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Research Article

High Risk Factors Associated With Early Childhood Hearing Loss: A 3-Year Review

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Purpose: In this study, we examined the association between risk factors for hearing loss and early childhood hearing status (normal hearing, congenital hearing loss, or delayed-onset hearing loss). Follow-up rates of audiologic care following passed or referred birth screens for children with risk factors were also examined.
Method: A retrospective data review was completed on 115,039 children born from 2010 to 2012. Data analyses included prevalence rates, odds ratios, and Fisher exact tests of statistical significance.
Results: Ninety percent of children were born with no risk factors for hearing loss; of those, 99.9% demonstrated normal hearing by 3 years of age. Of the 10% of children born with risk factors, 96.3% demonstrated normal hearing by age 3, 1.4% presented with congenital hearing loss, and 2.3% demonstrated permanent hearing loss by age 3. Factors that placed children at the highest risk of congenital hearing impairment were neurodegenerative disorders, syndromes, and congenital infections. Factors that placed children at the highest risk of developing permanent postnatal hearing loss were congenital cytomegalovirus, syndromes, and craniofacial anomalies.
Conclusions: Certain risk factors place a child at significantly greater risk of congenital hearing impairment or developing permanent hearing loss by age 3. Follow-up diagnostic testing should remain a priority for children with certain risk factors for hearing loss.

Prelingual hearing loss can negatively affect speech and language development, reading and writing skills, overall school performance, mental health, socialization, and other important aspects of development (e.g., Gurney et al., 2009; Moeller, 2000; Moeller, Tomblin, Yoshinaga-Itano, Connor, & Jerger, 2007; Yoshinaga-Itano, Coulter, & Thomson, 2000). For the two to three per 1,000 children who are born with hearing loss each year, early identification and intervention results in improved outcomes in all of these areas (Berninger & Westling, 2011). An important aspect of the early identification effort is universal newborn hearing screening (UNHS) programs, which have been implemented in all 50 states (Centers for Disease Control and Prevention, 2013).

As health care facilities have implemented UNHS programs, there has been growing interest in determining which infants to monitor during early childhood, as two per 1,000 children will develop hearing loss following the birth screen (Watkin & Baldwin, 2012). Without further monitoring, these children may remain undetected until signs of hearing loss manifest in speech-language, learning, or other developmental delays (Walker et al., 2014). It is important for Early Hearing Detection and Intervention (EHDI) programs to know which individuals are at risk of developing postnatal hearing loss and therefore should be monitored. Because of this, EHDI programs encompass more than just screening the hearing of infants at birth. Fundamental work to these programs is also tracking these individuals over time and examining the characteristics present in each child that contribute to hearing loss, particularly those that contribute to delayed-onset hearing loss.

The characteristics that contribute to the potential presence of hearing loss are described as risk factors. Risk factor information can help individual care providers determine hearing loss etiology, which is a benefit to the child and to public health. As a benefit to the child, knowing the etiology of hearing loss can lead to the provider being able to make more informed decisions about the

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course of treatment. As a benefit to public health, knowing the etiology of hearing loss allows EHDI programs to determine trends in developmental disabilities and the risks that are associated with these disabilities.

In their 2007 position statement, the Joint Committee on Infant Hearing (JCIH) identified 11 risk factors related to hearing loss in infants and children (JCIH, 2007). Eight of the 11 risk factors are primarily focused on delayed-onset hearing loss and thus are used to identify and monitor infants who pass their birth hearing screen but are at risk for developing hearing loss later in childhood. The 2007 JCIH statement recommends that all infants with a risk factor for hearing loss receive at least one audiologic assessment by 24 to 30 months of age, with more frequent and earlier monitoring of those with certain factors (e.g., craniofacial anomalies, family history of childhood hearing loss). The primary purpose of the current study was to examine the relationship between risk factors and hearing status (normal hearing, congenital hearing loss, or delayed-onset hearing loss). We sought to determine the prevalence of risk factors among newborns and the likelihood a child would be born with hearing loss or would develop hearing loss on the basis of his or her specific risk factor(s). A secondary purpose was to examine follow-up rates of audiologic care for children with risk factors in order to determine if infants with a risk factor for hearing loss were receiving the recommended audiologic assessment.

Although the JCIH recommendations are based on the likelihood of a risk factor causing hearing loss, studies establishing these risks are limited. The current literature focuses on the risk factors that place a child at an increased likelihood to develop delayed-onset hearing loss as opposed to being born with congenital hearing loss. Furthermore, only two recent literature reviews exist, and findings are mixed. For example, one meta-analysis completed by Vos, Senterre, Lagasse, Group, and Leveque (2015) evaluated risk factor studies from the years 2000 to 2015 by using the grading of recommendations, assessment, development, and evaluation (GRADE) assessment method to determine the level of evidence and strength of recommendation for each risk factor (Guyatt et al., 2008). Results revealed the following evidence levels for associations between a given risk factor and delayed-onset hearing loss: (a) Strong levels included congenital cytomegalovirus (CMV), toxoplasmosis, syphilis, or rubella; (b) moderate levels included a family history of hearing loss, hyperbilirubinemia, meningitis, or extracorporeal membrane oxygenation (ECMO) therapy; (c) weak levels included low Apgar scores; and (d) very low levels included congenital herpes, low birth weight, neonatal intensive care unit (NICU) stay, assisted ventilation, or ototoxic drugs. It is interesting to note that these results both confirm and conflict with those found in another comprehensive literature review. Beswick, Driscoll, and Kei (2012) evaluated 40 risk factor studies from the years 1973–2011. Results revealed the following evidence levels for associations between a given risk factor and delayed-onset hearing loss: (a) Strong levels included congenital CMV or ECMO therapy; (b) weak levels included genetic mutations, respiratory distress syndrome, or family history of hearing loss; and (c) no link included low birth weight or congenital toxoplasmosis. The discrepancies between these two comprehensive literature reviews are apparent: Although Vos et al. (2015) found a high level of evidence linking toxoplasmosis and hearing loss, Beswick et al. (2012) did not, and although Vos et al. (2015) found a moderate level of evidence linking ECMO and hearing loss, Beswick et al. (2012) found a stronger link. At the same time, there were also consistent findings: Both reviews found a high level of evidence linking congenital CMV and hearing loss, a moderate level linking family history and hearing loss, and little to no evidence linking low birth weight and hearing loss. These ambivalent findings illustrate the need for further large-scale research to examine the association between risk factors and postnatal hearing status. These comprehensive reviews that omitted congenital hearing loss also demonstrate the need for large-scale research to examine the association between risk factors and hearing loss present at birth. Although individuals with congenital hearing loss will likely be identified through the UNHS, determining the etiology is a critical component of public health. Because nongenetic factors (e.g., maternal infections, such as rubella, CMV, or herpes; toxins consumed by the mother during pregnancy; or birth injuries) account for approximately 25% of congenital hearing loss (American Speech-Language-Hearing Association, 2015), knowing the etiology of hearing loss allows EHDI programs to monitor and characterize trends in the risks that are associated with these developmental disabilities and, importantly, promote public health education and maternal safety practices.

No published studies to date have examined the relative risk of both congenital and delayed-onset hearing loss for a population of infants and toddlers who have one or more of the risk factors described by JCIH (2007). Only one such study, conducted by Beswick, Driscoll, Kei, Khan, and Glennon (2013), has examined which risk factor or combination of risk factors are most likely to predict postnatal hearing loss using odds ratios (ORs). In their study, 2,107 children who received a bilateral "pass" on the newborn hearing screen but had one or more risk factors for hearing loss were included and their hearing status examined. Only two risk factors, family history of hearing loss and craniofacial anomalies, predicted the occurrence of postnatal hearing loss in children. Results showed that family history of hearing loss made a child 1.92 times more likely to develop postnatal hearing loss than a child without a family history of hearing loss, and craniofacial anomalies made a child 2.61 times more likely to develop postnatal hearing loss than a child without craniofacial anomalies. With the exception of the Beswick et al. (2013) study, the literature linking risk factors and hearing loss are calculated using prevalence percentages that are based on a specific sample of individuals who have hearing loss and also have a risk factor or, conversely, a specific sample of individuals who have a given risk factor and if they developed hearing loss (i.e., frequency of occurrence) rather than calculating ORs (i.e., likelihoods). Because ORs are a measure

of association between an exposure and an outcome (i.e., these ratios represent the odds that an outcome will occur given a particular exposure in comparison to the occurrence in the absence of that exposure; Szumilas, 2010), it would be advantageous to use these statistical analyses when examining the impact of risk factors on hearing to understand likelihoods in addition to the frequency of occurrence.

The prevalence of those with hearing loss risk factors in the general population varies between 3% and 12% (e.g., Russ et al., 2002; Vohr et al., 2000; Wood, Davis, & Sutton, 2013). Of those individuals with at least one risk factor, the rate of hearing loss varies from 0% to 100%. Discrepancies in study findings have been vast and typically depend upon the location in which the given risk factor is studied; further, issues have been raised regarding sample sizes. For example, Weichbold, Nekahm-Heis, and Welzl-Mueller (2006) discovered that family history of hearing loss occurred at a rate of 2.86% (three out of 105 sampled) among individuals with hearing loss; in contrast, Beswick et al. (2013) discovered that family history of hearing loss occurred at a rate of 46.4% (26 out of 56 sampled). Another example includes congenital CMV, which was discovered in 7.4% (48 out of 651) of individuals by Dahle et al. (2000); 22% (13 out of 60) of individuals by Foulon, Naessens, Foulon, Casteels, and Gordts (2008); and 63% (77 out of 123) of individuals by Goderis et al. (2016). Because of the paucity of conclusive research examining hearing loss and JCIH risk factors, as demonstrated through comprehensive literature reviews by Beswick et al. (2012) and Vos et al. (2015), and incongruous results, such as the ones discussed above, prominent sources in the field of audiology have suggested that ongoing hearing monitoring for children with risk factors is unnecessary (e.g., Roush & Corbin, 2016).

In the state of Iowa, ongoing hearing monitoring for children with risk factors is recommended and outlined in Iowa Code Section 135.131, the same law that requires UNHS (Iowa Department of Public Health [IDPH], 2003). Mandatory hearing screening of all newborns has been implemented since 2004, with the exception of infants born with a condition that is incompatible with life or when there is active parent refusal of the hearing screen. This law mandates that any facility or health care professional is required to report to the IDPH the results of a hearing screen, hearing rescreen, or diagnostic assessment for any child younger than 3 years (IDPH, 2003) even when the outcome is normal hearing. The only allowable exception to reporting occurs when the hearing loss is a transient conductive hearing loss lasting less than 90 days in the best judgment of the practitioner. This exception will apply only if the child passed the initial hearing screening or rescreening or received a diagnostic assessment that resulted in normal hearing for both ears prior to the determination of the transient hearing loss. Since 2009, this legislation has also mandated the reporting of JCIH risk factors for all infants by providers who perform screenings and follow-up care. The parents and primary care provider of any child identified as having one or more risk factors receive a letter from the IDPH at 2 months of age indicating the need for a follow-up hearing screen at either 6 months or 24–30 months of age. In accordance with JCIH recommendations, the time at which follow-up care is recommended is based on the risk factor(s) present and their presumed likelihood of causing hearing loss (IDPH, 2008). This provides a unique opportunity to study the association between risk factors and congenital or delayed-onset hearing loss in a population of infants and toddlers.

Although it is strongly recommended that children with hearing loss risk factors return for follow-up audiologic care regardless of the birth screen outcome, it is certainly not required. Valuable resources are dedicated to notifying families of children with risk factors to return for follow-up, but no literature exists regarding the exact follow-up rates of these individuals. Although 2013 national EHDI data from the Centers for Disease Control and Prevention demonstrate that the national lost to follow-up rate for diagnosis was 32.1% (range = 0.0%–86.8%), with Iowa's lost to follow-up rate at 35.8%, there are no specific data regarding the follow-up rates for children with risk factors (Centers for Disease Control and Prevention, 2013). As there is an absence of these data, it is critical to determine the status of follow-up for children with risk factors so as to make appropriate recommendations for continuing to recommend follow-up care, examining factors related to loss to follow-up, or shifting recommendations for targeted follow-up procedures.

The current study aims to determine not only the prevalence of children with risk factors but also the likelihood of a child to present with hearing loss on the basis of his or her specific risk factor(s). Findings from this study, in conjunction with previous literature, may contribute to the growing body of literature regarding possible etiologies of hearing loss. Findings may also aid in shifting protocols for risk-monitoring programs, as issues with small sample sizes and inconsistent evidence related to various measures of risk have previously limited these recommendations. This study aims to answer the following questions:

1. What percentage of newborns is identified as having high risk factors associated with congenital or delayed-onset hearing loss?
2. What is the risk of congenital or delayed-onset hearing loss for infants and toddlers with risk factors relative to the risk for individuals without those risk factors?
3. What are differences in follow-up rates for children with risk factors (CWRF) who pass the newborn hearing screen and those who do not pass the newborn hearing screen?

Method

Data Extraction

The IDPH EHDI program utilizes an online database, Oz Systems eScreener Plus (eSP), to track all babies

born in the state of Iowa (IDPH, 2016). When a child is born, information including the birth location; date, time, and weight at birth; demographic information, presence or absence of risk factors for hearing loss (indicated by checking "yes" or "no" in the database); and hearing screening results are obtained from the infant's medical record and are entered into eSP. Each child's record is updated as more information becomes available (e.g., development of additional risk factors, additional hearing screenings, or diagnostic audiology information). All demographic and hearing health care information for each child under the age of 3 is included in eSP. All data from this study were retrieved from the eSP database, deidentified, and completed under the approval of the University of Iowa Institutional Review Board and through a data-sharing agreement with the IDPH. A list of risk factors documented for each individual in Iowa and the corresponding recommendation for audiologic assessment is located in Table 1.

Study Population

A retrospective population study was completed. All infants born in Iowa between January 1, 2010, and December 31, 2012, who received a hearing screen were included. All individuals included in this study reached their third birthday by the beginning of data collection and thus were considered to have complete records.

Data Analysis

Data extracted from eSP included information regarding birth nursery (i.e., well baby or NICU); hearing status (i.e., normal hearing or onset of permanent congenital or delayed hearing loss); risk factor presence or absence; and all audiologic results, including date and outcome of birth screen(s), hearing rescreen(s), and diagnostic evaluation(s). Presence of hearing loss or normal hearing was determined by the diagnosing audiologist for children who received an audiologic evaluation. For others, it was determined by the outcome of the last step in the screening and follow-up process. For example, a baby who passed the newborn hearing screen (NHS) and received no other follow-up was considered to have normal hearing for purposes of this study. A baby who did not pass the NHS and was later diagnosed with permanent hearing loss was considered to have congenital hearing loss. A baby who passed the NHS and was later diagnosed with permanent hearing loss was considered to have delayed-onset hearing loss.

Prevalence rates were calculated for hearing status given each risk factor. ORs and their 95% confidence intervals for congenital and delayed-onset hearing loss (before age 3 years) were calculated for each risk factor. ORs are a way to examine categorical data and describe the strength of the association between the risk factor and the hearing status outcome. Because the data examined are categorical in nature (i.e., outcome of hearing loss or outcome of

Table 1. Risk factors documented in the state of Iowa and their abbreviations.

Factor	Abbreviation
Parent or caregiver concern regarding hearing, speech, language, or developmental delay[a]	Concern
Family history of permanent childhood hearing loss[a]	Family Hx
Neonatal intensive care unit stay of greater than 5 days[a]	NICU
Extracorporeal membrane oxygenation[a]	ECMO
Assisted or mechanical ventilation	Vent
Exposure to ototoxic medications, including gentamicin, tobramycin, furosemide/lasix, chemotherapy	OtoMeds
Hyperbilirubinemia requiring exchange transfusion	Bili
Congenital cytomegalovirus[a]	cCMV
Congenital herpes	cHerpes
Congenital rubella	cRubella
Congenital syphilis	cSyph
Congenital toxoplasmosis	cToxo
Other culture-positive congenital infection	Cong Infect
Craniofacial anomalies, including cleft lip or palate, microtia, atresia, choanal atresia	CranioFac
Syndromes associated with hearing loss or progressive or late-onset hearing loss, including neurofibromatosis type II, Treacher Collins, Stickler, Pierre Robin Sequence, Goldenhar, CHARGE association, Usher syndrome, Waardenburg, Trisomy 21, Alport, Pendred, and Jervell and Lange-Nielsen[a]	Syndrome
Neurodegenerative disorder, including Hunter syndrome, sensory–motor neuropathies, Friedreich's ataxia, Charcot-Marie-Tooth syndrome[a]	Neuro Dis
Culture-positive postnatal infections associated with sensorineural hearing loss	Post Infect
Meningitis, bacterial or viral[a]	Mening
Head injury, especially basal skull or temporal bone fracture[a]	Head Inj
Apgar score 0–4 at 1 min	1Apgar
Apgar score 0–6 at 5 min	5Apgar
Birth weight lower than 1500 g	BW < 1500 g
Recurrent or persistent otitis media with effusion for greater than 3 months	OM > 3

[a]A child is recommended to see an audiologist for a hearing evaluation by 6 months of age; with the remaining factors, children are recommended to return at 24–30 months for audiologic follow up (Iowa Department of Public Health, 2008).

normal hearing) and certain risk factors only contained a small number of cases, the Fisher exact test was used to determine the level of statistical significance (du Prel, Rohrig, Hommel, & Blettner, 2010).

Results

What Percentage of Newborns Is Identified as Having High Risk Factors Associated With Congenital or Delayed-Onset Hearing Loss?

Between January 2010 and December 2012, 115,039 children were born in the state of Iowa and received an NHS. Of that number, 90% (n = 103,735) were identified as having no risk factors for hearing loss, and 10% (n = 11,304) were identified as having at least one risk factor for hearing loss (see Figure 1). It is important to note, while 90% of individuals were identified as having zero risk factors for hearing loss, this does not necessarily mean that these individuals did not in fact have risk factors for hearing loss but, rather, that risk factors were not reported, identified, or present by age 3. Among the 10% of those with identified risk factors, individuals had one to seven risk factors, and this breakdown can be seen in Figure 2. Figure 3 presents specific risk factors present in the study population. The most commonly occurring risk factors included ototoxic medication treatment in 54.3% (n = 6,137) of CWRF, NICU stay of greater than 5 days in 52.8% (n = 5,957), and family history of childhood hearing loss in 23% (n = 2,597). The numbers do not equal 100%, as 43% of the children presented with more than one risk factor.

Of the children with no reported risk factors, 99.9% (n = 103,640) had normal hearing up to age 3 years. Congenital hearing loss was present in 0.07% (n = 75), and 0.01% (n = 20) developed permanent hearing loss by age 3. Of the CWRF, 96.3% (n = 10,886) were documented as having normal hearing up to age 3 years. Congenital hearing loss was present in 1.4% (n = 163), and 2.3% (n = 255) developed hearing loss by age 3.

Table 2 displays prevalence rates for hearing loss among those with particular risk factors. The risk factors that were most commonly associated with congenital hearing loss (i.e., percentage of individuals with that specific risk factor who were identified with hearing loss from birth) included neurodegenerative disorders (66.7%, n = 2); syndromes (13.7%, n = 19); and congenital infections other than rubella, syphilis, herpes, toxoplasmosis, and CMV (10.5%, n = 4). The risk factors that were most commonly associated with delayed-onset hearing loss (i.e., percentage of individuals with that specific risk factor who presented with normal hearing at birth but were identified with hearing loss by age 3 years) included congenital CMV (18.8%, n = 3), syndromes (10.8%, n = 15), and craniofacial anomalies (9.9%, n = 22).

Figure 1. Breakdown of risk factors status and hearing status for study participants.

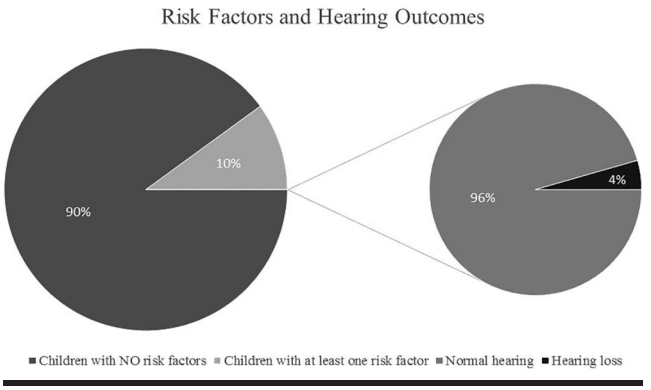
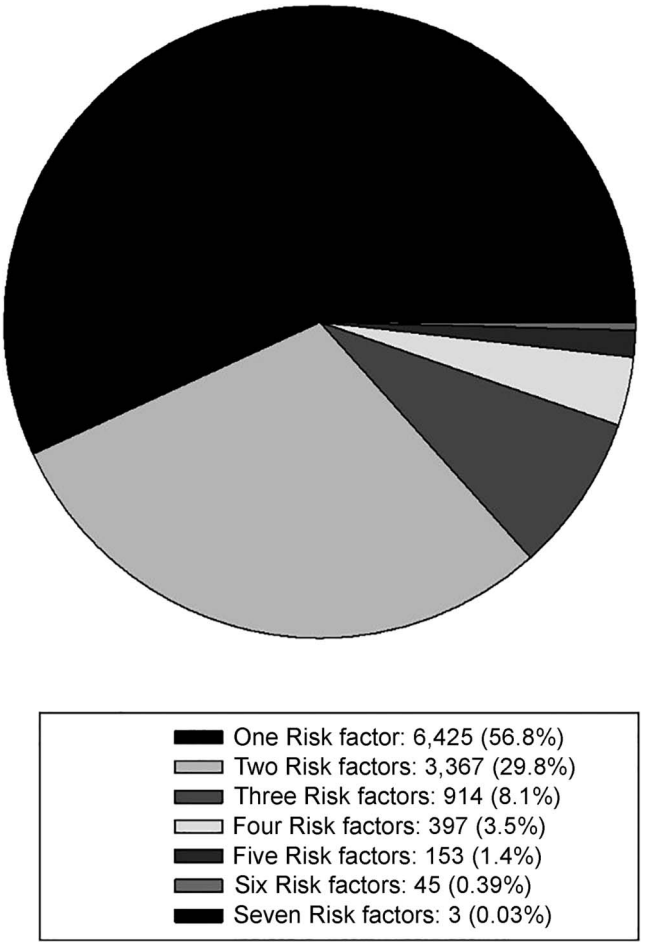


Figure 2. Number of risk factors present in each individual for those with one or more risk factors.



What Is the Risk of Congenital or Delayed-Onset Hearing Loss for Infants and Toddlers With Risk Factors Relative to the Risk for Those Without Risk Factors?

In addition to prevalence rates, ORs and their 95% confidence intervals were calculated for each risk factor (see

Figure 3. Risk factor presence and hearing loss in Iowa for the years studied. Hx = History; ECMO = extracorporeal membrane oxygenation; CMV = cytomegalovirus; BW = birth weight; OM = otitis media.

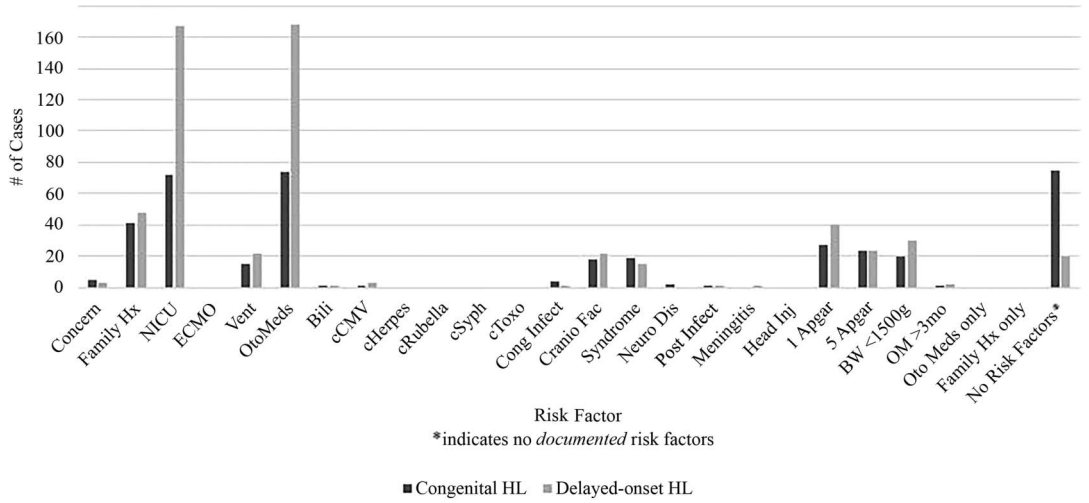


Table 3). If a risk factor has an OR of a given value (e.g., OR = 100), the odds that a child with that risk factor will have congenital hearing loss are 100 times greater than the odds of congenital hearing loss for a child without that risk factor. Risk factors that placed children at the highest risk of congenital hearing loss (i.e., largest OR in combination with highest statistical significance, $p < .001$) were neurodegenerative disorders (OR = 1,065.34), syndromes (OR = 104.57), and congenital infections (OR = 65.15). Risk factors that place a child at the highest risk of developing permanent postnatal hearing loss were congenital CMV (OR = 98.04), syndromes (OR = 58.38), and craniofacial anomalies (OR = 50.63).

Table 2. Risk factors present in the study population.

Risk factor	Total number with risk factor	Normal hearing, *n* (%)	Congenital HL, *n* (%)	Delayed-onset HL, *n* (%)	All hearing loss, *n* (%)
Concern	93	85 (91.4)	5 (5.4)	3 (3.2)	8 (8.6)
Family Hx	2,597	2,508 (96.6)	41 (1.6)	48 (1.8)	89 (3.4)
NICU	5,965	5,726 (96.0)	72 (1.2)	167 (2.8)	239 (4.0)
ECMO	3	3 (100.0)	0	0	0
Vent	555	518 (93.3)	15 (2.7)	22 (4.0)	37 (6.6)
Oto Meds	6,136	5,894 (96.1)	74 (1.2)	168 (2.7)	242 (3.9)
Bili	71	69 (97.2)	1 (1.4)	1 (1.4)	2 (2.8)
cCMV	16	12 (75.00)	1 (6.25)	3 (18.75)	4 (25.00)
cHerpes	2	2 (100.0)	0	0	0
cRubella	1	1 (100.0)	0	0	0
cSyphillis	1	1 (100.0)	0	0	0
cToxo	0	0	0	0	0
Cong Infect	38	33 (86.8)	4 (10.5)	1 (2.6)	5 (13.2)
Cranio Fac	222	182 (82.0)	18 (8.1)	22 (9.9)	40 (18.0)
Syndrome	139	105 (75.5)	19 (13.7)	15 (10.8)	34 (24.5)
Neuro Dis	3	1 (33.3)	2 (66.7)	0	2 (66.7)
Post Infect	35	33 (94.3)	1 (2.9)	1 (2.9)	2 (5.7)
Mening	18	17 (94.4)	0	1 (5.6)	1 (5.6)
Head Inj	17	17 (100)	0	0	0
1Apgar	1,314	1,247 (94.9)	27 (2.1)	40 (3.0)	67 (5.1)
5Apgar	537	489 (91.1)	24 (4.5)	24 (4.5)	48 (8.9)
BW < 1500 g	734	684 (93.1)	20 (2.7)	30 (4.1)	50 (6.9)
OM > 3	47	44 (93.6)	1 (2.1)	2 (4.3)	3 (6.4)
Oto Meds only	1,713	1,672 (97.60)	6 (0.35)	35 (2.00)	41 (2.40)
Family Hx only	2,358	2,281 (96.7)	35 (1.5)	42 (1.8)	77 (3.3)
No risk factors	103,735	103,640 (99.9)	75 (0.07)	20 (0.02)	95 (0.10)

Note. Included are prevalence rates for HL among those with a particular risk factor. HL = hearing loss; Hx = history; ECMO = extracorporeal membrane oxygenation; CMV = cytomegalovirus; BW = birth weight; OM = otitis media.

Table 3. Risk factors and the odds ratios associated with hearing status.

Risk factor	Hearing status	No	Yes	Odds ratio	95% confidence interval	*p* value
Concern	Normal	114,440	85			
	Congenital	212	5	31.754	12.757 to 79.040	< .001
	Delayed	292	3	13.820	4.4349 to 43.9960	< .001
Family Hx	Normal	112,017	2,508			
	Congenital	175	41	10.164	7.430 to 14.736	< .001
	Delayed	246	48	8.715	6.380 to 11.903	< .001
NICU	Normal	108,799	5,726			
	Congenital	144	72	9.500	7.151 to 12.622	< .001
	Delayed	127	167	24.985	19.806 to 31.519	< .001
ECMO	Normal	114,522	3			
	Congenital	217	0	0	0	1
	Delayed	295	0	0	0	1
Vent	Normal	114,007	518			
	Congenital	202	15	16.343	9.605 to 27.810	< .001
	Delayed	273	22	17.736	11.390 to 27.618	< .001
Oto Meds	Normal	108,631	5,894			
	Congenital	143	74	9.538	7.195 to 12.643	< .001
	Delayed	127	168	24.381	19.334 to 30.746	< .001
Bili	Normal	114,456	69			
	Congenital	216	1	7.680	1.062 to 55.544	.312
	Delayed	294	1	5.642	0.781 to 40.760	.450
cCMV	Normal	114,513	12			
	Congenital	216	1	44.179	5.720 to 341.250	.002
	Delayed	292	3	98.042	27.524 to 349.236	< .001
cHerpes	Normal	114,523	2			
	Congenital	217	0	0	0	1
	Delayed	295	0	0	0	1
cRubella	Normal	114,524	1			
	Congenital	217	0	0	0	1
	Delayed	295	0	0	0	1
cSyphillis	Normal	114,524	1			
	Congenital	217	0	0	0	1
	Delayed	294	1	389.537	24.308 to 6,242.460	< .001
cToxo	Normal	114,525	0			
	Congenital	217	0	0	0	1
	Delayed	295	0	0	0	1
Cong Infect	Normal	114,492	33			
	Congenital	213	4	65.154	22.883 to 185.509	< .001
	Delayed	294	1	11.801	1.609 to 86.565	.162
Cranio Fac	Normal	114,343	182			
	Congenital	199	18	56.827	34.335 to 94.053	< .001
	Delayed	273	22	50.629	32.023 to 80.045	< .001
Syndrome	Normal	114,420	105			
	Congenital	198	19	104.569	62.910 to 173.813	< .001
	Delayed	280	15	58.378	33.561 to 101.545	< .001
Neuro Dis	Normal	114,524	1			
	Congenital	215	2	1,065.340	96.242 to 11,792.635	< .001
	Delayed	295	0	0	0	1
Post Infect	Normal	114,492	33			
	Congenital	216	1	16.062	2.187 to 117.965	.085
	Delayed	294	1	11.801	1.609 to 86/565	.162
Mening	Normal	114,508	17			
	Congenital	217	0	0	0	1
	Delayed	294	1	22.911	22.911	.035
Head Inj	Normal	114,508	17			
	Congenital	217	0	0	0	1
	Delayed	295	0	0	0	1
1Apgar	Normal	113,278	1,247			
	Congenital	190	27	12.909	8.593 to 19.392	< .001
	Delayed	255	40	14.249	10.163 to 19.979	< .001
5Apgar	Normal	114,036	489			
	Congenital	193	24	28.999	18.800 to 44.732	< .001
	Delayed	271	24	20.653	13.478 to 31.646	< .001

(*table continues*)

Table 3. *(Continued).*

Risk factor	Hearing status	No	Yes	Odds ratio	95% confidence interval	*p* value
BW < 1500 g	Normal	113,841	684			
	Congenital	97	20	34.316	21.083 to 55.856	< .001
	Delayed	265	30	18.842	12.821 to 27.689	< .001
OM > 3	Normal	114,491	44			
	Congenital	216	1	12.047	1.652 to 87.828	.154
	Delayed	293	2	17.762	4.286 to 73.605	< .001
Oto Meds only	Normal	112,853	1672			
	Congenital	211	6	1.919	0.851 to 4.327	.188
	Delayed	260	35	9.086	6.363 to 12.974	< .001
Family Hx only	Normal	112,244	2281			
	Congenital	182	35	9.463	6.575 to 13.620	< .001
	Delayed	253	42	8.169	5.878 to 11.354	< .001

Note. Hx = history; ECMO = extracorporeal membrane oxygenation; CMV = cytomegalovirus; BW = birth weight; OM = otitis media.

Examination of Risk Factors in Combination

In this study, 43% of CWRF have more than one risk factor (see Figure 2). Attempting to examine all of the possible combinations of the risk factors results in more than four million different combinations, so one way to look at their combined effect is to count the number of risk factors each individual has. Table 4 presents the cumulative risk factor table. This table represents the hearing loss-onset likelihood on the basis of the number of risk factors present in a given individual. This table uses relative risk to compare the onsets with each other relative to normal hearing. For instance, the risk of congenital hearing loss with one risk factor is 41.38 and normal hearing is 57.35, so the relative risk is 41.38/57.35 = 0.72. Note that in Figure 4, the risk of congenital and delayed-onset hearing loss both increase as the number of risk factors increases. Using Table 4 to compare congenital versus delayed-onset hearing loss demonstrates how much the relative risk of congenital is higher than delayed. For instance, with three risk factors, congenital is 1.09 times higher than delayed, as 1.563/1.434 = 1.090. This is represented by the dashed black line in Figure 4. It is apparent that the risk of congenital and delayed-onset hearing loss are relatively the same until four or more risk factors, at which point congenital is greater and increases at a faster rate. The take-home message is that for those who have at least one risk factor, the risk of congenital or delayed-onset hearing loss increases with each risk factor when compared with normal. In addition, after about three risk factors, the risk is higher for congenital hearing loss than for delayed.

Table 4. Hearing loss-onset likelihood (OR) on the basis of number of risk factors present.

# of risk factors	1	2	3	4	5	6–7
Congenital HL	41.38	26.90	12.41	9.66	6.21	3.45
Delayed-onset HL	45.20	31.32	11.39	8.19	2.85	1.07
Normal hearing	57.32	29.78	7.94	3.31	1.25	0.37

Note. HL = hearing loss; OR = odds ratio.

Examination of Risk Factors in Isolation

Two risk factors in isolation were examined due to their well-established or equivocal association with childhood hearing loss and because they often occur alone: ototoxic medications and family history of hearing loss. Ototoxic medications in isolation was the third most commonly occurring risk factor (14.8%, $n = 1{,}713$). This risk factor demonstrated a higher rate of hearing loss than among the general population, as 2.4% ($n = 41$) of individuals were diagnosed with hearing loss by age 3. Of those children who received ototoxic medications and presented with hearing loss, 85.37% ($n = 35$) of cases were delayed in onset (see Figure 5). Further, ototoxic medication treatment alone demonstrated a significant relationship with congenital hearing loss (OR = 1.919, $p < .001$) and with delayed-onset hearing loss (OR = 9.086, $p < .001$).

Family history of hearing loss also demonstrated a higher rate of hearing loss than among the general population, as 3.3% ($n = 77$) of individuals were diagnosed with hearing loss by age 3 (see Figure 6). This risk factor demonstrated a significant relationship with congenital hearing loss (OR = 9.463, $p < .001$) and with delayed-onset hearing loss (OR = 8.169, $p < .001$).

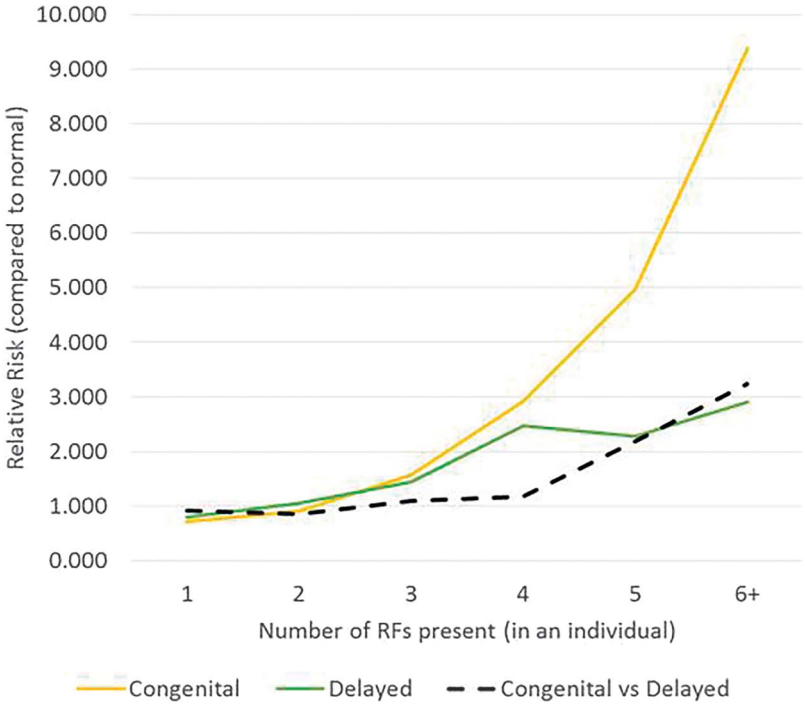
What Are the Differences in Follow-up Rates for CWRF Who Pass the NHS and Those Who Do Not Pass the NHS?

Follow-up rates for CWRF were examined (see Table 5) and compared using a chi-square test. Children who referred on the birth screening returned for an outpatient hearing screen (79%) significantly more frequently ($\chi^2 = 4{,}128.3$, $p < .001$) than did those who passed the birth screen (6%). Return rates for diagnostic testing were also significantly higher for those individuals who referred on the birth screening (43%–60%, $\chi^2 = 366.01$, $p < .001$) in comparison to those who passed the birth screen (21%).

Discussion

The primary purpose of the current study was to determine the prevalence of CWRF and hearing loss and

Figure 4. Risk factors in combination and the result on hearing status.



the likelihood of a child developing hearing loss on the basis of their specific risk factor(s). Between January 2010 and December 2012, 115,039 Iowa children received an NHS. Of the children with no reported risk factors, 99.9% demonstrated normal hearing up to age 3 years. Congenital hearing loss was present in 0.07%, and 0.01% developed permanent hearing loss by age 3. Of the CWRF, 96.3% were documented as having normal hearing up to age 3 years. Congenital hearing loss was present in 1.4%, and 2.3% developed hearing loss by age 3.

A secondary purpose was to examine follow-up rates of audiologic care for CWRF in order to determine if infants with a risk factor for hearing loss were receiving the recommended audiologic assessment. Children with risk factors for hearing loss who referred on the birth screening returned for an outpatient hearing screen and/or diagnostic testing significantly more frequently than did those who passed the birth screen. This may demonstrate the need for better education provided to the parents and health care providers regarding the association between risk factors and hearing loss, particularly for those with risk factors that are strongly associated with delayed-onset hearing loss. Current education practices for parents involve informing them that their child has a risk factor for hearing loss and instructing them to return at either 6 months or 24–30 months for a repeat hearing screening or hearing test. Parents subsequently receive a letter in the mail including this information. Improved education could involve explaining

Figure 5. Ototoxic medication exposure and hearing status.

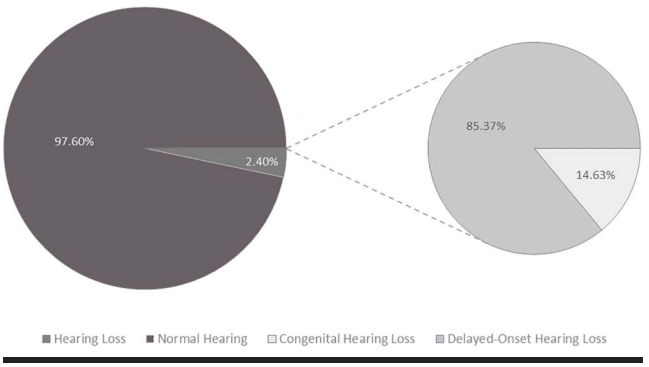


Figure 6. Family history of hearing loss and hearing status.

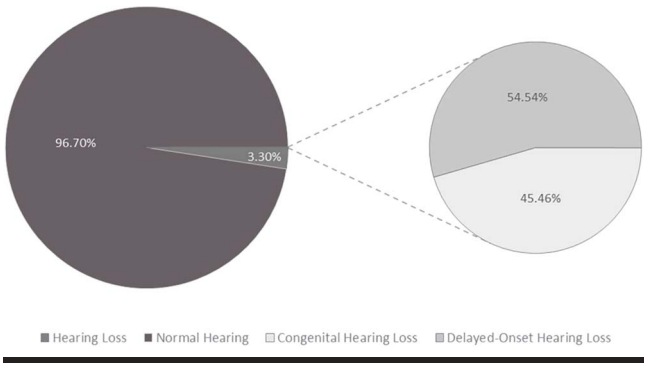


Table 5. Follow-up rates of audiologic care for children with risk factors.

Follow-up	Birth screen outcome	Returned for outpatient screen, *n* (%)	Returned for Dx testing, *n* (%)
Bilateral Refer	333	264 (79)	199 (60)
Unilateral Refer	480	379 (79)	205 (43)
Missed	85	72 (85)	22 (26)
Pass both	10,555	618 (6)	2,182 (21)
Total	11,453	1,333 (12)	2,608 (23)

Note. Dx = diagnostic (e.g., auditory brainstem response, behavioral audiometry).

the specific risk to their child (i.e., "Your child received ototoxic medications, and 4% of all children in Iowa who receive these antibiotics develop hearing loss by age 3. Because of this, we need you to come back to the hospital before age 3 so we can check to see if your child's hearing has changed.") Current education practices for providers involve a statement in the hearing screening clinical note that the child has a risk factor for hearing loss and will be contacted by the IDPH regarding follow-up testing. Improved education could involve explaining the specific risk to their patient, such as in the previous example, or more broadly, sharing data such as those presented in the current study through hospital in-service presentations for pediatric staff.

The Risk of Congenital or Delayed-Onset Hearing Loss for Infants and Toddlers With Risk Factors Relative to the Risk for Individuals Without Those Risk Factors

Iowa's EHDI legislation mandates that any individual working with a child must report risk factors and diagnostic audiologic evaluation results for all children up to 3 years of age. This legislation provides a unique opportunity to study the association between risk factors and congenital or delayed-onset hearing loss in a population of infants and toddlers. For babies born in Iowa from 2010 through 2012, we analyzed all risk factors to determine the likelihood of a child being affected by congenital hearing loss or delayed-onset hearing loss when the particular condition was present. Results indicated that the following were statistically significant risk factors in the occurrence of congenital hearing loss: neurodegenerative disorders, syndromes, congenital CMV, congenital infections, craniofacial anomalies, parent concern regarding hearing status, Apgar 0–6 at 5 min, NICU stay greater than 5 days, ototoxic medication treatment, low birth weight, assisted ventilation, Apgar 0–1 at 1 min, and family history of hearing loss. Results indicated that the following were statistically significant risk factors in the occurrence of delayed-onset hearing loss: congenital syphilis, syndromes, congenital CMV, craniofacial anomalies, parent concern regarding hearing status, Apgar 0–6 at 5 min, NICU stay greater than 5 days, ototoxic medication treatment, meningitis, low birth weight, otitis media for longer than 3 months, assisted ventilation, Apgar 0–1 at 1 min, and family history of hearing loss. It is apparent that there is significant overlap in the factors that cause both congenital hearing loss and delayed-onset hearing loss. Because of these findings, it is recommended that certain risk factors associated with hearing loss continue to be reported and targeted monitoring implemented. This information will not only continue to give insight into the causes of hearing loss, but will also allow for well-timed intervention and valuable parental and professional counseling. Risk factors including hyperbilirubinemia, congenital herpes, congenital rubella, and congenital toxoplasmosis likely no longer need to be reported and thus do not need to be monitored. Although not statistically significant, low numbers of reported cases make it equivocal to judge if meningitis and ECMO no longer need to be reported due to their known association with hearing loss.

Comparison of Current Findings to Existing Literature

Recent research (e.g., Hille, Van Straaten, & Verkerk, 2007; Kraft, Malhorta, Boerst, & Thorne, 2014; Pearson, Mann, Nedellec, Rees, & Pearce, 2013; Pourarian, Khademi, Pishva, & Jamali, 2012) did not find an association between specific JCIH risk factors and hearing loss (i.e., low birth weight, congenital infections, NICU stay greater than 5 days, ototoxic medication treatment, mechanical ventilation, syndromes, craniofacial anomalies). In contrast, the current study showed associations between these risk factors and hearing loss. The differences between the current study and others may reflect the need for a large sample size in order to detect small effects. Furthermore, the current study showed no association between hearing loss and congenital herpes, rubella, syphilis, or toxoplasmosis. In this case, the lack of association is due to the absence of such cases. Older studies showing associations between these diseases and hearing loss have been completed in less economically developed areas and often prior to widespread vaccinations against rubella, hence the previously reported increased incidence of hearing loss due to these diseases or infections (e.g., Roizen, 2003; Sellars & Beighton, 1983). This change validates that public health initiatives to reduce maternal and childhood infections and diseases have had a beneficial effect on childhood hearing.

Risk Factors in Combination

The demonstration of the association between risk factors and hearing loss may also reflect the need to further study the synergistic effect of risk factors in combination.

Many of these risk factors occur in combination (e.g., NICU stay greater than 5 days, assisted ventilation, and low birth weight; low Apgar score and ECMO therapy), with 43% of CWRF in this study having more than one risk factor. The current data suggest that as an individual has more risk factors present, it is more likely that he or she will have hearing loss than normal hearing. For those individuals who have at least one risk factor, the risk of congenital or delayed-onset hearing loss increases with each risk factor when compared with normal hearing. It is, however, difficult to compare how each risk factor compares to one another and to disentangle the effects of the presence of multiple risk factors as there are at least four million different combinations of risk factors. Hence, one way to examine their combined effects is to count the number of risk factors each individual has and compare the sheer number of risk factors between the different onsets. This information, in combination with the ORs for each specific risk factor, may allow the hearing health care professional or pediatrician to provide more informed recommendations for each individual's family in terms of risk monitoring (e.g., earlier hearing monitoring and/or more frequent monitoring) and the likelihood of a child developing hearing loss on the basis of their type and number of risk factors present.

Risk Factors in Isolation

Two risk factors were examined in isolation due to their high frequency of occurrence and known association or equivocal association with hearing loss. One of these factors was treatment with ototoxic medications due to the incongruous findings between hearing loss and ototoxic medications in previous studies (e.g., no association found by Hess et al., 1998, and Setiabudy et al., 2013; association found by Bielecki, Horbulewicz, & Wolan, 2011; Fuchs et al., 2016; Robertson, Tyebkhan, Peliowski, Etches, & Cheung, 2006; Zimmerman & Lahav, 2013) and the high number of babies who received ototoxic medications in the study population. In this study, treatment with ototoxic medications (when combined with other risk factors) was the most prevalent risk factor, and 3.9% of all hearing loss was associated with their use. This finding is well aligned with previous literature on this topic that has demonstrated positive associations between hearing loss and antibiotic use. When examining ototoxic medications in isolation, the risk factor was the third most commonly occurring. Even in isolation, ototoxic medications are a significant risk factor for hearing loss, demonstrating a higher rate of hearing loss than among the general population, as 2.4% of individuals were diagnosed with hearing loss by age 3. Of those children who received ototoxic medications and presented with hearing loss, 85.37% of cases were delayed in onset. Further, ototoxic medication treatment alone demonstrated a significant relationship with congenital hearing loss and with delayed-onset hearing loss. It is important to note that those individuals who received ototoxic medications and were identified with congenital hearing loss may have actually been born with hearing and developed hearing loss during their birth admission. This is a possibility because the "birth screen" is performed as close to discharge as possible, therefore following the completion of the antibiotic therapy. Further, the high OR associated with ototoxic medications and delayed-onset hearing loss highlights the importance of continued monitoring of children with this risk factor. Although these data do not provide information about type, dosage, or frequency of treatment, these data warrant further exploration of the link between hearing loss (particularly delayed-onset hearing loss) and ototoxic medications.

As approximately 60% of childhood hearing loss is genetic (Nance, 2003), the second risk factor examined in isolation was family history of childhood hearing loss. Family history is a significant risk factor for hearing loss, demonstrated by a higher rate of hearing loss than among the general population, as 3.3% individuals were diagnosed with hearing loss by age 3; this is even higher than the number of individuals who were diagnosed with hearing loss in the presence of ototoxic medication treatment only. This risk factor also demonstrated a significant relationship with congenital hearing loss and with delayed hearing loss. Although it is often assumed that a genetic hearing loss may be congenital, the present data show otherwise. Not only were the ORs nearly identical for congenital and delayed hearing loss with a family history of childhood hearing loss, the breakdown of onset was also nearly identical as well (45% congenital and 55% delayed onset). This highlights the importance of not only screening newborns at birth but also monitoring those with this risk factor until early childhood.

Recommendations

The findings outlined above indicate varied audiologic outcomes for children with risk factors but underscore the importance of continuing to utilize risk factor reporting as criteria to monitor individuals for audiologic follow-up. Although it was shown that 96% of all individuals with risk factors will likely retain normal hearing by age 3 years, resulting in potentially unnecessary evaluations for those children, the surveillance and follow-up provided for the 4% of children who will develop hearing loss is invaluable, critical, and worthy of this monitoring. Continued examination of risk factors in large-scale studies such as this will continue to lead to superior monitoring protocols to benefit all children screened at birth and particularly for those with risk factors for hearing loss.

Certain risk factors associated with hearing loss should continue to be reported. This information will not only continue to give insight into the causes of hearing loss, but will also allow for well-timed intervention and valuable parental and professional counseling and education. Other risk factors, including hyperbilirubinemia, congenital herpes, syphilis, rubella, and congenital toxoplasmosis, likely no longer need to be reported or monitored. Although not statistically significant, low numbers of reported cases make it equivocal to judge if meningitis and ECMO no

longer need to be reported due to their known association with hearing loss. Otitis media for longer than 3 months, postnatal infections, and head injuries are all postnatal risks and are often not reported in the EHDI database. Because there were so few accounts of these factors in this study, we cannot make a recommendation about if these risk factors should continue to be reported and audiologic follow-up warranted.

Limitations

One benefit of the Iowa eSP database is that many individuals enter data. Although this is an advantage as it ensures that there is a wide range of individuals completing records for each child, it is also a limitation of this study. Because there are nearly 400 individuals entering data, this may result in incomplete or inconsistent information entrance, and it is likely that the numbers presented in this study are actually an underestimate of the prevalence of risk factors. In addition to underestimating the prevalence of risk factors, it is also likely that the numbers presented in this study underestimate the number of individuals with hearing loss. Because the Iowa EHDI program only documents information in the eSP database until the child turns 3 years old, it is also possible that individuals developed hearing loss later in childhood and thus are not documented in this study. This is most likely among those individuals with congenital CMV, as it has been shown that hearing loss may not develop until later in childhood (Dahle et al., 2000). It is also certain that rates of CMV are highly underreported in this study. In a prospective study, Murph et al. (1998) found that 0.48% of Iowa newborns have congenital CMV. In the current study, only 0.01% of Iowa newborns were reported to have congenital CMV. Although CMV is the most common congenital infection in humans, 85%–90% of congenital CMV is asymptomatic (American Academy of Pediatrics, 2015) and thus a likely reason why the prevalence of congenital CMV among newborns was so low in this study. A further explanation of the low incidence of CMV reported in this study is due to the current CMV screening measures in place in Iowa. At present, there are no universal screening protocols in place for congenital CMV. If the incidence of congenital CMV is truly this underreported in the current study, it is certain that the prevalence of hearing loss due to this virus is also grossly underestimated in this study.

Loss to follow-up is a consistently reported statistic in NHS data and is due to a number of factors. In this study, loss to follow-up was also a limitation, and as a consequence, it is likely that there are undercounts of hearing loss. One example includes the infants reported as having ECMO. Although a larger number of children received ECMO treatment during the 3 years studied, only three "survived" the course of this extreme medical treatment and were reported in eSP. It is likely that there were more than three individuals who survived but that their ECMO risk status was not updated. These three also passed the UNHS. Of these three, two have no further tests on record, and one had documentation of normal hearing at 14 months of age with no further testing reported. In stark contrast, however, the literature has well documented the high incidence of delayed-onset hearing loss among individuals who received ECMO as compared with the general population (e.g., Cheung & Robertson, 1997; Fligor, Neault, Mullen, Feldman, & Jones, 2005; Murray, Nield, Larson-Tuttle, Seri, & Friedlich, 2011). In addition to this specific example and others of underreporting, documented follow-up rates can be seen in Table 4. The overall follow-up rate hovers between 12% and 23% for outpatient screening and diagnostic testing, demonstrating the possibility that, if anything, the prevalence of hearing loss is well undercounted.

Further, another area that is likely to have slight data imprecision is congenital hearing loss. For purposes of this study, *congenital* was defined as a refer on the hearing screen at birth and a subsequent diagnosis of permanent hearing loss. However, the birth screen is completed close to discharge, so it is possible that certain children, especially those who were long-term NICU inpatients, were born with normal hearing and subsequently lost their hearing during their course of treatment or stay. Although this does not necessarily make a large impact in terms of how we would treat the child audiologically and how it would affect our early intervention, it may affect recommendations for hearing health care in the NICU and, in the current study, is a potential source of data imprecision that is difficult to overcome.

Conclusions

The purpose of this study was to examine the association between risk factors for hearing loss and early childhood hearing status (normal hearing, congenital hearing loss, or delayed-onset hearing loss). After performing a retrospective data review of 115,039 children born over a 3-year time span, we reached the following conclusions:

- Certain risk factors put a child at significantly greater risk of having congenital hearing loss or developing hearing loss by age 3 years. This demonstrates the need for follow-up diagnostic testing to remain a priority for children with certain risk factors for hearing loss.
- The greater number of risk factors a child has, the more likely he or she is to have or develop hearing loss.
- Public health initiatives to reduce childhood infections and diseases have had a beneficial effect on childhood hearing.
- Awareness regarding and knowledge of associations between risk factors and hearing loss should be clearly communicated with families and health care professionals.

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