Vaccine Safety and Research

Allison Naleway, PhD
Stephanie Irving, MHS
Holly Groom, MPH

Center for Health Research
Kaiser Permanente

August 13, 2019
Overview

• Introduction to vaccine safety in the United States

• Overview of vaccine safety post-licensure programs
  • Vaccine Adverse Event Reporting System (VAERS)
  • Vaccine Safety Datalink (VSD)
  • Vaccine Injury Compensation Program (VICP)

• Challenges and discussion
Why study vaccine safety?

• Responsibility to identify and minimize risks; Vaccine Injury Act 1986

• Vaccination universally recommended or mandated

• Usually healthy people vaccinated (trials)
  • Pregnant women precluded

• Perceived risk of VAE > VPD

• WHO inclusion of vaccine hesitancy as a leading public health threat
Bonhoeffer, et al. 2002. The Brighton Collaboration: addressing the need for standardized case definitions of adverse events following immunization (AEFI)
Vaccine Clinical Trials

**Phase 1**
- 20-100 healthy volunteers
- Is this vaccine safe?
- Does this vaccine seem to work?
- Are there any serious side effects?
- How is the size of the dose related to side effects?

**Phase 2**
- Several hundred volunteers
- What are the most common short-term side effects?
- How are the volunteers’ immune systems responding to the vaccine?

**Phase 3**
- Hundreds or thousands of volunteers
- How do people who get the vaccine and people who do not get the vaccine compare?
- Is the vaccine safe?
- Is the vaccine effective?
- What are the most common side effects?
Vaccine Clinical Trials

**PHASE 1**
- 20-100 healthy volunteers
- Is this vaccine safe?
- Does this vaccine seem to work?
- Are there any serious side effects?
- How is the size of the dose related to side effects?

**PHASE 2**
- Several hundred volunteers
- What are the most common short-term side effects?
- How are the volunteers’ immune systems responding to the vaccine?

**PHASE 3**
- Hundreds or thousands of volunteers
- How do people who get the vaccine and people who do not get the vaccine compare?
- Is the vaccine safe?
- Is the vaccine effective?
- What are the most common side effects?
Vaccine Clinical Trials

• Strengths
  • Close, detailed follow-up
  • Requirement to provide data on common adverse reactions
  • Randomized, controlled designs

• Limitations
  • Not able to provide data on rare reactions, reactions with delayed onset, or reactions in subpopulations (premature infants, pregnant women, immunocompromised)
  • Non-standardized case definitions for adverse events
VAERS

Vaccine Adverse Event Reporting System

FDA/CDC collaboration since 1990

Reports of suspected vaccine adverse events from physicians, vaccine manufacturers, patients, etc.

Approximately 50,000 reports/year

Web-based reporting and public access to data (www.vaers.hhs.gov)
Have you had a reaction following a vaccination?

1. Contact your healthcare provider.
2. Report an Adverse Event using the VAERS online form or the new downloadable PDF. New!

Important: If you are experiencing a medical emergency, seek immediate assistance from a healthcare provider or call 9-1-1. CDC and FDA do not provide individual medical treatment, advice, or diagnosis. If you need individual medical or health care advice, consult a qualified healthcare provider.

¿Ha tenido una reacción después de recibir una vacuna?

1. Contacte a su proveedor de salud.
2. Reporte una reacción adversa utilizando el formulario de VAERS en línea o la nueva versión PDF descargable. Nuevo!
Report an Adverse Event

Online reporting is strongly encouraged. Please report clinically important adverse events that occur after vaccination of adults and children, even if you are not sure whether the vaccine caused the adverse event.

The Vaccine Adverse Event Reporting System (VAERS) accepts all reports, including reports of vaccination errors. Guidance on reporting vaccination errors is available if you have additional questions.

Knowingly filing a false VAERS report is a violation of Federal law (18 U.S. Code § 1001) punishable by fine and imprisonment.

Two Ways to Submit an Online Report to VAERS

Option 1 - Report Online to VAERS (Preferred)
Submit a VAERS report online. The report must be completed online and submitted in one sitting and cannot be saved and returned to at a later time. Your information will be erased if you are inactive for 20 minutes; you will receive a warning after 15 minutes.

Option 2 - Report using a Writable PDF Form
Download the Writable PDF Form to a computer. Complete the VAERS report offline if you do not have time to complete it all at once. Return to this page to upload the completed Writable PDF form by clicking here.

Checklist

What will I need to fill out the report?

- Patient information (age, date of birth, sex)
- Vaccine information (brand name, dosage)
- Date, time, and location administered
- Date and time when adverse event(s) started
- Symptoms and outcome of the adverse event(s)
- Medical tests and laboratory results (if applicable)
- Physician’s contact information (if applicable)
Information for Healthcare Providers

Safety monitoring in VAERS relies on receiving reports of vaccine adverse events from healthcare professionals. The following information provides guidance to healthcare professionals about how to submit accurate, complete and timely VAERS reports.

Guidance on Reportable Events

The National Childhood Vaccine Injury Act (NCVIA) requires healthcare providers to report:

- Any adverse event listed by the vaccine manufacturer as a contraindication to further doses of the vaccine; or
- Any adverse event listed in the VAERS Table of Reportable Events Following Vaccination [PDF - 75KB] that occurs within the specified time period after vaccination.

In addition, CDC encourages you to report any clinically significant adverse event that occurs in a patient following a vaccination, even if you are unsure whether a vaccine caused the event.

Follow-up Requests from VAERS

It is very important that VAERS reports are filled out as completely and as accurately as possible. If the CDC and FDA need additional information, you might be contacted by VAERS staff. These cases are usually serious adverse health events that require additional information, such as medical records, that will be helpful in better understanding the adverse event. Be sure to include the E-number or VAERS identification number when you send information back to VAERS. All records received by VAERS are kept confidential as required by law. (We do not recommend you send records by e-mail because email is not considered secure.) The patient’s consent is not required to release medical records to VAERS. Under the Health Insurance Portability and Accountability Act of 1996 (HIPAA), VAERS is considered part of a public health activity, and CDC and FDA are public health authorities collecting this data, thus individual authorization is not necessary before releasing information. If you have questions about how the HIPAA applies to VAERS, please visit the VAERS Privacy Policies and Disclaimers section.
VAERS: Data Flow

- Healthcare professionals
- Patients
- Parents and caregivers
- Vaccine manufacturers
- Others

VAERS downloadable data sets
(www.vaers.hhs.gov/data/index)

Posting of public VAERS data
(sensitive patient information removed)

CDC WONDER® VAERS database
(http://wonder.cdc.gov/vaers.html)

Data transmission to CDC and FDA

Report processing, MedDRA®
coding, data entry, quality
control, follow-up to obtain
health records, etc.
VAERS: Strengths and Limitations

Strengths

• National
• Timely and accessible
• Relatively inexpensive
• Generation of hypotheses/“signals”

Limitations

• Underreporting or biased reporting (timing, publicity, etc.)
• Mix of causal and coincidental events
• Inadequate reported data
• Lack of denominator or control group
• Not able to address causality or test hypotheses
VSD
Vaccine Safety Datalink

A collaborative project between CDC and 8 US health systems

Established in 1990

Allows for planned, post-licensure vaccine safety studies

Informs ACIP & national immunization policy
Analytic Approaches

• Identify adverse event outcomes in electronic health records
  • Relies on ICD diagnosis and codes (outpatient or inpatient)

• In-depth studies with medical record review
  • Validate vaccination history and outcomes data
    • Clinical adjudicators for chart review
    • Collect additional risk factor data, medication use

• Study designs
  • Cohort, case-control, self-controlled case series
VSD Studies

• Over 300 VSD-led publications
• Vast majority lead to null findings

• Study types
  • CDC priorities (Rapid Cycle Analysis)
  • Workgroup priorities
    • Pregnancy, Immune-compromised, Vaccine Schedule
  • Other priorities
    • Site-specific interest/expertise
    • Public concerns
Strengths of VSD

• Large sample size
• Geographic diversity
• Access to electronic health records
• Most participating sites have bidirectional exchange with state IIS
• Relatively quick and timely
• Longstanding; sites have great expertise
Limitations of VSD

• Dynamic cohorts – loss to follow up
• Expensive compared to passive surveillance
• Not large or diverse enough for some hypotheses
• Difficult to study potential VAEs with delayed or insidious onset
• Health plan members generally well-vaccinated so can be difficult to find controls
VSD Findings and Impact
• Rotavirus vaccine licensed by FDA in 1998 (RotaShield)
• In trials, intussusception noted, but not statistically significant
• Sep 1998-July 1999: 15 cases reported to VAERS
• Multistate case-control study and VSD cohort study launched (increased risk of 1-2/10,000)
• Results consistent with increase in cases identified; led to withdrawal of vaccine
VSD study identified increased risk of febrile seizure following MMRV vaccine, leading to change in wording of ACIP recommendation.

Alison Tse, Hung Fu Tseng, Sharon K. Greene, Claudia Vellozzi, Grace M. Lee, On behalf of the VSD Rapid Cycle Analysis Influenza Working Group
VSD Response to Public Concerns
Example: Safety of the immunization schedule

White Paper on studying the safety of the childhood immunization schedule in the Vaccine Safety Datalink

Jason M. Glanz, Sophia R. Newcomer, Michael L. Jackson, Saad B. Omer, Robert A. Bednarczyk, Jo Ann Shoup, Frank DeStefano, Matthew F. Daley

Assessing misclassification of vaccination status: Implications for studies of the safety of the childhood immunization schedule

Matthew F. Daley, Jason M. Glanz, Sophia R. Newcomer, Michael L. Jackson, Holly C. Groom, Marlene M. Lugg, Huong Q. McLean, Nicola P. Klein, Eric S. Weintraub, Michael M. McNeil
Example: Aluminum exposure
Example: Impact of vaccination on the immune system

JAMA | Original Investigation

Association Between Estimated Cumulative Vaccine Antigen Exposure Through the First 23 Months of Life and Non-Vaccine-Targeted Infections From 24 Through 47 Months of Age

Jason M. Glanz, PhD; Sophia R. Newcomer, MPH; Matthew F. Daley, MD; Frank DeStefano, MD, MPH; Holly C. Groom, MPH; Michael L. Jackson, PhD; Bruno J. Lewin, MD; Natalie L. McCarthy, MPH; David L. McClure, PhD; Komal J. Narwaney, MPH, PhD; James D. Nordin, MD, MPH; Ousseny Zerbo, PhD
**Example:** HPV vaccine and fertility

---

**Primary Ovarian Insufficiency and Adolescent Vaccination**

Allison L. Nalway, PhD,² Kathleen F. Mittendorf, PhD,² Stephanie A. Irving, MHS,² Michelle L. Henninger, PhD,² Bradley Crane, MS,² Ning Smith, PhD,² Matthew F. Daley, MD,², c Julianne Gee, MPH²

**BACKGROUND:** Published case series have suggested a potential association between human papillomavirus (HPV) vaccination and primary ovarian insufficiency (POI). We describe POI incidence and estimate POI risk after HPV; tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, adsorbed (Tdap); inactivated influenza (II); and meningococcal conjugate (MenACWY) vaccination.

**METHODS:** We searched Kaiser Permanente Northwest electronic health records for outpatient diagnoses suggestive of POI in female patients aged 11 to 34 years between 2006 and 2014. We reviewed and adjudicated the medical record to confirm diagnoses and estimate symptom onset dates. We excluded cases with known causes and calculated the incidence of idiopathic POI. We estimated risk by calculating hazard ratios and 95% confidence intervals (CIs).
Ongoing VSD Work

• Public health impact of the resurgence of vaccine-preventable diseases (pertussis, measles, mumps)
• Safety of combined/multiple vaccinations
• Vaccine safety within sub-populations: immunosuppressed, premature babies, pregnant women, malnourished
• Development of international surveillance systems and case definitions
• Incorporation of Immunization Information System (IIS) data
• HPV vaccine and autoimmune disease
• Safety profiles of new(er) vaccines: meningococcal B, 9-valent HPV, Shingrix
VSD, in Summary

• VSD plays a critical role in continuously monitoring post-licensure safety of vaccines
  • Successfully identifies even rare events

• Most studies lead to null findings; adverse events not detected

• Some studies conducted in response to public concerns

• More attention needed on how to improve messaging related to safety studies

VSD Publication Database:
https://www.cdc.gov/vaccinesafety/ensuring safety/monitoring/vsd/publications.html
VICTP
Vaccine Injury Compensation Program

- Response to manufacturers withdrawing from vaccine production
- Promotes vaccines as a public good
- Responsive to those who believe they’ve been injured
- Legal fees covered to ensure equitable access
Vaccine Injury Compensation Program

• 11 MDs from DHHS review cases and recommend either compensation or vaccine court

• Use of Vaccine Injury Table
  • “Presumed to be caused by vaccine, if no other cause is found”

• Most vaccines include the following AE as covered conditions/injuries:
  • Shoulder injury (2015)
  • Vasovagal syncope
  • Anaphylaxis
  • Included conditions based on scientific evidence (2012 IOM report); public meetings to discuss expansion of table

VICP Petitions, 1988-2019

20,728 petitions filed

17,923 adjudicated

6,597 (37%) compensated

11,326 (63%) dismissed

$4.1 billion total compensation payments

VICP Dispositions, by Year

Dispositions by Vaccine Type, 2006-2017
Influenza Vaccine-related Dispositions, 1988-2019
VICP, in Summary

• Vaccine Injury compensations are not determinations of causality

• Relative to the number of vaccine doses being administered, petitions are very uncommon

From 2006-2017:

• 70% of adjudicated petitions were a result of a “negotiated” settlement

• 1 petition compensated per 1 million distributed doses of vaccine
Take Home Message

Vaccine safety is being regularly monitored using appropriate and rigorous methodologies.
Challenges

• Efforts to be responsive to public concerns (e.g., publishing VAERS and compensation data) have sometimes resulted in mis-use or mis-interpretation of data

• Ongoing (and concerning) challenges around how to effectively communicate that vaccines are safe
Questions and Discussion

Allison.Naleway@kpchr.org
Stephanie.A.Irving@kpchr.org
Holly.C.Groom@kpchr.org

https://research.kpchr.org/