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Investigation of Predictors of Newborn Screening Refusal in a Large Birth Cohort in North Dakota, USA

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Abstract

Objectives The objective of this study was to identify maternal and provider predictors of newborn screening (NBS) refusal in North Dakota between 2011 and 2014. *Methods* Records of 40,440 live resident births occurring in North Dakota between 2011 and 2014 were obtained from the North Dakota Department of Health and included in the study. Factor-specific percentages of NBS refusals and 95% confidence intervals were computed for each predictor. Since the outcome is rare, multivariable Firth logistic regression was used to investigate maternal and provider predictors of NBS refusal. Model goodness-of-fit test was evaluated using the Hosmer–Lemeshow test. All analyses were conducted in SAS 9.4. *Results* Of the 40,440 live births, 135 (0.33%) were NBS refusals. 97% of the refusals were to white women, 94% were homebirths, and 93% utilized state non-credentialed birth attendants. The odds of NBS refusals were significantly higher among non-credentialed birth attendants ($p < 0.0001$), homebirths ($p < 0.0001$), and among those that refused Hepatitis B vaccination (HBV) at birth ($p = 0.047$). On the other hand, odds of NBS refusals were significantly ($p < 0.0001$) lower among women that had more prenatal visits. *Conclusions for Practice* This study provides preliminary evidence of association between NBS refusal and provider type, home births, and HBV refusal. Additional studies of obstetric providers, home births and women are needed to improve our understanding of the reasons for NBS refusal to better deliver preventive services to newborns.

Keywords Newborn screening · Parental refusal · Firth models · Logistic regression · North Dakota · Non-credentialed birth attendants · Homebirths · Lay midwives

Significance

What is already known on this subject? Although newborn screening (NBS) tests enhance early identification of newborns with potentially fatal and/or debilitating disorders, North Dakota state law allows parents to refuse NBS for any reason. While most studies on parental refusal of preventive services have focused on childhood vaccinations, little is known on parental refusal of preventive services during infancy.

What this study adds? North Dakota NBS and Vital Records data were utilized to identify maternal and provider predictors of NBS refusal. Study findings reveal that homebirths, refusal of Hepatitis B vaccine and non-credentialed providers were associated with NBS refusal.

Background

Newborn screening (NBS) refers to tests conducted on newborns for early detection of potentially fatal and/or debilitating disorders that can be identified through a few blood drops collected within a few days of life. With over 4 million newborns screened for congenital disorders each year in the United States (US), NBS remains the largest genetic screening program in the country (Green et al. 2006). Since the inception of the first screening test for Phenylketonuria (PKU) in the early 1960s, NBS has

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expanded to incorporate the screening for dozens of conditions, including but not limited to: amino acid disorders, fatty acid oxidation disorders, and endocrine disorders. As a result, over 6000 infants with genetic and/or metabolic disorders are detected through NBS tests each year (Centers for Disease Control and Prevention 2012). These allow for timely confirmatory diagnoses, referral, and treatment to avoid severe diseases or death (Centers for Disease Control and Prevention 2012).

In the United States, NBS is state-administered, with individual states taking ultimate responsibility in determining disorders to screen for, standards of practice, and the informed consent process on whether parents can opt-in or opt-out of NBS (American College of Medical Genetics Newborn Screening Expert Group 2006). Some states, such as Alaska and Hawaii, allow refusal of NBS services only for religious reasons; while others like North Dakota (ND) and Minnesota allow parents to refuse NBS for any reason (Newborn Screening Clearing House 2017). In ND, under ND Century Code (NDCC) § 25-17-02, parents who choose to refuse NBS are provided educational information on NBS by the attending care provider present at birth. The attending providers are required to submit a signed refusal form to the ND NBS Program (North Dakota Legislative Branch 2001).

Despite the well-established clinical efficacy of NBS (Grosse et al. 2016; Tran et al. 2007), the rate of parental refusal of NBS in ND has continued to rise. Given the important interaction that pregnant women have with their obstetric providers prior to, during, and after pregnancy, obstetric providers may play a critical role regarding how new mothers approach preventive measures, such as NBS (Committee on Genetics 2015; Larsson and Therrell 2002; Rose and Dolan 2012). With these issues in mind, the objective of this study was to identify maternal and provider predictors of NBS refusal.

Study Area

The study area included all 53 counties of ND which had a population ranging from 685,476 to 739,904 between 2011 and 2014, thereby remaining the fastest growing state in the nation. The racial distribution of ND is 87.9% White, 5.5% American Indian/Native American and 6.6% all other races. Approximately 3.6% of the residents are of Hispanic ethnicity (U.S. Census Bureau 2014). The study population included the cohort of live births occurring among ND residents between 2011 and 2014.

Conceptual Model for the Potential Predictors NBS

Predictors of NBS refusal are not well understood, therefore, our conceptual model showing the potential predictors of NBS refusal that guided our epidemiological/statistical modelling is shown in Fig. 1. This model is based on parental refusal literature, specifically, immunization refusal studies which have largely shown that parental vaccine refusal in the US is associated with higher income and educational levels, parental race, and regular use of alternative providers (such as chiropractors and naturopaths) (Dempsey et al. 2011; Marcewicz et al. 2017; Omer et al. 2009; Phadke et al. 2016; Sahni et al. 2014; Salmon et al. 2009; Schulte et al. 2014). Other maternal characteristics included in the conceptual model were maternal medical risk factors that have been identified by other studies as part of the criteria used by alternate obstetric providers, specifically midwives, in selecting low-risk clients for home or out-of-hospital births (Vedam and Kolodji 1995). Hepatitis B vaccination (HBV) at birth was included in the conceptual model because it was hypothesized that women who refuse preventive care like HBV for their infants would be more likely to refuse other preventive procedures like NBS compared to those who did not refuse the vaccine.

Data Sources and Management

NBS and birth certificate data were obtained for all births and NBS refusals occurring between 2011 and 2014 from the NDDoH. NBS refusal was defined as an infant whose parent or guardian had a written NBS refusal form signed and returned to the ND NBS Program.

Predictor Data

Data on potential predictors of NBS refusal were obtained from the birth certificate database. The variables extracted from this database included the maternal and infant health-related predictors presented in Table 1. Maternal socio-economic predictors such as maternal race, education, insurance status, and marital status were also obtained from the birth certificate database.

Information on birth attendant credentialing was also obtained from the birth certificate database and assigned to two distinct categories. The first category consisted of birth attendants who were licensed and overseen by a professional board in ND (North Dakota Legislative Branch 2016a, b). This category included birth attendants who self-reported as medical doctors (MD), doctors of osteopathic medicine (DO), or certified nurse midwives (CNM). The second category consisted of providers who identified themselves as

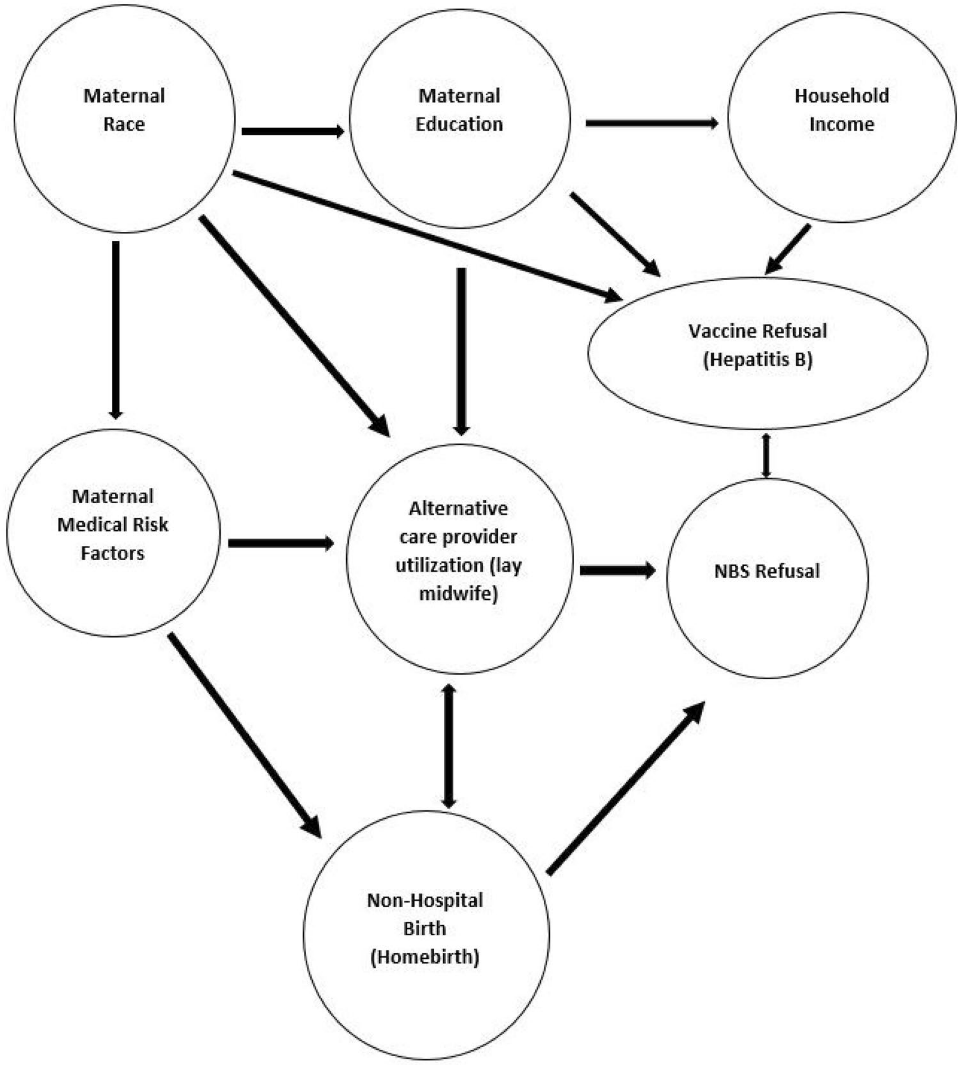

Fig. 1 Proposed conceptual model showing predictors of newborn screening refusal in North Dakota

an "other midwife" or "lay midwife". "certified professional midwives" (CPM) were also included in the non-credentialed category since they are not recognized or overseen by either the board of nursing or board of medicine in ND (North Dakota Legislative Branch 2016a, b). Registered and licensed provider names are publicly available in ND through the ND Board of Medicine and Board of Nursing websites. Therefore, missing credential information in the birth records were cross-referenced with the two licensing boards' websites to complete any missing provider credential information. The NBS Program also maintains a log of known lay midwives in the state. This was used to complete missing information on lay midwives. These combined efforts of identifying providers through the birth certificate database, the NBS lay midwives' log and the ND Boards of Nursing and Medicine, resulted in the correct classification of over 98% of all the births and the corresponding credential status of their birth attendants.

Information on household income is not collected on the ND birth certificate. However, NDDoH collects information on women who participate in the public benefit program for low income families called "Women, Infants and Children (WIC) Program" (North Dakota Department of Health 2016). Therefore, participation in the WIC program, was used as a proxy indicator of low household income. A binary variable indicating low household income (yes/no) was created based on participation in the WIC program. Women participating in the WIC program in ND also receive maternal education and counselling sessions on maternal and child health issues. Therefore, these variables along with maternal race, were considered as potential confounders and included in subsequent analyses.

Table 1 Demographic characteristics, by NBS status, of mothers of babies born in North Dakota between 2011 and 2014

Characteristic	NBS* refused	Percent	95% CI**	Non-refusal	Percent	95% CI**	Significant association
ND-born resident births (all)	135	0.33	(0.28, 0.39)	40,305	99.67	(99.61, 99.72)	
Provider type							
Non-ND credentialed	126	93.28	(88.97, 98.09)	91	0.44	(0.18, 0.27)	< 0.001
ND-credentialed	8	5.97	(1.91, 10.03)	40,129	99.56	(99.50, 99.63)	
Other/missing	**1**	0.75		85			
Place of birth							
Hospital/clinic/practitioner office	8	5.93	(1.89, 9.96)	40,003	99.33	(99.26, 99.41)	
Home birth	127	94.07	(90.04, 98.11)	268	0.67	(0.59, 0.74)	< 0.001
Socio-demographic factors							
Maternal race							
White	114	96.61	(93.30, 99.92)	33,385	85.28	(84.93, 85.63)	< 0.0001
Black/African American	***	***	(***,**)	1198	3.06	(2.89, 3.23)	
American Indian	***	***	(***,***)	3774	9.64	(9.35, 9.93)	
Asian/NH/PI	***	***	(***,***)	791	2.02	(1.88, 2.16)	
Missing	**17**			1157			
Maternal age groups							
<35	113	83.70	(77.39, 90.01)	36,273	90.00	(89.70, 90.29)	
>35	22	16.29	(9.99, 22.61)	4032	10.00	(9.71, 10.29)	0.01
Marital status							
In Wedlock	118	87.41	(81.74, 93.08)	27,154	67.15	(66.93, 67.85)	
Out of Wedlock	17	12.59	(6.92, 18.26)	13,136	32.48	(32.14, 33.06)	< 0.001
Maternal education							
Less than an associate's degree	84	69.42	(61.09, 77.75)	20,528	51.423	(50.94, 51.92)	< 0.0001
Associate's degree and above	37	30.48	(22.25, 38.91)	19,383	48.57	(48.08, 49.06)	
Missing	14			394			
Maternal WIC enrollment							
Yes	5	4.07	(0.53, 7.60)	10,678	27.49	(27.04, 27.92)	
No	118	95.94	(92.40, 99.47)	28,172	72.51	(72.07, 72.96)	
Missing	12			1455			
Payer/insurance status							
Third party payor	9	8.04	(2.92, 13.14)	25,099	62.18	(61.92, 62.86)	
Self-pay	103	76.30	(69.03, 83.56)	976	6.90	(6.65, 7.14)	< 0.0001
Other	23	17.04	(10.61, 23.46)	2776	2.42	(2.28, 2.58)	
Missing	0			77			
Maternal and infant medical risk factors							
Median number of prenatal visits	6.05		(5.61, 6.48)	10.67		(10.64, 10.71)	< 0.0001
Infant breastfed at birth							
Yes	134	99.26	(97.79, 100.00)	30,757	79.86	(79.46, 80.26)	< 0.0001
No	***	***	***	7758	20.14	(19.74, 20.54)	
Hepatitis B vaccine refusal							
Yes	80	59.26	(50.86, 67.65)	2900	7.20	(6.94, 7.44)	< 0.0001
No	55	40.74	(32.35, 49.14)	37,405	92.8	(92.55, 93.06)	
Precipitous delivery							
Yes	11	8.15	(3.53, 12.76)	959	2.38	(2.23, 2.53)	< 0.0001
No	124	91.85	(87.24, 96.47)	39,346	97.60	(97.5, 97.8)	
Previous C-section							
Yes	5	3.70	(0.48, 6.93)	5359	13.25	(12.96, 13.63)	
No	130	96.30	(93.07, 99.52)	34,946	86.70	(86.37, 87.03)	0.003
Maternal tobacco use							
Yes	***	***	(***,***)	4791	11.89	(11.57, 12.20)	
No	132	97.78	(95.26, 100.00)	35,514	88.11	(87.80, 88.43)	0.003

Table 1 (continued)

*Newborn screening

**95% confidence intervals

***Censored cases (i.e. cells with <5 subjects)

Statistical Analyses

Descriptive Statistics

Data were analyzed using SAS 9.4. Percentages and 95% confidence intervals were calculated for all categorical variables. Tests for normality (Kolmogorov–Smirnov) were conducted on the continuous variable, number of prenatal visits. Median and interquartile ranges were calculated for the two continuous variables since they were non-normally distributed.

Logistic Regression Model

Given the limited body of literature specific to NBS refusal, and utilizing the conceptual model shown in Fig. 1, model-building process was initiated by first assessing simple associations between predictor variables and NBS refusal using univariable Firth logistic regression models. All potential predictor variables that had univariable associations at an alpha-level of 0.10 level were considered for inclusion in the multivariable Firth logistic model which was then fit to the data using backwards elimination procedure. Firth logistic models were chosen for these data because the maximum likelihood estimation of the usual/ordinary logistic regression suffers from small-sample bias. Since there were small sample sizes associated with NBS, the Firth logistic regression provides better estimates than the usual/ordinary logistic regression models for these data (Georg Heinze and Schemper 2002). The advantage of the Firth model is that it uses penalized likelihood to reduce small-sample bias in maximum likelihood estimation (Firth 1993). In case of logistic regression, penalized likelihood also has the advantage of producing finite, consistent estimates of regression parameters in situations when maximum likelihood estimates do not exists due to complete or quasi-complete separation (Heinze 2006; Williams 2017). Confounding was assessed by examining whether the removal of a variable from the model resulted in a change of >20% in the coefficients of any of the other variables already in the model. Two-way interaction term between home births and provider type was assessed for significance in the final model. Hosmer–Lemeshow test was used to assess goodness-of-fit of the final model.

Results

Descriptive Analyses

Births eligible to participate in this study ranged from a low of 9211 in 2011, to a high of 11,005 in 2014, for a total of 40,440 births over the study period. The number of cases of NBS refusals ranged from a low of 23 in 2011 to a high of 47 in 2014, representing an over 100% increase in the count of cases of NBS refusal. The risk of NBS refusal over the same time period ranged from a low of 2.5 per 1000 live births in 2011 to a high of 4.3 per 1000 live births in 2014. As shown in Table 1, 0.33% (135/40,440) newborns had an NBS filed with the NDDoH. 93% of all NBS refusals were from women utilizing non-credentialed birth attendants compared to only 0.44% of non-credentialed providers among those who did not refuse NBS. Moreover, 94% of NBS refusals were associated with births occurring at home, compared to 0.7% of births occurring at home among those that did not refuse NBS. Note worth is the 157 homebirths attended by credentialed providers, none of which were NBS refusals. Approximately 97% of NBS refusals were to white women and, as expected from the racial distribution in ND, they also represented the majority in the non-refusal category at 85.2%. Interestingly, while about 90% of births among those accepting NBS were paid for by a third-party payer, 76.3% of the NBS refusals paid for their delivery out of pocket. Additionally, 59.3% of NBS refusals also refused HBV compared to only 7.2% among those not refusing NBS.

Firth Logistic Model Results

The effective analytic sample size used in the Multivariable Firth logistic regression was 37,559 new births, 121 of which were NBS refusals. Thus, the final Firth model used 93% (37,559/40,440) of all live births in the registry and 90% (121/135) of NBS refusal cases in the registry. Thus, the proportion of missing data is relatively small and is not expected to adversely affect study findings. Moreover, none of the categorical variables included in the final model had cell sizes <5. Based on the findings from the multiple Firth logistic model, deliveries attended by non-credentialed birth attendants had significantly higher odds of NBS refusal compared to those attended by a credentialed provider ($p < 0.0001$) (Table 2). Deliveries occurring at home also had significantly higher odds of NBS refusal compared to those occurring at birthing facilities ($p < 0.0001$). Infants who had recorded

Hepatitis B vaccine refusals had significantly higher odds of NBS refusal, compared to those that did not ($p=0.047$). The odds of NBS refusal were significantly ($p=0.02$) higher among infants born to women participating in WIC compared to those not participating in WIC. Babies born to women who had more prenatal visits had significantly ($p<0.0001$) lower odds of NBS refusal than those with fewer visits. Interestingly, although both non-credentialed providers ($p<0.0001$) and homebirths ($p<0.0001$) were significantly associated with higher odds of NBS refusal, no significant interaction between provider type and homebirths was observed indicating that the two variables work through different biological pathways in affecting NBS refusals. The Hosmer–Lemeshow goodness-of-fit test indicated that the model fit the data well ($\chi^2=4.23$; $p=0.84$).

Discussion

This study investigated predictors of NBS refusal and is the first of its kind to focus on maternal and provider determinants of NBS refusal and hence a scarcity of studies with which to compare the findings of our study. The rate of NBS refusal in ND was 0.33%, which is comparable to the 0.22% refusal rate of vitamin K prophylaxis in newborns, observed in Canada (Sahni et al. 2014). In our study, NBS refusal was higher among those utilizing non-credentialed providers and those that had homebirths. The fact that homebirths and provider type were both statistically significant in the final model suggests both are independent predictors of NBS refusal. Thus, the association between provider type and NBS refusal is not due to confounding by homebirths because if that was the case, there would be no significant association between provider type and NBS after controlling for homebirths in the model. If all the effects of provider type on NBS refusal was mediated through homebirths, then we would expect provider type to not have a significant association with NBS refusal when home-birth is added to the model. However, in our case both were significant in the final model implying that provider type has an independent association with NBS refusal (independent of home-births). Additionally, since the interaction between homebirths and provider type was non-significant it implies the predictors do not modify the effect of each other.

Table 2 Results of Firth logistic regression model assessing predictors of newborn screening refusal in North Dakota, 2011–2014

Predictor	Coefficient estimate	95% confidence interval	χ^2	p Value
Intercept	−2.5	−3.3 to −1.7	36.1	<0.0001
Non-credentialed provider (lay midwife)				
Yes	2.4	1.8–3.0	64.8	<0.0001
No	–		–	–
Home births				
Yes	1.6	1.0–2.2	26.3	<0.0001
No	–		–	–
Participated in women, infants and children program				
Yes	0.7	0.1–1.3	5.7	0.017
No	–		–	–
Number of prenatal visits	−0.3	−0.4 to −1.2	35.8	<0.0001
Hepatitis B vaccine refusal				
Yes	0.3	0.004–0.6	3.9	0.047
No	–		–	–

The association between NBS refusal and parental refusal of HBV is consistent with report from other studies evaluating the predictors of parental refusal of preventive services, such as, vitamin K prophylaxis, which have found that non-hospital births and those utilizing midwives had higher risk of vitamin K refusal (Hamrick et al. 2016; Marcewicz et al. 2017; Sahni et al. 2014). In their 2016 study on reasons for parental refusal of newborn vitamin K prophylaxis, for example, Hamrick, and others, reported that out-of-hospital births (birthing centers) had higher incidence of vitamin K refusal compared to those who had hospital deliveries (Hamrick et al. 2016). They also reported that parents who refused vitamin K were also more likely to refuse other prophylactic treatments such as Hepatitis B vaccine and erythromycin eye ointment for their newborns compared to those that did not refuse vitamin K (Hamrick et al. 2016). A key difference between our study and the one by Hamrick and co-workers was that birthing centers included in the latter investigation were staffed by only state-licensed practitioners (either certified nurse midwives or nurse practitioners). Sahni and others, in their 2014 study, also examined parental vitamin K prophylaxis refusal and reported that midwife deliveries had over eight-times [risk ratio (RR) = 8.4, 95% confidence interval (CI) 6.5–11.0] higher risk of vitamin K refusal compared to non-midwife deliveries. They also reported that home births had almost five-times (RR = 4.9, 95% CI 3.8–6.4) higher risk of vitamin K refusal than non-home births (Sahni et al. 2014). Given that non-credentialed providers in ND can only offer their services to women who choose to deliver at home, it is important to identify unique characteristics that lead women to choose homebirths. Boucher et al. investigated why women in the US deliver at home. The majority of respondents in their study were white women (87%) and most were married (91%). Additionally, 24% cited that the “desire to avoid medical interventions, routine procedures, and interferences” were their main criteria for choosing homebirth. (Boucher et al. 2009). This implies that women choosing homebirths are likely to refuse medical interventions (e.g. NBS) and are likely to seek providers likely to accommodate these preferences.

In this study, women refusing NBS were generally healthier during their pregnancies than those who accepted NBS, as evidenced by the lower percentages of maternal health-related risk factors, including smoking status, and histories of previous poor outcomes compared to those who did not refuse NBS. Those refusing NBS also had fewer prenatal visits, and were more likely to utilize non-credentialed birth attendants compared to those who did not refuse NBS. These findings are consistent with findings from other studies that reported that midwives tend to select homebirth clients who have low medical risks (Vedam and Kolodji 1995). This study found lower odds of NBS refusal among women who had more prenatal visits indicating the importance of following the recommendations of the American College of Obstetricians and Gynecologists on providing educational information to pregnant women on NBS during multiple prenatal visits (Committee on Genetics 2015; Larsson and Therrell 2002).

Given that the disorders screened for through NBS have the potential to cause severe morbidity and/or mortality, NBS refusal poses a unique challenge. New born screening is a multi-factorial process that can impose barriers to parents and providers alike (American College of Medical Genetics Newborn Screening Expert Group 2006). The process starts with the "education of parents and professionals; screening, which includes specimen collection, submission, and testing; follow-up of abnormal and unsatisfactory test results; confirmatory testing and diagnosis; medical management and periodic evaluation; and system quality assurance" (American College of Medical Genetics Newborn Screening Expert Group 2006). Future studies and efforts in NBS program planning should attempt to identify areas of improvement through each step, in order to encourage parents and providers alike to promote and accept NBS. Additionally, while NBS may not face safety concerns, storage of genetic material through the dried blood spot by state entities has raised ethical concerns for NBS programs. Most states, including ND, offer parents and legal guardians the option of retaining the dried bloodspot card after the screening has been conducted (Newborn Screening Clearing House 2017; North Dakota Legislative Branch 2001). Therefore, it is imperative for obstetric providers to fully inform new parents on all their options prior to and after NBS to alleviate these concerns and potentially minimize refusals.

Strengths

This study is the first of its kind to link NBS and birth certificate data in the U.S., and utilize this information to identify maternal and provider predictors of NBS refusal. Moreover, the ability to distinguish and include home births in this analysis was a key strength compared to recent similar studies, such as the vitamin K refusal study by Sahni and others, which attempted to study parental refusal issues, and cited this as a limitation (Sahni et al. 2014). Additionally, ND birth certificate data utilizes both self-reported variables, and variables extracted directly from maternal medical records by a medical certifier, hence minimizing self-reporting bias in the medical risk factor data. Furthermore, as demonstrated by Shoendorf and others, in their evaluation of vital statistics data to study perinatal health, use of these data is effective in minimalizing selection bias of samples and allows for study results that are representative of the birth population of interest (Schoendorf and Branum 2006).

Limitations

Since this was a retrospective study using secondary data, the predictors that could be investigated were limited to those available in the databases. Moreover, certain predictor were self-reported and hence prone underreporting bias. Additionally, some births may occur partially at home and completed at a hospital. Missing data in key variables was another study weakness. However, the proportion of missing data was relatively small and hence is not expected to adversely affect study findings. The fact that NBS refusal is a rare event also presented modeling challenges of small-sample bias. However, this was addressed using Firth logistic model that reduces small-sample bias. The small sample sizes may also affect the precision of the estimates. Thus, while this study is quite novel the findings should be interpreted with caution and further investigations are warranted to help strengthen the evidence. Lastly although the Health Department requires NBS refusal forms to be completed, there is no active tracking process for ensuring that parents that refuse NBS actually return the forms. These limitations notwithstanding, the findings of this study provide very useful information to guide future studies to help improve our understanding of the problem and hence improve provision of preventive services for newborns.

Conclusions

The results of this study have been successful in providing preliminary evidence of the association between NBS refusals and both home-births and provider type. Since NBS refusal has the potential to increase the chances of an infant's disorder being diagnosed late potentially resulting in complications or death, it is an area worth serious attention. Future studies will need to identify sub-populations that may have higher rates of NBS refusal, and explore patient and provider perspectives regarding NBS. They will also need to identify ways of addressing the problem in these populations.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval This study was reviewed and approved as exempt by both the ND Department of Health (NDDoH) (Approval Number: ND-014-42016) and the University of Tennessee, Knoxville Institutional Review Boards (IRB) (Approval Number: UTK IRB-17-04027-XM). Thus, the study has been performed in accordance with ethical standards laid down in the 1964 Helsinki Declaration and its later amendments. No identifying information was available in study data and all results are presented in aggregated form to ensure study subjects cannot be identified.

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