Vaccine Safety Monitoring Systems and Methods

October 2019 Advisory Committee on Immunization Practices (ACIP) meeting

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Immunization Safety Office
Centers for Disease Control and Prevention (CDC)

October 23, 2019
Overview

- Describe CDC vaccine safety monitoring systems
- HPV vaccine safety monitoring as a case study
- Broader national and international vaccine safety monitoring and research efforts
CDC Vaccine Safety Monitoring Systems
Safety is Part of Every Vaccine
Primary HHS organizations engaged in vaccine safety activities

- National Institutes of Health (NIH)
- Food and Drug Admin (FDA)
- Centers for Disease Control and Prevention (CDC)
- Health Resources and Services Admin (HRSA)

Other agencies and groups:
- DoD
- DVA
- IHS
- Manufacturers

Advisory Committees:
- NVAC
- ACIP
- VRBPAC
- ACCV

Immunization Safety Office (ISO)
CDC vaccine safety monitoring

1 office

VAERS Vaccine Adverse Event Reporting System
CISA Clinical Immunization Safety Assessment Project
VSD Vaccine Safety Datalink

Communication and response to inquiries is cross-cutting function
Two Ways to Report

1. **PDF Form**
   - Information about patient, healthcare provider and reporter, AEs, vaccines, preexisting medical conditions
   - Other information: date vaccinated, AE onset date, vaccine type, lot number, dose number
   - Anyone can submit a report
   - All reports accepted without judgment on causality
   - CDC encourages reporting as soon as possible, but no time limit on reporting

Direct link to PDF: [https://vaers.hhs.gov/pdf/VAERSForm_Aug2019.pdf](https://vaers.hhs.gov/pdf/VAERSForm_Aug2019.pdf)
Two Ways to Report

2. **Online Form**  
   - *preferred method*
   - Same fields as PDF form
   - Step-by-step visual guidance
   - Security and convenience

Direct link to online report form: https://vaers.hhs.gov/esub/index.jsp
Adverse events in the context of vaccine doses distributed for use in the United States

164.3 million non-flu vaccines* distributed (2017)
- 29,937 AE reports to VAERS
  - 1 report for every 5,488 doses distributed

159.1 million flu vaccines distributed (2018-19 season)
- 11,138 AE reports to VAERS
  - 1 report for every 14,284 doses distributed

*DT, DTaP, DTaP-Hep B – IPV, DTaP-HIB, DTaP-IPV-HIB, DTaP-IPV, DTP, DTP-HIB, EIPV, HEP A (Ped), HEP A (Adult), HEP AB, Hep B (Adult), Hep B (Ped), HEPB-HIB, Hib, HPV, MCV4, Measles, MenB, MENING (MPSV4), MMR, MMRV, Mumps, Pertussis, PPV23 (PNEUMO), PCV7, PCV 13, Rota, Rubella, Td, Tdap, TETANUS, Varicella, Zoster
VAERS monitoring: methods

- Signs, symptoms, and diagnoses coded using Medical Dictionary for Regulatory Activities (MedDRA) terms
- Clinical review of reports (includes medical records when available):
  - All serious\(^1\) reports
  - Selected conditions of special interest
- Trends and patterns of reports
- Reporting rates
- Empirical Bayesian data mining to detect disproportional reporting for vaccine-adverse event pairings

\(^1\)Based on the Code of Federal Regulations if one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization, permanent disability, congenital anomaly or birth defect (FDA routinely reviews all serious reports)
Vaccine Adverse Event Reporting System (VAERS)

**Strengths**
- National data
- Accepts reports from anyone
- Rapidly detects safety signals
- Can detect rare adverse events
- Data available to public

**Limitations**
- Reporting bias
- Inconsistent data quality and completeness
- Lack of unvaccinated comparison group
- Generally cannot assess causality

- As a hypothesis generating system, VAERS identifies potential vaccine safety concerns that can be studied in more robust data systems
VSD

Vaccine Safety Datalink

8 participating integrated healthcare organizations
Vaccine Safety Datalink (VSD)

- Established in 1990
- Collaboration between CDC and several integrated healthcare organizations
- Medical care and demographic data on over 12 million persons per year
- Links vaccination data to health outcome data
- Used for surveillance and research
VSD electronic files + chart review

Linked by study IDs

Enrollment and demographics
Birth and death certificate information & family linkage
Procedure codes
Hospital discharge diagnosis codes
Immunization records
Outpatient and clinic visits
Emergency room visits

Images created by Wilson Joseph, Megan Mitchell, Ananth, and Iga from the noun project
VSD methods

- Traditional epidemiologic studies
  - Descriptive analyses (e.g., background rates, vaccination coverage)
  - Cohort
  - Case-control
  - Self-control
- Tree-temporal scan data mining
- Rapid Cycle Analysis (RCA) for near real-time monitoring
Rapid Cycle Analysis (RCA) in VSD

A powerful surveillance tool

- Near real-time vaccine-safety monitoring (using sequential monitoring techniques)
- Employs an automated analysis of ICD-coded diagnoses from administrative data

**Design to detect statistical signals** (values above specified statistical thresholds)

- When a statistical signal occurs, CDC conducts a series of further evaluations, including traditional epidemiologic methods
- Chart-confirmation of diagnoses to confirm or exclude cases as true incident cases is a key part of statistical signal assessment

Not all statistical signals represent a true increase in risk for an adverse event
Vaccine safety monitoring

CISA
Clinical Immunization Safety Assessment

7 participating medical research centers*

- assist U.S. healthcare providers with complex vaccine safety questions about their patients
  CISAeval@cdc.gov†
- conduct clinical research

†More information about clinical consults available at http://www.cdc.gov/vaccinesafety/Activities/CISA.html

*Boston Medical Center, MA; Cincinnati Children’s Hospital Medical Center, OH; Columbia University, NY; Duke University, NC; Johns Hopkins University, MD; Kaiser Permanente Northern California, CA; Vanderbilt University TN
Case study of HPV vaccine safety
Timeline of CDC/ISO HPV vaccine safety monitoring and selected publications

Safety Monitoring

*VAERS 4vHPV safety surveillance, *JAMA*

VSD 4vHPV RCA

VAERS 4vHPV *

June 2006

2009

2011

2012

2013

2014

2015

2016

2017

2018

2019

2020

Reported AEs following 4vHPV, *J Womens Health*

-VAERS 4vHPV

RCA 4vHPV, *Vaccine*

VSD 9vHPV RCA

VAERS 9vHPV

Safety Studies

-HPV vaccine and CRPS, *Ebiomed*

-VTE and 4vHPV, *Vaccine*

-4vHPV and non-manufacturer pregnancy reports, *Vaccine*

-VSD 4vHPV

-VSD 9vHPV

-VTE


- Vaccination and 30-day mortality *Pediatrics*

- Maternal and infant outcomes after HPV vaccine, *Obset Gynecol*

- GBS and 4vHPV, *Vaccine*

- POTS and HPV in VAERS, *J Adol Health*

- Spontaneous abortion after inadvertent HPV vaccination, *Obset Gynecol*

- VAERS 4vHPV safety surveillance, *Vaccine*

- VAERS 2vHPV safety surveillance, *Br J Clin Pharm*

- POI and adolescent vac *Pediatrics*

- Type 1 diabetes and HPV vaccine, *Vaccine*

- Safety of 9vHPV among pregnant women in VAERS, *Vaccine*
Monitoring a recent vaccine: 9vHPV in VAERS and VSD
# Top 10 reported signs and symptoms after 9vHPV in VAERS, Dec 2014-Dec 2017

<table>
<thead>
<tr>
<th>Non-serious (n=7,058)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>529 (7)</td>
</tr>
<tr>
<td>Syncope</td>
<td>488 (7)</td>
</tr>
<tr>
<td>Headache</td>
<td>355 (5)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>316 (4)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>314 (4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>313 (4)</td>
</tr>
<tr>
<td>Pyrexia (fever)</td>
<td>283 (4)</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>273 (4)</td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>266 (4)</td>
</tr>
<tr>
<td>Pallor</td>
<td>235 (3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serious(^2) (n=186)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>63 (34)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>50 (27)</td>
</tr>
<tr>
<td>Nausea</td>
<td>48 (26)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>42 (23)</td>
</tr>
<tr>
<td>Pyrexia (fever)</td>
<td>35 (19)</td>
</tr>
<tr>
<td>Asthenia (weakness)</td>
<td>34 (18)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>33 (18)</td>
</tr>
<tr>
<td>Syncope</td>
<td>29 (16)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>26 (14)</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>26 (14)</td>
</tr>
</tbody>
</table>

\(^1\) As coded using the MedDRA preferred terms (PT); more than one code may be assigned to a single event

\(^2\) Based on the Code of Federal Regulations if one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization or permanent disability
Disproportional reporting of “syncope” was noted\(^1\)
- Syncope also was disproportionally reported for 4vHPV
- Syncope is a known and labeled adverse event\(^2\)

Other PTs signaled but do not represent an adverse event (i.e., drug administered to patient of inappropriate age, and other administration errors)

No other disproportional reporting for 9vHPV was noted

\(^1\) Data provided by FDA/CBER Division of Epidemiology
Summary of VAERS Review of 9vHPV safety

- VAERS received 7,244 reports following 9vHPV during the study period, December 1, 2014 – December 31, 2017
  - Most (97%) reports were non-serious
  - ~29 million 9vHPV doses were distributed in the United States
- No new safety signals or unexpected patterns were observed
- The safety profile of 9vHPV is consistent with data from pre-licensure trials and post-licensure data on 4vHPV
VSD RCA of 9vHPV: Design and Population

- Prospective cohort
- Enrolled in one of 6 participating VSD sites
- Males and females, 9-26 years old
## Pre-specified Adverse Events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Setting</th>
<th>Post-vax window</th>
<th>Primary comparison group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope</td>
<td>OP, ED, IP</td>
<td>Day 0</td>
<td>Concurrent</td>
</tr>
<tr>
<td>Injection site rxn, w/ and w/o day 0</td>
<td>OP, ED, IP</td>
<td>0-6, 1-6 days</td>
<td>Concurrent</td>
</tr>
<tr>
<td>Allergic Reactions</td>
<td>OP, ED, IP</td>
<td>0-2 ED, IP 1-2 for OP</td>
<td>Concurrent</td>
</tr>
<tr>
<td>Seizure</td>
<td>ED, IP</td>
<td>0-42 days</td>
<td>Concurrent</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>OP, ED, IP</td>
<td>0-2 days</td>
<td>Concurrent</td>
</tr>
<tr>
<td>Appendicitis</td>
<td>ED, IP</td>
<td>1-42 days</td>
<td>Historic</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>ED, IP</td>
<td>1-42 days</td>
<td>Historic</td>
</tr>
<tr>
<td>Guillain-Barré Syndrome (GBS)</td>
<td>OP, ED, IP</td>
<td>1-42 days</td>
<td>Historic</td>
</tr>
<tr>
<td>Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)</td>
<td>OP, ED, IP</td>
<td>1-180 days</td>
<td>Historic</td>
</tr>
<tr>
<td>Stroke</td>
<td>ED, IP</td>
<td>1-42 days</td>
<td>Historic</td>
</tr>
<tr>
<td>Venous Thromboembolism (VTE)</td>
<td>OP, ED, IP</td>
<td>1-42 days</td>
<td>Historic</td>
</tr>
</tbody>
</table>

*Historical comparison is based on VSD data from 2007-2014. Concurrent comparison is based on non-HPV vaccination visits during the surveillance period.*
Summary of findings in VSD RCA for 9vHPV

- Statistical signals occurred for several adverse events after 9vHPV
  - Syncope and injection site reactions were expected
  - All other signals were further investigated
- Signals for allergic reaction, pancreatitis, and appendicitis were not confirmed after further evaluation (e.g., diagnosis not verified)
Example of evaluating a specific outcome: Reports of death following HPV vaccine

- Death is the most concerning adverse event
- Frequent misconception that VAERS death reports represent causal associations, whereas:
  - A report filed to VAERS does not signify that the vaccine was the cause
  - A VAERS report only indicates a temporal relationship that an adverse event occurred sometime after a vaccination
Mortality Following 4vHPV: VAERS

- Surveillance period: January 2009-December 2015
- 92 reports of death
  - 61 hearsay reports: no medical information that could be verified
  - 2 reports mentioned cause of death but no patient or contact information provided
- 29 verified reports of death
- VAERS review of confirmed death reports found no pattern with respect to:
  - Time after vaccination, combination of vaccines administered or diagnoses at death
Mortality Following 4vHPV: VSD

- VSD conducted a study evaluating death among individuals 9-26 years from 2005 to 2011
- Medical records and coroners’ reports reviewed
- 13 deaths identified within 0-30 days following 4vHPV
  - 9 due to external causes; 2 unrelated to vaccination; 2 not sufficient evidence to confirm or rule out a causal association
- Rate of death following 4vHPV: 11.7 deaths per 100,000 PY
  - US published death rate for all causes among persons 15-24 years: 67.6 deaths/100,000 persons
- Risk of death was not increased during 30 days following 4vHPV vaccination (case-centered design)

Summary of VAERS and VSD findings on HPV vaccine

- No new safety concerns identified in VAERS or VSD RCA
- Epidemiologic studies in VSD found no increased risks for:
  - autoimmune and neurologic conditions
  - venous thromboembolism
  - mortality
  - pregnancy-related conditions
- Studies in progress in VSD: POTS, CRPS, CFS

POTS: Postural Orthostatic Tachycardia Syndrome
CRPS: Complex Regional Pain Syndrome
CFS: Chronic Fatigue Syndrome
Increasing focus on vaccine safety monitoring and research worldwide
Increase in vaccine safety publications

![Graph showing the increase in vaccine safety publications](image)

Courtesy of Edwin Asturias
Outcomes studied in postlicensure human papillomavirus vaccine safety evaluations and selected references

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Selected References</th>
<th>Vaccine</th>
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<tbody>
<tr>
<td>Autoimmune and neurologic diseases</td>
<td>Chao C. J Intern Med 2012</td>
<td>4vHPV</td>
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<td></td>
<td>Arnheim-Dahlstrom L. BMJ 2013</td>
<td>4vHPV</td>
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<tr>
<td></td>
<td>Grimaldi-Bensouda L. J Intern Med 2014</td>
<td>4vHPV</td>
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<td>Langer-Gould A. JAMA Neurol 2014</td>
<td>4vHPV</td>
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<td>Baxter R. Clin Infect Dis 2016</td>
<td>4vHPV</td>
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<td>Grimaldi-Bensouda L. J Autoimmunother 2017</td>
<td>4vHPV</td>
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<td>Sridhar G. Hum Vaccin Immunother 2017</td>
<td>4vHPV</td>
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<td>Miranda S. Vaccine 2017</td>
<td>4vHPV</td>
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<td>Hviid A. J Intern Med 2018</td>
<td>4vHPV</td>
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<td></td>
<td>Frisch M. Int J Epidemiol 2018</td>
<td>4vHPV</td>
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<td></td>
<td>Liu EY. CMAJ 2018</td>
<td>4vHPV</td>
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<td>Guillain-Barré syndrome only</td>
<td>Andrews NJ. Vaccine 2017</td>
<td>2vHPV</td>
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<td></td>
<td>Gee J. Vaccine 2017</td>
<td>4vHPV</td>
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<td></td>
<td>Deceuninck G. Expert Rev Vaccines 2018</td>
<td>4vHPV</td>
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<tr>
<td>Type-1 diabetes only</td>
<td>Klein NP. Vaccine 2019</td>
<td>4vHPV</td>
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<tr>
<td>Thromboembolism</td>
<td>Arnheim-Dahlstrom L. BMJ 2013</td>
<td>4vHPV</td>
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<td></td>
<td>Scheller NM. JAMA 2014</td>
<td>4vHPV</td>
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<td></td>
<td>Naleway AL. Vaccine 2016</td>
<td>4vHPV</td>
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<tr>
<td></td>
<td>Yih WK. Vaccine 2016</td>
<td>4vHPV</td>
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<td></td>
<td>Frisch M. Int J Epidemiol 2018</td>
<td>4vHPV</td>
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<tr>
<td>Multiple outcomes</td>
<td>Gee J. Vaccine 2011</td>
<td>4vHPV</td>
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<td>Klein NP. Arch Pediatr Adolesc Med. 2012</td>
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<td>Yih WK. AJE 2018</td>
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<td></td>
<td>Skufca J. Vaccine 2018</td>
<td>2vHPV</td>
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<td></td>
<td>Donahue JG. Pediatrics (in press)</td>
<td>9vHPV</td>
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<td>Primary ovarian insufficiency</td>
<td>Naleway AL. Pediatrics 2018</td>
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<td>Chronic fatigue</td>
<td>Feiring B. Vaccine 2017</td>
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<td>Schurink-Van’t Klooster TM. Vaccine 2018</td>
<td>2vHPV</td>
</tr>
<tr>
<td>Death</td>
<td>McCarthy NL. Pediatrics 2016</td>
<td>4vHPV</td>
</tr>
</tbody>
</table>

2vHPV, bivalent HPV vaccine; 4vHPV, quadrivalent HPV vaccine; 9vHPV, 9-valent HPV vaccine

aCase series, case reports and reports from passive reporting systems not included; bStudies focused on autoimmune outcomes, demyelinating or other neurologic conditions (most included many different outcomes including Guillain-Barré syndrome); cNaleway and Scheller studied only thromboembolism; other studies included many outcomes; dStudies not limited to autoimmune or neurologic outcomes

Courtesy of Lauri Markowitz
Conclusions

- Pre-licensure activities form the foundation of vaccine safety
- US has a comprehensive robust vaccine safety monitoring system
  - Essential to maintaining public confidence in vaccines
- Science is not sufficient in maintaining acceptance of vaccines
  - **Vaccinate with Confidence**: CDC’s strategic framework for strengthening vaccine confidence and preventing outbreaks of vaccine preventable diseases in the United States
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Thank you

For more information, contact CDC
1-800-CDC-INFO (232-4636)

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.