Hepatitis B birth dose effects on childhood immunization in the United States

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Abstract

Introduction

The Advisory Committee on Immunization Practices (ACIP) recommends administering the first dose of hepatitis B vaccine at birth, making it the first vaccine that many children receive. However, few studies examine whether children who miss the birth dose are at increased risk of vaccination delay. This study investigates birth dose as a determinant of up-to-date immunization status at 18 months, considering seven core childhood vaccine series: DTaP, polio, MMR, Hib, Hep B, varicella, and PCV13.

Methods

Cross-sectional data were collected in 2017 by National Immunization Survey – Child (NIS-Child), a nationally representative survey of 19-to-35-month-olds living the United States, and were analyzed in 2019. The primary outcome was combined 7-vaccine series (4:3:1:3:3:1:4) up-to-date status at 18 months. Doubly robust estimates of association were calculated using survey logistic regression and propensity scores estimated with boosted classification and regression trees (CART).

Results

Children who received the birth dose had 2.01 (95% CI 1.74, 2.33) times the odds of being up-to-date on the combined 7-vaccine series as children who did not. Odds ratios for all seven individual vaccine series were positive, ranging from 1.59 (1.28, 1.97) for MMR to 4.97 (3.97, 6.24) for hepatitis B.

Conclusions

Receiving the birth dose is positively associated with up-to-date status later in childhood, highlighting the importance of starting vaccination early. The association is insensitive to confounding by factors observed in NIS-Child, but investigation of unobserved factors – such as vaccine hesitancy– could provide critical information to guide intervention strategy.

Background

Since 2005, the Advisory Committee on Immunization Practices (ACIP) has recommended that the first dose of hepatitis B vaccine be administered at birth, making it the first vaccine that many children in the United States receive.[1,2] According to current (2019) ACIP recommendations, eight other vaccine series should begin between 2 and 12 months of birth: diphtheria, tetanus, and acellular pertussis (DTaP); inactivated poliovirus (polio); measles, mumps, and rubella (MMR); *Haemophilus influenzae* type B (Hib); varicella (VAR); pneumococcal conjugate vaccine (PCV13); rotavirus (RV); and hepatitis A.[2] With the exception of hepatitis A, all of these vaccine series should be completed before 19 months of age. A booster shot against DTaP, polio, MMR, and VAR should be administered between 4 to 6 years of age.

In 2016, 90.5% (95% CI 89.3-91.5%) of 19-to-35-month-olds in the United States were up-to-date on the hepatitis B vaccine series and 71.1% (69.5-72.7%) had received their first dose of hepatitis B vaccine within 3 days of birth.[3] 70.7% (69.2%-72.2%) of 19-to-35-month-olds were up-to-date on the combined 7-vaccine series (the 4:3:1:3:3:1:4 series) in 2016.[3] However, as this definition of "up-to-date" generously treats 35-month-olds the same as children who may be as much as 16 months younger, the proportion of children who go undervaccinated at some point early in life is likely much higher.[4]

As the first vaccine in the immunization schedule, receipt of the hepatitis B birth dose may serve as an indicator of future up-to-date vaccination status.[5–9] However, many of the determinants of birth dose receipt are also likely determinants of up-to-date vaccination status, and the relationship between birth dose and up-to-date status may be confounded by characteristics of

the child, the child's family, their health insurance, and their healthcare provider, among other factors.[10–17] To quantify the relationship between birth dose and up-to-date vaccination status independent of these potentially confounding factors, said factors must be taken into account in the study design.

This study investigates the relationship between receipt of the first dose of hepatitis B vaccine at birth and up-to-date vaccination status among children at 18 months of age using cross-sectional data from the 2017 National Immunization Survey (NIS). To adjust for potential confounders of this relationship, a propensity score weighting approach was employed to balance the characteristics of the "treated" (received hepatitis B vaccine birth dose) and "untreated" (did not receive birth dose) groups on these potential confounders.

Methods

Study Sample

Analysis was conducted in 2019 using the 2017 National Immunization Survey - Child (NIS-Child) dataset.[18] NIS-Child is a cross-sectional survey of noninstitutionalized children aged 19 to 35 months living in the United States conducted on an annual basis by the National Center for Immunization and Respiratory Diseases (NCIRD) with assistance from the National Center for Health Statistics (NCHS).[19]

Eligible households for the 2017 NIS-Child survey were selected using random-digit dialing (RDD) of cell and landline numbers from 60 geographic strata based on state and urban areas. Vaccination provider(s) were identified by a designated household respondent and contacted by

mail. If a child had at least one responding provider, or if the household respondent reported that the child had received no vaccinations, that child was classified by NIS-Child as having adequate provider data.[19] Out of the 28,465 children with a completed household interview, 15,333 (53.9%) had adequate provider data. Approximately 79% of children without adequate provider data were classified as such because their household respondent did not provide consent to provider contact or because they did not identify any providers.[19]

Of the 15,333 children classified by NIS-child as having adequate provider data, 290 (1.9%) had no responding vaccination providers and had a household respondent that reported no vaccines received.[19] These children are included by NIS-child in the adequate provider frame to better incorporate unvaccinated children into national estimates of vaccination coverage. However, as they are missing all data supplied by the healthcare provider (such as the characteristics of said provider(s) and confirmation that the birth dose was not received) these 290 children were excluded from analysis in this study, reducing the final sample to 15,043 children.

Measures

The NIS administered a two-part computer assisted telephone interview (CATI) to consenting respondents after selection. The first part of the interview identified households with eligible children and, if the household included an eligible child, selected the household member identified as being the most knowledgeable person with regards to the child's vaccination history. Demographic data – including information on the child, the child's family, and the child's insurance – were collected from this household respondent during the second part of the interview. The child's vaccination history and characteristics of their vaccination provider(s)

were obtained from the providers themselves via an Immunization History Questionnaire (IHQ) sent by mail to the provider(s) identified by the household respondent.

Hepatitis B birth dose was defined as a dose of hepatitis B vaccine administered within 3 days of birth. Up-to-date status for each vaccine series was determined at 18 months of age. Exact age in months at the receipt of a vaccine dose was determined by NIS-Child using provider-reported vaccine dose administration dates. Children who had received the recommended number doses for a given vaccine series before they turned 19 months of age were considered up-to-date for that series. One unique case is the Hib vaccine series, whose number of recommended doses depends on the vaccine manufacturer. For this vaccine, children were considered up-to-date on the Hib series if they had received 4+ doses of any type or 2+ doses of Merck types followed by 1+ dose of any type.

The primary outcome of interest was up-to-date status on the combined 7-vaccine series (4:3:1:3:3:1:4) at 18 months. The combined 7-vaccine series is defined as: 4+ doses DT-containing vaccine, 3+ doses polio-containing vaccine, 1+ doses measles-containing vaccine, 3+ or 4+ doses of Hib-containing vaccine (depending on the manufacturer), 3+ doses of hepatitis B-containing vaccine, 1+ doses of varicella-containing vaccine, and 4+ doses of pneumococcal-containing vaccine. Secondary outcomes included up-to-date status at 18 months on each of the individual (non-combined) vaccine series that comprise the combined 7-vaccine series.

Statistical Analysis

NIS-Child generated survey weights for sampled children with adequate provider data that take into account the probability of being sampled into the study, screener non-response, interview non-response, and provider non-response. The ultimate goal was to create a weighted sample distribution that was approximately representative of the source population. The complex survey weighting system employed by the NIS-Child may be explored in detail in other sources.[19,20]

Propensity scores were employed using inverse probability of treatment weighting (IPTW) to reduce bias due to confounding, increase the comparability of exposure groups, and ultimately estimate the population average treatment effect (PATE).[21–24] The probability that a subject received treatment (hepatitis B birth dose) was estimated using boosted classification and regression trees (boosted CART) with 20,000 iterations, shrinkage of 0.0005, 50% sampling fraction, and a stopping rule that minimizes the Kolmogorov-Smirnov test mean.[25,26]
NIS-Child survey weights were included as weights in the propensity score estimation model (as recommended by Ridgeway et al.[23]) as failure to take these weights into account may make final estimates more susceptible to bias.[23,24] Using the treatment probabilities generated in the boosted CART stage of analysis, IPTWs were created by calculating the inverse probability of treatment for each of the treated and the inverse probability of non-treatment for each of the non-treated subjects.[22] IPTWs were multiplied by the original survey weights as described by Ridgeway et al.[23] and DuGoff et al.[24] to create a composite weight to be used in the outcome models.

Doubly robust survey-weighted logistic regression models were fit using the composite weights to estimate the relationship between birth dose and up-to-date vaccination status. In addition to

propensity score adjustment using the composite weights, these doubly robust models also included potential confounders as covariables in the logistic regression model.[27]

Covariables were chosen for inclusion based demographic or provider characteristics identified by existing literature as having possible association either with birth dose or with up-to-date vaccination status.[10–17] An advantage of using propensity scores estimated with boosted CART is that a large number of variables may be considered when adjusting for confounding and the form of the relationship between those variables and the outcome need not be pre-specified.[25,28]

The full list of variables included in the propensity score model is as follows: child age at interview, child first born status, number of children in household, sex of child, race/ethnicity of the child, whether child ever received WIC benefits, current health insurance type for child, whether there was ever a break in health insurance for child, whether child born in or out of state of current residence, age of mother, education level of mother, marital status of mother, household income-poverty ratio, home ownership, number of responding vaccine providers, provider facility type, whether providers report to a state vaccine registry, and whether providers order vaccines from state/local health departments.

All analysis was conducted using R version 3.4.1.[29] Propensity scores were estimated using the twang package, version 1.5.[30] Survey logistic regression models and tests of covariable balance by birth dose status were conducted using the survey package, version 3.35-1.[31,32]

Results

A total of 11,268 (74.9%) children received the hepatitis B birth dose while 3,775 (25.1%) did not, representing a NIS-Child survey-weighted distribution of 74.5% and 25.5%. Summarizing variables with a survey-weighted p-value of less than 0.05: a greater proportion of children who received the birth dose, compared to those who did not, were born within their current state of residence (89.9% to 85.3%, $p < 0.001$), had a mother under the age of 30 (39.3% to 35.1%, $p = 0.035$), had an unmarried mother (38.5% to 30.5%, $p < 0.001$), received WIC benefits (54.1% to 50.4%, $p = 0.022$), had multiple responding vaccination providers (17.8% to 12.6%, $p < 0.001$), or had all (68.8% to 67.8%) or some (7.9% to 5.4%) providers that ordered vaccines from state or local health departments ($p = 0.005$). The balance of these potential confounders across birth dose status improved under the propensity score composite weights (Table 1). Under the new weights, observed population characteristics more closely mirrored one another across birth dose status. This represents evidence that the propensity score weights improve exchangeability across status, supporting the use these weights to control for confounding by the observed covariables.

Statistical evidence in all three model types (survey-weighted, propensity score weighted, and doubly robust) was consistent with a positive relationship between receipt of the hepatitis B birth dose and up-to-date vaccination status at 18 months of age for all individual vaccine series (Table 2). The relationship was strongest for the hepatitis B vaccine series, and children who had received the birth dose had 4.97 (95% CI 3.97, 6.24) times the odds of being up-to-date on the hepatitis B series as children who had not received the birth dose in the doubly robust model. The odds ratios (ORs) of other individual vaccine series ranged from 1.59 (1.28, 1.97) for MMR to 2.15 (1.67, 2.77) for polio. Birth dose was also positively associated with up-to-date status for the combined 7-vaccine series. Children who received the first dose of hepatitis B vaccine at

birth had 2.01 (1.74, 2.33) times the odds of being up-to-date on the combined 7-vaccine series at 18 months compared to children who did not receive the birth dose.

Discussion

In this analysis we examined the relationship between receipt of the first dose of hepatitis B vaccine at birth and up-to-date vaccination status at 18 months of age among children living in the United States using cross-sectional survey data. The results indicate that children who received the birth dose, compared to those who did not, had higher odds of being up-to-date on the DTaP, polio, MMR, Hib, hepatitis B, varicella, and PCV13 individual vaccine series. Furthermore, they also had higher odds of being up-to-date on the combined 7-vaccine series, suggesting a positive association between receipt of the birth dose and overall vaccination schedule adherence.

These results are consistent with the findings from Yusuf et al. who, using NIS-Child data from 1998, found that delayed administration of the first dose of hepatitis B vaccine was negatively associated with up-to-date status on the combined 4-vaccine series (DTaP, Polio, MMR, Hib).[5] Our study expands on the work by Yusuf et al. by examining individual vaccines and a more comprehensive combined series, demonstrating that the relationship persists across these new outcomes and is not driven by a single vaccine. A more contemporary examination of this relationship was also warranted. The 1998 NIS-Child data followed a sharp rise in hepatitis B vaccination coverage that began with the implementation of a universal childhood vaccination strategy against hepatitis B in 1991.[33] Birth dose coverage among 19-to-35-month-olds –

estimated to be approximately 54% in 1998 – has also increased, with annual estimates remaining consistently above 71% between 2012 and 2016.[3,5]

Several descriptive studies have also identified a positive relationship between early hepatitis B vaccination and up-to-date vaccination status later in childhood. The populations of these studies included: children born between 1991 and 1997 to families living in a low-income, predominantly Black neighborhood in Chicago;[7] children born between 2006 and 2010 in Michigan;[8] and children born in 2011 at North Carolina Women's Hospital.[9] While none of these studies methodologically considers what factors could explain the positive relationship between birth dose and up-to-date vaccination status, they do show that the relationship is present across the geography, demographics, and healthcare providers of their different samples, lending further support to the evidence in our study that birth dose effect persists despite these potentially confounding factors.

As seen in Table 2, the observed associations between birth dose and the individual and combined vaccine series were only marginally attenuated when potential confounders were taken into account in the propensity score weighted models (adjusted using propensity score weighting only) and doubly robust models (adjusted using propensity score weighting and multivariable regression). Using electronic health record data, a study by Fiks et al.[34] similarly found an association between immunization delay at 3 months and immunization delay at 24 months that remained strong even after multivariable adjustment.

One concern was that the relationship between certain variables and birth dose and may be nonlinear or modified by other characteristics. In the United States both high and low income have been indicated as barriers to vaccination, and global evidence indicates that the impact of education level on vaccination may vary depending on other individual factors.[35] Though it cannot take into account unmeasured variables that may impact the exposure-outcome relationship, an advantage of using boosted CART to estimate propensity scores is that it is capable of taking interactions and nonlinear relationships into account in its predictive model. This feature makes it an ideal tool for balancing children who received the birth dose and those who did not on potentially confounding characteristics given the data at hand.

Strengths of this study include use of a representative survey of children aged 19-35 months in the United States, incorporation of the complex survey design into the statistical analysis, use of provider-reported (as opposed to family-reported) vaccination data, and use of boosted CART as a nonparametric approach to propensity score estimation.

Limitations

If administering the first dose of hepatitis B vaccine at birth causes decreased vaccination delay, it would represent a meaningful secondary benefit to increasing birth dose coverage in the United States. However, evidence of a causal relationship between birth dose and up-to-date vaccination status is limited by the cross-sectional design of NIS-Child and failure to directly adjust for parent attitudes toward vaccination.

Parent attitudes toward vaccination are of particular concern because of their demonstrated ability to affect vaccination delay and potential ability to affect receipt of the birth dose. Opel et al. found that parents with high vaccine hesitancy scores had children who were under-immunized for 51% more days on average than children of parents with low scores.[15] In China, loss of confidence in the hepatitis B vaccine following media reports of infant death after receiving the vaccine led to decreased birth dose uptake among children born to both infected and non-infected mothers.[36] Understanding how failure to adjust for parent beliefs affects our estimates of effect is difficult without conducting a bias analysis because many of demographic variables associated with birth dose and up-to-date vaccination are also associated with parent beliefs about vaccination,[13,37] suggesting that the impact of belief on the propensity for receiving the birth dose could be imperfectly captured by the boosted CART model.

Interpretation of study results should also consider potential bias from selection and misclassification. The design of NIS-Child targets selection bias by building a statistical model that assigns survey weights for the subsample of subjects with adequate provider data.[20] When using these weights, estimates of national vaccination coverage appear to be little affected by selection.[38] Of perhaps greater concern is misclassification of both birth dose and up-to-date status due to incomplete vaccination records.[38] This mechanism of misclassification likely results in decreased sensitivity when determining both exposure and outcome status. To fully understand the impact of measurement error on the estimates of effect in this study a quantitative bias assessment may be warranted.

Conclusions

The evidence collected in this investigation supports a positive association between hepatitis B birth dose and up-to-date vaccination status at 18 months on seven core childhood vaccine series (DTaP, Polio, MMR, Hib, hepatitis B, varicella, and PCV13) and a combination of those series. This observed association is robust to confounding by the demographic and provider-based characteristics measured by NIS-Child. We recommend that future work examine the impact of vaccine hesitancy on the relationship between birth dose and up-to-date status.

As vaccine decision making by parents may begin prior to birth,[39] healthcare providers should consider prenatal resources for improving parent receptivity to child vaccination before the birth dose is missed. Further, providers should continue to provide immunization reminders to patients[40] and remain aware of the potential for increased risk of vaccine-preventable infection due to undervaccination[41,42] among children who miss the birth dose.

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Table 1: Survey and propensity weighted distributions of covariables by receipt of birth dose (N = 15,043).

	Survey weighted			Propensity score weighted		
Covariable	No birth dose	Birth dose	p[a]	No birth dose	Birth dose	p[a]
Number of children						
One	27.9%	28.6%	0.197	28.7%	28.5%	0.984
Two or three	57.2%	59.0%		58.4%	58.7%	
4 or more	14.9%	12.4%		12.9%	12.8%	
First born						
Yes	61.5%	60.3%	0.571	60.7%	60.5%	0.929
No	38.5%	39.7%		39.3%	39.5%	
Sex of child						
Male	53.8%	50.2%	0.073	51.8%	51.0%	0.643
Female	46.2%	49.8%		48.2%	49.0%	
Race/Ethnicity of child						
Hispanic	24.7%	27.8%	0.123	25.0%	26.8%	0.648
Non-Hispanic white	50.7%	45.5%		49.2%	47.0%	
Non-Hispanic Black	11.8%	13.1%		12.4%	12.8%	
Non-Hispanic other / multi-race	12.8%	13.6%		13.5%	13.4%	
Child received WIC benefits						
Yes	50.4%	54.1%	0.022	52.0%	53.2%	0.556
No	48.9%	44.9%		47.4%	45.9%	
Never heard of WIC	0.5%	0.2%		0.3%	0.3%	
Don't know	0.2%	0.7%		0.3%	0.6%	
Refused	0.0%	0.0%		0.0%	0.0%	
Gap in insurance[b]						
Currently insured	7.5%	6.7%	0.207	6.5%	6.7%	0.864
Never uninsured	90.0%	90.8%		91.2%	90.7%	
Currently uninsured	1.3%	1.8%		1.5%	1.7%	
Never insured	1.2%	0.8%		0.8%	0.9%	
Insurance provider type						
Private only	42.4%	41.6%	0.216	42.4%	42.1%	0.933
Any Medicaid	46.0%	48.5%		47.2%	47.6%	
Other insurance	9.0%	7.3%		8.0%	7.7%	
Uninsured	2.6%	2.6%		2.4%	2.6%	
Education (mother)						
Less than 12 years	17.7%	15.3%	0.127	15.4%	15.6%	0.873
12 years	20.8%	24.8%		22.7%	23.8%	

More than 12 years	22.8%	22.2%		22.6%	22.4%	
College Grad	38.7%	37.7%		39.4%	38.2%	
Maternal age group						
<= 29 years	35.1%	39.3%	0.035	37.3%	38.5%	0.532
>= 30 years	64.9%	60.7%		62.7%	61.5%	
Marital status						
Married	69.5%	61.5%	<.001	64.3%	63.2%	0.564
Never married/widowed	30.5%	38.5%		35.7%	36.8%	
Income-poverty ratio[c]	1.888	1.854	0.464	1.882	1.869	0.742
Geographic mobility						
Moved from different state	14.7%	10.1%	<.001	11.5%	11.0%	0.675
Didn't move from different state	85.3%	89.9%		88.5%	89.0%	
Home ownership						
Owned / being bought	51.5%	51.1%	0.816	51.8%	51.5%	0.976
Rented	44.5%	44.8%		44.3%	44.5%	
Other arrangement	3.4%	3.7%		3.5%	3.7%	
Refused	0.3%	0.1%		0.2%	0.1%	
Don't know	0.3%	0.2%		0.3%	0.2%	
Responding providers						
1	87.4%	82.2%	<.001	84.9%	83.3%	0.230
2	11.8%	16.2%		14.1%	15.2%	
3+	0.8%	1.6%		1.0%	1.5%	
Provider facilities[d]						
All public	13.2%	13.0%	0.055	12.5%	12.9%	0.981
All hospital	13.4%	13.8%		14.0%	13.8%	
All private	58.3%	54.9%		56.6%	55.7%	
All military / other	4.2%	3.4%		3.3%	3.6%	
Mixed	10.8%	14.9%		13.6%	14.0%	
Reports to vaccine registry[e]						
All providers	69.5%	68.3%	0.014	69.4%	68.5%	0.948
Some providers	5.1%	7.8%		6.7%	7.2%	
No providers	10.5%	8.1%		8.5%	8.6%	
Unknown/don't know	14.9%	15.8%		15.3%	15.7%	
Vaccines ordered from state/local health dept.[e]						
All providers	67.8%	68.6%	0.005	68.9%	68.4%	0.934
Some providers	5.4%	7.9%		6.7%	7.3%	
No providers	13.9%	10.2%		11.4%	11.1%	
Unknown/don't know	12.9%	13.3%		13.0%	13.3%	

[a] Rao-Scott Chi-Square test used to calculate p-values for categorical variables. Survey t-test used for continuous variables.

[b] Children classified as “currently insured” if presently insured but ever uninsured, “never uninsured” if presently insured and never uninsured, “currently uninsured” if presently uninsured but ever insured, and “never insured” if presently uninsured and never previously insured.
[c] Mean value. Determined from family income, number of persons in the household, number of children in the household, and the 2016 Census poverty thresholds.
[d] If a child had multiple responding providers of heterogeneous facility type, then the facility type set to "Mixed."
[e] If all responding providers reported affirmatively, category set to "all providers." If at least one (but not all) provider responded affirmatively, category set to "some providers." If all providers responded negatively, category set to "no providers." Otherwise, category set to "unknown."

Table 2: Associations between hepatitis B birth dose and up-to-date vaccination status at 18 months of age.

	Unadjusted survey weighted[a]			PS weighted[b]			Doubly robust PS weighted[c]		
Vaccine series	OR	95% CI		OR	95% CI		OR	95% CI	
DTaP	1.63	(1.37,	1.93)	1.56	(1.34,	1.82)	1.61	(1.38,	1.89)
Polio	2.41	(1.80,	3.23)	2.13	(1.66,	2.75)	2.15	(1.67,	2.77)
MMR	1.60	(1.27,	2.01)	1.57	(1.27,	1.94)	1.59	(1.28,	1.97)
Hib	1.72	(1.45,	2.05)	1.65	(1.41,	1.93)	1.69	(1.44,	1.99)
Hepatitis B	4.94	(3.87,	6.30)	4.78	(3.82,	5.99)	4.97	(3.97,	6.24)
VAR	2.08	(1.69,	2.57)	1.95	(1.60,	2.37)	1.99	(1.63,	2.43)
PCV 13	1.92	(1.60,	2.30)	1.82	(1.54,	2.15)	1.89	(1.59,	2.25)
Combined-7	2.01	(1.72,	2.36)	1.94	(1.68,	2.24)	2.01	(1.74,	2.33)
No hep combined 7	1.80	(1.53,	2.11)	1.71	(1.48,	1.97)	1.77	(1.52,	2.05)

[a] Univariable survey-weighted logistic regression using NIS-Child weights.
[b] Univariable survey-weighted logistic regression using IPTW and NIS-Child composite weights.
[c] Multivariable survey-weighted logistic regression using IPTW and NIS-Child composite weights.
For estimates in the form of risk ratios, see Table S3 in the supplement.

PS, propensity score; DTaP, diphtheria, tetanus, and acellular pertussis; Polio, poliovirus; MMR, measles, mumps, and rubella; Hib, *Haemophilus influenzae* type b, VAR, varicella zoster; PCV 13, pneumococcal conjugate vaccine 13; Combined 7 (also known as the 4:3:1:3:3:1:4), DTaP, Polio, MMR, Hib, Hepatitis B, VAR, and PCV 13 combined vaccine series; No hep combined 7, modified combined 7 series with hepatitis B dropped from up-to-date requirements.