Signal detection and signal strengthening in CDC's vaccine safety monitoring systems

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Vaccine Safety/VAERS Webinar
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Disclaimer

- The findings and conclusions in this presentation are those of the presenter and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC)

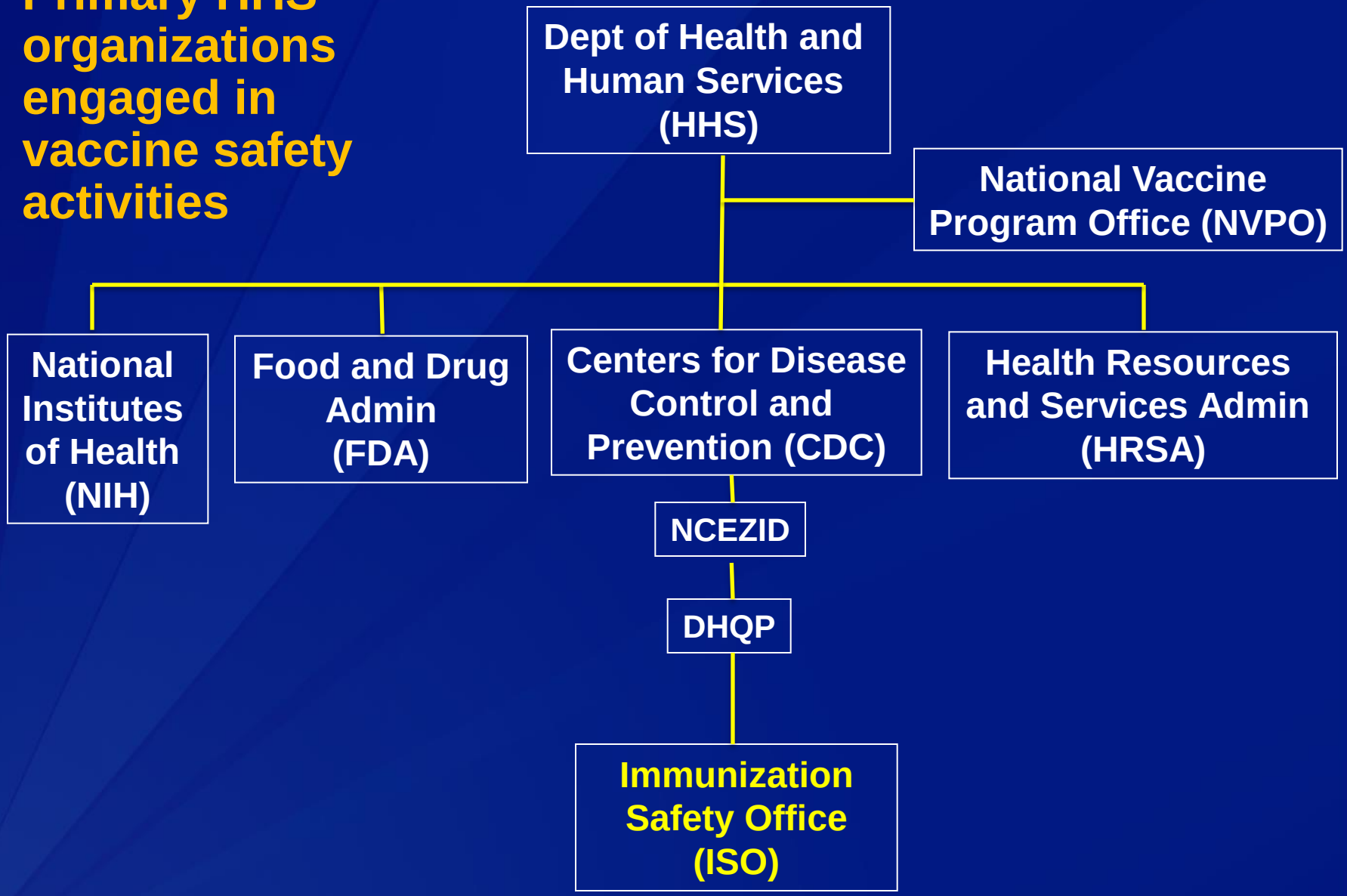
Agenda

- Overview of the Immunization Safety Office
- The US Vaccine Adverse Event Reporting System (VAERS)
  - Overview
  - Automated analyses
  - Clinical reviews
  - Reporting rates
  - Data mining (proportional reporting ratio and empirical Bayesian)
- The CDC's Vaccine Safety Datalink (VSD)
  - Overview
  - Rapid Cycle Analysis (RCA)

Why we monitor vaccine safety after licensure

- High safety standards expected for vaccines
  - People getting vaccinated are generally healthy (vs. ill for drugs) and many are children
  - 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

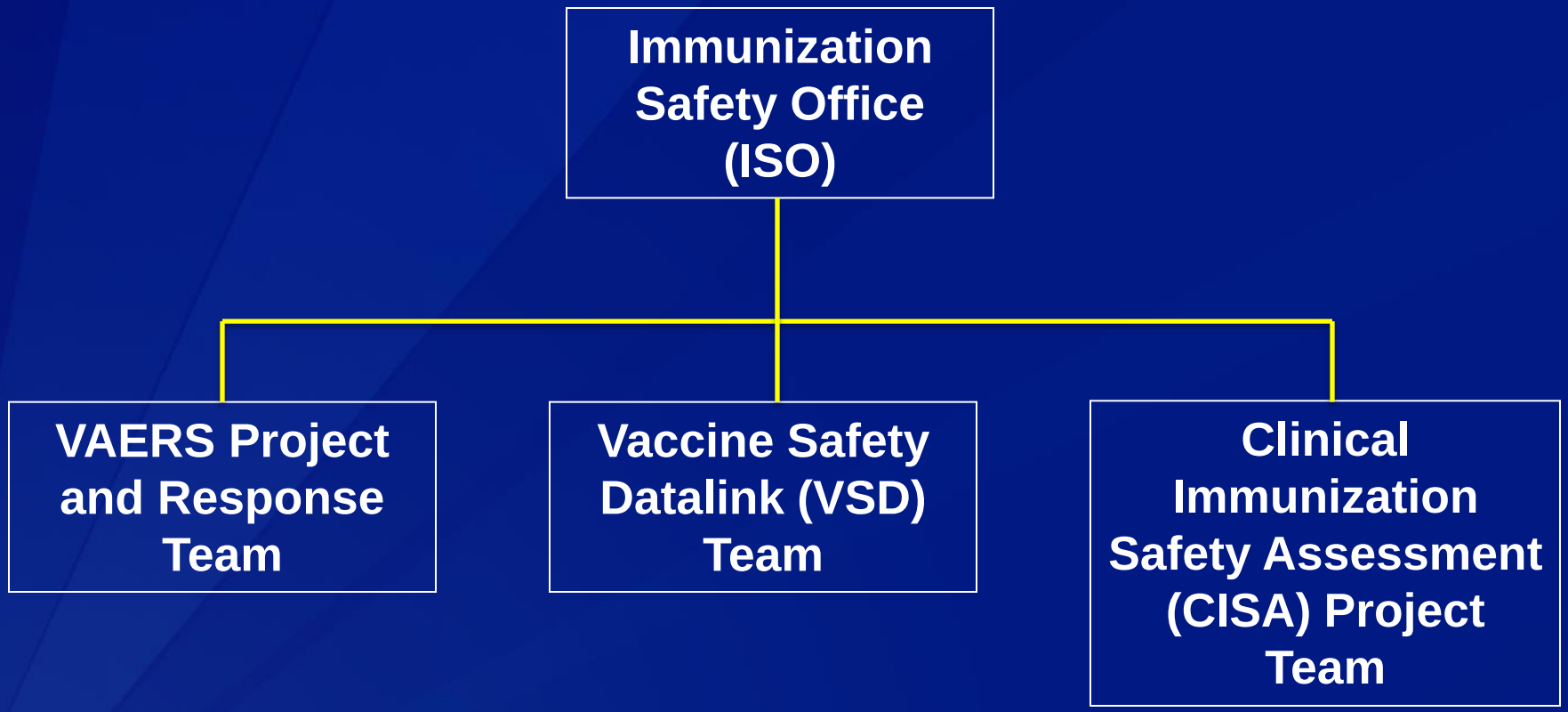
Primary HHS organizations engaged in vaccine safety activities



Federal agency primary roles

- **National Vaccine Program Office (NVPO)**
  - Strategic direction, interagency coordination
- **National Institutes of Health (NIH)**
  - Basic science and clinical research
- **Food and Drug Administration (FDA)**
  - Regulatory and enforcement activities
- **Centers for Disease Control and Prevention (CDC)**
  - Surveillance, research, prevention, education
- **Health Resources and Services Administration (HRSA)**
  - Administers the National Vaccine Injury Compensation Program

Immunization Safety Office (ISO)



ISO's post-licensure vaccine safety monitoring infrastructures

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

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 immunization in a timely way**
  - **Investigation of possible adverse events following immunization to determine causality and risk factors**
  - **Development of strategies for prevention of adverse events following immunization**
  - **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

What is a vaccine adverse event?

- Vaccine adverse event (or adverse event following immunization [AEFI])
  - Any untoward medical occurrence that follows vaccination and which does not necessarily have a causal relationship with the use of the vaccine
- May be any unfavorable or unintended condition
  - Sign, symptom, abnormal laboratory finding, disease
- In the United States an adverse event is considered serious based on the Code of Federal Regulations* if one of the following is reported:
  - Death, life-threatening illness, hospitalization or prolongation of existing hospitalization, permanent disability

* 21 CFR 600.80.

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.”*

*Safety of Medicines - A Guide to Detecting and Reporting Adverse Drug Reactions - Why Health Professionals Need to Take Action. Geneva, WHO, 2002 (http://apps.who.int/medicinedocs/en/d/Jh2992e/2.html)

Vaccine Adverse Event Reporting System (VAERS)

Vaccine Adverse Event Reporting System (VAERS)

- National spontaneous reporting system for adverse events (AE) after US-licensed vaccines
  - In recent years, received around 30,000 US reports annually
  - Accepts reports from healthcare providers, manufacturers and the public
  - Signs/symptoms of adverse event are coded using MedDRA* terms and entered into database
- Jointly administered by CDC and FDA since 1990
- Authorized by National Childhood Vaccine Injury Act of 1986

* http://www.meddra.org/

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VAERS Vaccine Adverse Event Reporting System

Search web site: Search

Report an Adverse Event | About VAERS | VAERS Data | Vaccine Resources | Information for Healthcare Professionals | Information for U.S. States and Territories | Information for Vaccine Manufacturers

The **Vaccine Adverse Event Reporting System (VAERS)** is a national vaccine safety surveillance program co-sponsored by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). VAERS is a post-marketing safety surveillance program, collecting information about adverse events (possible side effects) that occur after the administration of vaccines licensed for use in the United States.

VAERS provides a nationwide mechanism by which adverse events following immunization may be reported, analyzed, and made available to the public. VAERS also provides a vehicle for disseminating vaccine safety-related information to parents and guardians, health care providers, vaccine manufacturers, state vaccine programs, and other constituencies. more...

Have you or your child had a reaction following vaccination?

1. Contact your health care provider
2. Report the reaction
3. Submit Follow-Up Information
4. Visit the National Vaccine Injury Compensation (if appropriate)

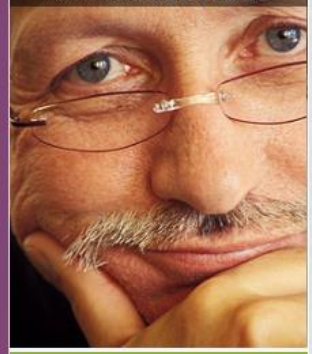
Important note: CDC and FDA do not provide individual medical treatment, advice, or diagnosis. If you need individual medical or health care advice, consult a qualified health care provider.

¿Ha tenido usted o su hijo una reacción adversa después de recibir una vacuna?

1. Contacte a su proveedor de salud
2. Reporte una reacción adversa
3. Visite el Programa Nacional de Compensación por Daños Derivados de Vacunas (si es necesario)

Search VAERS Data

VAERS Data last updated: 04/15/2015



Featured Resources

Seasonal Flu Update

- Summary of 2014-2015 Influenza Vaccine Information

Government Agencies

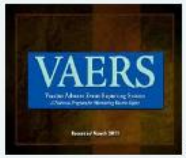
- Immunization Safety Office
- National Center for Immunization and Respiratory Diseases
- National Vaccine Injury Compensation Program
- National Vaccine Program Office
- Center for Biologics Evaluation and Research

Health Topics

- Vaccine Safety
- Immunization Schedules
- Preventing Flu with Vaccination
- Traveler's Health: Vaccinations
- Vaccine-Preventable Diseases
- CDC en Español: Inmunización

Browse All Vaccine Resources

VIDEO: An Overview of VAERS



This 10-minute video describes VAERS, who can report and how, and what happens after a VAERS report is submitted to CDC and the Food and Drug Administration (FDA).

VIDEO: Searching the VAERS Database

VAERS data is available to the public. This video demonstrates how to use the VAERS search tool.

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Call VAERS at (800) 822-7967 | Fax VAERS at (877) 721-0366
VAERS is co-sponsored by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA), agencies of the U.S. Department of Health and Human Services.

USA.gov | CDC | FDA

https://vaers.hhs.gov/index

Signal detection in VAERS

- **Signal detection / hypothesis generation**
  - **Detect new, unusual, or rare adverse events**
  - **Identify potential risk factors in vaccine recipients for particular types of adverse events**
  - **Monitor trends in known adverse events, particularly increases**
  - **Identify vaccine lots with increased numbers or types of reported adverse events (FDA lead)**

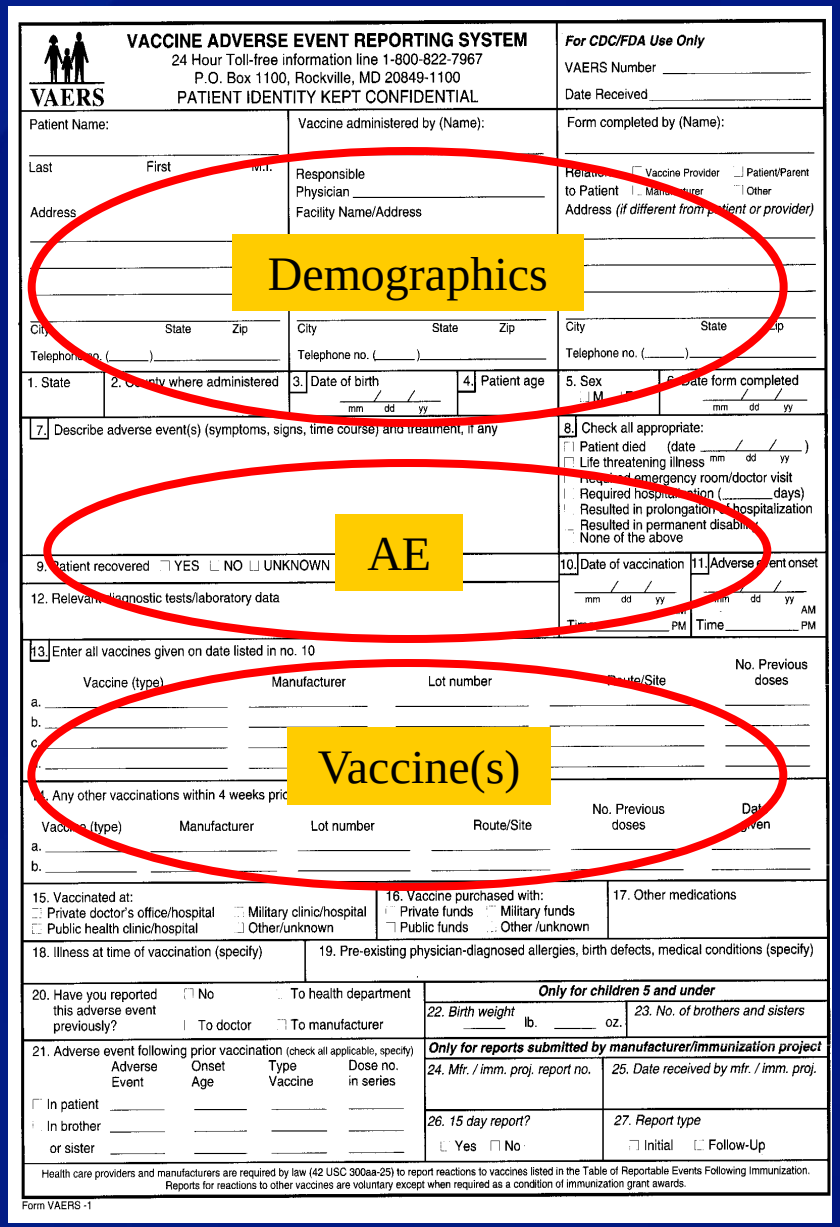
Submitting a VAERS report

- Mailed written hardcopy of paper form
- Faxed hardcopy
- Secure online submission (~30% of reports in recent years)
- 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

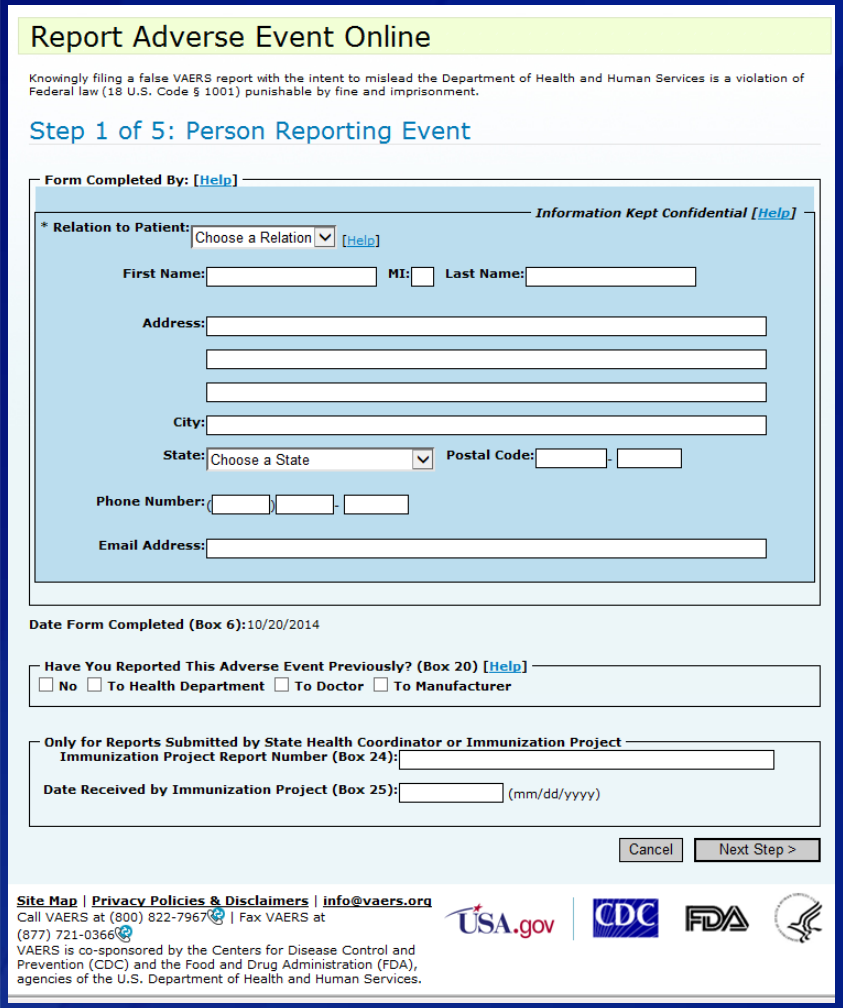
VAERS report form*

- 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
- Reports with incomplete information accepted
- All reports accepted without judgment on causality
- CDC encourages reporting as soon as possible, but no time limit on reporting



*Paper version (https://vaers.hhs.gov/resources/vaers_form.pdf) is called the VAERS-1 form

VAERS online reporting tool* (screen shots)



Report Adverse Event Online

Knowingly filing a false VAERS report with the intent to mislead the Department of Health and Human Services is a violation of Federal law (18 U.S. Code § 1001) punishable by fine and imprisonment.

Step 1 of 5: Person Reporting Event

Form Completed By: [Help]

Information Kept Confidential [Help]

* Relation to Patient: Choose a Relation [Help]

First Name: MI: Last Name:

Address:

City:

State: Choose a State Postal Code:

Phone Number: ( ) -

Email Address:

Date Form Completed (Box 6): 10/20/2014

Have You Reported This Adverse Event Previously? (Box 20) [Help]

No To Health Department To Doctor To Manufacturer

Only for Reports Submitted by State Health Coordinator or Immunization Project

Immunization Project Report Number (Box 24):

Date Received by Immunization Project (Box 25): (mm/dd/yyyy)

Cancel Next Step >

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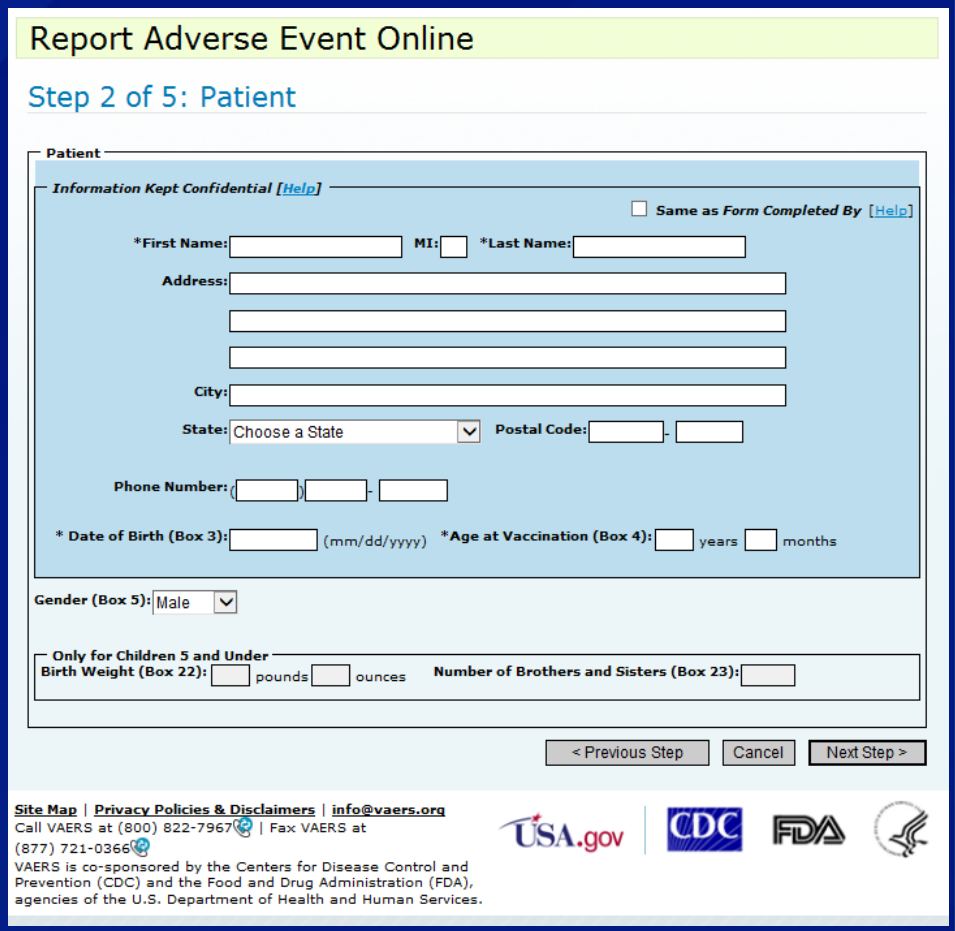
USA.gov CDC FDA



Report Adverse Event Online

Step 2 of 5: Patient

Patient

Information Kept Confidential [Help]

Same as Form Completed By [Help]

*First Name: MI: *Last Name:

Address:

City:

State: Choose a State Postal Code:

Phone Number: ( ) -

* Date of Birth (Box 3): (mm/dd/yyyy) *Age at Vaccination (Box 4): years months

Gender (Box 5): Male

Only for Children 5 and Under

Birth Weight (Box 22): pounds ounces Number of Brothers and Sisters (Box 23):

< Previous Step Cancel Next Step >

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USA.gov CDC FDA

*Online reporting form (https://vaers.hhs.gov/esub/step1) has same fields as the VAERS-1 form in a different presentation

Vaccine Adverse Event Reporting System (VAERS)[1]

Strengths

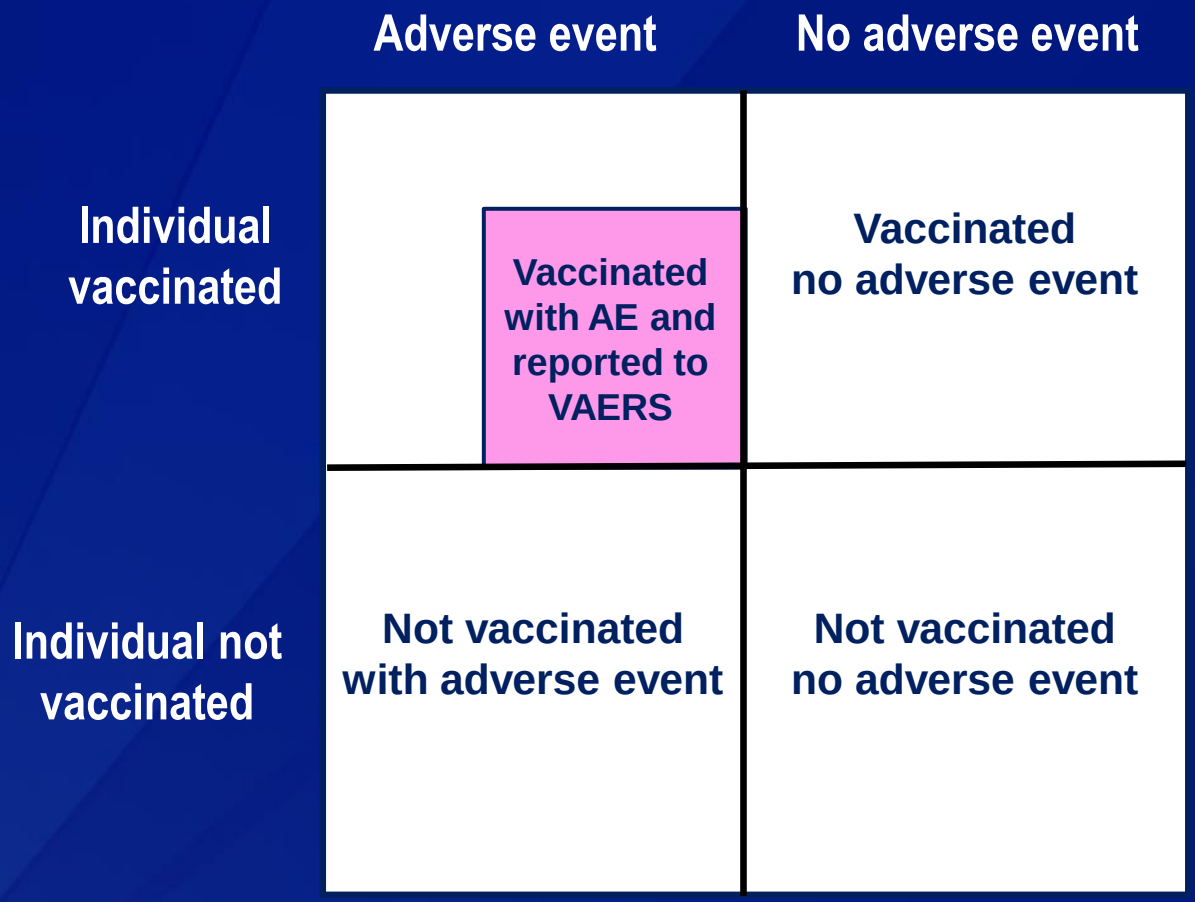
- National data; accepts reports from anyone
- Rapid signal detection
- Can detect rare adverse events
- Collects information about vaccine, characteristics of vaccinee, adverse event[2]
- Data available to public

Limitations

- Reporting bias
- Inconsistent data quality and completeness
- Lack of unvaccinated comparison group
- Generally cannot assess if vaccine caused an AE
- Pregnancy inconsistently reported

1. VAERS website: http://vaers.hhs.gov
2. Some reports have no adverse event

Limitations of VAERS data



- VAERS only contains partial data 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

Types of VAERS analyses

Automated analyses in VAERS

- Routinely conducted for influenza vaccine and for other CDC priority vaccines (e.g., human papillomavirus vaccine)
- Analyses focus on
  - Numbers of reports and proportions
    - Serious and non-serious reports
  - Pre-specified outcomes
  - Trends and historical comparisons (across years, across influenza seasons)
  - Specific vaccine products (e.g., new vaccines like recombinant and cell culture-based influenza vaccines)
- Looking for unusual or unexpected patterns
  - Increases in known AEs
  - Newly appearing AEs
  - Rare and/or serious AEs

Automated analysis for influenza vaccine and seizure reports (example)

Reporting trends of **SEIZURE** reports with onset interval 0-1 day
Following 2013-14 Inactivated seasonal influenza vaccines (IIV)[a]
Compared to 2012-13 Inactivated seasonal influenza vaccines (IIV) through 2003-04 (by season) (IIV)
By age-group and all ages, initial domestic reports only, VAERS reports as of 03/07/2014[b]

	6-23 mos		2 - 4 yrs		All ages	
Season	Total Reports	Seizure N (%)	Total	Seizure N (%)	Total Reports	Seizure N (%)
2013-14 IIV	158	29 (18.35%)	156	13 (8.33%)	5832	87 (1.49%)
2012-13 IIV	150	16 (10.67%)	148	10 (6.76%)	5451	67 (1.23%)
2011-12 IIV	267	83 (31.09%)	138	10 (7.25%)	5011	136 (2.71%)
2010-11 IIV	289	73 (25.26%)	214	15 (7.01%)	5862	138 (2.35%)
2009-10 IIV	246	36 (14.63%)	213	13 (6.10%)	4265	93 (2.18%)
2008-09 IIV	176	28 (15.91%)	144	6 (4.17%)	2910	61 (2.10%)
2007-08 IIV	219	49 (22.37%)	146	12 (8.22%)	2303	77 (3.34%)
2006-07 IIV	160	27 (16.88%)	129	2 (1.55%)	1802	41 (2.28%)
2005-06 IIV	157	23 (14.65%)	108	5 (4.63%)	1822	47 (2.58%)
2004-05 IIV	150	26 (17.33%)	69	3 (4.35%)	955	33 (3.46%)
2003-04 IIV	68	7 (10.29%)	101	2 (1.98%)	1438	20 (1.39%)

Automated analysis for influenza vaccine and Guillain-Barré syndrome (example)

Reporting trends of **GUILLAIN-BARRÉ SYNDROME (GBS)** reports
Following 2013-14 Inactivated seasonal influenza vaccines (IIV)[a]
Compared to 2012-13 Inactivated seasonal influenza vaccines (IIV) through 2003-04 (by season) (IIV)
By age-group and all ages, initial domestic reports only, VAERS reports as of 03/07/2014[b]

	6 mos - 17 yrs		18-64 yrs		65+ yrs		All ages	
Season	Total Reports	GBS N (%)	Total Reports	GBS N (%)	Total Reports	GBS N (%)	Total Reports	GBS N (%)
2013-14 IIV	1133	5 (0.44%)	4333	42 (0.97%)	2094	18 (0.86%)	7560	65 (0.86%)
2012-13 IIV	1106	7 (0.63%)	4285	44 (1.03%)	1810	17 (0.94%)	7201	68 (0.94%)
2011-12 IIV	1200	9 (0.75%)	3729	49 (1.31%)	1633	33 (2.02%)	6562	91 (1.39%)
2010-11 IIV	1415	5 (0.35%)	4422	63 (1.42%)	1951	57 (2.92%)	7788	125 (1.61%)
2009-10 IIV	1444	14 (0.97%)	3504	67 (1.91%)	839	37 (4.41%)	5787	118 (2.04%)
2008-09 IIV	978	3 (0.31%)	2202	22 (1.00%)	645	7 (1.09%)	3825	32 (0.84%)
2007-08 IIV	996	3 (0.30%)	1604	22 (1.37%)	582	15 (2.58%)	3182	40 (1.26%)
2006-07 IIV	743	3 (0.40%)	1250	23 (1.84%)	435	11 (2.53%)	2428	37 (1.52%)
2005-06 IIV	602	2 (0.33%)	1263	19 (1.50%)	512	8 (1.56%)	2377	29 (1.22%)
2004-05 IIV	443	0 (0)	540	7 (1.30%)	361	5 (1.39%)	1344	12 (0.89%)
2003-04 IIV	416	2 (0.48%)	1165	12 (1.03%)	397	5 (1.26%)	1978	19 (0.96%)

Clinical reviews

- **Clinical review of reports and medical records (if available) in VAERS may be performed to:**
  - **Evaluate unusual or unexpected reporting**
  - **Evaluate new vaccines or when new recommendations are made for existing vaccines**
  - **Monitor high priority conditions (e.g., anaphylaxis, miscarriage)**
  - **Evaluate data mining signals (signal assessment)**

In order to

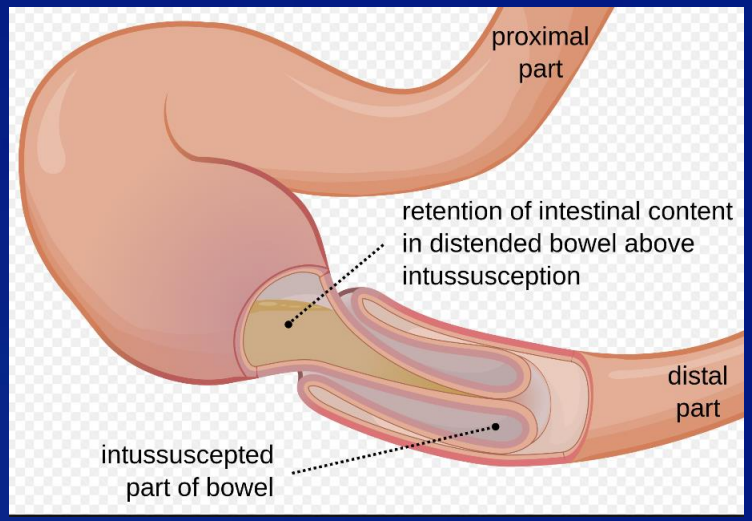
- **Characterize completeness and quality of reports**
- **Verify diagnoses**
- **Characterize clinical and laboratory features**
- **Assess other potential risk factors (e.g., co-administration of vaccines, underlying health conditions)**
- **Evaluate the interval between vaccination and the adverse event**

Reporting rates using VAERS data

- Uses vaccine doses distributed (or administered if available) to calculate reporting rates of specific AEs to VAERS
  - i.e., specific AE reported/100,000 doses distributed, or serious reports/100,000 doses distributed
- Compare with background rates from the literature or other sources
- If reporting rates for a specific AE approach or exceed background rates, it might require further assessment
- Because of under-reporting to VAERS, reporting rates must be interpreted cautiously
- Limitations include inability to assess if vaccine doses distributed are actually administered and to whom (i.e., ages, sex, etc.)

Reporting rates example: RotaShield® and intussusception (background)

- In August 1998 FDA licensed the rhesus-human rotavirus reassortant-tetravalent vaccine RotaShield®
- In March 1999 ACIP recommended universal infant vaccination with RotaShield®
- Within 9 months of licensure, reports to VAERS raised suspicions of a possible problem with intussusception



Reporting rates example: RotaShield® and intussusception (results - by May 1999)

- 9 cases of intussusception reported to VAERS
  - 8/9 cases after dose 1
  - 8/9 cases within 1 week of vaccination
  - Median age 4 months
  - 5 required surgical intervention

By comparison

- From Nov 1990 - Nov 1998 in VAERS
  - Only 3 cases intussusception reported following receipt of any other vaccine

Reporting rates example: RotaShield® and intussusception (observed v. expected cases)

Through July 1999

- Assumptions
  - 1.5 million doses of RotaShield® administered
  - Background rate: 51/100,000 infant-years*
- Expected: 14-16 cases within 1 week of vaccination by chance alone
- Observed: 12/15 VAERS reports with onset <1 week after vaccination
- Know VAERS reporting sensitivity <<100%
  - Reporting to VAERS that approaches background rate is concerning due to known underreporting to VAERS

* New York State Hospital discharges 1991-97

Data mining

- Definition: the process of collecting, searching through, and analyzing a large amount of data in a database, as to discover patterns or relationships*
- Since AE rates cannot be calculated from VAERS data, data mining techniques have been developed to assess for disproportional reporting in the VAERS database
- The proportional reporting ratio (PRR) and empirical Bayesian (EB) data mining are used for signal detection in VAERS

*Dictionary.com. *Dictionary.com Unabridged*. Random House, Inc. http://dictionary.reference.com/browse/data%20mining

Proportional Reporting Ratio (PRR)*†

- PRR is a statistic used to compare the proportions of AEs for a specific vaccine or vaccine type with proportions of AEs for other vaccines
- An AE with a higher proportion for a specific vaccine or vaccine type than for other vaccines might be considered a signal if the PRR exceeds a statistical threshold
- PRR does not estimate relative risk and can be unstable with small numbers
- A statistically significant PRR does NOT demonstrate the vaccine is associated with increased risk for the adverse event or that a new safety problem exists
- PRR findings may prompt further assessment to evaluate association

*Evans SJW, Waller PC, Davis S (2001). Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiology and Drug Safety 10:483-6.

†Iskander et al. Data mining in the US using the Vaccine Adverse Event Reporting System. Drug Saf. 2006;29:375-84.

Proportional Reporting Ratio (PRR)*

	Specific adverse event	All other adverse events
Vaccine of interest	a	b
All other vaccines	c	d

$$PRR = \frac{a/(a+b)}{c/(c+d)}$$

Criteria: PRR ≥ 2 , Chi^2 ≥4 and number of reports ≥3*

*Evans SJW, Waller PC, Davis S (2001). Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiology and Drug Safety 10:483-6.

Empirical Bayesian data mining*†

- Empirical Bayesian (EB) data mining is used by FDA to detect disproportional reporting in the VAERS database
- EB data mining assesses for adverse events reported more frequently than expected after a specific vaccine product compared with other vaccines in the VAERS database
  - Empirical Bayesian Geometric Mean (EBGM) is the point estimate for disproportionality
- EBGM has shrinkage toward the null based on a prior distribution derived from the entire VAERS database (i.e., a sample size adjustment)

*DuMouchel, W., Bayesian data mining in large frequency tables, with an application to the FDA spontaneous reporting system. Am Stat, 1999. 53: p. 177-190.

†Bate A, Evans SJ. Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiol Drug Saf. 2009;18:427-36.

Empirical Bayesian data mining

- A vaccine-adverse event pairing "signals" when a statistical threshold is reached (EB05>2) (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., nasal congestion after live attenuated influenza vaccine)
- Data mining findings may prompt further assessment to evaluate association

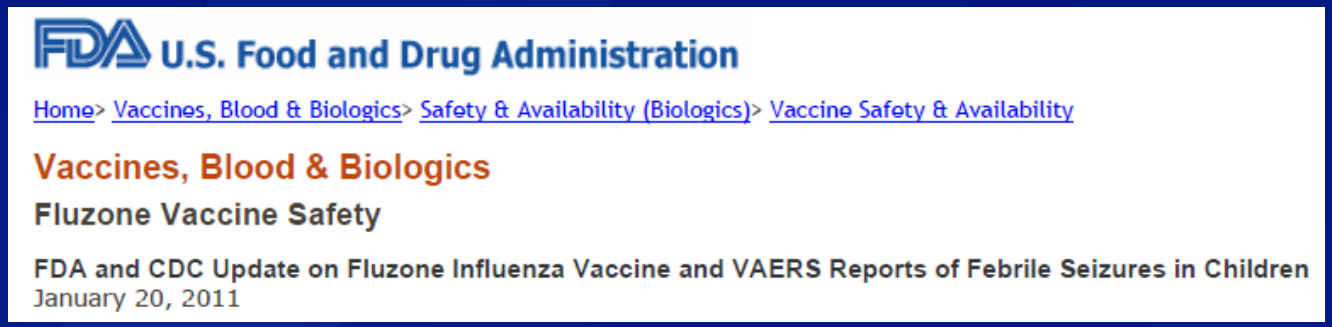
Data mining signal for febrile seizures after 2010-11 inactivated influenza vaccine (IIV3)

- 2010 Southern Hemisphere CSL IIV3 was associated with a transient increased risk for febrile seizures in young children*
  - In the US, IIV3 before 2010-11 season not previously associated with increased risk for febrile seizure
  - ACIP recommended for US 2010-11 season not using CSL vaccine for children aged <9 years; Fluzone® was the only recommended US 2010-11 IIV3 product for children aged 6-23 months
- During the 2010-11 influenza season FDA detected disproportional reporting (EB05>2) for febrile seizures following Fluzone® in young children in the VAERS database
- Clinical review showed VAERS reports had typical features of febrile seizures and all children recovered†

*CDC. *MMWR* Aug. 13, 2010. Update: Recommendations of the Advisory Committee on Immunization Practices (ACIP) Regarding Use of CSL Seasonal Influenza Vaccine (Afluria) in the United States During 2010-11. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5931a4.htm?s_cid=mm5931a4_w

†http://vaers.hhs.gov/resources/VAERSupdate_FebrileSeizures_Children.pdf

Data mining signal for febrile seizures after 2010-11 inactivated influenza vaccine (IIV3)


U.S. Food and Drug Administration

Home> Vaccines, Blood & Biologics> Safety & Availability (Biologics)> Vaccine Safety & Availability

Vaccines, Blood & Biologics

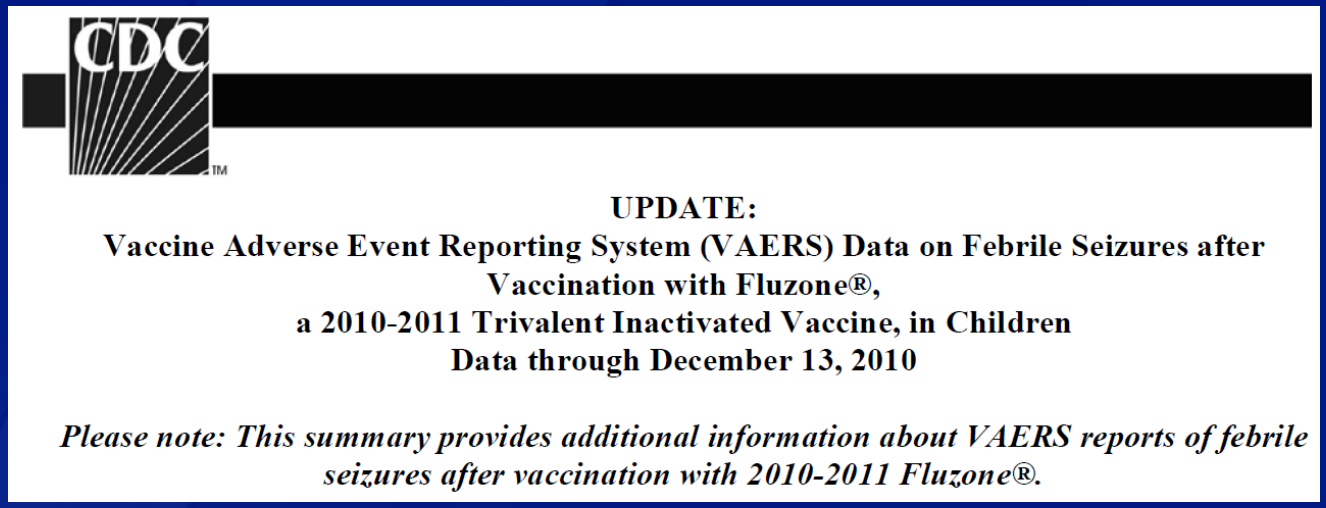
Fluzone Vaccine Safety

FDA and CDC Update on Fluzone Influenza Vaccine and VAERS Reports of Febrile Seizures in Children
January 20, 2011

"FDA and CDC have recently detected an increase in the number of reports to VAERS of febrile seizures following vaccination with Fluzone TIV… reported febrile seizures have primarily been seen in children younger than 2 years of age"

http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/ucm240037.htm

Data mining signal for febrile seizures after 2010-11 inactivated influenza vaccine (IIV3)



UPDATE:
Vaccine Adverse Event Reporting System (VAERS) Data on Febrile Seizures after Vaccination with Fluzone®, a 2010-2011 Trivalent Inactivated Vaccine, in Children
Data through December 13, 2010

Please note: This summary provides additional information about VAERS reports of febrile seizures after vaccination with 2010-2011 Fluzone®.

"FDA and CDC have recently become aware of an increased number of reports of febrile seizures after vaccination with Fluzone® … in children younger than 5 years of age in the United States, particularly in children aged 6-23 months. Fluzone® is the only product that is both licensed and recommended for 6-23 month olds in the United States this influenza season."

http://vaers.hhs.gov/resources/VAERSupdate_FebrileSeizures_Children.pdf

Data mining signal for febrile seizures after 2010-11 inactivated influenza vaccine (IIV3)

Vaccine 30 (2012) 2020–2023

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Brief report

Febrile seizures after 2010–2011 influenza vaccine in young children, United States: A vaccine safety signal from the vaccine adverse event reporting system

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ABSTRACT

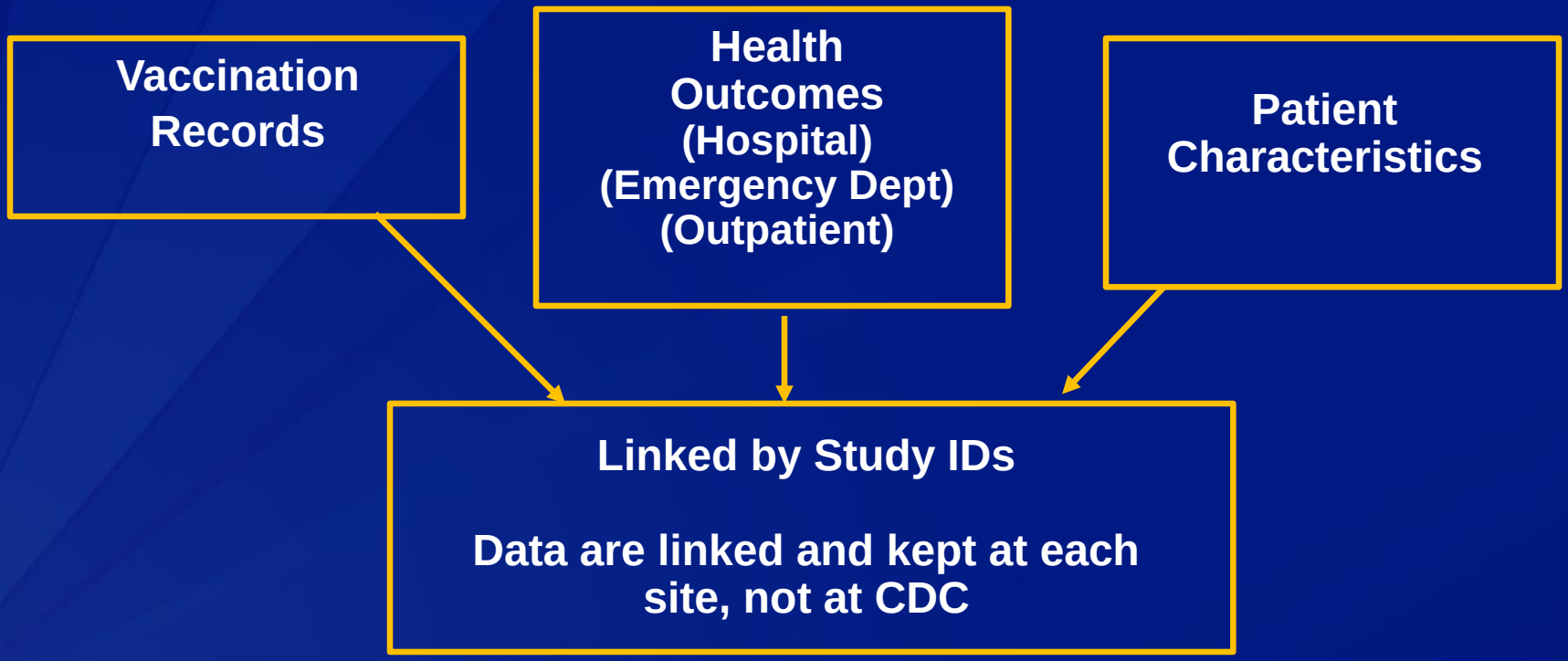
During the 2010–2011 influenza season, the Centers for Disease Control and Prevention and the Food and Drug Administration conducted enhanced vaccine safety monitoring for possible febrile seizures in all trivalent influenza vaccine (TIV) products in the United States using the Vaccine Adverse Event Reporting System (VAERS). We used Empirical Bayesian data mining techniques to assess disproportionate reporting after TIV and reviewed febrile seizure reports in children aged <5 years. On November 23, 2010, the combination of the coding term "febrile convulsion" and the Fluzone® TIV product exceeded a predetermined threshold in the VAERS database. By December 10, we confirmed 43 reports of febrile seizure following TIV in children aged 6–23 months. Clinical features of most reports were consistent with typical uncomplicated febrile seizures, and all children recovered. Further epidemiologic assessment of a

Leroy et al. Febrile seizures after 2010-2011 influenza vaccine in young children, United States: a vaccine safety signal from the vaccine adverse event reporting system. Vaccine. 2012 Mar 2;30(11):2020-3.

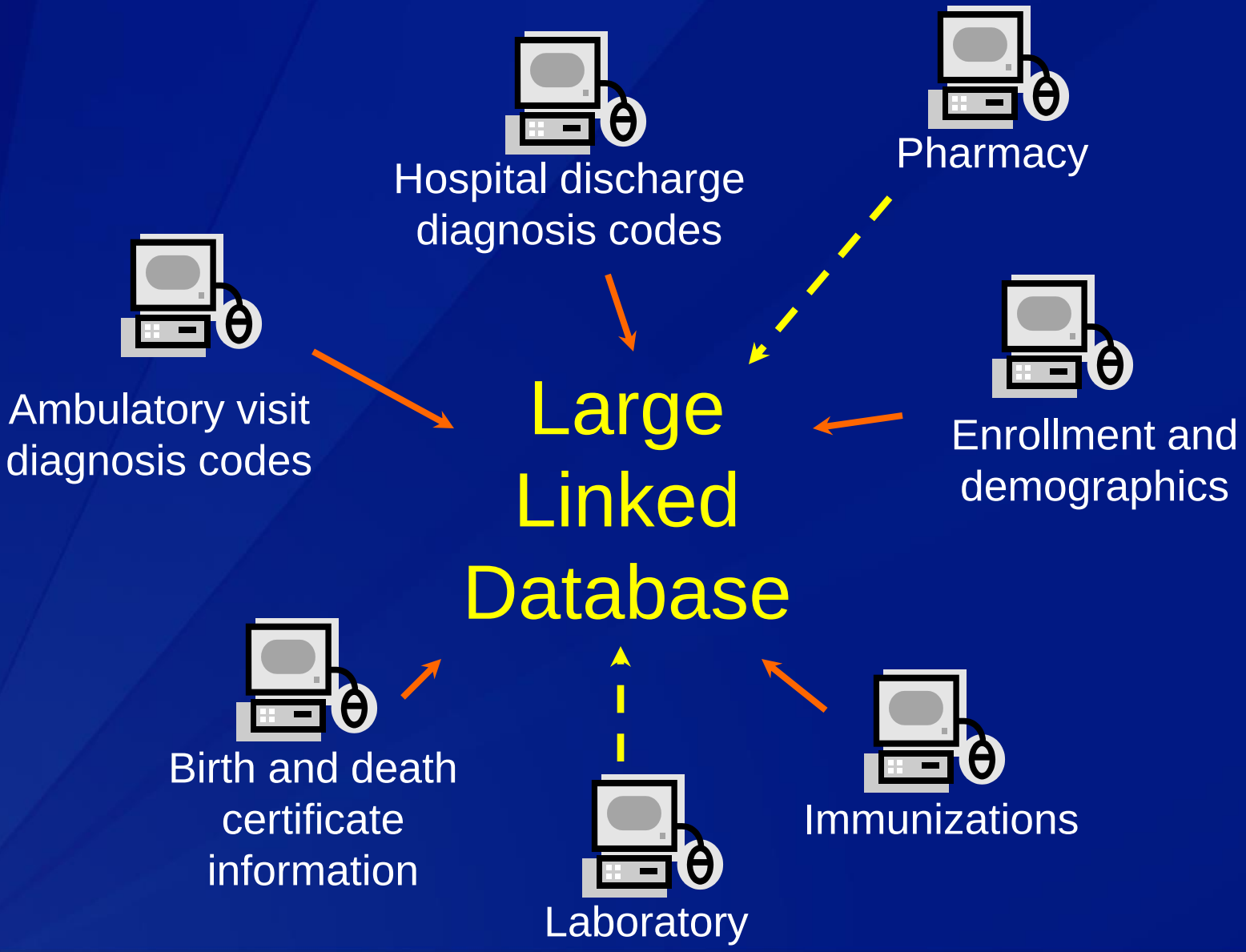
Vaccine Safety Datalink (VSD)

Vaccine Safety Datalink (VSD)

- Established in 1990
- Collaboration between CDC and 9 integrated healthcare plans
- Data on over 9 million persons per year (~3% of US population)
- Links vaccination data to health outcome data



VSD administrative data sources



Vaccine Safety Datalink (VSD)

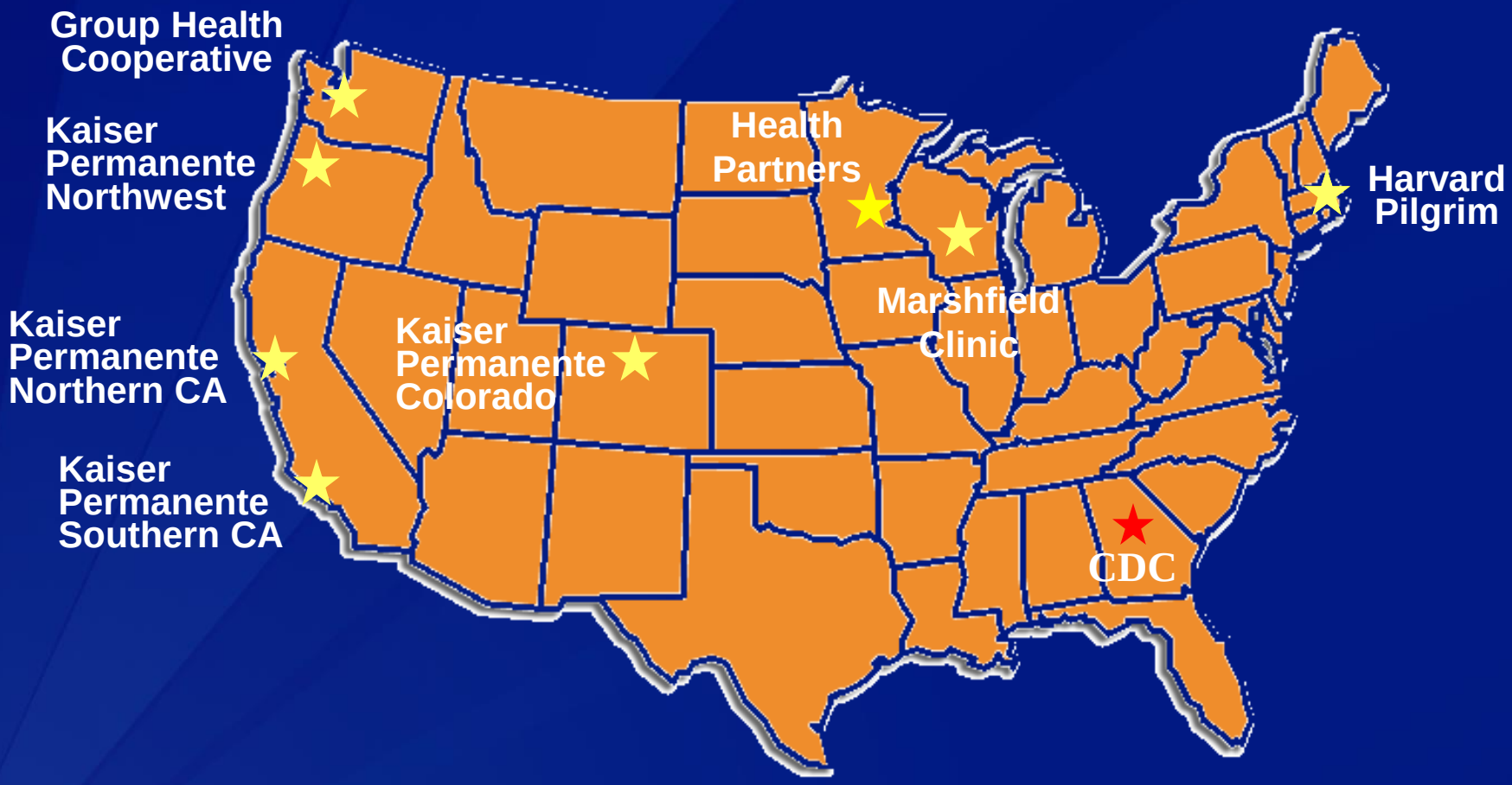
Strengths

- All medical encounters are available
- Vaccine registry data
- Can calculate rates
- Can assess risk of an AE
- 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

Vaccine Safety Datalink Sites in 2015



VSD Rapid Cycle Analysis (RCA)

- Developed to provide weekly near real-time assessment of the safety of newly licensed vaccines or new recommendations for existing vaccines
- Adverse events being monitored are pre-specified
- RCA is hypothesis testing, not data mining
- Findings of association using RCA are considered safety signals and further refinement of the analysis needs to occur once a signal is identified

Basics of VSD RCA

- For each vaccine, choose specific outcomes to monitor
- Each week, evaluate the number of outcomes in vaccinated persons
- Compare it to the expected number of outcomes based on a comparison group
- Adjust for repeated testing of the same data (maximized sequential probability ratio testing)
  - Null hypothesis – No excess risk
  - Alternative hypothesis – Increase in risk
  - The test statistic is the log likelihood ratio – depends on the observed vs. expected number of events

Choosing RCA outcomes

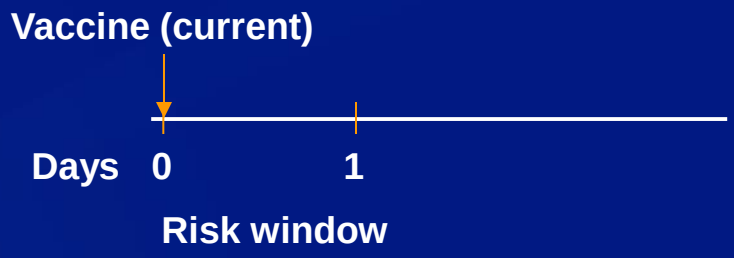
1. **Select outcomes based on plausibility**
   - Pre-licensure data
   - Known biologic properties of the vaccine
   - VAERS reports
   - Literature on this or similar vaccines

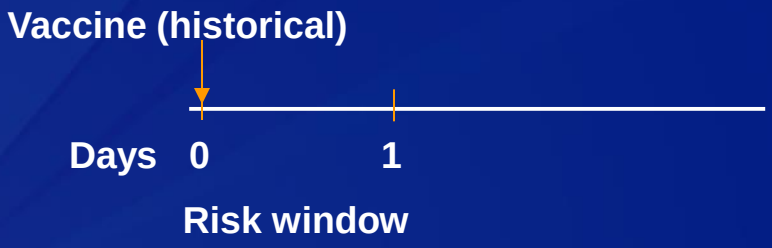
2. **Additional criteria**
   - Clinically well-defined
     - e.g., Guillain-Barré syndrome vs. “neurologic problems”
   - Acute-onset
   - Serious
   - Relatively uncommon

RCA methods

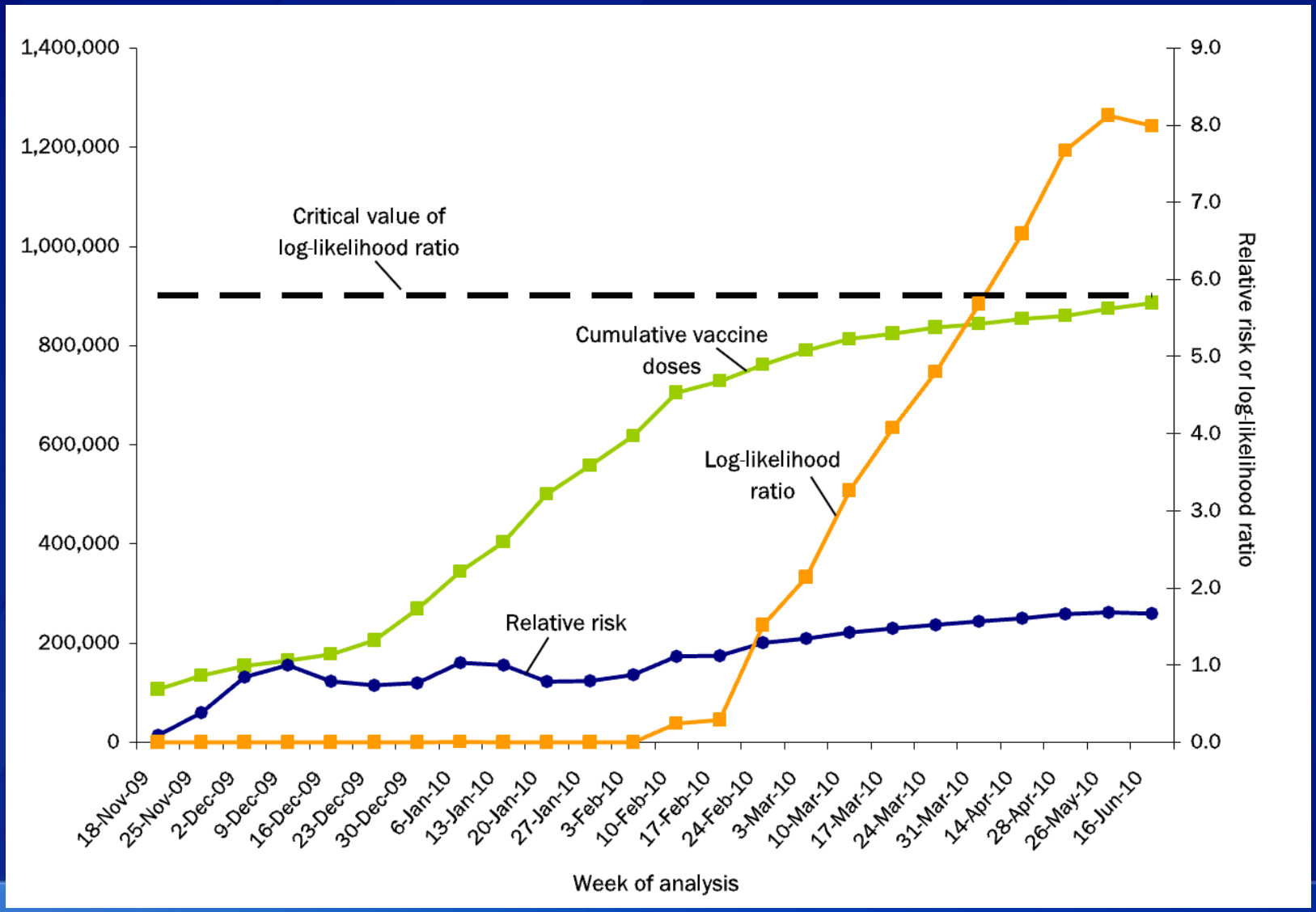
Self controlled design

Current vs. historical





Example of maximized sequential probability ratio testing (maxSPRT)



Example: Rapid Cycle Analysis signal for febrile seizures in young children following 2010-11 inactivated influenza vaccine

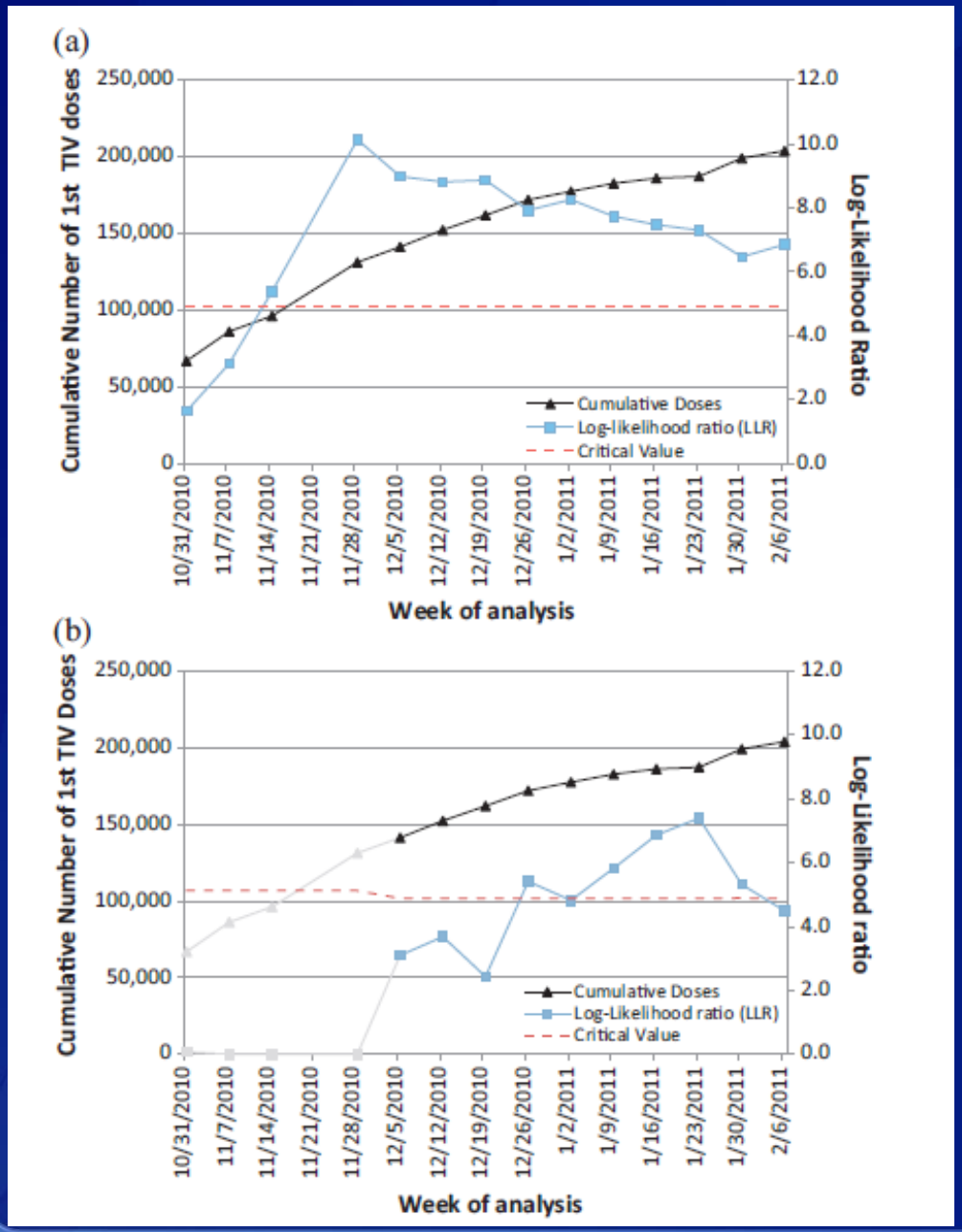
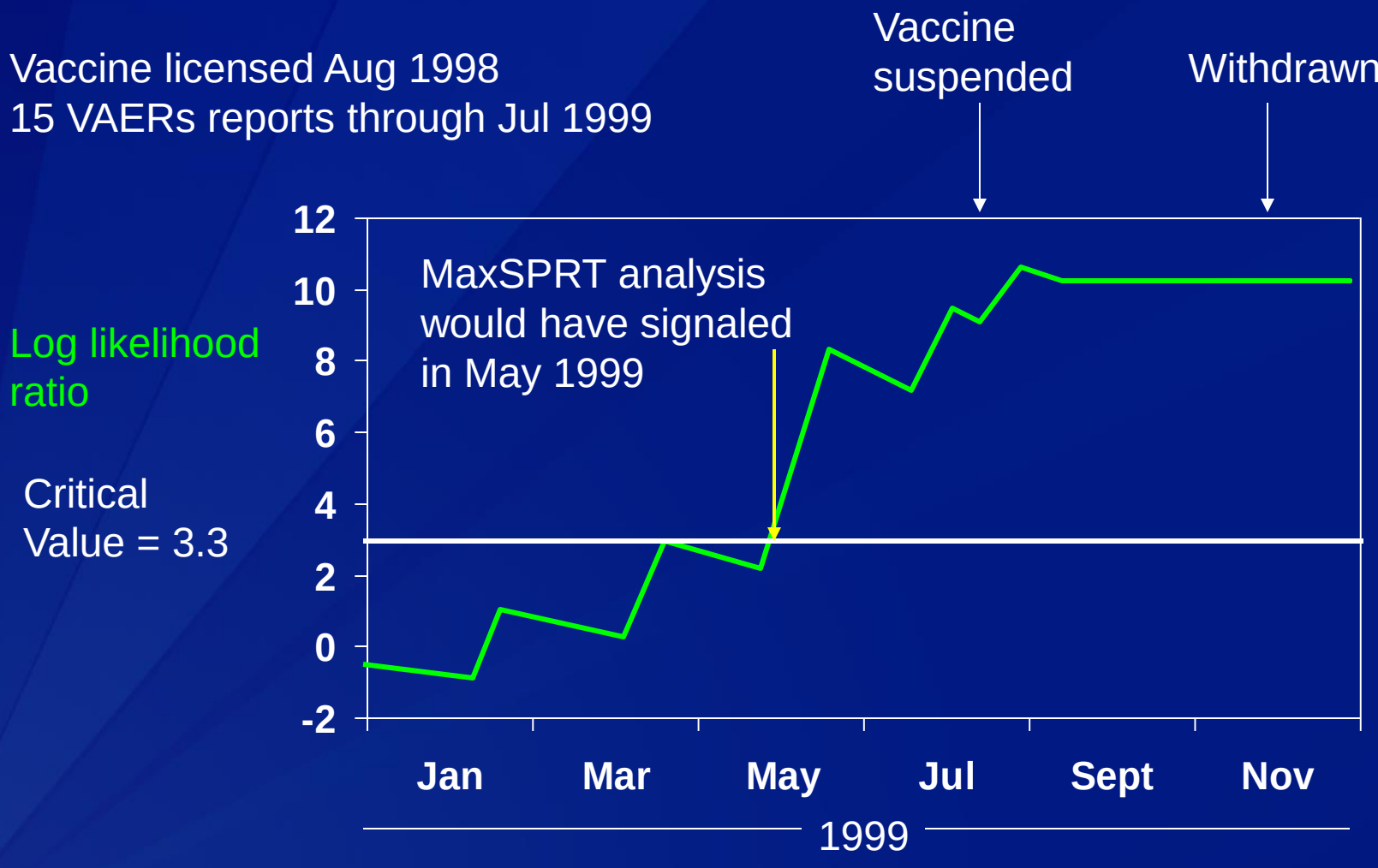


Fig. 1. Log-likelihood ratio during prospective surveillance for seizures following 1st dose trivalent inactivated influenza vaccine (TIV) in children ages 6–59 months for (a) current vs. historical and (b) self-controlled risk interval designs in the Vaccine Safety Datalink, August 1, 2010 to February 5, 2011. Critical value thresholds for signal identification are shown by the dashed lines. Control interval definition for self-controlled risk interval design was changed from 7–8 days to 14–15 days post vaccination beginning the week of analysis of 12/5/2010 to avoid overlap with the known increased risk of seizures in the 5–12 days following MMR and MMRV.

Tse et al. Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010-2011. Vaccine. 2012 Mar 2;30(11):2024-31.

Example: Rotashield® vaccine and intussusception (historical analysis)

Vaccine licensed Aug 1998
15 VAERs reports through Jul 1999



Summary

- Vaccine Adverse Reporting System (VAERS)
  - Automated analyses, clinical reviews, reporting rates, data mining
- Vaccine Safety Datalink (VSD)
  - Rapid Cycle Analysis
- Findings or signals do NOT demonstrate the vaccine is associated with increased risk for the adverse event or that a new safety problem exists
- Further assessment to confirm an increased risk or a new safety problem is usually required
- Signal assessment is often performed in the VSD using epidemiologic studies employing self-controlled methods with chart review or traditional methods (e.g., case control)*

*McNeil et al. The Vaccine Safety Datalink: successes and challenges monitoring vaccine safety. Vaccine. 2014 Sep 22;32(42):5390-8.

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Division of Healthcare Quality Promotion – Immunization Safety Office

Thank You

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Telephone, 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov Web: www.cdc.gov

Extra slides

Types of vaccine adverse events

Category	Cause
Vaccine quality defect-related reaction	due to one or more quality defects of the vaccine product including its administration device as provided by the manufacturer
Immunization error-related reaction	inappropriate vaccine handling, prescribing, or administration
Immunization anxiety-related reaction	arises from anxiety about the immunization
Vaccine product-related reaction	due to one or more of the inherent properties of the vaccine product
Coincidental event	something other than the vaccine product, immunization error, or immunization anxiety

Adverse reaction

- An adverse reaction is an adverse event that is caused by a vaccine
  - A body of scientific evidence exists to suggest that the vaccine cased the adverse event
- Examples of adverse reactions
  - Local: redness, swelling, pain at the injection site
  - Systemic: fever, myalgia

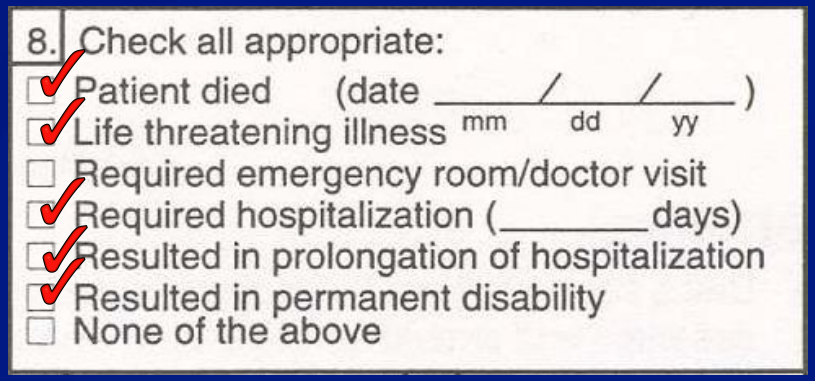
Why we monitor vaccine safety after licensure

- High safety standards expected for vaccines
  - Vaccines are usually administered to healthy people (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

VAERS follow-up

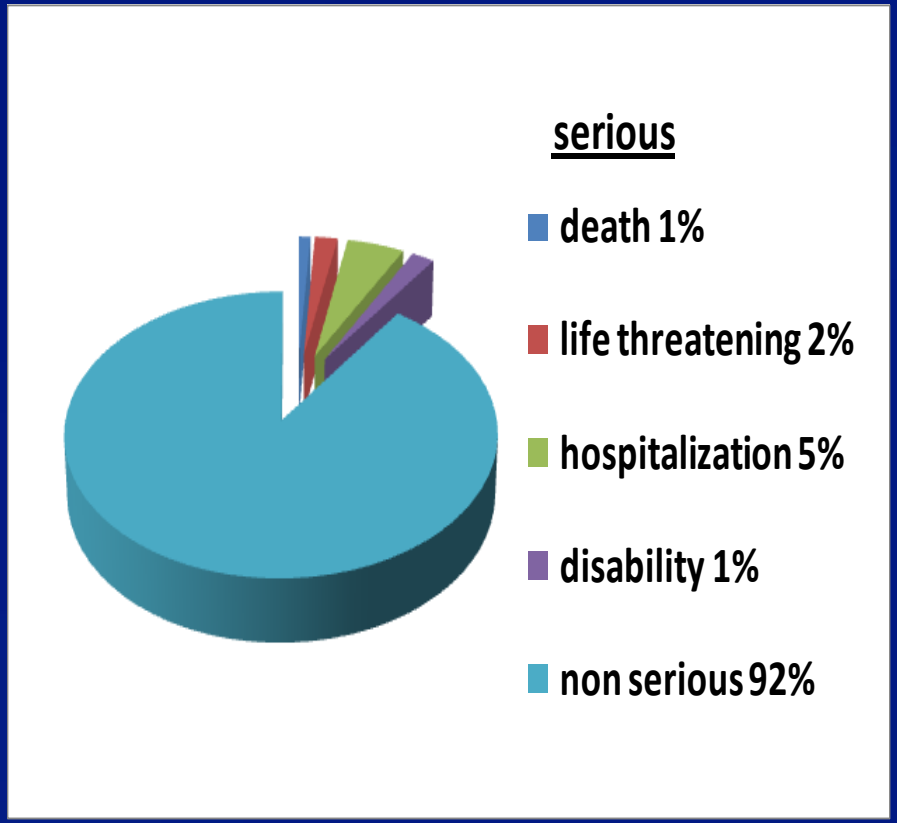
- VAERS staff follow up with health care providers on serious reports and certain selected reports of interest by phone to obtain
  - Medical records
  - Autopsy reports
- Medical officers review these medical records and VAERS reports
- Letter sent to reporters to check recovery status for all serious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

VAERS form Box 8 – Serious status

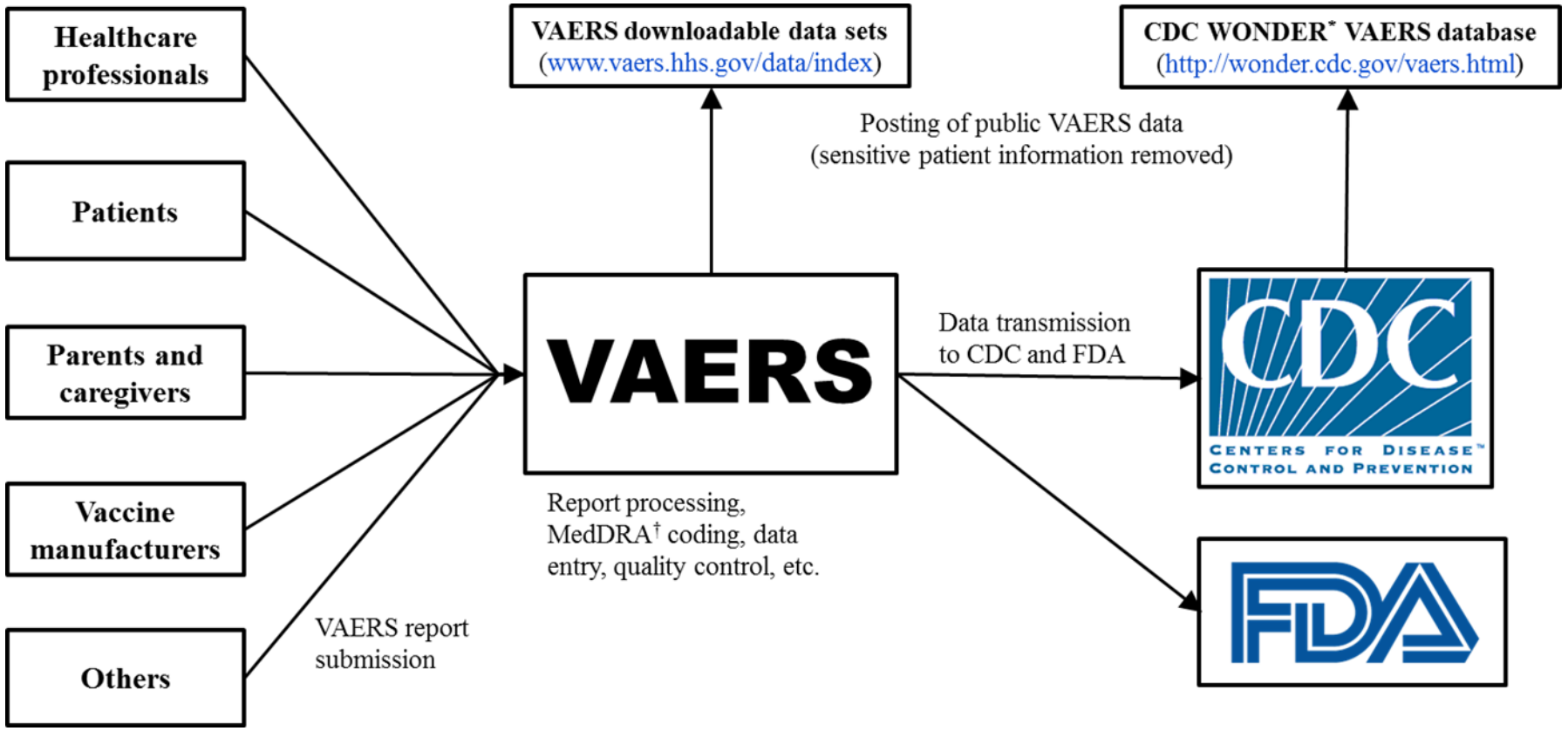

8. Check all appropriate:
- ☑ Patient died (date ___/___/___) mm dd yy
- ☑ Life threatening illness
- ☐ Required emergency room/doctor visit
- ☑ Required hospitalization (_____days)
- ☑ Resulted in prolongation of hospitalization
- ☑ Resulted in permanent disability
- ☐ None of the above

VAERS reports

- 92% of VAERS reports are “non-serious”
- 8% of VAERS reports are “serious”



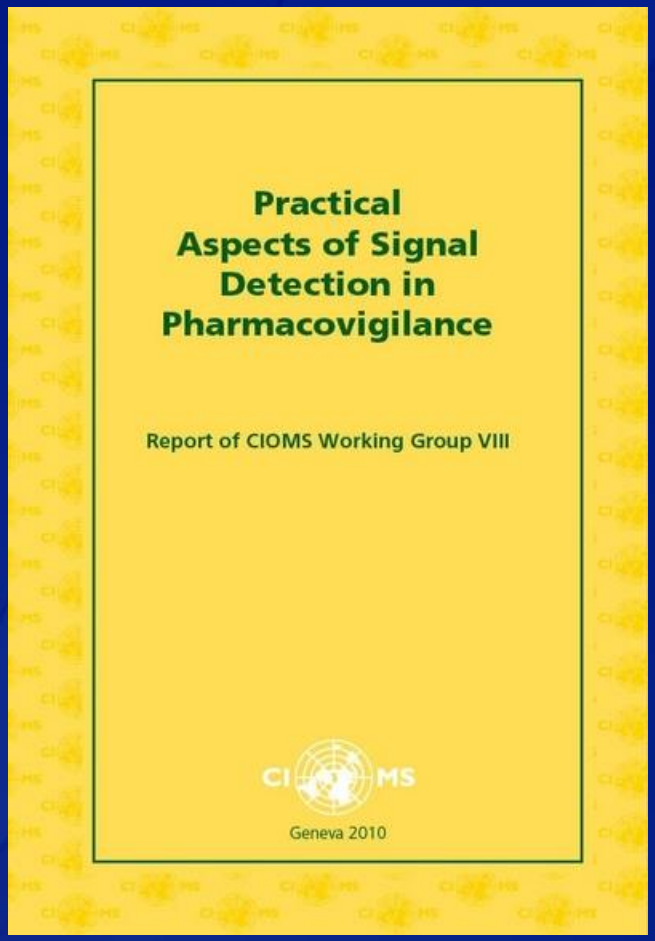
(VAERS) report submission and data flow



Detecting signals

- Spontaneous reporting systems are cornerstone
  - Particularly for rare or unusual adverse events
- Other sources
  - Literature, expert reviews, inquires, media, internet
  - Large linked databases
- Two main US systems
  - Vaccine Adverse Event Reporting System (VAERS)
  - Vaccine Safety Datalink (VSD)

Vaccine Safety Signal Management Guidance



Guidance for Industry
Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
March 2005
Clinical Medical

Vaccine safety signal management framework