Vaccine Safety Monitoring Systems and Methods

October 2019 Advisory Committee on Immunization Practices (ACIP) meeting

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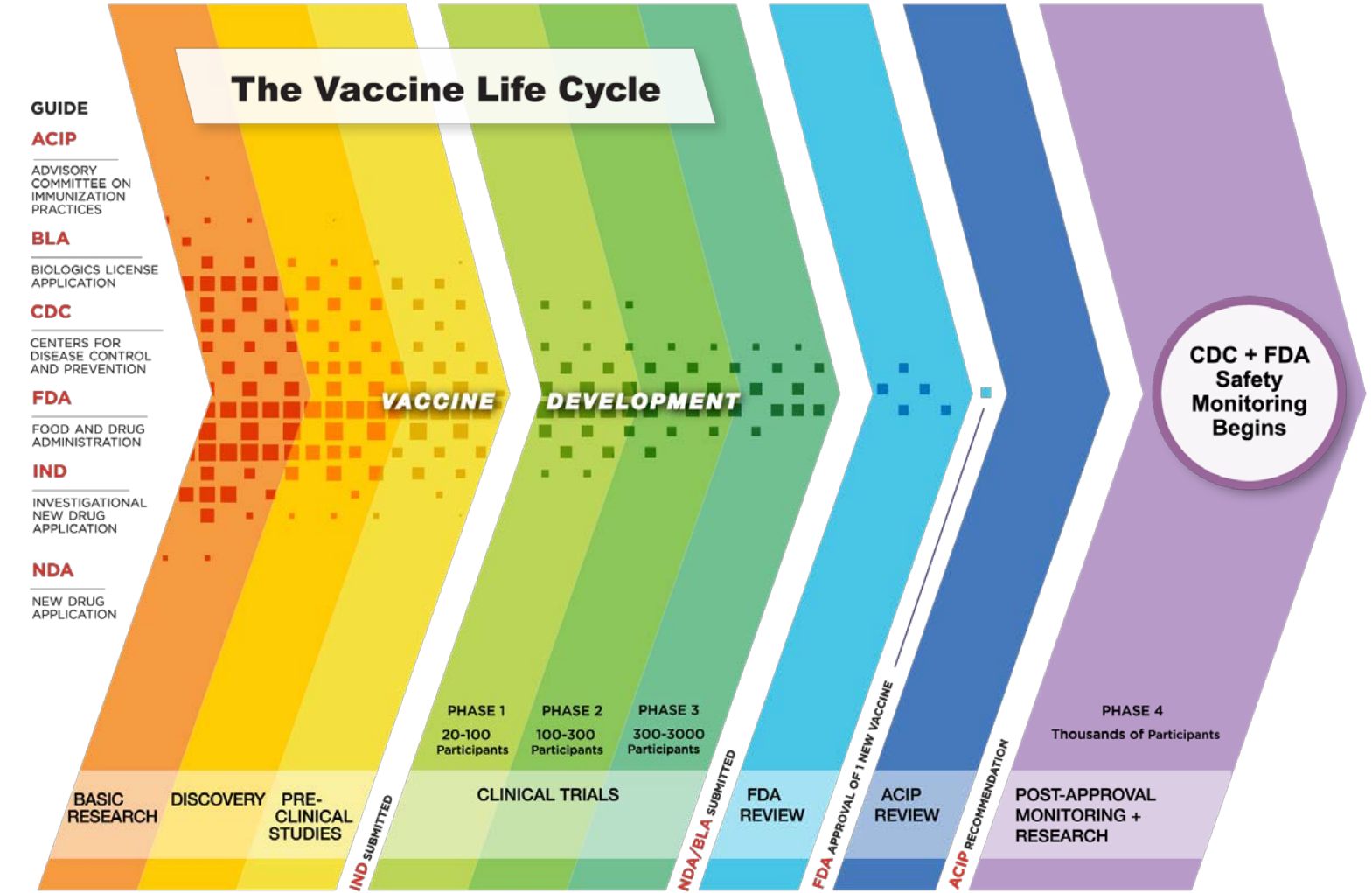
Overview

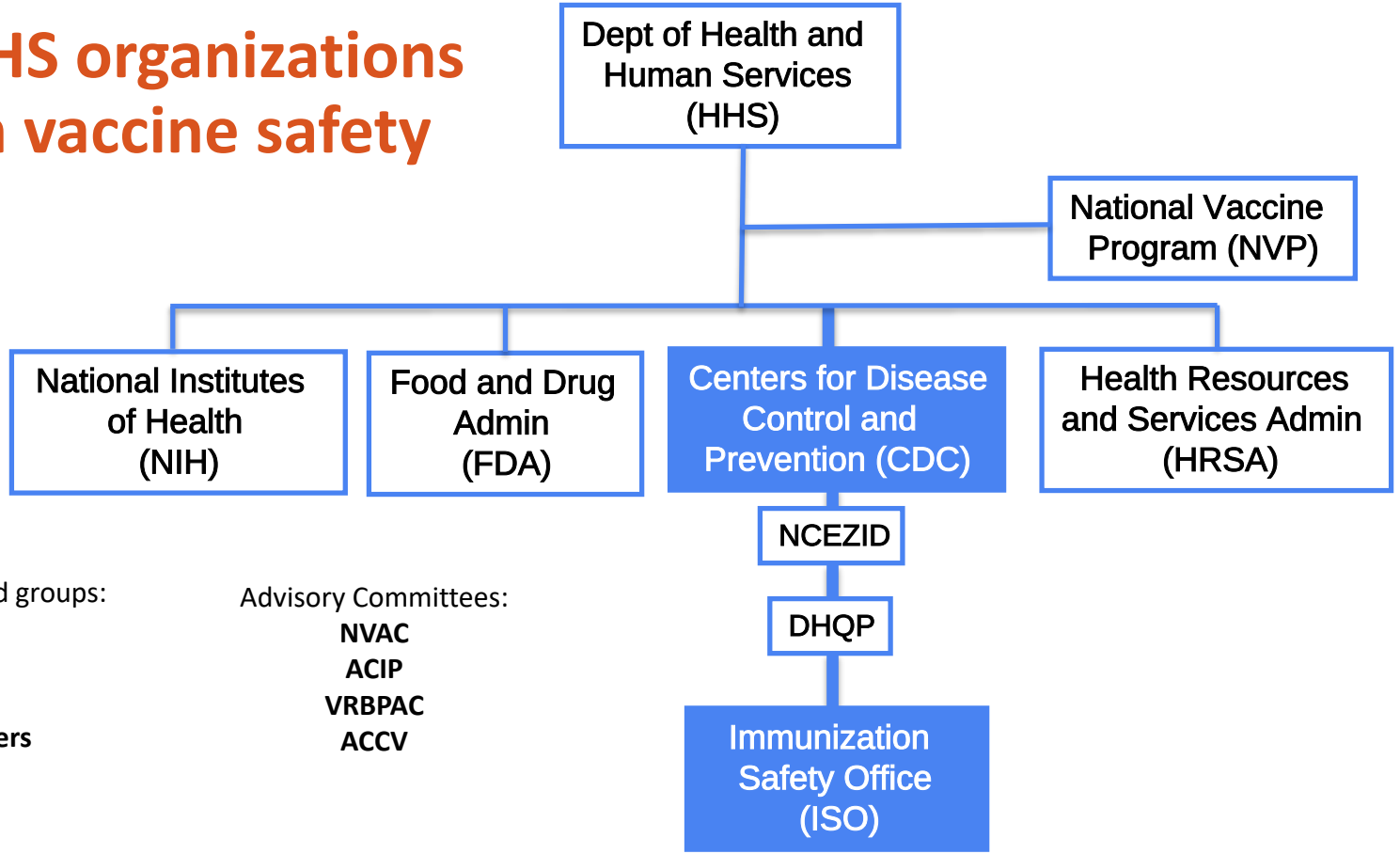
- Describe CDC vaccine safety monitoring systems
- HPV vaccine safety monitoring as a case study
- Broader national and international vaccine safety monitoring and research efforts

CDC Vaccine Safety Monitoring Systems



Safety
is Part of Every Vaccine

Primary HHS organizations engaged in vaccine safety activities



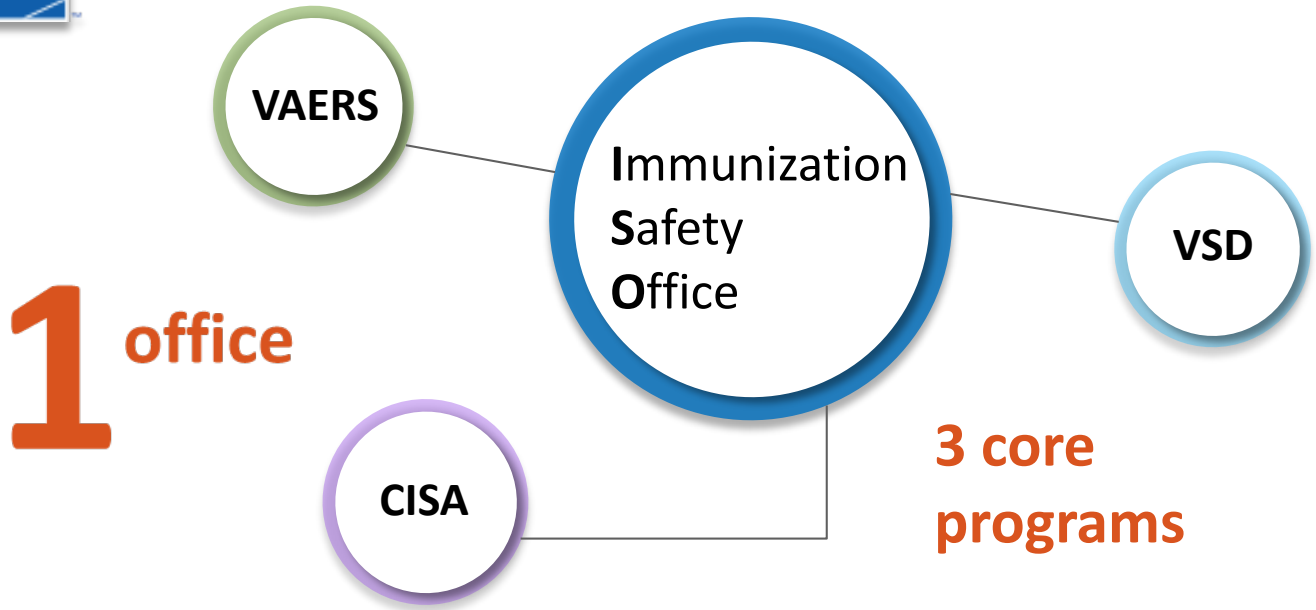
Other agencies and groups:

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

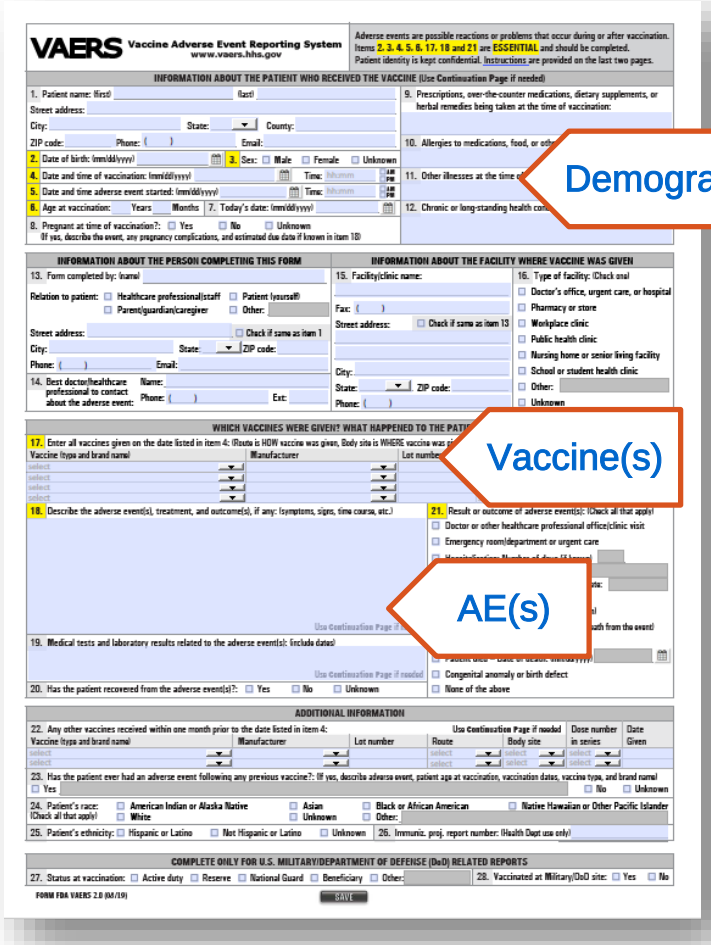
Co-managed by CDC and FDA

http://vaers.hhs.gov

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



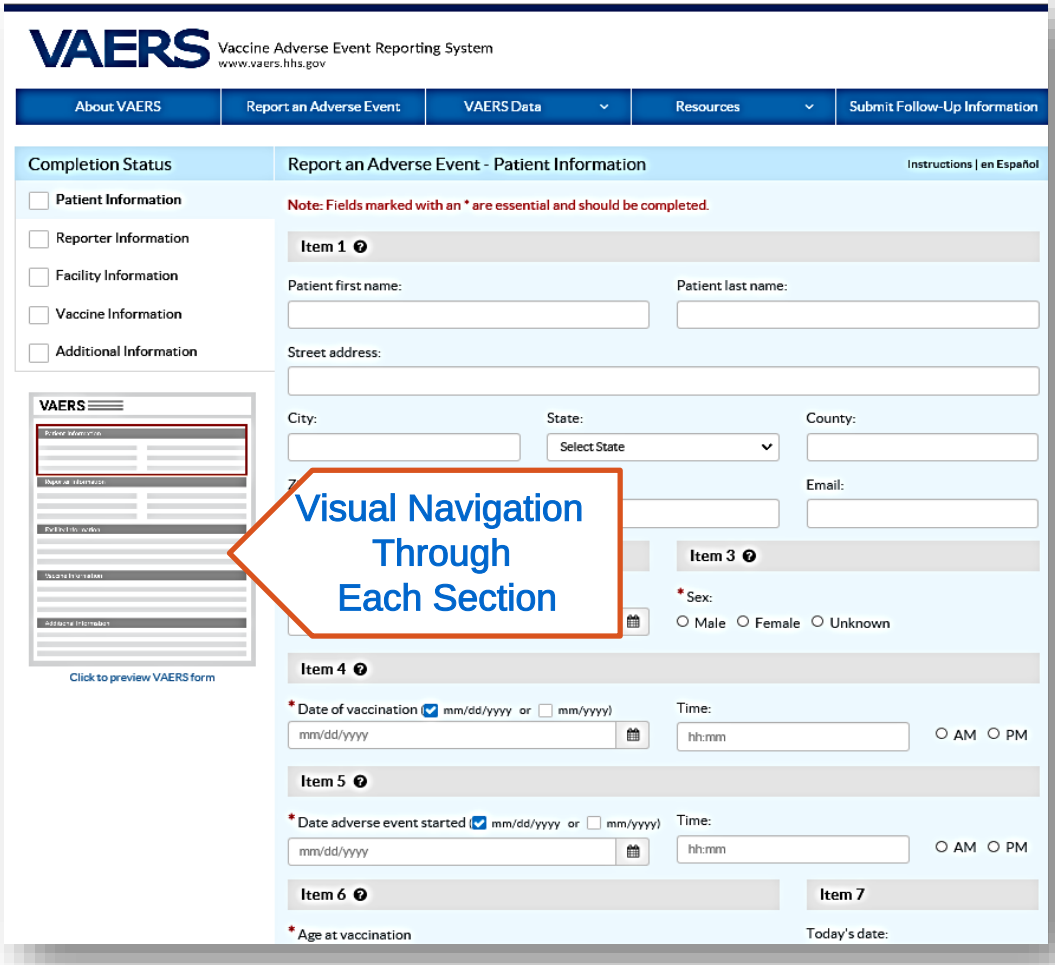
Direct link to PDF: https://vaers.hhs.gov/pdf/VAERSForm_Aug2019.pdf

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

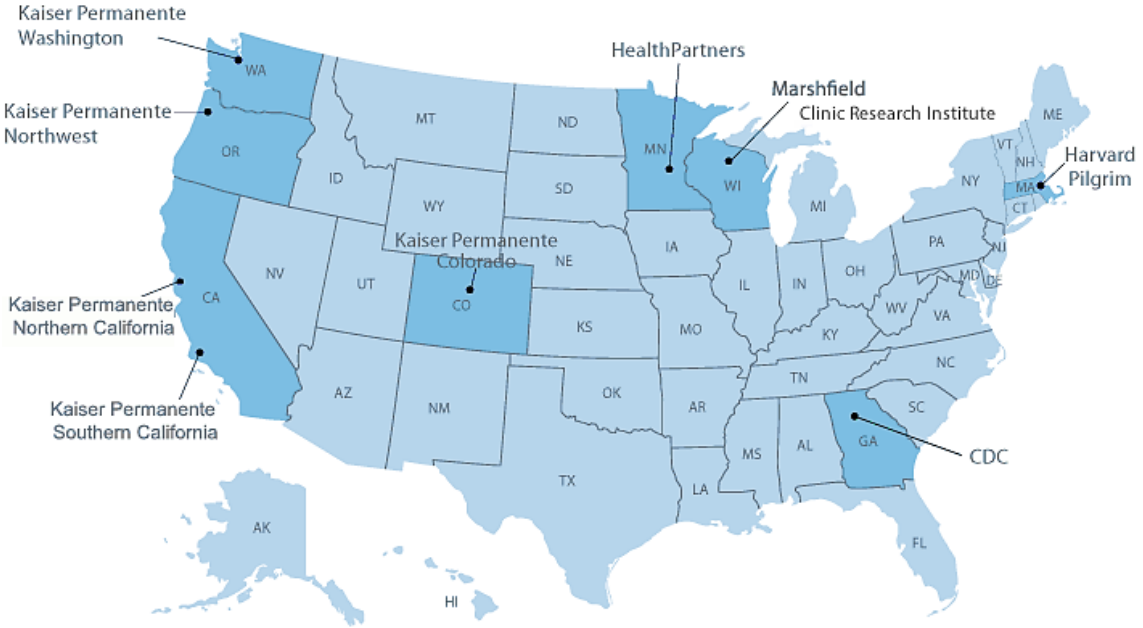
Limitations

- 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

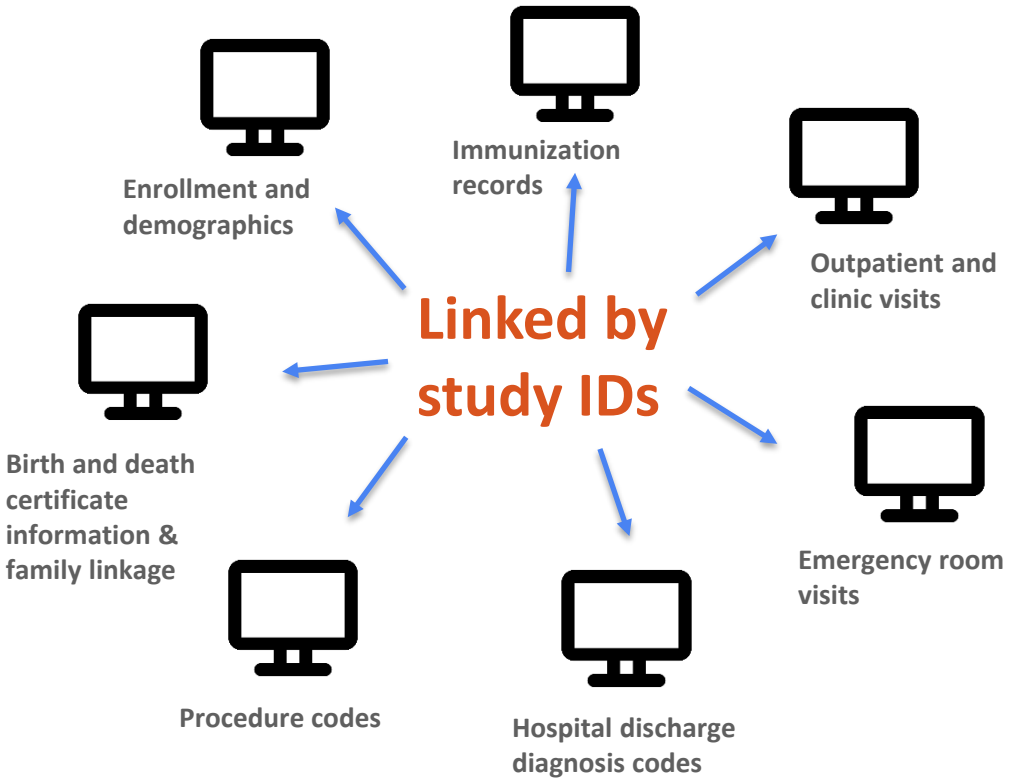


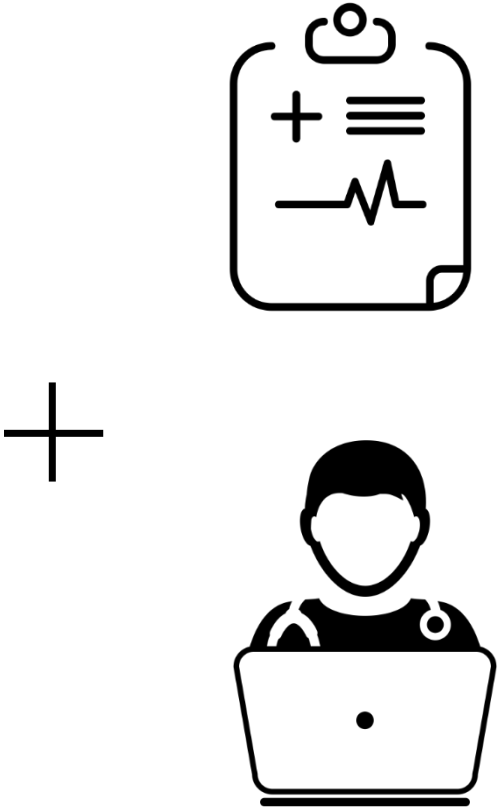
8 participating integrated healthcare organizations

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





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

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

vaccine safety experts

CISA

Clinical Immunization Safety Assessment

7 participating medical research centers*

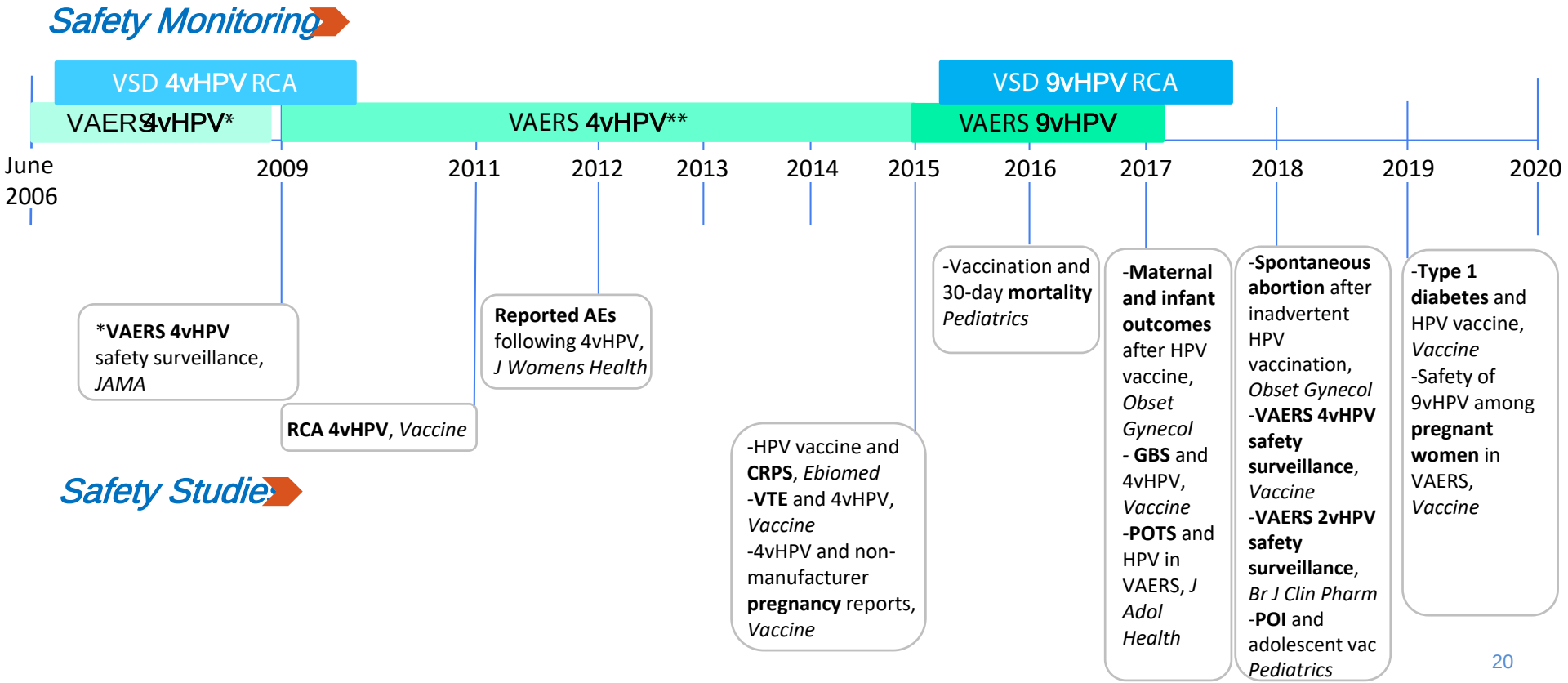
- assist U.S. healthcare providers with complex vaccine safety questions about their patients CISAeval@cdc.gov†
- conduct clinical research

*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

†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



Monitoring a recent vaccine: 9vHPV in VAERS and VSD

Top 10 reported signs and symptoms[1] 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 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

[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

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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)

McCarthy et al. Vaccination and 30-day mortality risk in children, adolescents, and young adults. Pediatrics 2016

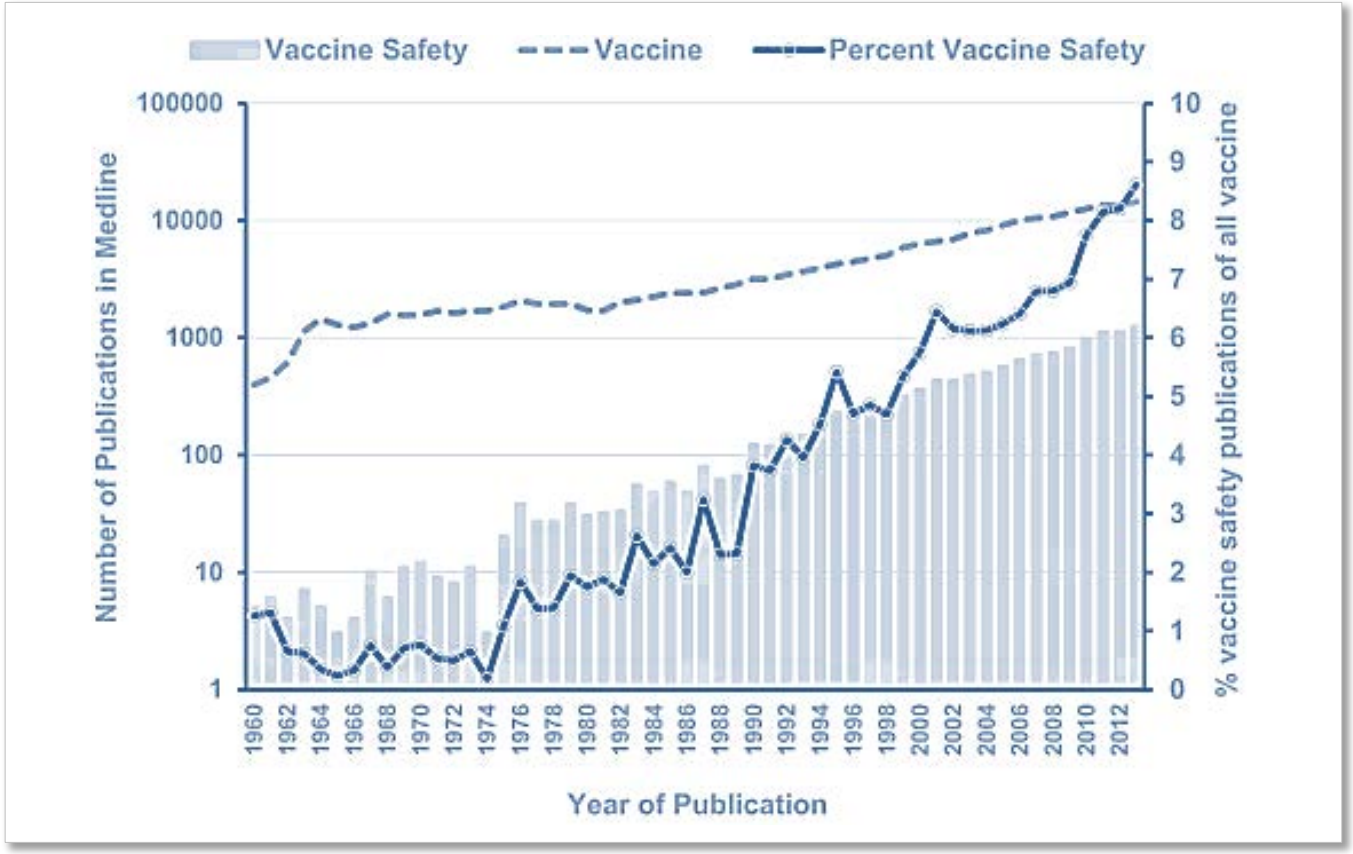
Summary of VAERS and VSD findings on HPV vaccine

- 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 post-licensure 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	2vHPC
	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, quadriavlent HPV vaccine; 9vHPV, 9-valent HPV vaccine

[a]case series, case reports and reports from passive reporting systems not included; [b]Studies focused on autoimmune outcomes, demyelinating or other neurologic conditions (most included many different outcomes including Guillain-Barré syndrome); [c]Naleway and Scheller studied only thromboembolism; other studies included many outcomes; [d]Studies 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

Acknowledgements

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Thank you

For more information, contact CDC
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TTY: 1-888-232-6348 www.cdc.gov