HHS Public Access

Author manuscript

Vaccine. Author manuscript; available in PMC 2019 July 13.

Published in final edited form as:

Vaccine. 2018 January 02; 36(1): 50–54. doi:10.1016/j.vaccine.2017.11.039.

Assessing the safety of hepatitis B vaccination during pregnancy in the Vaccine Adverse Event Reporting System (VAERS), 1990–2016

Pedro L. Moro, MD, MPH[1], **Yenlik Zheteyeva, MD, MPH**[2], **Faith Barash, MD, MPH**[3], **Paige Lewis, MSPH**[1], and **Maria Cano, MD, MPH**[1]

[1]Immunization Safety Office (ISO), Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Centers for Disease Control and Prevention (CDC)

[2]Community Interventions for Infection Control Unit, Division of Global Migration and Quarantine, NCEZID, CDC

[3]Center for Biologics Evaluation and Research, Food and Drug Administration (FDA)

Abstract

Background—The safety of hepatitis B vaccination during pregnancy has not been well studied.

Objective—We characterized adverse events (AEs) after Hepatitis B vaccination of pregnant women reported to the Vaccine Adverse Event Reporting System (VAERS), a spontaneous reporting surveillance system.

Methods—We searched VAERS for AEs reports involving pregnant women who received Hepatitis B vaccine from January 1, 1990–June 30, 2016. All reports and available medical records were reviewed by physicians. Observed AEs were compared to expected AEs and known rates of pregnancy outcomes to assess for any unexpected safety concern.

Results—We found 192 reports involving pregnant women following Hepatitis B vaccination of which 110 (57.3%) described AEs; 12 (6.3%) were classified as serious, one newborn death was identified in a severely premature delivery, and there were no maternal deaths. Eighty-two (42.7%) reports did not describe any AEs. Among pregnancies for which gestational age was reported, most women were vaccinated during the first trimester, 86/115 (74.7%). Among reports describing an AE, the most common pregnancy-specific outcomes included spontaneous abortion in 23 reports, preterm delivery in 7 reports, and elective termination in 5 reports. The most common non-pregnancy specific outcomes were general disorders and administration site conditions, such as injection site and systemic reactions, in 21 reports. Among 22 reports describing an AE among

Disclosures: No authors have a conflict of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the Food and Drug Administration.

Appendix A. Supplementary material

Supplementary data associated with this article has been provided

infants born to women vaccinated during pregnancy, 5 described major birth defects each affecting different organ systems.

Conclusion—Our analysis of VAERS reports involving Hepatitis B vaccination during pregnancy did not identify any new or unexpected safety concerns.

Keywords

adverse event; epidemiology; hepatitis B vaccine; surveillance; vaccine safety

Introduction

Five hepatitis B vaccines are licensed in the United States: two single antigen vaccines, Recombivax HB® (Merck & Co., Inc., Whitehouse Station, New Jersey) and Engerix-B® (GlaxoSmithKline Biologicals, Rixensart, Belgium) [1,2], and three combination vaccines, Twinrix® [HepA-HepB] (GlaxoSmithKline Biologicals, Rixensart, Belgium) [3], Comvax® [Hib-HepB] (Merck & Co., Inc., Whitehouse Station, New Jersey) and Pediarix® [DTaP-HepB-IPV] (GlaxoSmithKline Biologicals, Rixensart, Belgium) [4,5]. Comvax® and Pediarix® are indicated only for children [6].

The recommendations of the Advisory Committee on Immunization Practices (ACIP) for Hepatitis B vaccination during pregnancy state that this vaccine is not contraindicated during pregnancy. The indications for Hepatitis B vaccination are also applicable to pregnant women and these include: universal Hepatitis B vaccination for all unvaccinated adults in settings in which a high proportion of adults have risks for Hepatitis B infection (e.g., sexually transmitted disease/human immunodeficiency virus testing and treatment facilities). In other primary care and specialty medical settings in which adults at risk for Hepatitis B virus (HBV) infection receive care, health-care providers should inform all patients about the health benefits of vaccination, including risks for HBV infection and persons for whom vaccination is recommended, and vaccinate adults who report risks for HBV infection and any adults requesting protection from HBV infection [6,7].

Hepatitis B vaccines have a well-established safety record among infants, children, adolescents, and adults [6,7]. The most frequently reported adverse events (AEs) are pain at the injection site and fever [6]. Pregnancy is not a contraindication to vaccination [7]; however, there are limited data on the safety of Hepatitis B during pregnancy [8]. A review in the Vaccine Adverse Event Reporting System (VAERS) assessed the safety of Twinrix [9] in pregnancy and did not find any disproportionate reporting or unexpected AEs [9]. For the other hepatitis B vaccines, we are not aware of safety studies among pregnant women. To address this knowledge gap, we conducted a review of VAERS reports involving pregnant women for hepatitis B vaccines approved for use in women of reproductive age.

Materials and Methods

Vaccine Adverse Events Reporting System (VAERS)

VAERS is a national vaccine safety surveillance system, co-administered by the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC). It

receives spontaneous (passive) reports of AEs following vaccination [10] submitted by healthcare providers, vaccine recipients, vaccine manufacturers, and other reporters. The VAERS report form collects information on the age, sex, vaccines administered, AE experienced, medical conditions at the time of vaccination and medical history. Signs and symptoms in VAERS reports are coded using Medical Dictionary for Regulatory Activities (MedDRA) terms, a clinically validated, internationally standardized medical terminology [11]. AEs in a VAERS report may be assigned one or more MedDRA preferred terms (PT). A MedDRA PT is a distinct descriptor for a symptom, sign, disease, diagnosis, therapeutic indication, investigation, surgical, or medical procedure, or medical, social, or family history characteristic [12]. MedDRA PTs are not medically confirmed diagnoses. System Organ Class (SOC) is the highest level of the MedDRA hierarchy that provides the broadest classification for AEs [9] (e.g. nervous system disorders). The definition of serious reports, based on the Code of Federal Regulations, is a report that includes one of the following: death, life-threatening illness, hospitalization or prolongation of hospitalization, or permanent disability [13]. This definition is based on the reporter's assessment of the condition, and for pregnancy reports, it often is based on conditions in the mother and not necessarily the fetus or live born infant (e.g., a report of spontaneous abortion may not be classified as serious if it wasn't life threatening to the woman or did not result in hospitalization). Medical records are routinely requested for reports classified as serious and reported by non-manufacturers. Reports describing only a vaccination error (e.g., vaccine administered to a person who is of an age not recommended for vaccination) and no report of an AE are assigned appropriate MedDRA PTs for medication errors.

We searched the VAERS database for reports of pregnant women vaccinated in the United States with hepatitis B vaccine from January 1, 1990 through June 30, 2016. To identify pregnancy reports, we conducted an automated search using the following three approaches: i) MedDRA terms in two system organ classes (SOC), "Pregnancy, Puerperium, and Perinatal Conditions" and "Congenital, Familial, and Genetic Disorders"; ii) MedDRA PTs "Drug exposure during pregnancy", "Maternal exposure during pregnancy", and "Exposure during pregnancy"; and iii) a text string search for the term "preg" in the report. Reports that met at least one of these criteria were included for analysis. We included reports of women vaccinated with Hepatitis B vaccine during pregnancy where the primary AE being reported (or the focus of the report) was in the live born infant.

Clinical reviews

Physicians from the FDA (FB) and CDC (YZ, PM, MC) reviewed all United States reports identified through the automated search of the VAERS database to ascertain pregnancy status at time of vaccination, calculate gestational age, and characterize AEs. For each report, a primary diagnosis was assigned. If more than one AE was reported for the same individual, we assigned the diagnosis based on what we believed was the primary health event of concern, and classified the pregnancy-specific event as the primary event unless information suggested otherwise. Non-pregnancy-specific medical conditions were categorized by SOC. We excluded reports where upon review we determined the subject was not pregnant or that Hepatitis B vaccine was administered prior to the last menstrual period. Gestational age at the time of vaccination and at the time of the AE were calculated based

on: (1) clinical determination by the health care provider as stated in the report, (2) earliest ultrasound assessment (if the former was not available), or (3) last menstrual period, estimated delivery date, or estimated date of conception (if the first two options were unavailable) in the VAERS report and/or medical records. We used the following definition for trimesters: first (0–13 weeks), second (14–27 weeks), and third (≥28 weeks). Spontaneous abortion (SAB) was defined as fetal demise <20 weeks gestation; stillbirth was defined as fetal demise ≥20 weeks gestation, and preterm delivery was defined as a live birth <37 weeks gestation [14]. Observed AEs were compared to expected AEs and known rates of pregnancy outcomes to assess for any unexpected safety concern. Expected AEs were those deemed as such by subject matter experts [YZ, FB], and published sources [14,15].

Because VAERS is a routine, government-sponsored surveillance system that does not meet the definition of research, this investigation was not subject to institutional review board review or informed consent requirements.

Results

From January 1, 1990 through June 30, 2016, VAERS received 192 reports involving Hepatitis B vaccination of pregnant women. A total of 110 reports described AEs; the remaining 82 (42.7%) reports did not described an AE; in 48 of these 82 reports a live vaccine (contraindicated during pregnancy) was concomitantly administered and in one report the hepatitis B vaccine was given intravenously. A total of 12 (6.3%) reports were classified as serious. Characteristics of the pregnant women and AEs reported are shown in Tables 1 and Table 2. Most (191; 99%) reports involved administration of a single antigen Hepatitis B vaccine. In 93 (48.4%) Hepatitis B vaccine was given concurrently with other vaccines; 39 (43%) with known age were children and adolescents The top three vaccines given concurrently with Hepatitis B vaccine were varicella, measles, mumps, rubella, and hepatitis A vaccines, respectively. Vaccine manufacturers submitted the most reports (83, 43.2%) followed by healthcare providers (43, 22.4%).

Among 115 (59.9%) reports where information on trimester of pregnancy when vaccinated was available, 86 (74.7%) stated that Hepatitis B vaccine was received in the first trimester. A supplementary table shows the adverse events according to the trimester of vaccination. No maternal deaths were reported. One death in an infant of a woman vaccinated during pregnancy was reported; the child was born prematurely at 27 weeks gestation and died at 54 days of age. The infant presented with small perforations in the small intestine and had mild hyaline disease. The most common pregnancy-specific AEs were spontaneous abortion in 23 (20.9%) of 110 reports, followed by preterm delivery in 7 (6.4%) and elective termination of pregnancy in 5 (4.5%) reports. Circumstances surrounding elective termination was documented in one report, a fetus with Down syndrome and cardiac abnormalities detected in-utero. Among non-pregnancy-specific AEs, general disorders and administration site conditions (e.g., injection site and systemic reactions) were most commonly reported (20; 18.2%). We found 5 reports of birth defects, three of which involved cardiac defects, although different specific defects of the heart (Table 2).

Twelve reports classified as serious included: one maternal report each of urinary tract infection, pre-term delivery, hypertension, lupus, pharyngitis, spontaneous abortion, and elective termination; a report of intrauterine brain damage in the fetus; and one infant report each of encephalocele and orbital roof defect, deafness, hiccups, and meningitis.

Discussion

We do not know how many pregnant women in the United States have received Hepatitis B vaccine since 1990, as there is no national vaccination coverage data in pregnant women. A population-based study in the Vaccine Safety Datalink (VSD) estimated that during 2002–2009, Hepatitis B vaccine was administered at a rate of 3.7 doses per 1,000 pregnancies [16]. VAERS received 192 reports involving Hepatitis B vaccination of pregnant women or involving infants exposed in-utero during the analytic period January 1990 through June 2016. Conditions observed in reports were those we would expect (e.g., injection site reactions, spontaneous abortion) and vaccine administration errors (e.g. incorrect vaccine given) were common. Similar conditions have been reported to VAERS in pregnant women vaccinated with different vaccines [9,17,18]. SAB is relatively common during pregnancy, occurring at a background rate of 10%, and can reach 22% in women 34 years of age or older [15]. Given this relatively high background rate for SAB, we should expect to observe VAERS reports of SAB following maternal Hepatitis B vaccination due to chance alone (i.e., coincidental temporal association).

Due to the spontaneous and voluntary nature of VAERS reporting, information on trimester of pregnancy at vaccination was not always available, but in most (75%) reports where information was available, vaccination occurred during the first trimester. In 48 (25%) reports, Hepatitis B vaccine was administered simultaneously with other vaccines that are not recommended in pregnancy (e.g., Measles Mumps Rubella vaccine, Human Papillomavirus Quadrivalent Vaccine) [19], which suggests that when these women were vaccinated, pregnancy status was not ascertained and/or was not known (to the patient and the healthcare provider). Submission of VAERS report in such cases may have been motivated by concerns about the uncertainty of the potential effects of vaccination during pregnancy, rather than occurrence of an AE. Concomitant administration of multiple vaccines makes it difficult to draw conclusions about the relationship between AEs and specific vaccines. However, we did not find a concerning pattern of AEs in our sub-analysis where only a single antigen Hepatitis B vaccine was given.

The outcomes in infants whose mothers were vaccinated with Hepatitis B vaccine in pregnancy were diverse. We did not observe any cluster of specific infant AEs that would suggest a safety concern. The five reports of birth defects described various conditions involving four different organ systems.

Strengths of VAERS include its broad national scope and ability to rapidly detect rare AEs and safety signals [10]. However, as a spontaneous reporting system, it has important limitations, including reporting biases (over- or underreporting) and inconsistent quality and completeness of reports. Pregnant women who experience adverse outcomes in their fetuses or infants might be particularly susceptible to recall bias that influences decisions to report.

Events that occur close to the time of vaccination and medically serious events are more likely to be reported. In addition, VAERS does not collect data on the number of individuals vaccinated; therefore, it is not possible to calculate the incidence or prevalence of AEs. Due to these limitations, we generally cannot determine from VAERS data alone whether a vaccine caused an AE [10]. As it applies to pregnant women, the regulatory definition of a serious report is constrained by its singular focus on the vaccinated woman, not on the developing fetus or live born infant. For example, in our review, only one of 23 SAB reports were classified as serious because it involved hospitalization of the vaccinated patient (the pregnant woman). The remaining 22 were classified as non-serious because the report did not indicate that the vaccinated patient had been hospitalized.

Additional data on the safety of maternal Hepatitis B vaccination will be provided by an ongoing study of maternal and fetal adverse events after Hepatitis B vaccine in the VSD. Using data in VAERS, our safety review did not find any unusual or unexpected AE reporting patterns associated with Hepatitis B vaccination in pregnancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank CDC's Immunization Safety Office staff whose work allowed this activity to be conducted.

Funding/Support: The study was implemented by the Centers for Disease Control and Prevention (CDC) and Food and Drug Administration (FDA). The only funds used were from CDC and FDA budgets. This study had no external sponsors.

References

1. Recombivax HB® Hepatitis B vaccine (Recombinant) package insert, 1989 http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM110114.pdf
2. ENGERIX-B® [Hepatitis B Vaccine (Recombinant)] Package inserts, 1983 https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Engerix-B/pdf
3. Twinrix® [Hepatitis A &Hepatitis B (Recombinant) Vaccine] package insert, 2001 http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM110079.pdf
4. Comvax® [Haemophilus b Conjugate (Meningococcal protein conjugate) and Hepatitis B (recombinant) Vaccine] package insert, 1997 http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM109869.pdf
5. Pediarix® [Diphtheria and Tetanus Toxoid and Acellular Pertussis Adsorbed, Hepatitis B (Recombinant) and Inactivated Poliovirus Vaccine] package insert, 2002 http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM241874.pdf
6. Mast EE, Margolis HS, Fiore AE, Brink EW, Goldstein ST, Wang SA, Moyer LA, Bell BP, Alter MJ; Advisory Committee on Immunization Practices (ACIP). A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents. MMWR Recomm Rep. 2005 12 23;54(RR-16): 1–31.
7. Mast EE, Weinbaum CM, Fiore AE, Alter MJ, Bell BP, Finelli L, Rodewald LE, Douglas JM Jr, Janssen RS, Ward JW; Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC).. A comprehensive immunization strategy to eliminate transmission

of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. MMWR Recomm Rep. 2006 12 8;55(RR-16):1–33

8. Levy M, Koren G. Hepatitis B vaccine in pregnancy: maternal and fetal safety. Am J Perinatol. 1991 5;8(3):227–32. [PubMed: 1827584]
9. 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. 2014 6;210(6):561.e1–6 [PubMed: 24378675]
10. Shimabukuro TT, Nguyen M, Martin D, DeStefano F. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). Vaccine. 2015 8 26;33(36):4398–405. [PubMed: 26209838]
11. Medical Dictionary for Regulatory Activities. Available at: http://www.meddramsso.com/. Accessed April 28, 2011.
12. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals. http://www.ich.org/products/meddra.html.
13. Food and Drug Administration. 21 CFR Part 600.80. Postmarketing reporting of adverse experiences. Vol 62: Federal Register, 1997:52252–3.
14. Cunningham G, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ, Spong CY, eds. Williams obstetrics. New York (NY): McGraw-Hill Companies, Inc; 2010.
15. Black S, Eskola J, Siegrist CA, et al. Importance of background rates of disease in assessment of vaccine safety during mass immunization with pandemic H1N1 influenza vaccines. Lancet 2009;374:2115–22. [PubMed: 19880172]
16. Naleway AL, Kurosky S, Henninger ML, Gold R, Nordin JD, Kharbanda EO, Irving S, Craig Cheetham T, Nakasato C, Glanz JM, Hambidge SJ, Davis RL, Klein NP, McCarthy NL, Weintraub E. Vaccinations given during pregnancy, 2002–2009: a descriptive study.Am J Prev Med. 2014 2;46(2):150–7 [PubMed: 24439348]
17. Zheteyeva YA, Moro PL, Tepper NK, Rasmussen SA, Barash FE, Revzina NV, Kissin D, Lewis PW, Yue X, Haber P, Tokars JI, Vellozzi C, Broder KR. Adverse event reports after tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines in pregnant women. Am J Obstet Gynecol. 2012 7;207(1):59.e1–7 [PubMed: 22727350]
18. Moro P, Baumblatt J, Lewis P, Cragan J, Tepper N, Cano M. Surveillance of Adverse Events After Seasonal Influenza Vaccination in Pregnant Women and Their Infants in the Vaccine Adverse Event Reporting System, July 2010-May 2016. Drug Saf. 2017 2;40(2):145–152 [PubMed: 27988883]
19. CDC. Guiding principles for development of ACIP recommendations for vaccination during pregnancy and breastfeeding. MMWR Morb Mortal Wkly Rep. 2008;57(21):580. [PubMed: 18509303]

Table 1.

Characteristics of reports following hepatitis B vaccination during pregnancy in the Vaccine Adverse Event Reporting System (VAERS), United States, 1990 – 2016

Characteristic	
Total reports	192
Reports describing adverse events n (%)	110 (57.3)
Maternal age in years, median (range)[a]	24 (14 – 41)
Interval from vaccination to adverse event in days, median (range)[b]	3 (0 – 274)
Gestational age in weeks at time of vaccination, median (range)[c]	6 (1 – 39)
Serious adverse events, n (%)[d]	12 (6.3)
Type of reporter, N (%)[e]	
Manufacturer	83 (43.2)
Provider	43 (22.4)
Other	33 (17.2)
Patient/parent	14 (7.3)
Maternal age groups N (%)	
14 – 19 years	44 (22.9)
20 – 29 years	71 (36.9)
30 – 41 years	42 (21.9)
Vaccines administered, N(%)[f]	
Only Hepatitis B	99 (51.6)
Hepatitis B + Varicella	40 (20.8)
Hepatitis B + MMR	34 (17.7)
Hepatitis B + Hep A	21 (10.9)
Hepatitis B + HPV4	19 (9.9)
Trimester of pregnancy at time of vaccination (N=115)[g]**, N (%)**	
First (0 – 13 weeks)[h]	86 (74.7)
< 8 weeks gestation	53/65 (82%)
≥ 8 weeks gestation	12/65 (18%)
Second (14 – 27 weeks)	18 (15.7)
Third (28+ weeks)	11 (9.6)

[a] Maternal age unknown in 30 (15.6%) reports

[b] Interval unknown for 16 reports with adverse events

[c] Gestational age at time of vaccination is unknown for 99 reports

MMR: measles, mumps, rubella; hep A: hepatitis A

[d] A report is defined as serious when one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization, or permanent disability

[e] Type of reporter unknown in 19 (9.9%) reports

[f] Hepatitis B vaccines administered include: Engerix (93;46.7%), Recombivax (85;42.7%), no brand name (19;9.6%), Comvax (1;0.5%)

[g] Neither trimester nor gestational age was indicated in 77 reports

[h] Of 86 reports noting vaccination during the first trimester only 65 provided information on gestational age

Table 2.

Adverse events (AEs) following hepatitis B vaccination during pregnancy in the Vaccine Adverse Event Reporting System (VAERS), United States, 1990 – 2016 (N=110)

Adverse Events [≠]	N (%)
Pregnancy-specific AEs	**61 (55.4)**
Spontaneous abortion (<20 weeks gestation)	23 (20.9)
Preterm delivery (<37 weeks)	7 (6.4)
Elective termination	5 (4.5)
Vaginal bleeding	4 (3.6)
Failure to progress	4 (3.6)
Hypertension	3 (2.7)
Edema, swelling	3 (2.7)
Stillbirth (≥20 weeks gestation)	2 (1.8)
Chorioamnionitis	2 (1.8)
Premature labor	2 (1.8)
Pre-eclampsia	2 (1.8)
Other [a]	4 (3.6)
Non-pregnancy specific AEs [b]	**35 (31.8)**
General disorders and administration site conditions	20 (18.2)
Injection site reactions	7
Systemic reactions	12
Immune system disorders	7 (6.4)
Gastrointestinal disorders	2 (1.8)
Other [c]	6 (5.4)
Infant outcomes	**22 (20.0)**
Birth defects [††]	
Down's syndrome, cardiac abnormality	1
Encephalocoele and orbital roof defect	1
Tetralogy of Fallot	1
Undescended testicle	1
Absence of heart	1
Death from small bowel perforation and mild hyaline disease in preterm infant (27 weeks) [c]	1
Jaundice	3
Other [d]	13

Eighty-two reports with no adverse events after hepatitis B vaccination were submitted to VAERS but are not included above

[†]Adverse events are based on primary reported diagnoses identified during clinical review. One report may have more than one diagnosis if separate AEs are reported for the pregnant woman and her infant. Proportions calculated using only reports with adverse events (N=110)

[a]Other pregnancy specific adverse events include one report each of: Ectopic pregnancy, oligohydramnios, polyhydramnios

[b] Other non-pregnancy specific adverse events included one report each of urinary tract infection, injured arm, acute lymphocytic leukemia, pharyngitis, alopecia, atrial fibrillation

[c] Premature infant (27 weeks); presented small bowel with small perforations and mild hyaline disease and died at 54 days of age

[d] Other infant outcomes include one report each of chromosomal abnormalities, toxic neurologic effect of mercury poisoning in newborn, Apnea/brain hemorrhage, severe laryngomalacia in newborn/premature birth, intrauterine brain damage of foetus, cyanosis in infant, autism, deafness, hiccups/fussy/crying baby, meningitis in infant at 3 weeks, infant with broken clavicle, blisters in foot, large infant for vaginal delivery

[††] For birth defect reports vaccination took place during the first trimester (at 3–4 weeks gestation) for all reports except Down's syndrome for which the gestational age at the time of vaccination was not known.

[ǂ] The following AEs were reported following a sub-analysis of 72 pregnancy reports in which hepatitis B vaccine was administered without any concomitant vaccines:

1. Pregnancy outcomes: spontaneous abortion (15), vaginal bleeding (4), preterm delivery (2), elective termination (2), hypertension (2), stillbirth (2), premature labor (1), ectopic pregnancy (1), toxemia (1), fluid retention (1), polyhydramnios (1), edema (1), swelling (1)
2. Non-pregnancy outcomes: general disorders and administration site conditions (15), immune system disorders (4), gastrointestinal disorders (1), urinary tract infection, alopecia, atrial fibrillation; infant outcomes: jaundice (3), one report each of Tetralogy of Fallot, absence of heart, infant death, chromosomal abnormalities, toxic neurologic effect of mercury poisoning, intrauterine brain damage of fetus, cyanosis, autism, deafness, hiccups, broken clavicle