Vaccine Safety Monitoring and the CDC Immunization Safety Office

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Outline

- Background and overview of the Immunization Safety Office (ISO)
- ISO systems
  - Vaccine Adverse Event Reporting System (VAERS)
  - Vaccine Safety Datalink (VSD)
  - Clinical Immunization Safety Assessment (CISA) Project
- State Vaccine Safety Coordinator (VSC) program
- Example: febrile seizure signal detection and assessment
Background: Vaccine Safety Path

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

FDA licensure
- Vaccine is safe & effective
- Vaccine can be made safely

After licensure
- CDC* and FDA* conduct safety monitoring and studies

*Centers for Disease Control and Prevention; Food and Drug Administration
Definition of a signal in pharmacovigilance

“Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously.

Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.”

Why we monitor vaccine safety after licensure

- High safety standards expected for vaccines
  - Vaccinees 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
Primary HHS organizations engaged in vaccine safety activities

- Dept of Health and Human Services (HHS)
- National Vaccine Program Office (NVPO)
  - National Institutes of Health (NIH)
  - Food and Drug Admin (FDA)
  - Centers for Disease Control and Prevention (CDC)
  - Health Resources and Services Admin (HRSA)
  - NCEZID
  - DHQP
  - Immunization Safety Office (ISO)
Immunization Safety Office (ISO)

- VAERS Project and Response Team
- Vaccine Safety Datalink (VSD) Team
- Clinical Immunization Safety Assessment (CISA) Project Team
Immunization Safety Office (ISO) mission

To assess the safety of vaccines administered to children, adolescents and adults

- Comprehensive approach to vaccine safety includes
  - Surveillance to detect possible adverse events following vaccination in a timely way
  - Investigation of possible adverse events following vaccination to determine causality and risk factors
  - Development of strategies for prevention of adverse events following vaccination
  - Vaccine safety research
  - Timely communication and education to partners and the public

- Work with other Federal agencies and other organizations to further vaccine safety mission
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)
Selected ISO key activities

- Manage the VAERS contract/project
- Monitor newly recommended vaccines, new recommendations
- Monitor CDC priority vaccines
- Annual influenza vaccine monitoring
- Planned safety studies (VSD and CISA)
- Assess individual risk factors for AEs and clinical case reviews (CISA)
- Support ACIP data needs
- Pandemic influenza preparedness
- Public health response and response to inquiries
- Coordination with State health departments (State Vaccine Safety Coordinator program)
- Communication and education
## ISO’s post-licensure vaccine safety monitoring infrastructures

<table>
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<tr>
<th>System</th>
<th>Collaboration</th>
<th>Description</th>
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<tr>
<td>Vaccine Adverse Event Reporting System (VAERS)</td>
<td>CDC and FDA</td>
<td>US frontline spontaneous reporting system to detect potential vaccine safety problems</td>
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<tr>
<td>Vaccine Safety Datalink (VSD)</td>
<td>CDC and Healthcare Plans</td>
<td>Large linked database system used for active surveillance and research</td>
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<tr>
<td>Clinical Immunization Safety Assessment (CISA) Project</td>
<td>CDC and Academic Centers</td>
<td>Expert collaboration which conducts individual clinical vaccine safety assessments and clinical research</td>
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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

<table>
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<tr>
<th><strong>Strengths</strong></th>
<th><strong>Limitations</strong></th>
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<tr>
<td>National data; accepts reports from anyone</td>
<td>Reporting bias</td>
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<tr>
<td>Rapid signal detection; rare adverse events (AE)</td>
<td>Inconsistent data quality and completeness</td>
</tr>
<tr>
<td>Collects information about vaccine, characteristics of vaccinee, AE²</td>
<td>Generally cannot assess if vaccine caused an AE</td>
</tr>
<tr>
<td>Data available to public</td>
<td>Lack of unvaccinated comparison group</td>
</tr>
<tr>
<td></td>
<td>Pregnancy inconsistently reported</td>
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1. VAERS website: [http://vaers.hhs.gov](http://vaers.hhs.gov)
2. Some reports have no adverse event
Limitations of VAERS data

- VAERS only contains partial data on individual vaccinated with an AE (in pink cell; incomplete population data)
  - Not able to calculate rates of occurrence of adverse events
  - Not able to determine increased risk for adverse events
  - Not able to calculate vaccination coverage
Submitting a VAERS report

- Secure online submission (~30% of reports in recent years)
- Mailed written hardcopy of paper form
- Faxed hardcopy
- Via telephone through a VAERS customer service representative

- CDC is working with FDA on several initiatives to make enhancements to VAERS to facilitate electronic/online reporting
Vaccination error reporting guidance

The Vaccine Adverse Event Reporting System (VAERS) accepts all reports, including reports of vaccination errors. VAERS is primarily concerned with monitoring adverse health events and we encourage reporting of clinically significant adverse health events following vaccination. Using clinical judgment, healthcare professionals can decide whether or not to report a medical error at their own discretion. For example, a healthcare professional may elect to report vaccination errors that do not have an associated adverse health event, especially if they think the vaccination error may pose a safety risk (e.g., administering a live vaccine to an immunocompromised patient) or that the error would be preventable with public health action or education.

https://vaers.hhs.gov/esub/index
**VAERS report form**

- Information about patient, provider and reporter demographics, AEs, vaccines, preexisting conditions
- Other information: date vaccinated, vaccine type, lot number, dose number
- Reports with incomplete information accepted
- All reports accepted without judgment on causality
- Should report as soon as possible, but no time limit on reporting

*Online reporting form has same fields in a different presentation*
VAERS follow-up

- VAERS staff follow up with health care providers on serious reports and certain selected reports of interest by phone to obtain
  - Medical records
  - Autopsy reports
- Medical officers review these medical records and VAERS reports
- Letter sent to reporters to check recovery status for all serious reports with “no” or “unknown” recovery listed on initial VAERS form at 60 days and 1 year

VAERS form Box 8 – Serious status

- Patient died (date mm/dd/yy)
- Life threatening illness
- Required emergency room/doctor visit
- Required hospitalization (_________ days)
- Resulted in prolongation of hospitalization
- Resulted in permanent disability
- None of the above
Empirical Bayesian data mining in VAERS

- Empirical Bayesian data mining is used by FDA to detect disproportional reporting in the VAERS database
- A vaccine-adverse event pairing “signals” when a statistical threshold is reached (referred to as a data mining finding)
- A data mining finding does NOT demonstrate the vaccine is associated with increased risk for the adverse event or that a new safety problem exists
  - Some findings may be due to biases in reporting or to chance or other factors not related to an actual safety problem
  - Some adverse events are known, expected and accepted side effects (e.g., runny nose after live attenuated influenza vaccine)
- Data mining findings may prompt further assessment to evaluate association
Vaccine Injury Compensation Program*

- The Vaccine Injury Compensation Program (VICP) is administered by the Health Resources and Services Administration (HRSA)
- VICP is a no-fault alternative to the traditional tort system for resolving vaccine injury claims that provides compensation to people found to be injured by certain vaccines
- VICP is separate from the VAERS program and reporting an event to VAERS does not constitute filing a claim for compensation to the VICP
- Persons wishing to file a claim for compensation need to use the VICP process ([http://www.hrsa.gov/vaccinecompensation/fileclaim.html](http://www.hrsa.gov/vaccinecompensation/fileclaim.html))

*http://www.hrsa.gov/vaccinecompensation/index.html
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

Data on over 9 million persons per year (~3% of US pop)

- Annual birth cohort = 100k
VSD methodology examples

- **Traditional epidemiologic methods**
  - Descriptive epidemiology, case series, cohort study, case-control study

- **Rapid Cycle Analysis (RCA)**
  - Developed to provide weekly near real-time assessment of the safety of newly licensed vaccines or change in recommendations for current vaccines
  - Adverse events being monitored are pre-specified
  - Adverse events can also be added if a signal for an event (not already pre-specified) is identified from another system
  - Findings of association using RCA are considered safety signals and further refinement of the analysis needs to occur once a signal is identified
What happens when an RCA signal occurs?

- Rapid cycle analysis methods detect signals – values above specified statistical thresholds
- Not all signals represent a true increase in risk
- When a signal occurs, we conduct a series of evaluations using traditional epidemiologic methods
How we evaluate RCA signals

1. Check data quality
2. Check inputs, background incidences, i.e. temporal trends
3. Check whether comparison groups are defined appropriately
4. Conduct the analysis using a different control group (e.g., concurrent vs. historical) or different vaccine
5. Conduct a temporal scan to see if outcomes cluster during a post-vaccination time window
6. Conduct a definitive study using logistic regression analysis
7. Review charts to confirm or exclude cases as true cases
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**

**Strengths**
- Can implement prospective, multi-site clinical studies (hundreds of subjects)
- Expertise in vaccine safety and many clinical areas
- Access to special populations receiving vaccines
- Detailed clinical/data on patients
- Can collect biological specimens
- Ability to recruit controls

**Limitations**
- Sample size limited to study rare adverse events
- Potential challenges to recruit and retain subjects
- May not have access to vaccine records for vaccines given outside site
- Potential for lack of geographic or race/ethnicity diversity
- Clinical studies may be labor and resource-intensive
CISA evaluation for patient vaccine safety questions

- Healthcare provider email requests accepted at CISAeval@cdc.gov
- Providers notified within 1-2 weeks if case will be reviewed
- Whether a case is accepted for a CISA consultation or not, it is recommended that provider submit a report to VAERS
CISA Project sites and principal investigators (PI)

- **Boston Medical Center, MA**
  - PI: Colin D. Marchant, MD

- **Cincinnati Children's Hospital Medical Center, OH**
  - PI: Steven Black, MD

- **Columbia University, NY**
  - PI: Dr. Anne Gershon, MD and Philip LaRussa, MD

- **Duke Clinical Research Institute, Duke University, NC**
  - PI: Emmanuel “Chip” Walter, MD, MPH

- **Johns Hopkins University, MD**
  - PI: Neal Halsey MD

- **Kaiser Permanente Northern California (KPNC), CA**
  - PI: Roger Baxter, MD and Nicola Klein, MD, PhD

- **Vanderbilt Medical Center, TN**
  - PI: Kathryn M. Edwards, MD
Vaccine Safety Coordinator (VSC) Program

- Established in 2008
- Collaboration between CDC’s Immunization Safety Office and health departments
- VSCs are public health officials at Project Area* health departments and serve as vaccine safety liaisons as part of their duty
  - Most VSC reside in the immunization program
  - Many VSCs double as Immunization Program Manager and/or VAERS Coordinator

*The 62 CDC Public Health Emergency Preparedness Project Areas include the 50 US states, 4 major metropolitan areas (New York City, Chicago, Washington DC and Los Angeles County) and 8 US territories and freely associated island nations
Vaccine Safety Coordinator (VSC) program

- **Background/purpose**
  - Establish a Project Area health department vaccine safety point of contact (POC) in each of the 62 PHEP Project Areas
  - Facilitate effective pandemic influenza and emergency preparedness planning and response
  - Serve as CDC’s main POC for vaccine safety matters and as a liaison between the Immunization Safety Office/CDC and health department staff/leadership (routine ops and emergency response)
  - Serve as the health department POC and liaison on vaccine safety matters for local HDs, providers, and other partners
  - Serve as the “eyes and ears” for CDC on vaccine safety issues in the Project Area and coordinate with CDC on incident response
Vaccine Safety Coordinator (VSC) program

H1N1 Vaccine Safety Response

- During the H1N1 response, VSC duties included but were not limited to
  - Outreach and education to partners involved in vaccine safety monitoring (local health departments, hospitals/clinics, providers)
  - Establishing collaborations with other state and local health officials involved in the vaccination program
  - Frequent liaising with ISO staff to facilitate adequate exchange of information, prompt response to vaccine safety emergencies, and optimal risk communication
When to consider contacting CDC about vaccine adverse event reports

- Vaccine Safety Coordinators, Immunization Program Managers and other health department staff are welcome to contact CDC at any time about vaccine safety issues.

- Consider contacting CDC about:
  - Unusual or unexpected vaccine AE reports (e.g., death in a previously healthy child or young person, unusual neurologic symptoms)
  - Clusters of AEs (e.g., allergic reactions following vaccination at a single setting with a specific brand/lot of vaccine)
  - Events that may impact public confidence in vaccination programs
  - AE reports that may generate an increased level of media attention
  - When health departments want CDC laboratory and/or pathology support
  - When high ranking state/local health officials request an investigation

- CDC scientists and communications specialists may be able to provide technical support and assist in coordinating the response.
Febrile seizures following TIV, PCV13 and other childhood vaccinations:

Signal detection and assessment
Febrile seizures in young children following TIV and PCV13 (background/key events)

2010-11
- VAERS data mining signal for Fluzone; clinically relevant age group was in children 6-23 mo.*
- VSD Rapid Cycle Analysis (RCA) signal for TIV in children 6-59 mo.
- VSD TIV-PCV13 febrile seizure study**
  - Attributable risk for concomitant TIV+PCV13 peaked at 16 mo. with 45 additional febrile seizures per 100,000 children vaccinated

2011-12
- VSD RCA signal for TIV persisted (same formulation as 2010-11)
- Clinical Immunization Safety Assessment (CISA) Project TIV-PCV13 fever study***
  - Children 6-23 mo. who received TIV and PCV13 together at the same visit were about 3 times as likely to have a fever on days 0-1 compared with children who received TIV or PCV13 without the other product

2012-13
- No VSD RCA signal for TIV (formulation change(s) from 2010-11)

2013-14

Febrile seizures in young children following TIV and PCV13 (background/key events)

- Signal for febrile seizures following CSL TIV in Australia occurred during the 2010 Southern Hemisphere influenza season, which precedes the US influenza season.
- CDC and FDA routinely monitor for febrile seizures following TIV and were alerted to conduct enhanced monitoring in 2010-11 by the Australian experience.

Attributable risk estimates for febrile seizures following 1st dose TIV, 2010-11


*Vaccines may have been received concomitantly with non-TIV, non-PCV13 vaccines
Febrile Seizures in Children Following Vaccination with Influenza Vaccines and Pneumococcal Vaccines — 2010-2011 Influenza Season

During the 2010-2011 influenza season, there was enhanced focus on monitoring for febrile seizures after influenza (flu) vaccine in the United States because in Australia, during the 2010 Southern Hemisphere influenza season, one type of Australian influenza vaccine was associated with an increase in febrile seizures in young children.

CDC studied the healthcare visit records of more than 200,000 vaccinated children 6 months through 4 years of age through its Vaccine Safety Datalink project during the entire 2010-2011 influenza season. The analyses found that febrile seizures following inactivated influenza and PCV13 vaccines given to this age group did occur. The febrile seizures were most common in children ages 12 through 23 months when the two vaccines were given during the same healthcare visit. In this group, about one additional febrile seizure occurred among every 2,000 to 3,000 children vaccinated. The risk observed in U.S. children was considerably lower than that observed in Australia.

CDC, FDA, and the Advisory Committee on Immunization Practices (ACIP), reviewed vaccine safety data on febrile seizures in the United States following 2010-2011 inactivated influenza and pneumococcal conjugate (PCV 13) vaccines. After thoroughly evaluating the available information, CDC determined that no changes in the childhood immunization schedule were necessary.

Continued monitoring during the 2011-2012 influenza season detected increased febrile seizures following vaccination with inactivated influenza vaccine in young children, similar to the 2010-2011 influenza season.
Language added to the inactivated influenza vaccine
Vaccine Information Statement (VIS) following the CDC, FDA and ACIP review of the 2010-11 data*

**Moderate problems** following inactivated flu vaccine:

- Young children who get inactivated flu vaccine and pneumococcal vaccine (PCV13) at the same time may be at increased risk for seizures caused by fever. Ask your doctor for more information. Tell your doctor if a child who is getting flu vaccine has ever had a seizure.

[http://www.cdc.gov/vaccines/hcp/vis/vis-statements/flu.html](http://www.cdc.gov/vaccines/hcp/vis/vis-statements/flu.html)
Febrile seizures in young children following TIV and PCV13

- Questions to follow-up on from the 2010-11 febrile seizure signal
  - Did other vaccines besides TIV and PCV13 play any role?
  - Was there something unusual about the 2010-11 influenza vaccine that resulted in the increased risk for febrile seizures in young children?
    - What do the data prior to the 2010-11 influenza season show?

- ISO response was to conduct a multi-year study in VSD to assess all vaccines/combinations of vaccines, and their relationship to febrile seizures (results presented to ACIP on June 25, 2014)
### Attributable Risk (AR) Estimates for Combinations of Three Vaccines: TIV, PCV, DTaP-containing

<table>
<thead>
<tr>
<th>Vaccine(s) Received</th>
<th>IRR (95% CI)</th>
<th>AR* at 6 months</th>
<th>AR* at 12 months</th>
<th>AR* at 15 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 TIV</td>
<td>0.5 (0.2 – 1.0)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>2 PCV</td>
<td>1.8 (0.97 – 3.4)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>3 DTaP-containing</td>
<td>1 (0.5 – 2.3)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>4 PCV DTaP-containing</td>
<td>2.3 (1.4 – 3.8)</td>
<td>3</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>5 TIV DTaP-containing</td>
<td>3.5 (1.5 – 8.1)</td>
<td>6</td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td>6 TIV PCV</td>
<td>3.5 (1.1 – 11)</td>
<td>6</td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td>7 TIV PCV DTaP-containing</td>
<td>5 (2.5 – 9.9)</td>
<td>10</td>
<td>24</td>
<td>38</td>
</tr>
</tbody>
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* per 100,000 persons vaccinated.
- n/a: AR not calculated when IRR is not statistically significant.

Summary of updated VSD study

- The weight of the evidence and the consistency of the findings from the VSD analysis over several seasons suggest that:
  - When TIV is given alone, risk of febrile seizure is not increased
  - When TIV is given with PCV and/or DTaP, however, risk of febrile seizure is increased
  - Highest risk is when TIV + PCV + DTaP given together at 15 months of age
    - Attributable risk = 38 additional febrile seizures per 100,000 children vaccinated
    - Similar to febrile seizure risk seen with measles-mumps-rubella (MMR) vaccine

Simultaneous administration of TIV with PCV and/or DTaP vaccines appears to be associated with an increased risk for febrile seizures in young children.

This increased risk is transient (the day of to the day after vaccination [days 0-1]).

Although frightening for parents and caregivers, febrile seizures do not have lasting effects.

Getting recommended childhood vaccines during a single healthcare visit has important benefits:

- On-time vaccinations keep children protected against many infectious diseases, and providing multiple vaccinations in a healthcare visit minimizes the number of healthcare visits that parents, caregivers, and children must make.
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For more information please contact Centers for Disease Control and Prevention
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E-mail: cdcinfo@cdc.gov  Web: www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
Study Designs

- Self controlled design

- Current vs. historical

![Diagram showing study designs with vaccine risk windows and comparison windows.]

Days 0 1 14 15
Risk window

Vaccine

Days 0 1
Risk window

Vaccine (current)

Days 0 1
Risk window

Vaccine (historical)