Overview of the U.S. Vaccine Safety Surveillance Systems & Ongoing Scientific Activities to Monitor Maternal Vaccine Safety

Dr. Karin Bok
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# Pre-Licensure Vaccine Safety Activities

<table>
<thead>
<tr>
<th>Leading Institution</th>
<th>Vaccine Safety Scientific Activity</th>
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<tbody>
<tr>
<td>NIH</td>
<td>Identification and development of vaccine candidates</td>
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<tr>
<td>NIH</td>
<td>Design of novel vaccine strategies</td>
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<tr>
<td>NIH</td>
<td>Investigate the variability in human immune responses</td>
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<tr>
<td>NIH</td>
<td>Improve vaccine immunomodulators, administration, and formulations</td>
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<tr>
<td>FDA</td>
<td>Vaccine development</td>
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<tr>
<td>FDA</td>
<td>Study of pathogenicity</td>
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Why We Monitor Vaccine Safety After Licensure

- High safety standards expected for vaccines
- Vaccines generally healthy (vs. ill for drugs)
- Dual role of vaccinations
  - Individual protection
  - Societal protection (some vaccinations universally recommended or mandated)
- Pre-licensure trials are often too small to detect rare events and special populations may not be adequately represented
Post-licensure Vaccine Safety Monitoring Activities

- Rapidly identify new or rare adverse events of clinical importance
- Monitor changes in patterns for known adverse events
- Assess safety in special populations (e.g., pregnant women)
- Determine patient risk factors for particular adverse events
- Assess safety of vaccine lots (FDA)
Vaccination Safety Systems Working Together to Monitor & Test Maternal Immunization Safety

- **CISA (CDC)**
- **PRISM (FDA)**
- **VSD (CDC)**
- **MILVAX (DoD)**
- **VAERS (CDC and FDA)**
- **ADERS (VA)**

- 9 million
- 2.6 million
- 14 million
- 1 million
Vaccine Adverse Event Reporting System (VAERS)

- National spontaneous reporting system for adverse events after US-licensed vaccines
  - In recent years, received around 30,000 U.S. reports annually
  - Accepts reports from healthcare providers, manufacturers and the public
  - Signs/symptoms of adverse event coded and entered into database
- Jointly administered by CDC and FDA
- Authorized by National Childhood Vaccine Injury Act of 1986
Vaccine Adverse Event Reporting System (VAERS) (co-managed CDC and FDA)\(^1\)

**Strengths**

- National data; accepts reports from anyone
- Rapid signal detection; rare adverse events
- Collects information about vaccine, characteristics of vaccine
- Data available to public

**Limitations**

- Reporting bias
- Inconsistent data quality and completeness
- Generally cannot assess if vaccine caused an adverse event
- Lack of unvaccinated comparison group
- Pregnancy inconsistently reported

1. VAERS website: [http://vaers.hhs.gov](http://vaers.hhs.gov)
2. Some reports have no adverse event
Vaccine Safety Datalink (VSD)

- Established in 1990
- A collaborative project between CDC and 9 integrated healthcare organizations
- Allows for planned vaccine safety studies as well as timely investigations arising from
  - Hypotheses from medical literature and pre-licensure clinical trials
  - Reports to VAERS
  - Changes in immunization schedules, or the introduction of new vaccines
### Vaccine Safety Datalink (VSD)

**Strengths**
- All medical encounters are available
- Vaccine registry data
- Can calculate rates
- Can review medical records
- Tested algorithm to identify pregnancies
- Annual birth cohort = 100k

**Limitations**
- Sample size may be inadequate for very rare events
- Vaccines administered outside of medical home may not be captured
- Potential for lack of socioeconomic diversity
- Data lags

- Data on over 9 million persons per year (~3% of US pop)
- Links vaccination data to health outcome (outpatient, emergency dept., inpatient) and demographic data
Clinical Immunization Safety Assessment (CISA) Project

• Collaboration between CDC and 7 medical research centers
• Established by CDC to:
  • 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 adverse events following immunization (AEFI)
  • Conduct studies to identify risk factors and preventive strategies for AEFI, particularly in special populations
Clinical Immunization Safety Assessment (CISA) Project: Research

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Can implement prospective, multi-site clinical studies (hundreds of subjects)</td>
<td>• Sample size limited to study rare adverse events</td>
</tr>
<tr>
<td>• Expertise in vaccine safety and many clinical areas</td>
<td>• Potential challenges to recruit and retain subjects</td>
</tr>
<tr>
<td>• Access to special populations receiving vaccines</td>
<td>• May not have access to vaccine records for vaccines given outside site</td>
</tr>
<tr>
<td>• Detailed clinical/data on patients</td>
<td>• Potential for lack of geographic or race/ethnicity diversity</td>
</tr>
<tr>
<td>• Can collect biological specimens</td>
<td>• Clinical studies may be labor and resource-intensive</td>
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<tr>
<td>• Ability to recruit controls</td>
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Post-Licensure Rapid Immunization Safety Monitoring (PRISM)

- Established in 2009
- Uses data from National Health Insurance Plans and Immunizations Registries
- Links data between databases, performs epidemiological studies and establishes new statistical methods of analysis
  - Monitors the largest U.S. population cohort
  - Links states by using immunization registries
  - Synergistic with existing federal systems
Adverse Drug Event Reporting System (ADERS)

- VA’s, Web based
  - National Program – Initiated March 2007
  - Provider and patient reported AE’s
  - Medications and Vaccines
  - Over 400,000 reports
  - Linkage between VA ADERS and VAERS
  - Passive Surveillance: Weekly update identifying number, type, and sites of AE’s
VA ADERS links Medication and Vaccine Data

- Mortality Data
- VA Health Surveys
- Pharmacy Data
- Immunization Packages
- VA Patient Care Databases
# Ongoing Scientific Activities to Monitor Maternal Safety

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<th>Leading Agency/System</th>
<th>Scientific Activities</th>
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<tr>
<td>CDC</td>
<td>Assessing the Feasibility of Monitoring Influenza Vaccine Safety in Pregnant Women Using Text Messaging</td>
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<tr>
<td>CDC</td>
<td>Immune response to influenza vaccination and effect on reproductive hormones</td>
</tr>
<tr>
<td>CDC</td>
<td><strong>Clinical Study of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine (Tdap) Safety in Pregnant Women</strong></td>
</tr>
<tr>
<td>DoD</td>
<td>Support the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS), which is a system to identify as early as possible the circumstances in which a drug or immunization administered during pregnancy may cause harm. (flu and Tdap)</td>
</tr>
<tr>
<td>VA</td>
<td>End of Season Analysis for Flu and Outcomes of Interest</td>
</tr>
<tr>
<td>FDA</td>
<td>Two population-based studies of pregnancy safety. Further research will identify pregnancy outcomes and analyze rare birth defects.</td>
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CDC-NVPO Study: Clinical Study of Tdap Safety in Pregnant Women
Study Goals

• Compare the rates of local and systemic reactions following Tdap in pregnant women with non-pregnant women

• Assess rates of preterm and small for gestational age (SGA) births in women who received Tdap during pregnancy

• Explore differences in local and systemic reactions in pregnant women who are receiving their 1st Tdap versus those who have received Tdap in the past
Additional Study Goals

• Assess additional obstetrical and infant outcomes
  • Maternal or fetal death
  • Placental abruption
  • Postpartum hemorrhage
  • Pregnancy related hypertension
  • Gestational diabetes

• Evaluate health outcomes and growth parameters in infants born to women who received Tdap (first 6 months of life)

• Registered in www.clinicaltrials.gov (NCT02209623)
Maternal Immunization Safety Surveillance Challenges

- Enrolling susceptible populations in clinical trials
- Case-control studies on vaccines currently recommended for pregnant women (Flu and Tdap)
- Large cohorts that will enable studying rare adverse events (birth defects)
- Defining the endpoint of a vaccine safety clinical trial: creating consensus across trials nationally and globally
- Liability concerns when administering vaccines recommended for pregnant women only and/or intended to protect the baby
- Linking health records of pregnant women and infants to enable long-term follow up of infant
- Safety and regulatory requirements to obtain a indication specific for pregnancy
Maternal Immunizations: Paving the Road for New Vaccine Research and Development

- WHO and Brighton Collaboration: efforts with harmonizing definitions to assess safety of immunization during pregnancy
  - Dr. Flor Muñoz (Baylor College of Medicine)

- Overview of DMID’s consultative conferences on enrolling pregnant women in clinical trials of antimicrobials vaccines
  - Dr. Mirjana Nesin (NIH/NIAID/DMID)

- Regulatory issues of maternal immunization
  - Dr. Marion Gruber (FDA)

- Maternal immunization challenges and opportunities: perspective of vaccine developers and manufacturers
  - Ms. Phyllis Arthur (BIO)