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

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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

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Background

- On October 11, 2011 ACIP[a] voted to recommend that unvaccinated pregnant women receive a dose of Tdap
- On October 24, 2012 ACIP[b] voted to recommend the use of Tdap during every pregnancy irrespective of the patient's prior history of receiving Tdap. Optimal timing for Tdap administration is between 27 and 36 weeks gestation
- Tdap is not approved for repeat doses and ACIP has not previously recommended repeat doses in other populations
- No pre-licensure trials for Tdap were conducted in pregnant women

[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

Tdap in Pregnancy: Data from VAERS before Routine Recommendation

- 132 reports to VAERS in women who received Tdap[a] during pregnancy or infants exposed in utero (2005 - 2010)[b]
  - 77% of reports had Tdap during first trimester
  - 42% described no adverse event
- No unusual or unexpected pattern of maternal, fetal, or infant outcomes

Selected Outcomes	Number of reports
Spontaneous abortion	22
Fetal death	2
Preterm birth	2
Major birth defect	1 (gastroschisis)

[a] Zheteyeva et al. Safety of Tdap in pregnancy. *Am. J. Obstet Gyn*ecol. 2012;207:59.e1-7.
[b] Before routine recommendation for Tdap in pregnant women

Objective

- Describe adverse event reports submitted to the Vaccine Adverse Event Reporting System of pregnant women or their infants who received Tdap during 10/2011 – 01/2014 since ACIP recommendations

Methods

- Enhanced surveillance initiated November 26, 2012
- Search VAERS database for reports of pregnant women (or infants exposed in utero) after administration of Tdap (vaccinated during 10/11/2011- 01/31/2014):
  - "Exposure during pregnancy", "drug exposure during pregnancy" , "maternal exposure during pregnancy" and other specific pregnancy MedDRA* terms
  - Text string search for term 'preg'
- Serious reports classified based on Code of Federal Regulations: death, life threatening, hospitalization, prolonged hospitalization, permanent disability (exception: hospitalization for normal delivery)

* Medical Dictionary for Regulatory Activities

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

- Request and review medical records for ALL pregnancy reports associated with Tdap
  - Search of medical records for reports received since October 2011 (previous recommendation)
- Reports describing maternal and infant adverse events in the same report treated as separate reports
- Query the reporter/patient for prior administration of tetanus containing vaccine (Td/TT/Tdap)
- Descriptive analysis of adverse events reported

Preliminary Findings

Tdap in Pregnancy: Data from Enhanced VAERS Surveillance, 10/11/2011 - 01/31/2014

Characteristics	N (%)
Total Reports	**90**
Reports with no adverse events	20 (22)
Serious	14 (16)
Type of reporter	
Provider	34 (38)
Manufacturer	33 (37) [a]
Other	13 (14)
Patient/parent	10 (11)
Received Tdap alone	56 (62)

[a] **15 (16.7%) manufacturer reports came from same OBGYN practice**

Tdap in Pregnancy: Data from Enhanced VAERS Surveillance, 10/11/2011 - 01/31/2014

Characteristics	N (%)
Total Reports	**90**
Maternal age in years, median (range)	29 (13 - 42)
Onset interval to adverse event in days, median (range) (N=56)	1 (0 - 227)
Gestational age at time of vaccination in weeks, median (range), (N=72)	28 (1 - 40)
Gestational age at time of vaccination (N=73)	
First trimester (0-13 weeks)	14 (19)
Second trimester (14-27 weeks)	19 (26)
Third trimester (28+ weeks)	40 (55)

Safety of Tdap Vaccine in Pregnancy in VAERS: Pregnancy-Specific Adverse Events Reported, 10/11/2011 - 01/31/2014

Pregnancy specific adverse events	N = 26
Premature delivery (< 37 weeks)	5
Spontaneous abortion (< 20 weeks gestation)	4
Stillbirth (one with trisomy 12)	4
Gestational diabetes	2
Oligohydramnios	2
Preeclampsia	2
Chorioamnionitis	2
Polyhydramnios/macrosomia	1
Placenta previa	1
Abruptio placentae	1
Nausea and vomiting	1
Increased blood pressure	1

Safety of Tdap Vaccine in Pregnancy in VAERS: Infant or Fetal Adverse Events Reported, 10/11/2011 - 01/31/2014

Infant or fetal adverse events	N = 6
Ectopic kidney in newborn [a†]	1
Hypoplastic left heart syndrome [b†]	1
Polydactyly [c]	1
Intrauterine growth restriction	1
Neonatal respiratory disorder	1
Lockjaw in infant (insufficient information) [d]	1

[a] Pregnant patient vaccinated at 17 weeks
[b] Patient vaccinated at 1.4 weeks
[c] Patient vaccinated at 28 weeks
[d] Patient required hospitalization
† Major birth defects

Safety of Tdap Vaccine in Pregnancy in VAERS: Non-Pregnancy-Specific Adverse Events Reported, 10/11/2011 - 01/31/2014

Non-pregnancy specific adverse events	N = 38
Injection site reactions/pain in extremity/myalgia	19
Thrombocytopenia	4
Non-anaphylaxis allergic reaction	4
Systemic reactions (fever, chills, headache)	4
Guillain-Barré Syndrome [a]	1
Transverse myelitis [a]	1
Anaphylaxis [a]	1
Hypothyroidism	1
Pyrexia	1
Chronic hypertension [b]	1
Urinary tract infection	1

[a] Required hospitalization
[b] Fetus presented intrauterine growth retardation before maternal vaccination

Adverse Events Among the 10 Women with Known Prior Tdap Vaccination

Adverse event	Interval between current and previous Tdap vaccination
Stillbirth/trisomy 12 [a]	3.8 yrs
No adverse event	2.7
Increased blood pressure	2.6
Urinary tract infection	2.5
Systemic symptoms: headache, chills, fever	2.4
Arm pain	1.8
Oligohydramnios/premature delivery [a]	1.7
Injection site erythema/vaccination error [b]	159 days
No adverse event	29 days
Intrauterine growth restriction/vaccination error	7 days

[a] Required hospitalization
[b] Received 0.1 mL of Tdap subcutaneously instead of PPD

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 – Jan 2014)
Total Tdap pregnancy reports	132	90
Study period	5.5 years	2.3 years
Trimester of vaccination	First - 85 (77%) Third - 4 (4%)	First - 14 (19%) Third - 40 (55%)
Maternal age, median (range), years	22 (13 - 42)	29 (13 - 42)
Serious	6 (5%)	14 (16%)
Preterm birth	2 (2%)	5 (6%)
Spontaneous abortion	22 (17%)	4 (4%)
Stillbirth	2 (2%)	4 (4%)
Major birth defects	1 (1%)	2 (2%)
Injection site reactions/arm pain	6 (5%)	19 (21%)
No adverse event	55 (42%)	20 (22%)

[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

Summary

- Compared to the period prior to the routine recommendation for Tdap during pregnancy we noted the following after the routine Tdap recommendation during pregnancy in VAERS:
  - Increase in the proportion of:
    - Serious reports
    - Certain pregnancy-specific outcomes that occur after the first trimester (e.g. stillbirths, preterm deliveries)
    - Certain non-pregnancy specific outcomes (e.g. injection site reactions)
  - Decrease in the number of reports describing no adverse events
  - Most vaccinations during second and third trimester
- Changes in reporting patterns are likely due to new routine Tdap recommendation, increased awareness, and differences in the trimester of vaccination

Conclusions

- 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, with special emphasis on repeated doses of Tdap

Acknowledgements

Immunization Safety Office

- Frank DeStefano
- Tom Shimabukuro
- Karen Broder

Division of Reproductive Health

- Naomi Tepper

Division of Birth Defects & Developmental Disabilities

- Janet Cragan

Division of Global Migration and Quarantine

- Yenlik Zheteyeva

Extra Slides

Brands of Tdap administered

Brand	No. Reports
Adacel	51
Boostrix	29
Unknown brand	10
Total reports	90

Tdap pregnancy reports by year and safety profile

Year	No Reports	Serious	Serious Adverse Events
2012	44	8	Preterm delivery – 2 Preeclampsia -1 Oligohydramnios/preterm – 1 Guillain-Barré Syndrome -1 Anaphylaxis – 1 Transverse myelitis – 1 Lock jaw (infant) - 1
2013	37	4	Stillbirths - 3 Preterm delivery - 1

CISA Project Study: Clinical Study of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine (Tdap) Safety in Pregnant Women

- **Sites:** Vanderbilt University (lead site), Duke University (contributing site), and CDC plan to conduct a clinical study of Tdap safety in pregnant women
- **Primary Aim**
  - To compare rates of injection-site and systemic reactions after Tdap in pregnant women versus non-pregnant women
  - To assess rates of preterm and small for gestational age (SGA) births in women who received Tdap during pregnancy
- **Design**
  - Observational study in women receiving Tdap as part of usual care
  - Recruit pregnant women at ≥ 20 gestation receiving Tdap, particularly women receiving repeat Tdap, and non-pregnant receiving Tdap.
  - Assess reactogenicity events (e.g. injection-site reactions and fever) during 7 days after Tdap
  - Assess pregnancy outcomes
- **Timeline**
  - Anticipated starting study in June 2014 with approximately 20 months for enrollment (will be registered at Clinical.Trials.gov)