Vaccine Safety Monitoring in the United States

A System of Multiple Components with Contrasting Strengths and Limitations

Colorado Children's Immunization Coalition (CCIC)

Aurora, CO

September 14, 2017

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Disclosures

- Matthew F. Daley, M.D., has documented no financial relationships to disclose or conflicts of interest to resolve
- Matthew F. Daley, M.D., has documented that his presentation will not involve discussion of unapproved, off-label, experimental, or investigational use of any medical product

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Acronyms Used in Talk

Acronym	Full name
VAERS	Vaccine Adverse Event Reporting System
VSD	Vaccine Safety Datalink
PRISM	Post-Licensure Rapid Immunization Safety Monitoring
CISA	Clinical Immunization Safety Assessment
ACIP	Advisory Committee on Immunization Practices
AHRQ	Agency for Healthcare Research and Quality
CDC	Centers for Disease Control and Prevention
FDA	Food and Drug Administration
IOM	Institute of Medicine
RV1	Rotavirus vaccine, monovalent
RV5	Rotavirus vaccine, pentavalent
VIS	Vaccine Information Statement

Outline

- Vaccine safety “Life Cycle”
- Illustrative story
- Multi-faceted system: VAERS; VSD; PRISM; CISA
- Comprehensive reviews of the evidence regarding vaccine safety
- New frontiers

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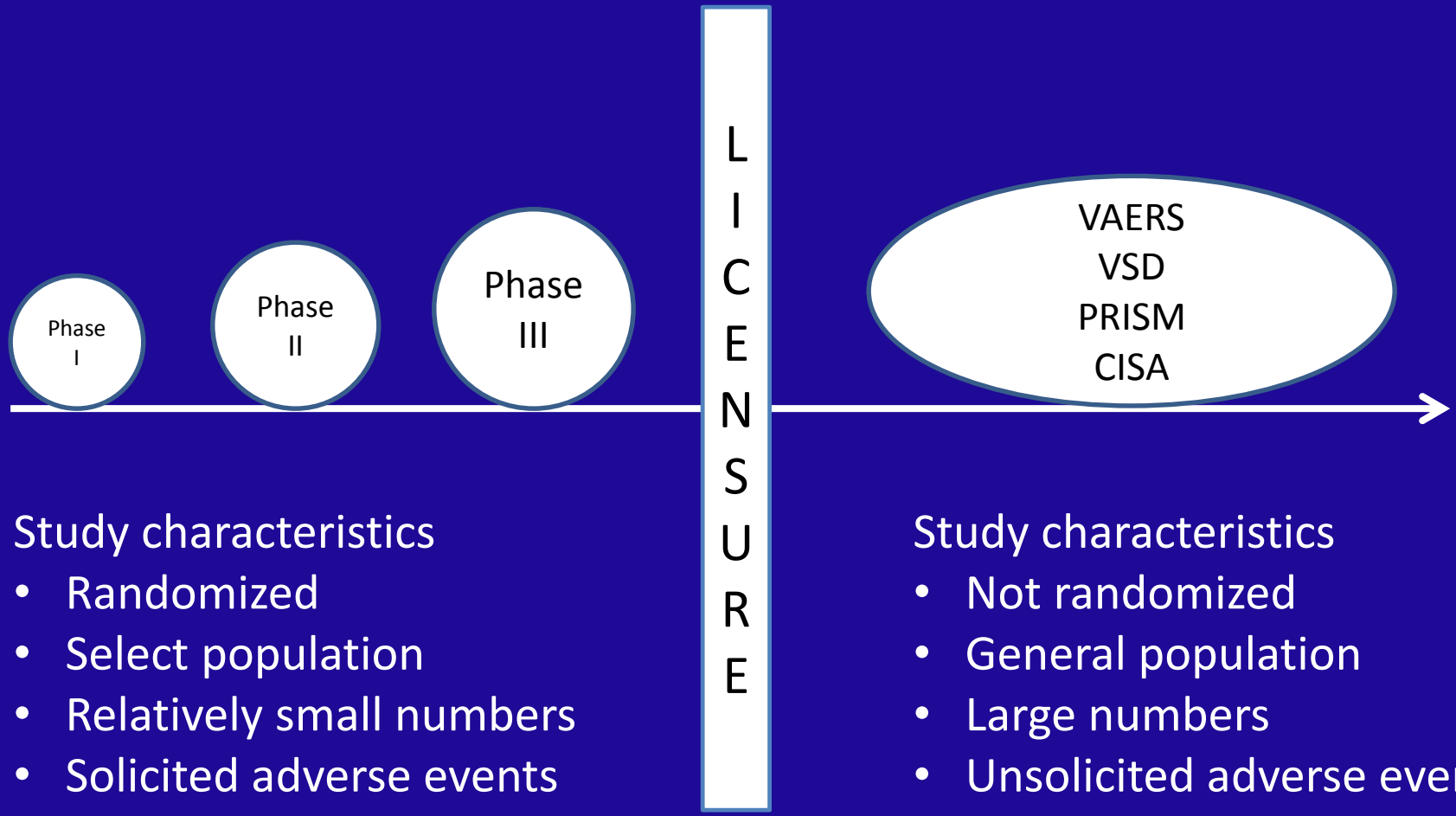
The Vaccine Safety "Life Cycle" (I)



Study characteristics
- Randomized
- Select population
- Relatively small numbers
- Solicited adverse events

Study characteristics
- Not randomized
- General population
- Large numbers
- Unsolicited adverse events

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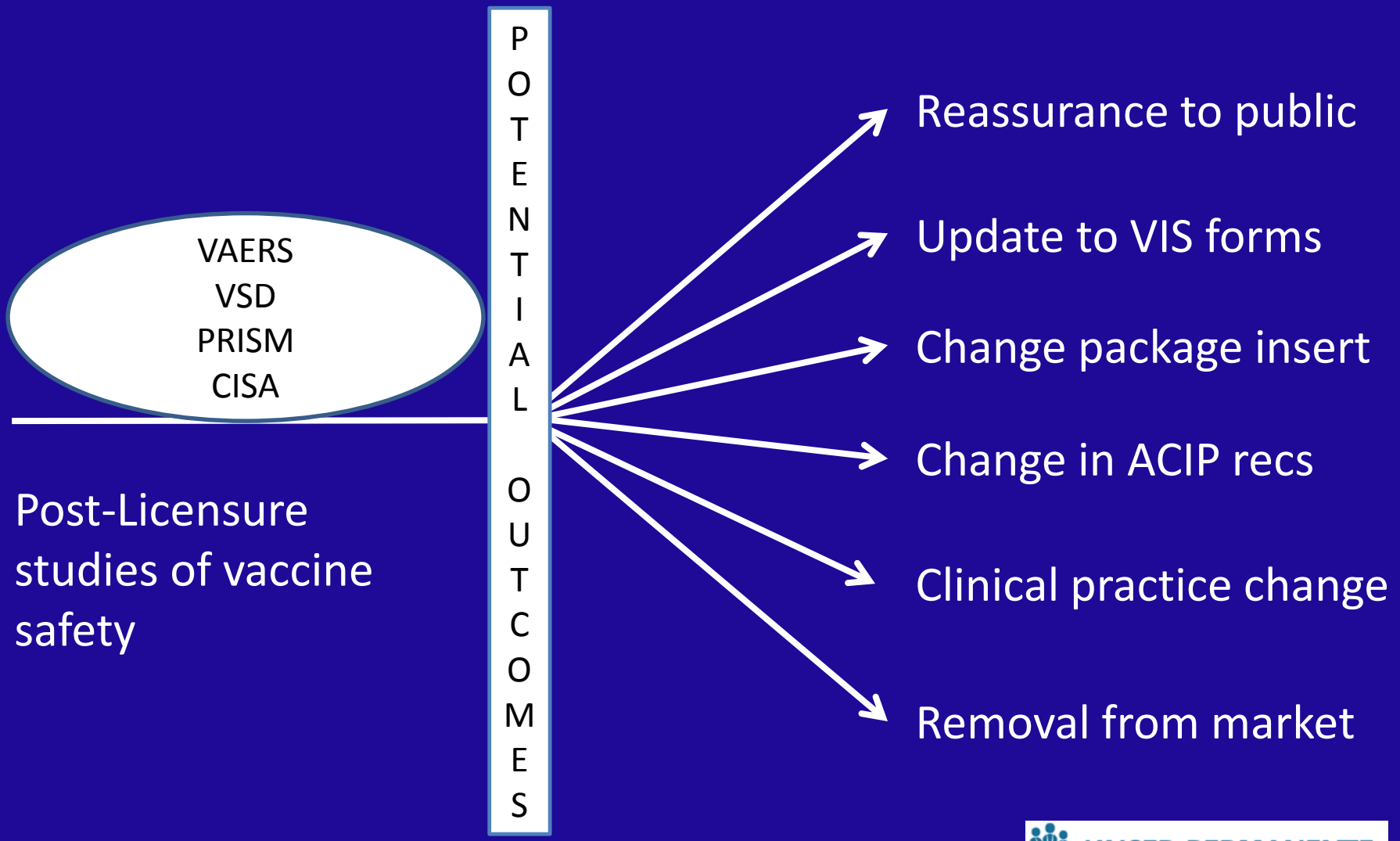
The Vaccine Safety "Life Cycle" (II)



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An Illustrative Story (I): Rotavirus Vaccine and Intussusception

- Pre-licensure trials (thousands of children) showed 5 cases of intussusception in vaccinated, 1 case in controls (not significant)
- Vaccine (RotaShield) licensed in 1998
- In May 1999 “signal” noted in Vaccine Adverse Event Reporting System: 9 cases in 6 months; cluster of 4 cases in April-May 1999
- “Signal” was hypothesis generating

Ref: CDC. MMWR 1999;48:577-81.

Follow-up Studies of VAERS "Signal"

- Test the following hypothesis
  - Is RotaShield vaccine associated with increased risk of intussusception?
- Studies initiated immediately after "signal"
  - Cohort study conducted in VSD, plus other sites
  - Case-control study conducted in 19 states, through state public health departments
- Thirty-fold increased risk for intussusception
- Vaccine withdrawn from U.S. market in 1999

Ref: 1) Kramarz et al. Pediatr Infect Dis J 2001;20:410-6.
2) Murphy TV et al. NEJM 2001;344:564-72.

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Attributes of U.S. Vaccine Safety Monitoring System, 1999

Attribute	VAERS	VSD	PRISM	CISA
National in scope	✓			
Relies on voluntary reporting	✓			
Patient population defined by enrollment		✓		
Does not rely on voluntary reporting		✓		
Case detection through diagnosis codes (ICD)		✓		
Case confirmation by manual record review		✓		
Neal real time surveillance				
Power to study relatively rare outcomes		✓		
Examination of individual patients				
Collection of genetic specimens				
Hypothesis generating	✓	✓		
Hypothesis testing		✓		

Overview of the Vaccine Adverse Event Reporting System (VAERS)

- Created in 1990
- Overseen jointly by CDC and FDA
- Spontaneous, voluntary, national reporting system which collects reports of adverse events occurring after vaccination
- Each year, VAERS receives ~ 30,000 reports

Ref: 1) Singleton et al. Vaccine 1999;17:2908-17. 2) CDC. MMWR Surveillance Summaries 2003:52(ss01);1-24. 3) Shimabukuro et al. Vaccine 2015;33:4398-405.

VAERS 2.0

- New process for reporting, started June 2017
  - Online reporting tool (preferred)
  - Or, can download and complete, then upload
- To what extent were there barriers, or loss of important data, with the old system?

Ref: 1) CDC. MMWR 2017;66:738. 2) vaers.hhs.gov, accessed September 7, 2017.

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

About VAERS | Report an Adverse Event | VAERS Data | Resources | Submit Follow-Up Information

Completion Status

- [ ] **Patient Information**
- [ ] Reporter Information
- [ ] Facility Information
- [ ] Vaccine Information
- [ ] Additional Information

Click to preview VAERS form

Report an Adverse Event - Patient Information

Instructions | en Español

Note: Fields marked with an * are essential and should be completed.

Item 1

Patient first name:

Patient last name:

Street address:

City:

State: Select State

County:

Zip code:

Phone:

Email:

Item 2

* Date of birth (mm/yyyy)

mm/dd/yyyy

Item 3

* Sex:

Male Female Unknown

Item 4

* Date of vaccination (mm/yyyy)

mm/dd/yyyy

Time:

hh:mm

AM

PM

Who Can Report to VAERS?

- Anyone can submit a report to VAERS
  - Health care providers
  - Vaccine manufacturers (different process)
  - Vaccine recipients
  - Parents or family members of individuals who have received a vaccine
- Some providers quite familiar with VAERS, others not

Ref: 1) Singleton et al. Vaccine 1999;17:2908-17. 2) CDC. MMWR Surveillance Summaries 2003:52(ss01);1-24.

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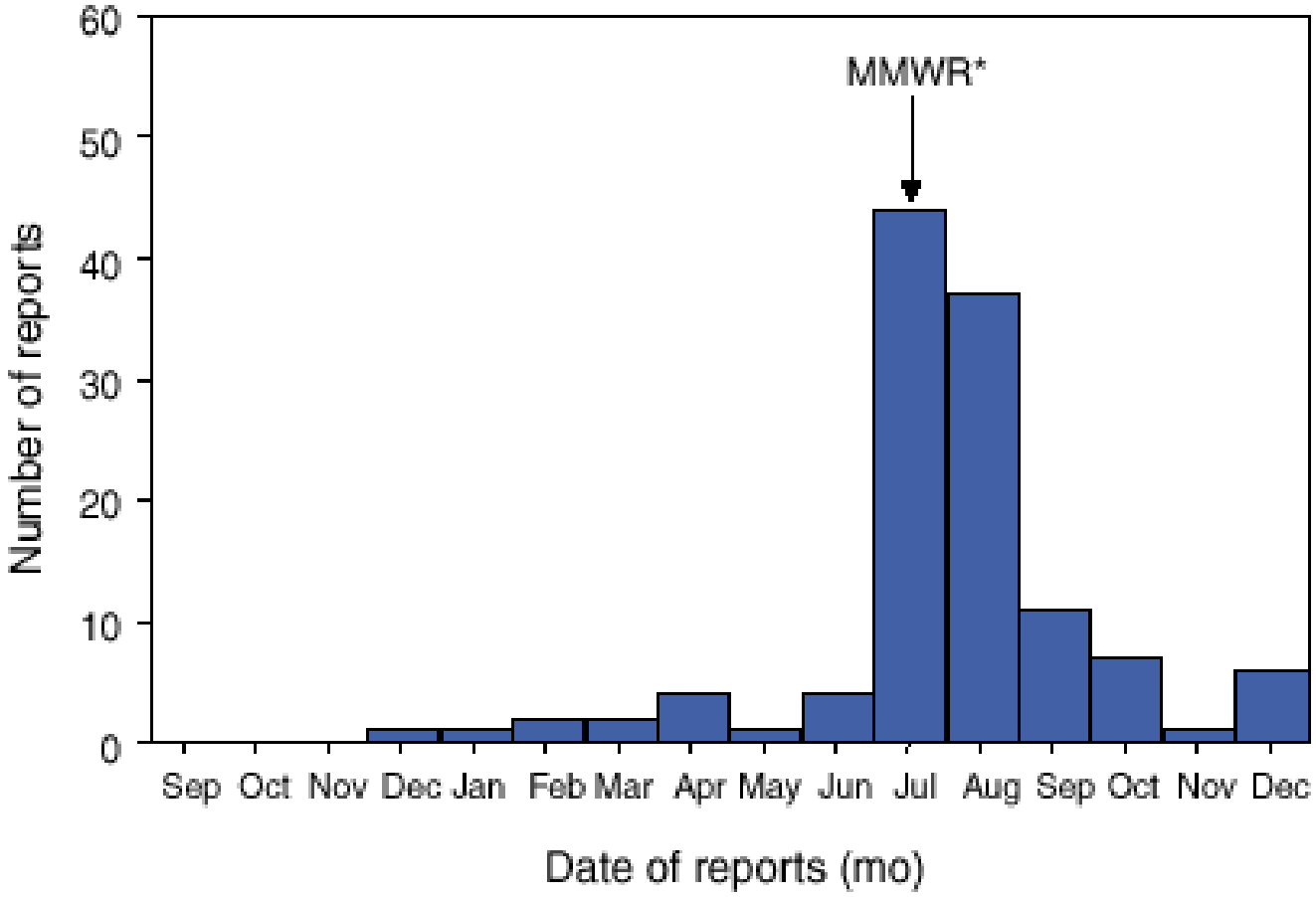
FIGURE 2. Number of intussusception reports after the rhesus rotavirus vaccine-tetravalent (RRV-TV) — United States, September 1998–December 1999



*CDC. Intussusception among recipients of rotavirus vaccine—United States, 1998–1999. MMWR 1999;48:577–81.

Ref: CDC. MMWR Surveillance Summaries 2003:52(ss01);1-24.

The Role of VAERS

- Can help identify unanticipated, new, rare adverse events
- Monitors trends of already known adverse events
- Monitors vaccine lot safety
- If unusually high number of adverse events after particular vaccine, “focused studies in other systems are done to determine if the adverse event is or is not a side effect of the vaccine”

Ref: 1) CDC. MMWR Surveillance Summaries 2003:52(ss01);1-24.
2) https://vaers.hhs.gov; accessed Feb 26, 2015

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Limitations of VAERS

- Under-reporting; over-reporting
- No denominator of vaccine doses given
- Virtually all conditions that can be vaccine adverse events (e.g., febrile seizures, Guillain-Barré syndrome) occur at a baseline rate in population
- No comparison group
- Cannot establish cause and effect

Ref: 1) Singleton et al. Vaccine 1999;17:2908-17. 2) CDC. MMWR Surveillance Summaries 2003:52(ss01);1-24.

VAERS Data Can Be Readily Misrepresented

Source: http://www.naturalnews.com/048573_measles_deaths_MMR_vaccine_immunization_dangers.html

Overview of the Vaccine Safety Datalink (VSD)

- Created in 1995
- Collaboration between 8 medical care organizations and CDC
- > 9 million children and adults under surveillance
- Integrated delivery systems, enrolled populations, electronic health records

Ref: Baggs et al. Pediatrics 2011;127:S45-S53.

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VSD: High Data Quality, Supports Multiple Study Designs

- Vaccine data highly accurate (unless vaccines given outside system)
- Case ascertainment
  - Search for specific electronic ICD diagnosis codes
  - Can confirm by manual review of electronic records
- Study designs
  - Cohort, case-control, self-control case series
  - All designs with comparison groups

Ref: Baggs et al. Pediatrics 2011;127:S45-S53.

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VSD: Rapid Cycle Analysis

- Developed to improve the timeliness with which potential adverse events are detected
- Beginning in 2006, weekly updating of vaccine and diagnosis data across VSD sites
- Sophisticated analytics developed: sequential probability ratio testing
- Example: detection of association between MMRV vaccine and febrile seizures

Ref: 1) Yih et al. Pediatrics 2011;127:S54-S64. 2) Klein et al. Pediatrics 2010;126:e1-8.

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The Broad Spectrum of VSD Work

- Autism: Thompson WW et al: Early thimerosal exposure and neuropsychological outcomes at 7 to 10 years. N Engl J Med 2007;357(13):1281-92.
- Rapid analyses: Klein NP et al: Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. Pediatrics 2010;126(1):e1-8.
- Under-immunization: Glanz JM et al: A population-based cohort study of undervaccination in 8 managed care organizations across the United States. JAMA Pediatr 2013;167(3):274-81.
- Data quality: Shui IM et al: Predictive value of seizure ICD-9 codes for vaccine safety research. Vaccine 2009;27(39):5307-12.
- Methods development: Xu S et al: Signal detection of adverse events with imperfect confirmation rates in vaccine safety studies using self-controlled case series design. Biom J;56(3):513-25.

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The Evolving Role of the VSD

- Prior to ~2006: traditional hypothesis testing; resource-intensive, slow
- Screening studies: hypothesis generating
- With development of system for monitoring in near real time (Rapid Cycle Analysis)
  - An evolution into an early detection system also
  - "Signals" from early detection system may need confirmatory studies

Ref: 1) Baggs et al. Pediatrics 2011;127:S45-S53. 2) Yih et al. Pediatrics 2011;127:S54-S64.

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Overview of the Post-Licensure Rapid Immunization Safety Monitoring (PRISM)

- Created in 2009
- Part of the FDA's Mini-Sentinel pilot and subsequent Sentinel program
- Relies on claims data from large national health insurers (Aetna, HealthCore, Humana, Optum)
- Sentinel: > 100 million individuals; not all Sentinel sites participate in PRISM
- Also collaborates with state immunization registries, for additional vaccination data

Ref: Nguyen M et al, Pharmacoepi and Drug Safety 2012;21(S1):291.

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PRISM Characteristics

- Accumulating evidence about accuracy of vaccination and health outcome data
- Can conduct manual record review to confirm case status, although can encounter delays in accessing medical records
- Also developed system for rapid vaccine safety assessments

Ref: Nguyen M et al, Pharmacoepi and Drug Safety 2012;21(S1):291.

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An Illustrative Story (II): Rotavirus Vaccine and Intussusception

- New rotavirus vaccines developed
- Large clinical trials:
  - RV5 (n=68,038), licensed in 2006
  - RV1 (n=63,225), licensed in 2008
- No increased risk for intussusception seen

Ref: 1) Vesikari T et al. N Engl J Med 2006;354:23-33. 2) Ruiz-Palacios et al. N Engl J Med 2006;354:11-22.

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Initial U.S. Studies of Intussusception

Study	Increasing Risk/Reporting
RV5 (VAERS/VSD[1])	No
RV5 (VSD, RCA[2])	No
RV5 (VSD, Cohort[3])	No
RV5 (VAERS[4])	Yes

Ref: 1) Haber P et al. Pediatrics 2008;121:1206-12. 2) Belongia EA et al. Pediatr Infect Dis J 2010;29:1-5. 3) Shui IM et al. JAMA 2012;307:598-604. 4) Haber P et al. Pediatrics 2013;131:1042-9.

International Observational Studies of Intussusception Risk

Study	Increased Risk	Dose 1 RR/OR	Dose2 RR/OR
RV5 (Australia[1])	Yes	5.26	NS
RV5 (Australia[2])	Yes	11.74	2.81
RV1 (Australia[1])	No	NS	NS
RV1 (Australia[2])	Yes	15.61	2.84
RV1 (Brazil[3])	Yes	NS	2.60
RV1 (Mexico[3])	Yes	5.80	NS
RV1 (Mexico[4])	Yes	6.49	NS

Ref: 1) Buttery et al. Vaccine 2011;29:3061-6. 2) Carlin JB et al. Clin Infect Dis 2013;57:1427-34. 3) Patel MM et al. N Engl J Med 2011;364:2283-92. 4) Velazquez FR et al. Pediatr Infect Dis J 2012;31:736-44.

Second Phase of U.S. Studies of Intussusception Risk

Rotavirus Vaccine Studied	VSD Study Results	PRISM Study Results
RV1	Increased risk for intussusception	Too few doses/low power
RV5	No risk for intussusception	Increased risk for intussusception
RV1 versus RV5	Higher risk after RV1 than after RV5	Not examined

Ref: 1) Weintraub ES et al. N Engl J Med 2014;370:513-9. 2) Yih WK et al. N Engl J Med 2014;370:503-12.

Synthesis

- "The very fact that it took more than 7 years to document a significant risk speaks to the relatively low rate of intussusception after immunization with either vaccine and the large populations required to assess this with confidence, as well as the need to have an established system in place to monitor such rare events."

Ref: Glass and Parashar. N Engl J Med 2014;370:568-70.

Where does CISA Fit In?

- CISA: Clinical Immunization Safety Assessment network
- Individuals, not populations
- “Understanding the role of human variation in vaccine adverse events”
- Health care providers can refer specific patients to CISA for clinical evaluation

Ref: LaRussa et al. Pediatrics 2011;127:S65-S73

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Objectives of CISA

- Study pathophysiology of adverse events
- Study risk factors, including genetic risk factors, for adverse events
- Provide clinical consultation to health care providers
  - Assess the likelihood that a particular adverse event was related to vaccination in individuals
  - Give recommendations for future vaccination

Ref: LaRussa et al. Pediatrics 2011;127:S65-S73

Published Case Reviews from CISA

Age	Vaccine(s)	Diagnosis	Time after vaccination	Past medical history	Causality
4 months	Rotavirus	Rotavirus positive chronic diarrhea (vaccine strain)	90 days	Later dx with SCID	Definite
4 months	IPV, DTaP, PCV7, Hib/Hep B	Abscess, sterile	21 days	None	Probable
16 years	DTaP, Hep B, IPV, Var	Periodic myalgia	< 1 day	Asthma	Probable
14 years	MCV4	Meningitis	7 days	Concussion	Unlikely

Ref: Williams et al. Vaccine 2011;29:6920-27.

Role and Future Potential of CISA

- To date, role primarily clinical
- Can also be hypothesis generating, and hypothesis testing
- Assessing genetic risk factors for adverse events following immunization
  - Rare adverse events; difficult to have adequate statistical power to assess risk factors
  - CISA has started a clinical registry and specimen repository (an immunization safety biobank)

Ref: LaRussa et al. Pediatrics 2011;127:S65-S73

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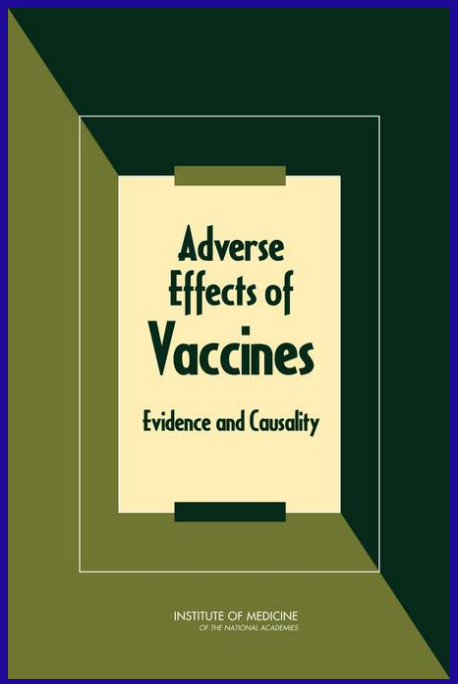
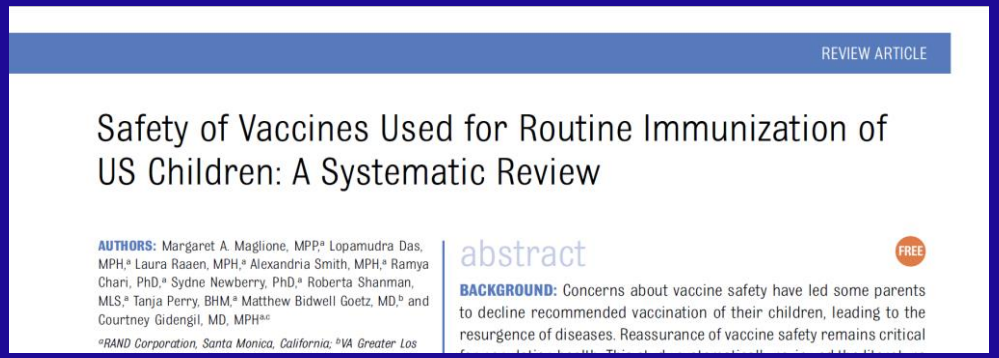
Systematic Reviews of Vaccine Safety




REVIEW ARTICLE

Safety of Vaccines Used for Routine Immunization of US Children: A Systematic Review

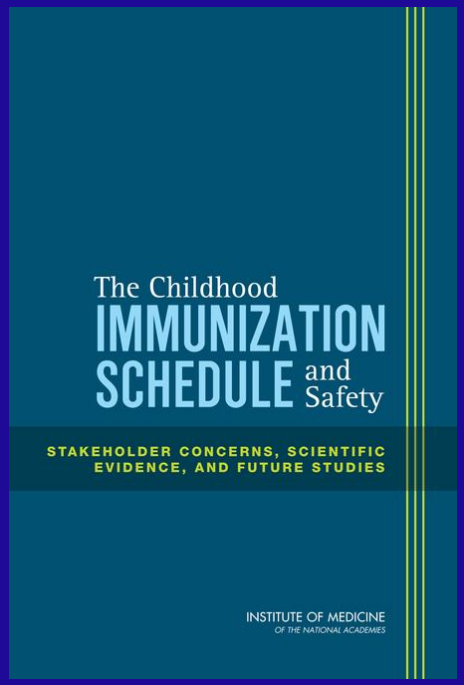
AUTHORS: Margaret A. Maglione, MPP,[a] Lopamudra Das, MPH,[a] Laura Raaen, MPH,[a] Alexandria Smith, MPH,[a] Ramya Chari, PhD,[a] Sydne Newberry, PhD,[a] Roberta Shanman, MLS,[a] Tanja Perry, BHM,[a] Matthew Bidwell Goetz, MD,[b] and Courtney Gidengil, MD, MPH[a,c]

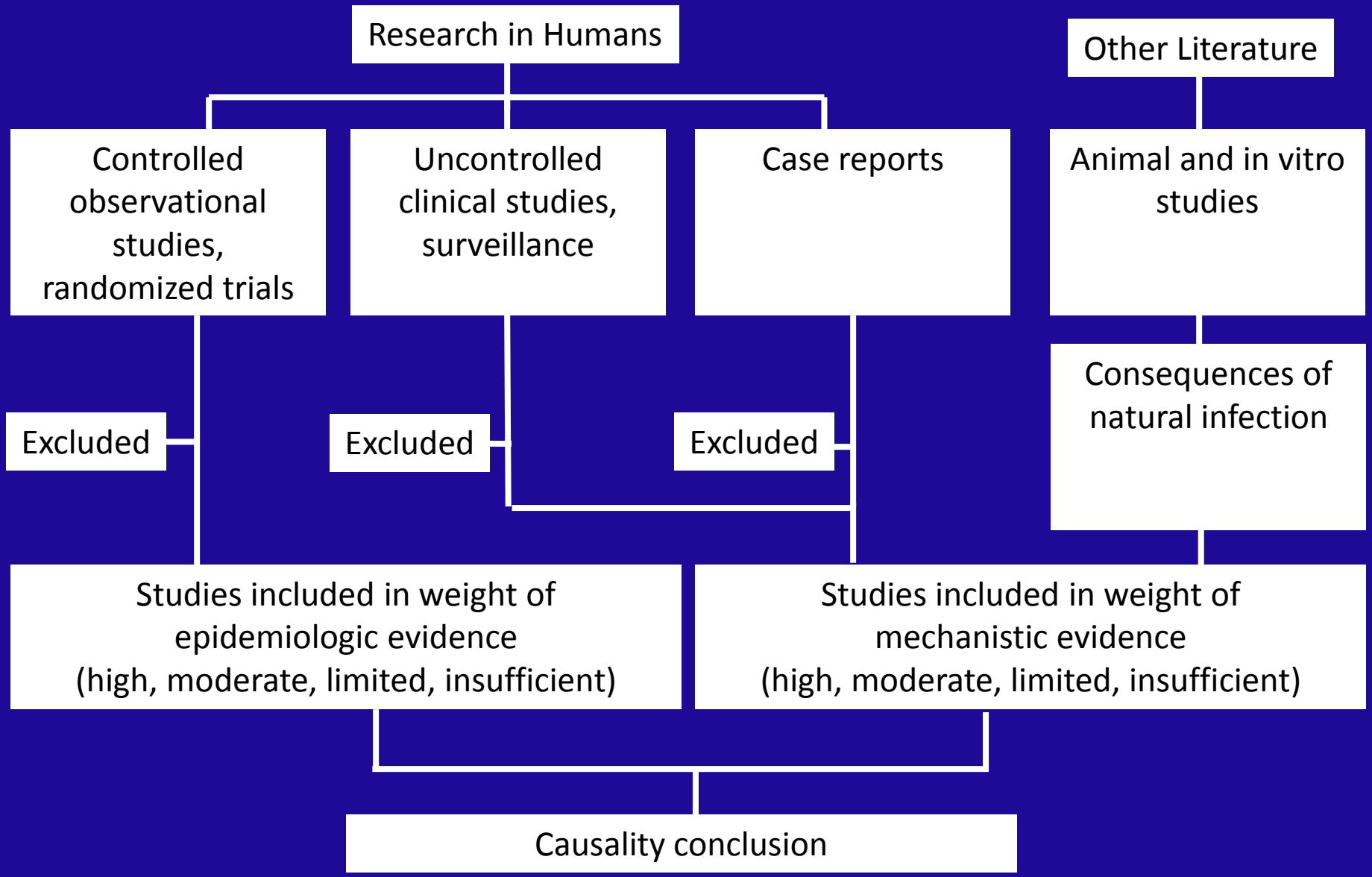
[a]*RAND Corporation, Santa Monica, California;* [b]*VA Greater Los*

abstract

FREE

BACKGROUND: Concerns about vaccine safety have led some parents to decline recommended vaccination of their children, leading to the resurgence of diseases. Reassurance of vaccine safety remains critical





Ref: IOM. 2012. Adverse effects of vaccines: evidence and causality. Washington, DC: The National Academies Press.

Role of Systematic Reviews

- "…to assess dispassionately the scientific evidence…"
  - At least 11 reviews by IOM in past 25 years
  - Periodic review of new evidence
  - New "set of eyes" on old evidence
  - Can address emerging concerns from the public
- Can set research priorities for the future

Ref: IOM. 2012. Adverse effects of vaccines: evidence and causality. Washington, DC: The National Academies Press.

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2012 IOM Safety Review

- Examined 8 different vaccines, 158 different adverse event-vaccine pairs (>12,000 articles)
- Evidence convincingly supported 14 specific vaccine-adverse event pairs, including
  - Varicella vaccine and disseminated vaccine strain viral infections
  - MMR vaccine and measles inclusion body encephalitis
  - MMR vaccine and febrile seizures
  - 6 different vaccines and anaphylaxis

Ref: IOM. 2012. Adverse effects of vaccines: evidence and causality. Washington, DC: The National Academies Press.

2012 IOM Safety Review

- "Evidence favors rejection of five vaccine-adverse event" associations
  - MMR vaccine and type 1 diabetes
  - DTaP vaccine and type 1 diabetes
  - MMR vaccine and autism
  - Inactivated influenza vaccine and asthma exacerbations
  - Inactivated influenza vaccine and Bell's palsy

Ref: IOM. 2012. Adverse effects of vaccines: evidence and causality. Washington, DC: The National Academies Press.

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AHRQ-Commissioned Review

- Updated IOM findings; also examined pneumococcal, rotavirus, Hib, IPV vaccines
- Strong evidence supporting association: MMR vaccine and febrile seizures; varicella vaccine and adverse events in immunodeficient individuals
- Strong evidence that MMR vaccine does not cause autism

Ref: Maglione et al. Pediatrics 2014;134:325-337

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IOM Review of Safety of Schedule

- Few studies have examined the safety of the schedule as a whole
- "The lack of conclusive evidence linking adverse events to multiple immunizations or other [schedule] exposures suggests that the recommended schedule is safe."
- Because of stakeholder concerns, further research is needed, depending upon epidemiologic evidence and biologic plausibility

Ref: IOM. 2013. The childhood immunization schedule and safety: stakeholder concerns, scientific evidence, and future studies. Washington, DC: The National Academies Press.

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What Was Learned from the Rotavirus Vaccine Story?

- Safety monitoring system in U.S. was “sensitive enough” to detect unanticipated adverse event
- Hypothesis testing RotaShield-intussusception association was resource-intensive; power an issue
- Provided pressure for evolution (as did new vaccines in mid-2000s, and FDA Amendments Act of 2007)
- Timeliness of risk assessment important
- Several independent systems needed for detecting “signals” and testing hypotheses

Attributes of U.S. Vaccine Safety Monitoring System, 2017

Attribute	VAERS	VSD	PRISM	CISA
National in scope	✓			
Relies on voluntary reporting	✓			
Patient population defined by enrollment		✓		
Does not rely on voluntary reporting		✓	✓	
Case detection through electronic ICD-9 codes		✓	✓	
Case confirmation by manual record review		✓	✓	
Neal real time surveillance		✓	✓	
Power to study relatively rare outcomes		✓	✓	
Examination of individual patients				✓
Collection of genetic specimens				✓
Hypothesis generating	✓	✓	✓	✓
Hypothesis testing		✓	✓	✓

Important Future Areas of Study

- Vulnerable sub-populations
  - Chronic health conditions
  - Pregnancy
- Genetic pre-disposition to adverse events following immunization
- Studying safety of the schedule as a whole
- Studying safety of vaccine ingredients

Summary and Conclusions

- U.S. has extensive, sophisticated system for monitoring safety of currently licensed vaccines
- Multiple components (VAERS, VSD, PRISM, CISA) with contrasting strengths and limitations
- Components are independent, yet work synergistically
- U.S. system also operates collaboratively within an international system of vaccine safety monitoring

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