# HOSPITAL-BASED IMPLEMENTATION OF NEWBORN HEARING SCREENING IN A COHORT OF INFANTS ADMITTED TO THE NICU: OUTCOMES AND IMPLICATIONS FOR POLICY AND PRACTICE

A Dissertation

by

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# ABSTRACT

Hearing loss affects approximately 1-3 live births per 1,000. Infants admitted to the NICU are at greater risk of hearing loss than infants in the newborn nursery. Family history, as well as very low birth weight and exposure to certain therapies such as assisted ventilation, are also risk factors associated with hearing loss. Many states mandate newborn screening for hearing loss after birth due to evidence that early diagnosis and intervention improve communication skills and school performance, but following these infants over time can be challenging.

This retrospective study describes temporal trends in primary screening outcomes including screening rates, loss to follow-up, and screen sensitivity and specificity. It also evaluated the likelihood of newborn hearing screening, loss to follow-up, false-positive and false-negative results, as well as hearing loss diagnosis among at-risk infants. Time-to-diagnosis for infants with and without screening was also assessed. The study utilizes a database of births and follow-up encounters for infants born in a large Texas integrated health system between 1996 and 2007.

Most newborn hearing screening program outcomes have improved since implementation in 1996. Outcomes differ by group, with black infants having higher probabilities of being lost to follow-up and receiving a false-positive result, but a lower probability of hearing loss than the overall study population. Infants diagnosed with persistent pulmonary hypertension had a higher probability of a false-negative result. Infants with craniofacial anomalies and neonatal infections have 5-7 times higher

probability of hearing loss than those without the diagnoses. The overall incidence of hearing loss among the study population was 5%. Survival estimates demonstrate that infants identified through screening have a higher probability of early diagnosis. Infants with false-negative screens have the same probability of early diagnosis as infants with no screen.

The study findings can inform both policy and practice. Newborn hearing screening leads to earlier diagnosis of infants with hearing loss, but improving targeted follow-up of high risk NICU infants may lead to earlier diagnosis of infants with delayed onset of hearing loss. Community-based providers can monitor high risk NICU infants after discharge for potential hearing loss.

# DEDICATION

I dedicate this dissertation to my family. Thank you for your encouragement and support of my ongoing desire for knowledge, and for always pushing me to do the best I can while still helping others. To my grandfather, Gordon C. Creel, PhD – I wish you were here to see this and to help me decipher Latin words.

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# CHAPTER I

# INTRODUCTION

Hearing loss affects approximately 1-3 live births per 1,000.[1] Early diagnosis of and intervention for hearing loss is critical since early intervention is linked to improved communication outcomes and school performance.[2-7] There are two types of hearing loss, conductive and sensorineural. Conductive hearing loss is caused by problems in the middle or outer ear.[8, 9] As an example, conductive hearing loss can be caused by a buildup of fluid within the middle ear, which is common in neonates. Conductive hearing loss can be reversible and may even resolve without treatment.[9] Alternatively, sensorineural hearing loss is caused by damage to the nerve endings that detect sound in the ear and is typically permanent.[8, 9] Either type of hearing loss can occur in one or both ears and may be congenital, syndromic, or nonsyndromic.[9] Infants and children may also be affected by a mix of both conductive and sensorineural hearing loss.[9] Hearing loss can also be progressive or have delayed onset.[8]

Infants admitted to the NICU are at greater risk of hearing loss than infants in the newborn nursery.[10] Family history, as well as very low birth weight and exposure to certain therapies such as assisted ventilation, are risk factors associated with hearing loss.[10] The US Preventive Services Task Force (USPSTF), the Joint Committee on Hearing (JCIH), and the Secretary's Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (SDACHDNC) have all recommended universal

newborn hearing screening,[1, 10, 11] due to the associated risks, the availability of screening technology, and efficacy of treatment options.[1]

Texas mandated universal newborn hearing screening in 1999[12] and HB 411 modified the newborn hearing screening program from an opt-in to an opt-out program in 2011.[13] HB 411 also outlined the process for follow-up of infants with a positive screen in 2011.[13]

In 2011, the Texas Early Hearing Detection and Intervention (TEHDI) program reported that 58.2% of newborns, infants, and children that needed follow-up care after newborn screening received such care.[14] This leaves 40.8% of children that were lost to follow-up due to: 1) truly not receiving any follow-up services, or 2) receiving services that were not reported to the TEHDI program.

This study evaluates hospital-based implementation of newborn hearing screening before and after the passage of HB 411. This study is a longitudinal, retrospective database analysis of health and development of infants admitted to the NICU after birth, a special population of children with unique needs and utilization patterns. Analyses are performed using a highly comprehensive database of birth admissions over the period 1988-2009, from a large single health care system in Texas, serving an ethnically and racially diverse rural and exurban population. This database contains key data from admission to discharge as well as linked diagnosis data from follow-up encounters through 2013. This database of over 50,000 infants, including more than 9,000 NICU admissions. Seventy-eight percent of infants admitted to this

NICU have associated follow-up encounters within the same health system available for analysis.

The primary outcomes of interest in the study are overall screening rates, loss to follow-up rates, screen sensitivity (and related false-negative rate), screen specificity (and related false-positive rate), and time-to-diagnosis for infants with hearing loss, adjusted for infant characteristics and clinical factors postulated as predictors of the outcomes. The specific aims and related hypotheses for the study include:

**Specific Aim 1: Describe existing database systems established to monitor and evaluate treatment of and outcomes in premature and low birth weight infants.**

Research questions: What current large-scale databases exist to allow research and quality improvement in treatment of premature and low birth weight infants? How do these compare with a single center database?

**Specific Aim 2: Assess temporal trends in screening rates, loss to follow-up, and test sensitivity and specificity after implementation of newborn hearing screening, and evaluate the likelihood of newborn screening, loss to follow-up, a false-positive result, a false-negative result, and hearing loss adjusting for infant characteristics and clinical factors.**

Hypothesis 1: Changes in policy and clinical practice improve newborn screening rates, loss to follow-up, and test sensitivity and specificity.

Hypothesis 2: The likelihood of receiving a newborn hearing screen, being lost to follow-up, receiving a false-positive screen result or false-negative screening results, and

receiving a diagnosis of hearing loss vary based on infant characteristics and clinical factors.

**Specific Aim 3: Evaluate time-to-diagnosis for infants that receive a positive screen result prior to hospital discharge, and identify correlates of earlier diagnosis.**

Hypothesis: Time-to-diagnosis is earlier in infants that receive a positive newborn screen, but still varies by group (e.g. race/ethnicity).

In Chapter II below, I summarize the existing literature related to infant and childhood hearing loss, universal newborn hearing screening recommendations and the program in Texas as well as the health system in which this study occurred, and the history of and challenges in studying outcomes for infants at high-risk of hearing loss and other developmental outcomes. Chapter III describes the methodology utilized to test the hypotheses described above. Chapters IV and V include the study results and a discussion of the findings and related implications for policy and practice.

# CHAPTER II

# LITERATURE REVIEW

This chapter summarizes the existing literature and research on hearing loss in infants and children. It also describes early detection of hearing loss and the efforts of state newborn hearing programs, recommendations for early intervention and hearing loss diagnosis, and known challenges in the long-term study of infants at greater risk of hearing loss.

## Risk Factors Associated with Hearing Loss

Risk for congenital, delayed onset, or progressive hearing loss in childhood may be increased by any of the following:[10] (a) family history, (b) NICU admission greater than five days or any of the following treatments within the NICU, regardless of length of stay – ECMO, assisted ventilation, exposure to ototoxic medications or loop diuretics, and hyperbilirubinemia, (c) in utero infection, (d) craniofacial anomalies, (e) physical findings associated with syndromes known to include hearing loss, (f) presence of certain syndromes associated with hearing loss, (g) neurodegenerative disorders, (h) post-natal infections such as bacterial meningitis, (i) head trauma, and (j) chemotherapy. The relative risk of each of these factors varies by study, however. Several recent studies have focused on examining the incidence of these risk factors in children with hearing loss[15-19]. Among these studies there is an inconsistency in results, suggesting that further study is necessary to fully understanding the contribution of certain risk factors to hearing loss in the first several years of life.

### *Infant and Maternal Characteristics Affecting Hearing Loss*

Other infant and maternal characteristics may also influence an infant's risk of hearing loss. Family history is a known risk factor for hearing loss.[10] Up to half of all hearing loss is attributable to genetic factors causing syndromes associated with hearing loss or increasing susceptibility to environmental factors that may cause hearing loss.[20] Studies suggest that the prevalence of hearing loss in children under the age of 20 may be higher in Hispanic infants and those in lower income households, but studies measuring these differences vary in design and study population.[21] Naarden and Decoufle found that low birth weight infants, specifically those born at less than 2,500 grams had a higher prevalence of bilateral sensorineural hearing loss, and that rates of hearing impairment were consistently higher among low birth weight black children compared to low birth weight white children.[22] Finally, NICU infants may be particularly susceptible to delayed-onset hearing loss.[23]

### *NICU Interventions Affecting Hearing Loss*

There are many advances in neonatology that have improved outcomes for infants born premature and/or at low birthweight. These infants have complex medical conditions and comorbidities associated with prematurity, respiratory distress for example, that significantly increase risk for mortality and morbidity. Technological interventions used to treat these infants in the NICU, such as assisted ventilation and extracorporeal membrane oxygenation (ECMO) therapy, have led to decreased mortality among low birth weight infants, but significant morbidities including hearing loss persist. In fact, an increased incidence of hearing loss among infants admitted to the

NICU has been observed.[24] The following sections summarize both assisted ventilation and ECMO therapy in an effort to demonstrate the effectiveness of new NICU interventions and their potential to increase the likelihood of hearing loss in infants admitted to the NICU. These examples were chosen since they are used to treat respiratory distress, which affects up to 7% of newborns and has a high incidence in preterm infants.[25] This current study focuses on implementation and outcomes of newborn hearing screening within a population of NICU infants and, therefore, a brief discussion of two associated risk factors is relevant.

The potential causes of respiratory distress include underdevelopment of the lungs, surfactant deficiency, transient tachypnea, infections, meconium aspirations syndrome, respiratory distress syndrome (hyaline membrane disease), and birth asphyxia.[25, 26] Among preterm infants, respiratory distress syndrome accounts for up to 30% of respiratory distress and may represent the greatest risk for mortality.[25] Treatment of respiratory distress varies depending on severity. Antenatal corticosteroids, surfactant administration, oxygenation, and, in severe cases, mechanical ventilation or ECMO are potential treatments.[26] Both assisted ventilation and ECMO are treatments primarily utilized in the NICU, and each is a known risk factor for hearing loss. Each of these neonatal treatment advances and their importance to studies of newborn hearing loss are described below.

**Assisted Ventilation**

Despite significant improvements in morbidity and mortality after the introduction of surfactant and increased use of antenatal steroids, the need for respiratory

support remains high among preterm infants.[27, 28] Assisted ventilation allows for the provision of respiratory support to infants who are unable to breathe well on their own. Assisted mechanical ventilation was first introduced in the 1960s and now includes a variety of mechanisms for ventilation, some more invasive (e.g. requiring intubation) than others.[28] Mechanical ventilation does have risks, including lung injury, pneumonia, chronic lung disease (including bronchopulmonary dysplasia), and mortality.[29, 30]

Limited population-based epidemiologic data exists on ventilation strategies and outcomes. However, the NICHD Neonatal Research Network has collected data on premature and low birth weight infants for over two decades and has been used for epidemiologic study. Among very low birth weight infants, the length of ventilation using intubation techniques has decreased over time as has the percent of infants with respiratory distress syndrome, although respiratory distress syndrome remains particularly high among extremely low birth weight infants (500-1000g).[31] Over the same time, mortality before discharge has decreased (although this study does not link decreased mortality to respiratory treatment improvements specifically) but morbidities such as bronchopulmonary dysplasia have not changed.[31]

Several studies have found possible associations between assisted ventilation and hearing loss in patients with congenital diaphragmatic hernia, although the incidence of hearing loss varied significantly by study.[32-34] In a Dutch study of risk factors for hearing loss in NICU graduates born at less than 30 weeks gestational age or with a birthweight less than 1000g, the authors found a significant association between assisted ventilation

of at least five days and hearing loss.[35] Similarly, a study from China found that NICU admission along with assisted ventilation was a risk factor for hearing loss.[36]

**Extracorporeal Membrane Oxygenation**

In extreme cases of neonatal respiratory distress, ECMO may be used as a mechanism for external life support. ECMO was first used successfully in 1976.[37] ECMO is used to bypass the heart and lung while maintaining respiratory function and blood oxygenation.[38] Clinical indications for ECMO include congenital diaphragmatic hernia, heart malformations, meconium aspiration syndrome, severe pneumonia, severe air leak syndrome, and severe pulmonary hypertension.[37, 38] ECMO is not indicated for very preterm or low birthweight infants. In most cases, infants with gestational age less than 34 weeks or birth weight less than 2000g are not candidates for ECMO, due to increased risk for and incidence of intracranial hemorrhage.[37]

ECMO use has declined since 1990, especially among patients with respiratory distress syndrome and sepsis or pneumonia.[37] Infants eligible for ECMO treatment are already at extreme risk for death given their underlying medical conditions, but additional risks associated with ECMO treatment include bleeding, due to the use of heparin, blood clot formation, intracranial hemorrhage, infection, and transfusion problems.[38] In the long-term, infants treated with ECMO may experience neurodevelopmental disorders such as cerebral palsy.[39] Despite these risks, approximately 77% of ECMO patients survive although this varies by condition for which ECMO was indicated.[37] A 2008 systematic review of ECMO trials found that use of ECMO provides strong benefit for infants in terms of mortality and decreased

likelihood of severe morbidity.[40] A cost-effectiveness study using data from the United Kingdom Collaborative ECMO Trial found that ECMO is cost-effective compared to conventional management.[41]

Associations between ECMO, and prolonged ECMO treatment, and hearing loss also appear to be positive.[42-44] Infants undergoing ECMO therapy demonstrate a greater risk of hearing loss, possibly associated with low levels of carbon dioxide in the blood prior to ECMO.[39] There is some evidence that ECMO therapy, especially, can result in delayed onset of hearing loss.[42-44] For example, one study found that approximately half of infants identified with sensorineural hearing loss after ECMO therapy has previously passed a hearing test.[42] Due to the potential for delayed onset, the JCIH has recommended additional audiologist assessment for infant with these risk factors, ideally between 24 and 30 months of age.[10]

Both neonatal technologies (assisted ventilation and ECMO) have an impact on early screening and, potentially, long-term outcomes related to hearing. Both technologies are used to save infant lives, thus leading to more infants living for a longer period of time. However, assisted ventilation and ECMO may also induce unfavorable long-term outcomes such as hearing loss. It is not clear whether or not treatment for respiratory distress or the underlying cause of respiratory distress (e.g. poor lung function which limits oxygen intake) actually lead to increased risk for hearing loss. Nonetheless, assisted ventilation and ECMO appear to be good indicators of risk for hearing loss, and there is enough evidence to warrant recommendations for universal

screening with targeted follow-up assessments for infants undergoing either treatment in the NICU.[1, 10]

## Universal Screening Programs

Early identification of and treatment for hearing loss is important for preventing and improving long-term problems with speech, language, and/or communication.[2-7] Treatments include interventions such as hearing aid placement and cochlear implants to provide amplification, as well as speech therapy. Early intervention using these treatments, or others as indicated, may also improve school performance.[7, 45]

In response to the growing body of evidence demonstrating the importance of early intervention, newborn screening for hearing loss has become prevalent across the United States and internationally. The US Preventive Services Task Force (USPSTF), the Joint Committee on Infant Hearing (JCIH), and the Secretary's Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (SDACHDNC) have all recommended universal newborn hearing screening.[1, 10, 11, 46] Most states, including Texas, have mandated universal newborn hearing screening or, if the state does not mandate screening, report high rates of screening for infants.

Newborn screening involves both biochemical screening tests using a small amount of blood taken from a newborn after birth and tested by the state, and point-of-care tests where technology is used at the bedside to screen for disorders such as hearing loss or critical congenital heart defects. In point-of-care screening, a technician, nurse, or other professional performs and interprets the screening result. There are two types of technologies typically used in universal newborn hearing screening programs,

otoacoustic emission testing (OAE) and auditory brainstem response testing (ABR). OAE testing relies on obtaining responses from the cochlea when sound is presented, while ABR is used to detect electrographic activity of sound as it moves along the auditory brainstem.[9]

In newborn screening, legal mandates, clinical practice guidelines, and screening technologies influence program administration, including documentation of follow-up, and clinical practice. The following paragraphs summarize laws, clinical practice guidelines, and changing screening technologies that have or may influence early detection of hearing loss.

Texas mandated universal screening in 1999 through House Bill 714, but the program did not require participation for hospitals with less than 1,000 births per year and required parents to opt-in to the screening with written consent.[12] The bill required full implementation by April 1, 2001, required informed consent from the parents, and outlined no specific protocols for screening infants admitted to the NICU. The bill also required birthing facilities that performed newborn hearing screening to report the screening results to parents, the newborn's physician, and the state health department.

In 2011, the Texas Legislature amended Chapter 47 of the Health and Safety Code with House Bill 411 to change the program to no longer require informed consent, thus mandating hearing screening unless the parents choose not to participate. Additionally, HB 411 specifically outlined the follow-up protocols and the responsibilities of both the state and birthing facilities.[13] The time frame of this study

does not allow for measuring outcomes after implementation of HB 411; however, its relevance to the study is important in terms of continued investigation.

The Joint Committee on Infant Hearing (JCIH), through its periodic statements, has recommended specific time frames within which infants should be screened, receive confirmatory testing, and receive intervention services.[10] In addition, the JCIH has recommended separate screening protocols for infants admitted to the NICU versus infants admitted to the well-baby nursery.[10] These practice guidelines are often disseminated through the peer-reviewed literature or professional meetings and may influence clinical practice before and after legal mandates require such practice. For example, the first JCIH statement on infant hearing screening was issued in 1995 through the journal *Pediatrics*.[47] The health system included in this study began newborn hearing screening, albeit not universally, in 1996, three years prior to HB 714 passing in Texas.

Birthing centers also make relevant organizational decisions or policies that influence screening outcomes. The health system in which this study was performed made decisions regarding staff training and use of specific screening protocols. We know from physicians working within the health system at the time that somewhere around the year 2001, the organization recognized a pattern of high false-positive rates. As a result, they implemented a staff training program to improve not only the screening protocol used but also interpretation of results.

Similarly, screening program outcomes may be impacted by the screening technology used to perform the hearing screen. In 2007, the JCIH recommended that

NICU infants be screened using ABR since their risk for hearing loss is greater than for non-NICU infants and the ABR testing methodology may be more sensitive to detecting the types of hearing loss for which NICU infants are at greatest risk.[10] In the health system where this study took place, we know that the change to ABR screening in the NICU occurred prior to 2007, but the exact date is unknown.

This study will look specifically at the timing of these policy mandates and organizational changes to identify whether or not they influenced screening program outcomes including screening rates, false-positive rates, and false-negative rates. Unfortunately measurement of the program effects of changing screening technology is not possible since the available records do not differentiate between screening technologies. However, this contextual information may help to explain results. In addition, the study looks at infant characteristics impacting the likelihood that an infant receives hearing screening, receives a false-positive result, or receives a false-negative result. Evaluation of screening program outcomes is important for quality improvement at the organizational-level and for informing future organizational and policy changes that impact hospital-based screening efforts. Success of screening programs, however, should not be measured solely at the point of intervention but should look at outcomes of the program after the infant leaves the hospital, where they presumably receive follow-up services to confirm a diagnosis of hearing loss and to treat the hearing loss if confirmed.

## Follow-up after a Positive Hearing Screen

Beyond screening for hearing loss, state programs are tasked with providing or ensuring follow-up for infants that fail the hearing screen. These follow-up services include confirmatory testing and enrollment in early intervention programs. Historically, newborn hearing screening programs have a high number of infants "lost to follow-up," ranging from approximately 35-45 percent from 2009 to 2012.[48] Other reports indicated that the rate of loss to follow-up may be as high as 50% of all infants with a positive hearing screen, but this includes both infants that do not receive follow-up services and those that are lost to documentation, meaning that the receipt of follow-up services is not documented and therefor the status of those infants is unknown.[49] In 2011, the Texas Early Hearing Detection and Intervention (TEHDI) program reported that 58.2% of newborns, infants, and children that needed follow-up care after newborn screening in Texas received such care.[14] This results in 40.8% of children that were lost to follow-up. Lower rates of loss to follow-up lead to an increasing number of infants with hearing loss being identified[50] and, presumably, receiving intervention services earlier.

A 2008 technical report issued by the American Speech-Language-Hearing Association described a systematic review of existing literature on factors associated with loss to follow-up. The working group that prepared the report cited three potential areas in which issues can arise that impact loss to follow-up, including systems issues such as communication between providers, family issues such as socioeconomic status, and quality assurance issues such as electronic systems for reporting follow-up status.[51]

Most relevant to this study are the individual-level factors that may influence receipt of follow-up services.

Several studies have examined the demographic and socioeconomic factors affecting whether infants receive follow-up services. Texas does not, at least publicly, report on loss to follow-up or enrollment in early intervention services by demographic or socioeconomic characteristics. However, a 2002 study from the Houston area compared newborn hearing screening and follow-up services at two centers, one serving a primarily indigent population and the other serving primarily private pay and Medicaid patients. The study found that infants born at the center serving mostly indigent patients were more likely to be lost to follow-up and less likely to be fitted for a hearing aid when one was indicated.[52]

The Centers for Disease Control and Prevention (CDC) produces an annual report on state newborn hearing screening and early intervention programs. Using their 2011 survey, demographic data indicate that the percentage of infants evaluated after a failed newborn hearing screen increased with increasing maternal age and increasing maternal education.[53] The percentage of infants evaluated after a failed newborn hearing screen varied by race/ethnicity, with infants of mothers of American Indian or Alaska Native and White Hispanic race/ethnicity having the lowest percentage.[53] The percentage of infants enrolled in early intervention services increased with increasing maternal age and increasing maternal education, but that it also varied slightly by race and ethnicity.[54]

A study of the Massachusetts newborn hearing screening follow-up program, which is statewide and multi-center, found that infants were more likely to be lost to follow-up if their mothers were non-white, received public insurance, smoked during pregnancy, or lived outside of the urban center (Boston).[55] Even though this study found that living outside of the urban center was a risk factor for being lost to follow-up, they found that living in or near the urban center actually decreased the odds of receiving early intervention services.[55]Other studies have found that socioeconomic factors, such as public insurance, decrease the likelihood of follow-up,[56-58] as well as infant race, infant birth weight, infant gender, and ventilator status.[51]

The potential for delayed onset hearing loss means that some infants may not screen positive for hearing loss during the newborn period, thus increasing the likelihood of a false-negative at the first newborn screen. To be fair, this probably should not be counted as a false-negative since, presumably, the disease may not have developed prior to screening. Rather, this demonstrates the importance of targeted follow-up for infants with known risk factors. Although targeted follow-up is recommended by JCIH, the high lost to follow-up rates in state newborn screening program create a challenge for following infants through diagnosis and intervention.

Future research on the etiology of newborn and childhood hearing loss is essential to improving screening, whether population-based or targeted, and long-term outcomes. Screening programs are currently focused on the newborn period and the potential for delayed onset may indicate a need to expand the scope of state newborn screening programs. Neonatal interventions such as ECMO are designed to decrease

mortality but may also be increasing morbidity, indicating a need for continued investigation into the pathophysiology by which clinical treatment causes hearing loss. This information may help researchers and providers identify clinical treatment modifications that reduce risk for hearing loss, and may assist screening programs in identifying appropriate time points for screening evaluations.

*Recommended Protocol for Newborn Hearing Screening and Follow-up*

The JCIH and the Centers for Disease Control and Prevention recommend a specific protocol for newborn hearing screening, and use this protocol to set national benchmarks for both quality improvement and Healthy People 2020. The protocol, titled "1-3-6," is as follows:[10, 59]

1. Infants will receive newborn hearing screening before 1 month of life.
2. Infants that fail the newborn hearing screen will receive audiologic evaluation by 3 months of age.
3. Infants that have confirmed hearing loss should be fit for amplification (if desired by the family) within 1 month of diagnosis.
4. Infants with confirmed hearing loss should be enrolled in early intervention services by 6 months of age.

States, including Texas, manage early intervention programs to assist families in enrolling infants into services that help with the child's speech, language, and social skills. This also includes connecting parents with other families affected by hearing loss. Additionally, the JCIH recommends that infants with risk factors associated with hearing loss, e.g. NICU admission, be monitored for hearing loss by their primary care

physician.[10] NICU follow-up clinics, where available, may also perform these hearing assessments.

There are group differences in receipt of follow-up services. Previous studies have examined time-to-treatment performance within systems. Sininger, et. al. found that infants that received newborn hearing screening received diagnosis of hearing loss, were fitted for a hearing aid, and were enrolled in early intervention earlier than infants not receiving a newborn hearing screen.[60] Spivak, Sokol, Auerback, & Gershkovich looked at referral for evaluation and fitting of hearing aids and found that less than one half of all infants were fit for a hearing aid on time (by 6 months of age).[56] They also found associations between unilateral hearing loss and late diagnosis and late hearing aid fitting as well as loss to follow-up; and conductive hearing loss and Medicaid coverage and an infant being lost to follow-up.[56] Knowledge of these differential effects of infant factors can inform future efforts to improve services delivery after newborn screening.

## Studying At-Risk Populations

Infants admitted to the NICU and specifically infants with LBW are at increased risk for hearing loss and other short- and long-term morbidities. Studying of the impacts of prematurity and LBW is challenging due to the relatively small number of infants born with prematurity and/or LBW, and the difficulty in following those infants long-term.

Each year, prematurity and LBW impact a small but significant proportion of all live births in the United States. In the United States and internationally, improving outcomes for these infants remains a high priority. Healthy People 2020 includes

objectives to reduce LBW and premature births.[61] These objectives include targets to reduce overall preterm births from 12.7% to 11.4% as well as specific objectives to reduce both very preterm and late preterm births by ten percent, and to reduce the number of LBW (8.2 to 7.8%), and very LBW (VLBW) infants (1.5 to 1.4%).[61]

In the United States, overall infant mortality has declined from 100 per 1,000 live births in 1900 to 6.05 per 1,000 births in 2011[62] while remaining one of the highest infant mortality rates among industrialized countries.[63] The development of medical and technological interventions has improved the survivability of premature and LBW infants. From 2000 to 2010 the infant mortality rate among preterm infants decreased from 37.88 deaths under age 1 per 1,000 live births to 34.22 per 1,000 live births, a decrease of almost 10 percent.[64] For infants born under 32 weeks, the mortality rate decreased almost eight percent from 2000 to 2010, from 180.95 per 1,000 live births to 165.57 per 1,000 live births.[64] While overall infant mortality rates have decreased, they are still comparatively high and short- and long-term morbidities associated with prematurity and LBW have persisted.[64, 65] There are a number of potential morbidities that affect nearly every organ system and include conditions such as poor neurodevelopmental outcomes, retinopathy of prematurity, severe intraventricular hemorrhage, hearing loss, bronchopulmonary dysplasia, respiratory distress syndrome, patent ductus arteriosus, necrotizing enterocolitis, and sepsis are associated with LBW and prematurity. These outcomes may be complicated by interventions to improve mortality such as ventilation[65-73], transfusions and catheters - common interventions provided during a typical neonatal intensive care unit (NICU) hospitalization.

Monitoring both short- and long-term outcomes of infants affected by preterm birth, LBW and VLBW is critical to advancing scientific and medical knowledge with respect to the development of more effective treatment guidelines, to improve quality of these treatments over time, and to minimize short- and long-term morbidities. Effective research can also inform integrated health care practices where surviving infants are treated through childhood and even into adulthood. However, studying infants affected by prematurity or LBW can be challenging due to small, single-center sample sizes, unknown quality of some administrative data, or limited availability of long-term follow-up data.

To address these challenges, a number of large-scale databases were developed to allow structured study of premature and LBW infants, including but not limited to those admitted to the NICU. In 1997, Wright and Papile summarized existing neonatal databases and their uses.[74] Their review provided detailed descriptions of four neonatal databases: the Kaiser Permanente Neonatal Minimum Data Set (KPNMDS), the Vermont Oxford Network (VON), the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NICHD NRN), and the National Perinatal Information Center (NPIC). Since 1997, there have been tremendous advances in neonatal care that have contributed to declines in infant mortality associated with prematurity or LBW, including the use of high-frequency ventilation and cooling caps. These clinical improvements are accompanied by an increasing number of studies aimed at evaluating neonatal intervention, understanding

the progression of disease, and investigating outcomes of those infants affected by prematurity or LBW.

*Existing Databases*

Of the four originally described by White and Papile, we are reviewing research progress using three, KPNMDS, NICHD NRN, and VON. The National Perinatal Information Center was not included in our review as their focus is on the perinatal period and not premature or LBW infants. The three databases have varying program goals, funding sources, strategies for data collection, and length of follow-up, but all focus on improving medical knowledge about and the quality of care provided to premature, LBW, and NICU admitted infants.

The Kaiser Permanente Neonatal Minimum Data Set (KPNMDS) originated in 1992 and is internally funded through the Kaiser Permanente (KP) system.[75] The KPNMDS was developed to obtain reliable data about the NICU admission, and to support research and quality improvement efforts. The database includes both inborn and outborn admissions to at least six KP NICUs in Northern California, although the total number of NICUs participating in KPNMDS has increased since Wright and Papile described the database in 1997. The KPNMDS includes data on the full NICU admission, and some prospective studies using KPNMDS data extend follow-up for months or years after discharge from the NICU. The primary criterion for inclusion in the database is NICU admission, not a specific birth weight or gestational age. KPNMDS supports both retrospective and prospective studies.

The Vermont Oxford Network (VON) originated in 1989 and seeks to "improve the quality and safety of medical care for newborn infants and their families through a coordinated program of research, education, and quality improvement projects."[76] VON maintains two international databases, the Very Low Birth Weight Database and the Expanded Database, with a total of over two million infant cases.[76] The Very Low Birth Weight Database includes inborn and outborn (if admitted within 28 days of birth) infants with birth weights below 1500 grams or gestational ages between 22 weeks 0 days and 29 weeks 6 days.[77] The Expanded Database includes all infants from the Very Low Birth Weight Database as well as infants born at more than 1500 grams and admitted to a NICU at a participating center, or "who die at any location in the center within 28 days of birth without first having gone home."[77] In 2012, VON reported 369 centers reporting data on 153,093 infants into the Expanded Database, and 909 centers reporting data on 60,007 infants into the VLBW Database.[77] VON members pay an annual membership fee and are eligible to use the data for studies, given strict adherence to data use guidelines set forth by VON leadership.[78] In general, VON includes infant data through discharge, death, or one year of age although some prospective studies using VON have longer follow-up periods. VON supports both retrospective and prospective studies. NICUs may apply to participate in VON using a membership application and must pay a membership fee.

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) began in 1986 and includes a registry to house data from multiple clinical trials funded through NICHD. NICHD

supports the NRN financially. Orginally, the NRN registry included data for inborn and outborn infants having a birth weight between 401 and 1500 grams.[74] Since 2008, the database has included only inborn infants with a gestational age between 22 0/7 to 28 6/7 weeks and/or a birth weight between 401 grams to 1000 grams.[79] It also includes follow-up data at 18-26 months, depending on the year of study and if the participating study site(s) assessed outcomes at such age as part of their research protocol.[74, 79] As of August 1, 2014, the NRN website listed 20 participating sites.[80] NICHD NRN supports both retrospective and prospective studies, specifically clinical intervention and epidemiologic studies funded through NICHD. Participation in the NICHD NRN requires funding through NICHD, which is typically provided through a competitive grant process.

All three databases use standardized forms and definitions for data submission by participating sites. In general, data use is open to participating sites contributing data to the database as long as database-specific requirements are met.

These databases have continued to expand and become more widely used since they were first reviewed in 1997. In the systematic review described under Specific Aim 1, I seek to provide a summary of how the databases are being used to advance scientific and clinical knowledge about the epidemiology of prematurity and LBW and the clinical treatment of those infants, in an effort to characterize the probability of using one of these databases to study screening for and diagnosis of newborn hearing loss. A further purpose is to offer clinical and health services researchers insight into how research on

preterm and LBW infants has evolved, and to offer strengths and opportunities for continued research using these and other databases.

# CHAPTER III

# METHODS

This study focuses on three specific aims, as outlined in Chapter 1. The description of methodology employed for each is described below.

## Specific Aim 1

**Specific Aim 1: Describe existing database systems established to monitor and evaluate treatment of and outcomes in premature and low birth weight infants.**

Research questions: What current large-scale databases exist to allow research and quality improvement in treatment of premature and low birth weight infants? How do these compare with a single center database?

Specific Aim 1 is motivated by the need to understand how existing, multi-center databases have been used to study the epidemiology of and outcomes for infants affected by LBW and prematurity. To achieve this, we employed a systematic review process to identify and characterize studies that have utilized data from one of three databases. The three databases of interest in the review are the Kaiser Permanente Neonatal Minimum Data Set (KPNMDS), the Vermont Oxford Network (VON), and the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network (NICHD NRN).

We conducted a literature search using PubMed and Google Scholar of studies published over the time period January 1990 to August 15, 2014. Search terms included official names for each of the databases and their abbreviations, if applicable. For

example, the Kaiser Permanente Neonatal Minimum Data Set was searched for using the full name as well as “KP Neonatal Minimum Data Set” and “Kaiser Permanente Neonatal MDS.” None of the databases were searched for simultaneously, although several studies were returned during separate database searches.

Article titles and abstracts were reviewed for inclusion in our study. Initial inclusion criteria only required that the article include the name of one of the three databases and there was some evidence from the abstract that the study used or participated in the database network. Initial results were compared with publication lists maintained by the database managers. Both VON and NICHD NRN maintained such lists, which were last reviewed on August 15, 2014. In both cases, additional studies were added into our review.

After title and abstract review, all articles were read to determine if the study used the database of interest as a data source for measuring the research question. The database could be used as a primary source of data or as a source of comparison or benchmark data. If either condition was true, the article was included in our study. Exclusion criteria included the following: descriptive articles summarizing database use or methodology, articles using similar but tangential databases such as the VON Encephalopathy Registry or Moderately Premature Infant Project database, articles referencing only definitions or tools (e.g. SNAP-II and SNAPPE-II) derived from or used within one of the databases, studies evaluating instrumentation or measurement technology, studies evaluating quality improvement processes implemented at study

sites participating in one of the database networks, review articles or meta-analyses, and non-English articles.

Studies were categorized as having either a retrospective or prospective study design. Retrospective studies were further sorted into categories based on use of the database as a primary data source or using it or its published findings as a comparison or benchmark for another study. A primary and secondary clinical focus area was also assigned to each individual study, in an effort to determine trends in research. To capture the overall clinical or outcome focus of the study, clinical focus area categories were applied first by the primary investigator, then reviewed by three other investigators for consistency.

The outcomes from Specific Aim 1 were reviewed when identifying and assessing the data source for the analyses in Specific Aims 2 and 3. The data elements of each database, as well as their stated length of follow-up on infants, were also considered. These factors were used to justify use of the single-center, longitudinal database used to analyze the hypotheses under Specific Aims 2 and 3.

## Specific Aim 2

**<u>Specific Aim 2:</u> Assess temporal trends in screening rates, loss to follow-up, and test sensitivity and specificity after implementation of newborn hearing screening, and evaluate the likelihood of newborn screening, loss to follow-up, a false-positive result, a false-negative result, and hearing loss adjusting for infant characteristics and clinical factors.**

Hypothesis 1: Changes in policy and clinical practice improve newborn screening rates, loss to follow-up, and test sensitivity and specificity.

Hypothesis 2: The likelihood of receiving a newborn hearing screen, being lost to follow-up, receiving a false-positive screen result or false-negative screening results, and receiving a diagnosis of hearing loss vary based on infant characteristics and clinical factors.

The study under Specific Aim 2 utilizes a retrospective database of NICU and newborn nursery admissions over the period 1989 to 2009, from a large single health care center in Texas. This database contains key data from admission to discharge, including the date of the newborn hearing screen and the bilateral hearing screen results. For infants with at least one NICU admission, records are linked to the inpatient and ambulatory electronic medical record (EMR) in the same health system, allowing for detailed follow-up information regarding diagnoses received and morbidities these infants face as they mature through childhood. This database houses information on 51,244 infants, including 9,219 infants with at least one NICU admission. Seventy-eight percent (78%) of all infants with a NICU admission have associated post-discharge follow-up encounters available for analysis. There is a mean of ten years of follow-up data on each infant for which follow-up is available. All patient and treatment factors as well as diagnoses were abstracted from this database.

This study included inborn and outborn births between 1996 and 2007. Infants born prior to 1996 were excluded from analysis since newborn hearing screening did not begin in the center until 1996. Infants born after 2007 were excluded because the data

were incomplete for years following 2007. Further exclusion criteria were applied for each outcome of interest. To assess loss to follow-up, infants who were never admitted to the NICU, died prior to discharge, or received no hearing screen were excluded from analyses. Infants with no follow-up were further excluded from analyses of test sensitivity and specificity. Table 1 includes the exclusion criteria and sample sizes for each measure described below.

**Table 1. Model Exclusion Criteria and Sample Sizes**

| Model | Exclusion Criteria | Final Sample Size |
|---|---|---|
| Screening Rates<br>Logistic Model for Receipt of Newborn Hearing Screen | Births prior to 1996 and after 2007 (n=21,498)<br>Remaining individuals with incomplete data | 28,335 |
| Loss to follow-up Rates<br>Logistic Model for Being Lost to Follow-up | Births prior to 1996 and after 2007 (n=21,498)<br>Non-NICU admissions (n=23,482)<br>Deaths prior to discharge (n=73)<br>Remaining individuals with incomplete data (n=667) | 5,102 |
| Sensitivity Rates<br>Specificity Rates<br>False-Negative Rates<br>False-Positive Rates<br>Logistic Model for Receipt of False-Negative Screen Result<br>Logistic Model for Receipt of False-Positive Screen Result | Births prior to 1996 and after 2007 (n=21,498)<br>Non-NICU admissions (n=23,482)<br>Deaths prior to discharge (n=73)<br>Infants with no follow-up (n=689)<br>Remaining individuals with incomplete data (n=767) | 5,002 |
| Logistic Model for Receipt of Hearing Loss Diagnosis<br>Cox Proportional Hazards Regression Model | Births prior to 1996 and after 2007 (n=21,498)<br>Non-NICU admissions (n=23,482)<br>Deaths prior to discharge (n=73)<br>Infants with no follow-up (n=689)<br>Remaining individuals with incomplete data (n=647) | 4,855 |

*Outcome Measures*

Specific Aim 2 explores temporal trends in four outcomes of interest to newborn hearing screening programs: screening rates, loss to follow-up, test sensitivity, and test specificity. The formulas used to calculate each of the outcomes are described below.

$$\text{Annual newborn hearing screening rate} = \frac{\#\ of\ infants\ receiving\ hearing\ screen\ in\ year_i}{\#\ of\ infants\ eligible\ for\ screening\ in\ year_i}$$

Screening completion, or receipt of a hearing screen, was measured by identifying whether or not an infant has a screening result recorded during their birth admission. If a result is present, screening completion was coded as "yes." The number of eligible infants was defined as the total number of infants admitted to either the NICU or newborn nursery.

$$\text{Annual loss to follow-up} = \frac{\#\ of\ infants\ receiving\ follow{-}up\ services\ after\ a\ positive\ screen}{\#\ of\ infants\ with\ a\ positive\ screen\ in\ year_i}$$

Receipt of follow-up services was defined as an infant having ever received follow-up within the health care system in which they were born. The screening result will be measured by analyzing the exiting hearing screen result from the infant's record. In the database, screening result is coded as PP (pass in both ears), FP or PF (pass in one ear and fail in one ear), or FF (fail in both ears). These results were recoded into pass (PP) or fail (FP, PF, or FF).

Sensitivity and specificity are typical measures of test or screening effectiveness. Sensitivity reflects the ability of a test to accurately identify individuals with the disease, and specificity indicates the ability of a test to accurately identify individuals without the

disease. These are closely linked to false-positive and false-negative rates. These outcomes were calculated using the following formulas:

$$\text{Annual test sensitivity} = \frac{\#\ of\ infants\ with\ hearing\ loss\ who\ had\ a\ positive\ screen\ in\ year_i}{total\ \#\ of\ infants\ screened\ in\ year_i and\ identified\ with\ hearing\ loss})$$

False-negative rate = 1 – sensitivity

$$\text{Annual test specificity} = \frac{\#\ of\ infants\ without\ hearing\ loss\ who\ had\ a\ negative\ screen\ in\ year_i}{total\ \#\ of\ infants\ screened\ in\ year_i without\ hearing\ loss}$$

False-positive rate = 1 – specificity

Confirmed hearing loss is defined as having a prevalent diagnosis as identified using ICD-9CM codes from the follow-up record. A total of 10 ICD-9CM codes were identified as primary codes for hearing loss.[81] These ten ICD-9CM codes are listed Table 2. Given the sample sizes in this study, hearing loss was coded as a binary variable if an individual was given any of these hearing loss diagnoses. Separate analyses were not performed for different types of hearing loss.

**Table 2. ICD-9CM Codes used to Identify Hearing Loss**

| |
|---|
| 389.00 Conductive hearing loss, unspecified |
| 389.10 Sensorineural hearing loss, unspecified |
| 389.11 Sensorineural hearing loss, bilateral |
| 389.12 Neural hearing loss, bilateral |
| 389.14 Central hearing loss, bilateral |
| 389.15 Sensorineural hearing loss, unilateral |
| 389.16 Sensorineural hearing loss, asymmetrical |
| 389.18 Sensorineural hearing loss of combined types, bilateral |
| 389.2 Mixed conductive and sensorineural hearing loss |
| 389.9 Unspecified hearing loss |

Specific Aim 2 also includes analyses to assess the likelihood of receiving a newborn hearing screen, receiving of a positive screen result, being lost to follow-up, receipt of a false-positive result, receiving a false-negative result, and receiving of a hearing loss diagnosis, adjusting for infant characteristics. Both infant characteristics and co-occurring diagnoses are included in the analysis. Co-occurring diagnoses were identified using ICD-9CM codes. Table 3 summarizes the factors assessed.

**Table 3. Infant Factors**

| |
|---|
| Birth Year |
| Gender |
| Birthweight |
| Race/Ethnicity |
| Length of Stay |
| Apgar (1 minute and 5 minute) |
| Treatment Factors associated with hearing loss or common in NICU |
| Ventilation Status |
| Oxygen Status |
| Primary Diagnoses from the birth encounter associated with hearing loss or therapies associated with hearing loss (e.g. ECMO) |
| Cytomegalovirus Dx (ICD-9CM: 771.1) |
| Craniofacial Anomoly Dx (ICD-9CM: 756.0) |
| Neonatal Infection Dx (ICD-9CM: 760.2, 771.82) |
| Hyperbilirubinemia Dx (ICD-9CM: 774.6, 774.2) |
| Sepsis Dx (identified through database notation, not diagnosis code) |
| Respiratory Distress Dx (ICD-9CM: 769) |
| Meconium Aspiration Dx (ICD-9CM: 770.12) |
| Persistent Pulmonary Hypertension Dx (ICD-9CM: 747.83) |

*Statistical Analyses*

**Temporal Trends**

Tests for temporal trends were performed to characterize the data and identify any year in which the outcomes were significantly different from the first year of

screening. Generalized linear models were used to test for trends in each of the rates from the first year of screening (1996) through 2007. All statistical analyses were performed using STATA 13.[82] Results with p-values less than 0.05 were considered significant. The empirical models are as described below.

*Annual Screening Rates*

Screening rates were calculated for each year and the model includes the admitting unit (newborn nursery or NICU) as a covariate. Birth year is used as a trend variable to mark changes. Attempts were made to use an indicator variable for pre- or post-policy change but these were excluded due to collinearity. The model specification is below:

$$Y = \beta_0 + \beta_1(X_1) + \beta_2(X_2) + \varepsilon$$

Where:

Y = Annual screening rate

$X_1$ = birth year

$X_2$ = admitting unit

*Annual Loss to Follow-up*

Rates of loss to follow-up were calculated for each year and only for infants admitted to the NICU. Again, covariates indicating policy changes were excluded due to collinearity, so birth year itself is used as a trend variable to mark changes. This was the only covariate included in the model. The model is defined below.

$$Y = \beta_0 + \beta_1(X_1) + \varepsilon$$

Where:

Y = Annual rate of loss to follow-up

$X_1$ = birth year

*Annual Test Sensitivity*

Sensitivity rates were calculated for each year and only for infants admitted to the NICU and with at least one follow-up encounter. Covariates indicating policy changes were excluded due to collinearity, and birth year itself is used as a trend variable to mark changes. The model is as follows.

$$Y = \beta_0 + \beta_1(X_1) + \varepsilon$$

Where:

Y = Annual sensitivity rate

$X_1$ = birth year

*Annual Test Specificity*

Specificity rates were calculated for each year and only for infants admitted to the NICU and will at least one follow-up encounter. Covariates indicating policy changes were excluded due to collinearity, and birth year itself is used as a trend variable to mark changes. The model specification are:

$$Y = \beta_0 + \beta_1(X_1) + \varepsilon$$

Where:

Y = Annual specificity rate

$X_1$ = birth year

## Prediction Models

Separate multivariate logistic regression models were used to assess the likelihood of an infant receiving a newborn hearing screen, being lost to follow-up, receipt of a false-positive result, receiving a false-negative result, and receiving of a hearing loss diagnosis, while adjusting for infant characteristics and birth year (as an indicator of policy/organizational change). These epidemiologic inquiries are useful for identify risk factors for the outcomes of interest. Robust standard errors were used to estimate variance of the maximum likelihood functions.

Where significant differences were identified, marginal effects were calculated to identify the difference in probabilities. Marginal effects are historically used in economic analysis but can be useful for interpreting results in health services research and weighing decision options.[83] Analyzing marginal effects allows researchers to determine the "incremental difference in outcomes between defined groups" (page 98).[84] Here, I use average marginal effects, which estimate the marginal effect based on the calculated average for each individual in the sample,[84] to contextualize the differences in terms of probability of outcomes for groups within each significant model covariate. The models for each analysis are presented below.

### *Receipt of Newborn Hearing Screen*

The outcome variable of interest in this model is receipt of a newborn hearing screen. This analysis was performed using infants admitted to both the newborn nursery and NICU, therefore the admitting unit is included as a covariate. The model also includes infant characteristics for adjustment.

$$Y = \beta_0 + \beta_1(X_1) + \beta_2(X_2) + \beta_3(X_3) + \varepsilon$$

Where:

Y = newborn hearing screen completion (1 = yes, 0 = no)

$X_1$ = birth year

$X_2$ = admitting unit

$X_3$ = vector of infant characteristics including gender, birthweight, race, Apgar scores, length of stay, oxygen status, ventilation status, and disorders reported as risk factors for hearing loss (see Table 3); in this model I also include an interaction for birth year and admitting unit

*Loss to Follow-up*

The outcome variable of interest in this model is lost to follow-up. This analysis was performed using infants admitted to only the NICU, as follow-up records are only available for the NICU population. While other studies have found that distance from urban centers was associated with receipt of follow-up services after hearing screening, the available location information (zip code) in our dataset was inconsistent and there were a large number of infants for which this information was missing. Therefore, distance was not included in our model.

$$Y = \beta_0 + \beta_1(X_1) + \beta_2(X_2) + \varepsilon$$

Where:

Y = screen result (1 = lost, 0 = not lost)

$X_1$ = birth year

$X_3$ = vector of infant characteristics including gender, birthweight, race, Apgar scores, length of stay, oxygen status, ventilation status, and disorders reported as risk factors for hearing loss (see Table 3).

*False-Positive Result*

The outcome variable of interest in this model is receipt of a false-positive result. This analysis was performed using infants admitted to only the NICU, as follow-up records are only available for the NICU population.

$$Y = \beta_0 + \beta_1(X_1) + \beta_2(X_2) + \varepsilon$$

Where:

Y = screen result (1 = false-positive, 0 = true-positive)

$X_1$ = birth year

$X_2$ = vector of infant characteristics including gender, birthweight, race, Apgar scores, length of stay, oxygen status, ventilation status, and disorders reported as risk factors for hearing loss (see Table 3)

*False-Negative Result*

The outcome variable of interest in this model is receipt of a false-negative result. This analysis was performed using infants admitted to only the NICU, as follow-up records are only available for the NICU population.

$$Y = \beta_0 + \beta_1(X_1) + \beta_2(X_2) + \varepsilon$$

Where:

Y = screen result (1 = false-negative, 0 = true-negative)

$X_1$ = birth year

$X_2$ = vector of infant characteristics including gender, birthweight, race, Apgar scores, length of stay, oxygen status, ventilation status, and disorders reported as risk factors for hearing loss (see Table 3)

*Confirmed Hearing Loss*

The outcome variable of interest in this model is receipt of a hearing loss diagnosis. This analysis was performed using infants admitted to only the NICU, as follow-up records are only available for the NICU population. Screen result and birth year were not included in the model since the neither is an associated cause of hearing loss.

$$Y = \beta_0 + \beta_1(X_1) + \beta_2(X_2) + \varepsilon$$

Where:

Y = hearing loss (1 = hearing loss diagnosis, 0 = no hearing loss diagnosis)

$X_1$ = birth year

X = vector of infant characteristics including gender, birthweight, race, Apgar scores, length of stay, oxygen status, ventilation status, and disorders reported as risk factors for hearing loss (see Table 3)

## Specific Aim 3

**Specific Aim 3: Evaluate time-to-diagnosis for infants that receive a positive screen result prior to hospital discharge, and identify correlates of earlier diagnosis.**

Hypothesis: Time-to-diagnosis is earlier in infants that receive a positive newborn screen, but still varies by group (e.g. race/ethnicity).

Specific Aim 3 centers around understanding whether or not receipt of a positive hearing screen is associated with earlier diagnosis of hearing loss, and identifies infant factors and comorbidities associated with earlier diagnosis. The study group included in this analysis included all infants admitted to the NICU in the health care center and having at least one follow-up encounter after discharge from the NICU. Infants born prior to 1996 and after 2007 were excluded from the study due to incomplete birth or follow-up data. A total of 5,502 infants were eligible for inclusion in the study. There were 647 infants with incomplete records on at least one of the variables, resulting in 4,855 infants included in the sample.

Infant characteristics of interest to the study include both demographic factors as well as those that have been shown to affect both hearing status and the likelihood of receiving follow-up services. Table 3 lists the infant characteristics included. Birth year is also included in the analysis as a categorical variable to identify trends in earlier diagnosis given policy and organizational changes. The presence or absence of diagnoses known to increase risk for hearing loss, either congenital or delayed-onset, were also included based on reports of the Joint Committee on Infant Hearing and other studies.[10, 15-19, 42] Both ventilation status and oxygen status were also included as treatment factors in the model.

Specific Aim 3 employs survival analysis with the Cox proportional-hazard regression technique.[85] This method accounts for the variable lengths of follow-up available for each individual and allows for censoring, which describes the point at

which the individual leaves the study and assumes future diagnosis is possible even though it was not captured in the study.

The time-to-event of interest in this study is the time between NICU discharge and hearing loss diagnosis. Discharge date was selected as the starting point for time measurement since the hearing screen is typically performed in the days prior to discharge and I assume that referral for confirmatory testing would be provided at that point. Diagnosis date was ascertained by identifying the first hearing loss diagnosis in the infant record and abstracting the associated date from the database. Individual records were coded as either having a documented hearing loss diagnosis or being censored after the date of their last follow-up encounter. Individual and treatment factors were included in the Cox Proportional Hazards model to identify correlates of early diagnosis. STATA software was used for analyses.[82] Results with p-values less than 0.05 were considered significant.

The proportional hazards assumption is inherent to the Cox Proportional Hazard regression model and states that the hazard for any one individual is proportion to the hazard for any other individual, and that this proportionality is constant over time.[85] The proportional hazards assumption was assessed by graphic modeling, specifically using log-log plots,[85] and using statistical tests performed with the *estat phtest* command in STATA 13. Both assessments found that that the baseline hazards for the categories of screen result (no screen, screen negative, screen positive) were not proportional and the proportional hazards assumption for this predictor was not met. As a result, a stratified Cox Proportional Hazards model was used to estimate differences in diagnosis based on

infant and treatment factors, presumably similar to the results from the logistic model evaluating risk factors associated with a hearing loss diagnosis (see Specific Aim 2). The model was stratified by screen result and, therefore, hazard ratios are not available for this variable. However, through stratification, all results are adjusted for screen status. Independent survival curves were prepared for each significant covariate, as well as for screen result. Log-rank tests for equality of survival curves were conducted to see if there were statistically significant differences in the survival estimates for different groups.

Median time-to-diagnosis and annual ranges, were also calculated for each year included in the study. These were plotted on a graph with a trend line to demonstrate the direction of changes over time.

### Limitations of Methodology

This methodology is limited by several factors. First, I use ICD-9CM codes as an indicator of disease. ICD-9CM codes can be unreliable due to the fact that they are applied for billing purposes and may not always be an accurate indicator of disease status.[86] Full chart reviews were impractical in the study and, therefore, disease status could not be confirmed. Second, one of the well-known risk factors for hearing loss is family history, which could not be measured using these data. As a result, the models may include some level of misspecification due to a known but unmeasurable confounder. Finally, test of goodness of fit produced non-significant results for all models except in the logistic models for receipt of a newborn hearing screen and receipt of a false-positive result. The sample sizes included in the analyses for each model were

large, which may bias goodness of fit results. However, this may indicate that the models are somehow misspecified.

# CHAPTER IV

# RESULTS

The results presented below are organized by specific aim. Sample sizes for each part of the study or individual model are noted in each section. A discussion of results and their implications for policy and practice are in Chapter V.

## Specific Aim 1

A final total of 343 studies published between 1990 and 2014 were included in the review. Figure 1 summarizes the abstraction process and the final number of studies included across databases.

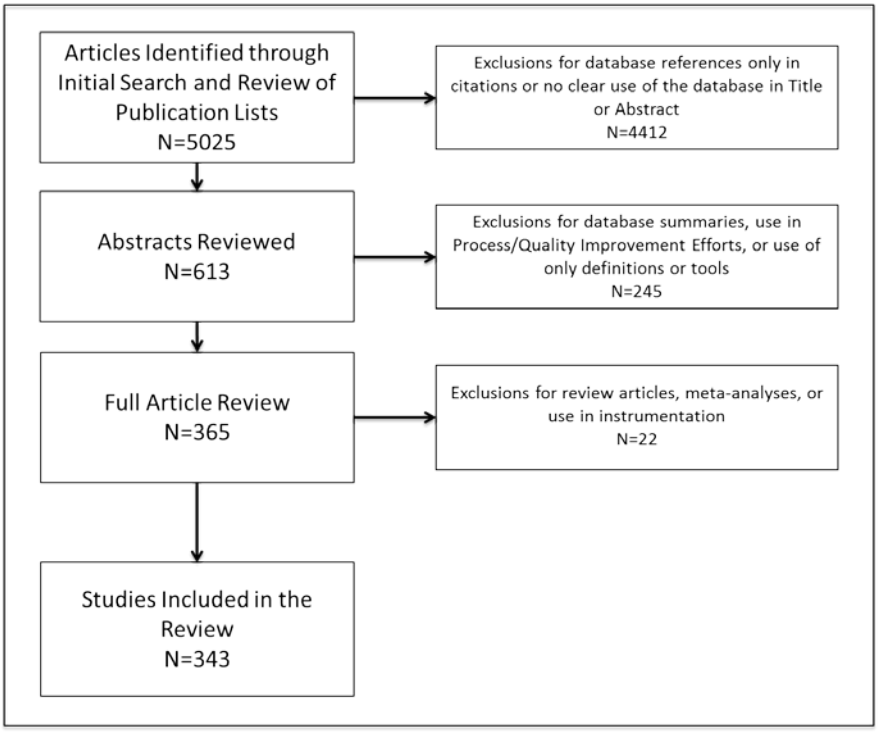


**Figure 1. Database Review, Study Abstraction Process**

The total number of publications using the databases has increased, from three in 1991 to 41 in 2013 (the last full calendar year included in our review). Both prospective and retrospective studies have also increased, with retrospective studies comprising more of the total number of studies in most years. Around 2005, there was a slight decline in the number of studies published, but publications began to increase again after 2006. Figure 2 summarizes the year-by-year results.

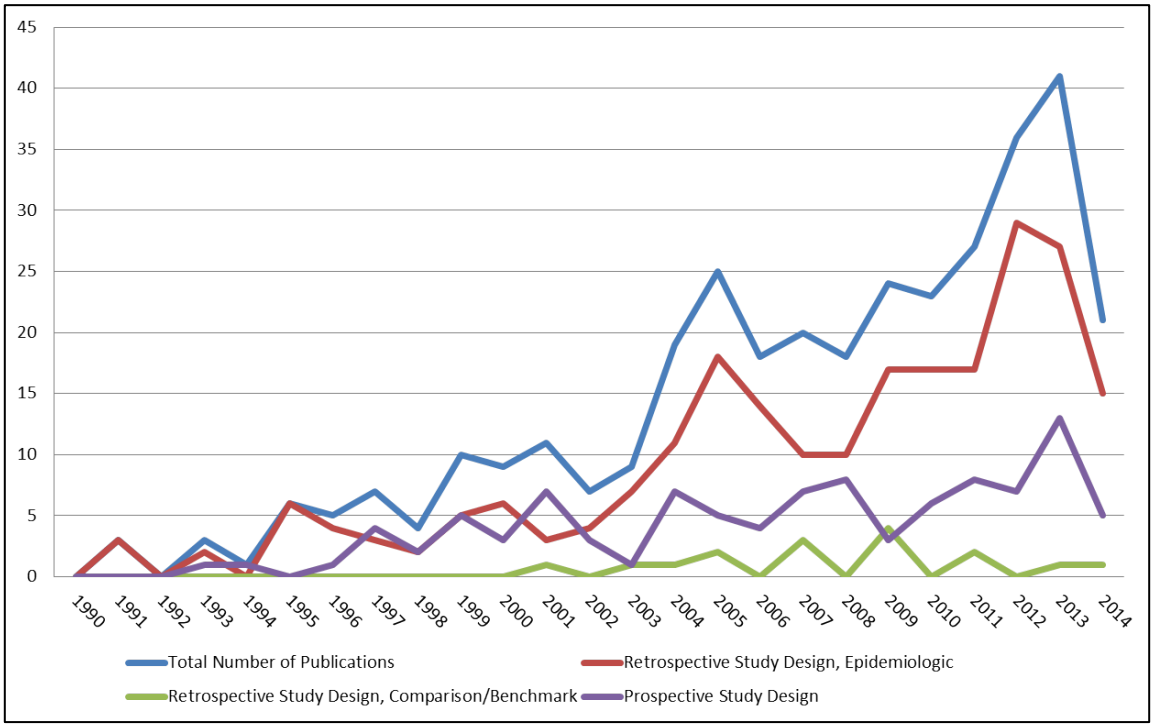


**Figure 2. Annual Publications by Study Design**

Seventy-one percent (71%) of the studies used a retrospective study design and these studies tended to have an epidemiologic focus. Among retrospective studies, the database was sometimes used as a comparison group or benchmark for a single-center

study. For example, Pietz, Achanti, Lilien, Stepka, and Mehta studied the incidence of necrotizing enterocolitis (NEC) in a single NICU over the course of twenty years. Their study looked specifically at the incidence of bowel perforation and NEC among a population of infants that were unlikely to have been treated with indomethacin, a nonsteroidal anti-inflammatory drug that can be used to treat very premature infants. Use of indomethacin in this particular NICU was discouraged and the authors emphasize the need to compare results to other centers that may use indomethacin more frequently. The study authors compared results from their NICU to overall results from VON, which likely included infants treated in NICUs employing more typical practice (for the time) of using indomethacin, and tested for differences in rates of NEC.[87] Alternatively, retrospective studies also used the databases to study population health research questions. For example, Stoll, et. al. utilized the NICHD Neonatal Research Network database to retrospectively examine trends in morbidity and mortality among LBW infants.[65] Smith, et. al., used the KPNMDS to study temporal trends in bronchopulmonary dysplasia rates over eight years.[88]

Approximately 31% of studies utilized a prospective study design where the database was used as a sampling frame, or was used to house study data and answer a specific clinical research question. In their study of neurodevelopmental outcomes among extremely LBW infants (i.e., < 2000 g), Mercier, et. al., used the VON database as a sampling frame from which infants were identified for follow-up assessments.[89] Lorch, Srinivasan, and Escobar published a study on the epidemiology of apnea and

brachycardia in premature infants, which used the KPNMDS as a primary data source throughout the infants' admission to the NICU.[90]

Studies focused on a variety of clinical conditions, interventions, and outcomes, with just over 70% of studies concentrating on ten categories (summarized in Table 4). The top ten areas of research focus were respiratory treatments/outcomes; neurodevelopmental, growth, or language outcomes; outcomes of very LBW or extremely LBW; encephalopathy; neonatal infections; intestinal disease; sepsis; antenatal corticosteriod treatment; retinopathy of prematurity, and hyperbilirubinemia. The remaining 30% of studies focus on other specific conditions and interventions and account for a large amount of diversity in study focus areas. Approximately 10% of the studies were in a category alone, leaving 90% in categories with two or more studies.

**Table 4. Primary Clinical Areas of Focus for Studies Using Multicenter Neonatal Databases**

| **Primary Clinical Focus Area** | **Count** | **Percent (%)** | **Citations** |
|---|---|---|---|
| Respiratory Treatments & Outcomes | 67 | 19.53% | 27, 70, 88, 91-153 |
| Neurodevelopmental, Growth, or Language Outcomes | 45 | 13.12% | 66, 69, 89, 154-195 |
| Outcomes of VLBW/ELBW | 39 | 11.37% | 65, 67, 68, 71, 72, 196-229 |
| Encephalopathy | 24 | 7.00% | 230-253 |
| Neonatal Infections | 18 | 5.25% | 254-271 |
| Intestinal Disease | 15 | 4.37% | 87, 272-285 |
| Sepsis | 14 | 4.08% | 286-299 |
| Antenatal Corticosteriod Treatment | 10 | 2.92% | 300-309 |
| Retinopathy of Prematurity | 8 | 2.33% | 310-317 |
| Hyperbilirubinemia | 8 | 2.33% | 318-325 |
| Other | 95 | 27.70% | 90, 326-420 |
| **Total** | **343** | **100%** | |

Among those studies in the top ten categories, some were given a secondary clinical focus area to further describe the research. This occurred frequently in the broader categories looking at outcomes. For example, studies focusing on respiratory treatment and outcomes may have specific research questions related to use of surfactant or comparing ventilation strategies. Studies of neurodevelopmental outcomes tended to have secondary clinical foci on specific clinical conditions such as NEC, intraventricular hemorrhage, or hyperbilirubinemia. Other top categories, such as intestinal disease, had fewer secondary categories due, presumably, to the focus of the topic area.

Studies in each category also varied in terms of the range of time in which they were published. The earliest published studies focus on intestinal disease and overall outcomes of VLBW and ELBW infants, and these tend to continue through the duration of time included in our review. Alternatively, studies of heart defects and encephalopathy using one of the three databases were not published until after 2000. Figure 3 below describes the range of years across which studies in the top categories were published.

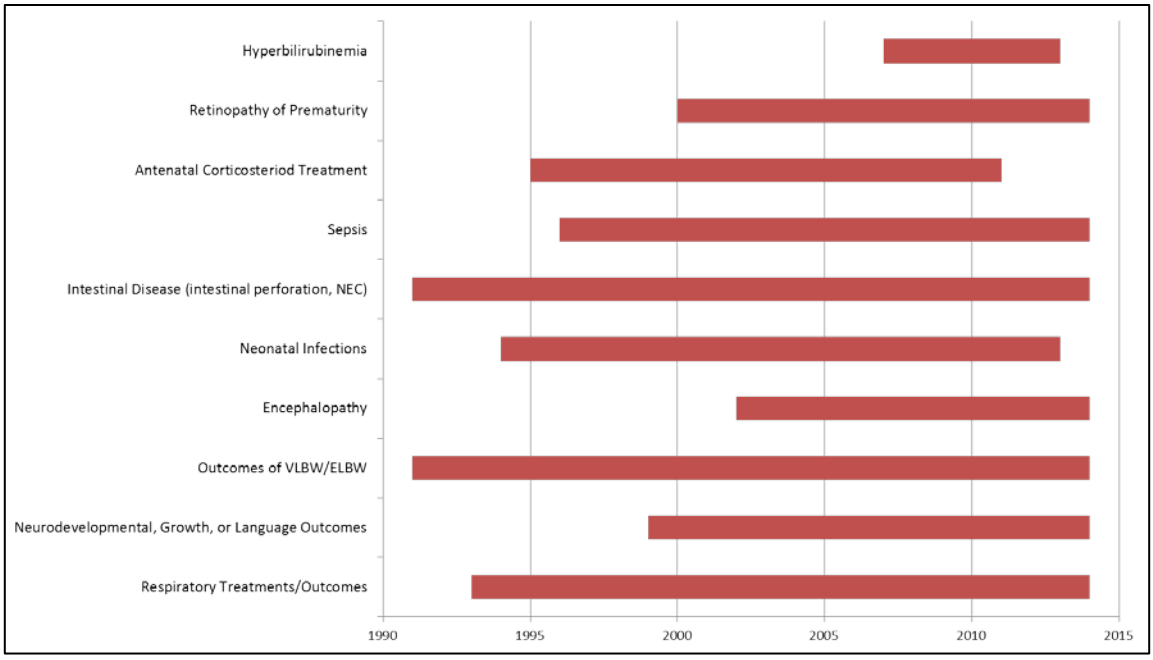


**Figure 3. Study Trends, Top Ten Clinical Focus Areas, 1990-2014**

Despite extensive datasets and the ability for diverse research aims, these databases are not ideal for all outcome studies of prematurity and low birth weight. In the context of this study of hearing loss among NICU infants, there are several specific concerns. First, there is limited evidence that hearing screening status is available for infants in any of the databases. Given my intent to assess implementation and outcomes of the screening policy, screening status is necessary. Second, these three databases do not report maintaining consistent long-term follow-up of infants. While some studies follow infants for extended periods of time, this is not a requirement for participation in the databases and, therefore, researchers cannot count on follow-up data on a large proportion of infants. Finally, and related to follow-up, hearing loss is a relatively rare disorder detected in newborns with an incidence rate of 1-3 per thousand in the general

population. To detect significant results in the NICU population, which is already small, I needed a large sample size. Although the three databases reviewed have a large number of included infants, there is likely a small number with hearing-related screen information or diagnoses after discharge from the hospital. Due to these concerns, I feel justified in using a longitudinal database from the single center where hearing screen results were documented routinely in the medical record and where there is a mean of ten years of diagnostic follow-up on infants receiving follow-up services within the center.

## Specific Aim 2

Here I present results for Specific Aim 2, which aims to look at temporal trends in newborn hearing screening, loss to follow-up, screen specificity and false-positive rate, and screen sensitivity and false-negative rate. In addition, I use logistic regression to predict the likelihood of an infant receiving a hearing screen, being lost to follow-up, receiving a false-positive and false-negative screen result, and receiving a diagnosis of hearing loss; and analyze the marginal effects in different groups.

### *Study Sample Profile*

The database used in this study of hearing screening and hearing loss includes a total of 51,244 infants either born or transferred into a single health care system in Central Texas between 1988 and 2009. There are statistically significant differences between the newborn nursery and NICU infants in all characteristics of interest, including the number receiving a newborn hearing screen. A larger proportion of infants were admitted to the newborn nursery, which might be expected since most babies are

born healthy and do not require a higher level of care. A larger proportion of females and black infants were admitted to the NICU than the newborn nursery. As might be expected, the NICU also had a greater proportion of infants with low birth weight and an early gestational age (see Table 5). Table 5 also denotes were there were missing data for each variable, which did impact the relative sample sizes for each separate analysis.

Only one set of analyses, temporal trends in and likelihood of newborn hearing screening, include infants from the newborn nursery. All other analyses required data on confirmed hearing loss and, therefore, only NICU infants were included in the samples those portions of the study. Table 6 includes descriptive statistics for infants with an without confirmed hearing loss during the study period of 1996-2007. A total of 285 infants (4.9 percent) in the sample had a diagnosis of hearing loss in their record. There were no differences in gender, Apgar scores, or several of the treatment factors or comorbidities between infants with and without hearing loss (see Table 6). The groups did differ in race/ethnicity, birth weight, whether or not they received a screen, ventilation status, length of stay, and in the diagnosis of a craniofacial anomoly.

**Table 5. Characteristics of Newborn Population Admitted to Health Care System between 1988 and 2009**

| | Newborn Nursery (n=42,025) | NICU (n=9,219) | *Statistically Significant Difference? (Newborn Nursery vs. NICU)* |
|---|---|---|---|
| **Gender** | | | |
| Male | 20,673 (49.19%) | 4,158 (45.10%) | *Overall p<0.001* |
| Female | 21,335 (50.77%) | 5,047 (54.75%) | |
| missing | 17 (0.04%) | 14 (0.15%) | |
| **Race** | | | |
| White | 15,077 (35.88%) | 3,514 (38.12%) | *Overall p<0.001* |
| Black | 4,276 (10.17%) | 1,387 (15.05%) | |
| Hispanic | 7,370 (17.54%) | 1,294 (14.04%) | |
| Other | 894 (2.13%) | 119 (1.29%) | |
| missing | 14,408 (34.28%) | 2,905 (31.51%) | |
| **Delivery Route** | | | |
| Vaginal | 34,209 (81.40%) | 5,704 (61.87%) | *Overall p<0.001* |
| Cesarean | 7,806 (18.57%) | 3,453 (37.46%) | |
| missing | 10 (0.02%) | 62 (0.67%) | |
| **Birthweight** | | | |
| >4,200g | 1,810 (4.31%) | 244 (2.65%) | *Overall p<0.001* |
| 2,500-4,199g | 39,146 (93.15%) | 3,761 (40.80%) | |
| 1,500-2,499g | 1,066 (2.54%) | 3,496 (37.92%) | |
| 1,000-1,499g | 2 (0.00%) | 995 (10.79%) | |
| <1,000g | 1 (0.00%) | 723 (7.84%) | |
| **Gestational Age** | | | |
| >37 weeks | 36,150 (86.02%) | 2,948 (31.98%) | *Overall p<0.001* |
| 35-37 weeks | 5,297 (12.60%) | 1,531 (16.61%) | |
| 32-34 weeks | 541 (1.29%) | 2,313 (25.09%) | |
| 28-31 weeks | 35 (0.08%) | 1,699 (18.43%) | |
| <28 weeks | 2 (0.00%) | 728 (7.90%) | |
| **Newborn Hearing Screen** | | | |
| Not screened | 18,254 (56.56%) | 5,883 (63.81%) | *Overall p<0.001* |
| Screened | 23,768 (43.44%) | 3,336 (36.19%) | |
| **Birth Year** | | | |
| Prior to 1996 | 14,396 (34.26%) | 2,875 (31.19%) | *Overall p<0.001* |
| After 1996 | 27,629 (65.74%) | 6,344 (68.81%) | |

**Table 6. Descriptive Statistics for Hearing Loss (HL) in the NICU cohort, 1996-2007**

| | Confirmed Hearing Loss (n=285) | No Confirmed Hearing Loss (n=5,480) | *Statistically Significant Difference? (HL+ vs -)* |
|---|---|---|---|
| **Gender** | | | |
| Male | 158 (55.44%) | 3,019 (55.04%) | *p>0.05* |
| Female | 127 (44.56%) | 2,461 (44.87%) | |
| missing | - | 5 (0.09%) | |
| **Race/Ethnicity** | | | |
| White | 185 (64.91%) | 3,017 (55.00%) | *p<0.001* |
| Black | 33 (11.58%) | 1,186 (21.62%) | |
| Hispanic | 58 (20.35%) | 1,155 (21.06%) | |
| Other | 8 (2.81%) | 101 (1.84%) | |
| missing | 1 (0.35%) | 26 (0.47%) | |
| **Birthweight** | | | |
| >4,200g | 10 (3.51%) | 153 (2.79%) | *p<0.001* |
| 2,500-4,199g | 130 (45.61%) | 2,441 (44.50%) | |
| 1,500-2,499g | 91 (31.93%) | 2,017 (36.77%) | |
| 1,000-1,499g | 28 (9.82%) | 509 (9.28%) | |
| <1,000g | 26 (9.12%) | 365 (6.65%) | |
| **Apgar Scores** | | | |
| 1 minute, mean | 7 | 7.41 | *p>0.05* |
| 5 minute, mean | 8.42 | 8.49 | *p>0.05* |
| **Hearing Screening** | | | |
| Not screened | 10 (3.51%) | 438 (7.33%) | *p=0.015* |
| Screened | 275 (96.49%) | 5,541 (92.67%) | |
| **Comorbidities and Treatments** | | | |
| Ventilation | 74 (25.96%) | 1,205 (20.15%) | *p=0.017* |
| Oxygen | 100 (35.09%) | 2,192 (36.66%) | *p>0.05* |
| Craniofacial Anomolies | 7 (2.46%) | 11 (0.18%) | *p<0.001* |
| Cytomegalovirus | 1 (0.35%) | 25 (0.42%) | *p>0.05* |
| Neonatal infection | 2 (0.70%) | 11 (0.18%) | *p>0.05* |
| Hyperbilirubinemia | 39 (13.68%) | 836 (13.98%) | *p>0.05* |
| Sepsis | 19 (6.67%) | 361 (6.04%) | *p>0.05* |
| Respiratory Distress | 54 (18.95%) | 1,027 (17.18%) | *p>0.05* |
| **Length of Stay** | | | |
| <=5 days | 78 (27.37%) | 2,097 (35.07%) | *p=0.008* |
| > 5 days | 207 (72.63%) | 3,882 (64.93%) | |

*Temporal Trends*

**Newborn Hearing Screening Rates**

Since the health care system implemented newborn hearing screening in 1996, the annual rate of infants receiving a screen has increased to rates between 90 and 100 percent. Prior to 2001, the rates varied by admitting unit, with infants admitted to the NICU having higher rates of newborn hearing screening than infants admitted to the newborn nursery. Since 2001, rates in both units stabilized and are above 90 percent. Between 1999, when the screening mandate was passed in the Texas Legislature, and 2001, when full implementation of the law was required, there was a reduction in the screening rates for both admitting units, with the newborn nursery having the sharpest decline. Figure 4 shows the trends in screening rates since 1996. The fitted line is included to demonstrate the direction of the trend in overall screening rates across both units. As the graph shows, newborn hearing screening rates increased over the priod 1996 to 2007.

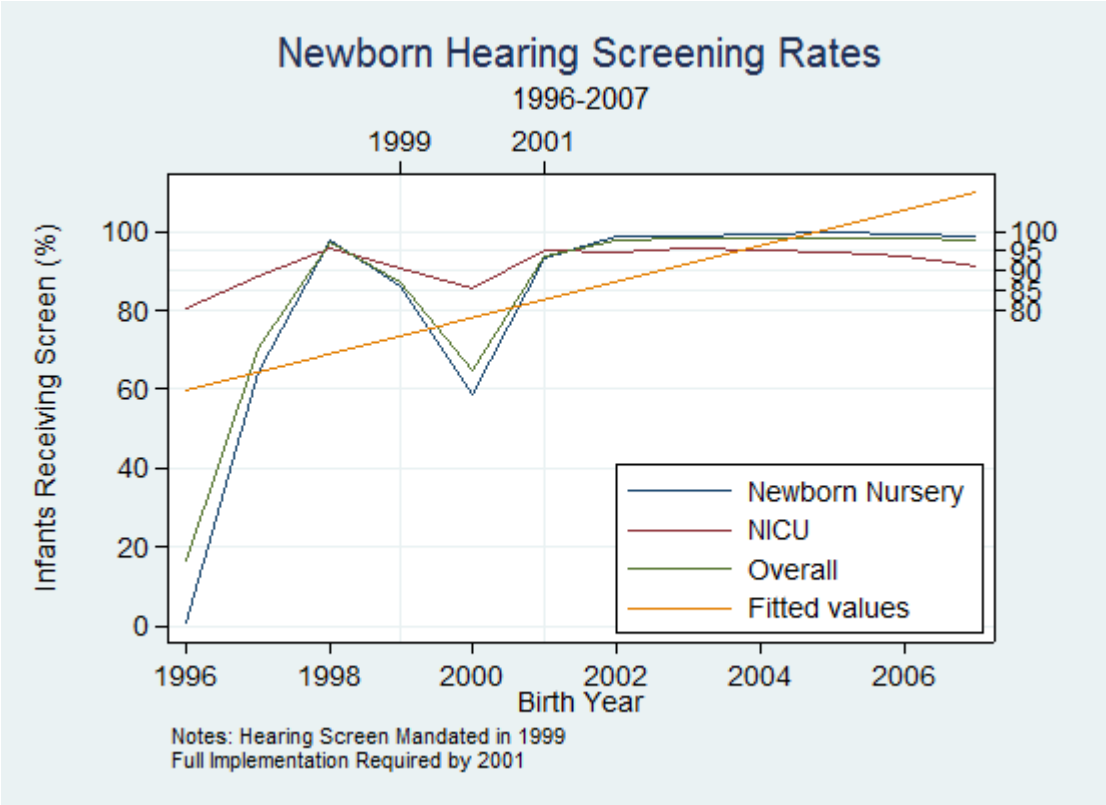


**Figure 4. Newborn Hearing Screening Rates, 1996-2007**

The generalized linear model showed that each year after 1996 had a statistically significant improvement in newborn hearing screening rates, compared to 1996 and adjusted for admitting unit (p-values all equal < 0.001). The NICU is also associated with higher screening rates (p-value<0.001).

**Loss to Follow-up Rates**

Annual rates of loss to follow-up for infants admitted to the NICU decreased over the time period 1996 to 2007, demonstrating that fewer infants with positive newborn hearing screens were being lost due to either receiving no follow-up or not having documentation of follow-up services within the system. In all years except for

1996 the annual rate of loss to follow-up was less than 15 percent, much lower than the reported rate for Texas (40.2 percent in 2011). Figure 5 shows the annual rates and included a fitted line to demonstrate their downward trend.

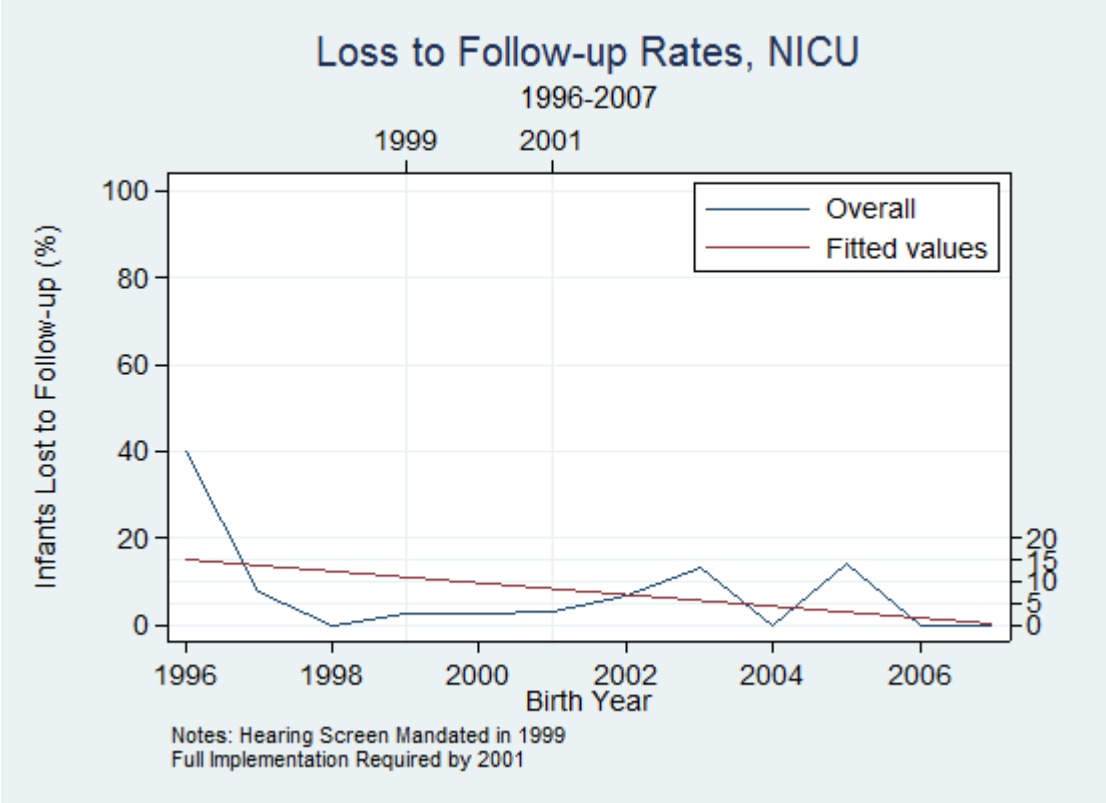


**Figure 5. Loss to Follow-up Rates, NICU, 1996-2007**

The generalized linear model testing for changes in the loss to follow-up rate showed that all years had statistically significant reductions in loss to follow-up compared to 1996 (p-value<0.001).

**Screen Specificity and False-Positive Rate**

Specificity of a screen or test indicates the extent to which the test accurately identifies individuals without the disease when they truly do not have the disease. In the case of newborn hearing screening, this is the ability of the screen to provide negative results to infants that do not have hearing loss.[421] The false-positive rate is the rate of infants that were identified through the screening program to potentially have hearing loss, but do not actually have hearing loss upon confirmatory testing (or, in this analysis, do not ever receive a hearing loss diagnosis). The higher the specificity, the lower the false-positive rate.[421]

The specificity of the screening program among NICU infants has maintained a high specificity rate, never going below 90 percent. As such, the false-positive rate as remained below 10 percent, with a high in 1999. Figure 6 shows the trends graphically. The fitted lines demonstrate that there is a general trend toward an increasingly higher specificity, while the false-positive rate has declined.

We know from conversations with physicians in the health system that they recognized a high false-positive rate around 1999-2000. In response, the organization implemented a new staff training to improve performance and interpretation of the newborn hearing screen. After 1999 the rates begin to decline and stabilize around 2000.

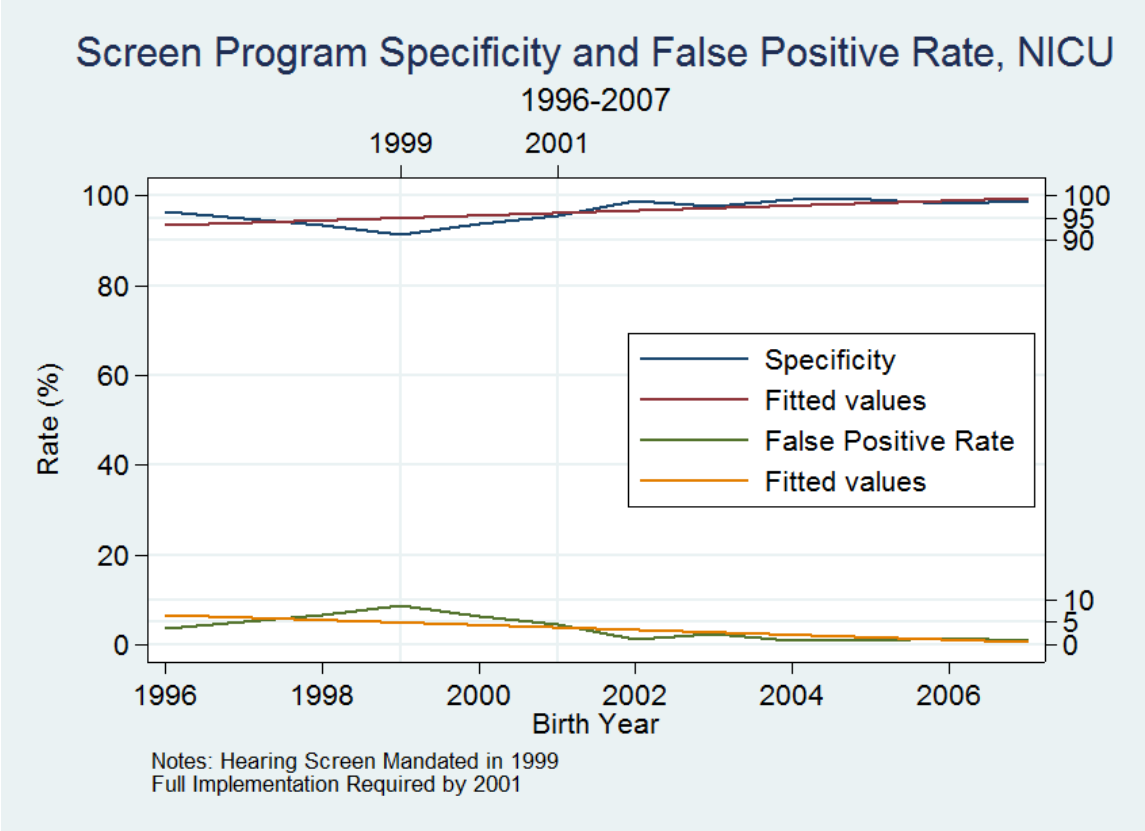


**Figure 6. Screen Program Specificity and False-Positive Rate, NICU, 1996-2007**

The generalized linear model shows that there has been fluctuation in the specificity and the false-positive rate over time. Specificity was lower in 1997, 1998, 1999, 2000, and 2001, compared to the year 1996 (p-values<0.001). In the following years (2002-2007), the odds of increased specificity are all greater than 1 (p-values<0.001), indicating higher specificity in all years compared to 1996.

Similarly, the false-positive rate was higher from 1997-2001, compared to 1996 (p-values=0.000). In 2002, the odds of a lower false-positive rate become lower than one and remain so through 2007 (p-values<0.001).

**Screen Sensitivity and False-Negative Rates**

The sensitivity of a screen or test is the extent to which the test accurately identifies individuals that have the disease of interest.[421] The false-negative rate is 1-sensitivity and represents the proportion of individuals that had a negative test or screen result but eventually received diagnosis of the disease.[421] Tests with high sensitivity rates will have low false-negative rates.[421]

In general, this study of newborn hearing screening found that the sensitivity of the screen was low over the study period and, similarly, that the false-negative rate remained quite high. There was variation over the years. Figure 7 shows the changes over time and includes fitted lines for both sensitivity and false-negative rates to demonstrate trend.

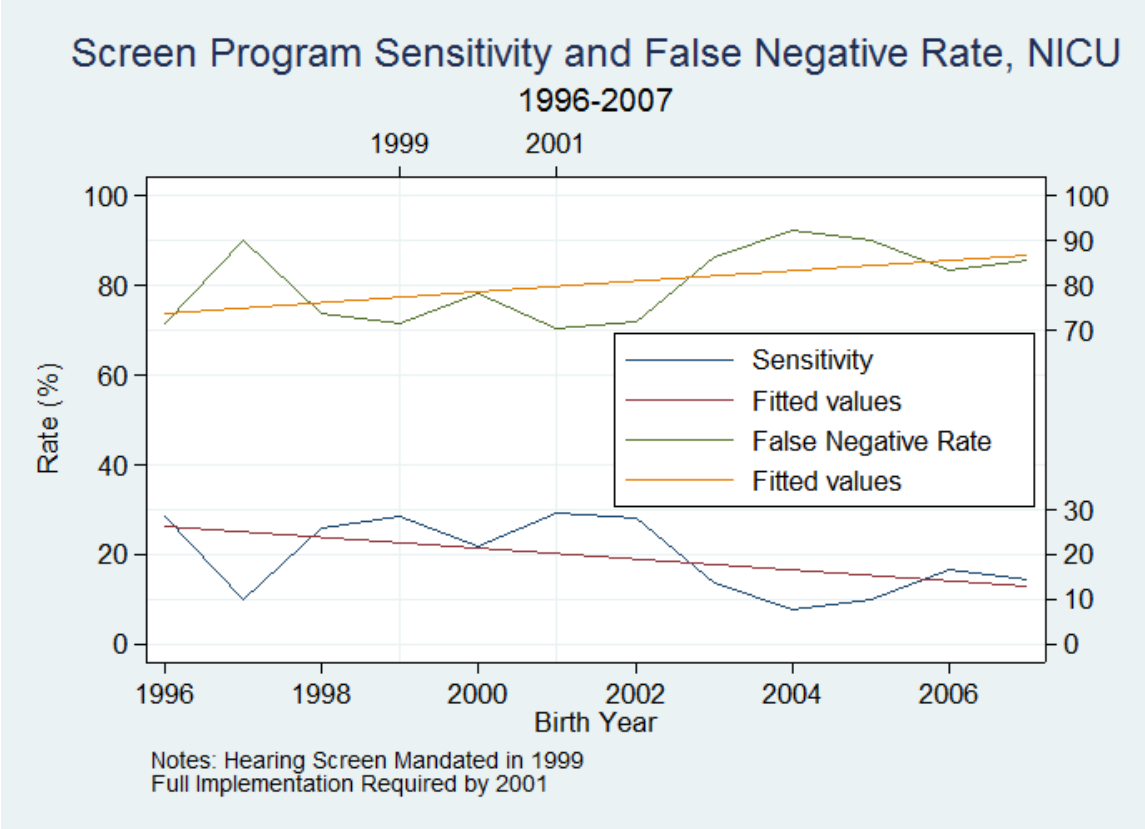


**Figure 7. Screen Program Sensitivity and False-Negative Rate, NICU, 1996-2007**

The generalized linear model shows that the odds of higher sensitivity were lower than one in all years except for 2001, compared to 1996 (p-values<0.001; year 1999 had exact same sensitivity as 1996). In 2001, the odds were slightly higher than 1 (1.04, p-value<0.001) and represent the highest annual sensitivity rate across the study period. The model to predict changes in false-negative rates shows that the odds of a higher false-negative rate were above one for all years except 2001, compared to 1996 (p-values<0.001). These results confirm that both the screen sensitivity and false-negative rate have not improved since the inception on newborn hearing screening

within the health care center in 1996 and may reflect the fact that NICU infants are at greater risk of delayed onset hearing loss.

### *Prediction Models*

Next, I extend the focus on these program outcomes and present results of five separate logistic regression models to predict the likelihood of receiving a newborn hearing screen, being lost to follow-up, receiving a false-positive or false-negative screen result, and receiving a hearing loss diagnosis, all adjusted for birth year and infant characteristics. The results are intended to further inform hearing screening programs, both universal and through targeted follow-up.

#### Likelihood an Infant Received a Hearing Screen

A total of 28,335 infants with complete data were included in our analysis of the likelihood an infant received a hearing screen. As noted previously, this is the one outcome in the study where inclusion of both the newborn nursery and neonatal intensive care units is possible, providing the opportunity to adjust for admitting unit.

Across the study sample and period, the mean probability that an infant received a hearing screen was 0.859. Neither gender or race was associated with increased odds of receiving a screen, nor was birth weight. Both birth year and admitting unit, and their

interaction, were significantly associated with receipt of a screen, as were the 5-minute Apgar score, length of stay, ventilation status, and a diagnosis of hyperbilirubinemia. Table 7 includes the regression results for these significant covariates.

Compared to the year 1996, infants born between 1997 and 2007 had greatly increased odds of receiving a hearing screen (OR range 118 to 19,169, p-values<0.0001). Infants admitted to the NICU were also more likely to receive a hearing screen (OR=118, p-value<0.0001). Higher 5-minute Apgar scores (OR=1.19, p-value<0.0001), a length of stay greater than five days (OR=13, p-value<0.0001), and a diagnosis of hyperbilirubinemia during the birth admission (OR=3.19, p-value<0.0001) were also associated with an increased odds of receiving a hearing screening. Infants that were on ventilation, regardless of the length, had lower odds of receiving a hearing screen (OR=0.25, p-value<0.0001). The interaction between birth year and admitting unit was significant in the model and each individual interaction was also significant, adding slight increases to the relative odds for each variable.

**Table 7. Results of Logistic Regression Analysis, Likelihood an Infant Received a Hearing Screen (n=28,335)**

| Variable | Odds Ratio | P-value | [95% Conf. Interval] | |
|---|---|---|---|---|
| **Birth Year (*referent is 1996)*** | | | | |
| **1997** | **152.47** | **<0.0001** | **100.92** | **230.35** |
| **1998** | **3651.24** | **<0.0001** | **2195.72** | **6071.61** |
| **1999** | **505.90** | **<0.0001** | **331.90** | **771.12** |
| **2000** | **118.43** | **<0.0001** | **78.48** | **178.72** |
| **2001** | **1181.78** | **<0.0001** | **759.79** | **1838.13** |
| **2002** | **8764.76** | **<0.0001** | **4747.52** | **16181.28** |
| **2003** | **5997.30** | **<0.0001** | **3431.09** | **10482.83** |
| **2004** | **10492.02** | **<0.0001** | **5487.39** | **20060.97** |
| **2005** | **19169.58** | **<0.0001** | **8891.42** | **41328.92** |
| **2006** | **10047.66** | **<0.0001** | **5442.53** | **18549.37** |
| **2007** | **6044.29** | **<0.0001** | **3524.46** | **10365.70** |
| **Admitting Unit (*referent is Newborn Nursery*)** | | | | |
| **NICU** | **188.37** | **<0.0001** | **109.41** | **324.32** |
| **Apgar (5 minute)** | **1.19** | **<0.0001** | **1.09** | **1.30** |
| **Length of stay >5 days** | **13.29** | **<0.0001** | **8.86** | **19.94** |
| **Ventilation** | **0.25** | **<0.0001** | **0.15** | **0.41** |
| **Hyperbilirubinemia Dx** | **3.19** | **<0.0001** | **1.67** | **6.10** |
| **Birth Year and Unit Interaction (*referent is 1996*NICU*)** | | | | |
| **1997#NICU** | **0.02** | **<0.001** | **0.01** | **0.03** |
| **1998#NICU** | **0.00** | **<0.001** | **0.00** | **0.01** |
| **1999#NICU** | **0.01** | **<0.001** | **0.00** | **0.01** |
| **2000#NICU** | **0.02** | **<0.001** | **0.01** | **0.03** |
| **2001#NICU** | **0.01** | **<0.001** | **0.00** | **0.02** |
| **2002#NICU** | **0.00** | **<0.001** | **0.00** | **0.00** |
| **2003#NICU** | **0.00** | **<0.001** | **0.00** | **0.00** |
| **2004#NICU** | **0.00** | **<0.001** | **0.00** | **0.00** |
| **2005#NICU** | **0.00** | **<0.001** | **0.00** | **0.00** |
| **2006#NICU** | **0.00** | **<0.001** | **0.00** | **0.00** |
| **2007#NICU** | **0.00** | **<0.001** | **0.00** | **0.00** |

The estimated marginal effcts of the significant variables are summarized in Table 8. The overall probability of receiving a hearing screen was 0.859. The average marginal effects provided in the table demonstrate the relative probability of the different groups described and, since they are all significant variables in the model, we can compare probabilities between groups. For example, an infant born is 1997 was over four times as likely to receive a hearing screen as an infant born in 1996 (probability of 0.698 in 1997 compared to probability of 0.157 in 1996). Similarly, infants born after 2002 were six times as likely to receive a hearing screen. The probability of receiving a hearing screen in the NICU was four percent higher (0.892) than the probability of receiving a screen in the newborn nursery (0.84). Infant that received assisted ventilation had an eight percent higher probability of receiving a hearing screen, although the reason for this difference is not clear. The probability of hearing screening for infants with a length of stay greater than five days was 10 percent higher than infant admitted for five or fewer days, possibly due to the extended amount of time during which the screen could be performed. A hyperbilirubinemia diagnosis was also associated with a five percent increase in the probability of screening.

**Table 8. Average Marginal Effects for the Logistic Model of Screening Receipt**

| Variable | Margin | P-value | [95% Conf. Interval] | |
|---|---|---|---|---|
| **Birth Year** | | | | |
| 1996 | 0.157 | <0.001 | 0.149 | 0.165 |
| 1997 | 0.698 | <0.001 | 0.679 | 0.717 |
| 1998 | 0.977 | <0.001 | 0.971 | 0.983 |
| 1999 | 0.873 | <0.001 | 0.860 | 0.887 |
| 2000 | 0.647 | <0.001 | 0.628 | 0.666 |
| 2001 | 0.941 | <0.001 | 0.932 | 0.951 |
| 2002 | 0.986 | <0.001 | 0.981 | 0.990 |
| 2003 | 0.984 | <0.001 | 0.979 | 0.988 |
| 2004 | 0.985 | <0.001 | 0.981 | 0.990 |
| 2005 | 0.986 | <0.001 | 0.982 | 0.991 |
| 2006 | 0.981 | <0.001 | 0.975 | 0.986 |
| 2007 | 0.969 | <0.001 | 0.960 | 0.978 |
| **Admitting Unit** | | | | |
| Newborn Nursery | 0.850 | <0.001 | 0.847 | 0.853 |
| NICU | 0.892 | <0.001 | 0.876 | 0.909 |
| **Length of Stay** | | | | |
| Five or less Days | 0.835 | <0.001 | 0.830 | 0.841 |
| Greater than 5 days | 0.933 | <0.001 | 0.926 | 0.940 |
| **Ventilation Status** | | | | |
| No Ventilation | 0.862 | <0.001 | 0.859 | 0.864 |
| Received Ventilation | 0.761 | <0.001 | 0.718 | 0.804 |
| **Hyperbilirubinemia Dx** | | | | |
| No hyperbilirubinemia | 0.858 | <0.001 | 0.856 | 0.861 |
| Hyperbilirubinemia | 0.908 | <0.001 | 0.889 | 0.927 |

### Likelihood an Infant is Lost to Follow-up

There were 5,102 eligible infants with complete data included in the analysis to determine the likelihood an infant is lost to follow-up. This includes only infants admitted to the NICU, since follow-up status could only be assessed for those infants. Compared to 1996, the odds an infant with a positive screen was lost to follow-up was

lower (ORs=0.19-0.37, p-values<0.0001) in all years except 1997, where the result was insignificant.

Infants born with a birthweight between 1,000 and 1,499 grams were less likely to be lost to follow-up than infants greater than 4,200 grams (OR=0.45, p-value=0.027), but no other birthweight categories had significant differences. Black infants had greater odds of being lost to follow-up (OR=1.34, p-value=0.013), while Hispanic infants had lower odds of being lost (OR 0.64, p-value=0.002) compared to whites.

Neither the 1-minute or 5-minute Apgar score, nor ventilation status were associated with an increased odds of being lost. Infants who received oxygen while in the NICU were more likely to be lost (OR=1.46, p-value=0.004). Infants that were admitted to the hospital for longer than five days had higher odds of being lost (OR=1.28, p-value=0.04). The only diagnosis form the birth encounter associated with loss to follow-up was hyperbilirubinemia, in which infants who received this diagnosis were less likely to be lost (OR=0.59, p-value=0.004). Table 9 includes the results of the logistic regression for significant variables.

**Table 9. Results of Logistic Regression Analysis, Likelihood an Infant is Lost to Follow-up (n=5,102)**

| Variable | Odds Ratio | P-value | [95% Conf. Interval] | |
|---|---|---|---|---|
| **Birth Year (*referent is 1996)*** | | | | |
| 1997 | 0.72 | 0.098 | 0.49 | 1.06 |
| **1998** | **0.28** | **<0.0001** | **0.18** | **0.44** |
| **1999** | **0.32** | **<0.0001** | **0.19** | **0.52** |
| **2000** | **0.19** | **<0.0001** | **0.12** | **0.32** |
| **2001** | **0.29** | **<0.0001** | **0.18** | **0.45** |
| **2002** | **0.30** | **<0.0001** | **0.20** | **0.47** |
| **2003** | **0.36** | **<0.0001** | **0.23** | **0.56** |
| **2004** | **0.26** | **<0.0001** | **0.16** | **0.42** |
| **2005** | **0.37** | **<0.0001** | **0.24** | **0.56** |
| **2006** | **0.33** | **<0.0001** | **0.21** | **0.53** |
| **2007** | **0.34** | **<0.0001** | **0.19** | **0.60** |
| **Birthweight (*referent is 2,500g-4,199g)*** | | | | |
| >4,200g | 1.08 | 0.794 | 0.61 | 1.92 |
| 1,500-2,499g | 1.07 | 0.542 | 0.86 | 1.32 |
| **1,000-1,499g** | **0.49** | **0.003** | **0.31** | **0.78** |
| <1,000g | 0.71 | 0.271 | 0.39 | 1.30 |
| **Race (*referent is White*)** | | | | |
| **Black** | **1.34** | **0.013** | **1.06** | **1.69** |
| **Hispanic** | **0.64** | **0.002** | **0.49** | **0.85** |
| Other | 0.63 | 0.288 | 0.27 | 1.47 |
| **Length of stay >5 days** | **1.28** | **0.04** | **1.01** | **1.62** |
| **Oxygen** | **1.46** | **0.004** | **1.13** | **1.90** |
| **Hyperbilirubinemia Dx** | **0.59** | **0.004** | **0.42** | **0.85** |

The overall probability of being lost to follow-up was 0.0919. After assessment of the average marginal effects, there were no differences in probability for infants born in 1996 or 1997; therefore, we are unable to compare probabilities across birth years. However, we can compare probabilities from individual years to the overall probability. Infants born from 1998 to 2007 had lower probabilities of being lost to follow-up that the sample as a whole. The probability of being lost to follow-up for black infants was three percent higher than that for the overall sample, and Hispanic infants had a lower probability of being lost. The probability of being lost for infants that received oxygen during their NICU admission was three percent higher than those that did not receive oxygen. Infants with a length of stay longer than five days had a two percent higher probability of being lost to follow-up than those with a shorter length of stay. Infants with a hyperbilirubinemia diagnosis had a lower probability two and half percent lower than those without the diagnosis. Table 10 includes the average marginal effects.

**Table 10. Average Marginal Effects for the Logistic Model of Being Lost to Follow-up**

| Variable | Margin | P-value | [95% Conf. Interval] | |
|---|---|---|---|---|
| **Birth Year** | | | | |
| 1998 | 0.072 | <0.001 | 0.048 | 0.095 |
| 1999 | 0.080 | <0.001 | 0.051 | 0.109 |
| 2000 | 0.051 | <0.001 | 0.030 | 0.071 |
| 2001 | 0.073 | <0.001 | 0.050 | 0.096 |
| 2002 | 0.077 | <0.001 | 0.054 | 0.100 |
| 2003 | 0.089 | <0.001 | 0.063 | 0.115 |
| 2004 | 0.066 | <0.001 | 0.043 | 0.089 |
| 2005 | 0.091 | <0.001 | 0.066 | 0.115 |
| 2006 | 0.084 | <0.001 | 0.058 | 0.110 |
| 2007 | 0.085 | <0.001 | 0.048 | 0.122 |
| **Birthweight** | | | | |
| 1,000-1,499g | 0.050 | 0.010 | 0.030 | 0.070 |
| **Race/Ethnicity** | | | | |
| Black | 0.120 | <0.001 | 0.101 | 0.140 |
| Hispanic | 0.063 | <0.001 | 0.049 | 0.078 |
| **Oxygen Status** | | | | |
| No Oxygen | 0.082 | <0.001 | 0.072 | 0.092 |
| Received Oxygen | 0.114 | <0.001 | 0.095 | 0.133 |
| **Length of Stay** | | | | |
| Five or less Days | 0.079 | <0.001 | 0.066 | 0.093 |
| Greater than 5 days | 0.098 | <0.001 | 0.088 | 0.108 |
| **Hyperbilirubinemia Dx** | | | | |
| No hyperbilirubinemia | 0.097 | <0.001 | 0.088 | 0.105 |
| Hyperbilirubinemia | 0.061 | <0.001 | 0.042 | 0.080 |

## Likelihood of a False-Positive Hearing Screen Result

A total of 5,102 eligible infants with complete data were included in the analysis to determine the likelihood of a false-positive screen result. It was not until the year 2002 that infants were at lower odds of receiving a false-positive screen. As mentioned

previously, the health care system had identified a high false-positive rate and implemented a staff training program to improve screening performance and interpretation. Likely a result of this organizational policy, infants born between 2002 and 2007 were less likely to receive a false-positive result (ORs=0.10-0.29, p-values with range of <0.0001 to 0.031). Table 11 includes the complete results of the regression analysis.

Gender was not associated with false-positive results but infants with a birth weight less than 1,000 grams (OR=4.66, p-value=0.013) and black infants (OR=1.49, p-value=0.048) had greater odds of a false-positive results. Those with a length of stay longer than five days were less likely to receive a false-positive result (OR=0.27, p-value<0.0001), as were infants that were on oxygen during their admission (OR=0.23, p-value<0.0001). Receipt of assisted ventilation (OR=2.60, p-value=0.008) and a diagnosis of persistent pulmonary hypertension (OR=44.15, p-value<0.0001) were associated with receipt of a false-positive result.

**Table 11. Results of Logistic Regression Analysis, Likelihood of a False-Positive Screen Result (n=5,002)**

| Variable | Odds Ratio | P>z | [95% Conf. Interval] | |
|---|---|---|---|---|
| **Birth Year (*referent is 1996)*** | | | | |
| 1997 | 0.73 | 0.41 | 0.34 | 1.56 |
| 1998 | 0.77 | 0.493 | 0.37 | 1.61 |
| 1999 | 1.35 | 0.412 | 0.66 | 2.75 |
| 2000 | 0.95 | 0.881 | 0.46 | 1.96 |
| 2001 | 0.52 | 0.104 | 0.24 | 1.14 |
| **2002** | **0.12** | **<0.0001** | **0.04** | **0.35** |
| **2003** | **0.29** | **0.01** | **0.11** | **0.74** |
| **2004** | **0.12** | **0.001** | **0.03** | **0.41** |
| **2005** | **0.10** | **0.001** | **0.03** | **0.37** |
| **2006** | **0.26** | **0.007** | **0.10** | **0.69** |
| **2007** | **0.18** | **0.031** | **0.04** | **0.85** |
| **Birthweight (*referent is 2,500-4,199g*)** | | | | |
| >4,200g | 1.06 | 0.903 | 0.40 | 2.81 |
| 1,500-2,499g | 1.11 | 0.635 | 0.73 | 1.68 |
| 1,000-1,499g | 1.30 | 0.560 | 0.54 | 3.11 |
| **<1,000g** | **4.97** | **<0.001** | **2.23** | **11.07** |
| **Race (*referent is White*)** | | | | |
| **Black** | **1.49** | **0.048** | **1.00** | **2.20** |
| Hispanic | 0.98 | 0.925 | 0.62 | 1.54 |
| Other | 1.00 | | | |
| **Length of stay >5 days** | **0.27** | **<0.0001** | **0.17** | **0.42** |
| **Ventilation** | **2.60** | **0.008** | **1.28** | **5.26** |
| **Oxygen** | **0.23** | **<0.0001** | **0.12** | **0.44** |
| **Persistent Pulmonary Hypertension Dx** | **44.15** | **<0.0001** | **6.61** | **294.76** |

The overall probability of a false-positive screen result was 0.0302. Again, since not every birth year was significant in the logistic model, marginal effects are interpreted relative to the overall probability. From 2002 to 2007, the probability an infant received a false-positive screen result was lower than the overall probability. Black infants had a slightly higher probability than that for the overall sample. The probability of a false-positive screen in infants born at less than 1,000 grams was three times the overall probability. Infants that received oxygen had a three percent lower probability of a false-positive result than those not receiving oxygen, but infants that received assisted ventilation had a three percent higher probability of a false-positive result than those with no ventilation. Infants with a length of stay greater than five days had a four percent lower probability of receiving false-positive result compared to infants with a shorter stay. The probability of a false-positive screen for infants with a diagnosis of persistent pulmonary hypertension was almost 14 times the probability for infants without the diagnosis. See Table 12 for the complete results on marginal effects.

**Table 12. Average Marginal Effects for the Logistic Model of Receipt of a False-Positive Screen Result**

| Variable | Margin | P-value | [95% Conf. Interval] | |
|---|---|---|---|---|
| **Birth Year** | | | | |
| 2002 | 0.009 | 0.016 | 0.002 | 0.016 |
| 2003 | 0.019 | 0.002 | 0.007 | 0.031 |
| 2004 | 0.008 | 0.056 | 0.000 | 0.017 |
| 2005 | 0.007 | 0.059 | 0.000 | 0.015 |
| 2006 | 0.017 | 0.005 | 0.005 | 0.030 |
| 2007 | 0.012 | 0.153 | -0.005 | 0.029 |
| **Race/Ethnicity** | | | | |
| Black | 0.039 | <0.001 | 0.028 | 0.050 |
| **Birth Weight** | | | | |
| <1,000g | 0.103 | <0.001 | 0.045 | 0.102 |
| **Oxygen Status** | | | | |
| No Oxygen | 0.043 | <0.001 | 0.034 | 0.052 |
| Received Oxygen | 0.011 | <0.001 | 0.006 | 0.016 |
| **Ventilation Status** | | | | |
| 0 | 0.027 | <0.001 | 0.022 | 0.032 |
| 1 | 0.063 | <0.001 | 0.029 | 0.096 |
| **Length of Stay** | | | | |
| Five or less Days | 0.058 | <0.001 | 0.044 | 0.072 |
| Greater than 5 days | 0.018 | <0.001 | 0.013 | 0.022 |
| **Persistent Pulmonary Hypertension Dx** | | | | |
| No Persistent Pulmonary Hypertenstion | 0.030 | <0.001 | 0.025 | 0.035 |
| Persistent Pulmonary Hypertenstion | 0.418 | 0.013 | 0.089 | 0.747 |

**Likelihood of a False-Negative Hearing Screen Result**

There were 5,011 eligible infants included in the analysis of false-negative results. Unlike the results for false-positive screens, there is not a specific year in which a change in the odds of a false-negative screen shift and remain so. In the years 2000, 2001, 2002, 2004, and 2007, infants had greater odds of receiving a false-negative screen result. Recall that NICU infants are at greater risk of hearing loss and that they are particularly susceptible to sensorineural hearing loss, which may have delayed onset. Hearing loss, in this study, was defined as the presence or absence of any hearing loss diagnosis, so we do not currently know if these false-negative results are due, in fact, to delayed onset, i.e. the infant truly did not have hearing loss at the time of their NICU admission.

Neither gender or birth weight had any association with false-negative results, but black infants had lower odds of receiving a false-negative screen (OR=0.32, p-value<0.0001). A longer length of stay (OR=1.86, p-value=0.001) and diagnosis of a neonatal infection (OR=10.65, p-value=0.002) were positively associated with receipt of a false-negative result. Table 13 summarizes these results.

**Table 13. Results of Logistic Regression Analysis, Receipt of a False-Negative Screen Result (n=5,002)**

| Variable | Odds Ratio | P-value | [95% Conf. Interval] | |
|---|---|---|---|---|
| **Birth Year (*referent is 1996)*** | | | | |
| 1997 | 2.71 | 0.082 | 0.88 | 8.34 |
| 1998 | 2.41 | 0.125 | 0.78 | 7.44 |
| 1999 | 2.21 | 0.181 | 0.69 | 7.10 |
| **2000** | **3.57** | **0.022** | **1.20** | **10.60** |
| **2001** | **3.15** | **0.039** | **1.06** | **9.36** |
| **2002** | **3.07** | **0.044** | **1.03** | **9.16** |
| 2003 | 2.66 | 0.085 | 0.87 | 8.08 |
| **2004** | **3.10** | **0.044** | **1.03** | **9.31** |
| 2005 | 2.27 | 0.147 | 0.75 | 6.89 |
| 2006 | 2.45 | 0.112 | 0.81 | 7.41 |
| **2007** | **3.28** | **0.048** | **1.01** | **10.68** |
| **Race (*referent is White*)** | | | | |
| **Black** | **0.32** | **<0.0001** | **0.19** | **0.53** |
| Hispanic | 0.77 | 0.155 | 0.53 | 1.10 |
| Other | 1.20 | 0.679 | 0.51 | 2.82 |
| **Length of stay >5 days** | **1.86** | **0.001** | **1.28** | **2.72** |
| **Oxygen** | **0.63** | **0.023** | **0.42** | **0.94** |
| **Neonatal Infection** | **10.65** | **0.002** | **2.37** | **47.94** |

The overall probability of a false-negative result was 0.0392. Compared to the overall probability, the probability of a false-negative result was higher in the years 2000, 2001, 2001, 2004, and 2007. Black infants had a lower probability of a false-negative result compared to the overall sample probability. Infants on oxygen had a one and a half percent lower probability of a false-negative result compared to infants with no oxygen, while infants with a longer length of stay had two times the probability of a

false-negative result compared to infants with a shorter stay. Infants that had a neonatal infection had a probability of a false-negative result over seven times higher than those without a neonatal infection (see Table 14).

**Table 14. Average Marginal Effects for the Logistic Model of Receipt of a False-Negative Screen Result**

| Variable | Margin | P-value | [95% Conf. Interval] | |
|---|---|---|---|---|
| **Birth Year** | | | | |
| 2000 | 0.051 | <0.001 | 0.030 | 0.072 |
| 2001 | 0.045 | <0.001 | 0.027 | 0.064 |
| 2002 | 0.044 | <0.001 | 0.026 | 0.062 |
| 2004 | 0.045 | <0.001 | 0.026 | 0.063 |
| 2007 | 0.047 | 0.001 | 0.020 | 0.075 |
| **Race/Ethnicity** | | | | |
| Black | 0.016 | <0.001 | 0.009 | 0.023 |
| **Oxygen Status** | | | | |
| No Oxygen | 0.046 | <0.001 | 0.037 | 0.055 |
| Received Oxygen | 0.030 | <0.001 | 0.021 | 0.038 |
| **Length of Stay** | | | | |
| Five or less Days | 0.026 | <0.001 | 0.019 | 0.034 |
| Greater than 5 days | 0.048 | <0.001 | 0.039 | 0.056 |
| **Neonatal Infection Dx** | | | | |
| No Neonatal Infection | 0.039 | <0.001 | 0.034 | 0.044 |
| Neonatal Infection | 0.284 | 0.050 | 0.000 | 0.569 |

## Likelihood of a Hearing Loss Diagnosis

Finally, 5011 infants with complete data were included in the analysis of risk factors associated with an eventual hearing loss diagnosis. The model, as described earlier, included demographic factors and clinical characteristics that have been shown in the literature to be associated with hearing loss or conditions/therapies associated with

hearing loss. One widely known risk factor, family history, was not measurable within this study and, therefore, is excluded from our analysis.

The overall incidence of hearing loss among the study population was 5.1 percent, which is higher than the reported incidence for the total population but not unlikely given the high risk of hearing loss among infant admitted to the NICU. Neither gender nor race were associated with a hearing loss diagnosis. Black infants had lower odds of hearing loss compared to white (OR=0.38, p-value<0.001), but there were no other differences by race/ethnicity. Among clinical indicators, Apgar scores, cytomegalovirus, hyperbilirubinemia, sepsis, and respiratory distress had no association with hearing loss.

Confirming the finding from other studies, length of stay greater than five days increased the odds of hearing loss (OR=1.68, p-value=0.002), as did assisted ventilation (OR=1.71, p-value=0.023). Receipt of oxygen decreased the odds of hearing loss (OR=0.59, p-value=0.005). Infants with a craniofacial anomaly had much greater odds of hearing loss (OR=12.89, p-value<0.001). Similarly, infants with a neonatal infection were also more likely to have hearing loss (OR=7.39, p-value-0.006). See Table 15 for complete results.

**Table 15. Results of Logistic Regression Analysis, Likelihood an Infant Receives a Hearing Loss Diagnosis (n=4,855)**

| Variable | Odds Ratio | P>z | [95% Conf. Interval] | |
|---|---|---|---|---|
| **Gender (*referent is Female*)** | | | | |
| Male | 1.01 | 0.955 | 0.78 | 1.31 |
| **Birthweight (*referent is >4,200g*)** | | | | |
| 2,500-4,199g | 1.07 | 0.856 | 0.51 | 2.23 |
| 1,500-2,499g | 0.75 | 0.075 | 0.55 | 1.03 |
| 1,000-1,499g | 1.07 | 0.790 | 0.65 | 1.78 |
| <1,000g | 1.33 | 0.392 | 0.69 | 2.58 |
| **Race (*referent is White*)** | | | | |
| **Black** | **0.38** | **<0.001** | **0.25** | **0.57** |
| Hispanic | 0.79 | 0.156 | 0.57 | 1.09 |
| Other | 1.35 | 0.435 | 0.64 | 2.85 |
| Apgar (1 minute) | 0.95 | 0.226 | 0.88 | 1.03 |
| Apgar (5 minute) | 1.04 | 0.646 | 0.88 | 1.22 |
| **Length of stay >5 days** | **1.68** | **0.002** | **1.20** | **2.34** |
| **Ventilation** | **1.71** | **0.023** | **1.08** | **2.72** |
| **Oxygen** | **0.59** | **0.005** | **0.40** | **0.85** |
| Cytomegalovirus Dx | 0.88 | 0.897 | 0.12 | 6.59 |
| **Craniofacial Anomoly Dx** | **12.89** | **<0.001** | **4.44** | **37.38** |
| **Neonatal Infection** | **7.39** | **0.006** | **1.79** | **30.53** |
| Hyperbilirubinemia Dx | 0.98 | 0.919 | 0.68 | 1.41 |
| Sepsis Dx | 0.92 | 0.776 | 0.52 | 1.62 |
| Respiratory Distress Dx | 0.79 | 0.295 | 0.52 | 1.22 |

The overall probability of hearing loss was 0.0506. Black infants had a two percent lower probability of hearing loss compared to the overall sample probability. Infants who received oxygen during their birth admission had a two and a half percent

lower probability of hearing loss compared to infants not receiving oxygen. Infants on ventilation had a three percent higher probability of hearing loss compared to infants with no ventilation. Infants with a length of stay greater than five days had a probability of hearing loss over two percent higher than those admitted for five or fewer days. The probability of hearing loss among infants with craniofacial anomalies was seven times the probability of those without craniofacial anomalies; and infants with a neonatal infection had a probability five times those without a neonatal infection (see Table 16).

**Table 16. Average Marginal Effects for the Logistic Model of Diagnosis of Hearing Loss**

| Variable | Margin | P-value | [95% Conf. Interval] | |
|---|---|---|---|---|
| **Race/Ethnicity** | | | | |
| Black | 0.025 | <0.001 | 0.016 | 0.034 |
| **Oxygen Status** | | | | |
| No Oxygen | 0.061 | <0.001 | 0.051 | 0.071 |
| Received Oxygen | 0.037 | <0.001 | 0.028 | 0.047 |
| **Ventilation Status** | | | | |
| No Ventilation | 0.046 | <0.001 | 0.040 | 0.053 |
| Received Ventilation | 0.076 | <0.001 | 0.049 | 0.104 |
| **Length of Stay** | | | | |
| Five or less Days | 0.037 | <0.001 | 0.028 | 0.046 |
| Greater than 5 days | 0.060 | <0.001 | 0.051 | 0.069 |
| **Craniofacial Anomaly Dx** | | | | |
| No Craniofacial Anomaly | 0.050 | <0.001 | 0.044 | 0.056 |
| Craniofacial Anomaly | 0.384 | 0.002 | 0.146 | 0.622 |
| **Neonatal Infection Dx** | | | | |
| No Neonatal Infection | 0.051 | <0.001 | 0.045 | 0.057 |
| Neonatal Infection | 0.269 | 0.046 | 0.005 | 0.534 |

## Specific Aim 3

In this final section of results, I present the findings from a survival analysis looking at the time-to-diagnosis of hearing loss. As summarized previously, earlier diagnosis of hearing loss can lead to better communication skills and school performance.[7, 45] The outcome of interest is the length of time between discharge and diagnosis of hearing loss, measured in 30 day periods for easy translation into years. Of note, the hazard of interest here is diagnosis and, contrary to many survival studies where death or disease may be the hazard, the presence of a hearing loss diagnosis is positive if we presume that earlier diagnosis leads to earlier intervention. A hazard ratio greater than one indicates a higher likelihood of diagnosis, compared to the reference group, during the time period of the study. Important here, and what is different from the prior analyses of hearing loss using logistic regression, is that these models are adjusted for screening status (negative result, positive result, no screen) in an effort to understand timing of diagnosis related to the screening program. Of note, follow-up records are available through the year 2013, so we have a minimum of six years of potential follow-up data and a maximum of 17 years for infants born 1996 to 2007.

First, I present the mean time-to-diagnosis for each birth year included in the study. Then, the Kaplan-Meier survival curves for hearing screen result are reviewed to demonstrate the differences in time-to-diagnosis for the different groups. Finally, I present results of a stratified Cox proportional hazards regression model, and then the Kaplan-Meier survival curves for factors associated with earlier diagnosis. Hazard ratios

are not available for hearing screen status as this variable violated the proportional hazards assumption and therefore, the model was stratified by screen status.

*Time-to-Diagnosis by Year*

The median time-to-diagnosis decreased from 1996 to 2007. In 1996 the median time-to-diagnosis was approximately 5.9 years (range: 1.3-11.1) and decreased to 3.3 years by 2007 (range: 0.8-5.5) (see Table 17 for annual means and ranges). An independent t-test for the difference in mean time-to-diagnosis before and after full implementation of the newborn screening mandate in Texas (2001) indicates that the means are significantly different and that the difference is greater than 0 (p-value=0.004). Figure 8 visually depicts this downward trend in time-to-diagnosis. While providing evidence of adownward trend, these results do not take into account the fact that infants born in different years have different lengths of follow-up.

**Table 17. Median Time to Hearing Loss Diagnosis, in Years**

| Birth Year | Median Time-to-Diagnosis, in years | Minimum | Maximum |
|---|---|---|---|
| 1996 | 5.9 | 1.3 | 11.1 |
| 1997 | 5.5 | 0.1 | 16.1 |
| 1998 | 4.3 | 0.7 | 14.8 |
| 1999 | 5.3 | 0.2 | 13.0 |
| 2000 | 4.9 | 0.3 | 11.1 |
| 2001 | 4.1 | 0.1 | 10.9 |
| 2002 | 4.3 | 0.1 | 10.9 |
| 2003 | 5.7 | 0.3 | 10.0 |
| 2004 | 3.9 | 0.8 | 9.0 |
| 2005 | 4.3 | 0.3 | 6.4 |
| 2006 | 4.9 | 0.1 | 7.1 |
| 2007 | 3.3 | 0.8 | 5.5 |

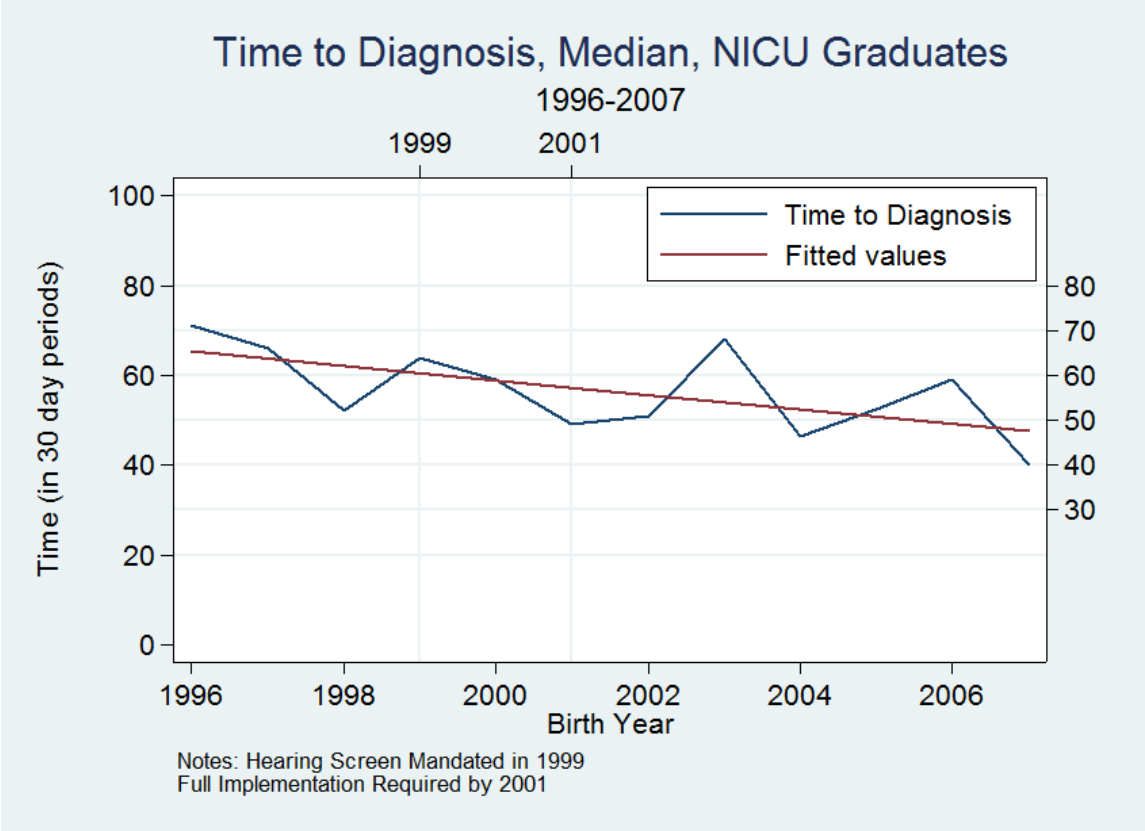


**Figure 8. Median Time-to-Diagnosis, NICU Graduates**

*Survival Estimates by Hearing Screen Status*

The Kaplan-Meier survival curve for hearing screen result (shown in Figure 9) shows that the probability of a hearing loss diagnosis early in the study period was greater among infants that failed the newborn hearing screen, suggesting that the screening program is leading to earlier diagnosis in infants who do have hearing loss. A log-rank test for equality of survival curves confirms that these curves are significantly different (chi2=181.51, p-value<0.0001). The findings under Specific Aim 2 suggested that the false-negative rate among NICU infants is somewhat high, possibly due to delayed onset of hearing loss or other unmeasured factors. In Figure 9, we can see that the survival curve for infants who had a negative screen result are very close to the curve for infants that did not receive a screen at all.

While the Kaplan-Meier survival curve demonstrates that infants identified through screening receive earlier diagnosis, it is also influenced by the low incidence of hearing loss and sensitivity of the screening test (sensitivity = 0.2 in the overall sample and highly variable by year). So we do not see a steeper downward slope of the survival curve for infants who failed the screen as we would expect with a higher sensitivity. In this cohort, the sensitivity is low possibly due to delayed onset hearing loss and the inability to determine if diagnosis occurred outside of the health system.

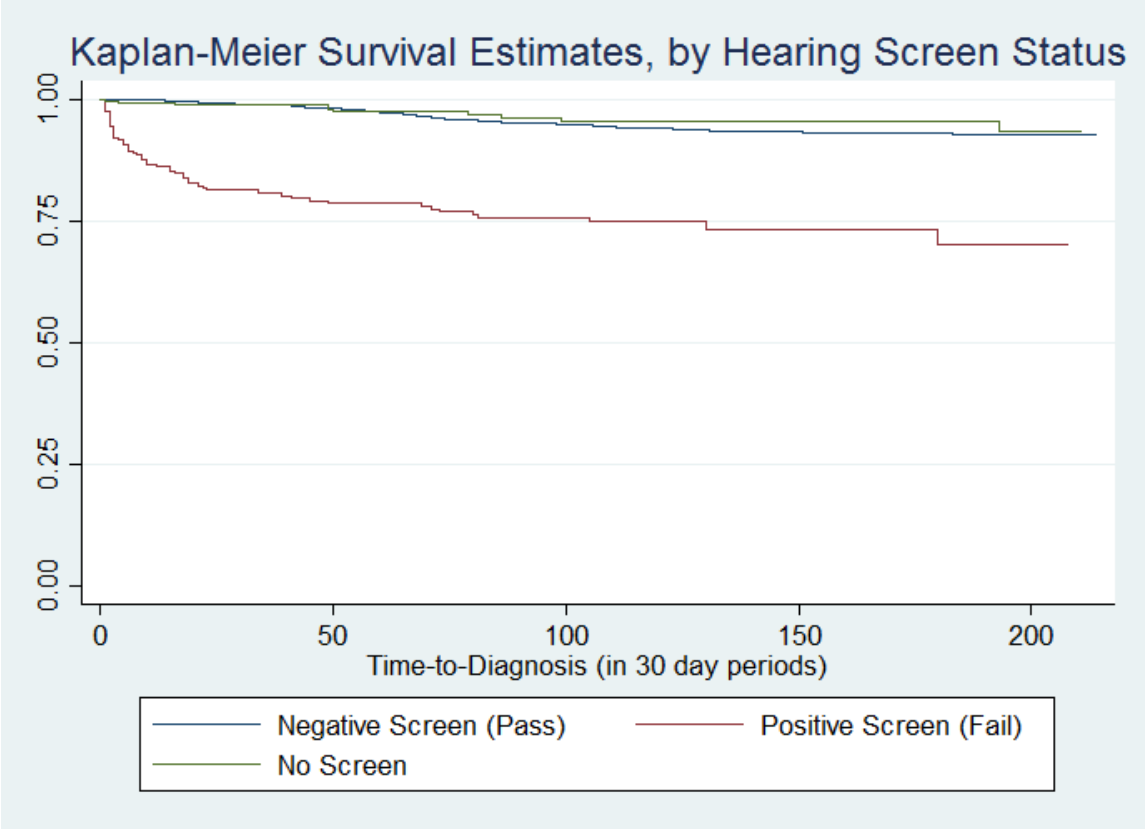


**Figure 9. Kaplan-Meier Survival Estimates, by Hearing Screen Status**

*Cox Proportional Hazards Regression*

A total of 4,855 eligible NICU infants with complete information, including 255 with a confirmed diagnosis of hearing loss, were included in the survival study. Infants born in the year 2000, and each subsequent year through 2007, were more likely to receive a hearing loss diagnosis during the monitored time period, compared to infants born in 1996. For example, the hazard ratio for the year 2007 is 4.55 (p-value=0.001)

indicating that infants with hearing loss that were born in 2007 were 4.55 times as likely as those born in 1996 to receive a hearing loss diagnosis during the period in which they received services in the health care system. As a reminder, these results are adjusted for hearing screen result using stratification. The complete results are available in Table 18.

The remaining significant predictors of hearing loss diagnosis confirm the prior results presented in the logistic model predicting hearing loss, with one exception. Infants with a length of stay greater than five days, those having received assisted ventilation during their admission, those with a craniofacial anomaly, and infants with neonatal infections were more likely to receive a hearing loss diagnosis during the study period, while black infants were less likely to receive a diagnosis (see Table 18). However, this analysis finds that infants in the racial category of "other" were more likely to receive diagnosis when adjusted for screening status (hazard ratio = 2.26, p-value=0.026).

**Table 18. Cox Proportional Hazards Model Results, Hearing Loss Diagnosis (n=4,855)**

| Variable | Hazard Ratio | P>z | [95% Conf. Interval] | |
|---|---|---|---|---|
| | | | | |
| 1997 | 2.07 | 0.085 | 0.90 | 4.74 |
| 1998 | 2.06 | 0.09 | 0.89 | 4.76 |
| 1999 | 1.73 | 0.229 | 0.71 | 4.24 |
| **2000** | **2.76** | **0.014** | **1.23** | **6.19** |
| **2001** | **3.02** | **0.007** | **1.35** | **6.76** |
| **2002** | **3.61** | **0.002** | **1.60** | **8.13** |
| **2003** | **2.49** | **0.033** | **1.07** | **5.77** |
| **2004** | **3.39** | **0.004** | **1.46** | **7.86** |
| **2005** | **3.20** | **0.008** | **1.36** | **7.55** |
| **2006** | **3.49** | **0.004** | **1.50** | **8.11** |
| **2007** | **4.55** | **0.001** | **1.81** | **11.48** |
| **Gender (*referent is Female*)** | | | | |
| Male | 1.00 | 0.981 | 0.78 | 1.29 |
| **Birthweight (*referent is 2,500-4,199g* )** | | | | |
| *>4,200g* | 1.06 | 0.862 | 0.52 | 2.19 |
| 1,500-2,499g | 0.79 | 0.117 | 0.58 | 1.06 |
| 1,000-1,499g | 1.16 | 0.534 | 0.72 | 1.86 |
| <1,000g | 1.40 | 0.283 | 0.76 | 2.59 |
| **Race (*referent is White*)** | | | | |
| **Black** | **0.41** | **<0.001** | **0.28** | **0.62** |
| Hispanic | 0.77 | 0.111 | 0.56 | 1.06 |
| **Other** | **2.26** | **0.026** | **1.10** | **4.64** |
| **Length of stay >5 days** | **1.93** | **<0.001** | **1.40** | **2.66** |
| **Ventilation** | **1.60** | **0.041** | **1.02** | **2.52** |
| **Craniofacial Anomoly Dx** | **4.58** | **<0.001** | **1.96** | **10.69** |
| **Neonatal Infection** | **5.24** | **0.023** | **1.25** | **21.86** |

*Survival Estimates for Significant Model Covariates*

The Kaplan-Meier Survival Curves presented below are for each of the significant variable from the Cox Proportional hazards regression model. Figure 10

shows that the probability of diagnosis early in the study period for infants categorized as having a racial category of other was higher than for the other groups (log rank test for equality: chi2=19.13, p-value=0.0003).

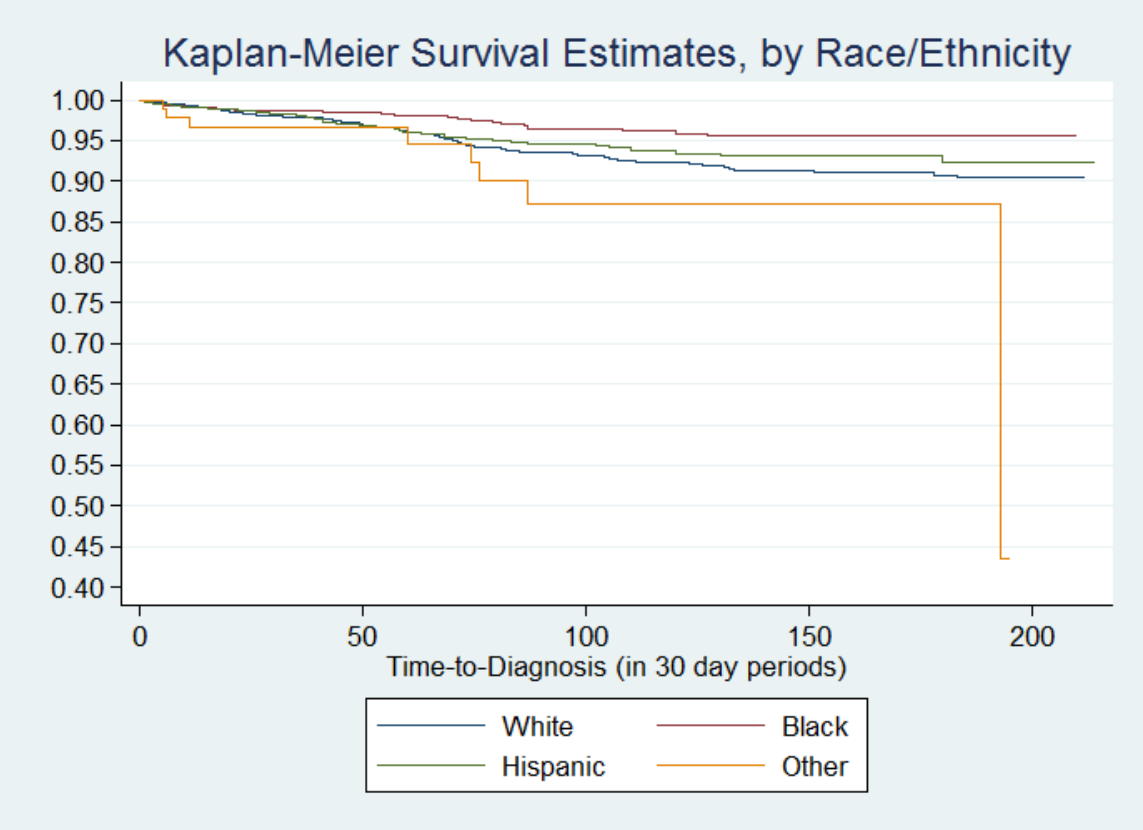


**Figure 10. Kaplan-Meier Survival Estimates, by Race/Ethnicity**

Figure 11 demonstrates that infants with a longer length of stay in the NICU also have a higher probability of early diagnosis than those with a stay five or fewer days (log rank test for equality: chi2=13.29, p-value=0.0003). Infants with longer lengths of stay

are likely sicker and require more frequent follow-up after discharge from the NICU, which may be the reason early diagnosis of hearing loss is more likely in this group.

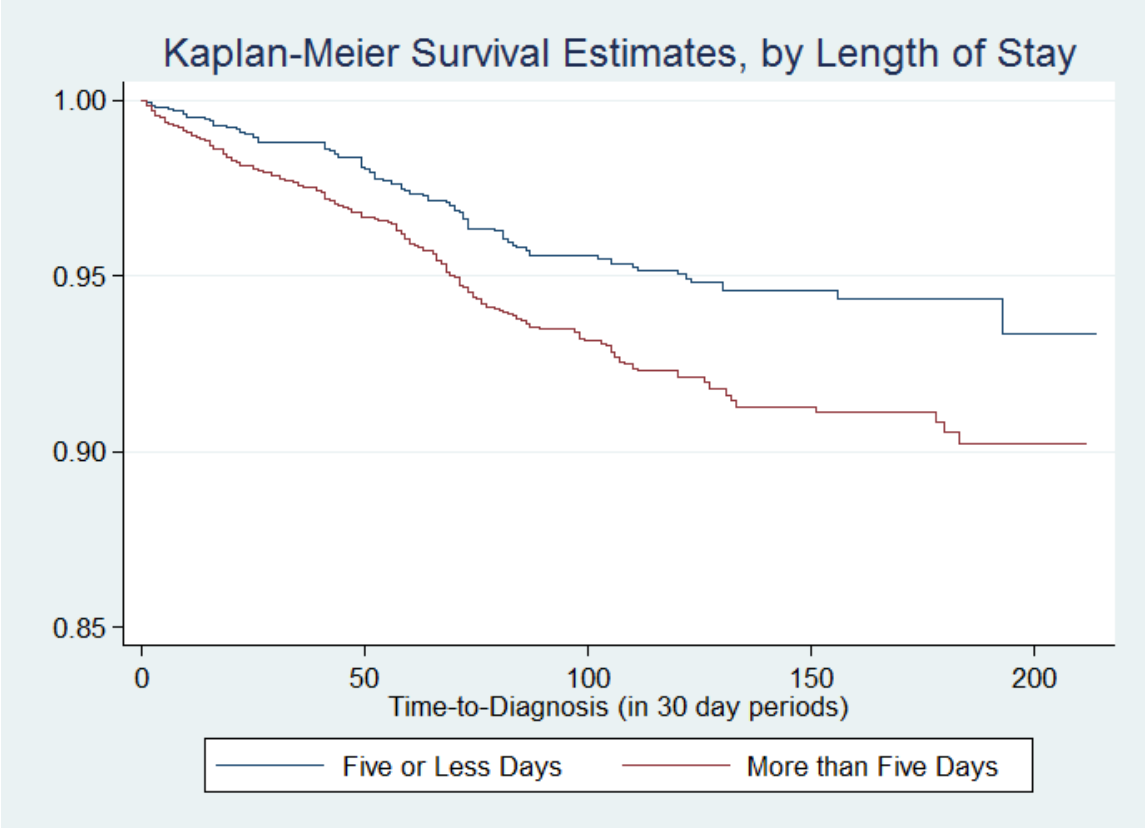


**Figure 11. Kaplan-Meier Survival Estimates, by Length of Stay**

Figure 12 shows that infants with diagnoses of craniofacial anomalies (log rank test for equality: chi2=63.53, p-value<0.0001) are more likely to receive earlier diagnosis of hearing loss. This diagnosis increases the likelihood of both hearing loss and of early diagnosis of hearing loss. Although neonatal infections increase the odds of

hearing loss (see Specific Aim 2), there is no difference in the survival functions for those infants with and without infections.

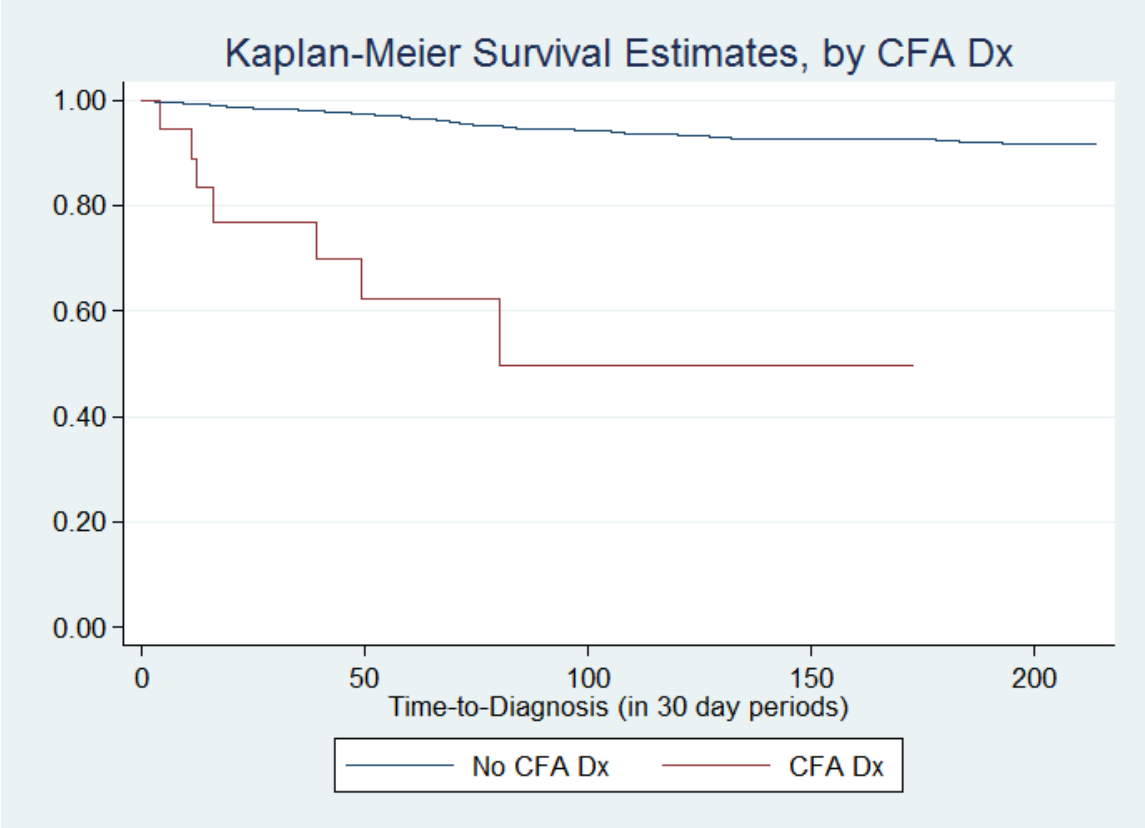


**Figure 12. Kaplan-Meier Survival Estimates, by CFA Diagnosis**

# CHAPTER V

# DISCUSSION AND CONCLUSIONS

Given the differing scope of methodologies used in Specific Aim 1 versus Specific Aims 2 and 3, the discussion below is separated into sections focusing first on the outcomes of the systematic review of neonatal databases and then on the findings from the portion of the study evaluating outcomes of newborn hearing screening.

## Specific Aim 1

Although birth outcomes such as prematurity and LBW may be relatively rare, infants with these outcomes and related conditions are more likely now than ever to survive their birth admission and receive community-based care in infancy and childhood. Often this care requires treatment of morbidities or chronic conditions associated with birth status or treatment thereafter, which motivates researchers to study short- and long-term outcomes that inform the practice of neonatology and pediatrics.

Three large databases focusing on premature, LBW, and/or very acutely ill neonates are available to researchers seeking to understand and improve birth and long-term outcomes for those infants. To date, an increasing number of studies using the three neonatal research databases have been published in the literature, and these studies use both prospective and retrospective research designs.

The studies include research in clinical areas important to advancing neonatal and pediatric medicine. For example, ten studies included in this review are part of the body of research on antenatal steroid use in mothers at risk of preterm delivery, and have

contributed to the body of research demonstrating both the risks and benefits of antenatal steroid use. Further, over 20 studies focus on encephalopathy, a condition affecting moderately premature infants. This is an important enough issue in neonatal medicine that an entirely separate registry was developed by the Vermont Oxford Network to allow for quality improvement and research efforts specific to encephalopathy. The diversity of studies published using one of the three databases is extensive and demonstrates the versatility that such databases provide to clinical and health services researchers.

The databases included in the review under Specific Aim 1 offer several advantages for researchers. First, each of the databases includes a large number of infants allowing for larger sample sizes and improved statistical power, especially when studying rarer conditions such as heart defects. Second, the databases include infants born or treated at multiple centers from diverse geographies, improving the likelihood of obtaining generalizable results in epidemiologic studies. Finally, the databases each have significant administrative guidelines and support, which provides researchers with valid and reliable data.

While a large proportion of studies focus on outcomes, there are variations in how long these outcomes are monitored within each database. The length of follow-up within each database varies, with many studies following infants through discharge from the NICU or hospital, and others, especially those with prospective data collection, follow infants into childhood. Nevertheless, consistent durations of long-term follow-up is currently limited. Researchers seeking to study disease epidemiology and long-term

outcomes may find opportunities with single center databases with smaller sample sizes. Single-center retrospective databases may offer data that are easier to obtain administratively and may be available for many years on each infant.

### *Study Limitations*

This review of studies utilizing data from existing neonatal databases expands on the work of Wright and Papile[74] and provides new information about how research on premature and LBW infants is evolving. The review is limited by a very focused search strategy that used the database names and abbreviations as the only search terms, which may have caused me to miss some studies that used the databases but did not reference the data source in the same way I searched. Even so, the search yielded 343 studies that were ultimately included in the review and I believe that this provides adequate power to show trends in this research area.

### *Implications for Research Practice*

Research into treatment and outcomes of premature and LBW infants is expanding, partially due to the availability of large, multicenter databases. The consistency of clinical conditions and neonatal outcomes studied since 1990 demonstrates that there are dedicated research agendas and resources that allow for long-term, and potentially replicable, studies within this population. Alternatively, the diversity of research topics and outcomes establishes an environment in which researchers can study new and innovative interventions or even some of the more rare conditions for which premature and LBW infants are at risk. These trends in neonatal research, specifically research focused on premature and LBW infants, offer a strong

foundation for future research efforts to inform neonatology, pediatric and perhaps even adult medicine with the remarkable improvements in survivability and improved long-term outcomes for these medically fragile infants.

The choice of a single center database for this study of newborn hearing screening was intentional and based on the fact that the database had data on hearing screening results and an average of ten years of follow-up on infants admitted to the NICU. Additionally, the database allowed for examination of epidemiologic trends in the outcomes important to newborn hearing screening since the data were systematically collected over the course of many years. The comprehensiveness of the available data and the extent of follow-up available (78 percent with confirmed follow-up, mean of 10 years) provided me with confidence in the internal validity of and ability to make inferences within the study.

**Specific Aims 2 and 3**

Implementation of newborn hearing screening within this single integrated health care system has improved since 1996, the first year of screening. Since then the proportion of infants receiving a screen has improved to steady rates around 98 percent in the final years of study. Screening rates were already improving prior to the 1999 passage of HB 714 in Texas, which required screening for all but the smallest hospitals and mandated full implementation by 2001. Between 1999 and 2001, the health system saw a slight decrease in screening rates and the cause of this is unclear, although it could be due to reassessment of organizational protocol to meet the requirements of the new law. After 2001, screening rates continued to steadily increase and stabilize. Screening

clearly targeted infants admitted to the NICU, presumably due to their increased risk, in the early years of the program, although screening rates in the newborn nursery were virtually equivalent to those in the NICU by 2001.

The health system also experienced a decrease in loss to follow-up over the study period. The system maintains a high rate of follow-up among infants admitted to the NICU, and this results of this study demonstrate that a high proportion of those infants are likely to have the opportunity for a hearing loss diagnosis within the system if they do, in fact, have hearing loss. Despite low overall rates of loss to follow-up, black infants are more likely to be lost to follow-up compared to white infants, suggesting that discharge planning for high-risk black infants may be useful in ensuring follow-up services after a positive hearing screen.

Over time, the specificity of the screen has improved, leading to a decrease in the relative number of false-positive results. Even with the general decline in false-positives, the rate had a period of increase in the late 1990s. Clinicians from the health system have advised that this increase was recognized and an organizational policy around staff training for quality improvement was implemented around 2000 or 2001. The data show that, after 2001, the false-positive rate improved to what is expected in a universal newborn hearing screening program, suggesting that organizational quality improvement initiatives can impact screening outcomes. After adjusting for birth year and other covariates, infants with extremely LBW, black infants, those that received assisted ventilation, and infants that received a diagnosis of persistent pulmonary hypertension were more likely to receive a false-positive screen result. This supports other study

findings that rescreening prior to discharge may reduce the rate of false-positives[422] and may further suggest that targeted rescreening is useful.

The sensitivity of the hearing screen, and associated false-negative rate, had less improvement over time and demonstrated less consistency across any given year. There is no single year where we observe a sustainable positive shift in the false-negative rate so this issue remains a prominent challenge, at least as of 2007. Infants with a longer length of stay and those with neonatal infections had an increased likelihood of a false-negative result, which indicates that targeted follow-up among these infants is important to ensure the earliest diagnosis possible. This assessment of false-negative rates may be biased due to the way in which I coded for hearing loss. All types of hearing loss are included and there is no differentiation between conductive, sensorineural, or delayed onset. The findings related to the high false-negative rate may be unusually high given the increased risk of delayed onset among NICU infants.[23] Further, it is not possible through the database to determine if there were post-discharge factors, such as head trauma, that led to hearing loss. In either case, the infants would not have had hearing loss during their birth admission and, therefore, a negative screen result at that time was probably accurate. As such, these results should be interpreted with some caution until future research determines the types of hearing loss actually diagnosed.

In this study, infants with a higher likelihood of hearing loss include those with craniofacial anomalies, neonatal infection, a length of stay greater than five days, and those receiving ventilation, confirming several risk factors cited by the JCIH, USPSTF, and other studies.[1, 10, 15-19] However, there was no difference in likelihood for infants

with hyperbilirubinemia or for those with LBW. Black infants had a lower probability of hearing loss in contrast to findings of other studies,[22] but they were also at higher risk of being lost to follow-up so diagnostic information may be missing. Receipt of oxygen is paradoxically associated with less likelihood of hearing loss, but there is no evidence from the literature that oxygen treatment is protective and there may be unmeasured clinical factors associated with these decreased odds. When adjusting for screening status in the Cox proportional hazards model, these results are mostly confirmed. However oxygen status no longer has an association with hearing loss while infants categorized as having "other race/ethnicity" have an increased likelihood of being diagnosed with hearing loss. Again, this may be due to unmeasured confounders since screening status is unlikely to have a causal relationship with hearing status.

Over the study period, the mean time-to-diagnosis has decreased and the difference prior to and after full implementation of HB 714 is statistically significant, although it was already declining. Infants that receive a positive hearing screen have a higher probability of early diagnosis, suggesting that the underlying motivations for universal newborn hearing screening are justified. Black infants have a slightly higher probability of later diagnosis, while infants categorized as "other race/ethnicity" have the highest probability of early diagnosis. Time-to-diagnosis for infants with certain risk factors for hearing loss (craniofacial anomalies, longer length of stay) are more likely to receive early diagnosis. Infants with a false-negative screen result had a probability of early diagnosis close to that for infants that had no screening at all. This may indicate

that targeted follow-up of high risk infants that did not fail the newborn hearing screen is a means to improving time-to-diagnosis.

### *Study Limitations*

This study includes several limitations. First, I was unable to include family history in the models due to unavailable data. This means the models are missing a well-documented risk factor for hearing loss, and a potential predictor of other outcomes such as loss to follow-up (presuming that families with a history of hearing loss are more aware of the need for early diagnosis and, therefore, are more likely to follow through with diagnostic assessment). Second, the study does not discern between types of hearing loss, which may impact interpretation of false-negative screen results. Infants documented in the study may actually have delayed onset hearing loss or other causes not related to the birth encounter, meaning that they were not likely to be identified through screening in the first place. Third, the data used in analysis are from the time period 1996 to 2007 and there could have been significant changes in program implementation and outcomes since that time. The 2007 JCIH statement includes a recommendation for routine follow-up and monitoring of high-risk infants, which may lead to earlier diagnosis among infants not identified through newborn screening after 2007, but was not measurable in the study.

Finally, this study focuses on implementation of screening within a single health system, potentially limiting the external validity or generalizability of the results to other centers or populations. Further, the health system began screening earlier than was mandated by law suggesting high levels of clinical and organizational motivation for

change possibly not true of all systems; and the center maintains a rate of follow-up that may not exist in other systems. This may limit the application of our results to other organizational or clinical settings. Even with these limitations, there are policy and clinical implications that arise.

### *Policy Implications*

The findings from this study provide further evidence in support of universal newborn hearing screening, namely the findings that hospital-based implementation is successful and that screening leads to earlier diagnosis for infants with hearing loss. Nevertheless, identification of hearing loss among high risk infants admitted to the NICU remains challenging. The high rate of false-negative screen results suggests that the JCIH recommendation for targeted follow-up and monitoring of high risk infants is justified. Coordination of efforts to ensure follow-up of these infants should be undertaken at both the state and organizational level.

Statewide rates of loss to follow up are high (approximately 40% in Texas in 2011), making the study of screening program outcomes difficult. However, studies within integrated health systems providing continuous care to infants after hospital discharge may provide insights into program success and opportunities for improvement.

As state newborn screening programs expand to include other point-of-care screening programs such as that for critical congenital heart disease, there is much to be learned from the history of newborn hearing screening. Facilitating quality improvement efforts, such as staff training programs, at local hospitals may be a particularly important component of any state law requiring universal screening at the bedside. Contrary to

traditional blood spot screening where state employees analyze, interpret, and follow-up on the screen, point-of-care screening shifts the burden of interpretation, parental notification, and referral to hospital staff.

### *Clinical Implications*

Clinicians and health systems can use the results of this study, and others, to identify opportunities to improve screening and follow-up. For example, infants with persistent pulmonary hypertension had a high probability of false-positive results so NICUs can consider rescreening prior to discharge to avoid time consuming and costly diagnostic testing. Similarly, targeted follow-up of infants with a length of stay longer than five days and those with neonatal infections may lead to earlier identification of hearing loss and earlier intervention. NICU follow-up clinics should continue to emphasize developmental screening, including that focused on assessing potential hearing loss.

Physicians can use the results of this study to identify infants at risk for any of the outcomes studied. Discharge planning should take into account the risk for false-positive and false-negative results into account. For example, the study finds that the probability of false-negative results were seven times higher for infants with neonatal infections compared to those without. This information may alert providers to the need for referral for follow-up despite the screening result, and in addition to the usual referral for general follow-up after NICU discharge. Similarly, community-based pediatricians caring for these infants after discharge and throughout childhood should be aware of infant and clinical risk factors that increase the risk of hearing loss, especially among

populations of infants with a high probability of false-negative screen results. The average marginal effects associated with the logistic models presented in this study may be particularly useful in clinical education and training, as they are easily interpretable and applicable to individual patients.

### *Future Research*

This study of hospital-based implementation of newborn hearing screening provides evidence for continuing universal newborn hearing screening, and makes recommendations for policy and practice. There are several opportunities for future research. First, this study should be expanded to include an analysis of the different types of hearing loss, specifically sensorineural hearing loss. NICU infants are at high risk of sensorineural hearing loss, which may have delayed onset. Analyses focused on the type of hearing loss may provide further explanation of the findings related to false-negative screen results and delayed time-to-diagnosis for infants with a false-negative.

Second, current procedural terminology (CPT) codes could be used to assess whether infants were receiving the intervention services as recommended by the JCIH. CPT codes would allow researchers to document services such as hearing and developmental assessments and receipt of amplification devices, potentially strengthening the general knowledge about factors associated with specific follow-up services, not just diagnosis.

Third, the study should be extended to the period after 2007 to identify progress in implementing Texas HB411, which provided follow-up guidelines and reporting requirements for hospitals and community-based practitioners. Finally, cost-

effectiveness studies could utilize the findings from this study, especially the marginal effects identified, to determine the marginal costs associated with outcomes such as false-positive and false-negative results among NICU populations.

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