HHS Public Access

Author manuscript

Birth Defects Res. Author manuscript; available in PMC 2019 May 21.

Published in final edited form as:

Birth Defects Res. 2017 July 17; 109(13): 1057–1062. doi:10.1002/bdr2.23622.

Major birth defects after vaccination reported to the Vaccine Adverse Event Reporting System (VAERS), 1990 - 2014

Pedro L. Moro[1], **Janet Cragan**[2], **Paige Lewis**[1], and **Lakshmi Sukumaran**[1]

[1]Immunization Safety Office, Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention (CDC)

[2]Division of Congenital and Developmental Disorders, CDC

Abstract

Background: Major birth defects are important infant outcomes that have not been well studied in the post-marketing surveillance of vaccines given to pregnant women. We assessed the presence of major birth defects following vaccination in the Vaccine Adverse Event Reporting System, a national spontaneous reporting system used to monitor the safety of vaccines in the United States.

Methods: We searched the VAERS database for reports of major birth defects during 1/1/1990 through 12/31/2014. We excluded birth defects from vaccines that had been studied in pregnancy registries or other epidemiological studies.

Results: We identified 50 reports of major birth defects; in 28 reports, the vaccine was given during the first trimester. Birth defects accounted for 0.03% of all reports received by VAERS during the study period; reported defects affected predominately the musculoskeletal (N=10) or nervous (N=10) systems. No unusual clusters or specific birth defects were identified after any vaccine evaluated.

Conclusion: This review of the VAERS database found that major birth defects were infrequently reported, with no particular condition reported disproportionally.

Keywords

birth defects; epidemiology; surveillance; vaccine; vaccine safety

Introduction

Major birth defects constitute important infant outcomes that have been assessed in a few post-licensure safety studies for vaccines given during pregnancy, such as influenza and tetanus toxoid, reduced diphtheria toxoid and acellular pertussis, adsorbed (A) (Tdap) vaccines [1,2]. In addition, other vaccines that are not recommended or contraindicated in

Corresponding author: Pedro L. Moro, MD, MPH, Immunization Safety Office, Division Of Healthcare Quality Promotion, Centers for Disease Control and Prevention, 1600 Clifton Rd, MS D26, Atlanta, GA 30333, Phone: (404) 498-0663, fax: (404) 498-0666, pmoro@cdc.gov.

Conflict of interest: None of the authors have a conflict of interest.

Publisher's Disclaimer: 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.

pregnancy have also been studied in pregnancy registries (e.g., measles, mumps, rubella vaccine (MMR), human papillomavirus vaccine (quadrivalent) (4vHPV), anthrax) [3–7]. These safety studies have found no associations between the selected vaccines and major birth defects. However, for vaccines not studied in pregnancy registries there are limited data on birth defects. Studies on the safety of Tdap, hepatitis A, and meningococcal vaccines in pregnancy reports from VAERS did not identify a pattern of concern for birth defects following these vaccines [8–10]. However, specific birth defects can be rare events, making their pharmacovigilance monitoring difficult. Exploring a national spontaneous reporting database, such as VAERS, more specifically to identify birth defects after maternal vaccination has the potential to identify concerns or associations between birth defects and certain vaccines. In addition, studying vaccines that are not routinely recommended in pregnancy is important since in many cases, the woman is vaccinated before she realizes she is pregnant and most birth defects occur early in pregnancy. The objective of this study is to assess VAERS reports of major birth defects after selected maternal vaccines and to describe the characteristics of these reports.

Methods

Vaccine Adverse Event Reporting System (VAERS)

VAERS is a national spontaneous reporting system established in 1990 that is co-administered by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration [11]. It has been described in more detail elsewhere. Briefly, VAERS data are monitored to detect new, unexpected, or rare vaccine adverse events (AEs), monitor increases in known AEs, or detect possible safety signals which may be further investigated in defined populations in other studies [11]. VAERS is not designed to assess causal associations between vaccines and AEs. While the VAERS report form collects demographic and health information, including information about the vaccination and AE experience [11], it does not specifically collect information on pregnancy status. However, this information may be included in free text fields. AE signs and symptoms recorded in each VAERS report are coded by trained staff using an internationally standardized terminology from the Medical Dictionary for Regulatory Activities (MedDRA) [12]. A symptom, sign or non-medical condition (e.g., social unrest) may be coded with a MedDRA code, also referred to as a ‘preferred term’. Reports may be coded as serious if the AE resulted in any of the following: death, hospitalization, prolonged hospitalization, life threatening illness, or permanent disability [13]. Medical records for serious reports in VAERS are routinely requested by a contractor and reviewed by physicians.

We searched the VAERS database for reports of birth defects in pregnant women who received a vaccine during pregnancy from January 1, 1990 through December 31, 2014. We conducted an automated search using methods previously published [8–10]. Briefly, we searched for MedDRA terms—“Drug Exposure During Pregnancy,” “Maternal Exposure During Pregnancy,” and “Exposure During Pregnancy”—in two System Organ Classes: “Pregnancy, Puerperium, and Perinatal Conditions” and “Congenital, Familial and Genetic Disorders.” Reports that had at least one of these criteria were included in the dataset for further evaluation. Non-US and duplicate reports were excluded.

Clinical Reviews

All US reports identified in the VAERS database using the search criteria above during the study period were reviewed by CDC medical officers to assess if they were indeed birth defects. Birth defects after (human papilloma virus) HPV, varicella, MMR, and anthrax were excluded from further analysis for two reasons: i) the safety of these vaccines has been studied and described in their respective pregnancy registries or through epidemiological studies; and ii) a substantial number of reports studied in pregnancy registries have also been submitted to VAERS; therefore, including these vaccines would duplicate the previous analyses and potentially lead to a distorted picture of the safety profile of these vaccines. For example, for 4vHPV, as many as 72% of pregnancy reports received by VAERS were from the manufacturer pregnancy registry [14]. A medical officer with expertise in birth defects was consulted to assist in the assessment of those reports where it was not clear if a birth defect was present and to classify them as major or minor defects. We identified the birth defect based on the description provided in the VAERS form and/or in the medical record, if it was available. We categorized each birth defect into a classification based on the organs and/or systems affected. If several birth defects affecting different systems were described, we classified those as multiple body systems.

Gestational ages at the time of vaccination and at the time of the AE were calculated based on the information provided in the VAERS form or medical record. We used the following definition for trimesters: first (0–13 weeks), second (14–27 weeks), and third (28+ weeks) [15].

Data mining

We used empirical Bayesian (EB) data mining [16] to identify birth defects reported more frequently than expected following any vaccine in the VAERS database. We used published criteria [17,18] to identify, with a high degree of confidence, vaccine-event pairs reported at least twice as frequently as would be expected (i.e., lower bound of the 90% confidence interval surrounding the EB geometric mean [EB05] >2). We clinically reviewed those reports containing preferred terms for birth defects that exceeded the data mining threshold noted above.

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

Results

During the period January 1, 1990 through December 31, 2014, VAERS received 440,529 reports, 158 (0.03%) of which were reports of major birth defects. Major vaccine types included: HPV (67), varicella vaccine (VAR) (25), MMR (12), anthrax (4), trivalent inactivated influenza vaccine (IIV3) (19), (Tdap) (7), tetanus and diphtheria toxoids adsorbed (A) (Td) (1), diphtheria and tetanus toxoids adsorbed (P) (DT) (2), diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (P) (DTaP) (1), hepatitis A (Hep A) or B (Hep B) (7), influenza H1N1 inactivated (5), quadrivalent meningococcal conjugate

vaccine (MenACWY) (3), quadrivalent inactivated influenza vaccine (IIV4) (1), typhoid (1), rubella (1), mumps (1), measles (1). One hundred eight reports of birth defects after HPV4, varicella, MMR, and anthrax vaccines were excluded from further analysis. Table 2 shows the body systems and specific conditions for the 50 remaining reports of major birth defects. Data mining analysis did not reveal disproportionate reporting for any birth defect in the VAERS database

Discussion

We found that over a 25-year reporting period, major birth defects were infrequently reported to VAERS, comprising 0.03% of all reports. We excluded from further analysis reports after HPV, varicella, MMR and anthrax vaccines since pregnancy registries or epidemiological studies have been implemented and conducted to assess the risk of birth defects following administration of these vaccines. For the other vaccines that we evaluated, we did not find increased or disproportionate reporting for any specific major birth defect during the study period. A limited number of studies have assessed the risk of birth defects after vaccination and have had reassuring findings. Most studies evaluated birth defects after influenza vaccines and have found no safety concerns [19–22]. A smaller number of studies have assessed Tdap vaccines given to pregnant women and no associations with birth defects have been noted [23–25]. A recent study in the Vaccine Safety Datalink found no increased risk of any birth defect among pregnant women vaccinated with Tdap [26]. A limitation of many of these studies is the heterogeneity in the definitions used for birth defects across studies, and the limited number of studies where the vaccine was given during the first trimester. For many studies, the relatively small sample size of pregnant women makes it difficult to assess for specific birth defects, which tend to be rare [21–22].

In this study we used a different approach by looking at VAERS, a spontaneous reporting system, to assess for possible increased occurrence of birth defects. An advantage of VAERS is that it is a national system, useful for studying rare adverse events following vaccination. The limitations of this system have been amply discussed elsewhere [11]. However, the spontaneous nature of VAERS, whereby conditions are reported after they occur and are recognized as possibly related to the vaccine, leads to underreporting of adverse events. For birth defects, there may be significant underreporting not only because of the spontaneous nature of VAERS, but also due to the period of time between vaccination and delivery, and the fact that many defects are not necessarily obvious or symptomatic immediately after birth. VAERS does not collect data on the number of vaccinees; therefore it is not possible to calculate the incidence or prevalence of adverse events. An approach to circumvent this problem is to assess for disproportionate reporting of an adverse event using data mining analysis. In this study we used empirical Bayesian data mining, which did not detect disproportionate reporting of a preferred term denoting a birth defect following any vaccination.

In conclusion, this review of the VAERS database for selected vaccines administered during pregnancy found no increased reporting for any birth defect. Further studies evaluating rates of birth defects following Tdap and influenza vaccinations will provide more specific

information on the occurrence of these events after recommended vaccines during pregnancy.

Acknowledgements

We thank CDC's Immunization Safety Office staff whose work allowed this activity to be conducted. We also thank staff from CSRA, Inc. for their work on this project.

References

1. Polyzos KA, Konstantelias AA, Pitsa CE, Falagas ME. Maternal Influenza Vaccination and Risk for Congenital Malformations: A Systematic Review and Meta-analysis. Obstet Gynecol. 2015 11;126(5):1075–84. [PubMed: 26444106]
2. McMillan M, Porritt K, Kralik D, Costi L, Marshall H. Influenza vaccination during pregnancy: a systematic review of fetal death, spontaneous abortion, and congenital malformation safety outcomes. Vaccine. 2015 4 27;33(18):2108–17. [PubMed: 25758932]
3. Goss MA, Lievano F, Buchanan KM, Seminack MM, Cunningham ML, Dana A. Final report on exposure during pregnancy from a pregnancy registry for quadrivalent human papillomavirus vaccine. Vaccine. 2015 6 26;33(29):3422–8. [PubMed: 25869893]
4. Current Trends Rubella Vaccination during Pregnancy -- United States, 1971–1988. MMWR. 1989 5 5;38(17):289–93. [PubMed: 2496289]
5. CDC. Measles, mumps, and rubella---vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 1998;47(no. RR-8).
6. Ryan MA, Smith TC, Sevick CJ, Honner WK, Loach RA, Moore CA, Erickson JD. Birth defects among infants born to women who received anthrax vaccine in pregnancy. Am J Epidemiol. 2008 8 15;168(4):434–42 [PubMed: 18599489]
7. Wiesen AR, Littell CT. Relationship between prepregnancy anthrax vaccination and pregnancy and birth outcomes among US Army women. JAMA. 2002 3 27;287(12):1556–60. [PubMed: 11911758]
8. Moro PL, Cragan J, Tepper N, Zheteyeva Y, Museru O, Lewis P, Broder K. Enhanced surveillance of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccines in pregnancy in the Vaccine Adverse Event Reporting System (VAERS), 2011–2015. Vaccine. 2016 4 29;34(20): 2349–53. [PubMed: 27013434]
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. Zheteyeva Y, Moro PL, Yue X, Broder K. Safety of meningococcal polysaccharide-protein conjugate vaccine in pregnancy: a review of the Vaccine Adverse Event Reporting System. Am J Obstet Gynecol. 2013 6;208(6):478.e1–6. [PubMed: 23453881]
11. 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]
12. Medical Dictionary for Regulatory Activities. Available at: http://www.meddra.org/
13. Food and Drug Administration. 21 CFR Part 600.80. Postmarketing reporting of adverse experiences. Federal Register. 1997;62:52252–3.
14. Moro PL. Safety of Human Papillomavirus Vaccines (Gardasil®) in Pregnancy in the Vaccine Adverse Event Reporting System. 17th Annual Vaccine Research Conference, April 28–30, 2014, Bethesda, Maryland.
15. Prenatal care In: Cunningham G, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ, Spong CY, eds. Williams' Obstetrics, 23rd ed New York: McGraw-Hill; 2010:189–214.
16. DuMouchel W Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system. Am Stat. 1999;53:177–90.

17. Szarfman A, Machado SG, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. Drug Saf. 2002;25:381–92. [PubMed: 12071774]

18. Martin D, Menschik D, Bryant-Genevier M, Ball R. Data mining for prospective early detection of safety signals in the Vaccine Adverse Event Reporting System (VAERS): A case study of febrile seizures after a 2010–2011 seasonal influenza virus vaccine. Drug Saf. 2013 7;36(7):547–56. [PubMed: 23657824]

19. Pasternak B, Svanström H, Mølgaard-Nielsen D, Krause TG, Emborg HD, Melbye M, Hviid A. Risk of adverse fetal outcomes following administration of a pandemic influenza A(H1N1) vaccine during pregnancy. JAMA. 2012 7 11;308(2):165–74. [PubMed: 22782418]

20. Chambers CD, Johnson D, Xu R, Luo Y, Louik C, Mitchell AA, Schatz M, Jones KL; OTIS Collaborative Research Group. Risks and safety of pandemic H1N1 influenza vaccine in pregnancy: birth defects, spontaneous abortion, preterm delivery, and small for gestational age infants. Vaccine. 2013 10 17;31(44):5026–32. [PubMed: 24016809]

21. Polyzos KA, Konstantelias AA, Pitsa CE, Falagas ME. Maternal influenza vaccination and risk for congenital malformations: A systematic review and meta-analysis. Obstet Gynecol. 2015 Nov; 126(5):1075–84.

22. McMillan M, Porritt K, Kralik D, Costi L, Marshall H. Influenza vaccination during pregnancy: a systematic review of fetal death, spontaneous abortion, and congenital malformation safety outcomes. Vaccine. 2015 4 27;33(18):2108–17. [PubMed: 25758932]

23. Shakib JH, Korgenski K, Sheng X, Varner MW, Pavia AT, Byington CL. Tetanus, diphtheria, acellular pertussis vaccine during pregnancy: pregnancy and infant health outcomes. J Pediatr. 2013 11;163(5):1422–6.e1–4. [PubMed: 23896191]

24. Berenson AB, Hirth JM, Rahman M, Laz TH, Rupp RE, Sarpong KO. Maternal and infant outcomes among women vaccinated against pertussis during pregnancy. Hum Vaccin Immunother. 2016 3 22:1–7.

25. Regan AK, Tracey LE, Blyth CC, Richmond PC, Effler PV. A prospective cohort study assessing the reactogenicity of pertussis and influenza vaccines administered during pregnancy. Vaccine. 2016 4 29;34(20):2299–304. [PubMed: 27038132]

26. DeSilva M, Vasquez-Benitez G, Nordin J, Kharbanda E. Presented by Sukumaran L. Maternal Tdap vaccination and structural birth defects in offspring. In: Meeting of the Advisory Committee on Immunization Practices (ACIP) 2016Available at: http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2016-06/tdap-02-sukumaran.pdf

Table 1.

Characteristics of reports of major birth defects (N=50)[†] reported to VAERS, 1990 – 2014

Maternal age in years, median (range)	28 (17–37)
Trimester of pregnancy at time of vaccination (N=45)	
First trimester (0–13 weeks), n (%)	28 (62.2)
Second trimester (14–27 weeks), n (%)	14 (31.1)
Third trimester (28+ weeks), n (%)	3 (6.7)
Type of vaccine given	
Trivalent inactivated influenza vaccine (IIV3)	14
Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed(Tdap)	6
Hepatitis B	5
2009 monovalent H1N1 inactivated influenza vaccine	4
Quadrivalent meningococcal conjugate vaccine (MCV4)	2
Quadrivalent inactivated influenza vaccine (IIV4)	1
Measles	1
Measles, rubella	1
Mumps	1
Rubella	1
Oral typhoid	1
Vaccines given in combination with others[*]	13

[†] Birth defects of vaccines already adequately studied in pregnancy registries or special studies were excluded (i.e., HPV4, varicella, MMR, anthrax)

[*] Included: two IIV3, Tdap and one each of IIV3, PPV; IIV3, HPV4; IIV3, H1N1 inactivated; IIV3, DTaP; DT, MMR; DT, IPV, MMR; MMR, Td; HPV4, Tdap; MNQ, Tdap; Hib-HepB, Varicella; HPV4, HepA

Table 2.

Number of infants with specific major birth defects and the body systems affected in reports submitted to VAERS, 1990–2014

Body system	N. vaccinated first trimester	N
Musculoskeletal system	**6**	**10**
• Polydactyly	**2**	3
• Clubbed feet	**1**	2
• Amelia (born without legs)	**1**	1
• One hand missing	**1**	1
• Congenital trigger finger	**0**	1
• Plagiocephaly	**0**	1
• Absent right radius	**1**	1
Nervous system	**7**	**10**
• Hydrocephalus	**3**	3
• Anencephaly	**1**	2
• Agenesis of corpus callosum	**1**	1
• Spina bifida	**0**	1
• Encephalocele Microcephaly	**2**	2
	0	1
Circulatory system	**4**	**6**
• Ventricular septal defect	**0**	1
• Tetralogy of Fallot	**1**	1
• Pulmonary hypertension, arteriovenous malformation	**1**	1
• Hypoplastic left ventricle	**1**	1
• Congenital heart disease	**0**	1
• Pulmonary atresia	**1**	1
Multiple body systems	**2**	**6**
• Pilonidal sinus; mildly deformed left ear lobe; left index finger with only half nail bed; mild micrognathia & nevus flammeus	**0**	1
	1	1
• Hypospadias; undescended testicle; skeletal abnormalities	**0**	1
• Ventricular and atrial septal defects; renal cyst	**1**	1
• Myotonic dystrophy/arthrogryposis; dilated bowel, possible bowel obstruction; cystic hygroma	**0**	1
• Congenital brain anomaly (not specified); claw hand	**0**	1
• Cleft lip and palate; echogenic focus in left cardiac ventricle		1
Chromosomal abnormalities, not elsewhere classified	**2**	**4**
• Down syndrome	**1**	1
• Possible Down syndrome	**0**	1
• Trisomy 12	**0**	1
• Trisomy 18	**1**	1
Eye, ear, face and neck	**2**	**4**
• Congenital deafness	**1**	3
• Right eye congenital glaucoma and cataract	**1**	1
Urinary system	**1**	**3**
• Hydronephrosis	**1**	2
• vEctopic kidney	**0**	1
Digestive system	**3**	**4**
• Pyloric stenosis	**2**	3
• Pyloric stenosis/imperforate anus	**1**	1
Respiratory system	**0**	**1**
• Congenital cystic adenomatoid malformation of the lung	**0**	1
Cleft lip and palate	**1**	**2**
• Cleft lip	**1**	1
• Pierre Robin sequence	**0**	1
Total	**28**	**50**