Update on the safety of maternal tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap)

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The findings and conclusions in this presentation are those of the authors and do not necessarily represent the views of CDC

Outline

- Background
- Enhanced Surveillance of Tdap Vaccine Safety in Pregnancy in the Vaccine Adverse Event Reporting System (VAERS)
- Maternal Pertussis Vaccination and Structural Birth Defects in Offspring
- Clinical Study of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine (Tdap) Safety in Pregnant Women
- Update on ACIP Pertussis Working Group Activities

Background

- **ACIP recommendations:**
  - **Unvaccinated pregnant women receive a dose of Tdap [a] (2011)**
    - **To provide infants with maternal transplacental passive antibody protection against pertussis during the early postnatal months**
    - **Infants are at highest risk of pertussis infection**
  - **Tdap during every pregnancy irrespective of prior history of receiving Tdap [b] (2012)**
    - **Optimal timing for administration: 27 - 36 weeks gestation**
- **At the time of the recommendation(s), limited data existed on the safety of Tdap vaccination in pregnancy**

[a] CDC. MMWR. October 21, 2011 / 60(41); 1424-1426. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6041a4.htm

[b] CDC. MMWR. February 22, 2013 / 62(07);131-135. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6207a4.htm

Background (cont.)

- During the 2012 deliberations, ACIP expressed the need for enhanced monitoring and safety studies of Tdap in pregnancy
- The CDC Immunization Safety Office implemented a comprehensive vaccine safety monitoring effort for maternal Tdap safety [c]
  - Enhanced surveillance in the Vaccine Adverse Event Reporting System (VAERS)
    - Clinical review of all Tdap pregnancy reports
  - Epidemiologic studies in the Vaccine Safety Datalink (VSD)
  - Clinical research in the Clinical Immunization Safety Assessment (CISA) Project
- In 2015, Tdap vaccination coverage during pregnancy among women who had a live birth was 42.1% vs. 27% in 2014 [d]

[c] Moro et al. Hum Vaccin Immunother. 2015;11(12):2872-9

[d] Pregnant Women and Tdap Vaccination, Internet Panel Surveys, United States, April 2014 and April 2015 (unpublished data)

CDC's Post-licensure Vaccine Safety Monitoring Systems

System	Collaboration	Description
Vaccine Adverse Event Reporting System (VAERS)	CDC and FDA	US frontline spontaneous reporting system to detect potential vaccine safety problems
Vaccine Safety Datalink (VSD)	CDC and 9 integrated healthcare systems	Large linked database system used for active surveillance and research, ~9.4 million members (~3% of US pop.) - Conducts monitoring and evaluation - Can calculate rates and risk estimates
Clinical Immunization Safety Assessment (CISA) Project	CDC and 7 medical research centers	Expert collaboration which conducts individual clinical vaccine safety assessments and clinical research

Safety of Tdap in Pregnancy in VAERS

- Surveillance in VAERS from October 2011 through June 2015 showed no new or unexpected vaccine safety concerns among pregnant women who received Tdap or their infants
- Part of these findings were presented at the February 2014 ACIP meeting and have been published [a]

[a] Moro PL, et al. Vaccine. 2016 Apr 29;34(20):2349-53

Safety of Tdap in pregnancy in VSD

Period	Sample size	Safety data
2010-2012 [a]	26,224 vaccinated 97,265 unvaccinated	▪ No increased risk of preterm birth, small for gestational age or hypertensive disorders ▪ Slight increased in risk of chorioamnionitis
2007-2013 [b]	29,155 vaccinated with Tdap (varying intervals from prior tetanus-containing vaccinations)	▪ No increased risk of acute adverse events (fever, allergy, and local reactions) or adverse birth outcomes (small for gestational age, preterm delivery, and low birth weight) for women who had a previous tetanus vaccination regardless of timing since prior tetanus containing vaccine
2007-2013 [c]	36,844 vaccinated 8,464 Tdap and IIV on same day 28,380 sequentially	▪ No statistically significant increased risk of fever or any medically attended acute adverse event in pregnant women concomitantly compared with sequentially ▪ No differences in both groups in pregnancy outcomes (e.g., Small for gestational age, low birth weight, preterm delivery)

[a] Kharbanda EO, et al. JAMA 2014;312:1897–904
[b] Sukumaran L, et al. JAMA. 2015;314(15):1581-1587
[c] Sukumaran L, et al. ObGyn. 2015;126(5): 1069–1074

Update on the Enhanced Surveillance of Tdap Safety in Pregnancy in the Vaccine Adverse Event Reporting System (VAERS)

VAERS: Spontaneous Reporting System Co-administered by the FDA and CDC

Strengths

- Rapid signal detection
- Can detect rare adverse events
- Generates hypotheses
- Encourages reports from healthcare providers and accepts reports from patients and others
- Data available to the public

Limitations

- Reporting bias (e.g., underreporting, stimulated reporting)
- Inconsistent data quality and completeness
- Not designed to assess if vaccine caused an adverse event (AE)
- Lack of unvaccinated comparison group
- No field for pregnancy: difficult to search for reports

Methods

- Surveillance initiated on November 26, 2012
- VAERS database searched for reports of pregnant women (or infants exposed in utero) after administration of Tdap (vaccinated during 10/11/2011- 5/6/2016)
- Requested and reviewed medical records for ALL pregnancy reports associated with Tdap (since October 2011)
- Query the reporter/patient for prior administration of tetanus-containing vaccine (Td/TT/Tdap)

Preliminary Findings

Tdap in Pregnancy: Data from VAERS Surveillance, 10/11/2011 - 5/6/2016

Characteristics	N (%)
Total Reports	**464**
Reports with no adverse events	196 (42)
Serious[a] reports	36 (8)
Type of reporter	
Manufacturer	251 (54)
Provider	106 (23)
Patient/parent	70 (15)
Other	27 (6)
Received Tdap alone	393 (85)
Reports of repeat Tdap doses	26 (5.6)

[a] Serious reports classified based on Code of Federal Regulations: death, life threatening, hospitalization, prolonged hospitalization, permanent disability (exception: hospitalization for normal delivery)

Tdap in Pregnancy: Data from VAERS Surveillance, 10/11/2011 - 5/6/2016 (cont.)

Characteristics	N (%)
Total Reports	**464**
Maternal age in years, median (range)	30 (13 - 42)
Onset interval to adverse event in days, median (range)	1 (0 - 255)
Gestational age at time of vaccination in weeks, median (range)	31 (1 - 41)
Gestational age at time of vaccination (N=382)	
First trimester (0-13 weeks)	34 (9)
Second trimester (14-27 weeks)	46 (12)
Third trimester (28+ weeks)	302 (79)

Safety of Tdap Vaccine in Pregnancy in VAERS: Pregnancy-Specific Adverse Events Reported 10/11/2011 - 5/6/2016

Pregnancy specific adverse events	N = 82
Premature delivery (< 37 weeks)	15
Stillbirth (one with trisomy 12)	13
Oligohydramnios	12
Gestational diabetes	10
Gestational hypertension	5
Spontaneous abortion (< 20 weeks gestation)	4
Failure to progress	4
Polyhydramnios	3
Chorioamnionitis	3
Preeclampsia	2
Other*	11

*Includes two reports of breech presentation and one each of placenta previa, abruption placentae, nausea and vomiting, premature rupture of membranes, preterm labor, contractions/sent to hospital, arrest of descent, prolonged labor, induction of labor due to fetal tachycardia

Safety of Tdap Vaccine in Pregnancy in VAERS: Infant or Fetal Adverse Events Reported 10/11/2011 - 5/6/2016

Infant or fetal adverse events	N = 21
Intrauterine growth restriction	8
Macrosomia	4
Neonatal demise (cause of death: umbilical cord occlusion with fetal vascular thrombus formation)	1
Polydactyly	1
Neonatal respiratory disorder	1
Lockjaw in infant	1
Pneumonia in infant	1
Large for gestational age	1
Hypoglycemia in infant	1
Fetal tachycardia	1
Decreased fetal movement	1

Safety of Tdap Vaccine in Pregnancy in VAERS: Major Birth Defects Reported 10/11/2011 - 5/6/2016

Major [a] birth defects	N = 4
Ectopic kidney in newborn [b]	1
Hypoplastic left heart syndrome [c]	1
Trisomy 12 [d]	1
Clubbed foot [e]	1

[a] Rasmussen S, et al. CID 2014;59(S7):S428-36
[b] Patient vaccinated at 17 weeks
[c] Patient vaccinated at 1.4 weeks
[d] Patient vaccinated at 28 weeks
[e] Time of vaccination not reported

Safety of Tdap Vaccine in Pregnancy in VAERS: Non-Pregnancy-Specific Adverse Events Reported, 10/11/2011 - 5/6/2016

Non-pregnancy specific adverse events	N = 172
Injection site reactions/pain in extremity/myalgia	74
Systemic reactions (fever, chills, headache)	31
Musculoskeletal and connective tissue disorders	14
Non-anaphylaxis allergic reactions	12
Thrombocytopenia	4
Guillain-Barré Syndrome	5
Anaphylaxis	4
Infections and infestations	5
Other [a]	23

[a] Other non-pregnancy specific adverse events included nine reports of general disorders and administration site conditions, seven reports of neurological conditions, three reports of abdominal pain/diarrhea, two reports of chronic hypertension, and one report each of depression and a dog bite

Reports of Repeat Tdap Doses Among Pregnant Women in VAERS

- Twenty-six reported to have received a previous dose of Tdap
- Interval between current and previous Tdap: 7 days - 9.4 years (median 1.8 years)
- Thirteen reports did not describe an adverse event (AE)
- AEs in 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
  - One report each of stillbirth with trisomy 12, maternal urinary tract infection, and maternal systemic reactions (e.g., fever, chills)

Conclusions

- In VAERS, no new unexpected vaccine safety concerns noted among pregnant women who received Tdap or their infants
- Limited number of pregnancy reports with repeat Tdap doses received by VAERS
- CDC will continue to monitor the safety of Tdap vaccine during pregnancy

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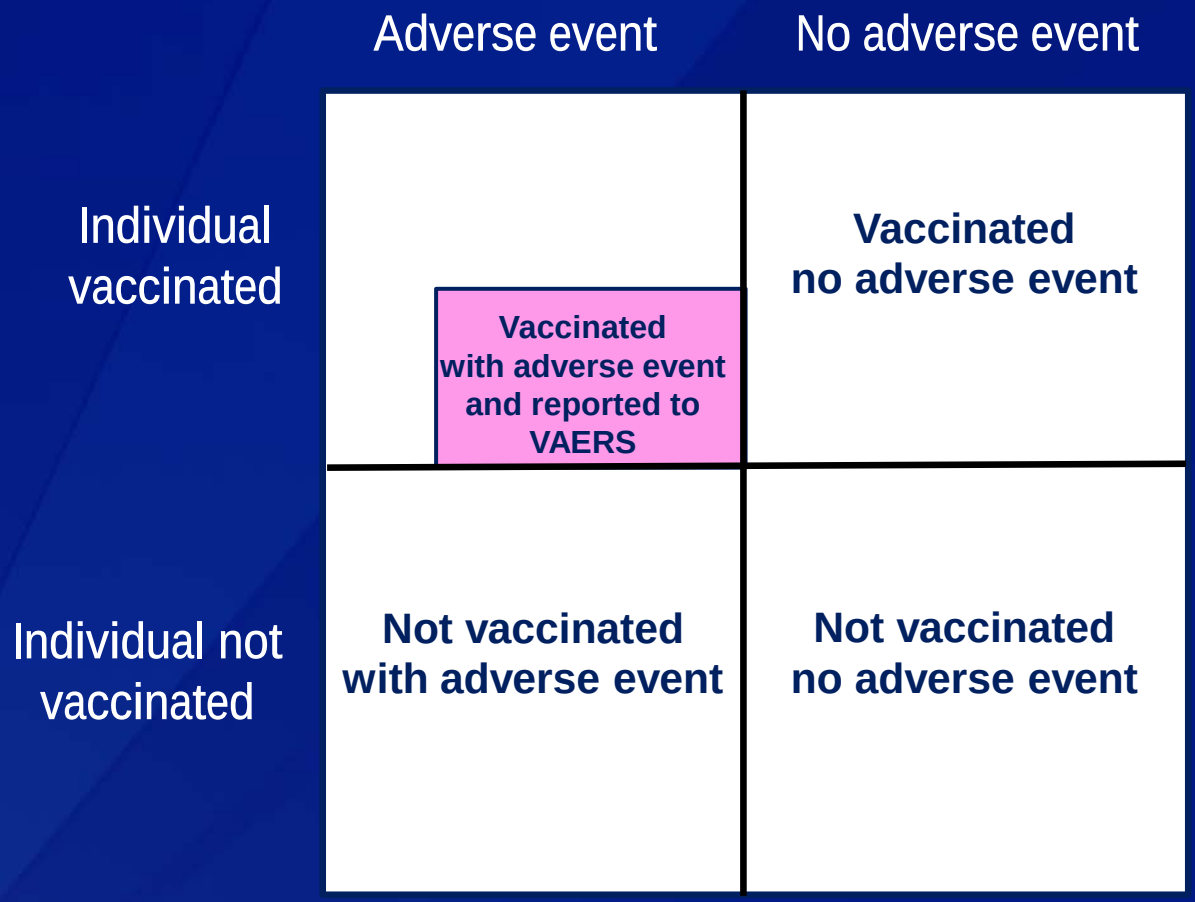
Extra Slides

Limitations of VAERS data



- **VAERS only contains partial data in pink cell (incomplete population data)**
  - **Not able to calculate rates of occurrence of adverse events**
  - **Not able to determine increased risk**
  - **Not able to calculate vaccination coverage**

Chorioamnionitis finding in the VSD*

- Magnitude of risk observed was small
- No increased risk of preterm birth, a major sequela of chorioamnionitis, was observed (risk may be due to residual confounding)
- Chorioamnionitis finding may reflect heterogeneity in the diagnosis:
  - Chart reviews revealed that a diagnosis of chorioamnionitis had only 50% positive predictive value (PPV) for having a clinical presentation consistent with chorioamnionitis
  - When this PPV was applied, the association between Tdap vaccination and chorioamnionitis was no longer significant

***Kharbanda et al. JAMA. 2014;312(18):1897-1904**

Safety of Tdap in Pregnancy in VAERS

	Before Routine Recommendation for Tdap during Pregnancy (Jan 2005 – June 2010) [a,b]	After Routine Recommendation for Tdap during Pregnancy (Oct 2011 – May 2016)
Total Tdap pregnancy reports	132	464
Study period	5.5 years	4.5 years
Trimester of vaccination	1st - 85 (77%) 3rd - 4 (4%)	1st - 34 (9%) 3rd - 302 (79%)
Maternal age, median (range), years	22 (13 - 42)	30 (13 - 42)
Serious	6 (5%)	36 (8%)
Preterm birth	2 (2%)	15 (3%)
Stillbirth	2 (2%)	13 (3%)
Spontaneous abortion	22 (17%)	4 (1%)
Major birth defects	1 (1%)	4 (1%)
Injection site reactions/arm pain	6 (5%)	74 (16%)
No adverse event	55 (42%)	196 (42%)

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

[b] Recommendation since 2008. 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