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Abstract

Objective

To investigate potential factors influencing initial length of hospital stay (LOS) for infants with neonatal abstinence syndrome (NAS) in Florida.

Methods

The study population included 2984 term, singleton live births in 33 Florida hospitals. We used hierarchical linear modeling to evaluate the association of community, hospital, and individual factors with LOS.

Results

The average LOS of infants diagnosed with NAS varied significantly across hospitals. Individual-level factors associated with increased LOS for NAS included event year ($P<0.001$), gestational age at birth ($P<0.001$), maternal age ($P=0.002$), maternal race and ethnicity ($P<0.001$), maternal education ($P=0.032$), and prenatal care adequacy ($P<0.001$). Average annual hospital NAS volume ($P=0.022$) was a significant hospital factor.

Conclusion

NAS varies widely across hospitals in Florida. In addition to focusing on treatment regimens, to reduce LOS, public health and quality improvement initiatives should identify and adopt strategies that can minimize the prevalence and impact of these contributing factors.

Introduction

Neonatal abstinence syndrome (NAS) is a constellation of signs of drug withdrawal most commonly occurring in newborns after in utero exposure to opioids.(1) Withdrawal signs develop in 55-94% of newborns exposed to opioids in utero.(1–5) From 2004 to 2014, the incidence of NAS in the United States (US) increased to 8.0 per 1000 hospital births representing a greater than 5-fold increase in infants born with NAS.(6) Paralleling national trends, Florida also witnessed an increase in the incidence of NAS from 1999 to 2013, from 0.4 to 6.3 per 1000 live births.(7)

Infants with NAS are at increased risk of birth complications,(8,9) admission to the neonatal intensive care unit (NICU),(9–11) and a prolonged hospital length of stay (LOS).(8,9,12) The average LOS of infants with NAS in the US between 2009 and 2012 was 17-23 days.(8) Contributory factors associated with increased LOS are maternal methadone use,(13–15) lack of adherence to treatment protocol, and lack of standardization in clinical management.(15,16) State Medicaid programs fund the hospital care of more than 80% of infants with NAS in the US.(6) Total annual hospital charges billed to Medicaid are estimated to be $1.5 billion.(8) This costly public health issue invites new strategies to lessen opioid morbidity among pregnant women and their infants.

To date, no studies have investigated the contribution of individual, hospital and community level factors to increased LOS for infants born with NAS. Such factors may explain the marked observed inter-hospital variation in LOS in Florida. The few studies evaluating LOS for NAS infants in the US have focused on total medical costs,(8,17,18) quantification of LOS,(10,19) comparison of LOS in infants with and without NAS,(10) and assessment of the

relationship of LOS to pharmacological treatment strategies.(13–16) Other studies have described reductions in the LOS of infants with NAS achieved by a focus on non-pharmacological management using the East, Sleep, Console approach.(20,21)

To fill this gap, we investigated to what extent individual, hospital, and community factors were associated with increased LOS that may explain the inter-hospital variation in LOS of infants diagnosed with NAS in Florida from 2010-2015.

Methods

We conducted a retrospective cohort study among newborn infants in Florida with a diagnosis of NAS who were discharged between January 1, 2010 and September 1, 2015, just prior to the transition to ICD-10-CM implementation. We linked birth certificate and hospital discharge administrative data. This included linking resident births in non-military or veteran administration hospitals using a valid social security number as a primary linkage variable. As this linkage was predominantly dependent on a valid social security number, mothers with an undocumented immigrant status were excluded. Florida Department of Health and Agency for Health Care Administration (AHCA) approved this use of the linked data file; the Florida Department of Health and University of South Florida institutional review boards approved the study.

Participants

The study was restricted to include infants with a NAS diagnosis by ICD-9-CM code 779.5 or 292.0 (n=8698) resulting in a NAS incidence rate of 3.9 per 1000 births. Of these we excluded the following (Figure 1): 3192 infants who were not admitted to Florida hospitals with level II or III NICUs; 1201 infants that were not term (37–41 completed weeks of birth gestation); 84

infants that were not singleton; 28 infants that were not live births weighing ≥2500 g; 529 infants with known preexisting fetal or placental conditions or significant anomalies or a diagnosis of NAS who might have been treated with opioids after birth for medical conditions such as hypoxic-ischemic encephalopathy, tracheoesophageal fistula, congenital diaphragmatic hernia, omphalocele, or gastroschisis. We also excluded 278 infants from 27 hospitals that had fewer than 20 NAS admissions over the study period, as well as 191 infants who were transferred to another hospital. Based on the American Academy of Pediatrics (AAP) recommendations that prenatally opioid-exposed neonates be monitored for a minimum of 5 days after delivery, we excluded 167 infants with a LOS less than 4 days as they were unlikely to have NAS.(1) To eliminate conditions requiring markedly prolonged hospitalizations, infants with a LOS greater than 80 days were also excluded. We noted that the average LOS of infants born with NAS being 17-23 days(8) and that only 7 of infants with NAS in our study experienced a LOS > 80 days and had associated comorbidities requiring longer LOS. There were 37 missing values not included in the study, resulting in our study population of 2984 infants with NAS.

Variables

We selected individual, hospital, and community factors for analysis based on existing literature, their clinical significance, and their ability to be abstracted from our data set. The study included the following individual factors: event year (2010 – 2015 [Q1-Q3]), birth gestational age (37 – 41 weeks), infant's sex (male, female), mother's age (<20, 20-29, 30+ years), mother's race/ethnicity (non-Hispanic white, other), mother's nativity (US born, other), mother's education status (≤ high school, > high school, unknown), marital status (married, not married), parity (no previous deliveries, ≥1 previous delivery, unknown), prenatal care (inadequate/unknown, intermediate, adequate/adequate plus), maternal smoking in 3rd trimester

(yes, no/unknown), and mother's insurance status (Medicaid/Medicaid Managed Care, other). Hospital factors included: hospital's highest NICU level (II, III), Pediatric residency program (no, yes), annual hospital birth volume (<3000, 3000+), average annual NAS volume (4-19, 20-51 infants), and urbanicity of hospital's geographic location (urban – *Large Central/Large Fringe Metro*, and non-urban – *Medium/Small Metro/Micro/Noncore/Unknown*). Community factors included: urbanicity of county where mother resided (urban – *Large Central/Large Fringe Metro*, and non-urban – *Medium/Small Metro/Micro/Noncore/Unknown*) and median family income among households with children in county where mother resided. Prenatal care categories were defined by the Kotelchuck Index, that measures prenatal care utilization based on timing of initiation of care and number of prenatal visits attended after initiation. Prenatal care utilization is defined as inadequate (<50% of recommended prenatal visits), intermediate (50-79%), adequate (80-109%), and adequate plus (≥110%).(22)

We combined maternal age groups into three categories due to small numbers in each group. Due to very small percentages of Hispanic, black, and other race/ethnicity categories, we dichotomized Maternal race and ethnicity variable into two categories as 'non-Hispanic white' and 'Hispanic, blacks, other'. We included maternal nativity as a variable because during the study period, 31% of all births in Florida were to foreign-born women.(23) For maternal insurance the 'other' category (i.e. self-pay, private insurance, and Tricare) was combined because the numbers were small in each group and there were no significant differences between these groups. We excluded missing and unknown values for maternal age, race and ethnicity, education level, and mother's parity that contributed less than 10% to variable frequency. The 'average annual NAS volume' variable was dichotomized based on the clinical belief that it was a reasonable threshold to separate lower experience from higher experience hospitals. Also, on

inspection of our data, 20 NAS admissions per year produced a natural break in the distribution histogram.

Statistical Analysis

We used hierarchical modeling with hospitals and counties as random effects due to the nested nature of contributing factors. However, the county level was not significant as a random term so was removed from the random effects. This analysis provided estimates of the variability in NAS LOS across hospitals (i.e., between-hospital variance) and factors associated with LOS. Using the glimmix procedure in SAS software version 9.4 (SAS Institute Inc, Cary, NC) and starting with a full model, non-significant ($P<0.05$) variables were removed sequentially in reverse order of significance (backwards and stepwise regression). We eliminated non-significant variables at every level in the model to maximize statistical power and increase the ability to identify key study variables at each level. We explored several models, comparing for the smallest Akaike Information Criterion (AIC) value which was used to assess the fit of the final model selected, and found the lognormal function produced the most parsimonious model to transform the skewed LOS data. Consequently, estimates from the final model were back transformed to their original units. The Intraclass Correlation Coefficient (ICC) was used to investigate the random term. Finally, as a sensitivity analysis, we re-ran the model using the maternal smoking in the 3rd trimester variable categorized as ‘Yes’, ‘No’, and ‘Unknown’.

Results

The study population consisted of 2984 infants with NAS born in 33 hospitals across Florida from January 1, 2010 to September 1, 2015. The number of infants diagnosed with NAS was greatest in 2014 (18.7%) and lowest in 2010 (13.6%). The majority of infants born with NAS were male (53.7%). The proportion of infants with NAS by gestational age was highest at 39

weeks (35.9%) and lowest at 41 weeks (6.2%) respectively. Most of these infants were born to mothers who were 20-29 years old (63.8%), non-Hispanic white (89.5%), US born (96.9%), not married (76.1%), and had an equivalent to or less than high school education (66.4%). Most of these mothers received inadequate/unknown prenatal care (43.3%, of which 13.6% were unknown), had at least one previous delivery (69%), did not smoke or smoking status was unknown in the 3rd trimester of the pregnancy (57.8%), and utilized Medicaid or Medicaid Managed Care as their mode of health insurance (85%). Among hospital level factors, most hospitals had an annual average of 20-51 infants with NAS (60.9%), were more likely to have a level III NICU (58.1%) than level II, had an annual total birth volume of less than 3000 births (57%), did not have a Pediatric residency program (67.2%), and were located in an urban geographic location (60.4%). Infants with NAS were more likely to be born to mothers who resided in an urban county (90.1%), and in counties where the average family income among households with children was $53,630.67 (±$7947; Table 1).

The median LOS for our study population was 16.0 days (IQR=7.0-26.0) and a mean of 18.7 (SD 13.6) days. The random effect of the hospital was tested and found to be significant ($P<0.001$). Amongst infants diagnosed with NAS, the average LOS varied predominantly within hospitals rather than between hospitals [ICC=0.038] (Figure 2).

The final multivariable model (Table 2) contained remaining significant individual and hospital factors associated with LOS. This model had the smallest AIC compared to other models that were explored (i.e. the quality of our model was the best compared to other statistical models for the given data). Individual factors included event year ($P<0.001$), gestational age at birth ($P<0.001$), maternal age ($P=0.002$), maternal race and ethnicity ($P<0.001$), maternal education ($P=0.032$), maternal insurance status ($P=0.066$), and prenatal care adequacy ($P<0.001$).

Average annual NAS volume (P=0.022) remained as a significant hospital factor in addition to the other variables included in the final model. Infant gestational age (18.4%), maternal prenatal care (17.7%), and hospital average annual NAS volume (14.3%) explained at least 50% of the final multivariable model. There were no significant community factors in the final model.

While the trend of each additional event year resulted in a decrease in hospital LOS (Figure 3), infants with NAS born in 2015 spent almost 3 days less in hospital than infants born in 2010. Additionally, each week increase in term gestational age at birth added almost an additional day of LOS for an infant with NAS. Infants with NAS born to mothers 20-29 years of age and 30 years or older had a 3-4 day difference in LOS compared to those born to mothers less than 20 years of age. Infants with NAS born to non-Hispanic white mothers had a longer LOS in hospital than those of Hispanic/black/other mothers. Likewise, infants with NAS born to mothers with a high school or lower education spent slightly longer in hospital than those whose mothers had a greater than high school education. Although not statistically significant, insurance status (P=0.066) was retained in the final model due to its clinical significance. Infants whose mothers used Medicaid/Medicaid Managed Care had a LOS longer than infants of mothers who used other types of insurance. The LOS of infants whose mothers received inadequate/unknown prenatal care or intermediate prenatal care was 1-2 days longer than the adequate/adequate plus prenatal care group, respectively. Hospitals with an average annual NAS volume of 4-19 infants reported a LOS of 13.5 (CI 11.9-15.3) days, almost 3 days longer than hospitals with an average annual NAS volume of 20-51 infants (LOS 10.8 (CI 9.2-12.8) days).

The sensitivity analysis where we examined maternal smoking in the 3rd trimester categorized as ‘Yes’, ‘No’, and ‘Unknown’, yielded a similar not significant result as the variable categorized as ‘Yes’ and ‘No/unknown’.

Discussion

Paralleling national data that demonstrate a marked progressive increase in the number of infants diagnosed with NAS,(8) the number of infants with NAS in Florida (not taking into account NAS cases excluded from this study) also increased from 405 births in 2010 to 559 births in 2014. Infants with NAS had longer hospital LOS compared to non-NAS infants and greater associated healthcare costs, which has a significant impact on local and statewide public health. Our finding is consistent with previous studies that report longer hospital LOS for infants with NAS.(8,9,12) Within the 33 delivery hospitals in Florida meeting inclusion criteria, LOS for infants with NAS varied significantly across hospitals, and was associated with a number of individual and hospital factors in Florida. Prior studies have shown that maternal methadone use, lack of adherence to treatment protocol, and lack of standardization in clinical management contribute to longer LOS.(13–16) Our study has identified infant and maternal factors (infant's year of birth, infant's gestational age at birth, maternal age, maternal race and ethnicity, maternal education, maternal prenatal care, and maternal insurance status), and a hospital factor (lower average annual hospital NAS volume) that also increase LOS in Florida.

Despite an increase in the number of infants born with NAS from 2010 to 2015, LOS for infants with NAS has decreased since 2010. This was likely due to a combination of guidelines and standardization of care of infants with NAS in Florida. Some strategies implemented during this period to improve national and statewide NAS response and surveillance included Florida becoming one of only four states that required NAS be a reportable condition,(24) the creation of the prescription drug monitoring program Electronic-Florida Online Reporting of Controlled Substance Evaluation Program (E-FORCSE) in 2009,(25) and initiatives aimed at improving physician prescribing practices in pregnant women and women of childbearing age, in addition

to providing educational and outreach resources.(24) Likewise, an increase in provider knowledge and experience in the field coupled with recommendations for standardization of opioid and NAS diagnosis, pharmacological and non-pharmacological interventions and management may be responsible for the decrease in NAS LOS,(1,26,27) in spite of an increasing prevalence during the study period in Florida.

At term gestation, each additional week of gestation resulted in a slight increase in hospital LOS. This finding runs counter to what one observes in infants without NAS and is likely due to decreasing risk of maturational complications. Infants with NAS born to mothers 20 years and older had a longer hospital LOS compared to those born to mothers younger than 20 years old. Our findings are consistent with studies in other states that have shown that infants with NAS are more likely to be born to mothers who are non-Hispanic white and covered by Medicaid/Medicaid Managed Care.(17,19) Additionally, our population-based study has shown that these same factors, including maternal high school education or less, are associated with a longer LOS for infants with NAS. Infants with NAS born to mothers who received below the recommended prenatal care level (i.e., inadequate/unknown or intermediate prenatal care) had a longer hospital LOS. Finally, NAS infants born at level II or III NICU hospitals with an average annual NAS volume of less than 20 births had a significantly longer LOS. NAS volume may be related to having more experience in providing the consistent quality of care required by these infants resulting in a decrease in LOS.(28)

Our analysis highlights a limited number of factors that are potentially modifiable and may be exploited to reduce the average LOS for infants with NAS at a statewide level. For example, there is a need to address prenatal care access and quality of prenatal care. This presents an important opportunity to not only identify opioid dependence during pregnancy, but

to address psychosocial needs and facilitate maintenance treatment and referrals to needed services for improved infant and maternal outcomes.(29) Additionally, using regionalization of care at hospitals that care for large numbers of infants with NAS may allow for standardization of management and lead to lower LOS.

Using hierarchical modeling to assess the factors that might have contributed to increased LOS among infants with NAS was unique to this study. Our findings are consistent with studies in other states that have shown that infants with NAS are more likely to be born to mothers who are non-Hispanic white and covered by Medicaid/Medicaid Managed Care.(17,19) Additionally, our population-based study has shown that these same factors are associated with a longer LOS for infants with NAS.

During the study period from 2010-2015 (Q3), NAS outcomes were reported using only ICD-9 codes. We did not wish to include later years during which time hospitals transitioned to using ICD-10 codes because the performance of these new codes had not been validated. Only recently have studies on the accuracy and completeness of clinical coding using ICD-10 been published.

Using birth certificate and hospital discharge administrative data resulted in limitations for this study. It did not allow for detailed exploration of the impact other factors potentially might contribute to LOS, such as the type of maternal opioid exposure, access to and adherence with opioid maintenance therapy, maternal co-exposures (e.g., anti-depressants, marijuana, gabapentin), infant treatment protocol, and social factors that may have delayed hospital discharge of the infant (e.g. abandonment, foster care placement). Also, unknown or inaccurate ICD-9 coding information may have resulted in misclassification of NAS diagnosis. However,

using population-based data do offer the best opportunities to assess many of the studied factors at multiple levels.(30) Finally, although most NAS cases are found in level II and level III NICUs, we excluded infants with NAS who were treated at these hospitals and were transferred to another hospital for further care. This resulted in 2.9% of infants with NAS meeting all other study screening criteria that were excluded from our study. Because this proportion of transfers excluded was small, and the LOS distribution for this group at level II and level III hospitals was similar to the LOS for infants included in the study, this exclusion was unlikely to skew our results.

We have identified individual and hospital factors that are associated with initial LOS for infants with NAS in Florida. Our study has also shown that most variation in NAS LOS occurred within hospitals rather than between hospitals. Therefore, in addition to focusing on treatment regimens, to reduce LOS, public health and quality improvement initiatives which are geared towards improvement within hospitals, should identify and adopt strategies to minimize the prevalence and impact of these contributing factors.

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Author Contributions: All authors conceptualized and designed the study. CR and TF conducted data analysis. CR drafted the initial manuscript and received critical input from TF, AM, MH, MB, RK, RW, and WS in the final manuscript.

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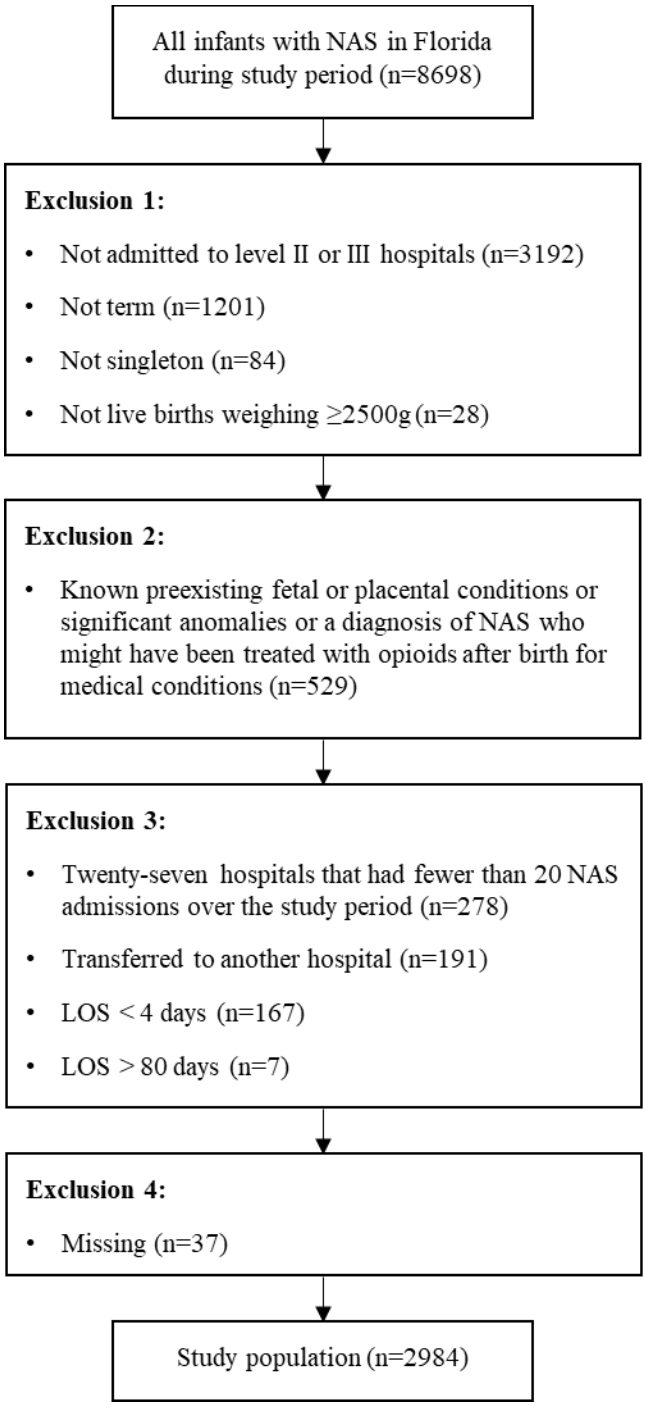


Figure 1. Flow diagram of infants with NAS included in the study

Table 1. Distribution of individual, hospital and community level factors among infants diagnosed with Neonatal Abstinence Syndrome in the study population vs non-NAS births: Florida, 2010-2015

Characteristics	Statistics	
	NAS Births	Non-NAS Births[a]
Total, n (%)	2984 (100)	23543 (100)
Individual factors		
Event year, n (%)		
2010	405 (13.6)	4000 (17.0)
2011	491 (16.5)	4006 (17.0)
2012	522 (17.5)	4164 (17.7)
2013	547 (18.3)	4096 (17.4)
2014	559 (18.7)	4201 (17.8)
2015*	460 (15.4)	3076 (13.1)
Gestational age, wk		
mean (sd)	38.7 (1.1)	38.7 (1.1)
Infant sex, n (%)		
Female	1383 (46.4)	10400 (44.2)
Male	1601 (53.6)	13141 (55.8)
Maternal age, n (%)		
<20 y	60 (2.0)	2012 (8.5)
20-29 y	1093 (63.8)	12312 (52.3)
30+ y	1021 (34.2)	9212 (39.2)
Maternal race and ethnicity, n (%)		
non-Hispanic white	2672 (89.5)	10917 (46.4)
Hispanic, black, other	312 (10.5)	12626 (53.6)
Maternal nativity, n (%)		
US born	2892 (96.9)	17290 (73.4)
Other	92 (3.1)	6253 (26.6)
Mother married, n (%)		
No	2272 (76.1)	12912 (54.8)
Yes	712 (23.9)	10630 (45.2)
Maternal education, n (%)		
≤High school	1980 (66.4)	12197 (51.8)
>High school	1004 (33.6)	11346 (48.2)
Maternal parity, n (%)		
No previous deliveries	925 (31.0)	12000 (51.0)
≥1 previous delivery	2059 (69.0)	11543 (49.0)
Prenatal care, n (%)		
Inadequate/unknown	1293 (43.3)	6029 (25.6)
Intermediate	484 (16.2)	3829 (16.3)
Adequate/adequate plus	1207 (40.5)	13685 (58.1)
Mother smoked in 3rd trimester, n (%)		
No/unknown	1724 (57.8)	22084 (93.8)
Yes	1260 (42.2)	1459 (6.2)

Maternal insurance status, n (%)		
Medicaid/Medicaid Managed Care	2536 (85.0)	13653 (58.0)
Other	448 (15.0)	9890 (42.0)
Hospitals factors		
Neonatal intensive care unit level, n (%)		
II	1249 (41.9)	7697 (32.7)
III	1735 (58.1)	15846 (67.3)
Annual hospital birth volume, n (%)		
<3000	1701 (57.0)	9518 (40.5)
3000+	1283 (43.0)	14025 (59.5)
Annual average NAS volume, n (%)		
4-19	1166 (39.1)	
20-51	1818 (60.9)	
Pediatric residency program, n (%)		
No	2006 (67.2)	14405 (61.2)
Yes	978 (32.8)	9138 (38.8)
Hospital urbanicity, n (%)		
Large Central/Fringe Metro[b]	1802 (60.4)	16486 (70.0)
Medium/Small Metro, Micro, Noncore, unknown[c]	1182 (39.6)	7057 (30.0)
Community factors		
County urbanicity, n (%)		
Large Central/Fringe Metro[b]	2690 (90.1)	21826 (92.7)
Medium/Small Metro, Micro, Noncore, unknown[c]	294 (9.9)	1717 (7.3)
Median family income among households with children, $		
mean (sd)	53630.67 (7947.0)	53807.80 (7091.2)
min,max		31137, 86838

*Q1-Q3

[a]Non-NAS births meeting inclusion/exclusion criteria

[b]Urban

[c]Non-urban

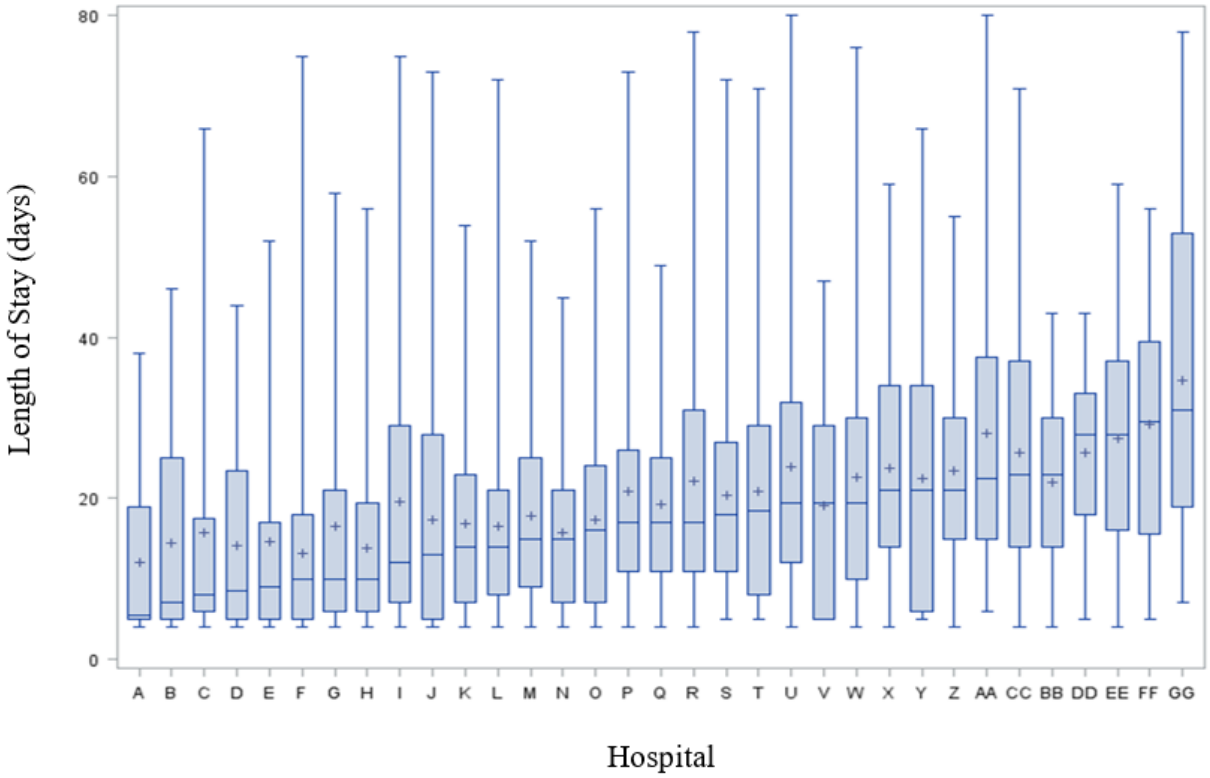


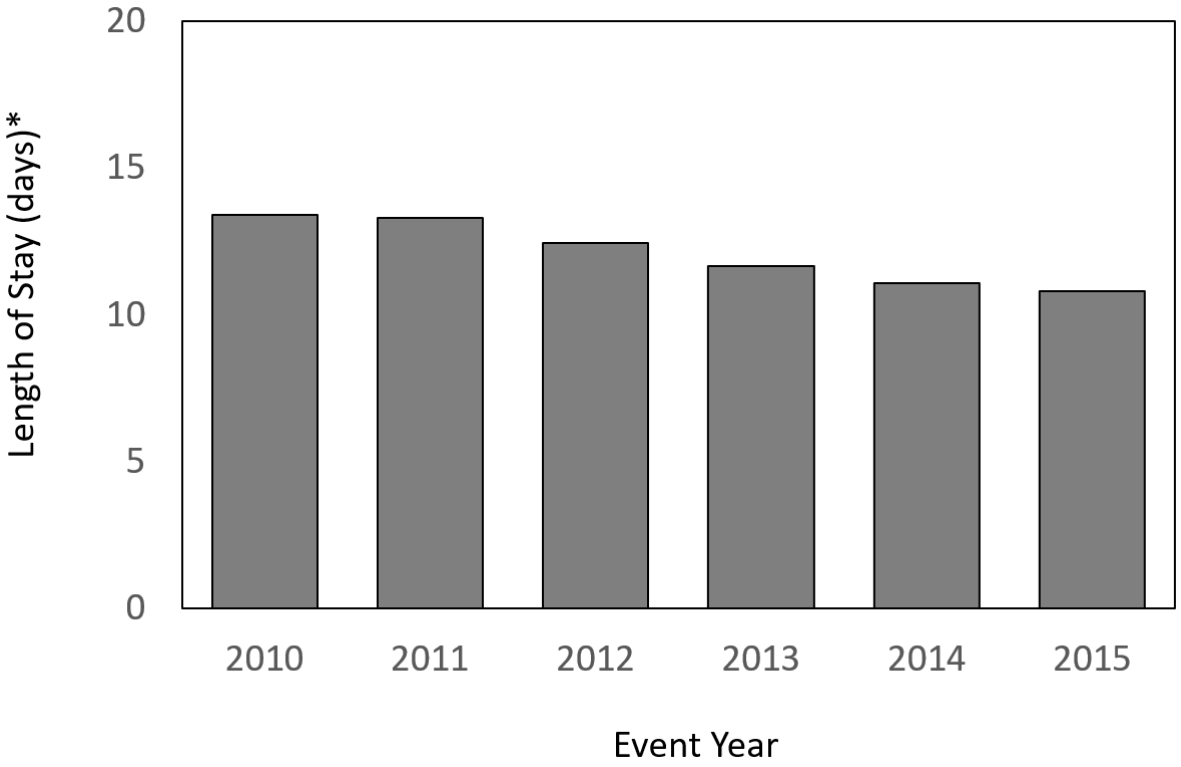
Figure 2. Variability of Neonatal Abstinence Syndrome length of stay by hospitals in Florida: 2010 – 2015. The plus sign in the middle of each box indicates the mean, the horizontal line in the middle of each box indicates the median, while the upper and lower borders of the box indicate the 75th and 25th percentiles, respectively. The whiskers above and below the box indicate the 90th and 10th percentiles.

Table 2. Parameter estimates of average length of stay from the final model: Florida, 2010-2015

Parameter	LOS (days)*	95% CI	P value
Maternal age			0.002
<20 y	9.8	8.0-12.0	
20-29 y	13.6	12.2-15.1	
30+ y	13.2	11.9-14.7	
Maternal race and ethnicity			<.001
Hispanic, black, other	11.2	9.8-12.8	
non-Hispanic white	13.0	11.7-14.6	
Maternal education			0.032
≤High school	12.4	11.1-14.0	
>High school	11.7	10.4-13.2	
Maternal insurance status			0.066
Medicaid/Medicaid Managed Care	12.5	11.1-14.0	
Other	11.7	10.3-13.3	
Prenatal care			<.0001
Inadequate/unknown	13.0	11.5-14.6	
Intermediate	12.1	10.6-13.7	
Adequate/adequate plus	11.2	10.0-12.6	
Average annual NAS volume			0.022
4-19	13.5	11.9-15.3	
20-51	10.8	9.2-12.8	

*Standard error = 1.1

Fit Statistics
AIC 6415.04
ICC 0.038



*2010 – 13.4 (CI 11.7-15.3)
2011 – 13.3 (CI 11.7-15.1)
2012 – 12.4 (CI 10.9-14.1)
2013 – 11.7 (CI 10.3-13.2)
2014 – 11.1 (CI 9.8-12.6)
2015 – 10.8 (CI 9.5-12.3)

Figure 3. Neonatal Abstinence Syndrome length of stay by event year.