



Vaccine Safety Monitoring Systems and Methods

October 2019 Advisory Committee on Immunization Practices (ACIP) meeting

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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

The Vaccine Life Cycle

GUIDE

ACIP

ADVISORY
COMMITTEE ON
IMMUNIZATION
PRACTICES

BLA

BIOLOGICS LICENSE
APPLICATION

CDC

CENTERS FOR
DISEASE CONTROL
AND PREVENTION

FDA

FOOD AND DRUG
ADMINISTRATION

IND

INVESTIGATIONAL
NEW DRUG
APPLICATION

NDA

NEW DRUG
APPLICATION

VACCINE

DEVELOPMENT

CDC + FDA
Safety
Monitoring
Begins

Safety
is Part of
Every
Vaccine

BASIC
RESEARCH

DISCOVERY

PRE-
CLINICAL
STUDIES

IND
SUBMITTED

PHASE 1
20-100
Participants

PHASE 2
100-300
Participants

PHASE 3
300-3000
Participants

CLINICAL TRIALS

NDA/BLA
SUBMITTED

FDA
REVIEW

FDA
APPROVAL OF 1 NEW VACCINE

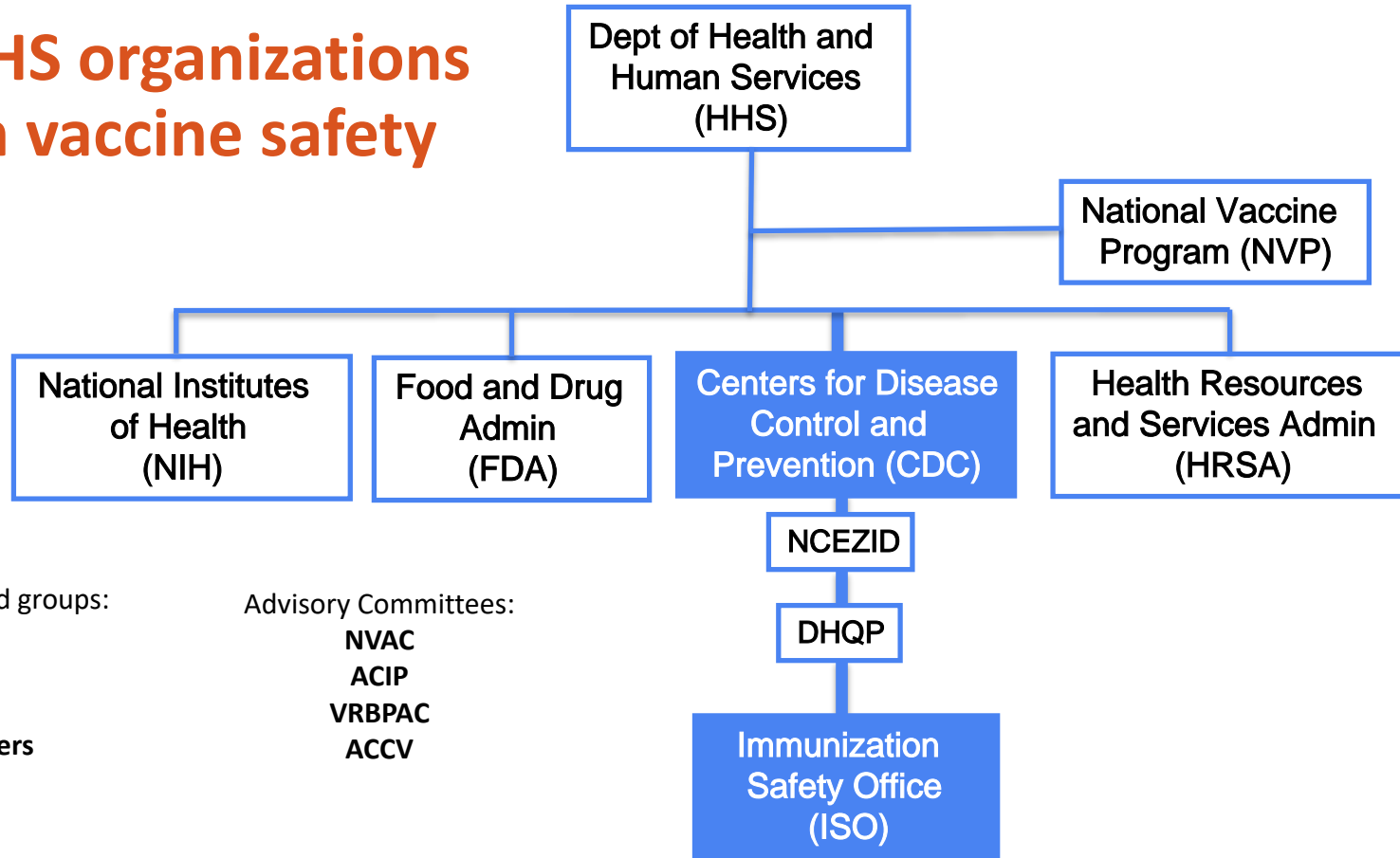
ACIP
REVIEW

ACIP
RECOMMENDATION

POST-APPROVAL
MONITORING +
RESEARCH

PHASE 4
Thousands of Participants

Primary HHS organizations engaged in vaccine safety activities



Other agencies and groups:

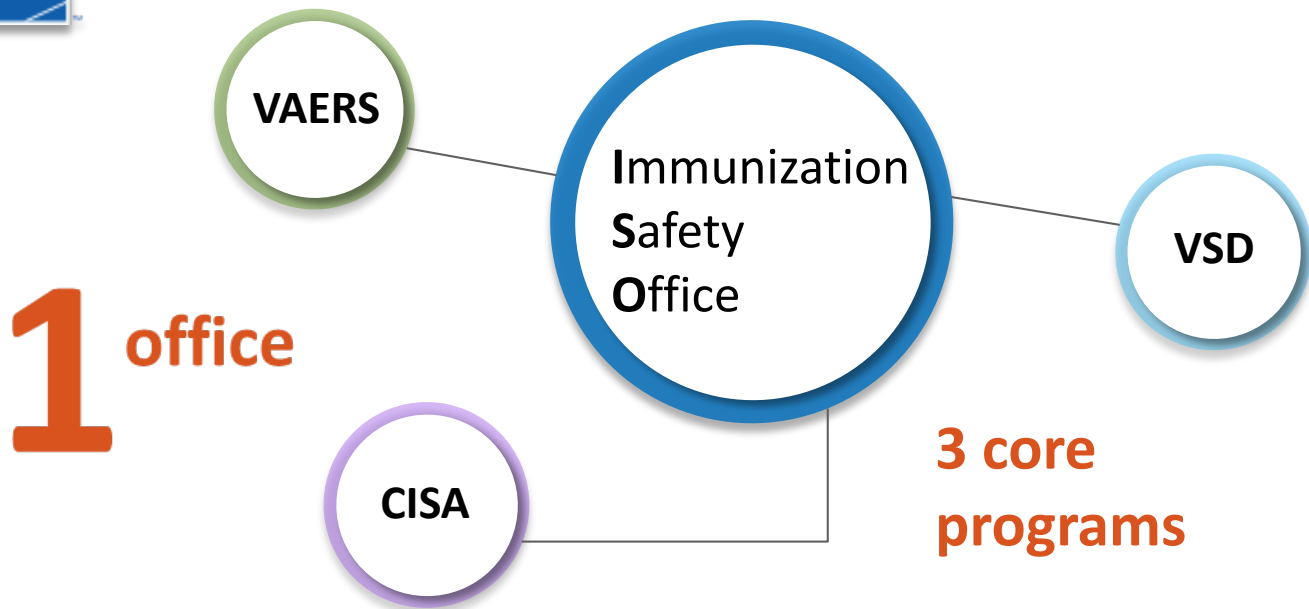
DoD
DVA
IHS
Manufacturers

Advisory Committees:

NVAC
ACIP
VRBPAC
ACCV



CDC vaccine safety monitoring



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**



VAERS

Vaccine Adverse Event Reporting System

Co-managed by
CDC and FDA

<http://vaers.hhs.gov>

VAERS Vaccine Adverse Event Reporting System
www.vaers.hhs.gov

About VAERS

Report an Adverse Event

VAERS Data

Resources

Submit Follow-Up Information

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!*



What is VAERS?



REPORT AN ADVERSE EVENT

Report significant adverse events after vaccination.



SEARCH VAERS DATA

Download VAERS Data and search the CDC WONDER database.



REVIEW RESOURCES

Find materials, publications, learning tools, and other resources.



SUBMIT FOLLOW-UP INFORMATION

Upload additional information related to VAERS reports.

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

VAERS Vaccine Adverse Event Reporting System
www.vaers.hhs.gov

Adverse events are possible reactions or problems that occur during or after vaccination. Items 2, 3, 4, 5, 6, 17, 18 and 21 are **ESSENTIAL** and should be completed. Patient identity is kept confidential. Instructions are provided on the last two pages.

INFORMATION ABOUT THE PATIENT WHO RECEIVED THE VACCINE (Use Continuation Page if needed)

1. Patient name: first (last)
Street address:
City: State: County:
ZIP code: Phone: () Email:

2. Date of birth: (mm/dd/yyyy) 3. Sex: Male Female Unknown
4. Date and time of vaccination: (mm/dd/yyyy) Time: (hh:mm) AM/PM
5. Date and time adverse event started: (mm/dd/yyyy) Time: (hh:mm) AM/PM
6. Age at vaccination: Years Months 7. Today's date: (mm/dd/yyyy)
8. Pregnant at time of vaccination?: Yes No Unknown
If yes, describe the event, any pregnancy complications, and estimated due date if known in item 10

9. Prescriptions, over-the-counter medications, dietary supplements, or herbal remedies being taken at the time of vaccination:
10. Allergies to medications, food, or other:
11. Other illnesses at the time of vaccination:
12. Chronic or long-standing health conditions:

INFORMATION ABOUT THE PERSON COMPLETING THIS FORM

13. Form completed by: (name)
Relation to patient: Healthcare professional/staff Patient (yourself) Parent/guardian/caregiver Other:
Street address: Check if same as item 1
City: State: ZIP code:
Phone: () Email:

14. Best doctor/healthcare professional to contact about the adverse event: Name: Phone: () Ext:

INFORMATION ABOUT THE FACILITY WHERE VACCINE WAS GIVEN

15. Facility/clinic name:
Fac: ()
Street address: Check if same as item 13
City: State: ZIP code:
Phone: ()

16. Type of facility: (check all that apply)
 Doctor's office, urgent care, or hospital
 Pharmacy or store
 Workplace clinic
 Public health clinic
 Nursing home or senior living facility
 School or student health clinic
 Other:
 Unknown

WHICH VACCINES WERE GIVEN? WHAT HAPPENED TO THE PATIENT?

17. Enter all vaccines given on the date listed in item 4: (Reason is HOW vaccine was given, Body site is WHERE vaccine was given)
Vaccine (type and brand name) Manufacturer Lot number
select select select
18. Describe the adverse event(s), treatment, and outcome(s), if any: (symptoms, signs, time course, etc.)
21. Result or outcome of adverse event(s): (check all that apply)
 Doctor or other healthcare professional office/clinic visit
 Emergency room/department or urgent care
 Medication (name, number of doses, if known)
19. Medical tests and laboratory results related to the adverse event(s): (include dates)
Use Continuation Page if needed
20. Has the patient recovered from the adverse event(s)?: Yes No Unknown
22. Any other vaccines received within one month prior to the date listed in item 4:
Vaccine (type and brand name) Manufacturer Lot number Route Body site Dose number Date given
select select select select select select
23. Has the patient ever had an adverse event following any previous vaccine?: If yes, describe adverse event, patient age at vaccination, vaccination dates, vaccine type, and brand name
 Yes No Unknown
24. Patient's race: American Indian or Alaska Native Asian Black or African American Native Hawaiian or Other Pacific Islander
 White Unknown Other:
25. Patient's ethnicity: Hispanic or Latino Not Hispanic or Latino Unknown 26. Immunity, prev. report number: (Health Dept use only)

COMPLETE ONLY FOR U.S. MILITARY/DEPARTMENT OF DEFENSE (DoD) RELATED REPORTS

27. Status at vaccination: Active duty Reserve National Guard Beneficiary Other:
28. Vaccinated at Military/DoD site: Yes No

FORM FDA VAERS 2.0 (M/19) **SAVE**

Direct link to 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

The screenshot displays the VAERS (Vaccine Adverse Event Reporting System) online report form. The header includes the VAERS logo and the text "Vaccine Adverse Event Reporting System www.vaers.hhs.gov". The navigation bar contains links for "About VAERS", "Report an Adverse Event", "VAERS Data", "Resources", and "Submit Follow-Up Information". The main content area is titled "Report an Adverse Event - Patient Information" and includes a note: "Note: Fields marked with an * are essential and should be completed." The form is divided into sections labeled "Item 1" through "Item 7". Item 1 includes fields for Patient first name, Patient last name, Street address, City, State (a dropdown menu labeled "Select State"), County, and Email. Item 3 includes a Sex field with radio buttons for Male, Female, and Unknown. Item 4 includes a Date of vaccination field with a calendar icon and a Time field with AM/PM options. Item 5 includes a Date adverse event started field with a calendar icon and a Time field with AM/PM options. Item 6 includes an Age at vaccination field. Item 7 includes a Today's date field. A visual navigation guide, represented by a blue arrow pointing to the right, is overlaid on the form with the text "Visual Navigation Through Each Section".

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

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 serious¹ 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

¹Based 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

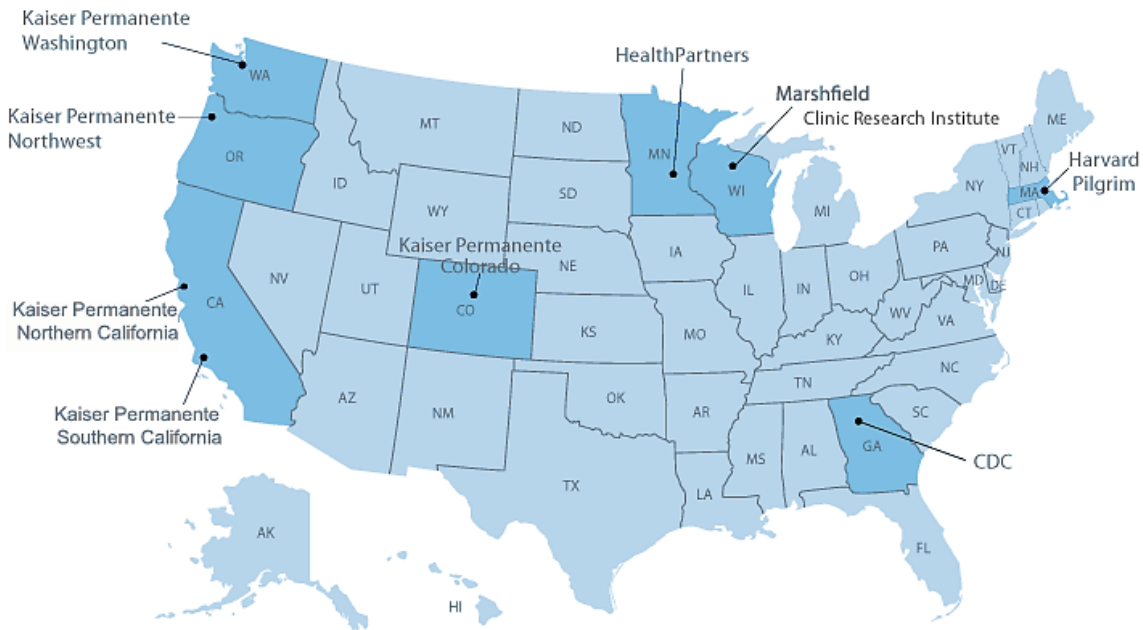
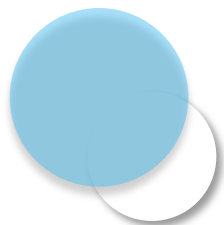
- Reporting bias
- Inconsistent data quality and completeness
- Lack of unvaccinated comparison group
- Generally cannot assess causality

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



VSD

Vaccine Safety Datalink

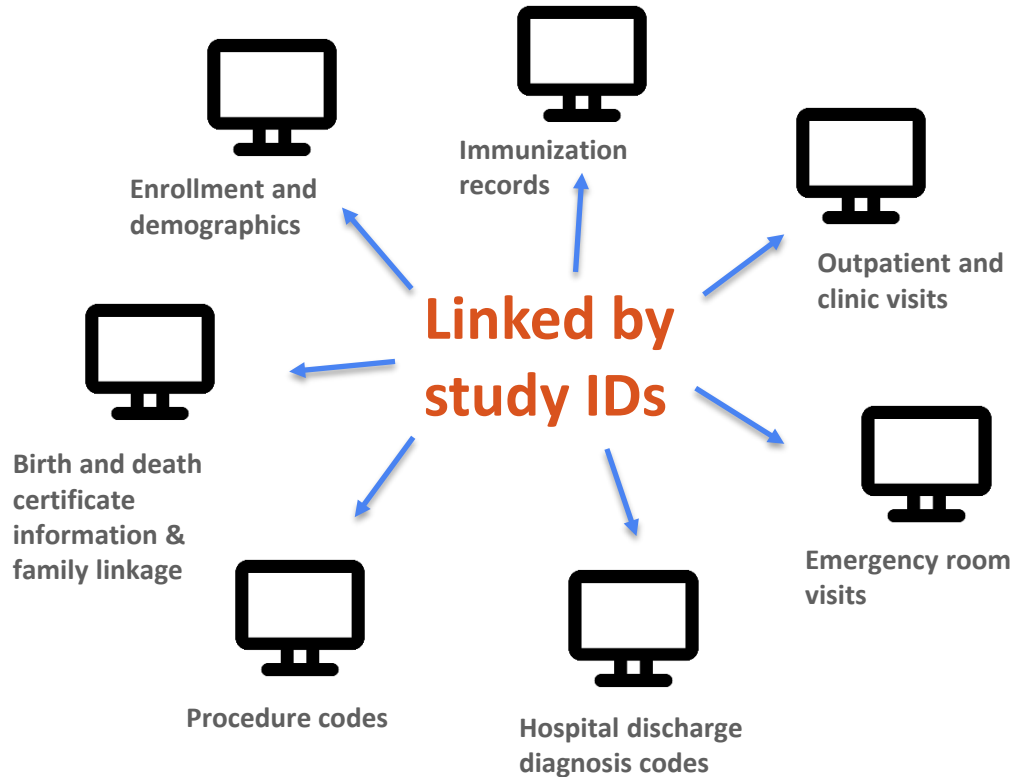


8 participating integrated healthcare organizations

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



+



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

Designed to detect statistical signals (values above specified statistical thresholds)

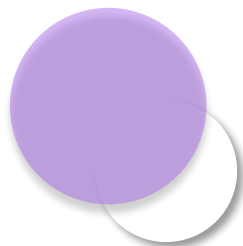
- When a statistical signal occurs, CDC conducts a series of further evaluations, including traditional epidemiologic methods
- Chart-confirmation of diagnoses to confirm or exclude cases as true incident cases is a key part of statistical signal assessment

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*

*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

vaccine safety experts

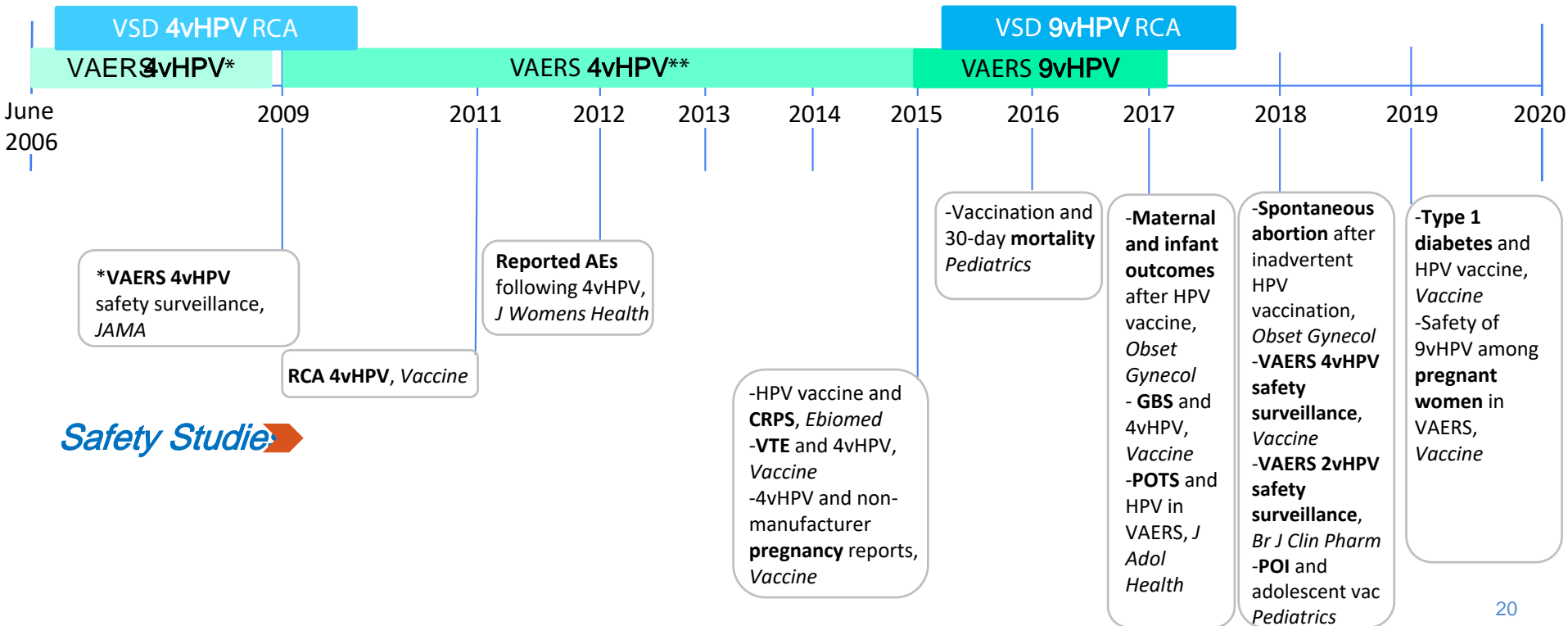
- assist U.S. healthcare providers with complex vaccine safety questions about their patients
CISAeval@cdc.gov[†]
- conduct clinical research

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

Case study of HPV vaccine safety

Timeline of CDC/ISO HPV vaccine safety monitoring and selected publications

Safety Monitoring



Safety Studies

Monitoring a recent vaccine: 9vHPV in VAERS and VSD

Top 10 reported signs and symptoms¹ after 9vHPV in VAERS, Dec 2014-Dec 2017

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

Serious ² (n=186)	N (%)
Headache	63 (34)
Dizziness	50 (27)
Nausea	48 (26)
Fatigue	42 (23)
Pyrexia (fever)	35 (19)
Asthenia (weakness)	34 (18)
Vomiting	33 (18)
Syncope	29 (16)
Abdominal pain	26 (14)
Loss of consciousness	26 (14)

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

VAERS Empirical Bayesian data mining for 9vHPV

- Disproportional reporting of “syncope” was noted¹
 - Syncope also was disproportionately reported for 4vHPV
 - Syncope is a known and labeled adverse event²
- 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

² Adverse Effects of Vaccines: Evidence and Causality, Institute of Medicine, Aug 2011 (<http://www.iom.edu/Reports/2011/Adverse-Effects-of-Vaccines-Evidence-and-Causality.aspx>)

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
- Surveillance period: 10/4/2015—10/3/2017
- Enrolled in one of 6 participating VSD sites
- Males and females, 9-26 years old

Pre-specified Adverse Events

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

*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

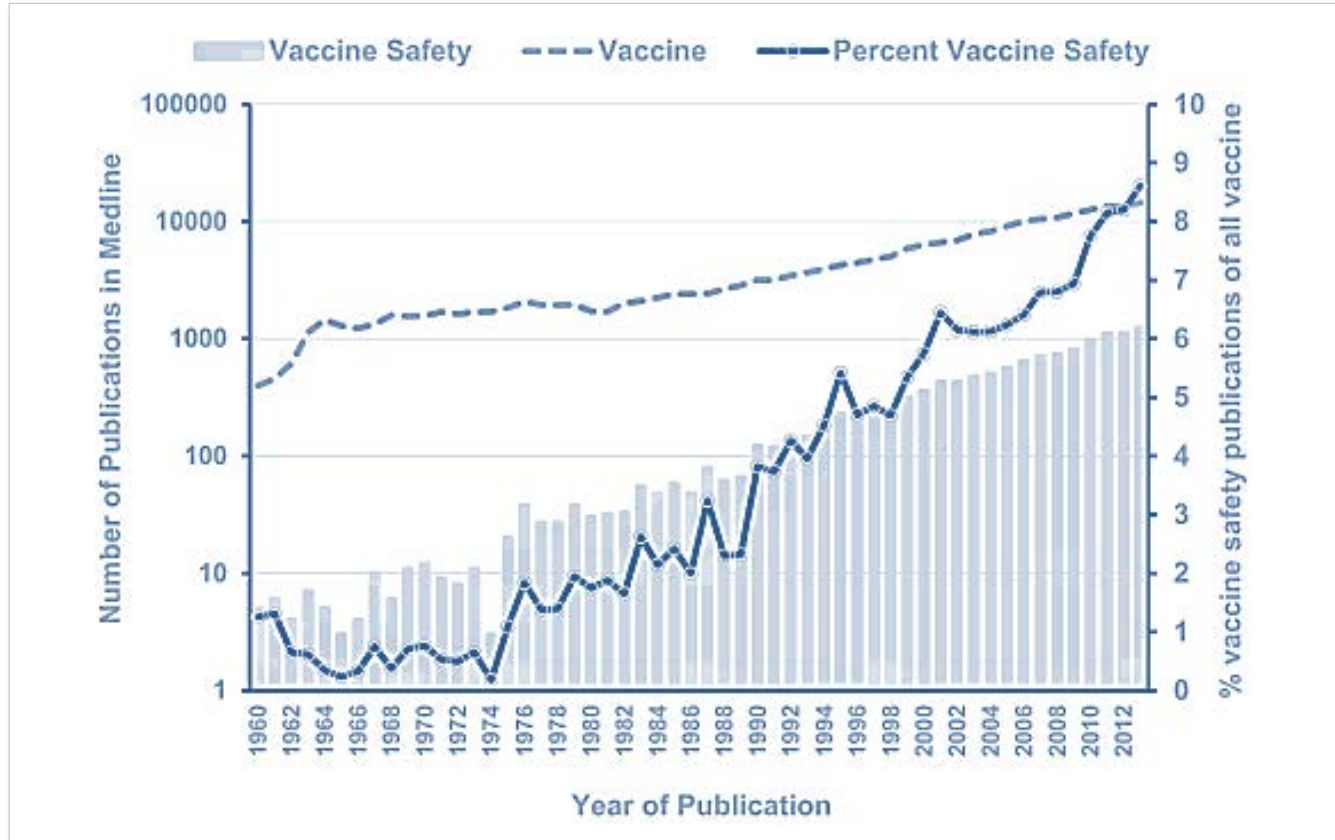
POTS: Postural Orthostatic Tachycardia Syndrome

CRPS: Complex Regional Pain Syndrome

CFS: Chronic Fatigue Syndrome

**Increasing focus on vaccine safety
monitoring and research worldwide**

Increase in vaccine safety publications



Courtesy of Edwin Asturias

Outcomes studied in postlicensure human papillomavirus vaccine safety evaluations and selected references^a

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

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)
TTY: 1-888-232-6348 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.

