



# A population-based study of maternal and infant factors influencing influenza vaccination among young children born in Colorado from 2008 to 2016



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## ABSTRACT

**Introduction:** Influenza causes significant morbidity among young children, and vaccination remains the best strategy to prevent disease. Understanding factors influencing early influenza vaccination uptake are important to identify strategies to increase vaccination rates.

**Objective:** To assess maternal and neonatal factors associated with influenza vaccination among first-born children within the first two years of life.

**Methods:** We conducted a retrospective population-based cohort study linking Colorado Birth Registry data and state immunization data of all live births between 2008 and 2016. The cohort was limited to singleton, first births. Multivariable logistic regression was used to assess associations between maternal and neonatal factors and influenza vaccination.

**Results:** Among 126,763 births meeting criteria for inclusion, 50.2% were vaccinated against influenza by two years of age. Mothers of unvaccinated children were older (27 vs 26 years,  $p < 0.0001$ ), married (67.8% vs 66.8%,  $p < 0.0001$ ), with a college education (38.8% vs 37.2%,  $p < 0.0001$ ). Influenza vaccination rates declined over time by birth year (30.5% in 2009 vs 6.8% in 2013,  $p < 0.0001$ ). Children admitted to the NICU receiving oxygen with 72 h of birth were 20% less likely to be vaccinated (RR = 0.8, 95% CI: 0.67–0.96) after adjusting for maternal age, race/ethnicity, education and preterm birth. Conversely, premature births were associated with an increase in influenza vaccination by age two years (RR = 1.1, 95% CI: 1.05, 1.15).

**Conclusions:** Among a large population-based cohort of mother-infant pairs in Colorado using birth and immunization registry data, there were statistically significant differences in maternal factors between unvaccinated and vaccinated children with influenza in the first 2 years of life, but the differences were too small to be clinically significant. Children admitted to the NICU were 20% less likely to be vaccinated, highlighting the need to target influenza vaccination in this population once eligible. Ongoing studies are needed to explore factors associated with early influenza vaccination.

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## 1. Introduction

Influenza infection results in a heavy burden of disease, and young children under the age of two years are particularly vulner-

*Abbreviations:* NICU, neonatal intensive care unit; CIMS, Colorado Immunization Information System; CDPHE, Colorado Department of Public Health and Environment; SD, Standard deviation; HS, High school; GED, General Education Diploma; CI, confidence interval; RR, risk ratios.

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able to complications resulting in hospitalization and death [1,2]. Annual influenza vaccination is recommended for all individuals aged six months of age and older, and is the best way to prevent influenza illness and decrease morbidity and mortality related to infection. However, during the 2015–2016 influenza season in the United States, vaccine coverage for children 6 months to 4 years of age was 70% [3]. A recent study suggests that influenza vaccination in children two years of age and younger is less than 50% [4].

An enhanced understanding of the factors associated with influenza vaccination refusal in children would be beneficial in

informing public health policy makers and to help target strategies to improve vaccination rates in these populations. There is limited data exploring maternal factors or infant factors at birth that may impact influenza vaccination in the first 2 years of life. Existing data show that low socioeconomic status, access to healthcare, as well as ethnicity and race are predictors of influenza vaccine status for children 3–24 months of age [4]. Studies show that the reasons for parental refusal are varied, with the most common reason from national survey data being the belief that influenza leads to only mild illness [5]. Data also indicate that influenza vaccine coverage among young children is higher among urban versus rural settings [6].

While national surveillance systems such as the national immunization survey provide useful data, they do not explore early infant or maternal factors that may influence vaccination in the early years of life. State-based immunization registries provide an opportunity to provide population-based assessments of vaccination status and can be linked with other state registry databases to provide more robust sociodemographic and clinical characteristics, thus providing a more comprehensive approach, enabling new factors to be explored outside the scope of national survey data, and providing opportunities for outreach. The objectives of this study were to determine sociodemographic maternal factors and neonatal factors (including term-birth, oxygen use and admission into the NICU) associated with uptake of seasonal influenza vaccination in the first two years of age.

## 2. Methods

We conducted a retrospective observational cohort study using the Colorado Department of Public Health and Environment (CDPHE) birth registry data and Colorado Immunization Information System (CIIS) data from 2008 to 2016. The birth registry database is a compilation of the Colorado Standard Certificate of Live Birth worksheet completed by hospital staff after every live birth in Colorado. Data collected includes sociodemographic information pertaining to the mother, father, prenatal period, delivery, and newborn outcomes during the hospital stay. The CIIS registry was implemented in 2007, and is accessible to physicians and clinics on a voluntary basis. From 2008 to 2016, 88–100% of children in Colorado who are 6 months to 5 years of age have two or more vaccines recorded in CIIS. Information from CIIS includes type of vaccination, date and time of vaccination, and refusal of vaccination, and all births in the state of Colorado are uploaded into the registry soon after birth.

The study population included mother-infant pairs with data available in the Colorado birth certificate registry and CIIS and who gave birth between 2008 and 2016. To attempt to limit the analyses to those children who were likely to have vaccination data available in the registry for the first two years of life, we restricted our population to mother-infant pairs from the birth certificate cohort with documented varicella vaccination logged in the CIIS registry. We selected varicella vaccination as a proxy measure for a child being in the registry since it is given at 12–15 months of age and is the vaccine with the highest rate of uptake among children in Colorado under the age of 2 years [7]. Individuals with missing data for residence, pre-natal care, other risk factors and covariates required for analyses were excluded from the study population. Additionally, only mothers with residence in the state of Colorado were included in the study population. We excluded infants born in 2006 and 2007, given the potential for low reporting in the first year of CIIS. We also limited the population to singleton births and first-time mothers to assure independence of the observations in our dataset.

Vaccinated individuals were defined as infants/young children with at least one influenza vaccination listed in the CIIS registry

within the first two years of infancy. Unvaccinated individuals were defined as infants with documented varicella vaccination in CIIS but who did not receive influenza vaccination in the first two years of life. The primary outcome was the child's receipt of at least one influenza vaccination within two years of age as documented by the CIIS registry. The primary explanatory variable was maternal county residence designation as rural, urban, or frontier, which was ascertained from county classification from birth certificate registry data and coded according to designations determined by the Colorado Rural Health Center. A secondary explanatory maternal variable was maternal receipt of prenatal care as a continuous variable, obtained from the birth certificate worksheet entry "total number of prenatal visits for this pregnancy". Newborn variables of interest obtained from the birth certificate included term birth (defined as 37 weeks or more), presence or absence of congenital anomaly, and admission to the neonatal intensive care unit (NICU) at birth. Consideration was given to several confounding factors a priori, which were determined to be associated with vaccination uptake. Based on previous literature, covariates included maternal age, race/ethnicity, and education level. In addition, univariate analyses assessed differences between the vaccinated and unvaccinated groups to identify additional confounders.

*Data Analysis:* Univariate analyses were conducted to assess for balance of demographic and clinical characteristics across vaccinated and unvaccinated groups, using an alpha value of 0.05. We used Chi-Square tests and Student t-tests to determine statistically significant differences in our study population to inform corrections for confounding in our models. Multivariable logistic regression was used to assess the association between maternal residence, receipt of prenatal care and child influenza vaccination. Logistic regression was used in a similar manner to address the associations with respect to infant factors. Logistic regression models were adjusted for confounders using the operational criteria of a 10% change in the crude beta estimate of the model. Risk ratios (RR) and 95% confidence intervals were calculated, and given the large sample size, even small differences between groups reach statistical significance with an alpha value of 0.05. Therefore, for the analyses,  $p < 0.01$  was defined as statistically significant [8], and a difference of  $\geq 5\%$  was considered clinically meaningful, based on reports of effective evidence-based strategies to increase vaccination rates [9]. SAS version 9.4 (Cary, NC) was used to perform analyses for this study. The Colorado Multiple Institutional Review Board deemed this study non-human subject research given that the dataset was de-identified, therefore informed consent was not required.

## 3. Results

Among 126,763 births in the final cohort, 50.2% ( $n = 63,572$ ) were vaccinated against influenza in the first two years of life (Fig. 1). The average age of mothers was 26.3 years and 67.3% of mothers were married at the time of their child's birth. These women averaged 10 (SD = 3.6) pre-natal visits and mostly identified as non-Hispanic white (63.4%). Among infants born, 51.5% were male, 7.3% ( $n = 9243$ ) were preterm while 8.3% ( $n = 10,453$ ) were admitted to neonatal intensive care unit (NICU) at birth.

There was no significant association between maternal residences in a rural or urban county with influenza vaccination. Mothers who did not vaccinate their children for influenza were older (26.5 years vs 26.2 years) and were more likely to have at least a college level education (38.8% vs 37.2%). There was a higher proportion of married women (67.8% vs. 66.8%) in the vaccinated group compared to the unvaccinated group. There was a significant difference in vaccination status by birth year, with a decrease in

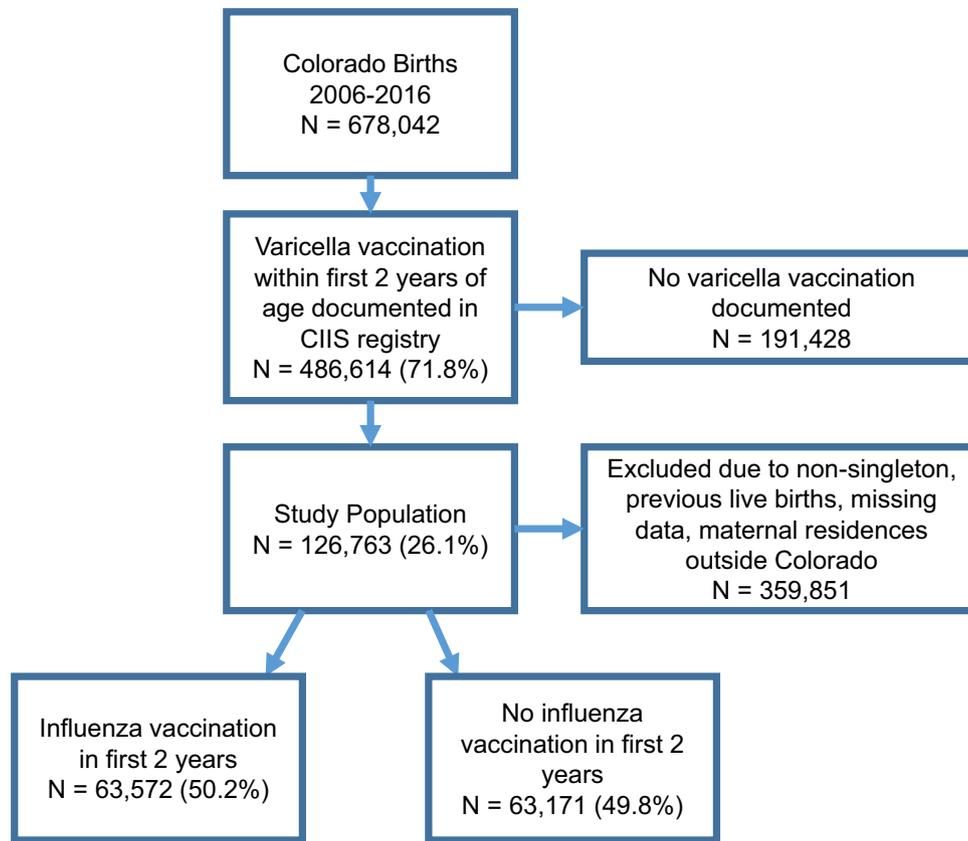


Fig. 1. Flow diagram of children born in Colorado from 2008 to 2016 included in the study cohort.

influenza vaccination rates over time (30.5% of children born in 2009 received early influenza vaccination, which decreased to 6.8% of children born in 2013 receiving early influenza vaccination ( $p < 0.0001$ ). A higher proportion of infants who were admitted to the NICU at birth (8.5% vs. 8.0%) and who received supplemental oxygen within the first 72 h of birth (2.5% vs 2.1%) were unvaccinated compared to vaccinated. While these differences were statistically significant ( $p < 0.01$ ), the differences observed were small (with the exception of birth year) and did not reach our threshold of clinical significance (Table 1).

Due to a significant interaction observed ( $p = 0.0023$ ) between maternal race/ethnicity and number of pre-natal visits, the results were stratified by race/ethnicity. There was a significant association between pre-natal visits and influenza vaccination among mothers who identified as Hispanic or other after adjusting for maternal age and education. Among Hispanic mothers, an increase in pre-natal visits was associated with a small decrease (Relative risk = 0.992, 95% CI 0.986, 0.998) in the incidence of early childhood influenza vaccination ( $p = 0.0084$ ) after adjusting for maternal age and education. Likewise, among mothers who did not identify as Hispanic, white non-Hispanic, or black non-Hispanic, an increase in pre-natal visits was associated with a 1.6% decreased likelihood (RR = 0.984, 95% CI 0.973, 0.996) of infant influenza vaccination ( $p = 0.0069$ ) after adjusting for maternal age and education.

Although the crude association between preterm birth and influenza vaccination initially showed no significant associations, when the model was adjusted for maternal age, race/ethnicity, education, and NICU admission, the association was significant (RR = 1.10, 95% CI: 1.05, 1.15). There were not enough individuals in the study population to assess the association between congenital anomaly and influenza vaccination. NICU admission was

associated with influenza vaccination and this association was modified by whether a child received supplemental oxygen within 72 h of birth ( $p = 0.04$ ). After adjusting for maternal age, preterm birth, and supplemental oxygen given at birth, children who were admitted to the NICU and given supplemental oxygen were 20% less likely to be vaccinated (RR = 0.80, 95% CI: 0.89, 0.96) against influenza in their first two years (Table 2).

#### 4. Discussion

We conducted a population-based cohort study of mother-infant pairs in Colorado over an 8-year period, using linked data from state immunization and birth registries to determine infant and maternal factors associated with influenza vaccination. Half the study population received influenza vaccination in the first 2 years of life. Vaccination rates by birth year decreased over time, but we did not observe differences in vaccination rates among urban versus rural populations. While we did find statistically significant differences with regards to maternal age, education, marital status, NICU admission and use of supplemental oxygen, the differences observed were too small to reach clinical significance. In adjusted analyses, a higher number of prenatal visits was associated with not being vaccinated within the first two years of life, whereas preterm birth was associated with being vaccinated. Similarly, the magnitude of these association were relatively small. Finally, in adjusted analyses, children admitted to the NICU at birth were 20% less likely to be vaccinated than children not admitted to the NICU.

While overall vaccination rates in our cohort are similar to national rates over the same time period [3], it was surprising to note that influenza vaccination rates within the first two years of

**Table 1**  
Maternal sociodemographic and clinical characteristics of children born in Colorado from 2008 to 2016 vaccinated and unvaccinated against influenza within the first 2 years of life.

Characteristic	Total study population (n = 126,743) N(%)	At least one influenza vaccination by age 2 yrs (n = 63,572) N(%)	No influenza vaccination by age 2 yrs (n = 63,171) N(%)	p-value
<i>Maternal factors</i>				
Maternal Age (mean ± SD)	26.3 ± 6.1	26.2 ± 6.1	26.5 ± 6.0	<0.0001
Number of Pre-natal visits (mean ± SD)	10.3 ± 3.6	10.3 ± 3.6	10.4 ± 3.6	0.048
Maternal Education (n, %)				
No high school diploma or GED	17,037 (13.5)	9190 (14.5)	7847 (12.5)	
HS diploma or GED	24,864 (19.6)	12,621 (19.9)	12,243 (19.4)	
Some college or Associate's degree	35,322 (27.9)	17,398 (27.4)	17,924 (28.3)	
Bachelor's degree or higher	48,096 (38.0)	23,600 (37.2)	24,496 (38.8)	
Unknown	1424 (1.1)	763 (1.2)	661 (2.9)	<0.0001
Maternal Race/Ethnicity (n, %)				
Non-Hispanic white	80,359 (63.4)	40,185 (63.2)	40,174 (63.6)	0.027
Non-Hispanic black	4764 (3.8)	2366 (3.7)	2398 (3.8)	
Hispanic	29,571 (23.3)	14,994 (23.6)	14,577 (23.1)	
Other	9261 (7.3)	4752 (7.5)	4509 (7.1)	
Unknown	2788 (2.2)	1275 (2.0)	1513 (2.4)	
Maternal marital status (n, %)				
Married	85,328 (67.3)	42,282 (66.8)	42,846 (67.8)	0.0007
Divorced/Separated	2060 (1.6)	1031 (1.6)	1029 (1.6)	
Never Married	39,175 (30.9)	19,954 (31.4)	19,221 (30.4)	
Widowed	55 (0.04)	31 (0.05)	24 (0.04)	
Unknown Status	125 (0.1)	74 (0.1)	51 (0.1)	
Residential County (n, %)				
Rural	15,211 (12.0)	7,752 (12.2)	7,459 (11.8)	0.096
Frontier	2448 (1.9)	1214 (1.9)	1234 (2.0)	
Urban	109,084 (86.1)	54,606 (85.9)	54,478 (86.2)	
<i>Infant factors</i>				
Birth year				<0.0001
2009	26,855 (21.2)	19,412 (30.5)	7443 (11.8)	
2010	26,190 (20.7)	19,667 (30.9)	6523 (10.3)	
2011	25,873 (20.4)	14,925 (23.5)	10,948 (17.3)	
2012	25,333 (20.0)	5277 (8.3)	20,056 (31.8)	
2013	22,492 (17.7)	4291 (6.8)	18,201 (28.8)	
NICU Admission (n, %)	10,453 (8.3)	5061 (8.0)	5392 (8.5)	0.0002
Pre-term Birth (n, %)	9243 (7.3)	4714 (7.4)	4526 (7.2)	0.121
Supplemental oxygen within first 72 h of birth (n, %)	2884 (2.3)	1335 (2.1)	1549 (2.5)	<0.0001

SD- Standard deviation.

HS- High school.

GED- General Education Diploma.

NICU- neonatal intensive care unit.

**Table 2**  
Association between Neonatal Intensive Care Unit admission, (stratified by oxygen receipt) and influenza vaccination within the first two years of life among children born in Colorado from 2008 to 2016.

	Relative Risk	95% Confidence interval
Overall study population <sup>a</sup>	0.95	(0.88, 0.99)
Stratified Results: Association between NICU admission and flu vaccination		
Received supplemental oxygen in first 72 h <sup>a</sup>	0.8	(0.67, 0.96)
Did not receive supplemental oxygen in first 72 h <sup>a</sup>	0.93	(0.89, 0.98)

<sup>a</sup> Adjusted for maternal age, race/ethnicity, education, and preterm birth.

age were decreasing by advancing birth year. This data is in contrast to national data demonstrating a slow increase in the percentage of children vaccinated against influenza aged between 6 months to 4 years of age over time [10], but state records demonstrate a plateauing of influenza vaccination in this age group [11]. The reason for our findings may reflect a growing vaccine-hesitant community, highlighting the importance of targeting expectant parents and families of young children regarding the benefits of influenza vaccination.

Another interesting finding was that influenza vaccination rates were similar between urban and rural families. National immunization survey data demonstrate that children under 3 years of age living in rural areas have lower immunization coverage for routine vaccines [12]. Other studies have shown that children from urban settings across the US have higher influenza vaccination rates compared with rural settings [6,13]. Locally, survey data in Colorado from a study of urban and rural primary care practices showed that, while attitudes regarding influenza vaccination were similar, there was a higher proportion of children who received influenza vaccination in urban (63%) versus rural (41%) children [14]. Since we attempted to identify children with immunization data captured in the state immunization registry, we may have biased our sample towards a group more willing to receive vaccinations, with fewer barriers that have been well described among rural populations towards accessing and receiving healthcare [15]. In our exploration of maternal factors, we found that higher maternal age, non-Hispanic white race, higher maternal education and married mothers were less likely to have children with influenza vaccination in early childhood, mirroring findings from studies of factors associated with intentional vaccine delay in children [16,17]. The phenomenon of higher education status is also being found with increasing frequency among studies of vaccine-hesitant families [18,19].

Interestingly, a higher number of prenatal visits was associated with lower influenza vaccination rates in young children, with a stronger association among children born to white non-Hispanic mothers. In contrast, studies of influenza and other childhood vaccinations demonstrate that children whose mothers used healthcare frequently were more likely to be vaccinated [20,21]. The magnitude of the association of our findings after adjusting for maternal education and age was small, but highlight the opportunity to target expectant mothers during prenatal visits regarding the benefits of childhood vaccination.

Analyses of neonatal factors associated with influenza vaccination demonstrated that pre-term infants were more likely to receive influenza vaccination, which is one of the groups of children considered at high-risk for complications from influenza, and thus is an important group to target [22]. However, after adjusting for maternal age and preterm birth, our findings also demonstrated that children who were admitted to the NICU and who received oxygen were less likely to receive influenza vaccination in early childhood. While we would expect that infants admitted to the NICU at birth may represent a more medically-vulnerable population that would also be targeted for vaccination, an Italian cohort study found similarly that there was a high-risk of vaccine delay among pre-term births requiring NICU admission [23]. Our findings highlight a second opportunity to educate families of neonates in the NICU regarding the benefits of influenza vaccination.

To our knowledge, our study is the first to link birth registry data with state influenza immunization data, providing a rich population-based dataset with which to explore early infant factors and comprehensive maternal sociodemographic factors which may influence early influenza vaccination uptake, while accounting for multiple important confounding variables. While other studies use survey data, relying on self-report, our dataset includes documented vaccination. Overall vaccination rates in our study were similar to data published in the literature [4,24], and influenza vaccination rates in Colorado are similar to national rates (Colorado influenza vaccination coverage has been consistently at the national average since 2010 [3]), so our study provides a representative sample of the US population, thus enhancing the generalizability of our findings. However, there are several limitations to this study that warrant discussion. Firstly, CHS is not used by all pediatric practices in the state of Colorado, and when first introduced, was not widely used. Thus, influenza immunization data may be missing from the registry, leading to misclassification bias. We attempted to overcome this issue by limiting our cohort to children with varicella vaccination data in the registry (which represents the vaccine with highest uptake among children less than two years of age in Colorado [25]), which may bias our cohort to a higher-vaccinated population, but may misclassify children whose vaccinations were not included in the registry after the first 12–15 months of age. Further, some of the birth registry data such as prenatal care received, is self-reported, which is less reliable, thus introducing recall bias. Next, we were not able to explore some key factors which influence vaccination uptake in young children. We were not able to compare influenza vaccination uptake among children who are otherwise complete on their routine childhood vaccines, compared with unvaccinated children or those on a delayed schedule, which may reveal important sociodemographic differences. We also did not have data regarding parental influenza vaccination status nor whether an influenza vaccine recommendation was made. Finally, we limited our population to first-time births, which also likely skewed our sample to younger maternal age, and maternal decisions about child influenza vaccination may change over time, which was not captured in our analyses.

## 5. Conclusion

In conclusion, among a population-based cohort of children born to first-time mothers in Colorado over an 8-year period, after adjusting for maternal sociodemographic characteristics and early perinatal factors, we did not find differences in influenza vaccination rates among urban and rural populations within the first 2 years of life. Children admitted to the NICU at birth were 20% less likely to be vaccinated against influenza in their early years of life. While other maternal and infant factors were statistically significant, the differences observed were small. Therefore, additional studies are warranted to assess factors associated with early influenza vaccination in children, to help target immunization strategies of this vulnerable pediatric population.

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## Conflict of interest

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