



Uptake and safety of hepatitis A vaccination during pregnancy: A Vaccine Safety Datalink study



Holly C. Groom^{a,*}, Ning Smith^a, Stephanie A. Irving^a, Padma Koppolu^a, Gabriela Vazquez- Benitez^b, Elyse O. Kharbanda^b, Matthew F. Daley^c, James G. Donahue^d, Darios Getahun^e, Lisa A. Jackson^f, Nicola P. Klein^g, Natalie L. McCarthy^h, James D. Nordin^b, Lakshmi Panagiotakopoulos^h, Allison L. Naleway^a

^aCenter for Health Research, Kaiser Permanente Northwest, Portland, OR, United States

^bHealthPartners Institute, Minneapolis, MN, United States

^cInstitute for Health Research, Kaiser Permanente Colorado, Aurora, CO, United States

^dMarshfield Clinic Research Institute, Marshfield, WI, United States

^eResearch and Evaluation, Kaiser Permanente Southern California, Pasadena, CA, United States

^fKaiser Permanente Washington Health Research Institute, Seattle, WA, United States

^gKaiser Permanente Vaccine Study Center, Kaiser Permanente Northern California, Oakland, CA, United States

^hImmunization Safety Office, Centers for Disease Control and Prevention, Atlanta, GA, United States

ARTICLE INFO

Article history:

Received 11 July 2019

Received in revised form 3 September 2019

Accepted 10 September 2019

Available online 20 September 2019

Keywords:

Vaccination

Hepatitis A

Pregnancy

Vaccine safety

Maternal immunization

ABSTRACT

Introduction: Infection with hepatitis A virus (HAV) during pregnancy, although uncommon, is associated with gestational complications and pre-term labor. Hepatitis A vaccine (HepA) is recommended for anyone at increased risk for contracting hepatitis A, including women at risk who are also pregnant. Limited data are available on the safety of maternal HepA vaccination.

Objectives: Assess the frequency of maternal HepA receipt and evaluate the potential association between maternal vaccination and pre-specified maternal and infant safety outcomes.

Methods: A retrospective cohort of pregnancies in the Vaccine Safety Datalink (VSD) resulting in live births from 2004 through 2015 was included. Pregnancies with HepA exposure were compared to those with other vaccine exposures, and to those with no vaccine exposures. Risk factors for contracting hepatitis A were identified up to one-year prior to or during the pregnancy using ICD-9 codes. Maternal and fetal adverse events were evaluated according to maternal HepA exposure status. Adjusted odds ratio (OR) were used to describe the association.

Results: Among 666,233 pregnancies in the study period, HepA was administered at a rate of 1.7 per 1000 (n = 1140), most commonly within the first six weeks of pregnancy. Less than 3% of those exposed to HepA during pregnancy had an ICD-confirmed risk factor. There were no significant associations between HepA exposure during pregnancy and gestational hypertension, gestational diabetes, pre-eclampsia/eclampsia, cesarean delivery, pre-term delivery, and low birthweight. There was a statistically significant association between HepA exposure during pregnancy and small-for-gestational age (SGA) infants (aOR 1.32, [95% CI 1.09, 1.60], p = 0.004).

Conclusions: The rate of maternal HepA vaccination was low and rarely due to documented risk factors for vaccination. HepA vaccination during pregnancy was not associated with an increased risk for a range of adverse events examined among pregnancies resulting in live births, but an identified association between maternal HepA and SGA infant outcomes, while likely due to unmeasured confounding, warrants further exploration.

© 2019 Elsevier Ltd. All rights reserved.

1. Introduction

Hepatitis A virus (HAV) infection during pregnancy, although uncommon (incidence of 1 per 1000 pregnancies) [1], has been found, in one study, to be associated with high rates of gestational complications and preterm labor with stronger associations noted

* Corresponding author at: 3800 N. Interstate Avenue, Portland, Oregon 97218oh, United States.

E-mail address: Holly.c.groom@kpchr.org (H.C. Groom).

for HAV infection during the second and third trimesters [2]. Few accounts of vertical transmission and intrapartum transmission (via contaminated blood or feces) exist, suggesting that mother-to-infant transmission of HAV can occur, but is extremely rare [3–6].

As a means to prevention, three Hepatitis A vaccines (HepA) have been shown to induce protective antibody levels in 94–100% of adults one month after receiving the first dose, and in 100% of adults following the second dose, which is recommended 6–18 months following the first dose [7]. HepA have also demonstrated effectiveness in reducing HAV transmission among children and adults based on analysis of trends in hepatitis A incidence following the Advisory Committee on Immunization Practices recommendation for routine vaccination of children in 1999 [7]. The Centers for Disease Control and Prevention (CDC) recommends vaccinating pregnant women who are previously unvaccinated (or of unknown vaccination status) and at high-risk of contracting hepatitis A, in order to prevent acute liver failure in the mother, and to minimize any potential risk for transmission of the virus to the fetus [8,9]. However, limited data are available on the safety of HepA receipt during pregnancy. Receipt of HepA during pregnancy may be prompted by a provider's concern over the presence of one or more risk factors for contracting hepatitis A, as detailed in Table 1. Maternal HepA administration may also occur inadvertently when a woman receives the vaccine for travel-related reasons or to catch-up on the routinely recommended vaccination schedule before she is known to be pregnant.

No previous large-scale, epidemiologic studies have systematically examined the safety of HepA administered during pregnancy or its association with maternal or fetal adverse events. One manuscript described 139 case reports to the Vaccine Adverse Event Reporting System (VAERS) over a 17-year period, describing events following receipt of HepA in pregnant women and did not find any concerning patterns of adverse events, either in pregnant women or their infants [10]. One recent study evaluated the risk of spontaneous abortion among pregnant women who received either a bivalent human papilloma virus (HPV) vaccine or HepA during pregnancy and found no increased risk of spontaneous abortion among women exposed to a HepA vaccine, in comparison to those receiving the HPV vaccine [11,12].

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 HepA 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

Table 1
High-risk indications for vaccination with HepA and corresponding ICD-9 codes.

High-risk indication for HepA	ICD-9 code
Chronic liver disease	571.x
Injection or non-injection drug use	304.x, 305.2–305.9
Clotting-factor disorder	286.x
Direct contacts with hepatitis A infection	NA
Occupational risk	NA
Travel to endemic countries	NA
Men who have sex with men*	NA

Abbreviations: HepA, hepatitis A vaccine; ICD-9, International Classification of Diseases- 9th edition; HAV, hepatitis A virus.

NA, Not available as ICD-9 code in HER.

* Not relevant for study population.

Datalink (VSD), a collaboration with the CDC [13]. 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. Study methods are similar to those used in a previous publication describing maternal Hepatitis B vaccination [14]. 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 to 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 in order to capture pre-pregnancy comorbidities as well as birth outcomes. Pregnancies were identified using a validated algorithm based on administrative, EHR, and claims data [15]. 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, within 30 days [15]. 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 birth-weight values (<300 g or >5000 g). Gestational age cut-offs were used to decrease errors in gestational age estimation and to remove infants with borderline viability who may be less likely to survive [2,16]. 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 CDC.

2.2. Measurement of exposure and covariates

Eligible pregnancies were assigned to one of three groups: (1) pregnancies where at least one dose of any of the three HepA licensed products was administered during the study period (*HepA vaccinated*); (2) pregnancies with no vaccines administered during pregnancy (*unvaccinated*); and (3) pregnancies that were not exposed to HepA, but were exposed to at least one other inactivated vaccine (*other vaccinated*). 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 HAV-immune status was not evaluated for this study, nor was HepA vaccination status prior to pregnancy.

The three groups were compared for differences in baseline demographic characteristics (age, race, educational background, marital status, gravidity, enrollment site) and three pre-specified high-risk HepA vaccine indications up to one year prior to and during pregnancy (chronic liver disease, clotting-factor disorder, and documented drug use and/or outpatient visit to chemical dependency or methadone use). 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 using International Classification of Diseases, Ninth Revision (ICD-9) codes assigned at inpatient or outpatient visits (Supplemental Table 1).

2.3. Reasons for vaccination

Given that several HepA indications could not be identified through ICD-9 codes documented in the EHR (e.g., occupational status, travel to and from endemic area), we conducted a single-site chart review of all HepA-exposed pregnancies to determine whether the presence of risk factors without associated ICD-9 codes may have contributed to decisions for maternal HepA

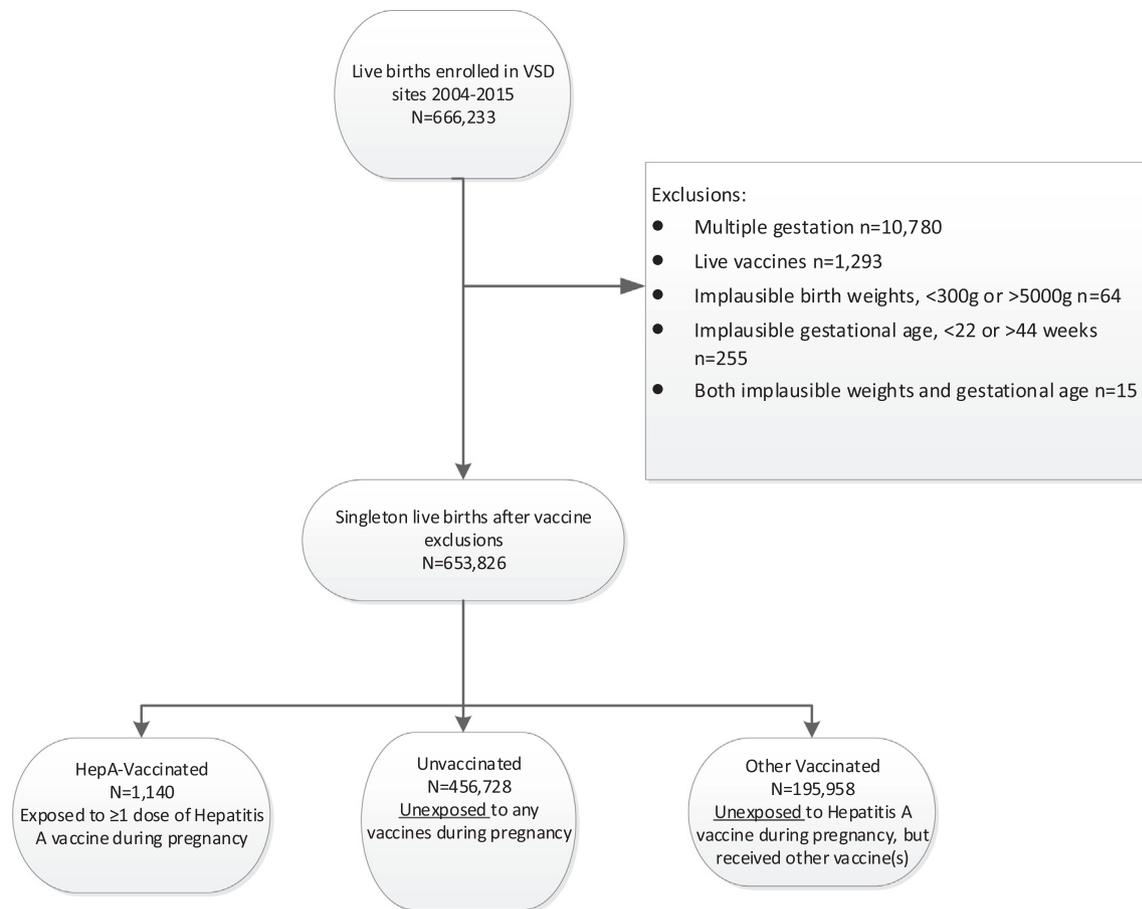


Fig 1. Study population of pregnancies with live birth outcomes in the VSD, 2004–2015.

administration, and to explore the frequency of catch-up vaccination of pregnant women before the pregnancy was confirmed. 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 HepA vaccination. Those with a positive pregnancy test prior to HepA receipt were defined as vaccination with ‘known’ pregnancy status; others were considered ‘unknown’ pregnancy status. The second step of chart review involved reviewing provider notes detailing any explanation for administering HepA during pregnancy. The five categorical options for explanations included: (1) perceived risk of exposure related to work, school, or household contacts (i.e., environments that could place the individual at risk of exposure); (2) travel to or from a country with endemic HAV circulation; (3) chemical dependence or methadone treatment; (4) catch-up vaccination for those who had not completed the 2-dose HepA series; and (5) unknown. Among those with provider notes detailing travel to an HAV-endemic region, information on other inactivated travel vaccines (e.g., typhoid) and prescription of anti-malarial medications was also abstracted, as pregnant women traveling to HAV-endemic areas may have other exposures (e.g., pharmaceutical prophylaxis, environmental exposures) that may place them at greater risk of adverse pregnancy outcomes [17,18]. Results from this review were used to describe the potential for misclassification of high-risk indications for acquiring hepatitis A when using only ICD-9 codes.

2.4. Measurement of maternal and fetal outcomes

In the absence of specific safety concerns about maternal HepA, 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 [19–21]. The adverse events of interest included the following common pregnancy-related complications identified using ICD-9 codes: gestational hypertension, gestational diabetes, preeclampsia/eclampsia, and cesarean delivery (Supplemental Table 1). Fetal adverse outcomes included pre-term birth (i.e., delivery before 37 weeks of completed gestation), low birth weight (<2500 g), and small for gestational age (SGA). 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 [22,23]. Fetal outcomes were identified from the mother’s chart or, for birthweight data, abstracted into the EHR from infant birth certificates, 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 post-partum period (Supplemental table 1).

2.5. Analysis

Since pregnancies were clustered within patients, General Estimating Equations (GEE) were used to first compare patient characteristics between the three study groups (except for pregnancy trimester at time of vaccination, which could only be compared between the *HepA vaccinated* and *other vaccinated* groups). To evaluate and compare maternal and fetal outcomes for HepA-exposed and unexposed pregnancies, the *unvaccinated* and *other vaccinated* groups were combined into a single unexposed comparison group. The GEE model was then used to evaluate potential associations between HepA and pre-specified study outcomes, controlling for

Table 2
Maternal characteristics based on vaccination status.

Characteristics	Group 1. HepA vaccinated (n = 1,140) %	Group 2. Unvaccinated* (N = 456,728) %	Group 3. Other vaccinated [†] (n = 195,958) %
Mean age (SD), years	29.0 (5.9)	30.1 (5.6)	30.2 (5.9)
<i>Age, years</i>			
<18	12.5	1.9	1.2
18–25	14.1	19.9	19.2
26–35	54.1	59.8	62.4
>35	19.3	18.4	17.2
<i>Marital status</i>			
Married	55.7	61.0	59.4
Single	26.1	21.4	23.0
Unknown	18.2	17.6	17.6
<i>Race</i>			
White	38.9	52.9	55.4
Black	8.3	7.1	5.8
Asian	29.6	14.5	15.1
Other	10.4	11.2	10.1
Unknown	12.9	14.3	13.7
<i>Study Site[‡]</i>			
A	4.7	5.4	4.8
B	3.7	5.4	5.6
C	0.6	2.0	1.9
D	52.5	40.0	40.5
E	4.8	5.5	4.8
F	33.7	41.7	42.4
<i>Education</i>			
< High school	6.4	3.6	2.7
High school graduate	5.8	10.6	10.3
>High school	67.3	67.3	68.3
Unknown	20.5	18.5	18.6
<i>Gravidity</i>			
1	42.7	29.3	35.7
2+	42.9	56.0	50.8
Unknown	14.4	14.7	13.7
<i>Trimester of vaccine exposure</i>			
1st (0–13 weeks)	69.0	NA	29.6
2nd (14–26 weeks)	26.2		35.4
3rd (27–42 weeks)	4.8		35.0
<i>Maternal vaccines received</i>			
Only HepA	30.2	NA	NA
1 other vaccine	41.1		71.3
≥2 other vaccines	28.8		28.6
Any travel vaccines ^{††}	15.4		<1.0
Any hepatitis A risk factor[§]	2.5	2.6	2.5
Clotting-factor disorder	0.00	0.18	0.00
Chronic liver disease	0.26	0.29	0.24
Injection-drug use	2.19	2.22	2.18
Visit to chemical dependency	1.6	1.7	1.6
History of HepA	0.00	0.01	0.00
Maternal alcohol use	12.1	13.1	17.9
Maternal Smoking	6.1	6.4	7.2

Abbreviations: HepA, hepatitis A vaccine; HAV, hepatitis A virus.

Bold face indicates high-risk indications for HepA vaccination.

* Pregnancies with no vaccine exposure during pregnancy.

[†] Pregnancies with no exposure to HepA 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 ICD-9 codes either during, or within 12 months preceding, the pregnancy.

^{††} Travel vaccines included any inactivated presentations of the following vaccines: Typhoid, Rabies, Japanese Encephalitis.

race, age, site, marital status, education, gravida status, maternal alcohol use, maternal smoking, and high-risk indications for HepA vaccination, including chronic liver disease, clotting-factor disorder, and injection drug use and/or outpatient visit to chemical dependency or methadone use.

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 1140 pregnancies resulting in live births were included in the *HepA vaccinated* group, 456,728 in the *unvaccinated*

group, and 195,958 in the *other vaccinated* group (Fig. 1). While pregnancies with HepA exposure (<1% of the study population) were significantly different across most descriptive characteristics when compared to pregnancies in either comparison group, the absolute percentage differences between groups were generally small (<5%; Table 2). Some noted exceptions, however, include higher proportions of women aged < 18 years and of Asian race among HepA-exposed pregnancies. Women with a HepA-exposed pregnancy were significantly more likely to be aged < 18 years and experiencing their first pregnancy, and nearly 30% of those vaccinated were Asian compared to only 15% in each of the comparison groups. In the *HepA vaccinated* group, 51% of HepA exposures occurred within the first six weeks of pregnancy (and 36% within the first three weeks), whereas for pregnancies with exposure to other vaccines (primarily influenza and Tdap vaccines), vaccinations were more evenly distributed across the trimesters. Of the 1140 HepA exposed pregnancies, 55.3% were exposed to ≥ 1 other vaccine(s) concomitantly with HepA. Fifteen percent, or 178, women vaccinated with HepA also received one (or more) inactivated vaccines (174/178 administered concomitantly) that are only recommended for travel, such as the typhoid vaccine, compared to < 1% of the *other vaccinated* group.

In this analysis, we were able to examine only three of the high-risk indications specified for maternal administration of HepA with ICD-9 codes across study sites: chronic liver disease, clotting-factor disorder, and documented drug use. The proportions of pregnancies with any of these high-risk indications, as documented in the 12 months preceding or during pregnancy, were very low for all three groups (<1% with chronic liver disease; <1% with clotting-factor disorder, and < 3% with documented injection drug use or chemical dependency) (Table 2). Women with HepA-exposed pregnancies had a lower prevalence of documented maternal alcohol use than did women in

either of the comparison groups (12.1% vs 13.1% and 17.9%); prevalence of maternal smoking was similar across all groups. Of note, about 12% of pregnancies occurred among women who had between six and eleven months of continuous enrollment, which may have impacted our ability to assess their high-risk status.

3.1. Reasons for vaccination

Of the 53 HepA exposed pregnancies reviewed at one site, 27 (51%) had documentation of a positive pregnancy test prior to vaccination, and the remaining 26 (49%) had an unknown pregnancy status at time of vaccination. Among those with a known pregnancy status at the time of HepA receipt, the most common reasons for vaccination were catch-up vaccination (either initiation or completion of the series) (41%), travel-related (33%), and perceived risk status (27%). Two women were considered high-risk because they had previously been diagnosed with hepatitis B virus (HBV) infection; two were vaccinated to meet work or school requirements; two were at risk due to infected household contacts, and one was exposed to a food related hepatitis A outbreak. In comparison, where pregnancy status was not known at the time of vaccination, the most common reasons for vaccination were catch-up vaccination (50%), followed by travel-related reasons (35%), and three (12%) were vaccinated for another perceived risk (one was HBV-positive, one was engaging in high risk sexual behaviors, and 1 was vaccinated to meet work or school requirements). Among those for whom the primary reason for HepA vaccination was travel-related ($n = 18/53$), only two received any additional travel vaccines (typhoid, inactivated for both individuals) and none appeared to have been dispensed anti-malarial medications.

Table 3
Association between maternal vaccination with HepA and adverse maternal and fetal outcomes among pregnancies resulting in live births.

Outcome	HepA Vaccinated (n = 1,140) % (n)	Not HepA Vaccinated * (N = 652,686) % (n)	Odds Ratio (95% Confidence Intervals)	
			Unadjusted	Adjusted [†]
<i>Gestational hypertension</i> [‡]				
No (ref)	96.1 (1096)	95.4 (622,562)		
Yes	3.9 (44)	4.6 (30,129)	0.83 (0.62–1.12)	0.85 (0.64–1.15)
<i>Gestational diabetes</i>				
No (ref)	88.8 (1012)	87.8 (572,829)		
Yes	11.2 (128)	12.2 (79,862)	0.91 (0.76–1.09)	0.93 (0.78–1.11)
<i>Pre-eclampsia/eclampsia</i>				
No (ref)	95.5 (1089)	95.5 (623,435)		
Yes	4.5 (51)	4.5 (29,256)	1.00 (0.75–1.32)	0.92 (0.69–1.24)
<i>Cesarean delivery</i> [§]				
No (ref)	70.2 (705)	70.6 (408,622)		
Yes	29.8 (299)	29.4 (170,189)	1.02 (0.89–1.17)	1.01 (0.91–1.13)
<i>Pre-term birth (<37 wks)</i> [§]				
No (ref)	93.4 (953)	92.8 (551,036)		
Yes	6.6 (67)	7.2 (42,875)	0.90 (0.71–1.16)	0.83 (0.65–1.07)
<i>Low birth weight (<2500 g)</i> [§]				
No (ref)	94.2 (954)	95.0 (563,460)		
Yes	5.8 (59)	5.0 (29,592)	1.18 (0.9–1.53)	1.05 (0.81–1.37)
<i>Small for gestational age at birth</i> [§]				
No (ref)	87.7 (887)	91.7 (541,265)		
Yes	12.3 (124)	8.3 (49,273)	1.54 (1.27–1.85)	1.32 (1.09–1.60)

Abbreviations: HepA, hepatitis A vaccine; wks, weeks.

* The two unexposed groups have been combined.

[†] OR adjusted for race, age, site, marital status, education, gravida, alcohol use, smoking status, 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 = 136, Unexposed N = 73,880); Gestational Age < 37 weeks (Exposed N = 120, Unexposed N = 58,780); Low birthweight (Exposed N = 127, Unexposed N = 59,639); Small for gestational age (Exposed N = 129, Unexposed N = 62,153).

3.2. Maternal and fetal outcomes

Given minimal differences in population characteristics between the two unexposed study groups, the *unvaccinated* and *other vaccinated* were combined into a single unexposed group for assessment of study outcomes. There were no significant associations between HepA exposure during pregnancy and gestational hypertension, gestational diabetes, pre-eclampsia/eclampsia, cesarean delivery, pre-term delivery, or low birthweight (Table 3). However, there was a significant association between HepA exposure during pregnancy and SGA infants, with a 12.3% SGA prevalence ratio among HepA vaccinated pregnancies compared to 8.3% among non-HepA vaccinated pregnancies. After adjusting for race, age, site, marital status, education, gravida, maternal alcohol use, maternal smoking, and high-risk conditions for HepA vaccination, there was an adjusted odds ratio for SGA of 1.32, (95% CI 1.09, 1.60, $p = 0.004$).

3.3. Post hoc analyses of HepA exposure and SGA

To further explore the association between HepA exposure during pregnancy and SGA, we conducted age- and race-stratified analyses since prior research has shown that SGA risk is increased in non-whites and younger (<26 years) and older (>39 years) women [24]. Consistent with these previous studies, we observed increased overall rates of SGA among women younger than age 26 years and non-white race in our population; the prevalence was specifically higher in Asian women. However, when we stratified our findings by race and age according to HepA exposure, the increased risk of SGA was instead concentrated in both white women and those 26 years of age and older (Supplemental Table 2). We did not observe a significantly increased risk for SGA among younger or non-white women vaccinated during pregnancy compared to those who were not vaccinated, however the aOR was elevated in each stratum. We also examined the proportion of SGA infants who were born pre-term (<37 weeks gestation) in each of our study groups; 4.8% of our HepA vaccinated group with SGA outcomes had pre-term births, compared to 10.8% of our unexposed (data not shown). Comparisons between those with SGA and non-SGA outcomes, among HepA vaccinated pregnancies, revealed a similar distribution by trimester of vaccination, where 69% of those with and without SGA outcomes were first-trimester vaccinations, and the remainder largely vaccinated in the second trimester (27% without SGA, 31% with SGA). (data not shown) Finally, we compared low birthweight outcomes by trimester of vaccination, comparing HepA vaccinated pregnancies to those with some other vaccination during pregnancy; the proportion of infants classified as low birthweight was not significantly different among those with, compared to those without, HepA vaccination during pregnancy, regardless of trimester of vaccination (data not shown).

4. Discussion

This study represents the first large-scale evaluation of administration patterns and select safety outcomes following maternal HepA vaccine administration. Using a network of large, integrated healthcare systems, our study confirmed that maternal vaccination with HepA is uncommon; <1% of over 650,000 singleton pregnancies were exposed to HepA. Since no specific maternal HepA safety concerns are noted in the literature we chose to examine a pre-specified set of commonly examined maternal and fetal outcomes. The maternal and fetal outcomes included in our analysis are not expected to be causally linked to maternal exposure to HepA vaccines and we found no significant associations between maternal

HepA and gestational hypertension, gestational diabetes, pre-eclampsia/eclampsia, cesarean delivery, pre-term birth, or low birth weight. We did, however, find an association for SGA, where 12.3% of HepA exposed compared to 8.3% of unexposed pregnant women had infants considered as SGA.

SGA is defined as infants whose birthweight is at or below the 10th percentile for a given gestational age. It is important to note that neither low birth weight nor pre-term birth were independently associated with HepA vaccination; only for birth weight relative to gestational age did we observe this effect. This, combined with the discordant sample sizes of our comparison groups, makes it difficult to interpret the clinical significance of a 4% absolute difference in SGA prevalence (12.3% of 1011 vs. 8.3% of 590,533 births).

The maternal risk factors for SGA are extensive and include a combination of genetic, environmental, or placental factors. Ethnicity, age, height, weight, maternal chronic hypertension, renal disease, and anti-phospholipid syndrome also influence risk [25]. Having a diagnosis of SGA does not necessarily impact infant viability; certain genetic (e.g., race) and environmental (e.g., high altitude) factors can predispose individuals to SGA without adversely impacting their long-term health [26–28]. Without capturing the full range of possible etiologies of the SGA outcome, we are limited in our ability to understand the implications of our study findings. As described by Savitz et al., an optimal study designed to measure the association between an exposure and an outcome such as SGA would account for all known risk factors and also include longitudinal information on the pregnancy, detailing ultrasound measurements of fetal growth from pregnancy onset [27]. Our analysis did not include such measurements, nor did it account for the presence of most of the established maternal risk factors. However, we were able to measure some indicators for HepA vaccination during pregnancy that were recorded with ICD-9 codes in the EHR (clotting-factor disorder, chronic liver disease, documented chemical dependency) and adjusted for these and other measurable confounders (race, age, site, marital status, education, gravida, maternal alcohol use, and maternal smoking) in our models. With an unadjusted odds ratio of 1.54 and an adjusted OR of 1.32, some amount of confounding was addressed in our adjustments. Nonetheless, we can expect that our study design has introduced some systematic bias due to differences in baseline risk factors between our study groups that, if we were able to identify and capture, may help explain the association between SGA and HepA exposure during pregnancy [16]. Furthermore, there is no evidence describing the biologic plausibility of the hepatitis A vaccine causing SGA, thus complicating efforts to evaluate this observed association.

Using the available data, we conducted some post hoc analyses to explore the finding for SGA stratified by two known risk factors, maternal age and race. We found the risk of SGA to be concentrated in white women ≥ 26 years of age. However, cell sizes within the HepA vaccinated group were small (<15) when stratified by age and race, especially for the < 18 and 18–25 years age groups. As shown in Supplemental table 2, the overall prevalence of SGA is highest among those aged < 26, but small sample size paired with adjustments lead to a non-significant finding among this younger age group. As a result, the significant finding for SGA among those aged ≥ 26 years of white race is potentially spurious and likely driven by the very large number of pregnancies in our non-HepA vaccinated group [29].

The chart review data collected suggests that many women who received HepA during pregnancy were vaccinated before they or their provider were aware of the pregnancy. However, about 40% of these women were vaccinated because they were planning travel to an HAV endemic region or had another risk factor for HAV infection, including exposure to HAV-infected individuals and personal HBV infection. For those where travel was the motivator

behind maternal HepA vaccination, there are potential exposures during travel to HAV-endemic countries, such as other infectious diseases, dehydration, animal bites, travel medications, stress, and dietary changes, which may have adverse impacts on pregnancy [18,30]. Malaria and Zika virus infections as well as travel to high altitudes have all been shown to be associated with increased likelihood of intrauterine growth retardation and/or SGA [31,32]. While we were not able to assess these other exposures directly, we did review receipt of other travel vaccines during pregnancy as a proxy for these potential exposures and found that 175 (15%) of our HepA vaccinees also received some other inactivated travel vaccine (predominantly inactivated typhoid) during pregnancy, compared to <1% of our comparison group. Results from a stratified analysis, excluding all pregnancies with exposure to travel vaccines from our exposure groups, resulted in an adjusted odds ratio for SGA of 1.30 (95% CI 1.05–1.61). Removing travel vaccine exposure did not change our finding for SGA following maternal HepA vaccination.

Most doses (69%) of HepA were administered during the first trimester and 51% were administered before the 7th week of pregnancy, which suggests that providers may not be aware of the pregnancy when HepA is administered. In the sample of records reviewed, most women who received HepA were catching up on routine vaccination and did not appear to have other known or documented risk factors for hepatitis A. While this may not be generalizable to the full study population, it suggests 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 had small numbers of HepA exposed pregnancies. We did not examine neonatal outcomes related to congenital anomalies or neonatal cholestasis, nor did we examine pregnancy loss. We did not have data on specific, known risk factors for each of the included outcomes and we did not collect information on medication exposures, which may have been an important detail to consider for a vaccine that is commonly administered for travel. 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 travel, or household or occupational exposure for the full population. The high-risk indications that we did attempt to identify in the EHR (e.g., injection drug use/drug dependence) are poorly reported and documented and are likely an under-representation of the true extent of these high-risk indications in our study population. Consistent with other vaccine safety studies among pregnant women, we included vaccine exposures that occurred anytime during pregnancy (weeks 1 through 37) without adjusting exposure windows by outcomes. It is possible that causal association between vaccine and outcomes differs by timing of exposure. However, a separate analysis restricted to vaccinations that took place in the first trimester (representing 69% of vaccinees) did not change the study findings (supplemental table 3). Studies that have examined factors associated with SGA have described various ways that external factors might introduce fetal growth restriction, but there is not consensus around the critical timepoint when those exposures lead to SGA [25,33]. One such study has suggested that biologic variation in fetal size largely manifests in the third trimester, and newborns who are considered SGA at term may be more likely to represent those who are constitutionally (rather than pathologically) small [34]. This may be an important distinction, given that 95% of SGA infants in our HepA exposed group were term (gestational age \geq 37 weeks), compared to 89% in our non-HepA exposed group. Finally, the imbalanced sample sizes, between vaccinated and un-vaccinated, may have spuriously introduced our single significant finding.

5. Conclusions

This large, multisite study provides evidence that HepA administration during pregnancy was not associated with increased risk of a range of adverse events examined among pregnancies resulting in live births. The intent of this study was to broadly summarize maternal and fetal outcomes following maternal HepA vaccination. The association between maternal HepA vaccination and SGA, while likely due to unmeasured confounding, may warrant further exploration.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Naleway has received research support from Merck & CO, and Pfizer. Dr. Getahun has received research support from Bayer AG. Dr. Klein has received research support from GlaxoSmithKlein, Merck & CO, Sanofi Pasteur, Pfizer, MedImmune, Protein Science (now Sanofi Pasteur), and Dynavax. Merck and GlaxoSmithKlein currently manufacture hepatitis A vaccines that are in use in the United States.

Acknowledgements

Funding for this study was provided by the Centers for Disease Control and Prevention, Contract 200-2012-53584. Findings and conclusions of this study are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. We would like to acknowledge the contributions of Project Managers and Data Managers from participating VSD sites. We would also like to extend our appreciation to Dr. Noele Nelson, the Acting Branch Chief in CDC's Division of Viral Hepatitis, for her review of, and contributions to, the final manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2019.09.043>.

References

- [1] Magriples U. Hepatitis in pregnancy. *Semin Perinatol* 1998;22(2):112–7.
- [2] Elinav E, Ben-Dov IZ, Shapira Y, et al. Acute hepatitis A infection in pregnancy is associated with high rates of gestational complications and preterm labor. *Gastroenterology* 2006;130(4):1129–34.
- [3] Watson JC, Fleming DW, Borella AJ, Olcott ES, Conrad RE, Baron RC. Vertical transmission of hepatitis A resulting in an outbreak in a neonatal intensive care unit. *J Infect Dis* 1993;167(3):567–71.
- [4] Tanaka I, Shima M, Kubota Y, Takahashi Y, Kawamata O, Yoshioka A. Vertical transmission of hepatitis A virus. *Lancet* 1995;345(8946):397.
- [5] Leikin E, Lysikiewicz A, Garry D, Tejani N. Intrauterine transmission of hepatitis A virus. *Obstet Gynecol* 1996;88(4 Pt 2):690–1.
- [6] McDuffie Jr RS, Bader T. Fetal meconium peritonitis after maternal hepatitis A. *Am J Obstet Gynecol* 1999;180(4):1031–2.
- [7] Fiore AE, Wasley A, Bell BP. Prevention of hepatitis A through active or passive immunization: recommendations of the advisory committee on immunization practices (ACIP). *MMWR Recomm Rep* 2006;55(RR-7):1–23.
- [8] Bridges CB, Woods L, Coyne-Beasley T. Advisory committee on immunization practices (ACIP) recommended immunization schedule for adults aged 19 years and older—United States, 2013. *MMWR Surveill Summ* 2013;62(Suppl 1):9–19.
- [9] CDC. Prevention of hepatitis A through active or passive immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 1999;48(RR-12):1–37.
- [10] Moro PL, Museru OI, Niu M, Lewis P, Broder K. Reports to the vaccine adverse event reporting system after hepatitis A and hepatitis AB vaccines in pregnant women. *Am J Obstet Gynecol* 2013.
- [11] Panagiotou OA, Befano BL, Gonzalez P, et al. Effect of bivalent human papillomavirus vaccination on pregnancy outcomes: long term observational follow-up in the Costa Rica HPV Vaccine Trial. *BMJ* 2015;351:h4358.

- [12] Herrero R, Hildesheim A, Rodriguez AC, et al. Rationale and design of a community-based double-blind randomized clinical trial of an HPV 16 and 18 vaccine in Guanacaste, Costa Rica. *Vaccine* 2008;26(37):4795–808.
- [13] McNeil MM, Gee J, Weintraub ES, et al. The Vaccine safety Datalink: successes and challenges monitoring vaccine safety. *Vaccine* 2014;32(42):5390–8.
- [14] Groom HC, Irving SA, Koppolu P, et al. Uptake and safety of Hepatitis B vaccination during pregnancy: a vaccine safety Datalink study. *Vaccine* 2018;36(41):6111–6.
- [15] Naleway AL, Gold R, Kurosky S, et al. Identifying pregnancy episodes, outcomes, and mother–infant pairs in the vaccine safety Datalink. *Vaccine* 2013;31(27):2898–903.
- [16] Vazquez-Benitez G, Kharbanda EO, Naleway AL, et al. Risk of preterm or small-for-gestational-age birth after influenza vaccination during pregnancy: caveats when conducting retrospective observational studies. *Am J Epidemiol* 2016;184(3):176–86.
- [17] Kourtis AP, Read JS, Jamieson DJ. Pregnancy and infection. *N Engl J Med* 2014;371(11):1077.
- [18] Rogerson SJ. Malaria in pregnancy and the newborn. *Adv Exp Med Biol* 2010;659:139–52.
- [19] Kharbanda EO, Vazquez-Benitez G, Lipkind H, Naleway A, Lee G, Nordin JD. Inactivated influenza vaccine during pregnancy and risks for adverse obstetric events. *Obstet Gynecol* 2013;122(3):659–67.
- [20] Kharbanda EO, Vazquez-Benitez G, Lipkind HS, et al. Maternal Tdap vaccination: Coverage and acute safety outcomes in the vaccine safety datalink, 2007–2013. *Vaccine* 2016;34(7):968–73.
- [21] Sukumaran L, McCarthy NL, Kharbanda EO, et al. Safety of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis and influenza vaccinations in pregnancy. *Obstet Gynecol*. 2015;126(5):1069–74.
- [22] Joseph KS, Kramer MS, Allen AC, Mery LS, Platt RW, Wen SW. Implausible birth weight for gestational age. *Am J Epidemiol* 2001;153(2):110–3.
- [23] Oken E, Kleinman KP, Rich-Edwards J, Gillman MW. A nearly continuous measure of birth weight for gestational age using a United States national reference. *BMC Pediatr* 2003;3:6.
- [24] Ananth CV, Balasubramanian B, Demissie K, Kinzler WL. Small-for-gestational-age births in the United States: an age-period-cohort analysis. *Epidemiology* 2004;15(1):28–35.
- [25] McCowan L, Horgan RP. Risk factors for small for gestational age infants. *Best Pract Res Clin Obstet Gynaecol* 2009;23(6):779–93.
- [26] Wilcox AJ. On the importance—and the unimportance—of birthweight. *Int J Epidemiol* 2001;30(6):1233–41.
- [27] Savitz DA, Hertz-Picciotto I, Poole C, Olshan AF. Epidemiologic measures of the course and outcome of pregnancy. *Epidemiol Rev* 2002;24(2):91–101.
- [28] Schlaudecker EP, Munoz FM, Bardaji A, et al. Small for gestational age: case definition & guidelines for data collection, analysis, and presentation of maternal immunisation safety data. *Vaccine* 2017;35(48 Pt A):6518–28.
- [29] Kuhberger A, Fritz A, Lerner E, Scherndl T. The significance fallacy in inferential statistics. *BMC Res Notes* 2015;8:84.
- [30] Saito M, Gilder ME, McGready R, Nosten F. Antimalarial drugs for treating and preventing malaria in pregnant and lactating women. *Exp Opin Drug Saf* 2018;17(11):1129–44.
- [31] Antony KM, Ehrental D, Evensen A, Iruetagoiena JI. Travel during pregnancy: considerations for the obstetric provider. *Obstet Gynecol Surv* 2017;72(2):97–115.
- [32] Mieske K, Flaherty G, O'Brien T. Journeys to high altitude—risks and recommendations for travelers with preexisting medical conditions. *J Travel Med* 2010;17(1):48–62.
- [33] McCowan LM, Figueras F, Anderson NH. Evidence-based national guidelines for the management of suspected fetal growth restriction: comparison, consensus, and controversy. *Am J Obstet Gynecol* 2018;218(25):S855–68.
- [34] Ananth CV, Vintzileos AM. Distinguishing pathological from constitutional small for gestational age births in population-based studies. *Early Hum Dev* 2009;85(10):653–8.