The Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD): New Initiatives

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Vaccine Adverse Event Reporting System (VAERS)

- Frontline national spontaneous reporting system for adverse events after US-licensed vaccines
  - 2006-2010 average reports per year ~29,000 (U.S.)
  - Accepts reports from healthcare providers, manufacturers and others
    - Reports accepted by web, mail, or fax
- Jointly administered by CDC and FDA
VAERS: Spontaneous Reporting System co-administered by the FDA and CDC

<table>
<thead>
<tr>
<th><strong>Strengths</strong></th>
<th><strong>Limitations</strong></th>
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<tr>
<td>➢ Rapid signal detection</td>
<td>➢ Reporting bias (e.g., underreporting, stimulated reporting)</td>
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<tr>
<td>➢ Can detect rare adverse events</td>
<td>➢ Inconsistent data quality and completeness</td>
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<tr>
<td>➢ Generates hypothesis</td>
<td>➢ Not designed to assess if vaccine caused an adverse event (AE)</td>
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<tr>
<td>➢ Encourages reports from healthcare providers and accepts reports from patients and others</td>
<td>➢ Lack of unvaccinated comparison group</td>
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<tr>
<td>➢ Data available to the public</td>
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Recent VAERS accomplishments

- Rapidly monitored >10,000 reports during the 2009-10 H1N1 response; provided first national safety data that was reassuring (MMWR article)
- Provided comprehensive data on safety of seasonal influenza vaccine useful to pandemic planning
- Provided timely data on safety of new vaccines (e.g., HPV, Tdap, MCV4, Rotateq)
VAERS - New Initiatives

1. Enhance ability to find signals
   - Data mining (FDA: Empirical Bayes, neural analysis, text mining)

2. Improve reporting efficiency and data quality
   - Web-based reports
   - Electronic manufacturer reports
   - Electronic health records linkages
   - Smart phone application for VAERS reports (pilot proposed)

3. Pilot novel adverse event surveillance systems beyond VAERS
   - Real Time Immunization Monitoring System (RTIMS)
   - Text messaging study (FluNet)

4. Focus on vaccine safety surveillance in pregnant women
Percentages above bars represent web-based percents of total report (primary and secondary US reports)

*Includes 2009-2010 H1N1 vaccine reports

Initiative to Improve Reporting Efficiency and Data Quality:
Trends of Total and Web-based VAERS Reports Following U.S. Licensed Vaccines, 2005 - 2010
Initiative to Improve Reporting Efficiency and Data Quality: 
Manufacturer Electronic Reporting to VAERS

- Since VAERS establishment in 1990, vaccine manufacturers have submitted reports mainly via fax and/or paper.

- In August 2009 FDA initiated the improvement of post marketing of safety products. This included harmonization of post marketing safety reporting regulation with international standards for electronic submission of safety information.

- ICH E2B is a data standard developed by the International Conference on Harmonization (ICH) for electronic transmission of Individual Case Safety Report (ICSR). The goal is for worldwide industry and regulators to communicate ICRS electronically and more efficiently using agreed upon data standards.

- Following 3 pilot projects with FDA and industry VAERS can accept manufacturer reports using E2B(R3) (including additional VAERS data elements).

- FDA is developing guidance for manufacturers to transmit their data electronically. The anticipated completion date of the guidance is May 2012.

- We anticipate that prior to May 2012 manufacturers will start to transmit the reports to FDA/CDC.

Initiative to Improve Reporting Efficiency and Data Quality: Electronic Medical Records

- **Goals:**
  - To develop and pilot test new and improved computer software to identify potential vaccine-related adverse events in electronic medical record (EMR) data and facilitate increased reporting to VAERS by healthcare providers
    - Builds on prior experience*

- **Use of prompts from the EMR data to identify potential vaccine-related adverse events and alert provider to consider reporting to VAERS**
  - Secondary aim: Determine if computer-prompted reporting to VAERS from EMRs will be acceptable to clinicians

- **Study proposal in development (CDC)**

Pilot Novel Adverse Event Surveillance Systems Beyond VAERS: Pilot Studies for H1N1 and Seasonal Influenza Vaccines

- **Real Time Immunization Monitoring System (RTIMS)**
  - Collaboration with Johns Hopkins University
  - Web-based prospective reporting

- **FluNet - Real-time Influenza Vaccine Surveillance using Text Messaging**
  - Collaboration between CDC and New York Presbyterian Hospital
  - Primary aim to assess feasibility of a text messaging-based, active vaccine surveillance network to detect seasonal/pandemic influenza vaccine-related adverse events in a timely fashion.

- **Both systems try to facilitate reporting to VAERS**
Focus on Vaccine Safety in Pregnant Women:
Maternal Adverse Event Assessment in VAERS

- Several studies are in progress

- VAERS limitations include usual limitations of this passive surveillance system and those specific for maternal surveillance:
  - No fields in VAERS form for identifying pregnant women
  - Low specificity of current search criteria for pregnancy reports
  - Reporting rates of adverse events difficult to calculate in pregnant women
Focus on Vaccine Safety in Pregnant Women: VAERS Pregnancy Studies

- Assessment of the safety of seasonal influenza vaccine in pregnant women, 1990 – 2009*
  - No unusual patterns of pregnancy complications or fetal outcomes were observed in reports of pregnant women after the administration of TIV or LAIV.

- Adverse Events following Administration to Pregnant Women of Influenza A (H1N1) 2009 Monovalent Vaccine
  - Review of reports to VAERS following H1N1 vaccination in pregnant women did not identify any concerning patterns of maternal or fetal outcomes

- Evaluation of the Safety of Tdap Vaccine Administered during Pregnancy
  - No safety concerns that may warrant further study were identified

- Enhanced Surveillance of Infant Outcomes in Pregnant Women following administration of H1N1 Live Vaccine
  - Study in progress

Vaccine Safety Datalink (VSD)

- A collaborative project among CDC and ten managed care organizations (MCOs)
- Data on >9 million persons (with a birth cohort of 95,000 annually)
- Computerized linked immunization and health care databases allow studies to be conducted rapidly and efficiently
- Allows for planned immunization safety studies as well as timely investigation of new safety signals
Selected VSD Findings

• VSD data reassured public confidence in vaccine safety
  – Safety of seasonal and H1N1 flu vaccines during 2009-10
  – No association between Hepatitis B vaccine and increased risk of multiple sclerosis or optic neuritis
  – No association between childhood vaccinations and type 1 diabetes mellitus
  – No association between thimerosal in vaccines and deficits in neuropsychological functioning or autism

• Detected or quantified risk
  – Intussusception following RotaShield®
  – Risk of anaphylaxis after vaccination
  – Risk of febrile seizures following MMRV vaccine
VSD Limitations

- Data not collected for research purposes
- Only detects health events that require health care
- Immunizations given outside the MCO may be missed
- Population may not be representative of general U.S. population
- Population size may not be adequate to rapidly evaluate very rare outcomes or outcomes in small sub-groups
VSD - New Initiatives

1. Population and data enhancements
2. Methods development
3. Safety of immunizations during pregnancy
4. Vaccine delayers/refusers/simultaneous vaccination
Population and data enhancements

- Increase size of population by adding health plans
  - 2 MCOs added this year
  - Pilot using claims database of large health insurer
  - *Coordinate with FDA PRISM system*

- Linkages with immunization registries
  - Capture immunizations (e.g., influenza) given outside MCO
  - 3 of 8 VSD sites were able to capture H1N1 immunization data electronically from state and local registries, and one site was able to capture the immunizations through a paper-based system
  - Remaining 4 sites encountered various obstacles (e.g., privacy and confidentiality laws, data quality concerns)
VSD - New Initiatives

Methods development

- Statistical methods (e.g., case-centered)
- Sequential testing
- Defining risk windows
  - Statistical methods to define empirically
  - Working group on \textit{a priori} definitions based on biological mechanisms (CISA collaboration)
VSD - New Initiatives

Safety of immunizations during pregnancy

- Pregnancy database development
  - Algorithm to link birth and maternal records
- Descriptive study of vaccinations occurring during pregnancy
- Several studies of safety of seasonal and 2009 H1N1 influenza vaccines during pregnancy
  - Local and systemic reactions
  - Complications of pregnancy
  - Spontaneous abortions
  - Other pregnancy outcomes
  - Birth outcomes
Simultaneous vaccination and safety of the immunization schedule

Some parents continue to have concerns about the safety of simultaneous vaccination

- Specific concerns that have not been substantiated by scientific research
- Ill defined worries (e.g., “too many, too soon”)
Summary of IOM Review of Multiple Immunizations and immune dysfunction

<table>
<thead>
<tr>
<th>Possible outcomes</th>
<th>Causality assessment</th>
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<tbody>
<tr>
<td>- autoimmunity (e.g., DM)</td>
<td>Reject</td>
</tr>
<tr>
<td>- increased infections</td>
<td>Reject</td>
</tr>
<tr>
<td>- allergy/asthma</td>
<td>Inadequate evidence</td>
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http://www.iom.edu/project.asp?id=4705
### Immunization Safety Office (ISO) Scientific Agenda: National Vaccine Advisory Committee (NVAC) recommendations

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<tr>
<th>RECOMMENDATION #7 (NVAC)</th>
<th>RESPONSE (ISO)</th>
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| NVAC added recommendation for an external expert committee, such as the Institute of Medicine, with broad methodological, design, and ethical expertise to consider strengths and weaknesses, ethical issues and feasibility including timelines and cost of various study designs to examine outcomes in unvaccinated, vaccine delayed and vaccinated children | - ISO and NVPO* are co-sponsoring such a review by IOM  
- Review process is just beginning |

*National Vaccine Program Office*
Parents who delay immunizations: A VSD feasibility study for evaluating safety

- **Background**
  - Unvaccinated children of parents who refused immunizations were 50% less likely to visit the clinic for an upper respiratory infection compared to fully immunized children.
  - Vaccine refusers had 12% fewer clinic visits than children who were up-to-date.

- **Studies on the safety of delayed schedules could be flawed if vaccine delayers and vaccine accepters have differential rates of healthcare utilization.**

- **VSD feasibility study**
  - Compare health utilization patterns of children on delayed vaccination schedules with children who receive on-time vaccinations
Current Example of Simultaneous Vaccination Safety Issue: Influenza Vaccine and Febrile Seizures

- New risk for febrile seizures identified in the 2010-11 season following influenza vaccination
  - Relative risk was substantially different from prior seasons
  - Upon review of seizure cases, concomitant vaccination with PCV13 was frequently noted
  - PCV13 vaccine became available for use in April 2010
Attributable Risk per 100,000, 12-23 mo

<table>
<thead>
<tr>
<th></th>
<th>PCV7*</th>
<th>TIV+PCV7*</th>
<th>TIV*</th>
<th>PCV13*</th>
<th>TIV + PCV13*</th>
<th>TIV*</th>
</tr>
</thead>
<tbody>
<tr>
<td>08/05 - 04/10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case(0-1)</td>
<td>36</td>
<td>16</td>
<td>13</td>
<td>11</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Doses</td>
<td>240,088</td>
<td>62,457</td>
<td>210,069</td>
<td>58,023</td>
<td>14,258</td>
<td>34,109</td>
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<td>05/10 - 01/11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case(14-20)</td>
<td>66</td>
<td>11</td>
<td>60</td>
<td>11</td>
<td>4</td>
<td>7</td>
</tr>
</tbody>
</table>

* +/- other non-TIV, non-PCV vaccines; assuming chart confirmation rate of 80%

Source: Grace Lee, ACIP 2/23/2011
## Concomitant Vaccines among Febrile Seizure Cases 6-23 months (N=20), 2010-11

<table>
<thead>
<tr>
<th>Vaccines given on same day</th>
<th>N = 20</th>
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<tbody>
<tr>
<td>TIV + PCV13 + MMR + HepA + Hib + DTaP</td>
<td>1</td>
</tr>
<tr>
<td>TIV + PCV13 + Hib + Rota + DTaP-HepB-IPV</td>
<td>3</td>
</tr>
<tr>
<td>TIV + PCV13 + MMR + Var + DTaP</td>
<td>2</td>
</tr>
<tr>
<td>TIV + PCV13 + MMR + Var + HepA</td>
<td>1</td>
</tr>
<tr>
<td>TIV + PCV13 + HepA + Var + DTaP</td>
<td>2</td>
</tr>
<tr>
<td>TIV + PCV13 + MMR + Hib + DTaP</td>
<td>1</td>
</tr>
<tr>
<td>TIV + MMR + Var + HepA + DTaP</td>
<td>2</td>
</tr>
<tr>
<td>TIV + PCV13 + HepA + Hib + DTaP</td>
<td>1</td>
</tr>
<tr>
<td>TIV + PCV13 + Hib + DTaP-HepB-IPV</td>
<td>1</td>
</tr>
<tr>
<td>TIV + PCV13 + Hib</td>
<td>1</td>
</tr>
<tr>
<td>TIV + PCV 13</td>
<td>2</td>
</tr>
<tr>
<td>TIV only</td>
<td>3</td>
</tr>
</tbody>
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Source: Grace Lee, ACIP 2/23/2011
Simultaneous Vaccinations and Febrile Seizures: Next steps in VSD

- Complete analysis of 2010-11 influenza vaccine +/- other concomitant vaccinations

- Design a study of the association between several vaccines and febrile seizures
  - Re-assess possible association of individual vaccines (e.g., DTaP) using revised risk windows
  - Assess possible associations with various concomitant vaccine combinations to the extent feasible
Acknowledgements

- Immunization Safety Office colleagues
  - Claudia Vellozzi
  - Karen Broder
  - Jerry Tokars

- Grace Lee, Harvard University