Vaccine Safety Surveillance

Frank DeStefano, MD, MPH, FACPM
Immunization Safety Office
Division of Healthcare Quality and Promotion
National Center for Zoonotic and Infectious Diseases
Centers for Disease Control and Prevention
Atlanta, GA
Background: Vaccine Safety Path

Before licensure
- Lab research
- Animal studies
- Studies in people

After licensure
Regulatory agencies conduct safety monitoring and studies

Licensure
Vaccine is safe & effective
Vaccine can be made safely
Evaluation of Vaccine Safety in Pregnant Women

- Pregnant women excluded from pre-licensure trials for U.S. licensed vaccines
- Evidence for vaccine safety based largely on post-licensure surveillance data and observational studies
U.S. Post-licensure Vaccine Safety Monitoring and Evaluation

- FDA post-marketing commitments by the manufacturer
  - Routine evaluation of clinically significant post-licensure adverse event reports
  - Requested post-licensure safety studies
  - Pregnancy registries
- U.S. public health authorities and regulatory agencies fund and/or conduct surveillance to monitor vaccine safety
# U.S. Post-licensure Vaccine Safety Systems

<table>
<thead>
<tr>
<th>System</th>
<th>Collaboration</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine Adverse Event Reporting System (VAERS)</td>
<td>CDC and FDA</td>
<td>Frontline spontaneous reporting system to detect potential vaccine safety issues</td>
</tr>
<tr>
<td>Vaccine Safety Datalink (VSD)</td>
<td>CDC and several integrated health care systems</td>
<td>Large linked database system used for active surveillance and research ~9.4 million members</td>
</tr>
<tr>
<td>Clinical Immunization Safety Assessment (CISA) Project</td>
<td>CDC and 7 academic centers</td>
<td>Expert collaboration that conducts individual clinical vaccine safety assessments and clinical research</td>
</tr>
<tr>
<td>Post-Licensure Rapid Immunization Safety Monitoring Program (PRISM)</td>
<td>FDA and 6 partner organizations</td>
<td>Large distributed database system used for active surveillance and research ~170 million individuals</td>
</tr>
</tbody>
</table>
The Vaccine Adverse Event Reporting System (VAERS)
Vaccine Adverse Event Reporting System (VAERS)

- National spontaneous reporting system for adverse events after U.S. licensed vaccines
  - Accepts reports from health care providers, manufacturers, and the public
  - Signs/symptoms of adverse event coded and entered into database
  - Received ~30,000 U.S. reports annually in recent years
- Jointly administered by CDC and FDA, authorized by National Childhood Vaccine Injury Act of 1986
- VAERS website: http://vaers.hhs.gov
VAERS Report Form*

- Information about patient, health care provider and reporter, adverse events (AEs), vaccines, pre-existing medical conditions
- Other information: date vaccinated, AE onset date, vaccine type, lot number, dose number
- Reports with incomplete information accepted
- All reports accepted without judgment on causality
- Current form does not contain a check box to indicate maternal immunization, but new form will

*Paper version ([https://vaers.hhs.gov/resources/vaers_form.pdf](https://vaers.hhs.gov/resources/vaers_form.pdf)) is called the VAERS-1 form
The Vaccine Safety Datalink (VSD)
Vaccine Safety Datalink (VSD)

- Collaboration between CDC and several integrated health care plans
- Data on more than 9 million persons per year
- Links vaccination data to health outcome data
- Algorithms to identify pregnancies and link babies to mothers

**Vaccination Records**

**Health Outcomes**
- (Hospital)
- (Emergency Dept)
- (Outpatient)

**Patient Characteristics**

Linked by Study IDs

Data are linked and kept at each site, not at CDC
Vaccine Safety Datalink Sites in 2016

Group Health Cooperative
Kaiser Permanente Colorado
Kaiser Permanente Northern CA
Kaiser Permanente Southern CA
Kaiser Permanente Northwest
Marshfield Clinic
Harvard Pilgrim
CDC
VSD Study of Safety of Repeat Tdap Vaccinations in Pregnancy

- **Aim:** To study the safety of Tdap vaccine in pregnant women by comparing adverse events with regard to intervals from prior tetanus containing vaccines
- **Time period:** 1/1/2007 - 11/15/2013
- **Population:** Pregnant women in VSD
- Outcomes identified from diagnoses received in hospital, ED, or outpatient clinic care visits

### VSD Study Acute Outcomes: Prior Tetanus <2 Years vs. >5 Years

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tdap + Prior Tetanus &lt;2 Years (N = 4,812)</th>
<th>Tdap + Prior Tetanus &gt;5 Years (N = 14,344)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (0-3 days)</td>
<td>1 (2.1)</td>
<td>5 (3.5)</td>
<td>0.70</td>
</tr>
<tr>
<td>Fever (0-7 days)</td>
<td>3 (6.2)</td>
<td>6 (4.2)</td>
<td>0.51</td>
</tr>
<tr>
<td>Local Reaction (0-3 days)</td>
<td>2 (4.2)</td>
<td>16 (11.2)</td>
<td>0.35</td>
</tr>
<tr>
<td>Local Reaction (0-7 days)</td>
<td>6 (12.5)</td>
<td>22 (15.3)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Rate in parentheses = N/10,000
Adverse Pregnancy Outcomes following Tdap Vaccine: Prior Tetanus <2 Years vs. >5 Years

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tdap + Prior Tetanus &lt;2 Years (N = 3,313)</th>
<th>Tdap + Prior Tetanus &gt;5 Years (N = 10,633)</th>
<th>Adjusted Relative Risk# (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm Delivery</td>
<td>218 (6.6%)</td>
<td>723 (6.8%)</td>
<td>1.15 (0.98, 1.34)</td>
<td>0.08</td>
</tr>
<tr>
<td>Low Birth Weight</td>
<td>156 (4.7%)</td>
<td>543 (5.1%)</td>
<td>1.10 (0.92, 1.32)</td>
<td>0.31</td>
</tr>
<tr>
<td>Small for Gestational Age</td>
<td>298 (9.0%)</td>
<td>996 (9.1%)</td>
<td>0.99 (0.87, 1.13)</td>
<td>0.88</td>
</tr>
</tbody>
</table>

* N/100 # adjusting for gestational age at Tdap vaccination in weeks, VSD site, length of enrollment (months), prenatal care utilization index, maternal comorbidity, pregnancy complication, and maternal age
VSD Study Conclusions

- No increased risk of adverse events or adverse birth outcomes in women who were vaccinated with Tdap in pregnancy when comparing intervals from prior tetanus containing vaccines.

- VSD findings, however, restricted to medically attended conditions and underestimate occurrence of local injection site reactions.
Clinical Immunization Safety Assessment (CISA) Project
Clinical Immunization Safety Assessment (CISA) Project

- **Collaboration**
  - CDC’s Immunization Safety Office (ISO), 7 medical research centers, other federal partners

- **Mission**
  - To improve understanding of adverse events following immunization (AEFI) at the individual-patient level

- **Goals**
  - Serve as a vaccine safety resource for consultation on clinical vaccine safety issues
  - Develop strategies to assess individuals who may be at increased risk for AEFI
  - Conduct studies to identify risk factors and preventive strategies for AEFI, particularly in special populations
CISA: Clinical Study of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine (Tdap) Safety in Pregnant Women

Courtesy of Kathryn Edwards, ACIP Presentation 2016.
CISA: Clinical Study of Tdap Safety in Pregnant Women

• **Aims:**
  • To compare rates of injection-site and systemic reactions after Tdap in pregnant women versus non-pregnant women
  • To explore differences in injection-site and systemic reactions in pregnant women who received Tdap before the current pregnancy vs. pregnant women who are receiving their first Tdap dose

• **Methods:**
  • Prospective observational study of women aged 18-45 years receiving Tdap as first or repeat doses at Vanderbilt and Duke University clinics
  • Prior Tdap/ Td/ TT history assessed by subject report and/or medical record/ registry
  • Rates of local and systemic reactions assessed during days 0-7 after Tdap using memory aid, with severity scales

*Study registered at ClinicalTrials.gov (NCT02209623)*
Rates of Moderate + Severe Reactions Among Pregnant Women With and Without Prior Tdap Receipt within 7 Days After Vaccination
CISA Study Conclusions

- 53% of the pregnant women received prior Tdap and rates of moderate/severe reactions were similar in pregnant women receiving the first or repeat Tdap vaccination
Conclusions on Maternal Vaccine Safety Surveillance

- Pre-licensure evaluation and good manufacturing practices are the foundation of vaccine safety.
- Pregnant women excluded from pre-licensure trials for U.S. licensed vaccines.
- Evidence for maternal vaccine safety relies on post-licensure surveillance and observational studies.
- The U.S. has a robust and comprehensive system to monitor and evaluate vaccine safety, including in pregnant women.