dyssynchrony. In our study, 24 (9.2%) patients were noted to have these findings and further follow-up is therefore necessary.

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Chapter 4

Correlation of hearing screening with developmental outcomes in infants over a 2-year period

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Abstract

Conclusion:
Evoked otoacoustic emission (OAE) and auditory brainstem response (ABR) results for hearing screening among infants have good concordance. However, good correlation with the Griffiths Developmental Scales remains to be desired.

Objective:
To correlate hearing screening outcomes of a cohort of infants with developmental outcomes at 6 and 12 months.

Subjects and methods:
A cohort of pregnant women was identified in several communities in a rural area (Bulacan province) from April 2002 to February 2003 as part of a population-based study determining maternal exposure to pollutants and infant outcomes, with a total follow-up of 2 years. Pregnant mothers were identified and followed up until delivery at a secondary, provincial hospital. Hearing screening was performed with OAEs and ABR. Mental development of infants was assessed at 6 and 12 months using Griffiths Mental Developmental Scales - locomotor, personal-social, hearing and speech, hand and eye coordination, performance tests.

Results:
Among the 1086 babies recruited, there were 724 with hearing assessment. Of these 724 babies, 565 had both OAE testing and ABR. Overall in 1130 ears, OAE and ABR testing showed an observed agreement of 99%, agreement due to chance of 96%, and kappa agreement of 79% (p=0.00) in diagnosing bilateral hearing losses. OAEs had a sensitivity of 86.4% (95% CI 64-96.4%) and a specificity of 99.4% (95% CI 98.6-99.7%). At the end of the study, there were 708/724 (97.8%) infants with normal hearing, 7/724 (1.0%) with unilateral hearing loss, 8/724 (1.1%) with bilateral mild hearing loss, and 1/724 (0.1%) with bilateral profound hearing loss, who demonstrated consistent mental delay throughout.
Follow-up rates for developmental examinations at 6 and 12 months were 98% and 81.25%, respectively. In these groups, there were 8 (1%) infants at 6 months and 18 (2.4%) at 12 months with developmental delay (Griffiths Mental Developmental Scales).

Introduction

The advent of new and affordable technology over the past years has helped to jumpstart newborn hearing screening programs worldwide, even in developing countries. Awareness among health practitioners and the public of the importance of hearing have increased 10-fold because of these concerted efforts to identify babies with hearing loss as early as possible, and in turn, provide early treatment and rehabilitation.

In our setting over the past 5 years, a number of hospitals have carried out newborn hearing screening programs, the majority of which were instituted in public and private tertiary hospitals in the nation's capital. However, these applied varied protocols and in the majority follow-through refer rates have been unreported but generally not good. Diagnostic technologies like otoacoustic emissions (OAEs) and auditory brainstem response (ABR) may still be relatively costly, more so with hearing rehabilitation whether with hearing aids and/or cochlear implantation. However, bringing these technologies as well as their benefits to the community where the majority of underprivileged patients are to be found would really be more meaningful in our case, where only 38% of births are within health facilities.[1]

Previous reports[2,3] have documented our experience in starting hearing screening at a tertiary hospital, with both OAEs and ABR at the neonatal intensive care unit, where there was a 29% bilateral 'refer' rate but on follow-up a mere 10% to special populations referred to our Ear Unit for hearing assessment. It remains to be seen whether hearing screening with OAE and ABR in a community-based study will be as accurate. Moreover, correlation with accepted developmental instruments may be advantageous in order to assess the impact of hearing loss (if any) on development during the early years of life. In this paper, we present our experience in hearing screening of babies at the community level using OAE and ABR. Results of developmental assessment of hearing and speech were then correlated with hearing screening results.

Subjects and methods

A cohort of pregnant women was identified in several communities in a rural area (Bulacan province) from April 2002 to February 2005 as part of a population-based study determining maternal exposure to pollutants and infant outcomes, with a total follow-up of 2 years. Pregnant mothers were identified and followed up until

delivery at a secondary, provincial hospital. Newborns underwent hearing screening with OAE (Welch Allyn® Audiopath EOAE Screener 29230) and ABR (Interacoustics EP15). Mental development of infants was assessed by a team of developmental pediatricians at 6 and 12 months using the Griffiths Mental Developmental Scales - locomotor, personal-social, hearing and speech, hand and eye coordination, performance tests.[4] The Griffiths Mental Developmental Scale is a test instrument administered by pediatricians from birth until 8 years of age, and measures motor maturity and development, ability to cope with routine situations in everyday living, auditory and speech functions, hand and finger motor mobility and eye and hand coordination, body consciousness, physical activity, and memory.

Results

There were 450 (54.4%) males, 375 (45.4%) females, and 2 (0.2%) ambiguous babies. Among the 1086 babies recruited, 724 underwent hearing assessment. Of these 724 babies, 565 had both OAE and ABR testing. Overall in 1130 ears, OAE and ABR testing showed an observed agreement of 99%, agreement due to chance of 96%, and kappa agreement of 80% (p=0.00) in diagnosing bilateral hearing losses. OAEs had a sensitivity of 86.4% (95% CI 64-96.4%) and a specificity of 99.4% (95% CI 98.6-99.7%) (Table 1-3).

Table 1: Concordance of otoacoustic emissions (OAEs) and auditory brainstem response (ABR) among 565 children, right ears.

	Auditory brainstem response		
Otoacoustic emissions	>40 dB	≤ 40 dB	Total
Refer	11	2	13
Pass	0	552	552
Total	11	554	565

Observed agreement = 0.99; sensitivity = 100% (67.9 - 100); agreement due to chance = 0.96; specificity = 99.6% (98.6 - 99.9); kappa = 0.91, p = 0.00; positive predictive value = 84.6% (53.7 - 97.3); negative predictive value = 100% (99.1 - 100).

Table 2: Concordance of otoacoustic emissions (OAEs) and auditory brainstem response (ABR) among 565 children, left ears.

	Auditory brainstem response		
Otoacoustic emissions	>40 dB	≤ 40 dB	Total
Refer	8	5	13
Pass	3	549	552
Total	11	554	565

Observed agreement = 0.99; sensitivity = 72.7% (39.3 - 92.7); agreement due to chance = 0.96; specificity = 99.1% (97.8 - 99.7); kappa = 0.66; *p* = 0.00; positive predictive value = 61.5% (32.3 - 84.9); negative predictive value = 99.5% (98.3 - 99.9).

Table 3: Concordance of otoacoustic emissions (OAEs) and auditory brainstem response (ABR) among 1130 ears, right and left.

	Auditory brainstem response		
Otoacoustic emissions	>40 dB	≤ 40 dB	Total
Refer	19	7	26
Pass	3	1101	1104
Total	22	1108	1130

Observed agreement = 0.99; sensitivity = 86.4% (64 - 96.4); agreement due to chance = 0.96; specificity = 99.4% (98.6 - 99.7); kappa = 0.88; *p* = 0.00; positive predictive value = 73.1% (51.9 - 87.6); negative predictive value = 99.7% (99.1 - 99.9).

At the end of the study, based on the ABR threshold results there were 708/724 (97.8%) infants with normal hearing, 7/724 (1%) with unilateral mild hearing loss, 8/724 (1%) with bilateral mild hearing loss, and 1/724 (0.1%) with bilateral profound hearing loss, who demonstrated consistent mental delay throughout. Thus, the total prevalence of hearing loss documented was 2.2%.

In all, 84% of babies were screened during the first 6 months of life, with 476 (77%) from 0 to 3 months and 43 (7%) from 4 to 6 months, and a further 6% from 6 to 9 months.

Follow-up rates for developmental examinations at 6 and 12 months were 98% and 81.25%, respectively. In these groups, there were 8 (1%) infants at 6 months and 18 (2.4%) at 12 months with developmental delay (Griffiths Mental Developmental Scales).[5]

There were 15 babies with hearing loss identified through ABR thresholds (Table 3) with 1 baby having bilateral profound hearing loss. In this group, there were 3/22 (14%) ears of babies with ABR thresholds >40 dB HL, with 'pass' responses in the OAE testing (false negative). Three of seven with unilateral mild hearing loss and two of five with bilateral mild hearing loss had low development scores, while

the baby with bilateral profound hearing loss had consistently poor development scores. Correlation of the different subdomains with hearing impairment did not yield much in the way of conclusions. However, correlation of the hearing screening results with the subdomain of speech and hearing showed good correlation.

The results of the study are summarized in Tables 4-9.

Table 4: Distribution of patients according to age screened

Age group (months)	Frequency	%
1-3	476	77.24
4-6	43	6.97
7-9	89	14.44
10-12	5	0.80
> 12	3	0.38
Total	616	100.0

Table 5: Distribution of patients with abnormal hearing tests

Patient	Otoacoustic emissions		ABR thresholds	
Unilateral mild	Right	Left	Right	Left
1	Refer	Pass	50	40
2	Pass	Pass	20	50
3	Refer	Refer	50	30
4	Pass	Pass	20	50
5	Pass	Refer	30	50
6	Pass	Refer	40	50
7	Refer	Pass	50	40
Unilateral moderate				
8	Refer	Pass	80	40
Bilateral mild				
9	Refer	Refer	50	60
10	Refer	Refer	50	50
11	Refer	Pass	60	50
12	Refer	Refer	50	50
13	Refer	Refer	50	50
14	Refer	Refer	60	60
Bilateral profound				
15	Refer	Refer	100	100

Correlation of hearing screening

Table 6: Distribution of hearing/language among patients with abnormal hearing tests

Patient	Hearing/language			
Unilateral mild	SQ 6 months	Percentile 6 months	SQ 12 months	Percentile 12 months
1	109	71	68	2
2	100	50	71	4
3	105	62	86	19
4	114	81	107	67
5	100	50	30	14
6	100	50	40	19
7	109	71	50	21
Unilateral moderate				
8	109	71	98	45
Bilateral mild				
9	109	71	93	35
10	109	71	94	35
11	105	62	94	35
12	105	62	104	60
13	82	13	83	14
14	91	29	-	-
Bilateral profound				
15	42.3	0.5	68.6	2

Table 7: Distribution of performance scores among patients

Patient	Performance			
Unilateral mild	SQ 6 months	Percentile 6 months	SQ 12 months	Percentile 12 months
1	96	40	84	16
2	86	19	84	16
3	91	29	84	16
4	101	52	123	92
5	91	29	91	29
6	106	65	76	7
7	101	52	83	14
Unilateral moderate				
8	62	1	90	27
Bilateral mild				
9	101	52	88	23
10	96	40	98	45
11	91	29	98	45
12	101	52	80	11
13	62	1	80	11
14	86	19	-	-
Bilateral profound				
15	53.84	0.5	90.1	27

Table 8: Distribution of general quotient scores among patients with abnormal hearing tests

Patient	General quotient*			
Unilateral mild	6 months		12 months	
1	101.2	Average	78.8	Low average
2	100	Average	95.6	Average
3	99.6	Average	89.9	Low average
4	111.6	High average	107.4	Average
5	105.8	Average	93.6	Average
6	103.8	Average	90	Average
7	106.6	Average	83.4	Low average
Unilateral moderate				
8	90.4	Average	93.4	Average
Bilateral mild				
9	113.4	High average	84	Low average
10	106.6	Average	100.8	Average
11	102	Average	98.6	Average
12	106.8	Average	97.2	Average
13	76.4	Low	81.6	Low
14	97.2	Average	-	-
Bilateral profound				
15	47.59	Very low	75.64	low

* Ref.[4]

Table 9: Distribution of general quotient in the Griffiths scale among babies

Griffiths scale	General quotient	
	6 months	12 months
≤ 70, abnormal	8 (0.1%)	18 (2.4%)
71-75, borderline	7 (0.9%)	12 (1.6%)
76-89, below average	51 (6.7%)	224 (29.8%)
90-110, average	518 (68.4%)	487 (64.8%)
111-119, above average	147 (19.4%)	10 (1.3%)
> 120	26 (3.4%)	0
Total	757	751*

* Six babies were lost to follow-up.

Discussion

Community hearing screening in a population-based study is an ideal methodology to determine the efficiency of a screening program. Data gathered, as well as logistics and other resources can be identified, which are valuable in formulating the work plan. It is hoped that this undertaking will be a prelude to our efforts to establish a national primary care newborn hearing screening program.

Our results showing bilateral profound hearing loss of 1 per 724 babies in a general population are still slightly higher than the usual 1 per 1000 proportional

rate often reported. It is interesting to note that even with active case identification, where the staff go house-to-house, in spite of the acceptable coverage rate, there are still a number of babies that were screened after 6 months. The value of universal hearing screening has been demonstrated in a recent report[6] of an 8-year follow-up of a controlled trial on universal newborn hearing screening which increased the proportion of all true cases of permanent childhood hearing impairment referred before the age of 6 months. Identification and referrals to an audiology unit have been improved. In addition, the value of parental education and awareness is emphasized and must be taken into consideration in establishing a community-based universal hearing screening program. Continuing the study to involve more parents and children would be ideal and will yield more information for our purpose.

In the general population, it is expected that the prevalence rate would be lower compared to the hospital or specialized care units, where sick babies are referred and have co-morbid conditions. In this setting, monitoring the mental development through the Griffiths Mental Development Scale (which is an accepted assessment instrument of the mental development of babies up to 2 years old) and correlating with hearing assessments would be interesting. We have seen that in our baby with a bilateral profound hearing loss (ABR thresholds of 100 dB HL) the mental development scores (total general quotient) and in all subscales (locomotor, personal social, hearing and speech, eye-hand coordination, and performance) are lower than the average. Among those with mild hearing loss, whether unilateral or bilateral, at least 40% exhibit lower than average mental development. Whether the lower than average mental development is a result of the hearing impairment remains to be seen with subsequent tests and continuous assessment of these infants. Using the hearing and speech scale, values from this group of patients show that most have lower percentile scores even among those with unilateral mild hearing loss. This implies that while it is important to prioritize bilateral severe hearing losses, we may be underestimating the adverse effect of mild hearing loss among babies in terms of mental development.[7] Assessment at 24 months is therefore desired.

Referrals of these babies for rehabilitation may still prove beneficial in the long-term outcome.

Conclusion

There seems to be a good correlation between newborn hearing screening outcomes and developmental outcomes, especially for babies with hearing impairment. Comparison of these outcomes of babies which had early identification and rehabilitation, even among babies with mild hearing losses, will provide evidence to support the practice of rehabilitating such children as early as possible.

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Chapter 5

Auditory brainstem response latencies of infants and maternal exposure to environmental toxic products

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Abstract

Objective:
To explore effects of pesticide exposure on the auditory system, specifically on hearing status based on auditory brainstem responses.

Methods:
A cohort of pregnant women was identified in several communities in a rural area from April 2002 to February 2003 and followed up until delivery. Mother-infant dyads were assessed for exposure to pesticides. Maternal and fetal exposures to environmental toxic products were determined by measuring levels in maternal hair and blood, and infant cord blood, hair, and meconium respectively. Hearing status was measured using otoacoustic emissions (OAE) and confirmed by diagnostic auditory brainstem responses (ABR) measured at 80, 60, and 40 decibels.Waves I, III, V were identified and absolute latencies measured, including inter-peak latencies from waves I-III, I-V, and III-V. Pesticide exposure was then correlated with latencies of Waves I, III, V, and interpeak latencies of waves I-III, I-V, and III-V. Hearing loss and pesticide exposures were correlated with Griffiths Mental Development Scores (GMDS).

Results:
Significant delays in the ABR wave latencies were noted in the group with exposure to pesticides. Propoxur was the most common toxic product detected in infants and meconium the best substrate for its detection. There was a 1.4% risk of hearing loss with exposure to propoxur (RR=0.52 (0.12-2.30), p = 0.06), a 6.25% risk with cypermethrin exposure (RR= 4.53 (0.61-33.64), p = 0.10) and 6.25% risk with pretilachlor exposure (3.13 (0.44-22.30), p = 0.07). Griffith's Mental Developmental Scale scores (GMDS-hearing and speech subscale and general quotient scores) were not significantly different between exposed and unexposed groups. However, three infants with positive exposures and hearing loss had below average, or low to average scores using this scale.

Conclusion:
Maternal exposure to environmental toxic products may affect the auditory pathway in infants at birth. Pregnant women should limit their exposure to such toxic products in order to avoid neurodevelopmental effects particularly on hearing because this is very important in the critical stage of language and speech development.

Introduction

In a tropical primarily agricultural country like the Philippines, environmental toxic products such as pesticides and insecticides abound in most homes given previous reports of high prevalence of infestations with pests such as flies(97.7%), roaches (89.8%) and mosquitoes (97.6%).[1] Use of these products is deemed justified when the significant prevalence of pests and vector-borne diseases is considered, whether in the farm or at home. The acute toxic effects of these products seen in acute poisoning have already been identified, and include effects on the central nervous system manifesting as varied neurological symptoms and behavioral changes.[2] Profound bilateral sensorineural hearing loss has been associated with peripheral neuropathy in the extremities following acute poisoning from combined mixture of 75% malathion and 15% metamidophos.[3]

The auditory pathway has also not been spared from neurotoxin effects of other substances such as lead[4,5, 6] cocaine[7], and methylmercury[8], as established with delayed brainstem auditory evoked potentials. Combined exposure to organophosphates and pyrethroid insecticides revealed an associated high frequency hearing loss in 57% of exposed Brazilian farm workers.[9] Central auditory dysfunction assessed through pitch pattern sequence and duration pattern sequence showed 56% of exposed workers with central hearing disorder and a relative risk of 7.58 for the group exposed to insecticides (95% CI 2.9-19.8) when compared to the non-exposed group.[10]

In the rural areas where numerous chemicals are released in the environment it would be sensible to assess the possibility that such exposures can also affect the auditory system. Constant use of these products results in sub-clinical exposure of humans albeit in much lower concentrations insufficient enough to cause acute toxic effects. Chronic sub-clinical effects seem difficult to assess considering the intricate measurement of use and subsequent exposure. Despite this, it is important to determine the presence of such products in a community, demonstrate exposure to such products, and identify possible short- and long term effects. This would help in regulating and possibly modifying behaviors regarding use of such products especially in pregnant women who may unduly increase the risks to the fetus with their exposure.

Previous studies[1,8] have shown that appropriate assessment of exposure may be performed through analysis of various biological matrices, of which maternal hair was found to be the most robust for detecting maternal exposure to pesticides and meconium found to be the most sensitive for establishing exposure in

infants.[1,8] These studies found propoxur to be the most common toxic product found in meconium in about 23.8 %.
Correlation of neuro-development determined through GMDS and hearing status by screening with OAE and ABR showed good correlation between the presence of hearing loss and developmental delay.[11] This study looks at the possible effects of pesticide exposure on the infantile auditory system specifically looking at changes in ABR wave latency measures in those with maternal and infant exposures to environmental toxic products.

Materials and methods

All pregnant women consulting at the Bulacan Provincial Hospital from April 2002 to February 2003 were identified and recruited to participate in the study. Study participants who did not consent and who failed to submit for follow-up were excluded. The study was approved by the Human Investigation Committees at both Wayne State University and the University of the Philippines Manila. Informed consent was obtained for collection of demographic information, blood and hair samples from the mothers and their infants, meconium samples from newborns, and newborn hearing screening and diagnosis using OAE with ABR testing. Maternal blood and hair samples were collected upon recruitment and delivery, while infant cord blood samples were obtained at birth, infant hair and meconium samples were obtained later in the nursery. To ensure sample adequacy for analysis, collection of samples were pursued in homes of the study participants. Hair was taken from the nape or base of the scalp with the size of a pencil eraser in diameter. Meconium was collected from diapers during the first 2 days of life. Methods of collection and preparation of specimens and measurement of pesticides in various specimens have been extensively described in previous articles related to the study.[1,8] Pesticides were measured in micrograms/deciliter.
Newborns of identified pregnant mothers underwent OAE (Welch Allyn® Audiopath EOAE Screener 29230) and ABR (Interacoustics EP15) testing and assessment of mental development by developmental pediatricians at 6, 12 and 24 months using the GMDS – locomotor, personal-social, hearing and speech, hand and eye coordination, and performance tests.[11] The presence of OAEs will show a ‘pass’ result, and the absence of OAEs will show a ‘refer’ result, suggesting normal and abnormal cochlear functions, respectively. ABR recorded with standard machine followed American National Standards Institute (ANSI) standards. Determination of the presence of wave V after introducing clicks sound

at different loud intensities (from 100 decibels (dB) to 30 dB) was performed. Evaluation of the ABR tracings to determine presence of waves I, III, V and their inter-peak latencies (I-III, I-V, III-V) in milliseconds were performed. Infants were classified as having normal hearing if wave V was present at or below 40 dB suggesting possible normal auditory pathway, and with hearing loss if wave V was present at greater than 40 dB suggesting possible abnormal auditory pathway. The latencies of wave I, III, V were determined to determine any delay in the appearance of the response, indicating possible insults in the auditory pathway. The samples were analyzed for commonly used pesticides: cyfluthrin, propoxur, chlorpyrifos, cypermethrin, pretilachlor, bioallethrin, malathion, diazinon, trans-fluthrin, lindane and DDT. The pesticides measured included most of the major ingredients of different preparations of insecticides and pesticides. In the Philippines, there are 17 various preparations such as sprays, vaporizer, mats, mosquito coils, moth bag and oil spray. Maternal and infant exposures to several pesticides and metabolites were correlated with auditory brainstem response latencies to determine possible associations.

Results

There were 686 newborns (365 males (53.2%) and 321 females (46.8%)) with data on maternal and infant exposure to pesticides and auditory brainstem responses. Mean age of babies on the day of testing is 2 months (±2.63), with 72.7% tested at 2 months. At 3 months 78.57% of all the babies could undergo ABR testing and 100% were tested by 12 months of age (Table 1).

Table 1: Distribution of newborns' age when ABR was performed (N=686).

Age in months	Frequency	%
1-3	539	78.57
4-6	50	7.29
7-9	89	12.97
10-12	8	1.17
Total	686	100.00

Mean : 2.41 months ± 2.63;
Range 11 months, 1-12
50th percentile at 1 month

Table 2: Laterality of newborns with Wave V threshold ≥40 dB (with hearing loss) (n=15).

Laterality	Frequency	%
Bilateral	7	46.66
Unilateral		
Right	4	26.67
Left	4	26.67
Total	15	100.00

Table 3: Overall mean auditory brainstem response latencies, right and left ears.

80 dB			
Parameters	Right	Left	p
Absolute wave			
Latencies			
I	1.50 (±0.30)	1.49 (±0.29)	0.19
III	4.23 (±0.33)	4.23 (±0.35)	0.67
V	6.47 (±0.40)	6.47 (±0.41)	0.65
Interpeak wave			
Latencies			
I-III	2.73 (±0.30)	2.76 (±0.30)	0.04
III-V	2.25 (±0.25)	2.24 (±0.25)	0.64
I-V	4.98 (±0.41)	4.99 (±0.41)	0.14
60 dB			
Parameters	Right	Left	p
Absolute wave			
Latencies			
I	2.21 (±0.43)	2.19 (±0.43)	0.08
III	4.80 (±0.48)	4.80 (±0.48)	0.31
V	6.92 (±0.47)	6.92 (±0.49)	0.98
Interpeak wave			
Latencies			
I-III	2.58 (±0.37)	2.61 (±0.36)	0.49
III-V	2.13 (±0.28)	2.10 (±0.24)	0.36
I-V	4.70 (±0.51)	4.69 (±0.50)	0.60
40 dB			
Parameters	Right	Left	p
Absolute wave			
Latencies			
I	2.93 (±0.42)	2.84 (±0.48)	0.42
III	5.38 (±0.41)	5.42 (±0.45)	0.002
V	7.53 (±0.49)	7.53 (±0.61)	0.42
Interpeak wave			
Latencies			
I-III	2.41 (±0.36)	2.54 (±0.35)	0.00
III-V	2.14 (±0.28)	2.13 (±0.32)	0.70
I-V	4.48 (±0.46)	4.60 (±0.47)	0.12

Fifteen infants were noted to have significant hearing loss , with 47% bilateral and only the right or left ear abnormal in 53% (Table 2). As shown in Table 3, the subjects had no differences in latency measures between the left and right sides for all the stimulation intensities utilized except for delay in IPL I-III on the left at 80 db stimulation, and wave III and IPL I-III significantly delayed in the left after 40 db stimulation. At 60 db, no differences were noted between the right and left ears. It was considered important to look at latency measures separately for the right and left to detect evidence of right and left differences and if present report these separately for comparison to those with notable hearing loss. As detailed in Table 4, there were nine pesticides with positive exposures measured in meconium, the best matrix for infant exposure with levels of propoxur, diazinon, malathion, bioallethrin, pretilachlor, DDT, cyfluthrin, cypermethrin, and DDE. The highest frequency of exposure was noted for propoxur at 21.2 % (165/777) of the infants.

Table 4: Frequency distribution of infants with positive maternal and infant environmental exposure to various pesticides

Pesticides	Maternal Hair (%)	Infant Hair (%)	Meconium (%)
Lead	25.8	9.9	0
Cadmium	0.2	9.9	0
Mercury	24.7	9.9	0
Arsenic	7.5	17.7	0
Malathion	0.9	0	0.3
Chlorpyrifos	0.1	0.1	0
Bioallethrin	9.0	0	0.3
Pretilachlor	0.1	0	0.8
DDT	0.2	0	0.5
Propoxur	9.9	0.3	21.2
Diazinon	0	0	0.1
Cyfluthrin	0	0	0.8
Cypermethrin	0	0	1.5
DDE	0	0	0.2

For maternal hair which is the best matrix for maternal exposure, there were ten pesticides with positive exposure includinglead, mercury, arsenic, cadmium, propoxur, malathion, chlorpyrifos, bioallethrin, pretilachlor, and DDT. However, evidence of exposure to only six pesticides such as arsenic, lead, cadmium, mercury, propoxur and chlorpyrifos were noted in infant hair.

Table 5 shows the ABR wave latency measures in infants with hearing loss defined as ABR wave V thresholds greater than 40 dB compared with those without hearing loss (< 40 dB ABR wave V threshold). This serves as a good reference for the next table that examines effects on ABR latencies following infant exposure to propoxur.

Table 5: Comparison of latencies of ABR parameters between infants with hearing loss (Wave V threshold > 40 dB) and without hearing loss (Wave V Threshold≤ 40 dB).

80 dB	Right			Left		
	(> 40 dB)	(≤ 40 dB)	p	(> 40 dB)	(≤ 40 dB)	p
Parameters	(n=11)	(n=677)		(n=11)	(n=677)	
Absolute wave						
Latencies						
I	1.79 (±0.52)	1.50 (±0.29)	.00	2.02 (±0.53)	1.48 (±0.27)	.00
III	4.38 (±0.50)	4.22 (±0.32)	.02	4.48 (±0.60)	4.23 (±0.34)	.00
V	6.53 (±0.60)	6.47 (±0.40)	.10	6.67(±0.71)	6.47 (±0.40)	.00
Interpeak wave						
Latencies						
I-III	2.58(±0.31)	2.73 (±0.30)	.54	2.46 (±0.22)	2.76 (±0.30)	.18
III-V	2.15 (±0.24)	2.25 (±0.25)	.91	2.20 (±0.22)	2.24 (±0.25)	.85
I-V	4.74 (±0.49)	4.66 (±0.35)	.27	4.98 (±0.41)	5.00 (±0.40)	.23
60 dB	Right			Left		
	(> 40 dB)	(≤ 40 dB)	p	(> 40 dB)	(≤ 40 dB)	p
Parameters	(n=6)	(n=677)		(n=11)	(n=677)	
Absolute wave						
Latencies						
I	2.23 (±0.37)	2.21 (±0.44)	.50	2.56 (±0.54)	2.18 (±0.43)	.27
III	4.89 (±0.46)	4.80 (±0.38)	.33	5.06 (±0.63)	4.80 (±0.48)	.08
V	6.91 (±0.69)	6.47 (±0.40)	.06	7.09 (±0.86)	6.91 (±0.49)	.00
Interpeak wave						
Latencies						
I-III	2.61 (±0.34)	2.58 (±0.37)	.73	2.44 (±0.20)	2.61 (±0.36)	.06
III-V	2.02 (±0.29)	2.13 (±0.28)	.61	2.03 (±0.33)	2.10 (±0.24)	.12
I-V	4.50 (±0.50)	4.70 (±0.51)	.94	4.51 (±0.45)	4.70 (±0.50)	.78
40 dB	Right			Left		
	(> 40 dB)	(≤ 40 dB)	p	(> 40 dB)	(≤ 40 dB)	p
Parameters	(n=11)	(n=677)		(n=11)	(n=677)	
Absolute wave						
Latencies						
I	2.87 (±0.14)	2.93 (±0.42)	.35	2.81 (±0.36)	2.84 (±0.49)	.77
III	5.33 (±0.47)	5.38 (±0.41)	.45	5.33 (±0.40)	5.42 (±0.45)	.78
V	7.44 (±0.70)	7.53 (±0.49)	.03	7.57 (±0.73)	7.53 (±0.61)	.34
Interpeak wave						
Latencies						
I-III	2.73(±0.42)	2.40 (±0.35)	.94	2.56 (±0.01)	2.54 (±0.35)	.06
III-V	2.11 (±0.51)	2.14 (±0.28)	.11	2.09 (±0.33)	2.13 (±0.32)	.47
I-V	4.76 (±0.52)	4.48 (±0.46)	.95	4.70 (±0.49)	4.59 (±0.47)	.81

The differences in latencies (Wave I, III, V) and interpeak latencies (IPLs I-III, I-V, III-V) in auditory brainstem responses between infants exposed (with positive pesticide exposure, maternal hair and meconium) and infants unexposed (with negative pesticide exposure, maternal hair and meconium) to propoxur are shown in Table 6. With propoxur exposure(as detected in meconium among infants) ABR testing at 80 db showed significant differences in the latency of wave III and IPL I-

III on the right, wave III, V and IPL I-III both on the left ears. No major differences were seen at 60dB and 40dB.

Table 6: Comparison of absolute wave latencies and interpeak wave latencies between infants with and without meconium exposure to environmental pesticide propoxur.

80 dB						
Latencies	Right			Left		
	Exposed	Unexposed	p	Exposed	Unexposed	p
I	1.50±.27	1.51±.31	.75	1.48±.27	1.49±.30	.75
III	4.16±.31	4.25±.33	.006	4.18±.35	4.25±.34	.03
V	6.43±.40	6.49±.40	.13	6.42±.44	6.49±.40	.08
Interpeak wave Latencies						
I-III	2.66±.30	2.75±.30	.002	2.70±.31	2.77±.30	.02
III-V	2.27±.24	2.24±.25	.24	2.25±.27	2.24±.25	.86
I-V	4.93±.43	4.99±.41	.19	4.94±.44	5.00±.40	.11
60 dB						
Latencies	Right			Left		
	Exposed	Unexposed	p	Exposed	Unexposed	p
I	2.17±.40	2.22±.45	.35	2.17±.35	2.19±.46	.69
III	4.79±.36	4.86±.39	.58	4.78±.49	4.80±.49	.63
V	6.93±.45	6.92±.48	.77	6.94±.49	6.92±.50	.66
IPL						
I-III	2.60±.38	2.58±.36	.71	2.60±.36	2.62±.36	.66
III-V	2.15±.23	2.12±.29	.29	2.13±.26	2.10±.24	.12
I-V	4.74±.49	4.70±.52	.49	4.70±.47	4.69±.5	.86
40 dB						
Latencies	Right			Left		
	Exposed	Unexposed	p	Exposed	Unexposed	p
I	2.90±.4	22.93±.43	.68	2.93±.47	2.81±.49	.11
III	5.39±.4	15.38±.42	.70	5.46±.43	5.41±.46	.27
V	7.54±.4	97.52±.50	.67	7.58±.56	7.52±.64	.32
IPL						
I-III	2.41±.39	2.41±.35	.99	2.49±.39	2.56±.34	.25
III-V	2.16±.22	2.14±.30	.47	2.11±.23	2.13±.35	.37
I-V	4.52±.52	4.47±.44	.49	4.59±.48	4.60±.47	.90

There were differences found sporadically in different waves and pesticides. In some cases exposure to certain pesticides was found in 1 or 2 infants only, yet effects could be more pronounced as in diazinon, found in meconium of only one infant with abnormal ABR wave V threshold greater than 80 db suggestive of severe to profound hearing impairment.

Correlating exposures to pesticides and hearing loss (Tables 7-9), 2 infants had exposure to propoxur, with a 1.4% risk of hearing loss, lower compared to the 2.7% risk of hearing loss in infants without exposure. On the other hand, 1 infant

exposed to cypermethrin had hearing loss, with a 6.25% risk, higher compared to the unexposed group of 1.34%. Remarkably, this infant had propoxur exposure as well. One infant had pretilachlor exposure and a mild unilateral hearing loss with a 6.25% risk compared to the unexposed group with 1.99% .

However, there were no significant differences noted between the exposed and unexposed groups with regards to GMDS-hearing and speech subscale and general quotient scores.

Table 7: Association of propoxur exposure with status of hearing (ABR threshold)

	Presence of wave V at		
Propoxur	>40dB	≤40dB	Total
(+)	2	141	143
(-)	14	411	525
Total	16	652	668

Riskexposed =2/143 (1.4%)
Riskunexposed =14/525 (2.7%)
Relative risk =0.52 (0.12-2/30) P=0.0565
1St Infant: Wave V at 80dB at the right (1.6ug/L)
2nd Infant: Wave at 100dB both ears (0.32ug/L)

Table 8: Association of cypermethrin exposure with status of hearing (ABR threshold)

	Presence of wave V at		
Cypermethrinexp	>40dB	≤40dB	Total
(+)	1	15	16
(-)	9	643	652
Total	10	658	668

Riskexposed =1/16 (6.25%)
Riskunexposed =9/643 (1.34%)
Relative risk =4.53 (0.61-33.64) P=0.1019
1st Infant: Wave V at 80dB at the right (2.82ug/L)

Table 9. Association of Pretilachlor exposure with status of hearing (ABR threshold)

	Presence of wave V at		
Pretilachlor	>40dB	≤40dB	Total
(+)	1	15	16
(-)	13	639	652
Total	14	644	668

Riskexposed =1/16 (6.25%)
Riskunexposed =13/652 (1.99%)
Relative risk =3.13 (0.44-22.30) P=0.0723
3rd Infant: Wave V at 50dB at the left (0.48ug/L)

Scrutinizing the 3 infants with exposures and hearing loss, there were low scores in GMDS scoring noted. In infant 1 with 2 exposures at unilateral moderate hearing loss, performance scores were low, although the general quotient scores were average at 6 and 12 months (Table 10). Infant 2 had propoxur exposure and

bilateral profound hearing loss, with below average scores (Table 11). Infant 3 had pretilachlor exposure and unilateral mild hearing loss, showing modest scores in hearing & speech and performance with average general quotient scores (Table 12).

Table 10: Griffith's Mental Development Scale of Infant 1
Infant 1 – positive exposure for propoxur&cypermethrin with moderate hearing loss

Scores	SQ	%tile	SQ	%tile
	6 mo	6	Mo	12 mo12 MO
Hearing/language Performance	109 62	71 1	98 90	45 27
General quotient	90.4 (average)		93.4 (average)	

Table 11: Griffith's Mental Development Scale of Infant 2
Infant 2 – positive for exposure to propoxur with bilateral profound hearing loss

Scores	SQ	%tile	SQ	%tile
	6 mo	6	Mo	12 mo12 MO
Hearing/language Performance	42.3 53.84	0.5 0.5	68.6 90.1	2 27
General quotient	47.6 (below average)		75.6 (below average)	

Table 12: Griffith's Mental Development Scale of Infant 3.
Infant 3 – positive exposure to pretilachlor with mild unilateral hearing loss

Scores	SQ	%tile	SQ	%tile
	6 mo	6	Mo	12 mo12 MO
Hearing/language Performance	100 106	50 65	86 76	19 7
General quotient	103.8 (average)		90 (average)	

Discussion

While measures of central auditory effects among workers exposed to organophosphates have been reported, this study looks at early auditory effects in newborns with maternal exposure to environmental products. Propoxur, cypermethrin and pretilachlor exposure may contribute to increased risk of hearing loss given possible effects on the fetus or newborns. Three (3/668, 0.45%) with positive exposure to environmental toxins had wave V thresholds >40 dB, 2 of which at ≥80dB, and 1/668 (0.15%) with multiple exposures had wave V threshold ≥80dB.

The risk of hearing loss with exposure to identified substances appears clinically significant whether these are subtle changes found in ABR wave latencies or wave V threshold elevations. The GMDS scores show good correlation at least among infants with hearing loss and documented exposures to toxins.

In this cohort, despite the rarity of the condition, there seems to be an association between exposure to propoxur, cypermethrin, and pretilachlor and hearing loss. It is important to delineate the effects of these exposures and eliminate other causes for the hearing loss. Further analysis using multivariate regression may be employed to include all possible variables that may contribute to hearing loss, so that individual effects may be quantified.

This study, along with published studies on OAE & ABRs from our center encouraged us to push for legislation to institute newborn hearing screening so that even in far-flung areas these babies can benefit from early identification and intervention for prevention of deleterious effects on neuro-development which include speech and hearing. The present study would be helpful in educating people in the community on the proper use of commonly available pesticides, in addition to motivating health regulatory bodies to further investigate effects, institute regulations in pesticide use, and conduct regular monitoring of burden of exposures.

Conclusion

Maternal exposure to some pesticides may contribute to an increased risk for hearing loss among infants in an agricultural community. Further monitoring of infants may be helpful to assess if these effects are reversible or permanent.

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Chapter 6

Cost-analysis of universal newborn hearing screening in the Philippines

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Abstract

Objective:
To undertake a cost analysis of screening, diagnostic and intervention strategies for bilateral permanent hearing loss with modeling performed to compare the projected costs of three newborn hearing screening options: passive, targeted and universal.

Method:
Both short-term and long-term costs for hearing screening centers and for families of hearing impaired children are projected based on calculations of the cost of hearing screening given local published prevalence of congenital hearing loss and the effectiveness of testing strategies.

Results:
Using published data on the prevalence of hearing loss and experience from a pilot universal newborn hearing screening project at a national tertiary hospital (Philippine General Hospital) benefits and savings from UNHS on a national scale greatly outweigh the immediate costs of testing and intervention.

Conclusion:
A universal newborn hearing programme will accrue more savings compared to a no screening or selective screening strategy when implemented even in a developing country like the Philippines. There is a need to emphasize increased awareness among professionals and parents, an efficient follow-up of cases and early hearing and speech rehabilitation for this UNHS to be truly cost beneficial both from an individual and societal perspective.

Introduction

Congenital hearing impairment which is bilateral profound or permanent congenital hearing loss (PCHL) occurs in 1.3 per 1000 Filipino newborns.[1] This rate is at par with rates of congenital hearing impairment worldwide.[2] Milder forms or unilateral hearing loss may also be associated with developmental delays thus increased surveillance is needed.[1] Early detection of hearing impairment is the key to early intervention which in turn may avoid the deleterious effects on psychosocial, linguistic, educational aspects of development.[3] Thus it is important that babies

with hearing impairment be identified by age 6 months, so that early intervention can be given and they can develop mentally as their normal hearing peers.[4] While there may be countries where age at intervention may not be correlated with linguistic advantages this may be due to cultural differences in how young children are treated in terms of language development.[5] Ruben (2000) emphasized the high cost of hearing loss to society which in the U.S. comprised about 2.5% of the GDP.[6] Other studies that compared targeted screening versus universal newborn hearing screening showed the latter to be more cost effective given the high cost of educating a hearing impaired child. Targeted screening seems to be more attractive in terms of less cost for testing compared to universal newborn hearing screening. However, when overall costs for intervention and education are considered for those whose hearing loss are diagnosed late, universal newborn hearing screening proves to be more cost effective.[7,8] This study describes a developing country perspective on the cost of universal newborn hearing screening versus a targeted or selective newborn hearing screening strategy.

Methods

Short-term and long-term costs for hearing screening centers and for families of hearing impaired children are projected as well as societal costs. Calculations included cost of hearing screening given local published prevalence of congenital hearing loss and the effectiveness of testing strategies. It should be pointed out in the Philippines most of the costs for hearing screening, diagnosis and intervention are borne by individual patients or their families as third party payers do not pay for such services except for cochlear implantation which is a surgical procedure covered by the Philippine Health Insurance Corporation. Cost of hearing aids nor cochlear implant devices as well as speech therapy and auditory training are likewise not covered.

Newborn Hearing Screening Options

In many cases there are three options for detection of hearing impairment in newborns: no screening or passive detection; early screening for high-risk babies only or targeted or selective newborn hearing screening (TNHS or SNHS); or early screening for all babies or universal newborn hearing screening (UNHS).

The first option of passive detection will obviously result in delay in detection, with age at diagnosis of hearing impairment usually by 2 to 3 years old. A retrospective

analysis by Canale and co-workers reported the mean age of identification of severe to profound hearing loss who were not screened at 29 months of age.[9] In this scenario, the intervention, whether by hearing aids or surgery, is then expected to be also delayed.

The second option tests only those who are high-risk based on existence of the following factors[10] as described by JCIH (2007) shown in Table 1.

Table 1: 2007 JCIH Criteria for High Risk of Congenital Hearing Loss

caregiver concern regarding hearing, speech, language or developmental delay;
family history of permanent childhood hearing loss;
neonatal intensive care of more than 5 days or any of the following regardless of length of stay: extracorporeal membrane oxygenation or ECMO [which is similar to a heart-lung machine], assisted ventilation, exposure to ototoxic medications [or drugs that are toxic to the ear such as] (gentamicin and tobramycin) or loop diuretics (furosemide/Lasix) and hyperbilirubinemia [jaundice] that requires exchange transfusion [replacement of blood or plasma];
in utero [prenatal and maternal] infections, such as cytomegalovirus, herpes, rubella, syphilis, and toxoplasmosis;
craniofacial anomalies [deformities], including those that involve the pinna, ear canal, ear tags, ear pits, and temporal bone anomalies
physical findings such as white forelock, that are associated with a syndrome known to include a sensorineural or permanent conductive hearing loss;
syndromes associated with hearing loss or progressive or late-onset hearing loss, such as neurofibromatosis, osteopetrosis, and Usher syndrome; other frequently identified syndromes include Waardenburg, Alport, Pendred, and Jervell and Lange-Nielsen;
neurodegenerative disorders, such as Hunter syndrome, or sensory motor neuropathies, such as Friedrich ataxia and Charcot-Marie-Tooth syndrome;
culture-positive postnatal infections associated with sensorineural hearing loss, including confirmed bacterial and viral (especially herpes viruses and varicella) meningitis;
head trauma, especially basal skull/temporal bone fracture that requires hospitalization; chemotherapy.

This second strategy of selective or high-risk screening, although more economical in terms of number of babies to test, may not be cost-effective due to the high number of false-negatives (or wrongly labeled as normal when child is hearing impaired) based on risk factor history alone. Also it usually misses those children who may be hearing impaired but do not exhibit any risk factors. Studies have shown the proportion of such children may even be higher than those with risk factors and have hearing impairment.[11] The Wessex Universal Neonatal Screening Trial Group diagnosed those with permanent childhood hearing loss who had risk factors such as stay in the NICU or low birth weight, infections in only about 8% giving support to the need for objective screening to be applied universally to newborns.[12] Another study showed that the proportion of children

without risk factors may even be higher than those who are high-risk and have hearing impairment, with as much as 78% of newborns who fail hearing screening as having no risk factors.[13] A study by Olusanya highlighted the operational constraints that will limit its effectiveness and the limited evidence with respect to the validity of high risk factors especially in resource poor countries where such TNHS have been recommended.[14]

The third strategy, UNHS, is more comprehensive since it tests all babies, and ideally should catch all newborns with hearing impairment, whether high-risk or not. However in the real setting, while 29% of the NICU babies at the Philippine General Hospital had a bilateral refer rate the follow-up rates for second testing may be low, with as much as 73% of patients who require second testing lost to follow-up[15,16] in a related study done at the Philippine General Hospital NICU. Also the screening test has a false-positive rate of 13.6% and false-negative rate (labeled as normal when actually hearing-impaired) of 0.6%.[1] It should be noted that the false-positive rate may mean additional testing which are unnecessary since the child is not hearing-impaired, while a low false-negative rate implies that only a small proportion of babies who are truly hearing-impaired are mislabeled.
Previous studies in the United States have been done in order to assess the cost-effectiveness of UNHS vs. high-risk screening only. The estimated cost of detection per child who is hearing-impaired was $ 4,609 for UNHS vs. $ 8,239-9,920 for TNHS.[17] In a later study, it was shown that, the total cost of detection in case of no screening was $ 69,000; TNHS resulted in incremental savings of $16,400 per infant while UNHS yielded an incremental savings of $ 44,300 per infant whose deafness was diagnosed by age 6 months.[8] Similarly in Germany selective newborn hearing screening would at first seem economical but when the number of missed diagnosis and the consequent delay in language development and the other interventions are factored in, UNHS proves to be more cost effective.[7] In Brazil where prevalence of sensorineural hearing loss was 0.96:1000, the cost of hearing screening was US$ 7.00 and the annual cost of universal newborn hearing screening program was US$ 26,940.47.[18]

Projected Costs for Screening Centers

Initial costs for screening centers would be capital-intensive due to equipment acquisition. For most, an otoacoustic emissions (OAE) or automated auditory brainstem response equipment will constitute the required machines in a Newborn Hearing Screening center. The OAE test takes only a few minutes to test in a quietly resting baby though the AABR requires a slightly longer duration for testing.

In most Philippine hospitals OAE is used as an initial test. For those who fail the initial OAE screening, a second OAE test is recommended, preferably within one month of the first test. For those who fail both OAE tests, confirmation either by ABR or ASSR is recommended. OAE has good concordance with ABR among Filipino neonates[19] thus its utility as a screening tool has a proven track record. An OAE machine may cost P230,000 (Exchange rate of 1 USD = PhP40), while an AABR averages P700,000. An ABR and ASSR machine can cost 800,000 to 1800000 pesos respectively. These machines are durable and can last more than ten years with very little maintenance costs though may need calibration on an annual basis. Automated ABR has been recommended abroad as more practical for initial screening due to its lower false-positive rate and better cost-effectiveness as compared to OAE.[16] However we have no current data as to its sensitivity and specificity as a screening tool among Filipinos and on-going studies have just started. Although initial capital layout for equipment seems large, the actual cost becomes cheaper as more babies are screened over years of use, because the costing is reflected as the initial capital plus operating expenses divided by the total number of newborns screened. Operating expenses would likely constitute salaries of technicians and disposable supplies. In Manila, the standard salary for one technician would be P8000/month. Disposable supplies include batteries, alcohol, cotton, office supplies, etc. which may total at least P1000/month. Given that the initial capital and operating expenses will be the standard price for at least five years, the total cost for a screening center may then be at least 2,138,000 pesos.

Modeling using the pilot results form the Philippine General Hospital

From October to December 2007, a single technician was able to screen 995 babies or 75% of all newborns at the Philippine General Hospital or PGH (Table 2).

Of those screened, 10.5% had a “refer” result and thus required a second OAE test to confirm hearing impairment. However, of 104 babies only 27% followed up. Of those who followed up, only one child was confirmed by OAE to have a hearing impairment. This may mean that we could have missed another 2-3 hearing-impaired children who failed the first OAE test but did not come back for a second test. If these numbers are projected to a 5-year period, a single technician should be able to screen 23,886 babies, (at 90% screening rate) plus at least 2507 children for a second OAE test (at 10.5% refer rate). Once the program is entrenched, there is a tendency to improve coverage due to greater public

awareness and improved testing mechanisms to a 95% screening rate and 4% refer rate with about 80% follow-up or "recall" rate.

Table 2: Pilot OAE Screening of Babies at the Philippine General Hospital, October-December 2007

Total No. of Babies Born in one quarter+	1,327
Number of Babies Screened in one quarter	995
Rate (Actual) Screening	75% (995/1,327)
Total Rate of Screening in 5 years	90% (1,194 babies)
Ideal Rate of Screening after 5 years	95% (1,261 babies)
Initial Refer Rate obtained	10.6% (104 babies)
Ideal Refer Rate	4% (48 babies or 4% of 1,194)
Follow-up or Recall Rate obtained	27% (104/995)
Ideal Follow up Rate	80% (80% of 48 babies or 38)

If we were to use the data above as basis for capital (i.e. without costing for place of testing/rent/bills, etc.) and number of hearing-impaired children detected over 5 years, the cost of detecting a hearing-impaired child on second OAE screening is at least P63,000 (Table 3).

Table 3: Cost Calculations based on Projections of Baseline Data from the Philippine General Hospital

Total babies born in one quarter	=1327
At 90% (Ideal Rate) of 1327	= 1,194
Projected for 1 year	= 1,194 x 4 quarters /year = 4,777
Projected for 5 years	= 23,886(4777 x 5 years)
With 4% Refer Rate	= 955
80% Follow Rate for Initial Refer Patients	= 764
Total Number of babies Tested for 5 years (80% Follow-up Rate)	= 24,650 (P87 per OAE test)
Total Number of Babies Tested for 5 years With 100% Follow-up	= 24,841 (P86 per OAE test)
Based on Prevalence of PCHL	= 34 babies with PCHL in 5 years
Average cost per HI child	P62,882

If follow-up testing will have improved rates, that is at 100%, the cost of early detection may go down to P58000 per hearing-impaired child.

The usual cost for OAE in testing centers is currently P300, while the ABR or ASSR test varies from P800 to P2,000. Based on the computations above, the actual cost (without inflation) for screening a large volume over five years, if packaged at 2 OAE tests plus 1 ABR test, may amount to only P87 per child.

Projected Costs for Individuals

The impact of the previous calculation becomes more obvious if we were to compare the costs at an individual level. The change in expected impact and cost happens at two levels: (1) early detection, i.e. by age 3 months; and (2) early intervention, i.e. by age 6 months. If a child who is hearing-impaired is not screened by age 3 months, chances are high that the hearing impairment will be detected much later, usually at age 2-3 years, when the parent already sees the speech and language development to be much delayed compared to other children. If no intervention is done, then the lost opportunity to go to mainstream schools or the requirement for special education has a high price tag, which easily reaches hundreds of thousands of pesos over a period of 10 years. This has a snowball effect, which results in difficulty in acquiring a job in adulthood or underemployment, not just because of speech and language impairment but also poorer mental development compared with hearing individuals, and also less socialization capabilities and probably emotional problems from isolation and depression. We can arbitrarily assign a value of P30,000 per year for special education for 10 years, and lost income of P100,000 per year for 40 years, for a total of P4.3 million over a lifetime. Please note however that this is a very conservative estimate with no additional costing for inflation. If a child is diagnosed to have hearing impairment by age 6 months but intervention is not given early enough, then we can assume that the cost is similar to the previous scenario, plus the additional cost of testing. There are also cases in which intervention is given at later than 1 year and some improvement in speech and language is seen, however their development is still not at par with hearing children.[4] There will be a late diagnosis by age 2-3 years and special education services will be needed for a longer period of time. Compared to the previous estimate this will be higher because of additional costs from additional intervention.

If a child is diagnosed to have hearing impairment by age 6 months and intervention is given immediately, then the chance of developing normal speech and language development is much higher and may be expected to be near

normal if the hearing impairment is mild to moderate. Currently one hearing aid may range between P10,000 to P100,000 depending on the model. If we take the average cost of P30,000 - P45,000 for one ear, then those requiring hearing aids for both ears would require about P60,000 - P90,000 for optimal development. For those with moderate to severe hearing impairment lifetime use of hearing aids will be expected along with intensive speech rehabilitation and special education services. If we assume that replacement of the unit is required every 5-10 years, then the cost for hearing aids alone over a 60-year period would amount to at least P240,000-720,000 (plus batteries). Compared to the scenario with no intervention, this translates to a lifetime savings at the individual level of about P3.3 to 4 million. In some cases of severe to profound hearing loss, instead of hearing aids, cochlear implantation is required. Cochlear implantation involves the surgical insertion of an electrode into the inner ear of a severe-to-profoundly deaf child so that through electrical stimulation the neural cells can conduct impulses to the brain and hearing restored. The rate for the entire treatment now runs at about P1.2 million. Since the technology is still new (only 15 years in the Philippines), it is hard to say how many times a cochlear implantee would need re-implantation, and most patients would probably prefer no additional surgery. If we assume that a re-implant is required, perhaps due to technological advances or wear-and-tear, but will be done only after 30 years, then the cost would double over a 60-year period, which would amount to savings of P1.9 million. However only 60% of the children can be mainstreamed and 40% will still need special education services for at least five years to 10 years. Thus If we also assume that no re-implantation is required, then the savings would be higher at P3.1 million less the cost of special education (P30,000 x 10 years or P300,000) or about P2.8 million pesos. The prospect for employment for the deaf child is less than a normal hearing child but if implanted at an early age with sufficient language development will be better than for those who are deaf without any speech development at all. Thus at the individual level, a simple diagnostic exam with a basic cost of P87 can actually save an individual or family millions of pesos if done at the newborn period!

Projected Costs for National Program

If we try to imagine the costs and savings of the previous calculations on a national scale, then we have to take into account the prevalence of congenital hearing impairment in the country and the sensitivity and specificity of OAE as a screening test. Studies have shown the cost effectiveness of a screening intervention to be largely dependent not only on the cost per patient but also the baseline prevalence (Risk) of hearing impairment.[21] As previously reported, the

prevalence of bilateral profound hearing impairment among Filipino newborns is 1 in 724, or 0.14%.[1] If we include those with unilateral and mild-to-moderate hearing loss, the prevalence is 16/724 or 2.2%. However those with unilateral or milder forms of hearing loss may not necessarily require intervention. Still they may be diagnosed using the OAE as a screening test, thus we use the higher prevalence estimate in our succeeding estimation. In the same report, the sensitivity or chance of detecting a truly hearing-impaired child using OAE (as compared to the gold standard, ABR) is 86.4%, while the specificity or chance of detecting a hearing child as normal is 99.4%.

Following the method of Gorga and Neely[22], to estimate the cost-savings of a screening program, the posterior probabilities of each test result has to be computed, as follows:

P_{00} = P(normal) x P(pass|normal) = 0.98 x 0.99 = 0.97

P_{11} = P(impaired) x P(fail|impaired) = 0.02 x 0.86= 0.019

P_{01} = P(normal) x P(fail|normal) = 0.97x 0.006 = 0.006

P_{10} = P(impaired) x P(pass|impaired) = 0.02 x 0.136 = 0.003

The immediate cost for the first two outcomes that is *normal+pass*(C_{00}) and *impaired+pass*(C_{10}) is equal to the screening test, which we may assign as P200. This is because after the test, no other intervention is expected. For a *normal-fail* result, the cost (C_{01}) includes unnecessary testing with ABR, which when added to the screening OAE test, amounts to P2,000 (50 US dollars) The cost of *impaired+fail* result is negative because of savings from early detection of hearing impairment, since we prevent delayed language and speech. We can assign this value (C_{11}) as -P4.3 million. With these assumed probabilities and costs, we can compute the expected cost of the test per baby:

$$\text{Expected Cost} = C_{00} \times P_{00} + C_{11} \times P_{11} + C_{01} \times P_{01} + C_{10} \times P_{10}$$

$$= P300 \times 0.97 - P4{,}300{,}000 \times 0.019$$

+ P2000 x 0.006 + P300 x 0.003= -P82,000

Since the result has a negative value, this means that in the long-term the OAE screening test exceeds immediate costs when probabilities of each test outcome is applied. The value is the expected cost each time the screening test is administered. If about 1.8 million Filipinos are born yearly, then the benefit of performing a hearing screening test on every baby would be about P147.2 billion. This shows that the projected savings over 60 years or over the long term greatly exceeds the immediate cost of performing UNHS. Also if we compare the cost of testing each baby born in a year (i.e. P300 x 1,800,000 = P540,000,000) versus the total savings amortized on a yearly basis (i.e. P147,239,000,000 / 60 = P2,453,988,630), then it can be easily shown that the newborn screening program

would be cost-effective even on the first year of national implementation. On the other hand the cost of UNHS will likely lead to other health interventions to be displaced such that further examination of this cost and incorporation into existing health promotion and primary and secondary prevention programmes will need to be seriously considered.

Discussion

A review of literature has shown that risk factor screening alone while seemingly attractive in terms of cost for a developing country with scarce resources likely will entail more loss both from an individual and societal perspective considering the high cost of delayed intervention with hearing amplification, special education and speech rehabilitation. From this study both the projected costs that took into consideration the local prevalence of bilateral permanent hearing loss and the effectiveness of OAE as an objective hearing screening test showed significant cost benefit. The main problem, however, is the lack of awareness among Filipinos, even among physicians, of the need to refer newborns for hearing screening.[23] Even if a public hospital like the Philippine General Hospital is utilized as a model savings can still be obtained despite a less than ideal follow up or recall rate. The age of referral of only 30% at less than one year of age previously reported will likely improve.[1] Increased awareness among parents, health professsionals with an efficient testing and high recall rate will result in the substantial savings calculated in this study. For the initial implementation of the UNHS in the Philippines all the main islands of Luzon, Visayas and Mindanao should have screening diagnostic and intervention centers strategically placed in the first year. Within two years an additional 14 centers will need to be added such that all 17 regional hospitals in the country will be fully equipped to accept infants who have failed an initial hearing screen. The challenges of implementing a UNHS in the Philippines seem daunting but given the advantages to the family and the hearing impaired individual himself and society in general the implementation on a national scale may prove to be a worthwhile undertaking indeed.

Conclusion

Universal newborn hearing screening is a cost-effective strategy that should merit support from government as a program for promotion of hearing health among

Filipinos. Our estimates clearly show the huge financial benefits from the individual, family and societal perspectives that could be reaped from such a program if the required support services are provided, both with early detection and early intervention measures. Notwithstanding the cost of UNHS, further examination with respect to implications on funding of existing programs and as implemented in other developing countries with incorporation into the existing programmes for maternal and child health and newborn care such as that of using the immunization platform will still need serious consideration. The current projections in cost have been made possible through the availability of local data on prevalence and effectiveness of testing strategies. Based on pilot studies, cost benefit will be assured if good follow-up can be maintained for those who fail the initial OAE screen and if low false-positive rates can be achieved by technicians, which underscores the importance of increased public awareness, training of health practicioners, and timely interventions.

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Chapter 7

GJB2 variants and auditory outcomes among Filipino cochlear implantees

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Abstract

Objectives:
To determine the prevalence of gap junction beta-2 (*GJB2*) or connexin 26 (*CX26*) variants in Filipino cochlear implantees, and to describe radiologic findings, audiologic results and auditory performance after cochlear implantation (CI).

Methods:
Thirty cochlear implantees with unknown etiology for congenital severe-to-profound hearing loss and 30 controls provided venous blood samples for study. Radiologic evidence of temporal bone abnormalities, residual hearing status and post-CI auditory performance are described. Statistical analysis was performed for hearing thresholds before and after CI and for Parent Evaluation of Auditory/Oral Performance in Children (PEACH) scores based on the presence of cochlea-vestibular anomalies, age at CI and time since CI. Genomic DNA was extracted from venous blood, PCR-amplified and sequenced for *GJB2* variants.

Results:
One patient was compound heterozygous (c.[35delG];[235delC]) for *GJB2* variants. The variants p.Gly4Asp, p.Val27Ile and Val37Ile were identified in both patients and controls, including two implantees who were homozygous for p.Val27Ile and p.Val37Ile. No significant association was found between post-CI improvement in threshold or PEACH scores and the following variables: age at CI, duration of hearing aid use prior to CI, presence of cochleovestibular anomalies and completeness of electrode insertion. Although no significant change in audiometric thresholds due to time since CI was detected, PEACH scores were significantly improved with longer implant use at all conditions (quiet, noise and overall; $p<0.05$).

Conclusions:
The prevalence of causal *GJB2* variants in Filipino cochlear implantees is low (3.3%). Within this population the allele frequencies of the p.Val37Ile variant in patients and controls is >10%, which supports a non-pathogenic role for this variant. The low prevalence of *GJB2* variants precluded any association testing with CI outcome, although our results suggest better auditory outcome with longer CI use. Future genetic studies within the Filipino population should be able to control for population admixture.

Introduction

Mutations in the gap junction beta-2 (*GJB2*) gene, which encodes the connexin 26 protein that is important for potassium recycling and for hair cell depolarization/ repolarization, are the most common cause of congenital hearing loss of genetic origin in many populations.[1-2] Among different ethnic groups, there is great variability in genotype-phenotype correlations; for example, specific variants such as c.35delG are more prevalent in Caucasians[1], c.167delT among Ashkenazi Jews[3] and c.235delC among Asian populations.[4] In many developed countries, *GJB2* sequencing has become routine for genetic screening in hearing-impaired neonates. In contrast, in developing countries like the Philippines, infections (rubella, labyrinthitis, meningitis) and ototoxicity comprise about 50% of the known causes of congenital hearing loss, while in 24% the etiology remains idiopathic.[5] It is believed that some cases of hearing loss in the latter group may be due to genetic mutations, although the proportion is not as high as in developed countries. In this report, the *GJB2* gene was sequenced in Filipino cochlear implantees with bilateral severe-to-profound hearing loss of unknown etiology and in control subjects. Radiologic abnormalities, pre-implant residual hearing and auditory performance are also described. Given the challenges to access cochlear implant services in the country, our cohort of cochlear implantees provides a unique opportunity to study prevalence rates for hearing impairment genes among Filipinos and auditory outcomes after cochlear implantation (CI). The study results will be useful for genetic counseling, prognostication and formulation of a national policy for hearing care.

Materials and methods

Patient recruitment and clinical evaluation

The study was approved by the University of the Philippines Manila-National Institutes of Health Ethics Review Board prior to study initiation. Informed consent was obtained from adult subjects and parents of pediatric cochlear implantees. From an initial pool of 100 cochlear implantees, 30 cochlear implant recipients with bilateral severe-to-profound hearing loss of no definitive etiology from perinatal and maternal history, as well as 30 adult control subjects (median age 32 years, range 21-59), all of Filipino descent, were enrolled in the study. Otoscopic and audiometric screening of control subjects was performed and normal hearing results were obtained. For the cochlear implantees, all medical records including

radiologic and audiometric evaluation were reviewed. CI was performed by a single surgeon, and audiometric and speech evaluation was performed in one center. Within a soundproof setting, pure-tone thresholds for the pediatric patients were obtained by auditory steady-state response using a Biologic NavPro (Mundalein, Illinois, USA) machine. In the adult patients, audiometric evaluation based on the standard Hugh Westlake method was performed using a MADSEN Aurical Plus audiometer (Denmark). When computing the averages of the hearing thresholds, a default value of 120 dB was used to indicate profound hearing loss that is beyond the audiometer limits. In the patients with bilateral CI, thresholds for the better hearing ear were used.

Auditory outcomes were rated by Categories of Auditory Performance (CAP)[6] and Parent Evaluation of Auditory/Oral Performance in Children (PEACH) scales[7]. CAP is an index consisting of eight performance categories arranged in the order of increasing difficulty, with category 8 as highest performance. The parents of the pediatric cochlear implantees were asked to fill out a PEACH questionnaire[7].

Statistical analysis was performed for improvement in hearing thresholds and PEACH scores based on the presence of temporal bone anomalies, successful electrode insertion, duration of hearing aid use prior to CI, age at CI and time since CI. Improvement in hearing thresholds was derived by subtracting averaged pre-CI thresholds from averaged post-CI thresholds. The Mann-Whitney-Wilcoxon rank sum test for dichotomous independent variables and Spearman's correlation test for linear independent variables were performed using R[8].

DNA extraction, PCR-amplification and direct sequencing

Genomic DNA was extracted from whole blood using the Qiagen QIAamp DNA Blood Midi Kit (Qiagen, Valencia, Calif., USA). The coding exon (exon 2) of the *GJB2* gene was sequenced for all participating subjects. PCR primers 5' - gAAgTCTCCCTgTTCTgTCC – 3' (forward) and 5' - AATCTAACAACTgggCAATg – 3' (reverse) were designed with NetPrimer software (Premier Biosoft International, Palo Alto, Calif., USA).

PCR was performed in 45-µL reaction mixtures, each containing 1 X PCR buffer (20 mM Tris-HCl, pH 8.4; 50 mM KCl), 2.5 mM $MgCl_2$, 0.2 mM of each deoxy-nucleotide, 0.2 µM each of the forward and reverse primers, 3 U Taq DNA polymerase (Invitrogen, Carlsbad, Calif., USA) and 1.5 µL gDNA. PCR conditions were as follows: initial denaturation for 4 min at 94°C; 38 cycles of denaturation at 94°C for 30 s, annealing at 67.6°C for 30 s and extension at 72°C for 50 s; and a final extension for 10 min at 72°C. Amplicons were then sequenced bidirectionally.

For patient samples in which only one variant in exon 2 of *GJB2* was found, sequencing of exon 1 and adjacent intronic regions of the gene was performed.

Results

Clinical Description

Of 30 cochlear implantees, 14 were male and 16 female. The median age at CI was 4 years 7 months (range 15.5 months to 27 years; average age at CI 7 years). Nineteen patients were implanted on the right ear, 7 in the left ear, and 4 bilaterally. All patients were implanted with MED-EL devices, except for 1 patient who received a Cochlear Nucleus Freedom Contour device.

Half of the patients had normal cochleovestibular findings by CT and/or MRI scans including 3 with unilateral high-riding jugular bulb. Nine patients (30%) had enlarged vestibular aqueducts (EVA), 1 patient had bilateral Mondini dysplasia and another implantee had bilateral malformed cochleae with incomplete partition. A child with bilaterally malformed cochleae, vestibules and semicircular canals also had congenitally absent cochlear and inferior vestibular nerves in the right ear. Three implantees showed evidence of superior semicircular canal dehiscence.

For 3 children, only auditory brainstem response or auditory steady-state response results were available, which showed bilateral severe-to-profound hearing loss. Among 27 patients with preoperative hearing thresholds, the average across frequencies 0.5-4kHz was 106.6 $\pm$ 12.0 dB (median 111, range 80-120). Post-operatively the average across frequencies for aided thresholds was 38.9 $\pm$ 10.4 dB (median 38.8, range 25-80). This means an improvement in hearing of 66.7 $\pm$ 16.6 dB on average (median 71.2, range 31.8-95). Of 3 adult implantees (age >20 years), 2 had a CAP score of 7, while 1 had a CAP score of 6. The child with bilateral inner ear malformations and right eighth nerve aplasia was implanted in the left ear and had PEACH scores of 4% for quiet, 10% for noise and 7% overall conditions. For 24 other children with PEACH scores, the average scores were as follows: quiet condition, 74.1 $\pm$ 21.3% (median 81, range 21-96); noise condition, 66.0 $\pm$ 25.5% (median 67.5, range 0-100); overall condition, 70.5 $\pm$ 22.6% (median 75, range 16-98).

The presence of temporal bone abnormalities, successful electrode insertion and length of pre-CI hearing aid use did not significantly influence post-CI threshold improvement and PEACH scores. When plotted against age at CI and time since CI [Figure 1], no significant relationship with post-CI improvement was found in the threshold. Likewise, no significant change in PEACH scores was detected based

on age at CI. On the other hand, PEACH scores were significantly associated with time since CI at all conditions (quiet, R=0.54, p<0.01; noise, p<0.05; overall, R=0.49, p<0.05) [Figure 1].

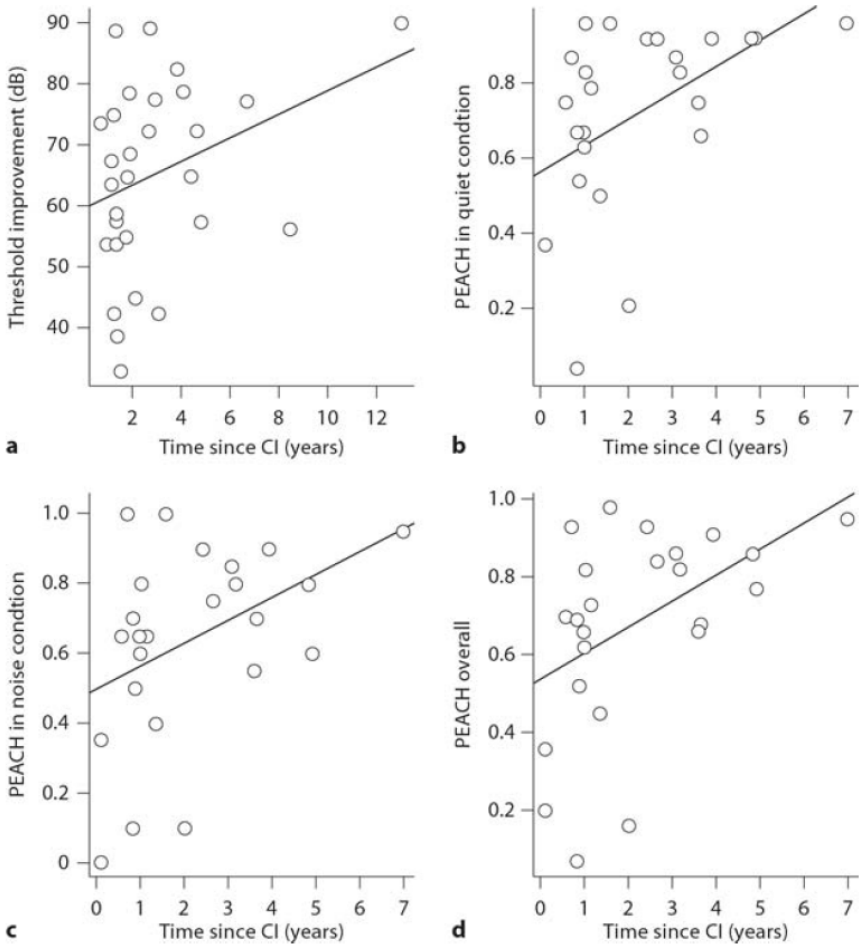

Figure 1: Correlation plots for improvement in auditory thresholds and PEACH scores based on time since CI. (a) Difference between pre- and post-CI thresholds versus time since CI (R=0.25, NS). (b) PEACH scores in the quiet versus time since CI (R=0.54, p=0.005). (c) PEACH scores in the noise condition versus time since CI (R=0.42, p=0.04). (d) Overall PEACH scores versus time since CI (R=0.49, p=0.015).

GJB2 Genotypes

Of 30 cochlear implantees who were sequenced for *GJB2*, only 3 patients were homozygous or compound heterozygous for *GJB2* variants [Table 1]. One implantee was compound heterozygous for the c.35delG and c.235delC mutations. A second implantee was homozygous for the p.Val37Ile variant. However, the p.Val37Ile variant was found in the heterozygous state at high allele frequencies in both patients (10%) and controls (11.7%; Table 1). One implantee was homozygous for p.Val27Ile, while 2 controls carried both the p.Val27Ile and

p.Glu114Gly variants in the heterozygous state. Previous reports have concluded that p.Val27Ile was a polymorphism, either as a single variant or within a haplotype with p.Glu114Gly.[9-10]. Another known variant, p.Gly4Asp[11], was identified in the heterozygous state in both implantees and controls at allele frequencies of 3.3 and 5%, respectively. Sequencing of exon 1 of *GJB2* in 9 implantees who were heterozygous for a single variant in exon 2 did not detect additional variants.

Table 1: *GJB2* genotypes among Filipino cochlear implantees and control subjects

GJB2 Genotype	Implantees	Controls
c.[35delG];[c.235delC]	1	0
p.[(Val37Ile)];[(Val37Ile)]	1	0
p.[(Val27Ile)];[(Val27Ile)]	1	0
p.[(Val27Ile;Glu114Gly)]	0	2
p.[Gly4Asp];[=]	2	3
p.[Val27Ile];[=]	1	0
p.[Val37Ile];[=]	6	7
None	18	18
Total	30	30

The patient who was compound heterozygous for c.[35delG];[235delC] was partly of Spanish descent. Based on oral history, multiple individuals from both sides of the patient's family also have hearing impairment. His temporal bone CT revealed bilateral EVA (fig. 2a). Although he was implanted in the right ear at the age of 6 years, he had been using hearing aids since he was 2 years old. He had excellent post-CI thresholds (average 41.2 dB; fig. 2b) and PEACH scores of 90-92% at all conditions.

The implantee who was homozygous for p.Val37Ile had EVA in the left ear (fig. 2c) and was implanted bilaterally at the age of 4 years. His average for aided thresholds was 25 dB (fig. 2d) and his PEACH scores ranged from 66-70%.

Discussion

Whether the p.Val37Ile variant damages hearing function or not remains controversial. This variant has been associated with mild-to-moderate hearing impairment in multiple individuals.[12]. Bioinformatics analysis using Polyphen-2[13] predicts the possibly damaging effect of the variant, while the SIFT[14] program labels p.Val37Ile as tolerated. On the other hand, functional studies indicate that

the p.Val37Ile variant disables induction of the formation of homotypic gap junction channels in *Xenopus* oocytes and may even have a dominant negative effect.[15-16] However, the allele frequency in both patients and controls in this study is >10%, and thus p.Val37Ile may be considered a common variant among Filipinos. It also appears to be equally prevalent among hearing-impaired individuals and controls in East Asian populations.[11,17]

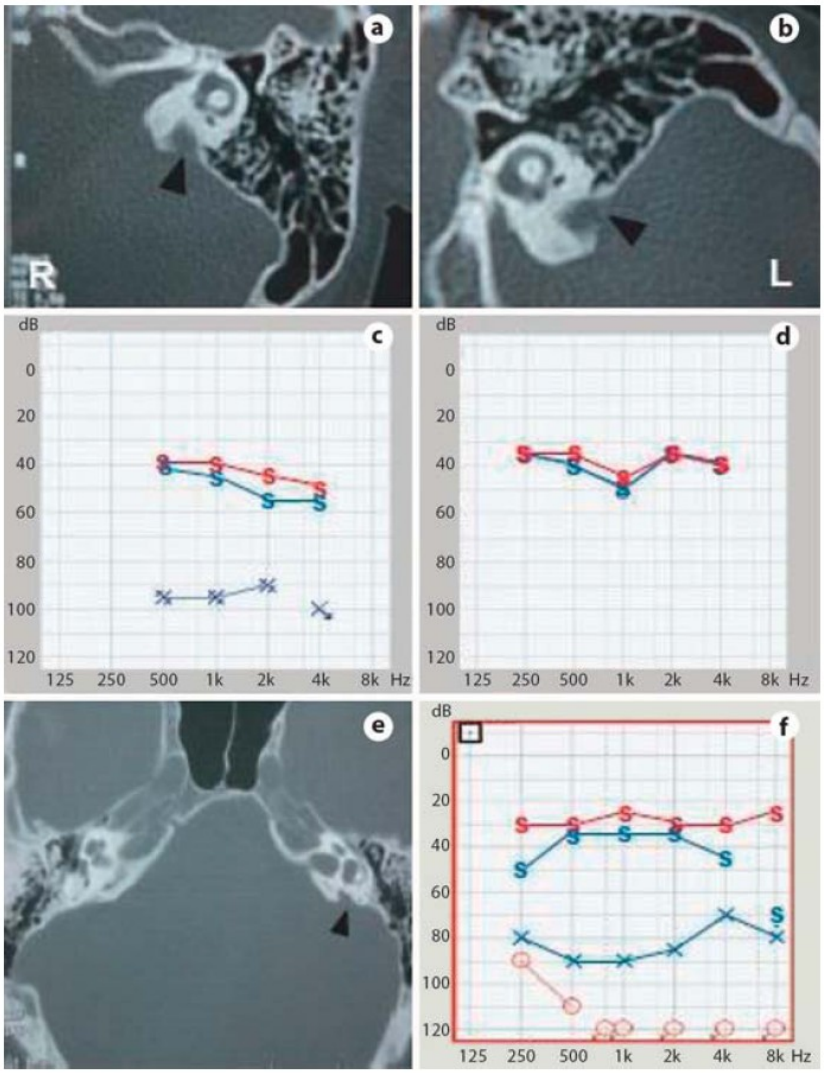

Figure 2: (a-b) Temporal bone CT showing bilaterally enlarged vestibular aqueducts (EVA, black arrowheads) in the patient with the GJB2 c.35delG/c.235delC genotype. (c) Visual reinforcement audiometry (blue with multiple hash) in the same patient at the age of 5 years showed severe hearing impairment, while aided thresholds (letter S) indicated hearing within the speech spectrum. Red, right ear; blue, left ear.
(d) Thresholds further improved 3.5 years after CI in the right ear. (e) Temporal bone CT of the patient who is homozygous for the GJB2 p.Val37Ile variant (black arrowhead). (f) Unaided thresholds indicated profound hearing loss in the right ear (red circles) and severe hearing impairment in the left ear (blue crosses). Thresholds obtained with hearing aids (blue S) were within the hearing range at 500-4,000 Hz but not at 500 and 8,000 Hz. Implant-aided thresholds (red S) were within the speech range across all Frequencies

Likewise both the p.Val27Ile and p.Val37Ile variants have high allele frequencies in Indonesians[18] and Malaysians[19]. Given this evidence, it is possible that the patient in this study was homozygous for the p.Val37Ile variant because of high variant allele frequencies within the population, and that the profound hearing loss in this patient has a different etiology.

Because only 1 patient carried recessive *GJB2* mutations in two alleles, the prevalence of hearing impairment due to *GJB2* variants within this cohort of Filipino cochlear implantees is low (3.3%). The prevalence of causal variants in *GJB2* is similarly low in other Southeast Asian countries Indonesia[18] and Malaysia[19], where the Filipino population originated historically. Since *GJB2* variants are not a common cause of hearing impairment within the Filipino population, *GJB2* sequencing will not be cost-effectient as a genetic screening tool.

Although the *GJB6* gene is known to cause hearing impairment through digenic inheritance with *GJB2*[20], the *GJB6* gene was not tested in this study. Similarly, only a few individuals were sequenced for exon 1. Worldwide, the prevalence rates for mutations within *GJB2* exon 1 and *GJB6* remain low, and such mutations are only common in individuals from select populations who have heterozygous mutations in *GJB2*.[21-23]

Earlier studies suggested better post-CI outcomes in children with *GJB2* mutations[24-25], but more recent studies demonstrate that such outcomes in *GJB2*-positive children are mainly due to duration of CI use or younger age at implantation.[26-27] Although the number of pediatric cochlear implantees in this study was small, we were able to show an improvement in PEACH scores with increasing time since CI, but not with age at implantation.

Due to the low prevalence of *GJB2* mutations, it was not possible to test if there is an association between the presence of *GJB2* mutations and post-CI auditory outcomes. However, merely increasing the sample size may not be a cost-efficient strategy in conducting future genetic research. The identification of the c.35delG and c.235delC variants in 1 individual due to mixed ancestry may reflect population admixture within the general Filipino population, which is to be expected from the country's migration and colonization history. This forebodes difficulties in designing case-control studies for this population and can result in false-positive associations due to population admixture. Thus, future genetic studies within the Filipino population require a study design and statistical analysis that properly control for population admixture and substructure.

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Chapter 8

General Discussion

General Discussion

Affecting at least 1.5 per 1000 live-births, congenital hearing loss remains as one of the most common congenital disorders in children (Parving ,1999). Given the pervasive individual disadvantages from psychosocial, educational and economic as well as the societal perpectives, efforts at early detection of childhood prelingual deafness should be pursued (Ruben, 2000). Following the principles laid out earlier by Wilson and Junger in 1968 and Davis and co-workers in 1997 newborn hearing screening can pose a number of challenges (Davis et al., 1997; Wilson and Junger,1968). Embarking on newborn hearing screening entailed the much needed epidemiological studies in the Philippines with the end view of determining the practicality and value of universal newborn hearing screening (UNHS). The Joint Committee on Infant Hearing (JCIH) in 1982 already considered the problems related to delayed diagnosis of childhood deafness and recommended identification by the age of 3-6 months (JCIH, 1982). A high risk register was then proposed since otoacoustic emissions (OAE) testing protocols had just been introduced (Kemp, 1978). Subsequently after about 8 years, the JCIH recommended the use of OAE to facilitate the early detection of hearing loss in newborns (JCIH, 2000; JCIH 2007).

Chapters 2 and 3 highlight the earlier studies carried out at the University of the Philippines Manila – Philippine General Hospital on the subject of hearing screening in neonates and very young children. In Chapter 2 the sickest babies at the neonatal intensive care unit of University of the Philippines- Philippine General Hospital were tested using OAE and it was noted that 29% had bilateral refer rates. The associated risk factors were determined and low birth weight and male gender were found to be significant (Chiong et al., 2003). A related study showed that only 8% of the babies who referred were brought back for retesting and 75% of them eventually passed (Quintos et al., 2003). As a national university hospital, most pregnant women who come to this hospital have had poor perinatal care, with pregnancy related complications and come from the very poor socioeconomic strata. Another related study soon from our center identified retrospectively the common etiologic basis of severe to profound deafness among cochlear implantees and showed maternal Rubella as the most common at 32% while other infections such as chronic otitis media (4%), meningitis and labyrinthitis (4%) and ototoxicity would cumulatively approximate 50% of the preventable causes of profound deafness consistent with the report of Alberti (Chiong, 2006;Chiong and Villanueva, 2012; Alberti, 1996). Similarly, risk screening alone will likely miss out

on 42% of hearing impaired children such that the need for more objective screening with OAE for example will be justified (Wrightson, 2007).

In Chapter 3 we report on 379 children referred to the Ear Unit of the Philippine General Hospital during a ten month period. These were children with notable delay in speech or whose pediatricians suspected the possible presence of hearing loss. The age of referral was more than 12 months in 63% and only 32 % percent between 5-12 months of age. This shows that most of the children were diagnosed beyond the age at which diagnosis and intervention are ideally provided without the deleterious consequences on speech and language development. In this chapter we also demonstrated good concordance of OAE and ABR. Most screening centers will likely be able to afford only to buy OAE equipment given the cost of ABR equipment in our setting. Indeed as reported by others the sensitivity and specificity of OAE vis-a vis the ABR as a gold standard was noted to be very good (Llanes & Chiong, 2004). On the other hand we also were interested in knowing how many of those who would have a flat ABR response might have some residual response with ASSR. A related study also from our center pegged this at 85% with the possibility of an objective way of choosing which ear gets the hearing aid amplification initially considering that most families could only afford to buy one hearing aid (Tan et al., 2009).

Chapters 2 and 3 delved with testing children in an academic tertiary hospital and so there was still the need to determine the prevalence of hearing loss in newborns in the community setting. Chapter 4 showed this to be 1.38 per 1000 livebirths (Chiong et al., 2007). This rate is similar to the reported prevalence rates on newborn hearing loss worldwide. If we are to consider unilateral and mild hearing loss the rate increases to 22 per 1000 live-births (an 18 fold increase). However given that the ABR testing done to confirm the level of hearing was performed above the age of 3 months in more than 40%, the percentage of children with temporary hearing loss (eg. from otitis media) could not be clearly ascertained. Nevertheless, using the Griffith's Mental Development Scoring it was noted that even those with mild or unilateral hearing loss had a developmental delay compared to those with normal hearing during the first two years of life. These children have been followed for another three years and it would be interesting to know whether such initial delays would be overcome as the children grew older. A study to look at outcomes in terms of development in the longer term is being planned.

Other etiologic factors responsible for the delayed auditory development in some of these children might include pesticides as most of the children tested came from an agricultural community where pesticides and insecticides were commonly used either to increase crop yields or reduce vector borne diseases. In Chapter 5, changes in ABR latency measures were studied among infants and correlated with the exposure to some of these environmental toxic products (Chiong et al., 2012). The matrices for determination of exposure among mother-infant dyads were noted to be maternal hair for exposure of mothers and meconium for infants being most robust (Ostrea et al., 2008; Ostrea et al., 2009). Propoxur noted to be the most prevalent neurotoxic product effected some changes in some latency measures between the exposed and non-exposed group suggesting an effect in the auditory system. This indeed highlights a need for increasing the awareness among the "at risk" population. The need to formulate effective strategies in this regard and the outcomes could be the subject of more studies in the future. Interestingly, as opposed to the initial experience in the hospital based screening of the NICU babies this study however showed that with community workers directly in touch with the mothers more than 90% of the babies could be tested within 9 months. Thus this community based strategy had an advantage over the hospital based testing. Along with the fact that only 40% -70% of births take place in hospital facilities in the Philippines (Philippine Fact Sheet,2010), a community based screening programme need to be formulated. As most of the rural areas will not have objective hearing screening equipment in hospitals an alternative hearing screening test had to be developed. Earlier screening methodologies described in literature such as the infant distraction test were revisited (Ewing & Ewing, 1944). In the UK these tests were being done at 8-9 months by a health visitor attending until objective testing using otoacoustic emissions tests became in widespread use (McCormick, 1983; McCormick, 2002). The accuracy of a human voice test ("BAAH") compared to OAE was good and increased to more than 65% the possibility of a diagnosing hearing impairment when a response was positively identified (Abes et al., 2012; Garcia et al., 2012). This paves the way for the possibility of training community health workers on both risk factors and the "BAAH" test in places where OAE equipment are not available. This alternative test need not preclude objective testing as it will defeat the purpose of universal newborn hearing screening. However cognizant of the limited resources in some remote islands without these equipment and the fact that procurement of such may take a long time still a fifty percent chance of detecting a child who needs closer monitoring might still be considered valuable with increased awareness of the parents and caregivers tasked to monitor the babies in these areas. Otherwise,

where some of the babies are found to fail to respond to this initial test, health workers will need to refer them to the nearest locality or hospital where the service can be provided.

Chapter 6 describes the cost analysis of a universal newborn hearing screening programme based on the data found in Chapters 2, 3 and 4. It was important to review how other countries whether developed or developing found UNHS to be cost effective. However as highlighted by these studies, prevalence rates and population at risk and the cost of services within the particular health system will have a lot of bearing on the eventual cost of carrying out such a programme. Selective or targeted hearing screening would appeal mostly to developing countries such as Sub-Saharan Africa and Southeast Asia (including the Philippines) where resources are limited and expenditure for health remain below the stipulated WHO rate of 5% of GDP. However as highlighted by several authors operational constraints would render selective screening to be not as cost-effective as that of a UNHS and that existing programmes within the health system of a country could well be utilized to cut the cost of rendering UNHS such as using immunization as a platform for the provision of this service (Olunsaya, 2011). In Germany, when cost of education and other interventions are considered universal newborn hearing screening is shown to be more cost-effective (Neumann et al., 2006). The cost analysis showed substantial savings could be obtained with the universal newborn hearing screening in the Philippines even during the first year of full implementation (Chiong et al., 2012).

The results of the studies described in this thesis were used to advocate for the legislative mandate to carry out a universal newborn hearing screening programme. In 2007 the first position paper was submitted to congress and Senator Loren B. Legarda filed Senate Bill 2390(23) using as a basis the results of the studies described in Chapters 2, 3 and 4. In two years the law mandating Universal Newborn and Early Intervention Act of 2009 was enacted. The Newborn Hearing Screening Reference Center as stipulated in the IRR (Implementing Rules and Regulations) approved by the Department of Health in 2010 is now busy formulating the protocols, registry, training and laboratory proficiency methodologies needed to carry out the mandate(Appendix 1) (Department of Health, 2010).

Indeed the early detection of childhood deafness is expected to lead to early intervention. These two tasks could be formidable in a setting where geographic

(the country has 7100 islands), infrastructure, low awareness regarding deafness prevention, lack of manpower aggravated by migration of professionals (Cheng et al., 2002) and cost issues of screening, diagnosis and treatment seem insurmountable. Nevertheless technological advances in hearing rehabilitation have come our shores and shown a glimmer of hope for some of these children. Thus it is hoped that with early detection of hearing loss more will benefit from early intervention and better choices for parents and families would be made available.

Corollary to this, genetic screening for early detection of hearing loss and its etiologic basis has been introduced in some countries. GJB2 or connexin 26 mutation is the most common cause of non-syndromic sensorineural hearing loss. GJB2 variants were studied among Filipino cochlear implantees (CI) and showed the prevalence at 3.3% mutation rate. This was not as high as that reported in other countries (Chiong et al., 2012) and the GJB2 variants noted can be explained on the basis of racial admixture in the context of Philippine colonial history. The prevalence of causal variants in *GJB2* is similarly low in other Southeast Asian countries such as Indonesia (Snoeckx et al., 2005) and Malaysia (Zainal et al., 2012) from which historically the main population of the Philippines originated. It also highlights the fact that genetic screening as espoused in other countries may not be that significant for the early diagnosis of hearing loss in childhood. Additionally, no effect of GJB2 mutation on the performance with cochlear implantation (CI) based on PEACH scoring (Ching & Hill, 2007) was noted. Other mutations such as SLC26A4 are now under investigation and another ongoing study looking at the identification of genes responsible for chronic otitis media are just some of the studies that have been formulated in order to possibly determine and look at the causes of early onset hearing loss among the most vulnerable segment of a growing population in our country where about 2 million babies are born each year.

This thesis summarizes the work done in our institution for the last ten years which started with epidemiologic studies on hearing impairment among neonates and young children, the age of identification, some of the risk factors and common etiologic causes and correlation of the hearing impairment with developmental milestones. We investigated the ability of OAE, ABR and ASSR to diagnose these children in our setting. We also studied alternative behavioural hearing screening testing that could be utilized in areas where no such objective audiologic testing could be carried out. The auditory effects of maternal exposure to environmental

toxins during pregnancy was likewise investigated with respect to ABR wave latency changes following maternal and fetal exposure as measured in several matrices with both maternal hair and meconium as most robust for the mother-infant dyads. Lastly the cost analysis of UNHS was investigated based on evidence on local prevalence data and cost of diagnostic and intervention services within the current health system. Initial studies on genetic basis for congenital hearing loss showed that GJB2 mutations accounted for only 3.3% of those with severe to profound hearing loss undergoing cochlear implantation with no impact on auditory performance with cochlear implantation. In contrast to other developed countries, this puts into question the importance of genetic screening in our setting.

A developing country perspective on the early detection of childhood deafness is provided and how research evidence can be utilized successfully for developing national policy and legislation to address this important health issue is demonstrated. A manual of operations is now being finalized in preparation for full implementation on a national scale (CONHSCA,2012) by year 2013.

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Chapter 9

Summary

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Summary

The importance of early detection, diagnosis and intervention for congenital hearing loss is well supported by the fact that it is one of the most common congenital disorders and is known to lead to deleterious effects with impact on the individual's overall psychosocial, educational and speech and language development. Given that established principles for hearing loss screening in newborns and infants are well justified, some developed countries have been able to mandate universal newborn hearing screening (UNHS) since the early 90's. In the case of developing countries it has been contended that risk factor and targeted or selective newborn hearing screening methods would be more practical with less cost. However as proven by numerous studies this strategy will miss out on about 50% of those with significant hearing impairment. The Philippines is in the medium development category ranking 112th of 187 countries on the basis of the human development index as of 2010. As in most developing countries primary prevention takes precedence over secondary or tertiary prevention measures given the limited resources for health care. Its growing population will likely magnify further the effects and toll on the economy of missed opportunities to ameliorate the lifelong and significant effects of congenital hearing loss. Universal newborn hearing screening as espoused in most reports could provide mitigation but adoption of the models in most developed countries will likely not be applicable given that the Philippines is an archipelago of 7100 islands and 40-70% of births are home born and not hospital based. This thesis provides a developing country framework and a systematic approach to how a universal newborn hearing screening programme could be operationalized given the foregoing realities including a burgeoning population growth with 1.8 million babies born on an annual basis.

The second chapter of this thesis highlights the pragmatic approach of first looking at the sickest babies in a tertiary academic center neonatal intensive care unit and the proportion of babies who would fail a distortion product OAE test. There was note of a 29% "refer" rate with low birth weight and male gender as the most significant risk factors. The greatest challenge was how to have the babies return for a follow up confirmatory test as only 8% could be recalled for a retest of whom 75% eventually passed. The third chapter looked at the agreement between OAE and ABR testing. A fairly good concordance could be established between the two. Additionally this study showed that referral for diagnosis of congenital hearing loss was delayed in the majority of cases. With only about 30% being referred at age

below one year of age data showed hearing loss diagnosis is beyond the six months ideal age of intervention compatible with age appropriate speech and language development. This is further supported by the fact that EHDI (Early Hearing Detection and Intervention) programmes from the U.S. for example will mandate that NHS(newborn hearing screening) be done within 48 hours before hospital discharge will miss out on the majority as most of the babies in the country especially in the rural araes are home born. However for a UNHS programme to be developed it was important to establish local prevalence of bilateral permanent congenital hearing loss. The Philippines remains to be a predominantly agricultural country as the study detailed in Chapter 4 that reports a community based prevalence of 1.4 per 1000 livebirths with bilateral permanent congenital hearing loss proved to be within the reported prevalence from other countries. The impact on early development within the first two years of life of various degrees of hearing loss and even unilateral hearing loss was also noted to be significant based on the Griffith's Mental Development Scale. Chapter five looked at the effects of maternal and fetal exposure to environmental toxic products on the ABR wave latencies highlighting the hazards of pesticides and insecticides on overall auditory development. The effect of exposure on latency changes on ABR was measured in robust matrices such as maternal hair for mothers and meconium for the infants. There was a significant difference found between the exposed and non-exposed groups using these several matrices as an index of maternal and infant exposure to pesticides that although already banned in Europe still remain commercially available in the Philippines. Propoxur was determined to be the most prevalent toxin in this cohort of mother-infant dyads.

In Chapter six the cost analysis of a universal NHS in the Philippines was undertaken in order to establish the feasibility of this hearing health programme using the findings on local prevalence of hearing loss seen in Chapter three and the costs of equipment, personnel salaries and other expenses relative to the loss of income and educational cost of speech and aural rehabilitation. It was noted that there would be substantial savings that could accrue from a universal NHS programme even in a country like the Philippines.

There were four related studies done at our center that may be considered as supporting the findings of this thesis. One is the study by Quintos et al. (2003) that reported only 8% recall rate for those who failed initial OAE testing in the neonatal intensive care unit in our center. This highlights the difficulty of ensuring a follow-up study with patients hailing from afar as the referral base of patients in our

center is in fact national. Perhaps a community based approach will be more effective as also supported by Chapter 4 where more than 90% of infants could be examined within nine months of birth where community health workers could provide encouragement to the mothers to bring their babies for testing. With respect to confirmatory tests with ABR(auditory brainstem response) following an OAE ”refer” result another study by Tan et al. (2009) reported that 85% of those with flat ABR had residual responses seen on ASSR (auditory steady state response) test. This highlights the potential value of a more comprehensive frequency specific and more robust electrophysiologic method of determining residual hearing in those with flat ABR findings which may be important where cost issues could delay provision for binaural hearing amplification (still an out of pocket expense). The third study by Garcia et al. (2011) provides a framework for the use of the voice test (BAAH) as an alternative test along with questionnaire risk factor screening for use in places where such OAE, ABR and ASSR equipment are still not available so that more than half of the babies with significant hearing impairment can still be identified. Lastly the study on GJB2 among Filipino cochlear implantees (Chiong et al., 2013) that showed a low 3.3% prevalence of this mutation among profoundly deaf subjects with unknown etiology for deafness may be interpreted as likely putting into question the practicability of a genetic screening in the Philippines even as this is now espoused in other developed countries having high prevalence of GJB2 mutations as the cause of congenital hearing loss.

This thesis documents the need for a systematic approach for building up the evidence from a developing country perspective on the value of early detection of hearing loss in children, the need for developing the UNHS as a potential method for facilitating the early diagnosis of childhood deafness as a way of ensuring that early intervention can be instituted and how this may be facilitated even with the operational constraints of lack of equipment and audiologic professionals for example. The findings of Chapters 3 to 5 served as a basis for a law that mandated universal newborn hearing screening in the country that will be introduced in phases for the next 5-10 years.

Samenvatting

Het belang van een vroege opsporing, diagnose en behandeling van een aangeboren doofheid wordt nog versterkt, omdat het om een van de meest frequente aangeboren ziekten gaat. Evenzo omdat een onbehandelde aangeboren slechthorendheid/doofheid zo een schadelijk effect heeft op de persoonlijke taal- en spraakontwikkeling en daarmee op de persoonlijke psychosociale ontwikkeling van een persoon. Nadat het belang van de screening bij neonaten en kinderen vanwege gehoorverlies voldoende was aangetoond, werd de neonatale/vroegkinderlijke gehoorscreening sinds het begin van de negentiger jaren in de afgelopen eeuw al in sommige ontwikkelde en geïndustrialiseerde landen als een verplichte routine screening ingevoerd.
In de ontwikkelingslanden is er om praktische redenen voor gekozen om alleen en dan pas gericht op het bestaan van een gehoorverlies te screenen wanneer er sprake is van een verhoogd risico op de aanwezigheid van een slechthorendheid/ doofheid. In talrijke studies is echter aangetoond dat met een dergelijke beperkte screeningsopzet zo een 50% van de kinderen met een ernstig gehoorverlies gemist wordt. De Filippijnen valt op grond van de ontwikkelingsstandaard (Human development category and index) in de middencategorie van landen met een plaats tussen nummer 112-187. Op grond van de beperkte budgetten beschikbaar voor gezondheidszorg heeft, evenals in de ontwikkelde landen, primaire preventie in de gezondheidszorg een hogere prioriteit in verhouding tot de secundaire en tertiaire zorg. Door toepassing van een zo beperkt screeningsprogramma vanwege vroegkinderlijke slechthorendheid/ doofheid zal het aantal gemiste gevallen van een vroegtijdige opsporing door een te verwachten bevolkings-toename nog verder gaan toenemen. Door deze gemiste kansen om zo in individuele gevallen de negatieve effecten van vroegkinderlijke slechthorendheid/ doofheid op iemand zijn persoonlijke ontwikkeling te helpen verlichten, zullen de totale kosten voor de economie op landelijk niveau gaan toenemen. Een verschuiving van gezondheidszorgbudgetten naar de primaire preventieve gezondheidszorg wordt beoogd. Een algehele invoering van een bevolkings-onderzoek op neonatale gehoorscreening in de Filippijnen zal nog op praktische problemen in de uitvoering stuiten, omdat de Filippijnen uit een archipel van 7100 eilanden bestaat en omdat 40-70% van de bevallingen thuisbevallingen zijn.

Dit proefschrift handelt over hoe in een ontwikkelingsland, zoals de Filippijnen, systematisch een bevolkingsonderzoek op neonatale gehoorscreening zou kunnen worden ingevoerd, weliswaar rekening houdend met de al genoemde

logistieke beperkingen bij een groeiende bevolking met thans al 1.8 miljoen nieuw geborenen/jaar.

Het **tweede hoofdstuk** van dit proefschrift richt zich eerst op een praktische aanpak door allereerst de zieke baby's in een tertiair universitair neonatale intensieve care unit op hun gehoor te onderzoeken en door zo na te gaan welke baby's falen bij de oto-akoestische emissie (OAE) test. Bij 29% van hen was dit het geval. De belangrijkste risico verhogende factoren waren een laag geboorte-gewicht en het mannelijk geslacht. Het bleek buitengewoon problematisch om deze kinderen met een negatieve OAE-test opnieuw te kunnen zien voor een vervolgtest op hun gehoor. Slechts 8% uit die groep bleek opnieuw getest te kunnen worden en driekwart van hen had vervolgens alsnog een goede uitslag.

Het **derde hoofdstuk** gaat over de mate van gelijkwaardigheid tussen de otoacoustische emissie (OAE) test en Auditory Brainstem Response (ABR) test. Een redelijk goede overeenkomst werd tussen beide testmethoden gevonden. Tegelijkertijd toonde deze studie aan dat de meerderheid van de dove/slecht-horende kinderen te laat verwezen werden voor deze diagnostiek. Slechts 30% van deze kinderen bleek verwezen te zijn voor het eerste levensjaar. Dit terwijl de leeftijd van 6 maanden de gewenste ideale leeftijd voor diagnose is om een passende spraak- en taalontwikkeling te kunnen bereiken. Het programma voor bevolkingsonderzoek om vroegkinderlijke doofheid/slechthorendheid (Early Hearing Detection and Intervention=EHDI) in de Verenigde Staten op te sporen kent als voorschrift dat het gehooronderzoek bij de neonaat (NHS=Newborn Hearing Screening) binnen 48 uur na de geboorte en in ieder geval voor ontslag uit het ziekenhuis verricht is. In de Filippijnen daarentegen - in het bijzonder in de landelijke gebieden - hebben de meeste bevallingen thuis plaats.
Voor het ontwikkelen en opzetten van het neonatale gehoorscreeningsprogramma in de Filippijnen was het nodig eerst de prevalentie van een beiderzijds voorkomend gehoorverlies te leren kennen. Landbouw is in de Filippijnen de belangrijkste economische activiteit. In **hoofdstuk 4** wordt aangetoond dat de prevalentie van een beiderzijds voorkomend blijvend gehoorverlies 1.4 op de 1000 levend geborenen is, wat valt binnen de voor andere landen gemelde prevalenties. Gehoorverliezen, zowel dubbelzijdige als enkelzijdige, die na de geboorte en wel in de eerste twee levensjaren ontstaan, blijken volgens de Griffith's Mental Development Maatstaf van groot belang te zijn.
In **hoofdstuk 5** werden aan de hand van auditieve hersenstam responsies (ABR) de effecten van de maternale en foetale expositie aan in de omgeving

voorkomende schadelijke stoffen bestudeerd. Dit om de nadruk te leggen op de gevaren van deze pesticiden en insecticiden op de ontwikkeling van het auditieve systeem. Deze toxische stoffen werden gemeten in het hoofdhaar van de moeder en de meconium van de neonaten. Er bleek een significant verschil te bestaan tussen de aan deze toxische stoffen geëxposeerde en de niet daaraan geëxposeerde groepen personen, wat als index werd gebruikt om de expositie aan deze toxische stoffen uit te drukken. Het is opmerkelijk dat het gebruik van deze toxische stoffen in Europa al is uitgebannen, terwijl deze insecticiden en pesticiden op commerciële basis in de Filippijnen nog beschikbaar zijn. Propoxur bleek het meest voorkomende toxische stof in dit cohort van moeder-kind koppels.

In **hoofdstuk 6** wordt een kosten-batenanalyse opgesteld voor het algemene bevolkingsonderzoek op neonatale gehoorscreening (NHS) in de Filippijnen om de haalbaarheid van dit bevolkingsonderzoek in financiële zin te achterhalen. De in hoofdstuk 3 gevonden prevalentie van dubbelzijdige aangeboren slechthorendheid/doofheid werden hierbij als grondslag gebruikt. Als kosten werden geteld de kosten van de materiële testuitvoering, de salariële kosten en de overige kosten als gevolg van een verlies aan eigen inkomsten en de hoge kosten van revalidatie vanwege de spraak- en gehoorontwikkeling. Geconcludeerd werd dat aanzienlijke besparingen – ook in de Filippijnen – zullen resteren wanneer een algemeen bevolkingsonderzoek vanwege neonatale gehoorscreening zal worden opgestart.

In ons universitaire centrum in Manilla werden nog 4 andere dan de in dit proefschrift opgenomen originele studies verricht. Een van deze vier studies is de publicatie van Quintos et al. (2003), die meldt dat slechts 8% van de neonaten die eerder onvoldoende resultaat behaalden bij een OAE-test - uitgevoerd in een centrum voor neonatale intensive care - opnieuw voor vervolgtesten verschenen. Aangezien het geografische verwijzingsgebied voor dit neonatale intensive care centrum het geheel van de Filippijnen beslaat, benadrukt deze bevinding nog eens hoe moeilijk het is bij zo een specifieke geografische gegevenheid om een follow-up in deze gehoorscreening zeker te stellen.
Mogelijk zal een algemeen bevolkingsonderzoek in zijn regionale opzet hier effectiever blijken. De in hoofdstuk 4 vermelde bevindingen suggereren dit omdat in die studie 90% van de kinderen jonger dan 9 maanden oud op hun gehoor onderzocht kon worden. Regionale medewerkers in de gezondheidszorg wisten toen de moeders te enthousiasmeren om hun baby's op hun gehoor te laten testen.

In een andere van deze vier bijdragen ditmaal van Tan et al. (2009) worden de uitkomsten van de ABR (Auditory Brainstem Response) na een eerdere negatieve uitslag bij Otoacoustische Emissie test besproken. Bij 85% van hen met een vlakke curve bij hersenstamaudiometrie (ABR) werden toch nog enige responsies gevonden bij de ASSR (Auditory Steady State Response) test. Dit benadrukt nog eens de potentiële waarde van een dergelijke meer frequentie specifieke en robuuste electrophysiologische testmethode om alsnog restgehoor aan te tonen wanneer de ABR geen gehoorresten meer weet aan te tonen. Immers omwille van onkosten (voor eigen rekening) zou anders in dergelijke gevallen een vroege dubbelzijdige hoortoestelaanpassing bij de jonge baby te lang uitgesteld kunnen worden met als later gevolg weer onnodig andere hoge kosten voor gehoor-revalidatie.

De derde van deze vier studies van Garcia et al. (2011) verschaft een kader voor het gebruik van de stemtest (BAAH) als een alternatieve test te gebruiken in combinatie met de risicofactoren - vragenlijst om op geografische afgelegen plaatsen te gebruiken in geval de andere methoden van OAE, ABR en ASSR niet beschikbaar zijn. Op die manier kunnen zo dan tenminste nog meer dan de helft van de vroegkinderlijke slechthorende/dove kinderen vroegtijdig opgespoord worden.

Tenslotte, de vierde van deze vier publicaties, ditmaal van Chiong et al (2013) toont dat slechts 3.3% van de in de Filippijnen met een cochleair implantaat gerevalideerde kinderen met een onbekende oorzaak voor hun vroegkinderlijke doofheid een pathogene mutatie voor GJB2 heeft. Dit roept voor dit moment voor de Filippijnen de vraag op of een genetische screening voor GJB2 (DFNB1) in de Filippijnen wel zinvol is, als de prevalentie van deze oorzaak voor vroegkinderlijke slechthorendheid/doofheid in de Filippijnen werkelijk zo laag is. Voor andere ontwikkelde landen blijkt een dergelijke incidentie als verklaring voor het gehoorverlies (DFNB1) veel hoger (20-50%) te zijn.

Dit proefschrift toont het nut om door een systematische aanpak evidentie te verschaffen om ook in ontwikkelingslanden vroegtijdig vroegkinderlijke slecht-horendheid/doofheid te willen opsporen. Evenzo wordt aangetoond dat een algemeen bevolkingsonderzoek voor neonatale gehoorscreening een goede mogelijkheid is om vroegtijdig vroegkinderlijke slechthorendheid/doofheid op te sporen om aldus een vroege interventie ter revalidatie va het gehoor te bewerkstelligen. Dit kan dus zelfs al ten dele lukken bij gebrek aan de benodigde

technische audiologische infrastructuur en bij gebrek aan audiologisch geschoolde professionals.

De in hoofdstuk 3 en hoofdstuk 5 beschreven bevindingen vormen de basis voor het tot stand brengen van een wet in de Filippijnen, die het landelijk opstarten van een bevolkingsonderzoek voor neonatale gehoorscreening regelt en wel binnen een periode te tellen vanaf nu 5-10 jaar.

Curriculum Vitae

The author was born on 11th June 1961 in Manila. She completed her Bachelors of Science Major in Zoology summa cum laude at the University of the Philippines Diliman in 1981. She received the Dean's Medal of Excellence from the College of Arts and Sciences, the University President's Pin in recognition of academic excellence and was inducted into the Phi Sigma Biological Sciences Honor Society and the Phi Kappa Phi Honor Society. She then finished 4 years of medical studies in the same university as one of the most outstanding graduates in clinical clerkship with a doctorate in medicine degree obtained in 1985. She qualified into the straight internship programme in internal medicine followed by 4 years of otolaryngology-head and neck surgical residency training at the University of the Philippines – Philippine General Hospital, the largest and premiere training institution in medicine in the country. She was awarded Most Outstanding Resident in Otolaryngology in 1990. She became well regarded as an active researcher with a number of her research papers distinguished by awards by the Philippine Society of Otolaryngology-Head and Neck Surgery over the years 1987-2011. A travel bursary with the Japan-Philippine Friendship Programme for young scientists in 1989 and her residency training which was completed in 1990 was followed by a research fellowship in otology at the Massachusetts Eye and Ear Infirmary- Harvard Medical School in Boston, USA under the tutelage of Prof. Dr. Joseph B. Nadol, Jr. then a one year clinical fellowship in neurotology with Prof. Julian Nedzelski at the Sunnybrook Health Sciences Center, University of Toronto, Canada. During these years she published many papers in otology and neurotology-skull base surgery. She returned to the Philippines with an appointment as a Clinical Assistant Professor in 1993 and established an academic practice in the same university hospital where she trained. She obtained her Diplomate in Otolaryngology-Head and Neck Surgery and Fellowship from the Philippine Society of Otolaryngology – Head and Neck Surgery in 1994. She was one of the pioneers of cochlear implantation in the Philippines along with Prof. Wolfgang Arnold in 1997 and did the first bilateral cochlear implantation in 2003 and electroacoustic stimulation in 2008. She was appointed Clinical Associate Professor in the University of the Philippines College of Medicine and later as Research Associate Professor at the National Institutes of Health University of the Philippines Manila. She was named most outstanding researcher in the University of the Philippines Manila in 2002. This was the time when she began her researches on newborn hearing screening and became an advocate for early detection of hearing loss and intervention. In 2004 she and her colleagues from

the Philippine National Ear Institute started collaborating with the Department of Education teaching public school nurses the use of the penlight and the tuning fork for ear examination and hearing screening in school children with about 7-8 million elementary students being examined on an annual basis since 2006 to 2010. Following a number of publications both internationally and locally she was awarded Most Outstanding ENT Professional in Research in 2006 by the Philippine Society of Otolaryngology-Head and Neck Surgery. She was one of five awardees as the Outstanding Filipino Physician in 2007 given by the Jaycee Senate International, the Department of Health and the Philippine Health Insurance Corporation. She was also a recipient of the Dangal ng Lipi Award (Health Category) in 2008. As the founding president of the Philippine Academy of Neurotology Otology and Related Sciences (2006-2012) and a former Vice President and member of the Board of Trustees of the Philippine Society of Otolaryngology and then Deputy Director of the Philippine National Ear Institute she was instrumental in formulating the position paper that formed part of the explanatory note for the filing of a senate bill on Universal Newborn Hearing Screening in the Philippines in 2008 then signed into Republic Act 9709 in 2009. She was given the scientific productivity award as University Scientist I in 2011 and named by the U.P. Medical Alumni Society as Outstanding Educator in 2012. She was also awarded an outstanding alumni award by the Holy Spirit Academy of Malolos for 2012. During the preparation of this thesis she was also appointed as founding director of the National Institutes of Health- Newborn Hearing Screening Reference Center and as Assistant Vice Chancellor for Planning and Development of the University of the Philippines Manila. She is the General Secretary of the Asean Academy of Neurotology Otology and Audiology as well as the Regional Secretary of the International Federation of Otolaryngological Societies (IFOS) for Western Pacific, Southeast Asia and Oceania.

Recently she has been appointed as Vice Chancellor for Planning and Development of the University of the Philippines Manila.

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List of abbreviations

AABR:	Automated Auditory Brainstem Response
ABR:	Auditory Brainstem Response
ANSI:	American National Standards Institute
ASSR:	Auditory Steady State Response
CAP:	Categories of Auditory Performance
CONHSCA:	Collaboration on Newborn Hearing Screening Advocacy
CI:	Cochlear Implantation
DDE:	Dichlorophenyldichloroethylene
DDT:	Dichlorodiphenyltrichloroethane
DPOAE:	Distortion-Product Otoacoustic Emissions
EOAE:	Evoked Otoacoustic Emissions
EHDI:	Early Hearing Detection and Intervention
EVA:	Enlarged Vestibular Aqueduct
FM:	Frequency Modulated
GDP:	Gross Domestic Product
GJB2:	Gap Junction Beta 2
GMDS:	Griffith's Mental Development Scales
GNI:	Gross National Income
HDI:	Human Development Index
HRR:	High Risk Registry
IPL:	Interpeak Latency
JCIH:	Joint Committee on Infant Hearing
NHS:	Newborn or Neonatal Hearing Screening
NICU:	Neonatal Intensive Care Unit
OAE:	Otoacoustic Emissions
PCHL:	Permanent Congenital Hearing Loss
PEACH:	Parent Evaluation of Oral/Aural Performance in Children
SNHS:	Selective Newborn Hearing Screening
TNHS:	Targeted Newborn hearing Screening
UNDP:	United Nations Development Program
UNEP:	United Nations Environment Program
UNHS:	Universal Newborn Hearing Screening
USPSTF:	United States Preventive Services Task Force
WHO:	World Health Organization