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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

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Abstract

Background: In October 2011, the Advisory Committee on Immunization Practices (ACIP) issued updated recommendations that all pregnant women routinely receive a dose of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine. **Objectives:** We characterized reports to the Vaccine Adverse Event Reporting System (VAERS) in pregnant women who received Tdap after this updated recommendation (2011-2015) and compared the pattern of adverse events (AEs) with the period before the updated recommendation (2005-2010).

Methods: We searched the VAERS database for reports of AEs in pregnant women who received Tdap vaccine after the routine recommendation (11/0½011-6/30/2015) and compared it to published data before the routine Tdap recommendation (01/0½005-06/30/2010). We conducted clinical review of reports and available medical records. The clinical pattern of reports in the post-recommendation period was compared with the pattern before the routine Tdap recommendation.

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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

Results: We found 392 reports of Tdap vaccination after the routine recommendation. One neonatal death but no maternal deaths were reported. No maternal or neonatal deaths were reported before the recommendation. We observed an increase in proportion of reports for stillbirths (1.5% to 2.8%), and injection site reactions/arm pain (4.5% to 11.9%) after the recommendation compared to the period before the routine recommendation for Tdap during pregnancy. We noted a decrease in reports of spontaneous abortion (16.7% to 1%). After the 2011 Tdap recommendation, in most reports vaccination (79%) occurred during the third trimester compared to 4% before the 2011 Tdap recommendation. Twenty-six reports of repeat Tdap were received in VAERS; 13 did not report an AE. One medical facility accounted for 27% of all submitted reports.

Conclusions: No new or unexpected vaccine AEs were noted among pregnant women who received Tdap after routine recommendations for maternal Tdap vaccination. Changes in reporting patterns would be expected, given the broader use of Tdap in pregnant women in the third trimester.

Keywords

adverse events; epidemiology; Tdap; pregnancy; surveillance; vaccine safety

Introduction

Tetanus, diphtheria, and acellular pertussis vaccine (Tdap) was licensed by the Food and Drug Administration (FDA) in 2005 for booster immunization against tetanus, diphtheria, and pertussis for adolescents and adults and is available in the United States from two manufacturers: Adacel (Sanofi Pasteur, Swiftwater, PA) [1] and Boostrix (GlaxoSmithKline Biologicals, Rixensart, Belgium) [2]. Pertussis incidence is highest among infants less than 6 months, in whom it may cause serious and life-threatening complications. Prior to 2011, ACIP had recommended using Tdap in the immediate postpartum period in women who did not previously receive Tdap to protect both mothers and infants from pertussis [3]. At the time, ACIP did not routinely recommend use of Tdap in pregnant women, but recommended that providers consider use in certain situations that included instances when a pregnant woman has insufficient tetanus or diphtheria protection until delivery, or is at increased risk for pertussis [3]. In June 2011, the Advisory Committee on Immunization Practices (ACIP) recommended using a single dose of Tdap for pregnant women who previously had not received Tdap in order to provide the young infant with maternal transplacental passive antibody protection against pertussis during the early postnatal months [4]. In October 2012, ACIP further recommended administration of one dose of Tdap during each pregnancy, irrespective of the woman's prior history of receiving Tdap [5]. To maximize maternal antibody response and passive antibody transfer to the infant, ACIP recommended that the optimal timing of Tdap vaccination was between 27 to 36 weeks of gestation, although it could occur at any time during pregnancy. The Centers for Disease Control and Prevention (CDC) implemented enhanced safety monitoring of Tdap given during pregnancy. A previous study in the Vaccine Adverse Event Report System (VAERS) [6] before the 2011 and 2012 Tdap recommendations, found no unusual or unexpected pattern of maternal, fetal, or infant outcomes in reports of pregnant women who received Tdap vaccine during

pregnancy. In 2010 before Tdap was recommended for pregnant women, approximately 12.7% of pregnant women in managed care patient populations were vaccinated [7]. By 2013, 2 years after this recommendation was made, this increased to 41.7% [7].In the current study, we assessed adverse event reports after Tdap vaccination reported to VAERS in pregnant women or their infants following the 2011 and 2012 ACIP recommendations and compared these reporting patterns with those before the Tdap recommendations in pregnancy.

Materials and Methods

Vaccine Adverse Event Reporting System (VAERS)

VAERS is a national spontaneous reporting system co-administered by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) since its establishment in 1990 [8]. VAERS accepts reports from healthcare providers, vaccine manufacturers, and the general public, on adverse events (AEs) associated with vaccines licensed in the United States. Vaccination errors with no AE may also be reported (e.g., inappropriate dose administered). VAERS is not designed to assess causal associations between vaccines and AEs. VAERS data are monitored to detect new, unexpected, or rare vaccine AEs, monitor increases in known AEs, or detect possible safety signals which may be investigated in defined populations in other studies [9]. The VAERS report form collects demographic and health information, including information about the vaccination and AE experience [10]. It does not specifically collect information on pregnancy status, but 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) [11]. VAERS reports may also be coded as serious using the definition of the Code of Federal Regulations [12], if any of the following conditions occur: death, hospitalization, prolongation of hospitalization, life-threatening illness, persistent or significant disability. For the current study, we did not consider serious those reports where the pregnant woman was hospitalized for a normal delivery. Medical and immunization records were requested for all reports, irrespective of seriousness criteria.

We searched the VAERS database for reports of pregnant women who received Tdap in the United States, with or without other vaccines, between October 11, 2011 and June 30, 2015. We conducted an automated search using methods previously published [13,14]. Briefly, we searched for MedDRA terms in two System Organ Classes (SOC) “Pregnancy, Puerperium, and Perinatal Conditions” and “Congenital, Familial and Genetic Disorders”, the MedDRA terms “Drug Exposure during Pregnancy”, “Maternal Exposure during Pregnancy”, and “Exposure during Pregnancy”, and a text string search for the term “preg” in the report. Reports that had at least one of these criteria were included in the dataset for further evaluation. Foreign and duplicate reports were excluded. We compared these findings with published safety data of Tdap vaccine in pregnant women during 2005-2010 before the current recommendation [6].

Clinical Reviews

All US reports identified in the VAERS database during the study period were reviewed by CDC medical officers to confirm pregnancy status at time of vaccination, estimate gestational age and characterize AEs. We included reports on infants born to women who received Tdap vaccine during pregnancy. For each report we assigned a primary diagnosis. If more than one AE was reported for the same individual, we assigned the diagnosis based on what we believed was the primary clinical event of concern and assumed the primary event was the pregnancy-specific event unless information suggested otherwise. Complex reports were reviewed by physicians on the study team with expertise in obstetrics and neonatology. If a VAERS report described AEs in more than one person, we noted the different AEs but did not treat the reports separately. Reports that indicated the reported subject was not pregnant or that Tdap vaccine was administered prior to the last menstrual period were excluded.

Gestational age at the time of vaccination and at the time of the AE was calculated based on 1) clinical determination of healthcare provider, 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 2 options were not available) found in 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) [15]. Spontaneous abortion (SAB) was defined as a fetal demise prior to 20 weeks gestation; stillbirth was defined as fetal demise at or after 20 weeks gestation and preterm birth was defined as a live birth before 37 weeks gestation.

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 and informed consent requirements.

Results

During October 11, 2011 through June 30, 2015, VAERS received a total of 8,795 US reports after Tdap vaccination; 418 reports met the criteria of pregnancy reports using the automated search. Seventy-six of these reports were excluded after further review because they did not receive Tdap during pregnancy. After the clinical review, 392 reports were identified as true pregnancy reports and were used for further analysis. Medical and vaccination records were obtained for 304 (77.6%) and 309 (78.8%) reports, respectively. Twenty-seven (6.9%) reports were classified as serious. Eleven reports described maternal and infant/fetal outcomes. One neonatal death immediately after birth was reported; the cause of death described in the medical records was umbilical cord occlusion with fetal vascular thrombus formation. No maternal deaths were reported.

Characteristics of VAERS reports are presented in Table 1. A majority of the reports (239, 60.9%) were received from manufacturers. In 329 (83.9%) reports Tdap was the only vaccine received. The median maternal age was 29 years. Information to determine the trimester of Tdap exposure was available for 333 (84.9%) reports. Among reports where trimester at time of vaccination was known, 264 (79.2%), indicated that Tdap vaccines were administered during the third trimester of pregnancy. Two hundred-thirty four (59.7%)

reports indicated administration of Adacel. One hundred eighty-two (46.4%) reports did not describe an AE.

Two hundred ten (53.6%) reports described at least one AE. The most frequent pregnancy-specific outcome was oligohydramnios in 12 (3.1%) followed by stillbirth and preterm delivery with 11 (2.8%) reports each. The most frequent non-pregnancy specific outcomes were injection site reactions, in 47 (11.9%) reports and systemic reactions (e.g., fever, chills) in 17 (4.3%) reports. There were 14 (3.6%) reports each of musculoskeletal and connective tissue disorders and immune system disorders (e.g., allergic reactions). Among immune system disorders, four were anaphylaxis reports, three of which were physician verified.

Sixteen reports (5.0 %) indicated adverse infant or fetal outcomes, which include the infant death mentioned above as well as four reports of birth defects: i) ectopic kidney in a newborn whose mother received Tdap at 17 weeks gestation; ii) hypoplastic left heart syndrome in an infant whose mother received Tdap early during the first trimester; iii) trisomy 12 identified through chromosomal analysis of the fetal tissue from one stillbirth; and iv) club foot in infant whose time of exposure to Tdap was unknown.

One hundred seven (27.3%) reports were submitted from a single facility. Reporters from this facility assumed that all reports of pregnant women, including those without an AE, had to be reported to VAERS. Pregnancy-specific outcomes from this facility (n=38) included: 11 reports of oligohydramnios, six reports each of preterm delivery and gestational diabetes, three reports each of pregnancy induced hypertension, failure to progress, and chorioamnionitis, two reports of preeclampsia and one report each of polyhydramnios, arrest of descent, breech presentation and premature rupture of membranes. Non-pregnancy specific outcomes (n=10) included four reports of thrombocytopenia, two reports of chronic hypertension, and one report each of Bell's palsy, gastroenteritis, depression, and hypothyroidism. Infant outcomes (n=14) included: four reports of macrosomia, three of intrauterine growth restriction, and one report each of clubbed foot, neonatal demise (described above), polydactyly, neonatal respiratory disorder, pneumonia in infant, large for gestational age, and decreased fetal movement. Fifty-one reports did not describe an AE.

Reporting patterns before (2005-2010) and after (2011-2015) the routine recommendation for Tdap during pregnancy

Table 2 shows characteristics of reports before (2005-2010) [6] and after (2011-2015) the routine recommendation for Tdap during pregnancy. Between 2005-2010 and 2011-2015, there was an increase in the proportion of stillbirth reports (from 1.5% to 2.8%) and injection site reactions (from 4.5% to 11.9%), and a decrease in the number of reports describing spontaneous abortions (from 16.7% to 1.0%). A much larger proportion of vaccinations (79.2%) in the reports after the routine Tdap recommendation occurred during the third trimester compared to the period before (4%) the routine Tdap recommendation.

Prior receipt of Tdap among pregnant women

Twenty-six reports (6.6%) described pregnant women who had also received at least one dose of Tdap vaccine before the current pregnancy. The interval between the current and previous Tdap vaccination varied from 7 days to 9.4 years (median 1.8 years). Eight reports

with an interval of Tdap doses of 6 months or less comprised vaccination errors, six of which described the erroneous administration of two doses of Tdap during the same pregnancy. Among the 26 reports, 13 did not describe an AE and the AEs in the other 13 reports included: four reports of injection site pain or arm pain; two reports each of oligohydramnios, intrauterine growth restriction/poor fetal growth, and elevated blood pressure/abdominal pain; and one report each of stillbirth with trisomy 12, maternal urinary tract infection, and maternal systemic reactions (e.g., fever, chills).

Discussion

During 2011 through 2015, following the routine recommendation for Tdap vaccination during pregnancy, we identified 392 reports of pregnant women or their infants that were submitted to VAERS after Tdap administration (109 reports per year), accounting for approximately 3.6% of all US reports after Tdap during this period. We did not find any unusual or unexpected increase in the number of reports or in the pattern of maternal, fetal or infant AEs when we compared the pattern of events to the period 2005-2010 (22 reports per year), when Tdap was not routinely recommended for use in pregnant women. In addition, we did note that almost a third of reports were submitted from one medical center which also accounted for half of pregnancy-specific AEs.

The changes noted in the safety profile of Tdap in pregnant women after the routine recommendation compared to the period before the routine recommendation are likely due to broader use of Tdap during the third trimester of pregnancy, in line with the routine recommendation [6]. The small increase in the proportion of stillbirths and decrease in the proportion of SAB are expected findings given the predominance of third trimester reports. The proportion of major birth defects reported after the routine recommendation remained similar to the previous period before the recommendation. However, this kind of AE may be under-reported in a passive surveillance system such as VAERS given the relatively long interval between vaccination and recognition of a birth defect. Among non-pregnancy specific AEs, the most commonly reported conditions were injection site reactions in 11.9% of reports, which is consistent with the period before the routine recommendation when these reactions were also the most common non-pregnancy specific AEs reported; these findings are also consistent with pre-licensure Tdap studies that found that injection site reactions were the most common reactions among non-pregnant Tdap recipients [1,2]. In our review we identified a limited number of reports of repeat Tdap doses following the routine recommendation from October 2012 of one dose of Tdap in each pregnancy. Most of the repeat dose Tdap reports we identified comprised vaccination errors with no AE reported. We are unable to make any assessment of the safety of repeat Tdap doses in pregnant women based on the small number of reports.

The Vaccine Safety Datalink (VSD), a collaborative project between CDC and nine integrated health care systems, also monitored the safety of Tdap vaccine in pregnant women following the routine recommendation. A study in two VSD sites did not find an increased risk of hypertensive disorders of pregnancy, preterm birth or small for gestational age [16]. However, a small but statistically significant increased risk of chorioamnionitis among pregnant women who received Tdap was noted. In our current review of VAERS

reports, we only found two reports of chorioamnionitis which is a similar finding to the period before the routine Tdap recommendation when a very small number of chorioamnionitis AEs were reported [6]. It is also consistent with a study of the entire VAERS database covering a period of 24 years which found that chorioamnionitis AEs was infrequently reported for any vaccine [17].

As a national surveillance system, VAERS may be used to detect signals of potential vaccine safety concerns, which can be further explored in carefully designed epidemiological studies. VAERS has inherent limitations of all passive surveillance systems including underreporting, reporting biases, and inconsistency in quality of reports [9]. Some of these limitations were noted in our review as we observed that almost a third of reports originated from one facility which accounted for half of all pregnancy-specific conditions. Events occurring temporally closer to the time of vaccination are more likely to be reported to VAERS [9]. Therefore, VAERS data must be interpreted with caution and cannot generally be used to assess causality [9]. The regulatory definition of a serious report in VAERS can have limitations as it may not reflect the true severity of an outcome. For example, in our review, six stillbirth reports were coded as serious because the mothers were hospitalized, whereas three were coded as non-serious because the report did not indicate the mother had been hospitalized. An important limitation of VAERS is its inability to calculate the incidence or prevalence of AEs because data on the number of pregnant women vaccinated is not collected. A proxy for incidence or prevalence are crude reporting rates which may be calculated if data on the number of Tdap doses administered or distributed for use among pregnant women is known. Data on Tdap vaccination coverage during pregnancy, however, are limited [20,21], which makes it difficult to estimate reporting rates for pregnancy conditions using VAERS.

Following the new Tdap recommendation in pregnancy, additional data from post-marketing surveillance studies have become available and have provided reassuring evidence on the safety of Tdap vaccine during pregnancy. In addition to the VSD study mentioned above [16], two retrospective cohort studies of pregnant women in Utah and Texas assessed pregnancy and infant outcomes following receipt of Tdap vaccine [22,23]. One study identified 138 women among 162,448 pregnancies, and these were compared to an unvaccinated control group of 552 pregnant women [22]. There were no significant differences in rates of spontaneous abortion or elective abortion, preterm birth, gestational age at birth, or birth weight between the groups; there was no increase in adverse outcomes identified in infants born to women receiving Tdap vaccine compared with infants of unexposed mothers [22]. A second study compared pregnancy outcomes among 7,152 women who received Tdap at 32 weeks gestation or later and 226 who declined to receive Tdap [23]. There was no difference in stillbirths, major birth defects, chorioamnionitis, 5-minute Apgar score, cord blood pH, or rates of neonatal complications noted. An observational cohort study in the UK Clinical Practice Research Datalink [24] examined the safety of pertussis vaccination (DTaP-IPV;REPEVAX®) in 20,074 pregnant women compared to a matched historical unvaccinated control group. No increased risk of stillbirth and predefined AEs (maternal and neonatal death, pre-eclampsia and eclampsia, antepartum and postpartum hemorrhage, fetal distress, uterine rupture, placenta previa, vasa previa, caesarean delivery, low birth weight, and neonatal renal failure) were observed.

A recent retrospective cohort study at seven VSD sites of 29,155 pregnant women who received Tdap found that among women who received Tdap vaccination during pregnancy, there was no increased risk of acute adverse events or adverse birth outcomes for those who had been previously vaccinated less than 2 years before or 2 to 5 years before compared with those who had been vaccinated more than 5 years before [25]. Another retrospective study also in the same seven VSD sites and during the same period of time assessed the safety of Tdap and influenza vaccines given concomitantly and sequentially [26] to pregnant women. Among 36,844 pregnancies in which Tdap and influenza vaccines were given, in 8,464 (23%) pregnancies both vaccines were given concomitantly and in 28,380 (77%) sequentially. There were no differences in preterm delivery, low birth weight, or small for gestational age neonates between women vaccinated concomitantly compared with sequentially in pregnancy.

Additional studies to assess the safety of repeat Tdap doses in pregnancy are currently being conducted at CDC and will provide important safety information for use of this vaccine in pregnancy. This review of the VAERS database during the period after the routine Tdap recommendation in pregnancy (2011-2015) did not find any unexpected increase in the number or pattern of AEs among pregnant women or their infants vaccinated with Tdap. Data from various surveillance systems and epidemiological studies support the safety of Tdap vaccination during pregnancy.

Conclusion

We identified no safety concerns in this comprehensive review of VAERS reports after routine Tdap vaccination was recommended in pregnant women. Findings from our review are consistent with data from other monitoring systems and epidemiological studies which have found a favorable safety profile for Tdap vaccine use during pregnancy.

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Condensation of the paper: Review of adverse events reported to the Vaccine Adverse Event Reporting System in women who received tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccines during pregnancy during 2011-2015 after the routine Tdap recommendation did not find any concerning safety patterns

Table 1.

Characteristics of VAERS reports received following Tetanus toxoid, reduced diphtheria-toxoid, and acellular pertussis (Tdap) vaccine in pregnant women, United States, after Tdap vaccine was routinely recommended during pregnancy (October 2011- June 2015) (N=392)[†]

Characteristic	
Tdap administered alone[a], n (%)	329 (83.9)
Maternal age in years, median (range)[b]	29 (13-42)
Interval from vaccination to adverse event in days, median (range)[c]	1 (0-255)
Gestational age in weeks at time of vaccination, median (range)[d]	31.0 (1-41)
Reports of serious adverse events, n (%)[e]	27 (6.9)
Trimester of pregnancy at time of vaccination (N=333)[f], N (%)	
First (0 – 13 weeks)	29 (8.7)
Second (14 – 27 weeks)	40 (12.0)
Third (28 + weeks)	264 (79.2)
Brand name of Tdap vaccine, N (%)	
Adacel	234 (59.7)
Boostrix	130 (33.2)
Unknown	28 (7.1)
Type of reporter, N (%)	
Manufacturer[g]	239 (60.9)
Provider	85 (21.7)
Patient/parent	49 (12.5)
Other	19 (4.8)

[†]392 reports described 403 adverse events; 6 reports described maternal and infant outcomes; 107 (27.3%) reports originated in a single obstetrical practice.

[a]Other vaccines given with Tdap included human papilloma virus vaccine (12;3.1%), and Tdap with meningococcal conjugate vaccine (7;1.8%).

[b]Age was missing for 13pregnant woman.

[c]Interval unknown for 11 reports.

[d]Gestational age at time of vaccination is unknown for 61 reports.

[e]A serious report is defined as such when one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization, or permanent disability [12]

[f]Trimester at time of vaccination is unknown for 58 reports.

[g]In 197 (82.4%) reports submitted by the manufacturer, the reports originated from the provider

Table 2.

Reports of adverse events following Tdap vaccination during pregnancy during 2005-2010 and 2011-2015, VAERS

	Before Routine Recommendation for Tdap during Pregnancy (January 2005 – June 2010) [a,b]	**After Routine Recommendation for Tdap during Pregnancy (October 2011 – July 2015)**
Total Tdap pregnancy reports	132	392
Trimester of vaccination	First - 85 (77%) Third - 4 (4%)	First - 29 (8.7%) Third - 264 (79.2%)
Maternal age, median (range), years	22 (13 - 42)	29 (13 - 42)
Serious [c] adverse event	6 (4.5%)	27 (6.9%)
Stillbirth	2 (1.5%)	11 (2.8%)
Preterm birth	2 (1.5%)	11 (2.8%)
Spontaneous abortion	22 (16.7%)	4 (1.0%)
Major birth defects	1 (0.8%)	4 (1.0%)
Injection site reactions/arm pain	6 (4.5%)	47 (11.9%)
No adverse event	55 (41.7%)	182 (46.4%)

[a] Zheteyeva et al. Safety of Tdap in pregnancy. Am. J. Obstet Gynecol. 2012;207:59.e1-7

[b] From 2008-2011. ACIP did not routinely recommend use of Tdap vaccine in pregnant women, but recommended that providers consider use in certain situations that included instances when a pregnant woman has insufficient tetanus or diphtheria protection until delivery, or is at increased risk for pertussis

[c] Based on definition of the Code of Federal Regulations [11], if any of the following conditions occur: death, hospitalization, prolongation of hospitalization, life-threatening illness, persistent or significant disability