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Uptake and safety of Hepatitis B vaccination during pregnancy: A Vaccine Safety Datalink study★

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Abstract

Introduction: Hepatitis B virus (HBV) infection acquired during pregnancy can pose a risk to the infant at birth that can lead to significant and lifelong morbidity. Hepatitis B vaccine (HepB) is recommended for anyone at increased risk for contracting HBV infection, including pregnant women. Limited data are available on the safety of HepB administration during pregnancy.

Objectives: To assess the frequency of maternal HepB receipt among pregnant women and evaluate the potential association between maternal vaccination and pre-specified maternal and infant safety outcomes.

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Conflict of interest statement

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Methods: We examined a retrospective cohort of pregnancies in the Vaccine Safety Datalink (VSD) resulting in live birth outcomes from 2004 through 2015. Eligible pregnancies in women aged 12–55 years who were continuously enrolled from 6 months pre-pregnancy to 6 weeks postpartum in VSD integrated health systems were included. We compared pregnancies with HepB exposure to those with other vaccine exposures, and to those with no vaccine exposures. High-risk conditions for contracting HBV infection were identified up to one-year prior to or during the pregnancy using ICD-9 codes. Maternal and fetal adverse events were also evaluated according to maternal HepB exposure status.

Results: Among over 650,000 pregnancies in the study period, HepB was administered at a rate of 2.1 per 1000 pregnancies (n= 1399), commonly within the first 5 weeks of pregnancy. Less than 3% of the HepB-exposed group had a high-risk ICD-9 code indicating need for HepB; this was similar to the rate among HepB unvaccinated groups. There were no significant associations between HepB exposure during pregnancy and gestational hypertension, gestational diabetes, pre-eclampsia/eclampsia, cesarean delivery, pre-term delivery, low birthweight or small for gestational age infants.

Conclusions: Most women who received maternal HepB did not have high-risk indications for vaccination. No increased risk for the adverse events that were examined were observed among women who received maternal HepB or their offspring.

Keywords

Hepatitis B vaccine; Vaccine safety; Pregnancy

1. Introduction

Hepatitis B virus (HBV) infection during pregnancy can pose a substantial risk to infants at birth. Perinatal transmission of HBV can occur if the mother acquired acute hepatitis B during late pregnancy or in the early postpartum period, or if the mother is chronically infected with HBV [1]. Vertical transmission from mothers who are positive for both HBV surface antigen (HBsAg) and HBV e-antigen (HBeAg) exceeds 90% and, in the absence of postexposure prophylaxis, between 70% and 90% of infected infants develop chronic infection by age 6 months, which increases the lifetime risk for cirrhosis and hepatocellular carcinoma [1–3].

The hepatitis B vaccine (HepB) is universally recommended as part of the routine immunization schedule for children [4]. To minimize the risk of maternal infection and vertical transmission, women who are susceptible (e.g., unvaccinated) to HBV and who have certain high-risk behaviors or conditions that increase their risk for contracting HBV infection are recommended to receive HepB during pregnancy. HepB administered as either a singleantigen (Recombivax HB® or Engerix-B®) or a combination vaccine with Hepatitis A (Twinrix®), is effective in reducing the risk of acquiring HBV infection [3,5]. Risk factors for contracting HBV infection include a range of behavioral (e.g., high-risk sexual activity, drug use), comorbid, occupational, household, and travel-related factors [6,7]. Although safety data are limited, HepB is considered safe and the benefits to protecting both the

mother and the fetus from acquiring HBV infection are considered to outweigh any potential risks of vaccination during pregnancy [8,9].

Receipt of HepB during pregnancy may be intentional, prompted by a provider's concern over the presence of one or more risk factors for contracting HBV. Maternal HepB administration may also occur inadvertently, when a woman is vaccinated without knowledge of pregnancy status. For these reasons, there is value in continuing to assess the safety of maternal HepB administration to understand how exposure affects pregnancy outcomes. However, there are limited studies on the safety of HepB administration during pregnancy. Two small studies evaluated maternal and fetal outcomes following maternal vaccination with HepB and found no evidence of associated adverse events, but the studies were underpowered to detect associations with potentially serious outcomes [1,10]. One additional descriptive study summarized reports to the Vaccine Adverse Events Reporting System following maternal receipt of HepB and did not find any concerning patterns of adverse events [11].

We evaluated 11 years of data from six integrated health systems, with the aim of describing vaccine administration patterns and evaluating the potential association between vaccination with HepB during pregnancy and pre-specified maternal and infant safety outcomes among women with live births.

2. Methods

2.1. Study design and population

The study population was drawn from members of six integrated healthcare systems participating in the Vaccine Safety Datalink (VSD), a collaboration with the Centers for Disease Control and Prevention (CDC). The six participating sites from five states (California, Colorado, Oregon, Washington, and Wisconsin), provide comprehensive medical care to health plan members, and document patient encounters within electronic health record (EHR) systems. Data from the respective EHR systems were used to identify a retrospective cohort of eligible pregnancies with start dates from January 1, 2004 through December 31, 2014 among women aged 12–55 years who were continuously enrolled in the health plan from 6 months prior to pregnancy through 6 weeks after the pregnancy ended in a live birth. Pregnancies were identified using a validated algorithm based on administrative, EHR, and claims data. Comparisons to medical record abstraction have shown that the pregnancy episode algorithm has 99% agreement for live birth pregnancy designation, and 98% agreement for gestational age [12]. Exclusion criteria were established for multiple gestation pregnancies, pregnancies with exposure to live virus vaccines, and pregnancies with implausible gestational age (<22 or >44 weeks) or birthweight values (<300 g). Gestational age cutoffs were used to decrease errors in gestational age estimation and to remove infants with borderline viability who may be less likely to survive [13]. Women could experience multiple pregnancies over the study period and thus have more than one pregnancy included in the analysis (Fig. 1). The study protocol was reviewed and approved by Institutional Review Boards at each participating study site and the Centers for Disease Control and Prevention.

2.2. Measurement of exposure and covariates

Eligible pregnancies were assigned to one of three groups: (1) pregnancies where at least one dose of HepB (Recombivax[®], Engerix[®] or Twinrix[®]) was administered during the study period and during pregnancy (*HepB vaccinated*); (2) pregnancies with no vaccines administered during pregnancy (*unvaccinated*); and (3) pregnancies that were not exposed to HepB, but were exposed to at least one other inactivated vaccine (*other vaccinated*) [14]. To correct for potential misclassification due to uncertainty of the pregnancy onset date and to limit inclusion of postpartum administrations, we included vaccines administered 8 days after last menstrual period (LMP) through 7 days before pregnancy end date. Provider assessment of HBV-immune status was not evaluated for this study.

The three groups were compared for differences in baseline demographic characteristics (age, educational background, marital status, gravidity, enrollment site) and three pre-specified high-risk vaccine indications up to one year prior to and during pregnancy (chronic liver disease, injection drug use and/or outpatient visit to chemical dependency or methadone use, and sexually transmitted infections) (Table 1). Maternal use of alcohol and tobacco, in the 12 months prior to and during pregnancy were also assessed as behaviors that could impact maternal and fetal outcomes. All diagnoses were identified from International Classification of Diseases, Ninth Revision (ICD-9) codes assigned at inpatient, emergency department, or outpatient visits (Supplementary table).

2.3. Reasons for vaccination

Given that several HepB indications could not be identified through ICD-9 codes documented in the EHR (e.g., occupational status, risk of exposure from HBV-positive household contact, travel to and from endemic areas, sexual activity), we conducted a single-site chart review of all HepB-exposed pregnancies to determine whether the presence of risk factors may have contributed to decisions for maternal HepB administration, and to explore the frequency of inadvertent maternal vaccination. This chart review was conducted by a single reviewer in a two-step process. First, we assessed whether providers were aware that the patient was pregnant at the time of maternal HepB; referred to as either ‘known’ or ‘unknown’ pregnancy status. Those with a positive pregnancy test prior to HepB receipt were defined as vaccination with ‘known’ pregnancy status. The second step of chart review involved reviewing provider notes in the EHR of each HepB-exposed pregnancy, detailing any explanation for administering HepB during pregnancy. The six categorical options for explanations included the following four high-risk indications: (1) work or school-related requirements (e.g., health care worker, student in health-related specialty); (2) travel to or from a country with endemic hepatitis B circulation; (3) risk of exposure due to a HBV-positive household member; (4) chemical dependence or methadone treatment; plus two categories for non high-risk factors: (5) catch-up vaccination for those who had not completed the 3-dose HepB series; and (6) unknown. Results from this review were used to highlight the potential for unmeasured confounding when using only ICD-9 codes to identify which individuals had one or more high-risk indications for vaccination.

2.4. Measurement of maternal and fetal outcomes

In the absence of specific safety concerns about maternal HepB, outcomes and exposure periods were selected a priori, as informed by previous safety studies of seasonal influenza and tetanus-diphtheria-acellular pertussis vaccination during pregnancy [14–16]. The adverse events of interest included the following common pregnancy-related complications: gestational hypertension, gestational diabetes, preeclampsia/eclampsia, and cesarean delivery. Fetal adverse outcomes among only infants of live births included pre-term birth (i.e., delivery before 37 weeks of completed gestation), low birth weight (<2500 g), and small for gestational age. Fetal outcomes were identified from the mother's chart and included outcomes up to 6-weeks post-partum. As described in the supplementary table, each outcome had a pre-specified timeframe and setting (e.g., inpatient or outpatient) during the pregnancy or postpartum period. Small for gestational age (SGA) was determined by using a referent standard for expected weights according to gestational age at birth. Births less than the 10th percentile for the expected weight-to-gestational age were classified as SGA [17,18].

2.5. Analysis

Since pregnancies were clustered within each patient, General Estimating Equations (GEE) were used to first compare patient characteristics between the three study groups (except for pregnancy trimester at vaccination, which could only be compared between *the HepB vaccinated* and *other vaccinated* groups). To evaluate and compare maternal and fetal outcomes for HepB-exposed pregnancies and HepB non-exposed pregnancies, the *unvaccinated* and *other vaccinated* groups were then combined into a single unexposed comparison group. The GEE model was then used to evaluate potential associations between HepB and pre-specified study outcomes, controlling for patient characteristics and high-risk indications for vaccination, including: chronic liver disease, injection drug use and/or outpatient visit to chemical dependency or methadone use, and sexually transmitted infections.

A binomial model with a logit link function was used to model the binary outcomes and estimate the odds ratios (OR) and associated 95% confidence intervals (CI) before and after adjusting for potential confounding factors. Exchangeable covariance structure was specified to account for the correlation among multiple pregnancies by the same patient. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

3. Results

A total of 1399 pregnancies resulting in live births were included in the *HepB vaccinated* group, 456,728 in the *unvaccinated* group, and 195,704 in the *other vaccinated* group (Fig. 1). While pregnancies with HepB exposure (<1% of the study population) were significantly different across most descriptive characteristics compared to pregnancies in either comparison group, the absolute percentage differences between groups are generally small (<3%) (Table 2). Women with a HepB-exposed pregnancy tended to be slightly younger and experiencing their first pregnancy. In the *HepB vaccinated* cohort, 71% of HepB exposures occurred in the first trimester of pregnancy, 51% of which occurred within the first 5 weeks

of pregnancy (data not shown), whereas for pregnancies with exposure to other vaccines (primarily influenza and Tdap vaccines) vaccinations were more evenly distributed across trimesters (30%, 35%, and 35% for 1st, 2nd, and 3rd trimesters, respectively).

In this analysis, we were able to examine only three of the high-risk indications specified for maternal administration of HepB: chronic liver disease, injection drug use, and STI diagnoses. The prevalence of other high-risk indications could not be assessed as there are not corresponding ICD-9 codes. The proportions of pregnancies with any of these high-risk indications, as documented in the 12 months preceding or during pregnancy, were very low (<1% with chronic liver disease; <3% with injection drug use or documented chemical dependency; and <2% with a documented STI) for all three groups (Table 2). Pregnancies with HepB exposure had significantly higher rates of chronic liver disease (0.9% vs. <0.4% in both comparison groups), and higher rates of STI diagnoses than the *unvaccinated* and *other vaccinated* groups, although these rates were all very low (1.6% in HepB vaccinated vs. 1.0% in unvaccinated and 0.8% in other vaccinated). Women with HepB-exposed pregnancies had lower rates of documented maternal alcohol use than did women in the *other vaccinated* comparison group (11.8% vs. 17.9%); rates of maternal smoking were similar across all groups.

3.1. Reasons for vaccination

Of 72 charts identified and available for review from one study site, we found that providers were not aware of the patient's pregnancy status at the time of vaccination for 32% of *HepB vaccinated* pregnancies (23/72) (data not shown), meaning that there was no indication of a positive pregnancy test prior to vaccination. Where pregnancy status was known at the time of vaccination (n = 45 or 63% of cases), the most common reasons for vaccination were work- or school-related requirements (40%), followed by catch-up vaccination, either as initiating or completing the HepB vaccine series (38%), and travel (13%). In comparison, where pregnancy status was not known at the time of vaccination, the most common reasons for vaccination were catch-up vaccination (44%), travel (26%), and work- or school-related requirements (22%). Chemical dependency (known pregnancy status) or having a hepatitis B infected household contact (unknown pregnancy status) were noted as the primary reasons in only 2 of 72 (3%) HepB vaccinated cases. It was unclear if pregnancy status was known or unknown in 4/72 (6%) cases.

3.2. Maternal and fetal outcomes

Given minimal differences in population characteristics between the three study groups, the two unexposed groups (*unvaccinated* and *other vaccinated*) were combined into a single unexposed group for assessment of study outcomes. There were no significant associations between HepB exposure during pregnancy and gestational hypertension, gestational diabetes, pre-eclampsia/eclampsia, cesarean delivery, pre-term delivery, low birthweight or small-for-gestational age infants (Table 3).

4. Discussion

This study represents the first large-scale evaluation of administration patterns and select safety outcomes following maternal HepB administration. Using a network of large, integrated healthcare systems, our study confirmed that maternal vaccination with HepB is uncommon; <1% of over 650,000 singleton pregnancies were exposed to HepB in an 11-year period. Since there is not specific maternal HepB safety concerns noted in the literature, we chose to examine a pre-specified set of commonly examined maternal and fetal outcomes. We found no significant associations between maternal HepB and hypertension, gestational diabetes, pre-eclampsia/eclampsia, cesarean delivery, pre-term birth, low birth weight, or small for gestational age.

Characteristics of exposed pregnancies resulting in live births were comparable to the unexposed; differences that were observed were statistically significant but quite small (data not shown). The low rate of EHR-documented high-risk indications for vaccination with HepB among our *HepB vaccinated* pregnancies (4.4%), implies that almost all maternal HepB was due to an indication that was not easily identified within the EHR (i.e., household risk, healthcare worker status, travel to or from an endemic area, catch-up vaccination, etc.), or may have been inadvertently timed during pregnancy. Most doses (71%) of HepB were administered during the first trimester and 50% were administered before the 6th week of pregnancy, which also supports the possibility that HepB administered during pregnancy often represents inadvertent administration.

The extent to which maternal vaccination with HepB in our study population occurred due to risks associated with occupational status, household risk, travel to- or from an endemic area, or was related to sexual activity, is unknown. Data from NHIS 2016 show that among individuals (both male and female) with a high-risk indication for HepB, those with occupational risk (i.e., health-care personnel) and travel-related risks have the highest HepB coverage (61% and 31%, respectively, in 2016) [19], which likely means some proportion of vaccinees in our study population also had these high-risk indications. It is possible health systems that serve populations from highly endemic countries (i.e. central Asian republics, Southeast Asia, etc.) may be more likely to vaccinate these women, regardless of pregnancy status, given that the majority of chronic HBV infections in the United States are among Asians and Pacific Islanders [5]. We did not include a racial/ethnic breakdown of our study population due to concerns around incomplete capture, however Asians are 15% of the total VSD study population (in comparison to 5% in the United States, overall) [20].

Findings from our single-site chart review revealed that 32% of maternal vaccination appeared to be inadvertent, as there was no mention of pregnancy found in the EHR at the time of vaccination. Chart review also determined that the most common risk factor among those intentionally vaccinated during pregnancy was occupational or student status (40%); a similar proportion had no high-risk indication for vaccination and were instead vaccinated as catch-up for routine vaccination (38%). Women who received HepB as part of routine vaccination had no other known or documented risk factors for HBV which suggests that providers are comfortable with maternal vaccination and may prefer to take opportunities to vaccinate even in the absence of a high-risk indication for vaccination.

Our study had several limitations. Even with an 11-year study period, we have small numbers of HepB exposed pregnancies. The maternal and fetal outcomes included in our analysis are not expected to be causally linked to maternal exposure to HepB vaccines. Study findings are intended to reassure providers and patients that common adverse pregnancy outcomes were not associated with vaccine exposure. We did not examine outcomes related to congenital anomalies, nor did we include pregnancies with non-live birth outcomes. Any possible association between maternal HepB exposure and non-live birth outcomes was not addressed in this study. Using ICD-9 codes to identify high-risk indications for vaccination limited us to identifying those behaviors or conditions that have corresponding ICD-9 codes; we were unable to identify or describe vaccine indications related to sexual exposure, or household or occupational exposure. Even those high-risk indications that we did attempt to identify in the EHR from one study site (e.g., injection drug use, STI infection) are poorly reported and documented and are likely an under-representation of the true extent of these high-risk indications in our study population. As such, there is the potential for unmeasured confounding in this analysis. Data have shown that 54% of newly acquired hepatitis B cases are associated with high-risk sexual activity (i.e., multiple partners), or injection-drug use [21]. Nevertheless, it is possible, that by including STI diagnoses, we were able to ascertain risks associated with sexual activity for some proportion of our vaccinated population. We included pregnant women that were undergoing dialysis but did not describe these pregnancies separately, even though hemodialysis is among the high-risk indications for vaccination with HepB. The rationale for its exclusion is that pregnancy is extremely uncommon among women with chronic kidney disease and, when it does occur, often results in significant adverse fetal outcomes [22]. We therefore anticipate that excluding this diagnosis does not impact our study findings.

This large, multisite study provides evidence that HepB administration during pregnancy does not increase risk for adverse events examined among pregnancies resulting in live births. Given low rates of known high-risk indications for maternal vaccination, it is expected that vaccination with HepB in early pregnancy is commonly occurring as part of routine vaccination and not necessarily due to a high-risk indication; this is true whether or not pregnancy status was known at the time of maternal vaccination. Regardless of the vaccination intent, our findings are consistent with those of previously published studies and provide added reassurance that it is safe to administer HepB to pregnant women both with and without high-risk indications for vaccination.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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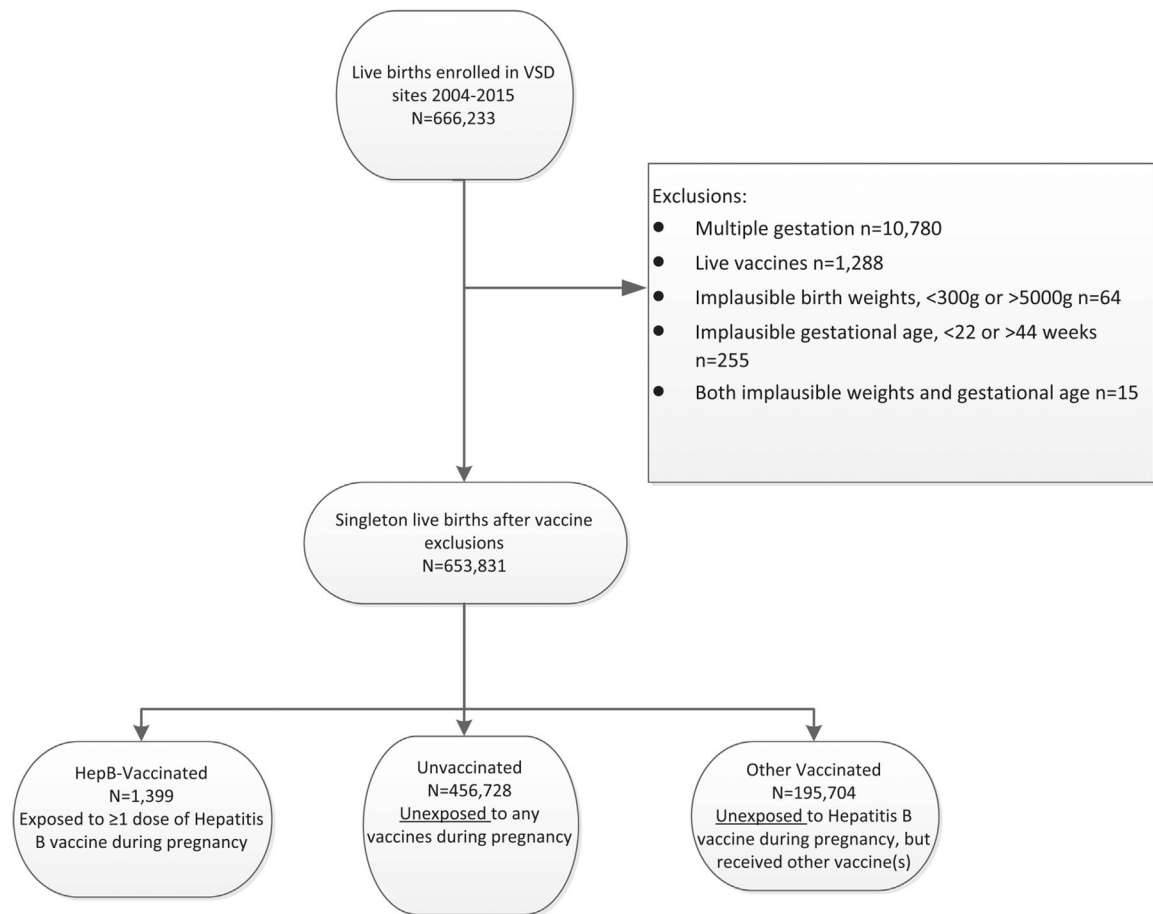


Fig. 1. Study population of pregnancies with live birth outcomes in the VSD, 2004–2015.

Table 1

High-risk indications for vaccination with HepB and corresponding ICD-9 codes.

High-risk indication for HepB	ICD-9 code
Chronic liver disease	571.x
Injection or non-injection drug use	304.x, 305.2–305.9
<i>Evaluated/treated for STI</i>	
Syphilis	091.0
Gonorrhea	098.0, 098.1, 098.2, 098.3
Chlamydia	099.41, 099.5
Trichomoniasis	131.0
Genital Herpes	054.1x
Hepatitis C Virus	070.51, 070.54, 070.70
HIV (acute, chronic, unspecified)	042.x
Hemodialysis patient	Not included [*]
Diabetes	Not included [†]
Developmentally disabled in LTCF	NA
Household contacts of HBV- chronically infected	NA
Occupational risk	NA
>1 sex partner in past 6 months	NA
Men who have sex with men	NA
Travel to endemic countries	NA

Abbreviations: HepB, hepatitis b vaccine; ICD-9, International Classification of Diseases-9th edition, STI, sexually transmitted infection; HIV, Human immunodeficiency virus; LTCF, long term care facility; NA, Not available as ICD-9 code in EHR

^{*} Pregnancies where hemodialysis was occurring were not enumerated given the low likelihood of pregnancy among women undergoing hemodialysis.

[†] Diabetes was not included as a high-risk indication for HEPB until 2012, at the very end of our study period.

Table 2

Maternal characteristics based on vaccination status.

Characteristics	Group 1. HepB- vaccinated (n = 1399) %	Group 2. Unvaccinated* (N = 456,728) %	Group 3. Other vaccinated† (n = 195,704) %
Mean age (SD), years	29.9 (5.9)	30.1 (5.6)	30.2 (5.9)
<i>Age</i>			
<18	2.1	1.9	1.2
18–25	20.4	19.9	19.1
26–35	59.7	59.8	62.4
>35	17.7	18.4	17.3
<i>Marital status</i>			
Married	57.5	61.0	59.4
Single	25.2	21.4	23.0
Unknown	17.2	17.6	17.6
<i>Study Site‡</i>			
A	5.4	5.4	4.8
B	3.2	5.4	5.6
C	1.9	2.0	1.9
D	47.0	40.0	40.5
E	5.6	5.5	4.8
F	36.9	41.7	42.4
<i>Education</i>			
<High school	2.8	3.6	2.7
High school graduate	7.8	10.6	10.3
>High school	70.4	67.3	68.3
Unknown	19.0	18.5	18.8
<i>Gravidity</i>			
1	37.3	29.3	35.7
2+	48.0	56.1	50.9
Unknown	14.7	14.6	13.4
<i>Trimester of vaccine exposure</i>			
1st (0–13 weeks)	71.0	NA	29.6
2nd (14–26 weeks)	23.4	NA	35.4
3rd (27–42 weeks)	5.6	NA	35.0
<i>Maternal vaccines received</i>			
Only HepB	33.2	NA	NA
1 other vaccine	43.7	NA	61.9
2+ other vaccines	23.1	NA	38.1
Any HBV risk factor§	4.4	3.4	3.1
Chronic liver disease	0.9	0.3	0.2
Injection-drug use	2.3	2.2	2.2
Visit to chemical dependency	2.2	1.7	1.6

Characteristics	Group 1. HepB- vaccinated (n = 1399) %	Group 2. Unvaccinated* (N = 456,728) %	Group 3. Other vaccinated [†] (n = 195,704) %
Any sexually-transmitted infection	1.6	1.0	0.8
HIV	0.3	<0.1	<0.1
Herpes Simplex Virus	0.8	0.7	0.6
Hepatitis C Virus	0.4	<0.1	<0.1
Maternal alcohol use	11.8	13.1	17.9
Maternal Smoking	6.9	6.4	7.2

Bold face indicates high-risk indications for HepB vaccination.

At least 1 cell size too small (expected frequency < 5).

Abbreviations: HepB, hepatitis b vaccine; HBV, hepatitis B virus; HIV, Human immunodeficiency virus; SD, standard deviation.

*Pregnancies with no vaccine exposure during pregnancy.

[†]Pregnancies with no exposure to HepB during pregnancy, but with exposure to >1 other vaccine.

[‡]Sites were not identified for reasons of confidentiality.

[§]Pregnancies with any of the individual high-risk indications, based on presence of ICD9 codes either during, or within 12 months preceding, the pregnancy.

Table 3

Association between maternal vaccination with HepB and adverse maternal and fetal outcomes among pregnancies resulting in live births.

Outcome	HepB-Vaccinated (n = 1399) % (n)	Not HepB-Vaccinated* (N = 652,432) % (n)	aOR (95% CI) [†]
<i>Gestational hypertension</i> [‡]			
No (ref)	95.1 (1331)	95.4 (622,327)	
Yes	4.9 (68)	4.6 (30,105)	1.02 (0.80–1.30)
<i>Gestational diabetes</i>			
No (ref)	87.2 (1220)	87.8 (572,621)	
Yes	12.8 (179)	12.2 (79,811)	1.06 (0.91–1.23)
<i>Pre-eclampsia/eclampsia</i>			
No (ref)	95.0 (1329)	95.5 (623,195)	
Yes	5.0 (70)	4.5 (29,237)	1.07 (0.84–1.36)
<i>Cesarean delivery</i> [§]			
No (ref)	70.0 (864)	70.6 (408,463)	
Yes	30.0 (370)	29.4 (170,118)	1.01 (0.91–1.13)
<i>Pre-term birth (<37 wks)</i> [§]			
No (ref)	91.6 (1173)	92.8 (550,816)	
Yes	8.4 (107)	7.2 (42,835)	1.14 (0.94–1.39)
<i>Low birth weight (<2500 g)</i> [§]			
No (ref)	93.9 (1200)	95.0 (563,214)	
Yes	6.1 (78)	5.0 (29,573)	1.21 (0.96–1.52)
<i>Small for gestational age at birth</i> [§]			
No (ref)	90.6 (1156)	91.7 (540,996)	
Yes	9.4 (120)	8.3 (49,277)	1.13 (0.94–1.37)

Abbreviations: HepB, hepatitis B vaccine; wks, weeks.

* The two unexposed groups have been combined.

[†] OR adjusted for demographics and presence of any high-risk condition(s).

[‡] Includes those diagnosed with 'Gestational Hypertension' and/or 'Hypertension during Pregnancy'.

[§] Pregnancies with missing outcome values were removed from Unexposed and Exposed denominators, including: Cesarean (Exposed N = 165, Unexposed N = 73,851); Gestational Age < 37 weeks (Exposed N = 119, Unexposed N = 58,781); Low birthweight (Exposed N = 121, Unexposed N = 59,645); Small for gestational age at birth (Exposed N = 123, Unexposed N = 62,159).