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Research article

Missed hepatitis B birth dose vaccine is a risk factor for incomplete vaccination at 18 and 24 months

Peyton Wilson[a,*], Genevieve Taylor[b], Jamie Knowles[c], Elizabeth Blyth[d], Jeff Laux[e], Jacob Lohr[d], Ravi Jhaveri[a]

[a] Department of Pediatrics, Division of Infectious Diseases, University of North Carolina, 038 MacNider Hall, CB #7231, United States
[b] Department of Pediatrics, Division of Neonatal Perinatal Medicine, University of North Carolina, United States
[c] School of Medicine, University of North Carolina, United States
[d] Department of Pediatrics, University of North Carolina, United States
[e] The North Carolina Translational and Clinical Sciences Institute, United States

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SUMMARY

Objectives: To determine whether missing the HepB birth dose vaccine is a risk factor for incomplete vaccination later in childhood.

Methods: This was a retrospective cohort study of infants born over one year at an academic medical center. The "not vaccinated at birth" group consisted of all infants who did not receive the HepB birth dose vaccine by seven days of life, while the "vaccinated at birth" group included infants who did receive the birth dose. The primary outcome was vaccination status at 18 months of age, determined from the state vaccination registry.

Results: Infants "not vaccinated at birth" had lower vaccination rates. At 18 months, 44% of the "vaccinated at birth" group received all recommended vaccines, compared with 23% of the "not vaccinated at birth" group ($p < 0.001$); at 24 months, rates were 65% and 45%, respectively ($p < 0.001$). Over 80% of the variability in vaccination completions were related to a single latent variable, which is most likely vaccine hesitancy/refusal.

Conclusions: Infants who miss the HepB birth dose vaccine are at risk for under-immunization by 18 and 24 months of age. This suggests that parents likely form opinions about vaccines long before the birth of their child; therefore, efforts to influence attitudes must begin earlier.

Introduction

Childhood vaccination is an effective public health measure that averts millions of cases of preventable infectious diseases.[1] Unfortunately, rates of vaccination among children in the United States have stalled and fallen short of national goals in recent years, attributable in part to the growing movement of vaccine hesitancy.[2–4] Refusal of and delays in vaccination have been associated with disease outbreaks in the U.S.[5,6] The first opportunity that parents have to accept or refuse a vaccine for their child occurs when the hepatitis B virus (HepB) vaccine is offered in the newborn period.

With approximately one million people living with chronic HepB infection in the U.S., it remains a significant cause of morbidity and mortality.[7,8] Beginning in 1991, the Advisory Committee on Immunization Practices (ACIP) recommended HepB vaccination as a three-dose series for all infants, which contributed to a 68% decrease in HepB prevalence among children.[9,10] In 2005, the ACIP revised its recommendations to emphasize initiation of the HepB vaccine series *at birth*, to protect the large number of infants born to HepB-positive mothers with unknown Hep B surface antigen (HBsAg) at time of delivery.[11] In 2016, based on data indicating increased protection against HepB vertical transmission, the ACIP shortened the recommended interval for the birth dose of vaccine to the first 12 h of life for infants born to women with known HepB. They stressed the advantages of seizing the opportunity to vaccinate infants while still in the nursery rather than relying on a subsequent office visit that could be missed or delayed.[12] The

Abbreviations: AAP, American Academy of Pediatrics; ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; DTaP, Diphtheria, Tetanus & acellular Pertussis; HepB, Hepatitis B Virus; Hib, *Haemophilus influenza* type b; IPV, Inactivated Poliovirus; MMR, Measles, Mumps and Rubella; NCIR, North Carolina Immunization Registry; NV, "not vaccinated at birth"; PCV13, Pneumococcal Conjugate; RV, Rotavirus; VAR, Varicella; YV, "vaccinated at birth".

* Corresponding author.
E-mail address: peyton_wilson@med.unc.edu (P. Wilson).

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American Academy of Pediatrics (AAP) has strongly endorsed the ACIP's policy in the strategy by recommending that *all* infants receive the vaccine within the first 24 h of life in order to eliminate HepB transmission in the U.S.

Previous studies have demonstrated that infants who receive the first dose of HepB vaccine at birth are more likely to complete the three-dose HepB vaccine series.[13,14] However, what has not been adequately studied is whether refusal of the birth dose of HepB is the first indication of vaccine refusal or vaccine hesitancy. Parents often challenge pediatricians as to why their baby should receive the vaccine in the nursery rather than waiting until the first office visit, especially if the mother knows she is negative for HepB. Providers often assume that these parents will ultimately have their infants vaccinated, but there are few studies that demonstrate whether these infants actually complete the primary vaccine series by 18 months. A more complete understanding of parental decisions about vaccine refusal will be key to determining the ideal timing for vaccination counseling. We hypothesize that HepB birth dose refusal is an early telltale sign that parents will refuse other vaccines. In this study, we used hospital birth records cross-referenced with the state immunization registry to determine whether failure to receive the birth dose of HepB vaccine indicates an increased risk of incomplete vaccination at 18 months of age.

Methods

Study design

This retrospective study of infants born at North Carolina Women's Hospital between January 1st and December 31st, 2011 compared the rate of completion of the primary vaccine series among infants who did and did not receive the birth dose of HepB vaccine.

Exposure

The exposure was defined as failure to receive the birth dose of HepB vaccine. The "not vaccinated at birth" (NV) group was composed of all infants born at North Carolina Women's Hospital during the study period (January 1, 2011 through December 31, 2011) who *did not* receive the birth dose of HepB vaccine in the hospital by day-of-life seven. The "vaccinated at birth" group (YV) was a control group of infants born during the same time period who *did* receive the HepB vaccine within the first week of life. The reason for using a random, unmatched sample of vaccinated infants was to have a control group as representative as possible of vaccinated children, and birth dates of infants in the YV group were relatively evenly distributed throughout the year-long study period. We chose not match by geography because of known differences in vaccination practices by geographical location. Day-of-life seven was chosen *a priori* as the cut-off point for receipt of the birth dose to include infants with delayed nursery discharge (i.e. late preterm infants or those with a prolonged nursery stays) while excluding infants weighing less than 2,000 grams at birth (for whom the first dose of HepB vaccine is not recommended until one month of age) from the exposure group. The HepB birth dose has been recommended as part of the standard of care for all infants born at North Carolina Women's Hospital for over a decade. Parents must actively refuse the vaccine in order for their infants not to receive it.

Study setting and population

The study was conducted at North Carolina Women's Hospital, a public academic hospital that provides care for patients from a wide catchment area throughout the state, including those in medically underserved areas. An estimated 3600 babies are born at North Carolina Women's Hospital annually. Based on an analysis of historical data within this hospital (unpublished data), approximately 20% of infants do not receive the birth dose of HepB vaccine, implying that approximately 720 infants would be in the NV arm of the study.

Data acquisition

Data were collected with assistance from the Carolina Data Warehouse for Health (CDW-H). The dataset included patient identifiers such as name, date of birth, medical record number, race, and address. Once compiled by CDW-H, data were then securely transmitted to collaborators at the North Carolina Immunization Registry (NCIR) to determine each infant's vaccination status. See **Supplement 1** for more information about the NCIR database. Data-use agreements were signed by both CDW-H and NCIR, and the Institutional Review Board at the University of North Carolina at Chapel Hill approved this study.

Outcomes

The primary outcome for this study was vaccination status at 18 months of age. According to the Centers for Disease Control's (CDC) Advisory Committee on Immunization Practices (ACIP), infants should receive the following vaccinations by 18 months: HepB (3 doses), Rotavirus or RV (2-3 doses), Diphtheria, Tetanus & acellular Pertussis or DTaP (4 doses), *Haemophilus influenza* type b or Hib (3-4 doses), Pneumococcal conjugate or PCV13 (4 doses), Inactivated Poliovirus or IPV (3 doses), Measles, Mumps and Rubella or MMR (1 dose), and Varicella or VAR (1 dose).[15] To assess if vaccination completion rates differed by whether infants received the birth dose of HepB vaccine, we compared each patient's vaccination records to the ACIP's vaccination schedule according to the version of the vaccine that the patient was given (e.g., Hib vaccine can be a 3-dose or 4-dose series depending on which formulation is given). To allow for the possibility of delayed vaccination, we also assessed completion by 24 months. The patient was recorded as complete for a given vaccine series if the required doses were completed by 18 or by 24 months. Hepatitis A and influenza vaccinations were not included in the analysis because neither is considered part of the primary vaccine series and because of low national coverage rates.[16,17]

Statistical methods

We determined the proportions of patients who completed each vaccine series as well as the full primary series. These proportions were tested for differences by group using chi-squared tests. Differences in vaccine patterns between the groups were also analyzed with chi-squared tests. Details of exploratory analyses including a principal component analysis and a propensity score analysis to control for potential confounders are included in **Supplement 1.** We used alpha = 0.05 as our threshold for significance. All analyses were conducted in R,[18] in conjunction with several add-on packages.[19–21]

Results

Of 3579 infants born at North Carolina Women's Hospital in 2011, 746 (20.8%) did not receive the birth dose of HepB vaccine by day of life seven. For the control arm, we randomly selected 749 infants who did receive the HepB birth dose. Of these 1495 records requested, 1436 infants (96%) were matched to NCIR records, with

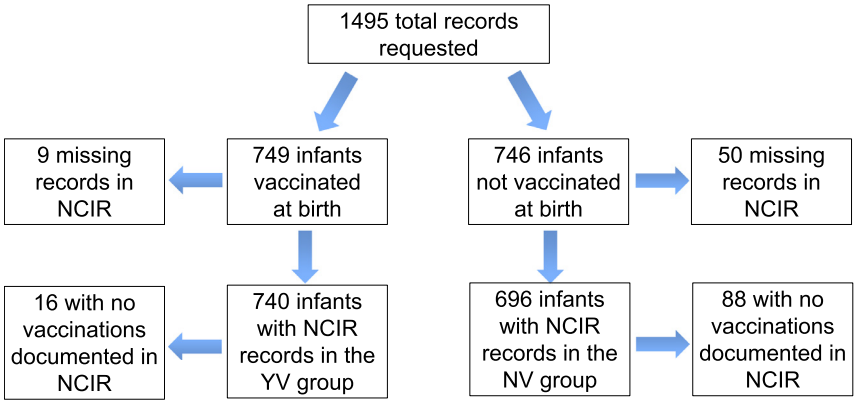

Fig. 1. Flowchart of data acquisition.

740 in the YV group and 696 in the NV group. A total of 88 infants (13%) in the NV group had no recorded vaccinations in NCIR, compared with 16 (2%) in the YV group ($p < 0.001$). We know that the latter 16 had at least one vaccination (i.e., the HepB birth dose within the first week of life); this implies that the NCIR data are incomplete, but there is no evidence that recorded inaccuracies differ by our exposure. Fig. 1 is a flow chart that represents the data acquisition process. Overall, 51% of the infants were male. Race was unknown for many infants (47%); of those indicated, 77% were Caucasian, 20% were African–American and 3% were Asian. Infants in the NV group were statistically significantly more likely to be Caucasian ($p < 0.001$).

By 18 months, 44% of infants in the YV group completed the primary vaccine series, compared with 23% of infants in the NV group (difference = 0.21, 95% CI [0.16,0.26], $p < 0.001$). In order to account for later vaccine administration, we re-evaluated vaccination status at 24 months and found increased rates overall but persistent differences between the groups (65% & 45%, respectively, difference = 0.21, 95% CI [0.15,0.26], $p < 0.001$). For each individual vaccine type, the rate of vaccination in the YV group was significantly higher than the rate of vaccination in the NV group at both 18 and 24 months (Fig. 2). At 18 months, 88% of infants in the YV group completed the 3-dose HepB vaccine series, compared with 64% of infants in the NV group (difference = 0.25, 95% CI [0.21,0.29], $p < 0.001$). This pattern of higher vaccination rates in the YV group compared with the NV held true for the other vaccines that comprise the primary series (Fig. 2). These patterns held true after adjusting for potential confounders (**Supplement 1).**

Infants in the NV group were also far more likely to have no recorded vaccinations in NCIR compared to the YV group (19% vs. 7%, respectively; difference = −0.12, 95% CI [−0.15,−0.08], $p < 0.001$). Parental objection does not appear to be due specifically to the HepB vaccine. We examined the 254 infants from the NV group who did not complete the HepB series in order to determine the completion rates of all other vaccines compared to the YV group. If the objection were specific to the HepB vaccine, we would expect the other completion rates to be similar, but instead the difference was highly significant with only 11% of the NV group completing all other vaccines versus 45% in the YV group (difference = 0.34, 95% CI [0.29,0.40], $p < 0.001$).

We then determined the most commonly occurring patterns of vaccinations (Fig. 3). With 2^8 possible combinations of vaccine statuses, there were 256 possible data patterns that could occur for a child in our dataset. However, the observed patterns of vaccine completions were highly concentrated: 148 patterns (56%) do not appear in our data at all. Four patterns were exhibited by ≥ 100 children, and only 16 had ≥ 10 instances. The two most common patterns of vaccination were completely vaccinated (34%) and no vaccine completions (13%).

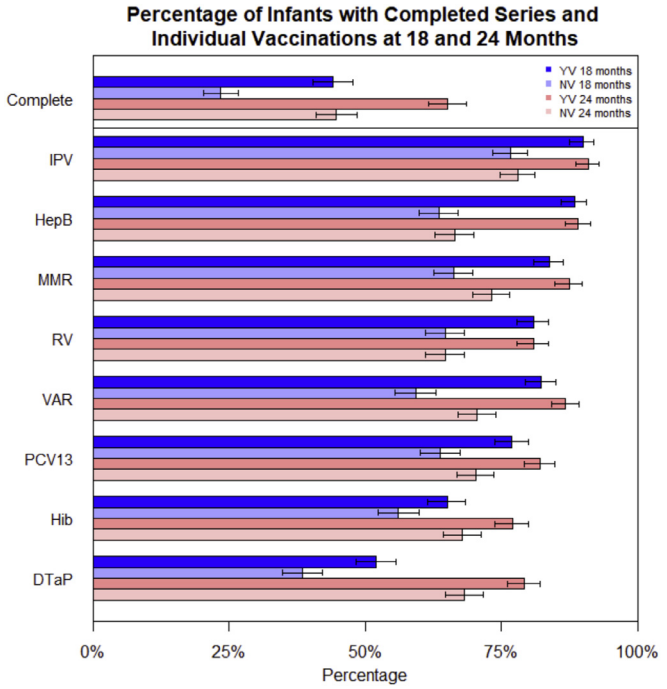

Fig. 2. Percentage of infants with completed series and individual vaccinations at 18 and 24 months. Symbols represent the percentage of patients having received the entire series ("Complete") of individual vaccinations as recommended by the ACIP. Blue represents vaccination completion rates for those who received the birth dose of HepB; red represents the rates of refusers. Circles connected by dashed lines are rates at 18 months and triangles connected by solid lines refer to 24 months. The vaccines are listed from left to right in descending order by overall completion rates. The error bars are exact 95% confidence intervals around the observed percentage. Abbreviations: IPV, Inactivated Poliovirus. HepB, Hepatitis B Virus. MMR, Measles, Mumps and Rubella. RV, Rotavirus. VAR, Varicella. PCV13, Pneumococcal Conjugate. Hib, Haemophilus influenza type b. DTaP, Diphtheria, Tetanus & acellular Pertussis.

Discussion

AAP and ACIP guidelines strongly recommend initiation of the 3-dose HepB vaccine series within the first 24 h of life.[11,12] Unfortunately, in this era of vaccine hesitancy,[4] too many children are either incompletely vaccinated or unvaccinated. It is important to identify risk factors for incomplete vaccination in order to counsel parents and to improve adherence to AAP and ACIP guidelines.

Our data support the hypothesis that failure to receive the birth dose of HepB vaccine is a risk factor for incomplete vaccination at 18 and 24 months of age. The statistically significant difference between vaccination rates in the NV and YV groups held true not

Panel A: All Infants

Rank	DTaP	Hib	PCV13	VAR	RV	MMR	HepB	IPV	Count
1	✓	✓	✓	✓	✓	✓	✓	✓	489
2	✗	✗	✗	✗	✗	✗	✗	✗	187
3	✗	✓	✓	✓	✓	✓	✓	✓	139
4	✗	✗	✓	✓	✓	✓	✓	✓	110
5	✗	✗	✗	✗	✓	✗	✓	✓	49
6	✗	✗	✗	✓	✓	✓	✓	✓	42

Panel B: YV Infants

Rank	DTaP	Hib	PCV13	VAR	RV	MMR	HepB	IPV	Count
1	✓	✓	✓	✓	✓	✓	✓	✓	326
2	✗	✓	✓	✓	✓	✓	✓	✓	79
3	✗	✗	✓	✓	✓	✓	✓	✓	75
4	✗	✗	✗	✗	✗	✗	✗	✗	54
5	✗	✗	✗	✗	✓	✗	✓	✓	32
6	✗	✗	✗	✓	✓	✓	✓	✓	23

Panel C: NV Infants

Rank	DTaP	Hib	PCV13	VAR	RV	MMR	HepB	IPV	Count
1	✓	✓	✓	✓	✓	✓	✓	✓	163
2	✗	✗	✗	✗	✗	✗	✗	✗	133
3	✗	✓	✓	✓	✓	✓	✓	✓	60
4	✗	✗	✓	✓	✓	✓	✓	✓	35
5	✗	✓	✓	✗	✓	✓	✓	✓	33
6	✓	✓	✓	✓	✓	✓	✗	✓	27

Fig. 3. Most commonly occurring patterns of vaccination. The patterns of vaccinations that appear most often in our dataset. The checks imply that the indicated vaccination series was completed by 18 months, whereas the x's mean they were not listed as complete by that time.

only for the HepB vaccine series, but across all other vaccine series. Therefore, refusal of the HepB vaccine at birth is an important indicator of future under- or unimmunized status. The strength of this study was the use of hospital-wide birth records combined with state immunization registry records to assess vaccination at multiple time points.

The principal component analysis (**Supplement 1**) and vaccine patterns data imply that there is a single tendency to vaccinate or to not vaccinate, rather than parents preferring certain vaccines over others. By three different criteria (parallel analysis, scree analysis, and Kaiser's criterion), only one principal component accounted for the majority (82%) of the variability in our data, with the remaining 18% of the variability presumably due to random error. This implies that whatever lies behind the decision to refuse the initial birth dose of HepB vaccine is the same factor that lies behind decisions about refusal of other vaccines. To further this argument, Fig. 3 reveals that patients tended to be either completely vaccinated, almost completely vaccinated, or have no vaccine series completed. Our speculation is that there is no direct causal connection between refusal of the birth dose of HepB and future vaccinations. However, refusal of the birth dose vaccine may be the first tangible indication that parents are vaccine hesitant and this information could serve as a warning sign to pediatricians that an infant is at risk for under-immunization.

These data are consistent with the notion that parents have already formed their opinions about vaccination long before facing the HepB birth dose decision. Previous studies have highlighted that parents form opinions about vaccination during the prenatal period.[22–24] Furthermore, a recent study demonstrated that receipt of positive information about vaccinations during pregnancy does not affect timeliness of infant immunization.[25] As such, future efforts optimally should focus on young adults prior to childbearing. It is of utmost importance that these conversations begin as early as possible so as to influence parental decisions and prevent the cycle of incomplete vaccination.

Our study has some limitations to consider. First, as a single-center study, our results may not be generalizable to the larger U.S. population. However, UNC healthcare is a public academic medical

center that provides care to a diverse patient population throughout all 100 counties in North Carolina. Second, when no vaccines were listed in NCIR, we are not able to label these patients as "unvaccinated" with certainty. There could be several reasons for the absence of vaccinations in the NCIR system, such as an infant's family moving to a different state with a separate registry, a child's death, a clerical error, or truly unvaccinated status. Clerical error must have played at least a small role in our study, as 16 infants in the YV group (who received the HepB vaccine in the nursery at North Carolina Women's Hospital) had no immunizations documented in NCIR. While these factors may have played a minor role, they should not account for the large differences between our two cohorts. Third, incongruences between the CDW-H database and the NCIR database led to missing data. However, NCIR was able to match 96% of all records received from CDW-H, which allowed for a vigorous analysis of our birth cohort. Fourth, rates of vaccination in our study were below the nationally reported averages. The 2014 National Immunization Survey (NIS) documented rates of up to 80.8% (± 6.9%) for completion of the primary vaccine series among children living in North Carolina.[26] However, these national averages are based on children aged 19–35 months, compared with the 18 and 24 month cutoffs that we used in our study. While the differences are most likely due to the different endpoints, our data could reflect more accurate sampling compared to the telephone surveys utilized in the NIS. Alternatively, these differences could be related to limited access to healthcare in a subset of medically underserved patients who seek care at UNC, a public hospital that serves a large catchment area in North Carolina. Finally, race and socio-economic status (SES) were largely missing from our dataset. Previous studies have demonstrated relationships between race or SES and vaccination status,[27,28] but due to missing data we are not able to comment on this.

Future efforts should focus on determining reasons for refusal of the birth dose of HepB vaccine, novel techniques to improve timely receipt of HepB and other vaccine series, methods for improving prenatal conversations about vaccination, and consideration of a national immunization registry to allow for a more complete assessment of vaccination status of children.

Conclusions

Our study demonstrated that failure to receive the birth dose of HepB vaccine predicts incomplete vaccination with both the HepB vaccine series and the primary vaccine series at 18 and 24 months of age. Furthermore, our analysis suggests that a single underlying parental tendency toward or against vaccination underlies the variability in vaccination. Future efforts for increased uptake of the birth dose of HepB should target pre-pregnancy and prenatal visits as crucial decision-making periods regarding vaccination.

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Potential conflicts of interest

The authors have no conflicts of interest relevant to this article to disclose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2018.09.014.

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