Vaccines Under the Microscope: How can we know they are safe?

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NDSU CENTER FOR IMMUNIZATION RESEARCH AND EDUCATION

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Disclosure

Dr. Carson has no relevant financial relationships with ineligible companies to disclose.

Objectives

1. Recognize how safety is prioritized in the vaccine development and approval process.

2. Identify the differences between vaccine safety surveillance systems in the U.S. and how they collaborate to assess potential safety signals.

3. Review historical examples of how vaccine surveillance systems have successfully identified and responded to safety concerns.

Comparison of 20th Century Annual Morbidity and Current Morbidity: Vaccine-Preventable Diseases

Disease	20th Century Annual Morbidity†	2021 Reported Cases ††	Percent Decrease
Smallpox	29,005	0	100%
Diphtheria	21,053	0	100%
Measles	530,217	9	> 99%
Mumps	162,344	157	> 99%
Pertussis	200,752	1,609	> 99%
Polio (paralytic)	16,316	0	100%
Rubella	47,745	3	> 99%
Congenital Rubella Syndrome	152	0	100%
Tetanus	580	19	97%
Haemophilus influenzae	20,000	15*	> 99%

† JAMA. 2007;298(18):2155-2163

†† Centers for Disease Control and Prevention. National Notifiable Diseases Surveillance System, Weekly Tables of Infectious Disease Data. Atlanta, GA. CDC Division of Health Informatics and Surveillance. Available at: Weekly statistics from the National Notifiable Diseases Surveillance System (NNDSS). (cdc.gov). Accessed on January 5, 2022; for diphtheria, case count as reported by CDC Program.

* *Haemophilus influenzae* type b (Hib) < 5 years of age. An additional 7 cases of Hib are estimated to have occurred among the 157 notifications of *Haemophilus influenzae* (< 5 years of age) with unknown serotype.

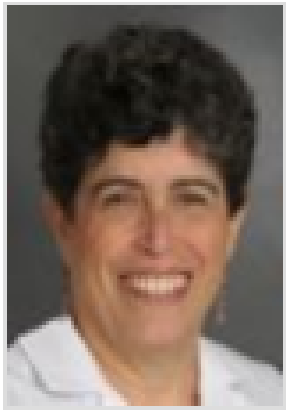
PERSPECTIVE

Faith in vaccines falls 10 percentage points in US poll

January 16, 2020

Prior to COVID!

ADD TOPIC TO EMAIL ALERTS



Sharon Nachman

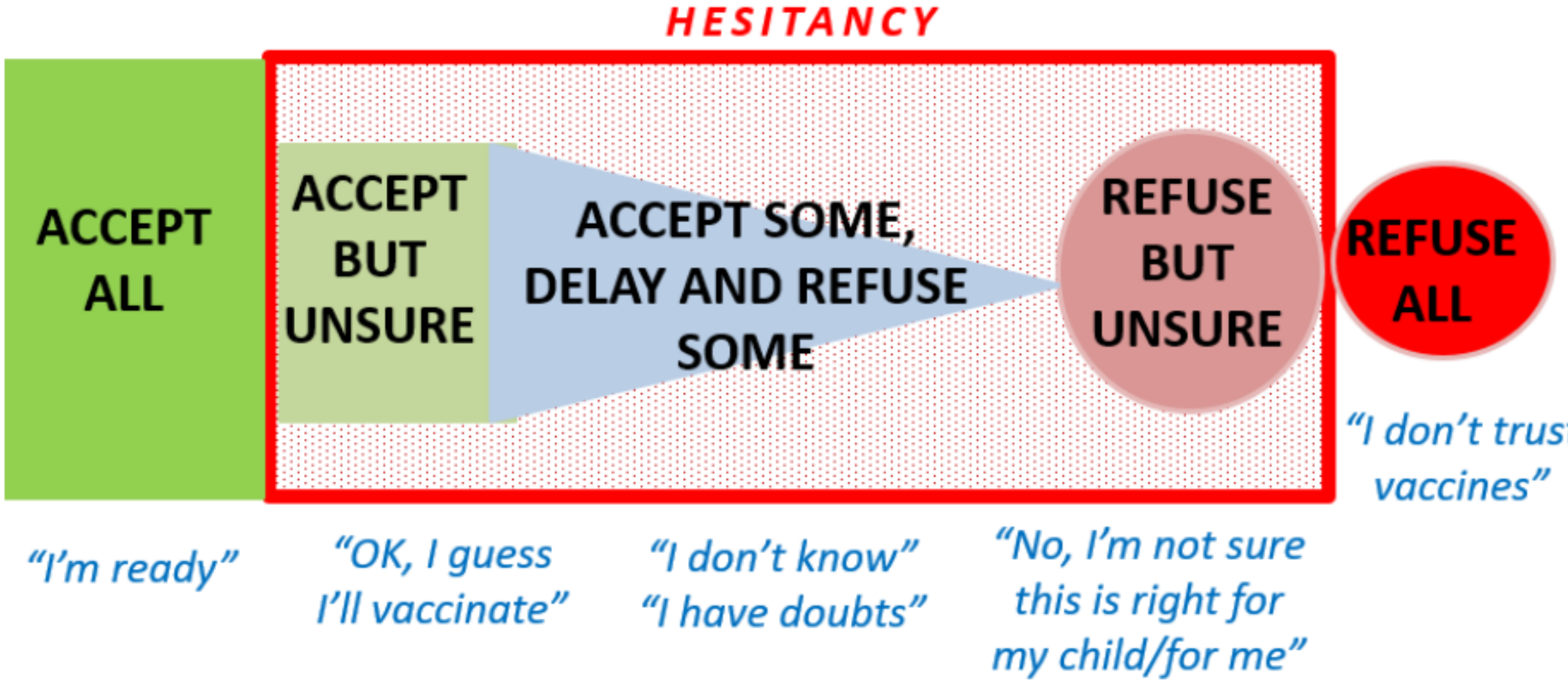
The percentage of Americans who feel strongly that parents should get their children vaccinated has dropped by 10 percentage points since 2001, according to a Gallup poll. The poll showed that only 45% of Americans believe vaccines do not cause autism in children.

https://www.healio.com/news/pediatrics/20200116/faith-in-vaccines-falls-10-percentage-points-in-us-poll

Vaccine Confidence: A Growing Challenge

50-60% of Americans have concerns about vaccine safety.

Piot P, Larson HJ, O'Brien KL, et al. Immunization: vital progress, unfinished agenda. Nature. 2019;575(7781):119-129
https://pubmed.ncbi.nlm.nih.gov/31695203/


HESITANCY
ACCEPT ALL
ACCEPT BUT UNSURE
ACCEPT SOME, DELAY AND REFUSE SOME
REFUSE BUT UNSURE
REFUSE ALL
"I don't trust vaccines"
"I'm ready"
"OK, I guess I'll vaccinate"
"I don't know" "I have doubts"
"No, I'm not sure this is right for my child/for me"

https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019

npr

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Shots HEALTH NEWS FROM NPR

PUBLIC HEALTH

Disneyland Measles Outbreak Hits 59 Cases And Counting

January 22, 2015 · 12:24 PM ET

LISA ALIFERIS

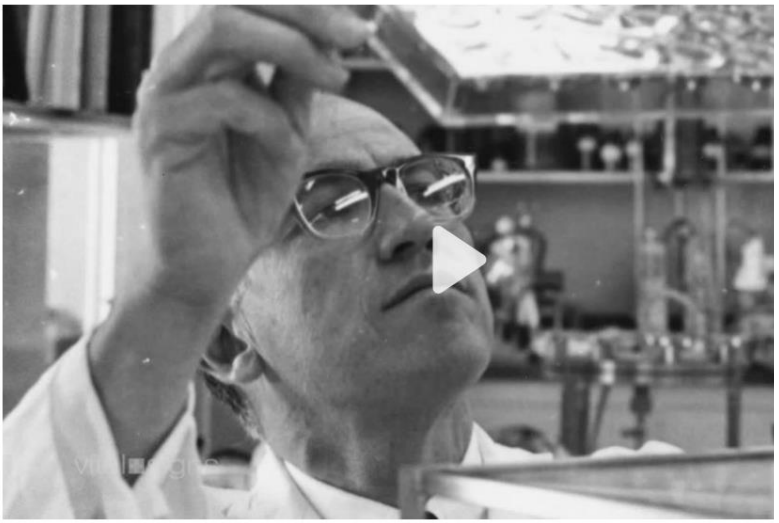
FROM KQED

CNN health | Life, But Better | Fitness | Food | Sleep | Mindfulness | Relationships

Polio makes a comeback in the Philippi years after the country was declared fr the disease

By Katie Hunt, CNN

Updated 11:46 AM EDT, Thu September 19, 2019

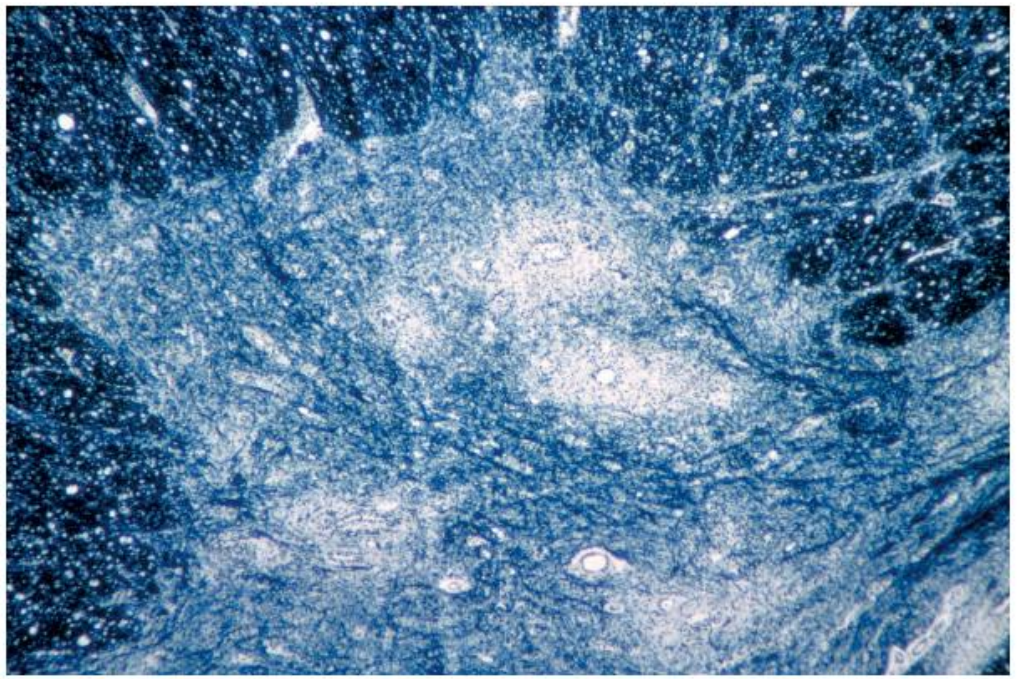


The New York Times

First Polio Case in Nearly a Decade Is Detected in New York State

A man who lives in Rockland County was infected by someone who received the oral polio vaccine, which is no longer used in the United States, officials said.

Give this article



This 1964 microscope image shows damage from the polio virus to human spinal cord tissue. CDC, via Associated Press

MINNESOTA

AP Center for Infectious Disease Research and Policy

pective | Infectious Disease Topics | Antimicrobial Stewardship | Ongoing Programs

COVID-19 | Flu Vaccines Roadmap | MERS-CoV | Chronic Wasting Disease

es cases hit 1,234 as Brooklyn outbreak er

s Reporter | CIDRAP News | Sep 03, 2019

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for Disease Control and Prevention new measles infections, raising 34 cases in 31 states.

e has been affected since the CDC's number of active outbreaks has ur, down from six noted last week.

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iated Press

on children to be vaccinated st polio in Africa after outbreak awi

2, 2022 at 7:41 a.m. ET

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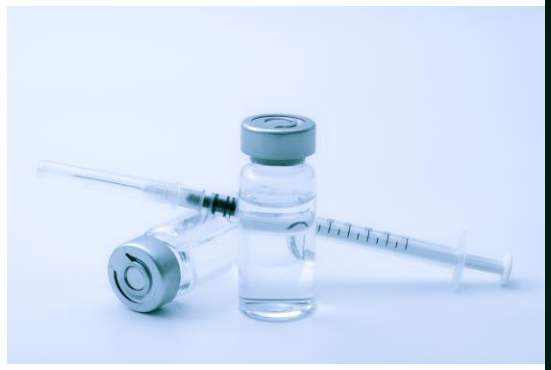
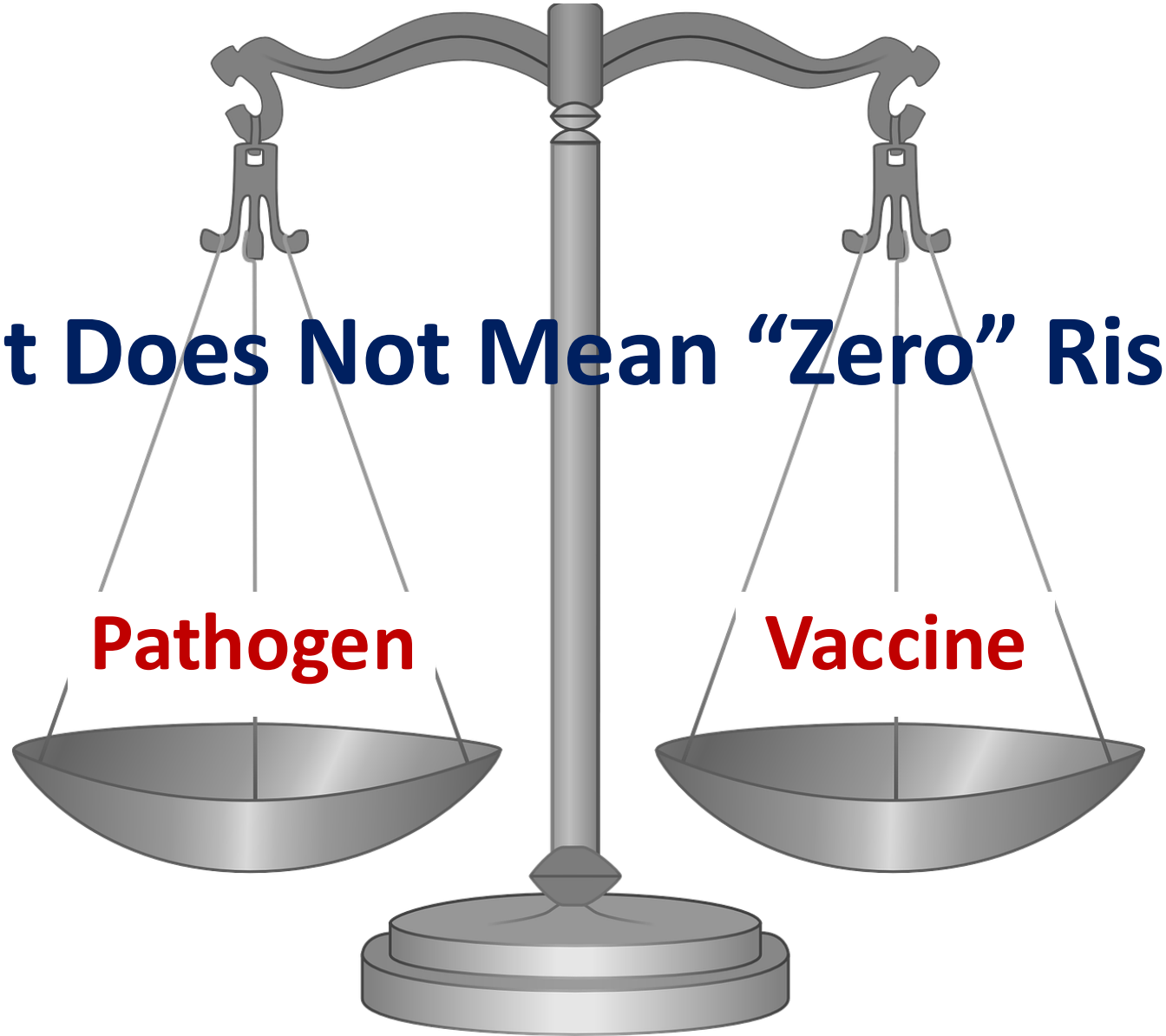
SAFETY + EFFICACY



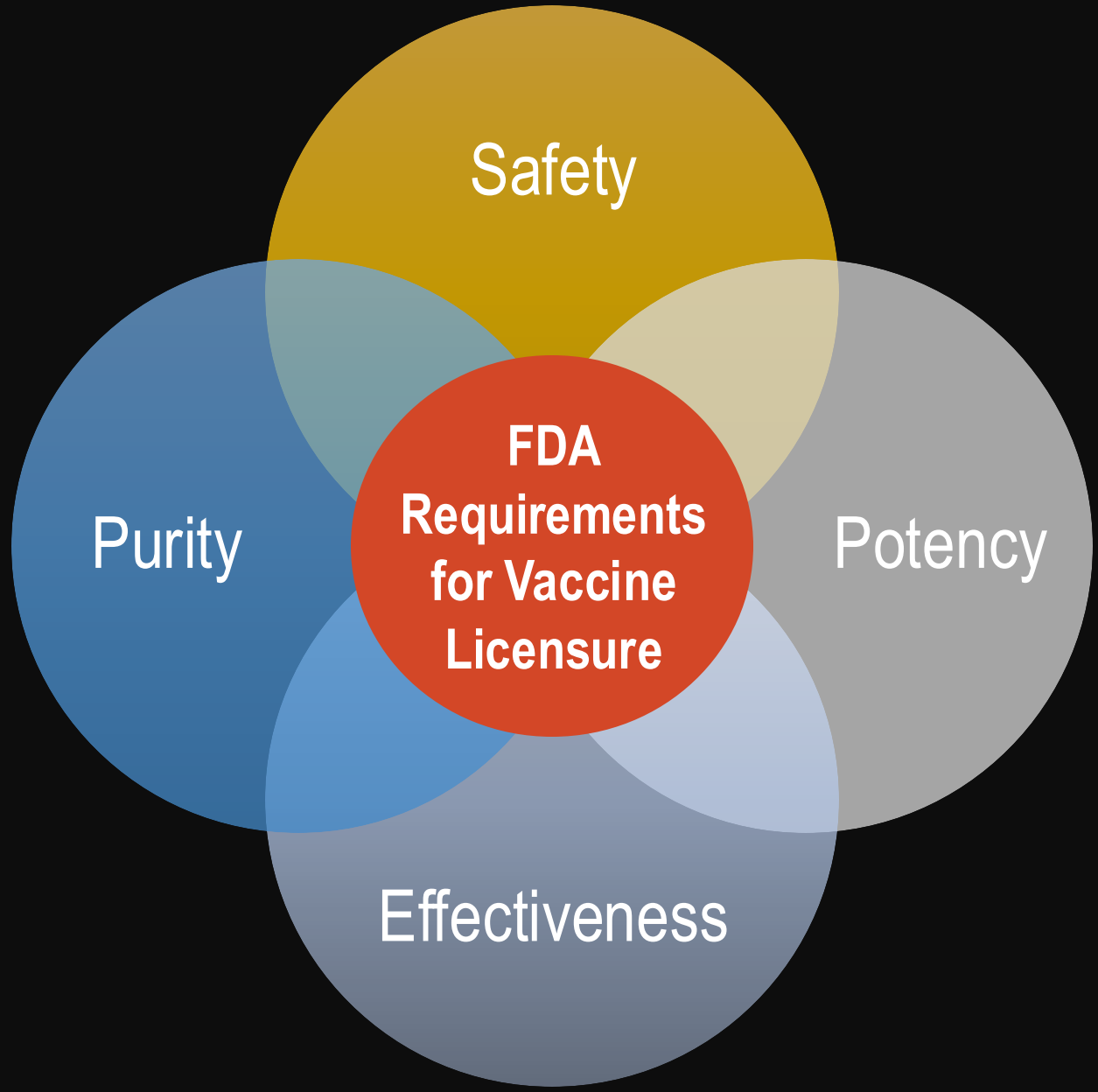
What does “Safe” Mean?



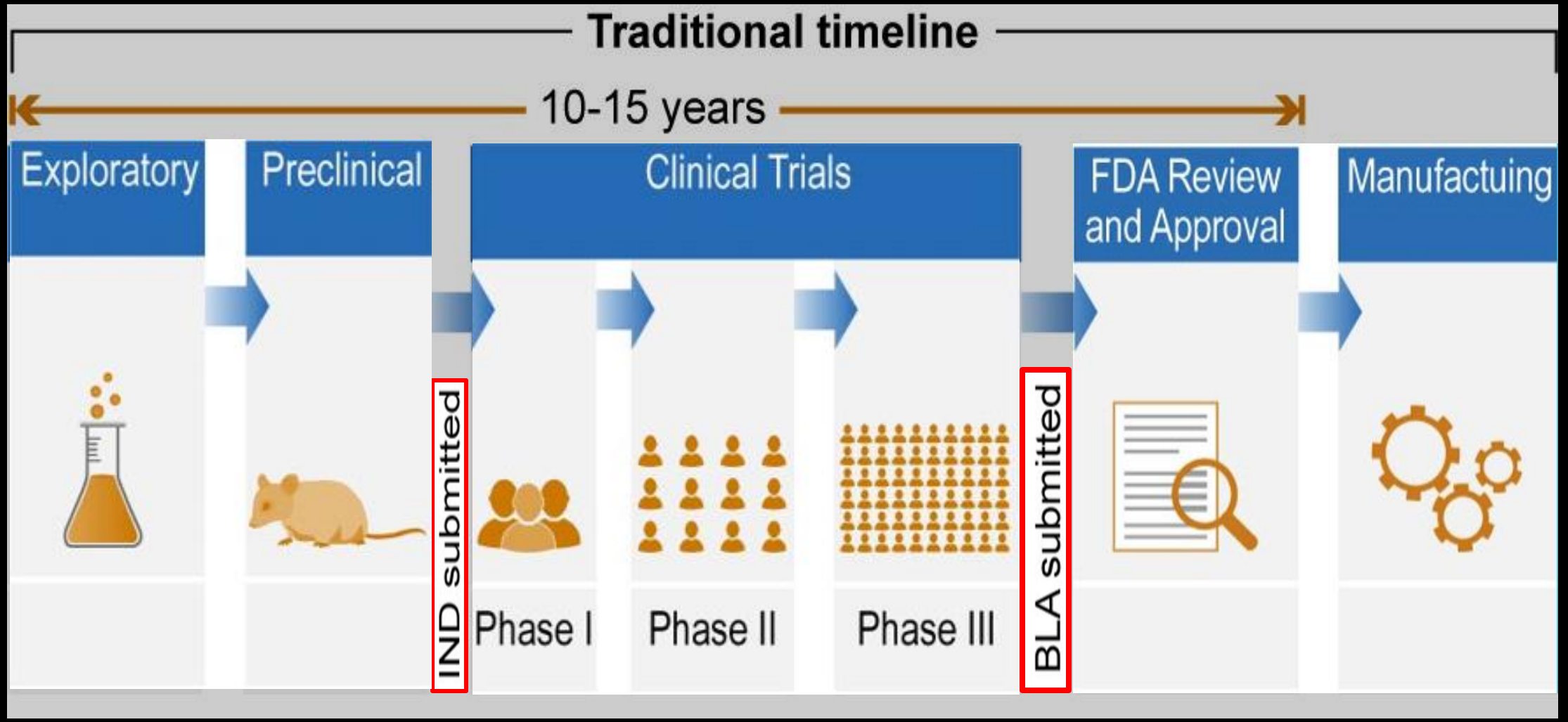
It Does Not Mean “Zero” Risk


The Journey of a Vaccine:
From Development to Public Availability

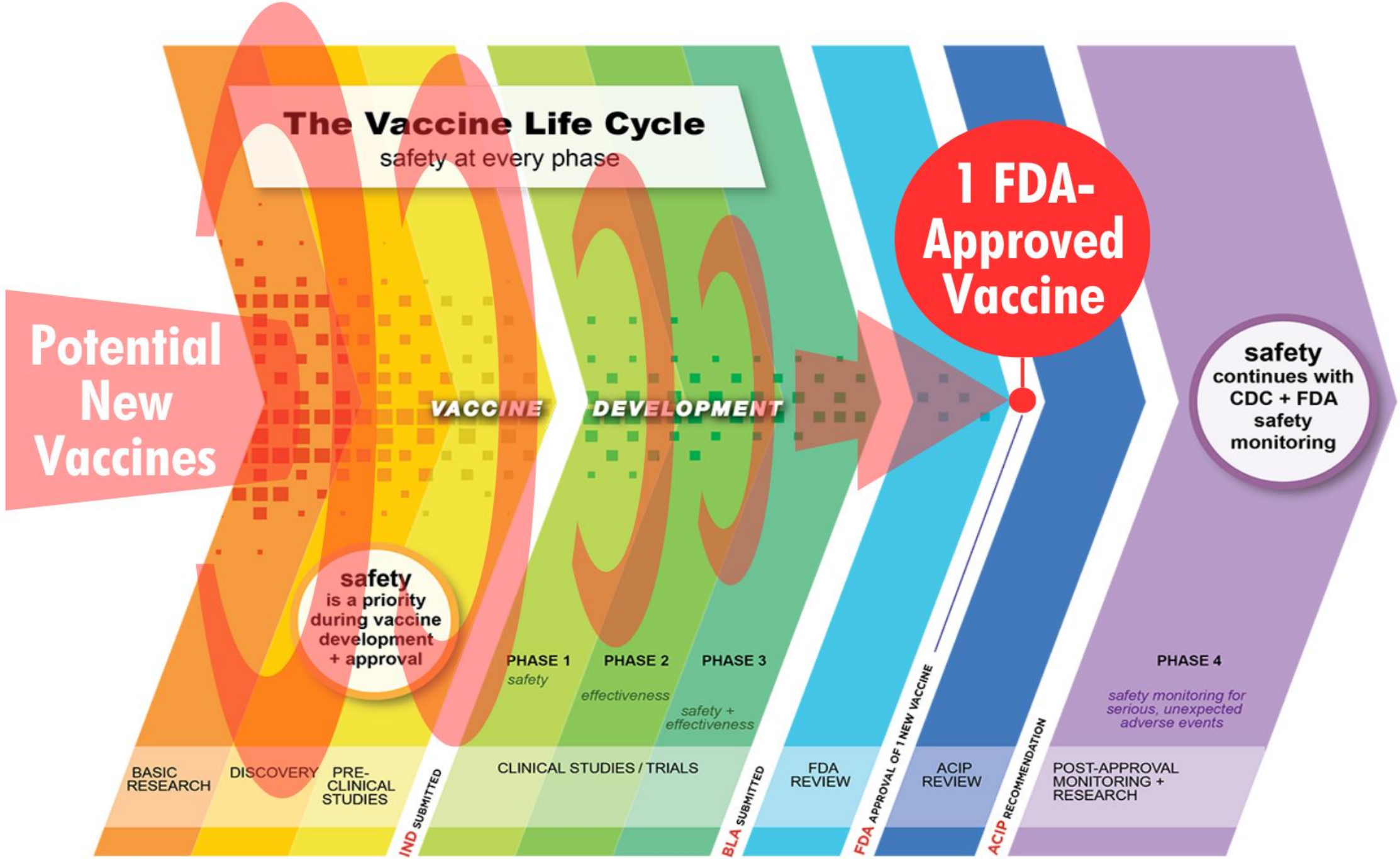
The FDA must license a vaccine before it can be used in the U.S.



Vaccine Development – Traditional Timeline



https://www.flickr.com/photos/usgao/49948301848



https://www.cdc.gov/vaccines/basics/how-developed-approved.html

Comparing Vaccine Randomized Controlled Trials

Vaccine (Developer)	Type of Vaccine	Protects Against	Approval Year	Was there a Control?	Phase III n
Rotashield	Live, attenuated	Rotavirus		Placebo (tissue culture medium)-controlled trial	4413
Daptacel	Combination	Diphtheria, Tetanus, Pertussis	2002	DT vaccine placebo-controlled trial	10,575
Gardasil	Subunit	HPV	2006	Saline or Aluminum Hydroxyphosphate Sulfate placebo-controlled trial	22,938
Rotarix	Live, attenuated	Rotavirus	2008	Placebo-controlled trial	80,427
Prevnar 13 - pediatric	Inactivated	Pneumococcal Disease	2010	Saline placebo-controlled trial	49,296
Spikevax (Moderna)	mRNA	COVID-19	2022	Saline placebo-controlled trial	30,420
Comirnaty (Pfizer)	mRNA	COVID-19	2021	Saline placebo-controlled trial	43,998
Jcovden (J&J)	Viral Vector	COVID-19		Saline placebo-controlled trial	44,325

U.S. Food and Drug Administration. (2021). FDA Approval Information for Comirnaty (Pfizer-BioNTech). Retrieved from FDA website;
ClinicalTrials.gov. (2022). Study Results for Phase III Trials of Moderna Spikevax.
Centers for Disease Control and Prevention (CDC). (2010). Rotavirus Vaccines: Rotashield and Rotarix Clinical Data.

STRENGTHS & LIMITATIONS OF PHASE I-III FDA APPROVAL PROCESS

STRENGTHS

- Stepwise safety and efficacy assessment
- Rigorous
- Phase III Randomized Controlled Trials
  - Decrease bias
  - Better group equivalence
  - True vaccine effects (both efficacy and risks)
  - Powered to detect efficacy and common adverse events

LIMITATIONS

- Can't detect very rare AEs
- Can't detect very late or delayed AEs
- Expensive and difficult
- Take a very long time
- Pediatric populations and pregnant women often studied much later

*AE = "adverse event" = any negative or untoward event following the administration of a vaccine. Includes true AEs due to the vaccine and events that coincidentally follow vaccination

Delayed Side Effects?

In the history of all vaccines licensed in the U.S., no serious side effects have been found after 6-8 weeks

Finding Rare Events: Rule of 3

Statistical shortcut: You can be 95% confident that your sample size (N) can detect events at a rate of 3/N or greater

Example:

Phase III trial for Pfizer mRNA vaccine -
N = 22,000 in vaccine arm

3 / 22,000 = .0136% = 1:7333

We can have 95% confidence that we detected any SAE occurring at a rate ≥ 1:7333

In addition, one must then statistically compare the event rate in the vaccine arm with same event rate in the non-vaccine arm

Adverse Events Associated with Vaccination

Vaccine	Event	Risk
Any	Anaphylaxis	1 : 1,000,000
Influenza (Inactivated)	G-B Syndrome	1-10 : million
MMR	ITP	1 : 40,000
MMR MMRV	Febrile Seizures 12-47 mos old	1 : 2,500 1 : 1,250
RRV-TV (Rotashield)	Intussusception	1 : 11,000
RV1 and RV5 (Rotateq)	Intussusception	1: 100,000

Bohlke. Pediatrics 2003;112:815;
Mantadakis. J Pediatr 2010;156:623; Peter. Pediatrics 2002;110:e67;
Klein. Pediatrics 2010;126:e1ACIP Meeting. June 2013

POST-LICENSURE VACCINE SAFETY MONITORING SYSTEMS IN THE U.S.

Question

Which of the following best describes the key difference between VAERS and VSD?

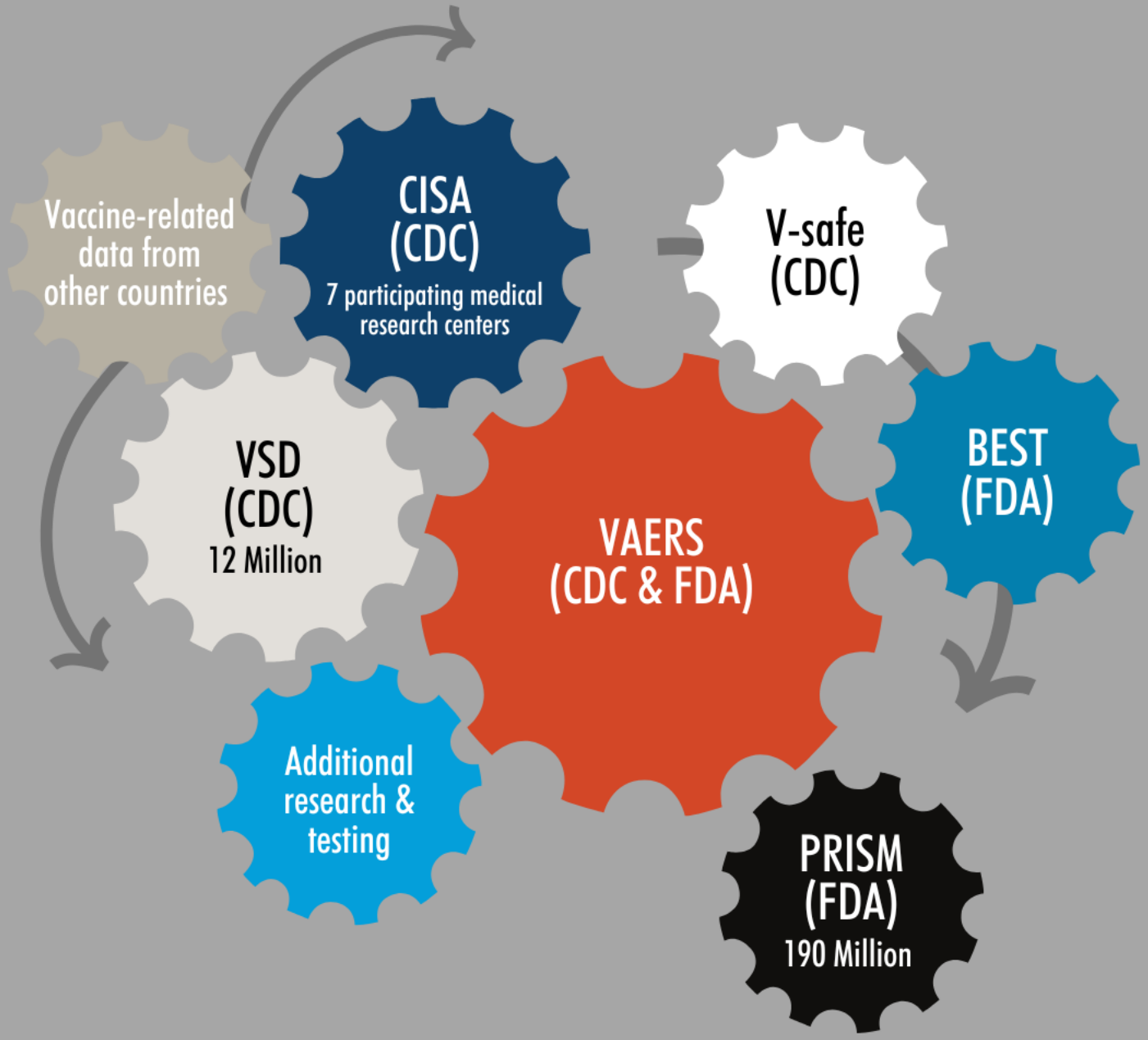
A) Both systems rely on active data collection

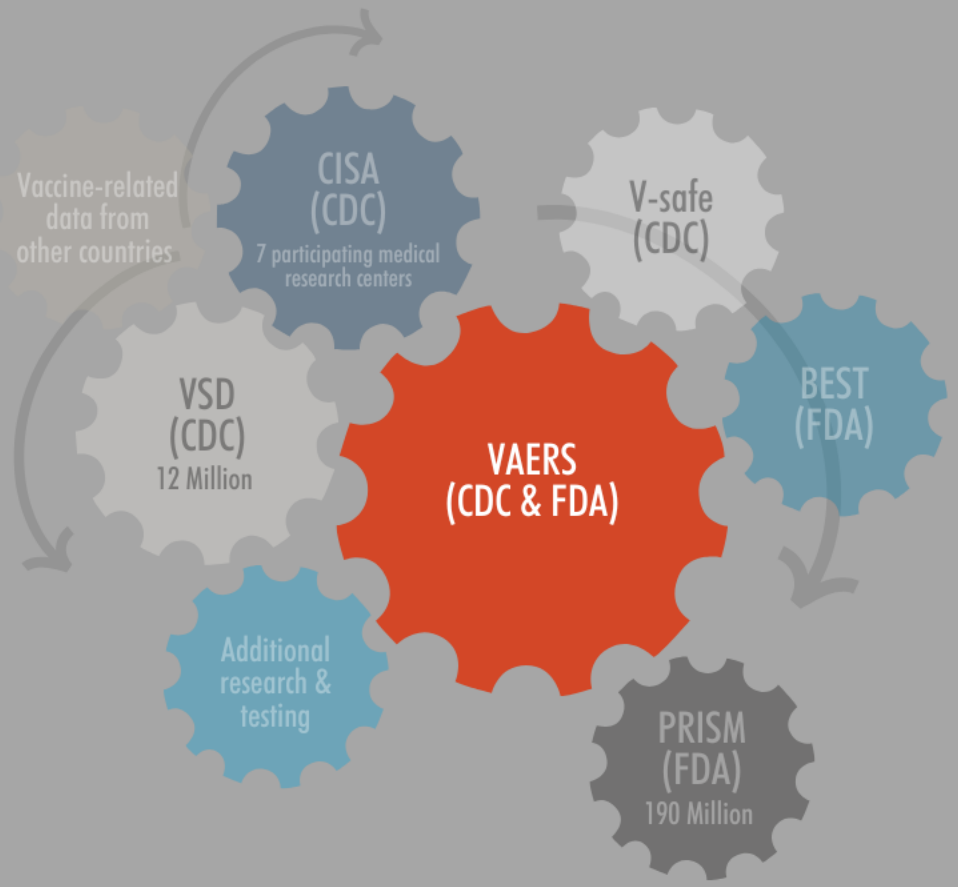
B) VAERS is a passive reporting system, while VSD actively monitors healthcare data

C) VSD focuses only on childhood vaccines, while VAERS covers all ages

D) VAERS is the only system that can establish causality between vaccines and adverse events

Vaccine Safety Monitoring Systems in the U.S.





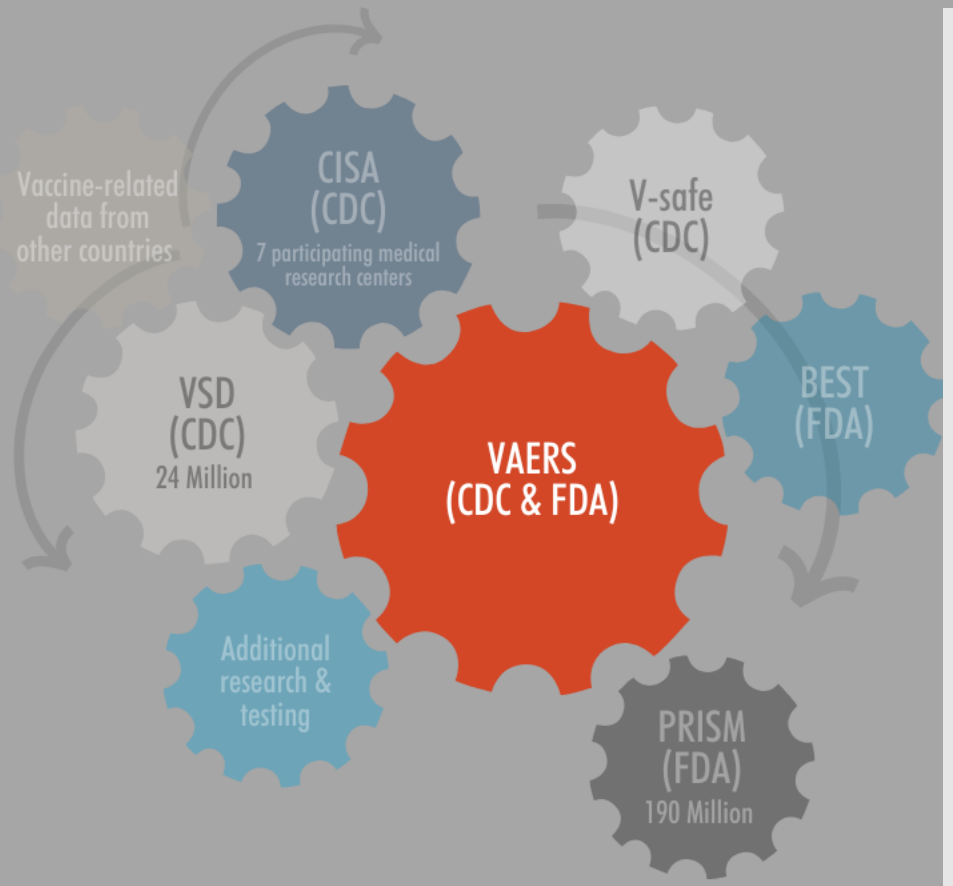
Vaccine Adverse Event Reporting System (VAERS)

VAERS

- Used by the FDA and the CDC to collect reports of adverse events that happen after vaccination
- **Passive reporting system**: The system relies on individuals and healthcare providers to send in reports of adverse health events following vaccination
- Scientists monitor VAERS reports to identify adverse events that need to be **studied further**
- Reports of adverse events that are followed up on with additional research:
  - Unexpected events
  - Appear to happen more often than expected


VAERS

VAERS: Strengths & Limitations



STRENGTHS

- Anyone can submit reports to VAERS (wide net)
- Serves as an early warning/hypothesis-generating system

LIMITATIONS

- Passive surveillance, doesn't capture all adverse events, no true denominator
- There is no control group to compare rates in vaccinated vs unvaccinated population
  - Cannot determine causality, only can raise questions
- Reports may lack details or contain errors

UNITED STATES

How a CDC Database Is Fueling Global Anti-Vaccination Sentiment

By Corbin Duncan April 6, 2021

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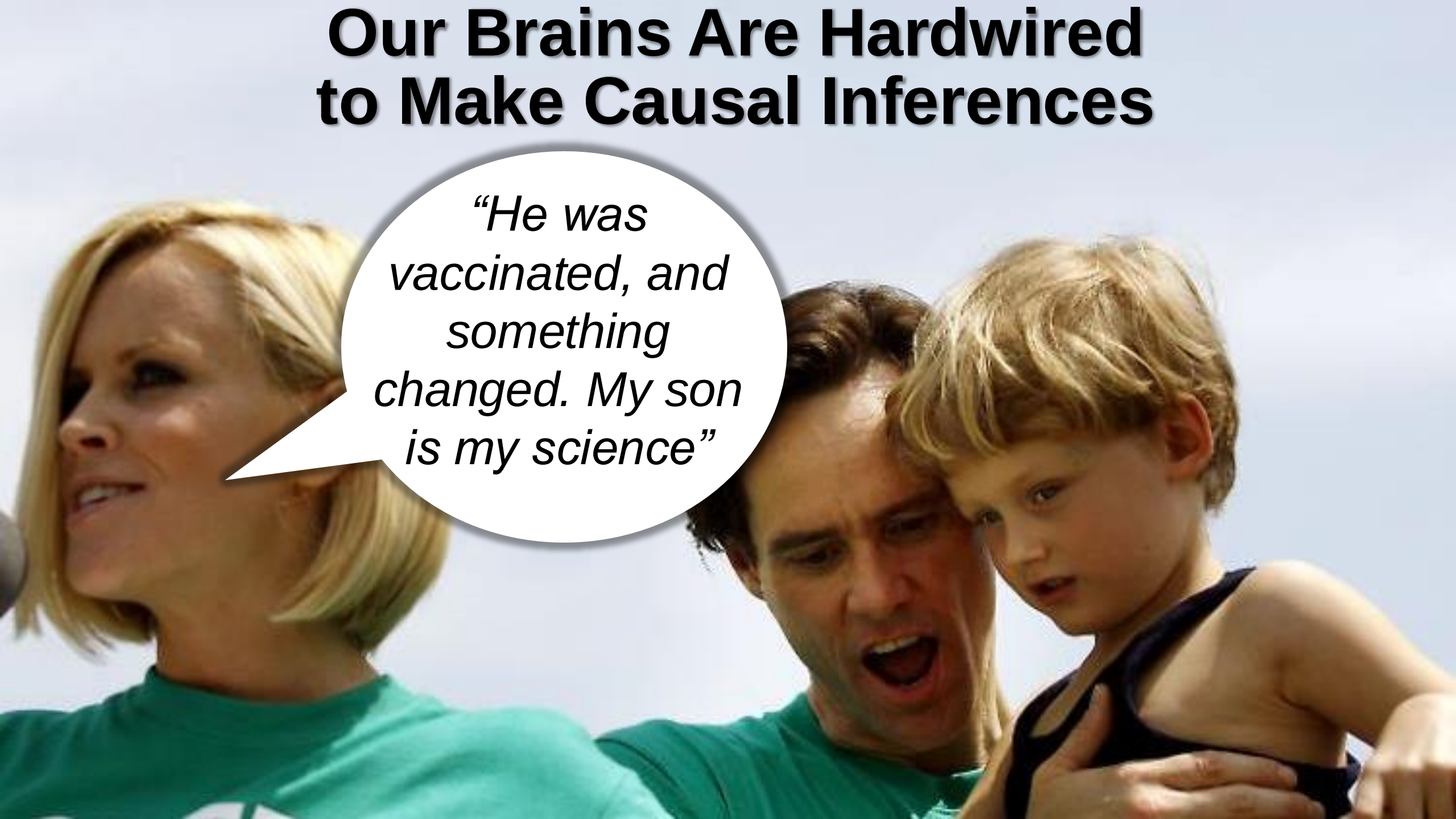
HARVARD POLITICAL REVIEW

Tuesday, June 15, 2021

Misinformation and Confusion around VAERS

Our Brains Are Hardwired to Make Causal Inferences



"I have heard that over 9,000 people have died after the COVID-19 vaccine...Is this true?"

NO!

From vs. after... what is the difference?!

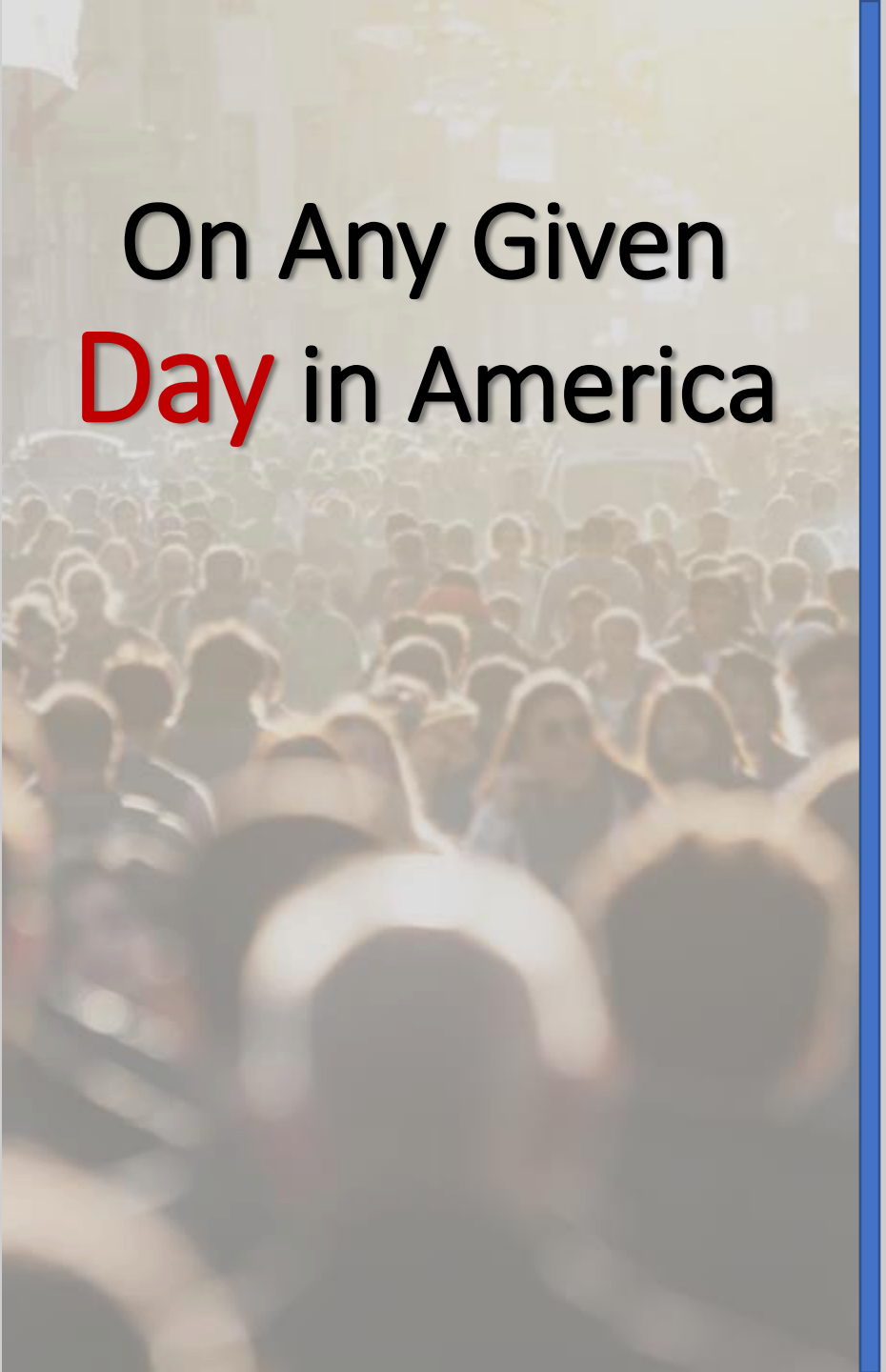
“Post-Hoc Ergo Propter Hoc”

Correlation ≠ Causation

DEADLY CHOICES

HOW THE ANTI-VACCINE MOVEMENT THREATENS US ALL

PAUL A. OFFIT, M.D.

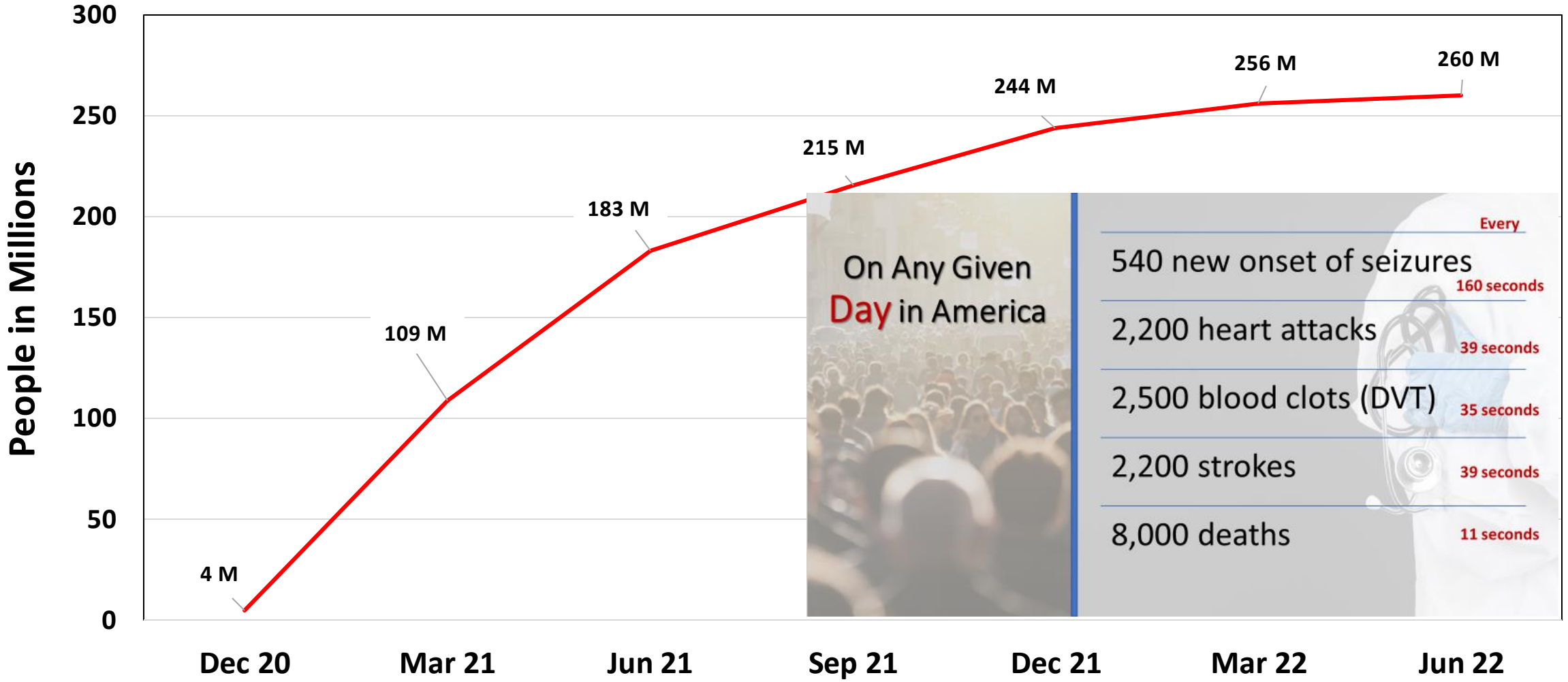


On Any Given Day in America

	Every
540 new onset of seizures	160 seconds
2,200 heart attacks	39 seconds
2,500 blood clots (DVT)	35 seconds
2,200 strokes	39 seconds
8,000 deaths	11 seconds

1. https://emedicine.medscape.com/article/1609294-overview#a4 ; 2. https://www.ncbi.nlm.nih.gov/books/NBK83160/
3. https://www.cdc.gov/blood-clots/toolkit/impact-of-blood-clots.html; 4. https://www.ahajournals.org/doi/full/10.1161/CIR.0000000000000350
5. https://www.cdc.gov/nchs/fastats/deaths.htm

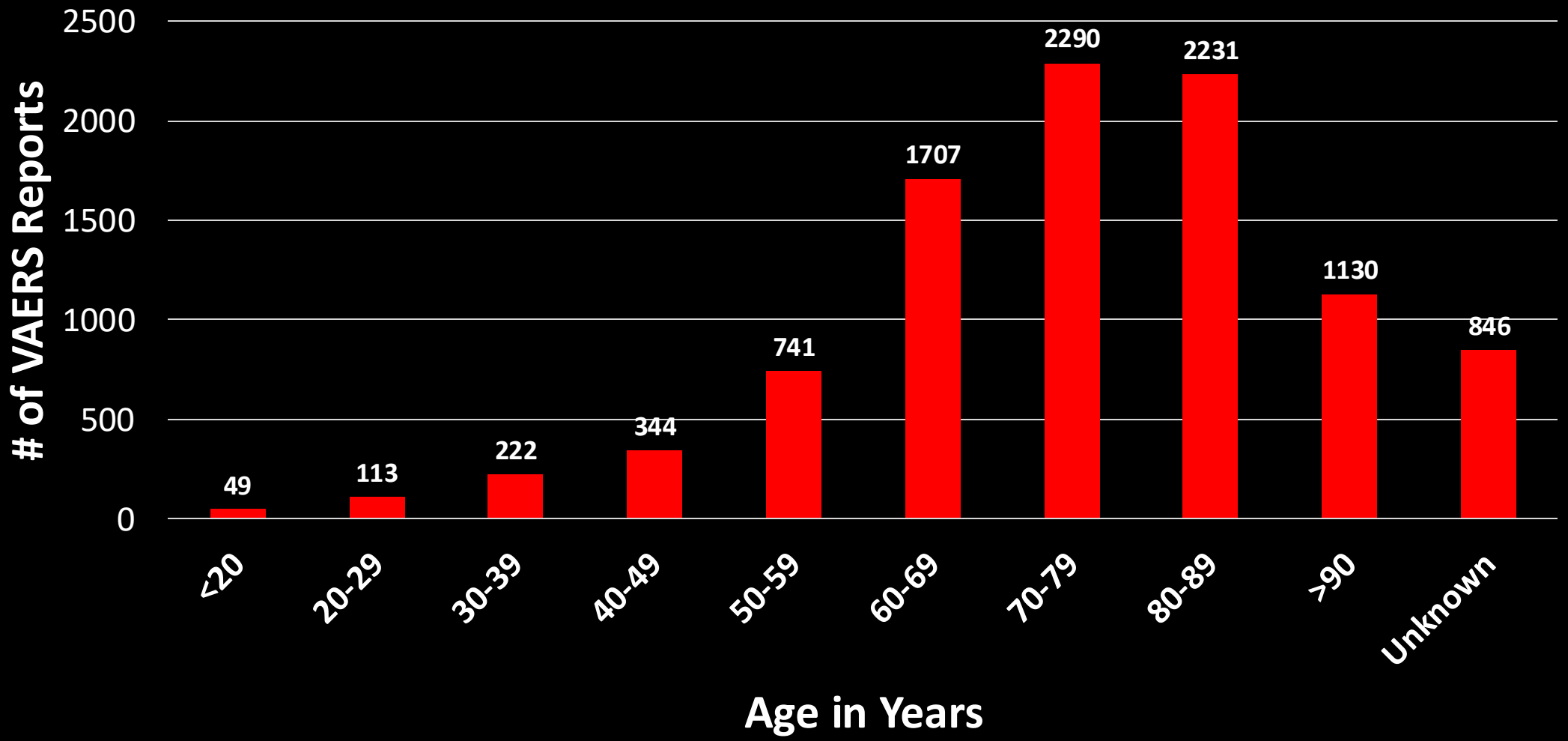
Cumulative Count of U.S. Population with at least One Dose of COVID-19 Vaccine



https://covid.cdc.gov/covid-data-tracker/#datatracker-home

American Heart Association. (2022). Heart Disease and Stroke Statistics—2022 Update: A Report From the American Heart Association. Retrieved from American Heart Association

Overwhelming Majority of COVID VAERS Reported Deaths are in Elderly (N=9763)*



* The report of an adverse event to VAERS is not documentation that a vaccine caused the event. Data through 11/17/21

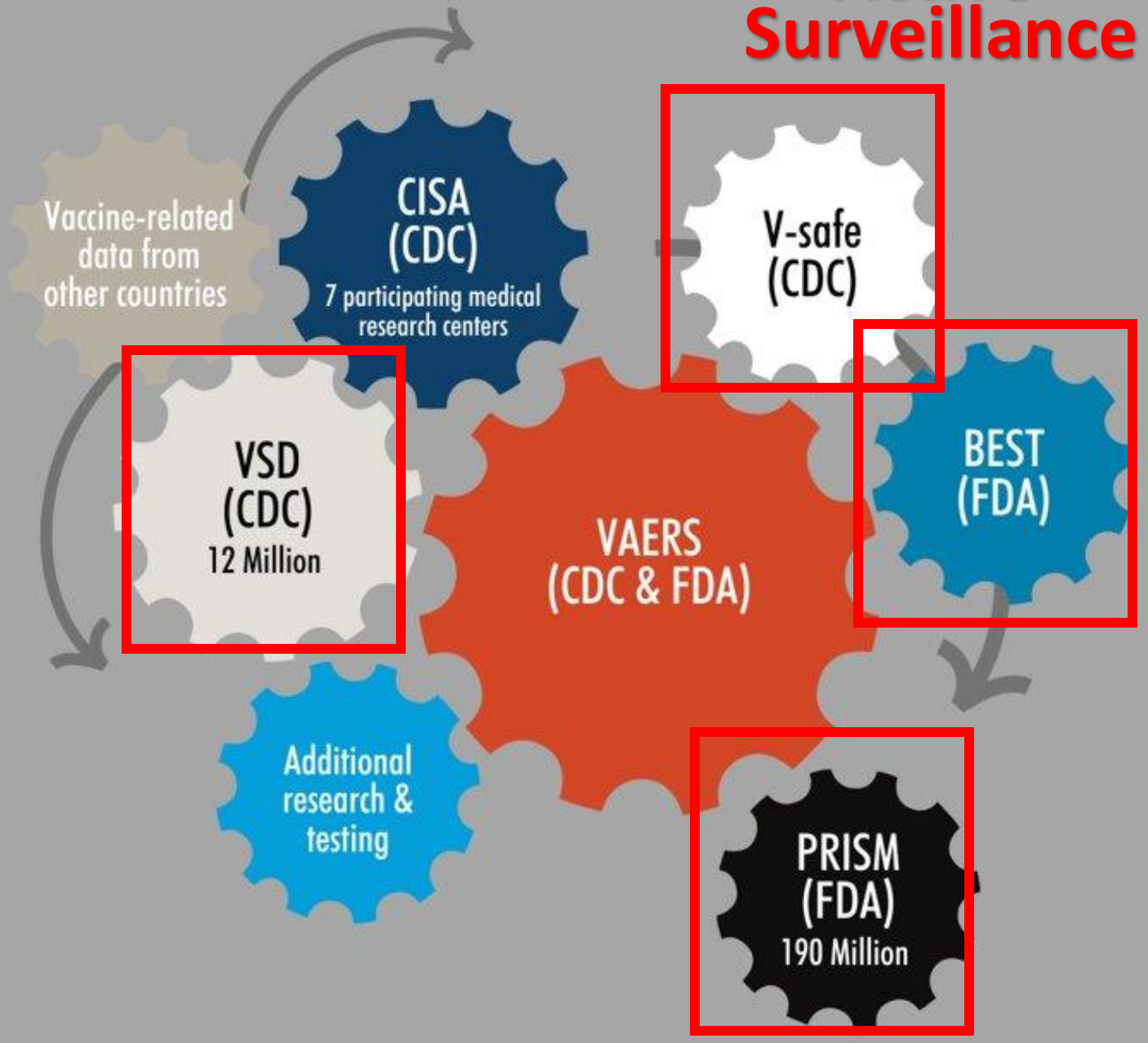
vaers.hhs.gov


SIGNAL

Vaccinated Group

Control Group

Vaccine Safety Monitoring Systems in the U.S.



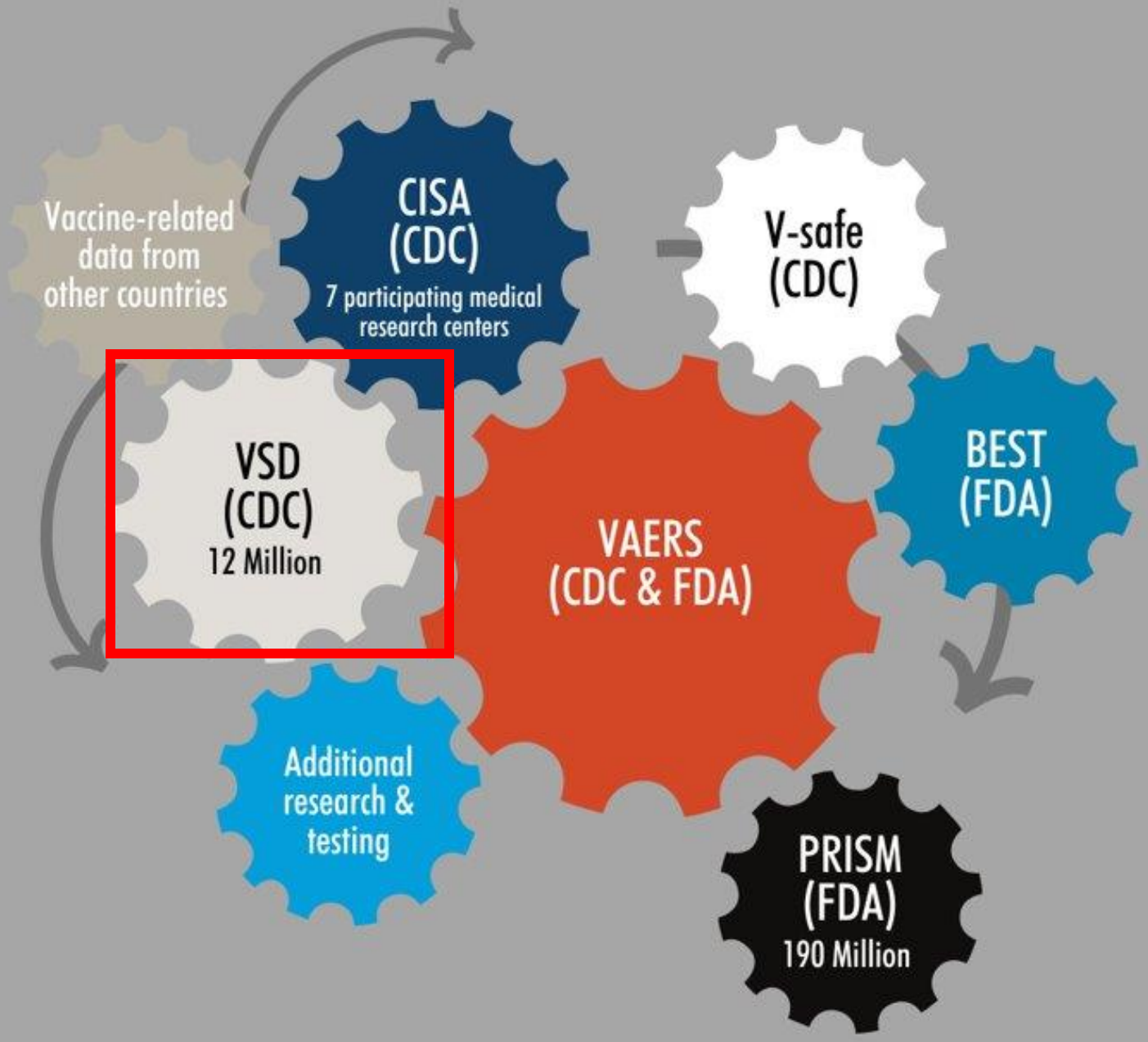
Passive Surveillance

- Unsolicited reports of adverse events sent to a central database or health authority
- In the U.S., these are received and entered into the Vaccine Adverse Event Reporting System (VAERS) that is co-managed by FDA and CDC

Active Surveillance

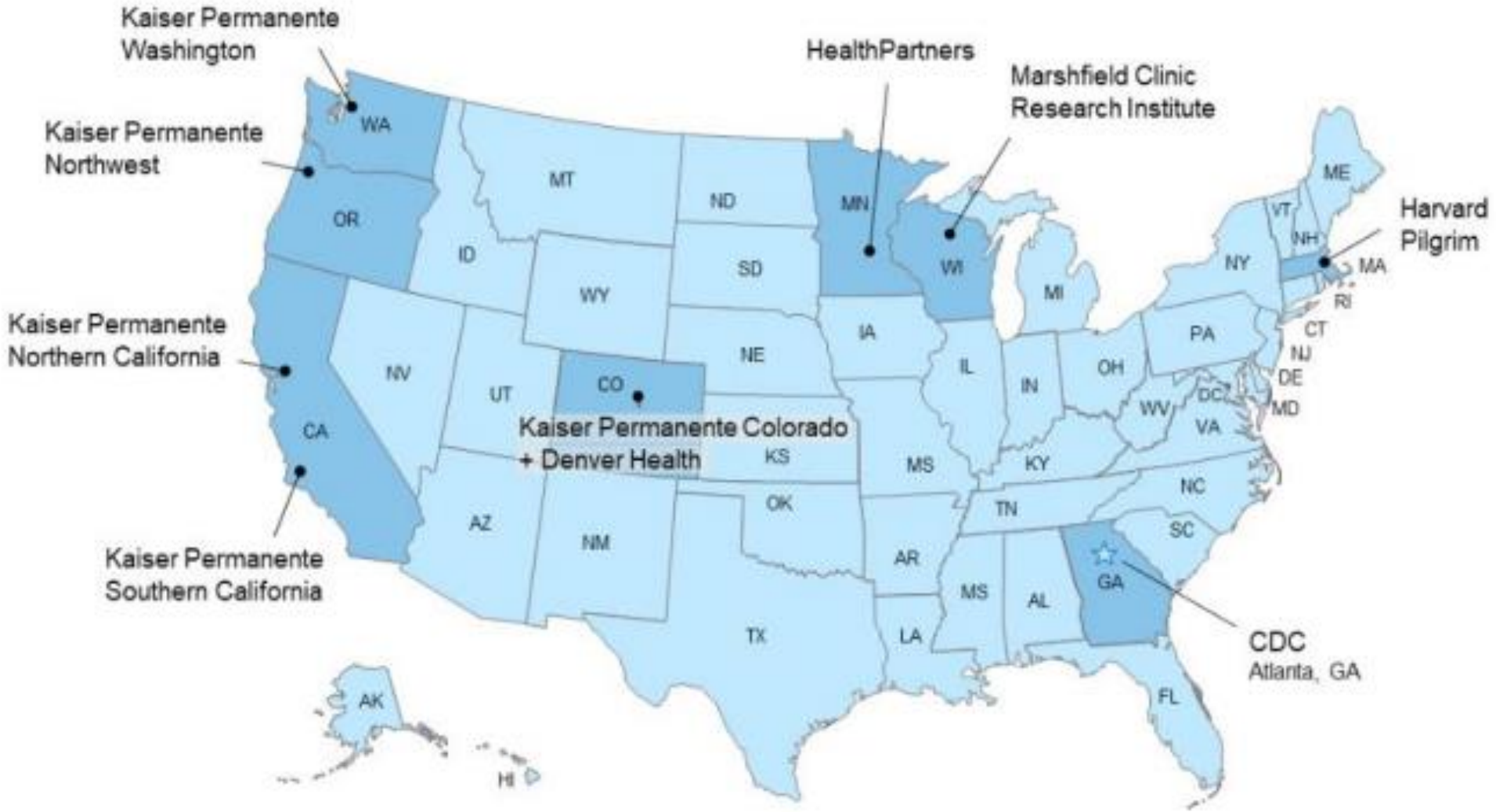
- Proactive assessment
- Variety of large databases
- “Captive” population (truer denominator)
- Data are used to verify safety signals from VAERS or to detect additional safety signals
- Done with VSD, PRISM, BEST, and V-SAFE systems

Vaccine Safety Monitoring Systems in the U.S.



VSD

Vaccine Safety Datalink



9 participating integrated healthcare organizations

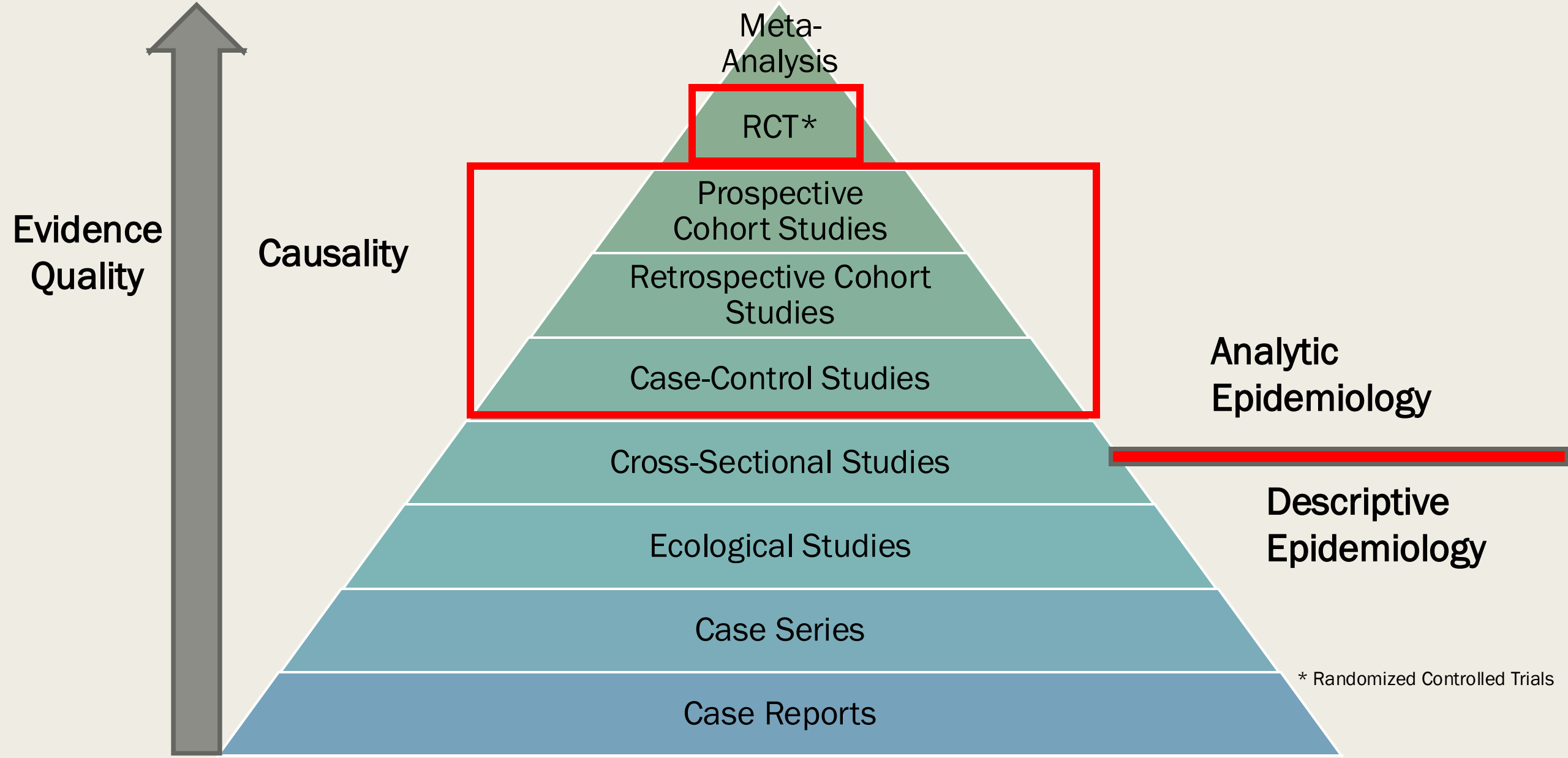
data on over **12 million** persons per year

https://www.cdc.gov/vaccine-safety-systems/vsd/index.html

Vaccinated Group

Control Group

Evidence Hierarchy of Epidemiological Study Design



JAMA | Original Investigation

Surveillance for Adverse Events After COVID-19 mRNA Vaccination

Nicola P. Klein, MD, PhD; Ned Lewis, MPH; Kristin Goddard, MPH; Bruce Fireman, MA; Ousseny Zerbo, PhD; Kayla E. Hanson, MPH; James G. Donahue, DVM, PhD; Elyse O. Kharbanda, MD, MPH; Allison Naleway, PhD;

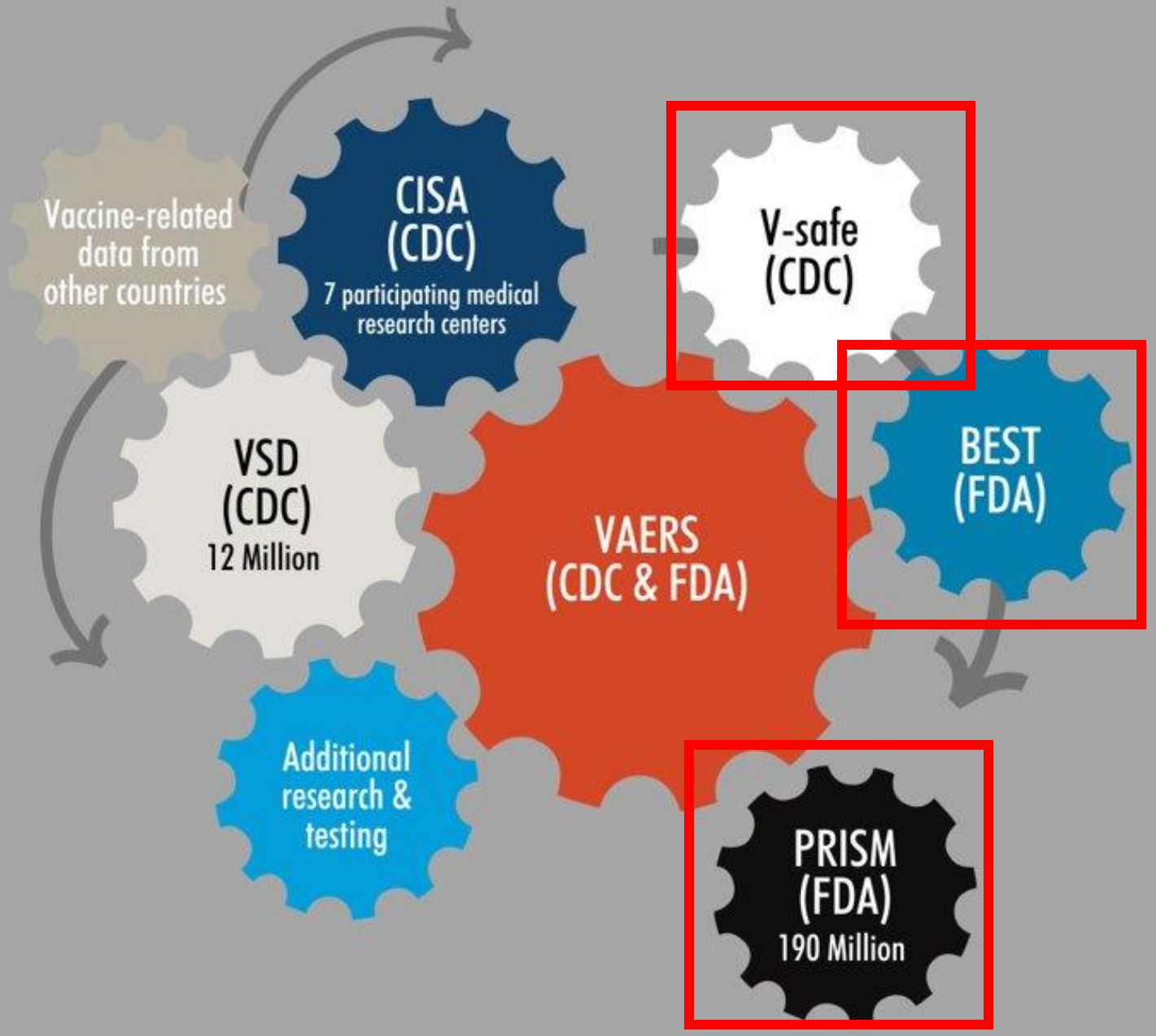
JAMA. doi:10.1001/jama.2021.15072
Published online September 3, 2021.

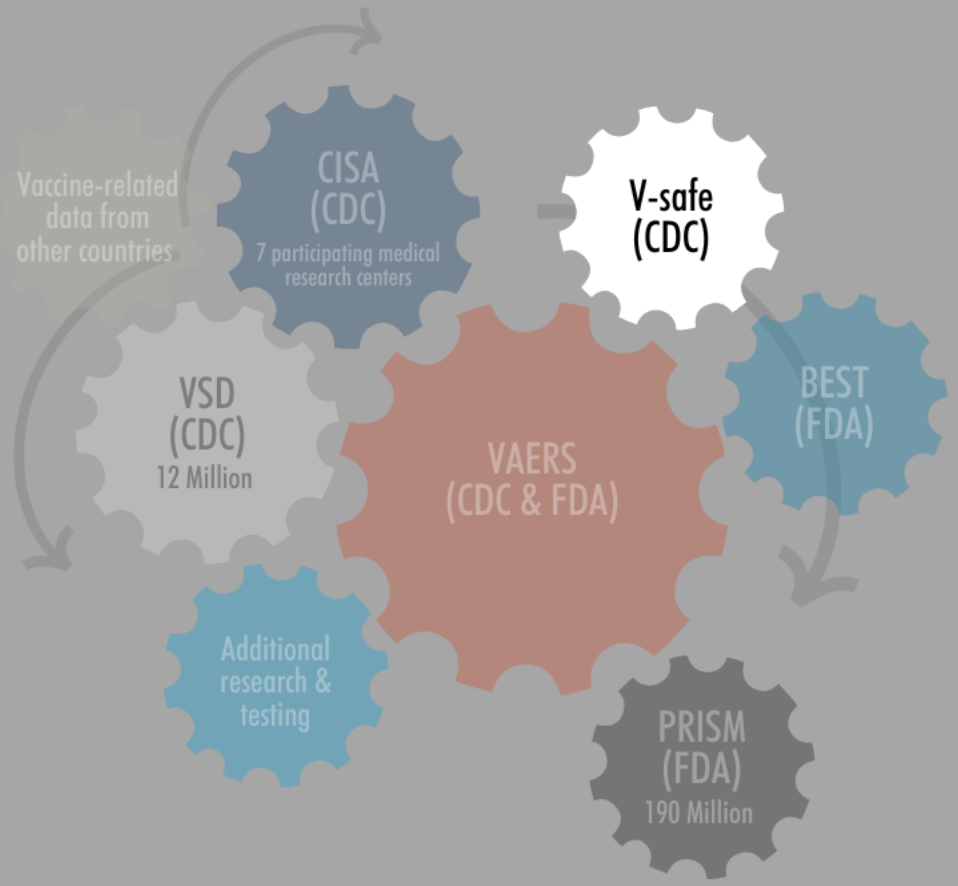
Table 1. Outcomes for Rapid Cycle Analysis of COVID-19 mRNA Vaccines

Outcomes	Risk interval, d	Setting	Exclude if COVID-19 positive in the interval before vaccination, d[a]
Comparative analyses	1-21		
Acute disseminated encephalomyelitis		Emergency department, inpatient	NA
Acute myocardial infarction		Emergency department, inpatient	30
Appendicitis		Emergency department, inpatient	NA
Bell palsy		Emergency department, inpatient, outpatient	30
Cerebral venous sinus thrombosis		Emergency department, inpatient	30
Convulsions/seizures		Emergency department, inpatient	30
Disseminated intravascular coagulation		Emergency department, inpatient	42
Encephalitis/myelitis/encephalomyelitis		Emergency department, inpatient	30
Guillain-Barré syndrome		Emergency department, inpatient	NA
Immune thrombocytopenia		Emergency department, inpatient, outpatient	30
Kawasaki disease		Emergency department, inpatient	NA
Myocarditis/pericarditis		Emergency department, inpatient	30
Pulmonary embolism		Emergency department, inpatient	30
Stroke			
Hemorrhagic		Emergency department, inpatient	30
Ischemic		Emergency department, inpatient	30
Thrombosis with thrombocytopenia syndrome[b]		Emergency department, inpatient	30
Thrombotic thrombocytopenic purpura		Emergency department, inpatient	30
Transverse myelitis		Emergency department, inpatient	NA
Venous thromboembolism		Emergency department, inpatient, outpatient	30
Descriptive monitoring only	Monitoring period, d		
Acute respiratory distress syndrome	0-84	Emergency department, inpatient	42
Anaphylaxis	0-1	Emergency department, inpatient	NA
Multisystem inflammatory syndrome in children/adults	0-84	Emergency department, inpatient	NA
Narcolepsy/cataplexy	0-84	Emergency department, inpatient, outpatient	NA

- 11,845,128 doses of mRNA vaccines in 6.2 million individuals
- No increased risk of any of the conditions except:
  - Myocarditis in 12-29 y.o. (3.7x increase)
  - Rare anaphylaxis (5-8 per million)

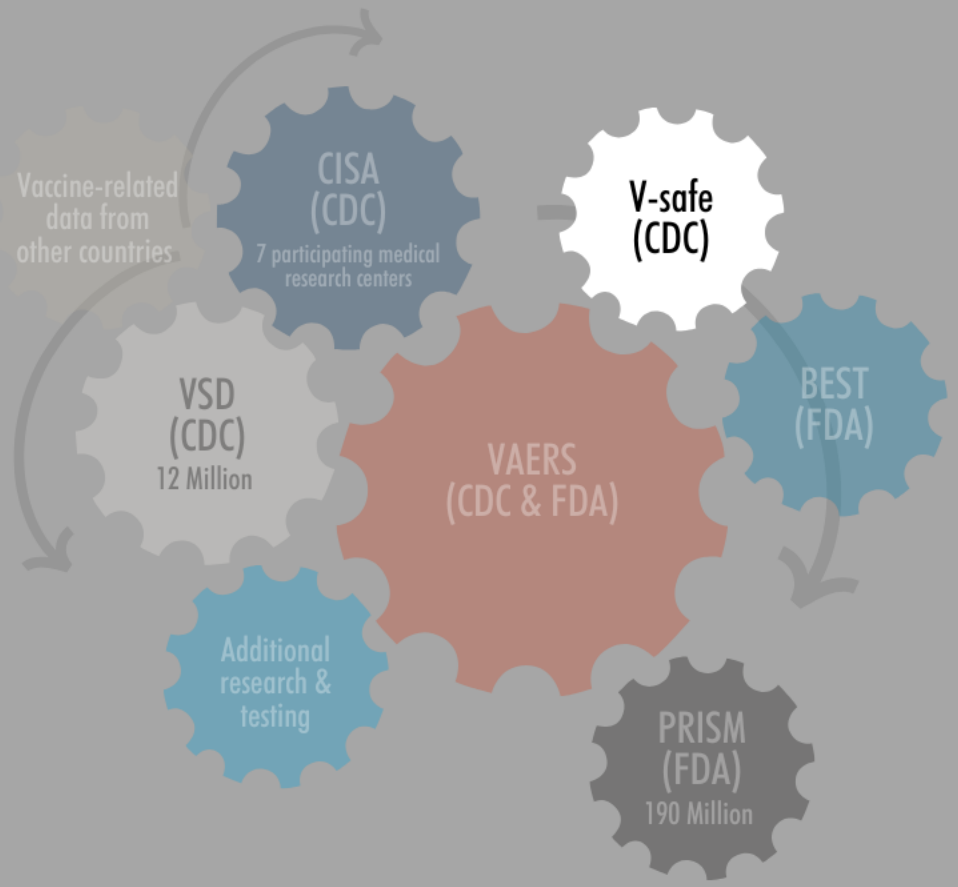
Vaccine Safety Monitoring Systems in the U.S.




Vaccine-related data from other countries
CISA (CDC)
7 participating medical research centers
V-safe (CDC)
VSD (CDC)
12 Million
VAERS (CDC & FDA)
BEST (FDA)
Additional research & testing
PRISM (FDA)
190 Million

V-safe

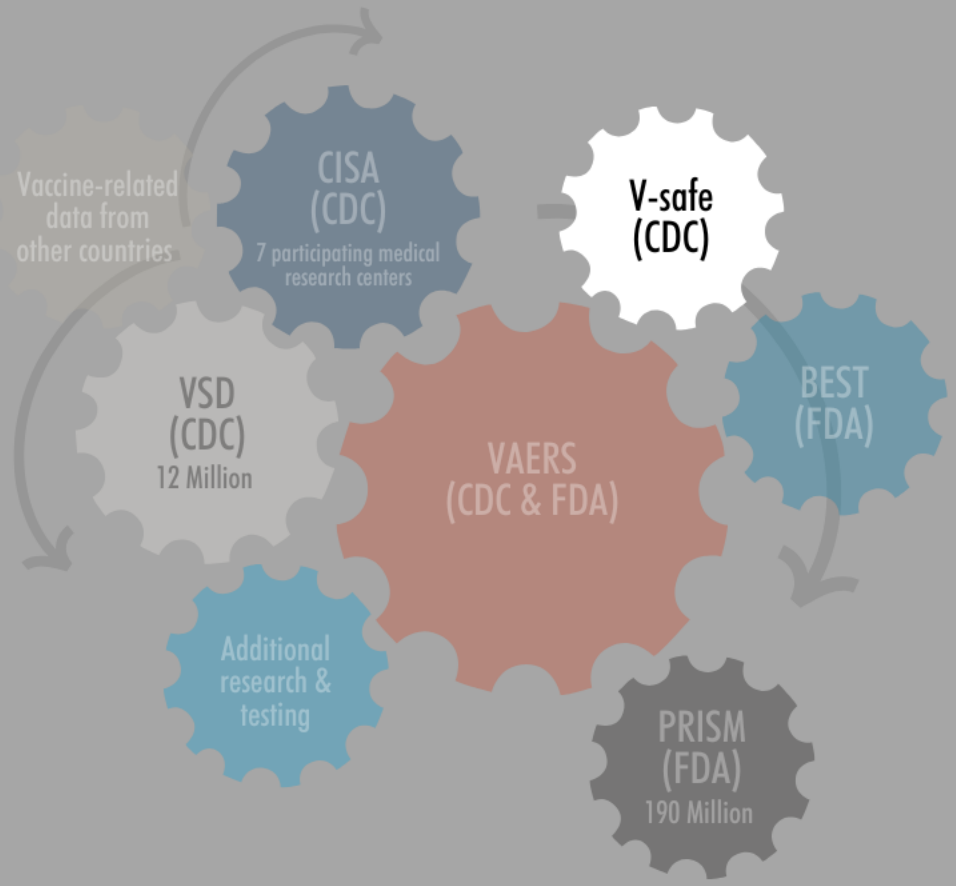
V-safe: What is it?



- Voluntary CDC smart phone-based monitoring program for COVID-19 vaccine safety in the US
- Since its launch in December 2020:
  - 10.1M v-safe participants completed more than 151M health surveys about their experiences following COVID-19 vaccination
  - v-safe data have been included in more than 20 scientific publications
- New version of v-safe will launch later in 2023 - will allow users to share their post-vaccination experiences with new vaccines

https://www.cdc.gov/vaccine-safety-systems/v-safe/index.html

V-safe Strengths & Limitation

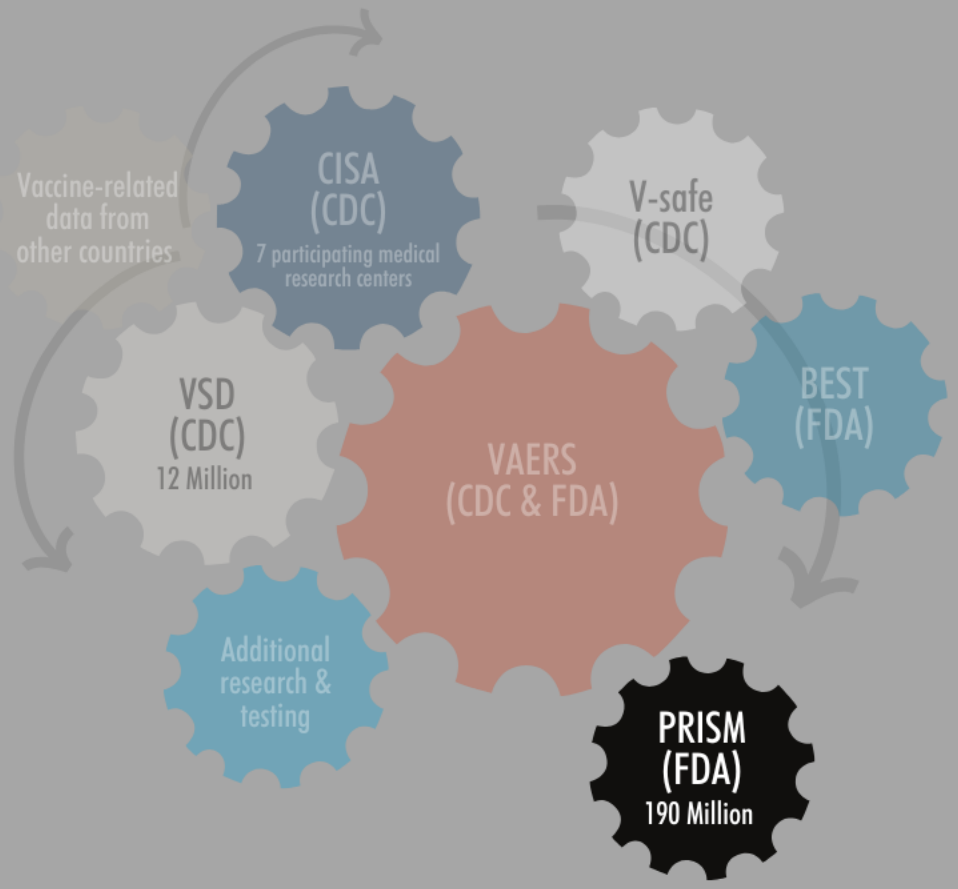


STRENGTHS

- Anyone can enroll in v-safe
- Another way to quickly validate safety data from clinical trials or identify potential safety issues
- Regular reminders to complete a survey help to capture more safety data
- CDC can follow-up with participants and submit VAERS reports, as needed

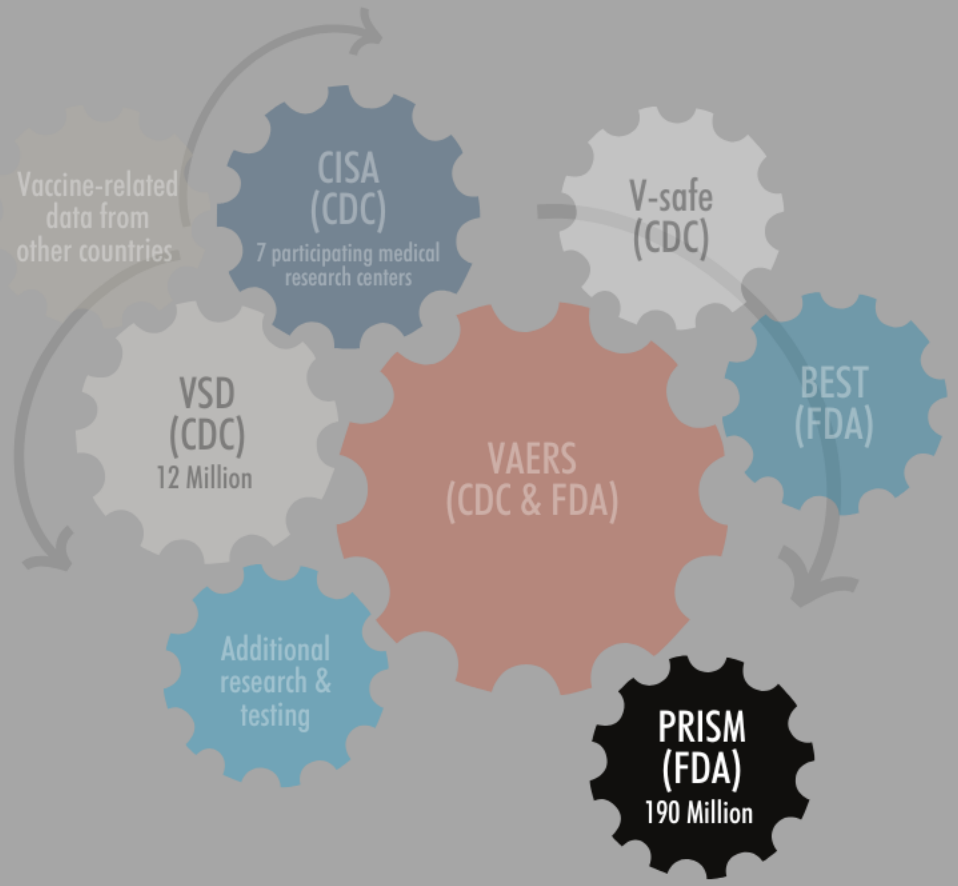
LIMITATIONS

- V-safe data may not properly represent the post-vaccination experiences of the entire population



Post-licensure Rapid Immunization Safety Monitoring System (PRISM)

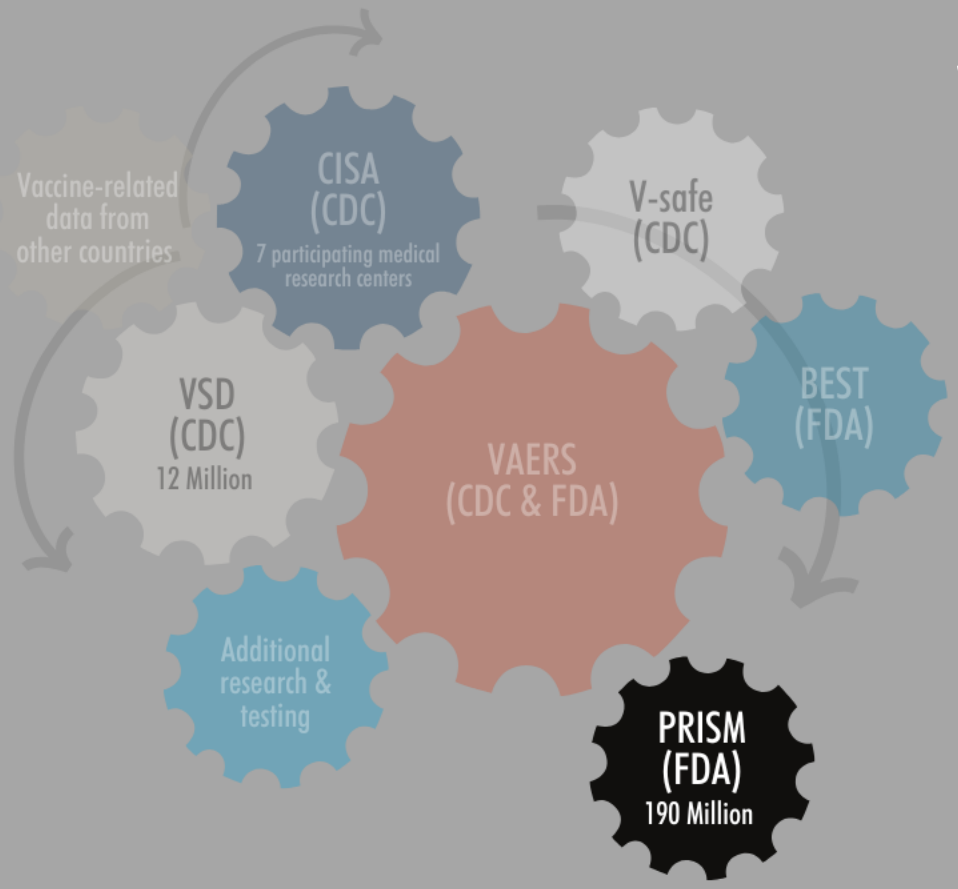
PRISM: What is it?



- The largest vaccine safety surveillance system in the U.S., with access to information for over 190 million people
- Uses a database of health insurance claims to identify and evaluate possible safety issues for licensed vaccines

https://www.sentinelinitiative.org/keywords/prism
https://www.sentinelinitiative.org/sites/default/files/Methods/Sentinel_PRISM_Vaccine_Effectiveness_White_Paper.pdf

PRISM: Strengths & Limitations

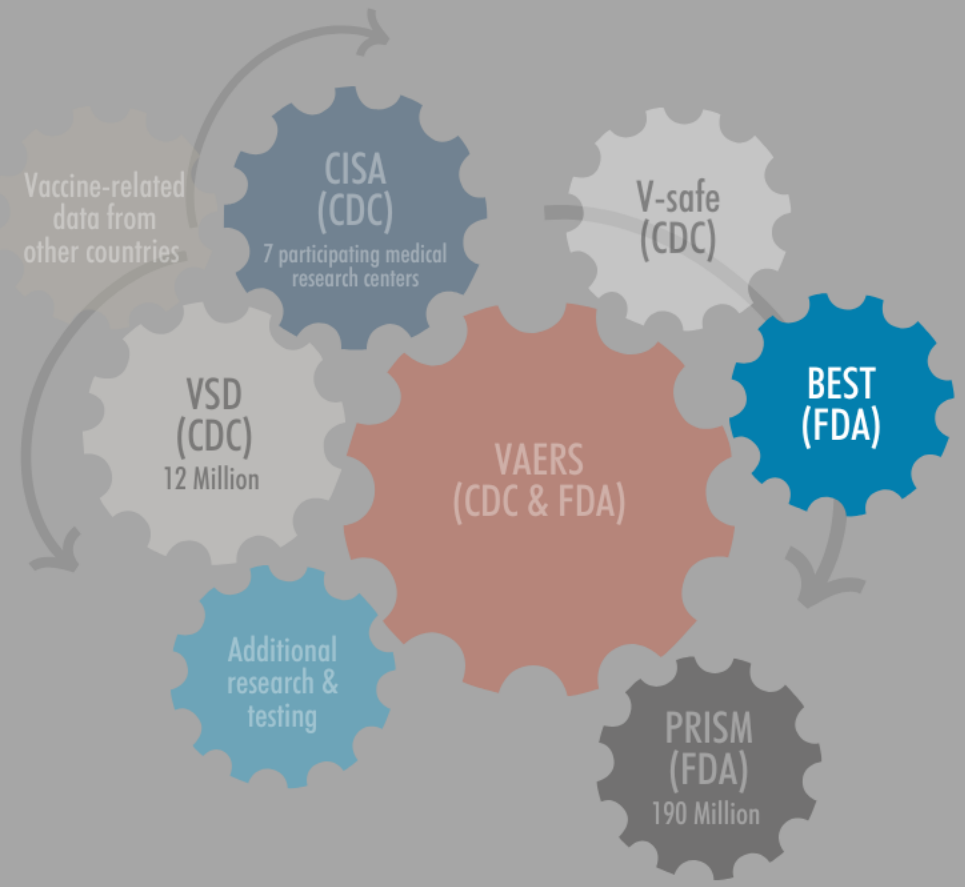


STRENGTHS

- Covers 190 million people
- PRISM uses a database of health insurance claims to identify and evaluate possible safety issues for licensed vaccine

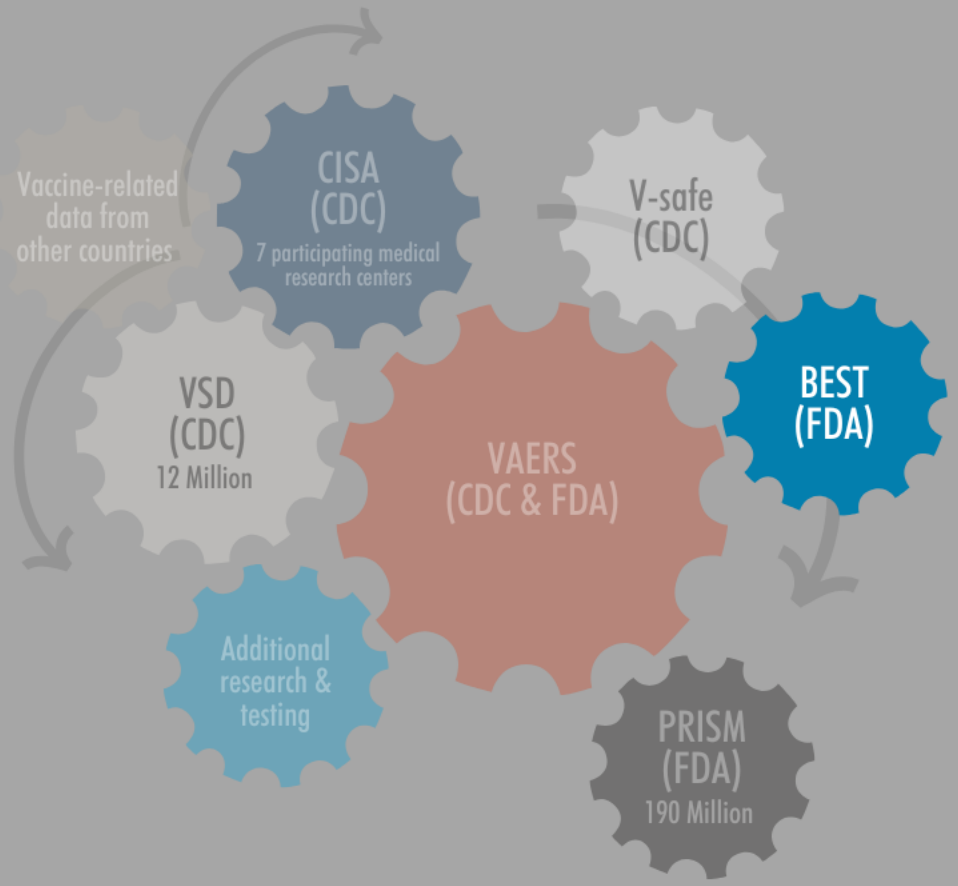
LIMITATIONS

- Lag in time for accessing the PRISM data
- Medicare population is not as well represented in PRISM
- May not be representative of those without insurance coverage



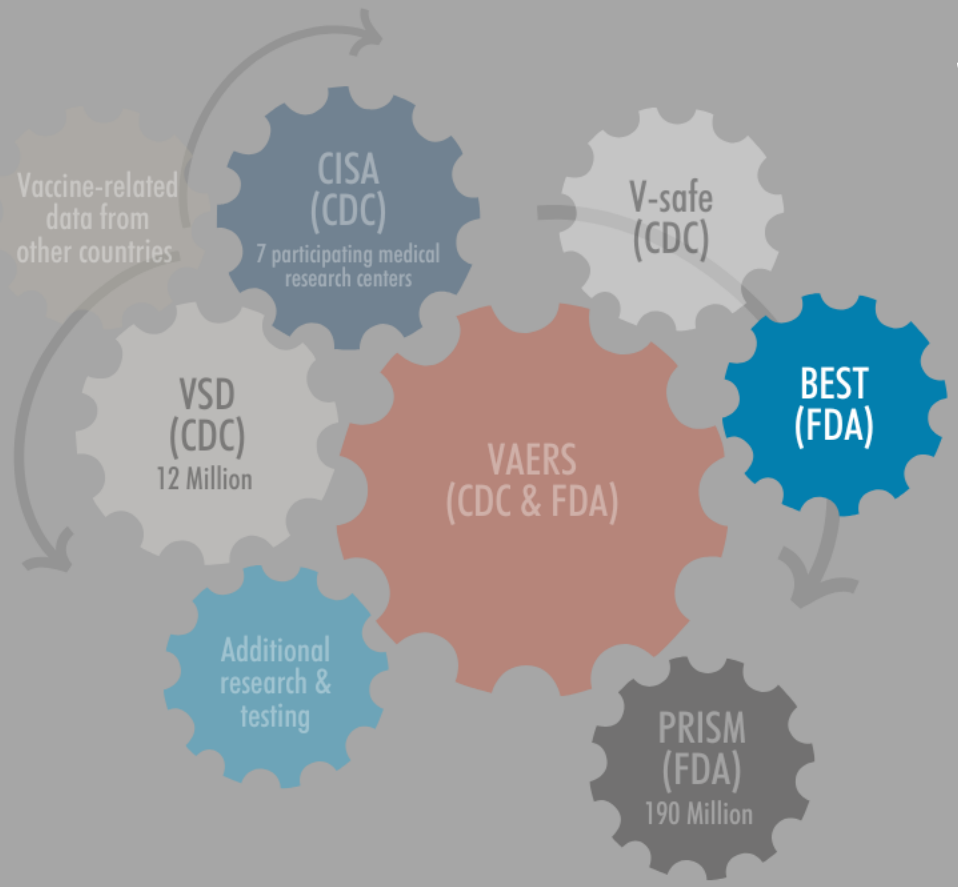
The Biologics Effectiveness and Safety (BEST) Initiative

BEST Initiative: What is it?



- Active system managed by the FDA
- Complement the VSD and v-safe for conducting surveillance of adverse events following vaccination
- Dataset includes large-scale claims data, electronic health records (EHR), and linked claims-EHR

BEST Initiative: Strengths & Limitations



STRENGTHS

- Near real-time analysis with available data
- Use of a control group, allowing for the comparison of adverse events in those who did and did not receive a vaccine (can compare vaccinated to unvaccinated)
- Ability to assess safety of vaccine in sub-populations (ex. those with pre-existing conditions, pregnant women)

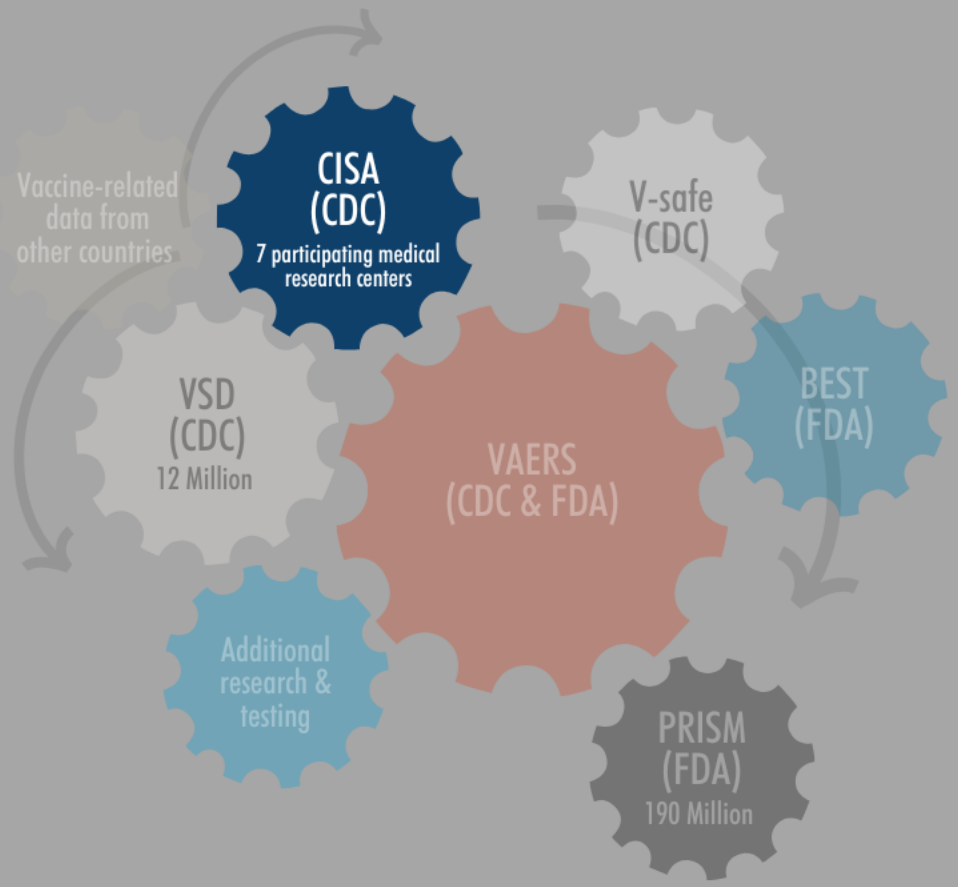
LIMITATIONS

- May not be representative of those without insurance coverage
- Cannot determine if an association between an adverse event and vaccination is causal

Safety Monitoring System Populations

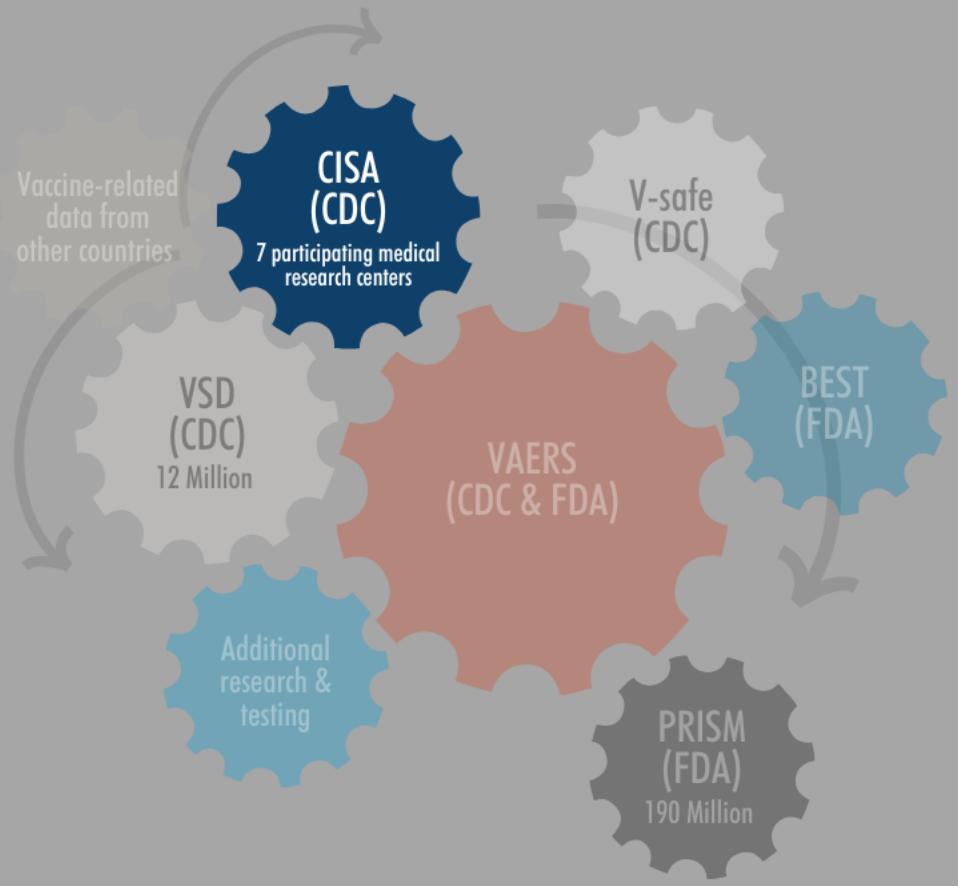
Monitoring System	Population Description	Population Total
VAERS (CDC & FDA) VA ADERS DoD VAECS CDC NHSN	General US Population, VA and DoD patient populations, NHSN acute care and LTCFs	320M people
V-safe (CDC)	All COVID-19 and mpox vaccine recipients are eligible	~10M participants
VSD (CDC)	Patients enrolled in any of the 9 VSD integrated health systems	12M patients
FDA-CMS	Medicare recipients (90+% of 65 yoa in US, including 650K LTCF residents)	~50M beneficiaries 65+yoa
BEST & PRISM (FDA)	Insured patients in BEST & PRISM sites	~190M patients
VA EHR & data warehouse	Enrolled VA patients	6.4M veterans
DoD DMSS	Active duty military (limited info on beneficiaries [ex family members retirees])	163M records
Genesis HealthCare (Brown U. & NIH-NIA)	Long-term care facility residents	~35,000 long stay residents

https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2020-12/COVID-04-Shimabukuro-508.pdf



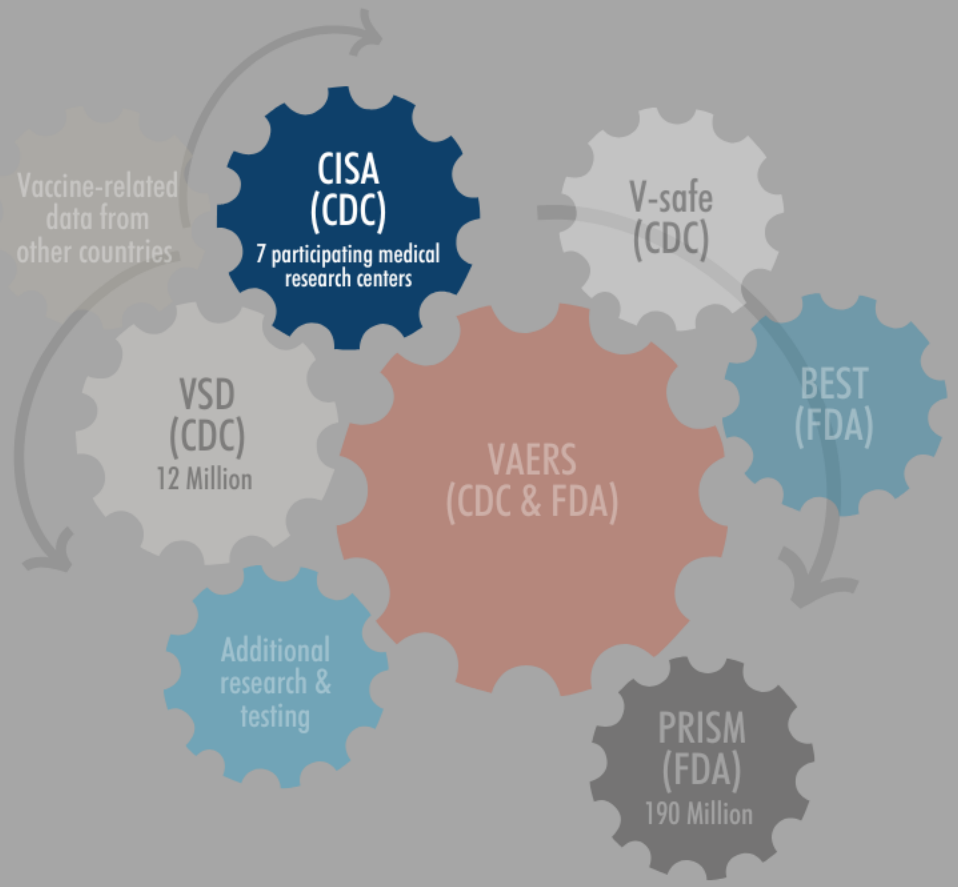
Clinical Immunization Safety Assessment Project (CISA)

CISA: What is it?



- A national network of vaccine safety experts from the CDC, seven medical research centers, and other partners
- The project addresses vaccine safety issues, conducts high quality research, and assesses complex clinical adverse events following vaccination through active surveillance

CISA: Strengths & Limitations



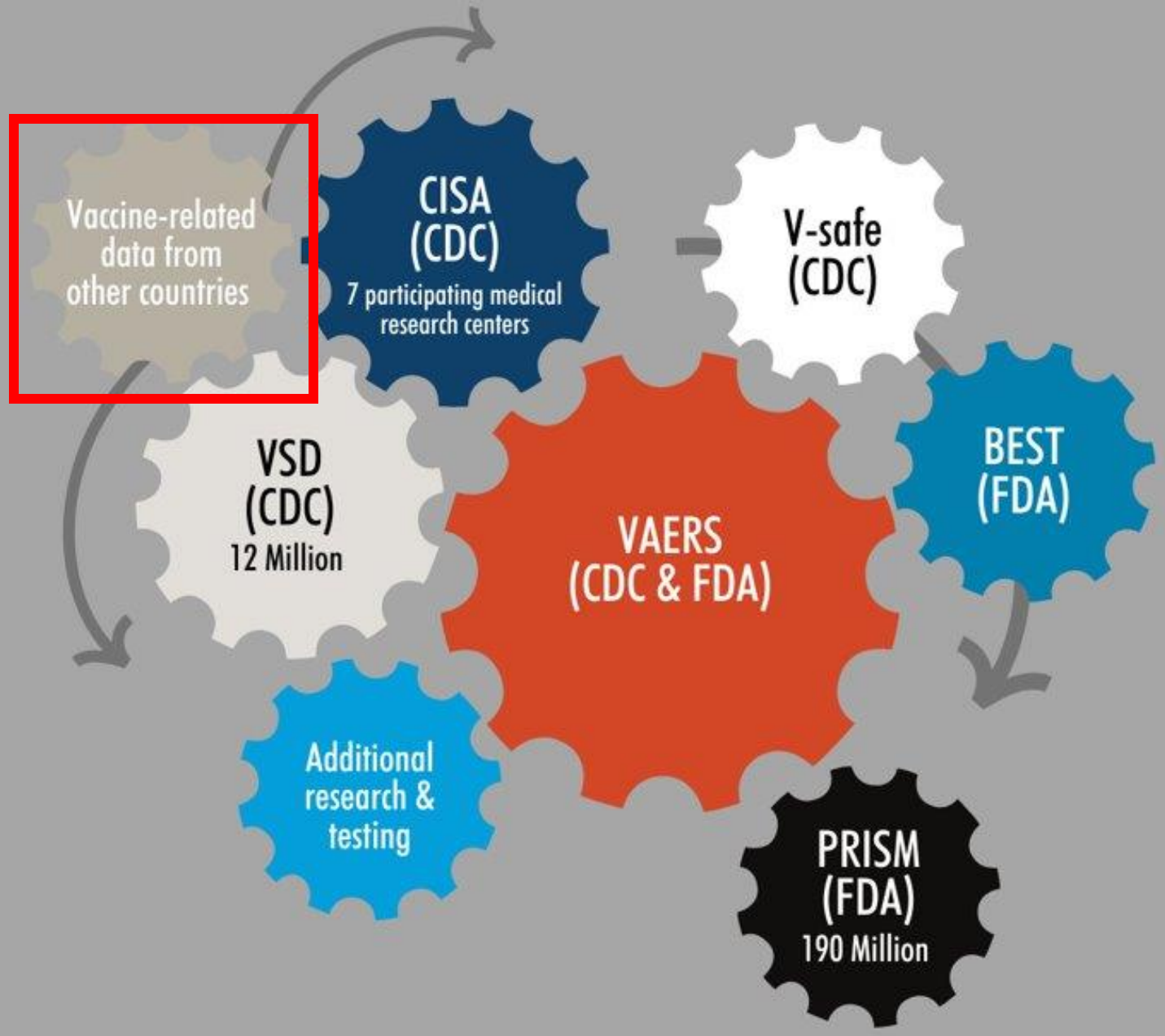
STRENGTHS

- Serves as a vaccine safety resource for U.S. health care providers and assist CDC and its partners in evaluating emerging vaccine safety issues
- Can implement prospective, multi-site clinical studies with hundreds of subjects and has the ability to recruit controls
- Can assess vaccine safety in sub-populations
- Receives detailed clinical data on patients and can collect biological samples from patients

LIMITATIONS

- Small sample sizes limits CISA's ability to study rare adverse events
- Clinical trials can be labor and resource intensive, and it can be challenging to recruit and retain subjects

Vaccine Safety Monitoring Systems in the U.S.



Vaccine-related Data from Other Countries: Examples

THE LANCET

Articles

Effectiveness of the Ad26.COV2.S vaccine in health-care workers in South Africa (the Sisonke study): results from a single-arm, open-label, phase 3B, implementation study

Linda-Gail Bekker, Nigel Garrett, Ameena Goga, Lara Fairall, Tarylee Reddy, Nonhlanhla Yende-Zuma, Reshma Kassanjee, Shirley Collie, Ian Sanne, Andrew Boulle, Ishen Seocharan, Imke Engelbrecht, Mary-Ann Davies, Jared Champion, Tommy Chen, Sarah Bennett, Selaelo Mametja, Mabatlo Semenya, Harry Moultrie, Tulio de Oliveira, Richard John Lessells, Cheryl Cohen, Waasila Jassat, Michelle Groome, Anne Von Gottberg, Engelbert Le Roux, Kentse Khuto, Dan Barouch, Hassan Mahomed, Milani Wolmarans, Petro Rousseau, Debbie Bradshaw, Michelle Mulder, Jessica Opie, Vernon Louw, Barry Jacobson, Pradeep Rowji, Jonny G Peter , Azwi Takalani, Jackline Odhiambo, Fatima Mayat, Simbarashe Takuva, Lawrence Corey, Glenda E Gray, and the Sisonke Protocol Team, on behalf of the Sisonke Study Team

Summary

Background We aimed to assess the effectiveness of a single dose of the Ad26.COV2.S vaccine (Johnson & Johnson) in health-care workers in South Africa during two waves of the South African COVID-19 epidemic.

Methods In the single-arm, open-label, phase 3B implementation Sisonke study, health-care workers aged 18 years and older were invited for vaccination at one of 122 vaccination sites nationally. Participants received a single dose

Lancet 2022; 399: 1141–53

See Comment page 1095

The Desmond Tutu HIV Centre, Cape Town, South Africa

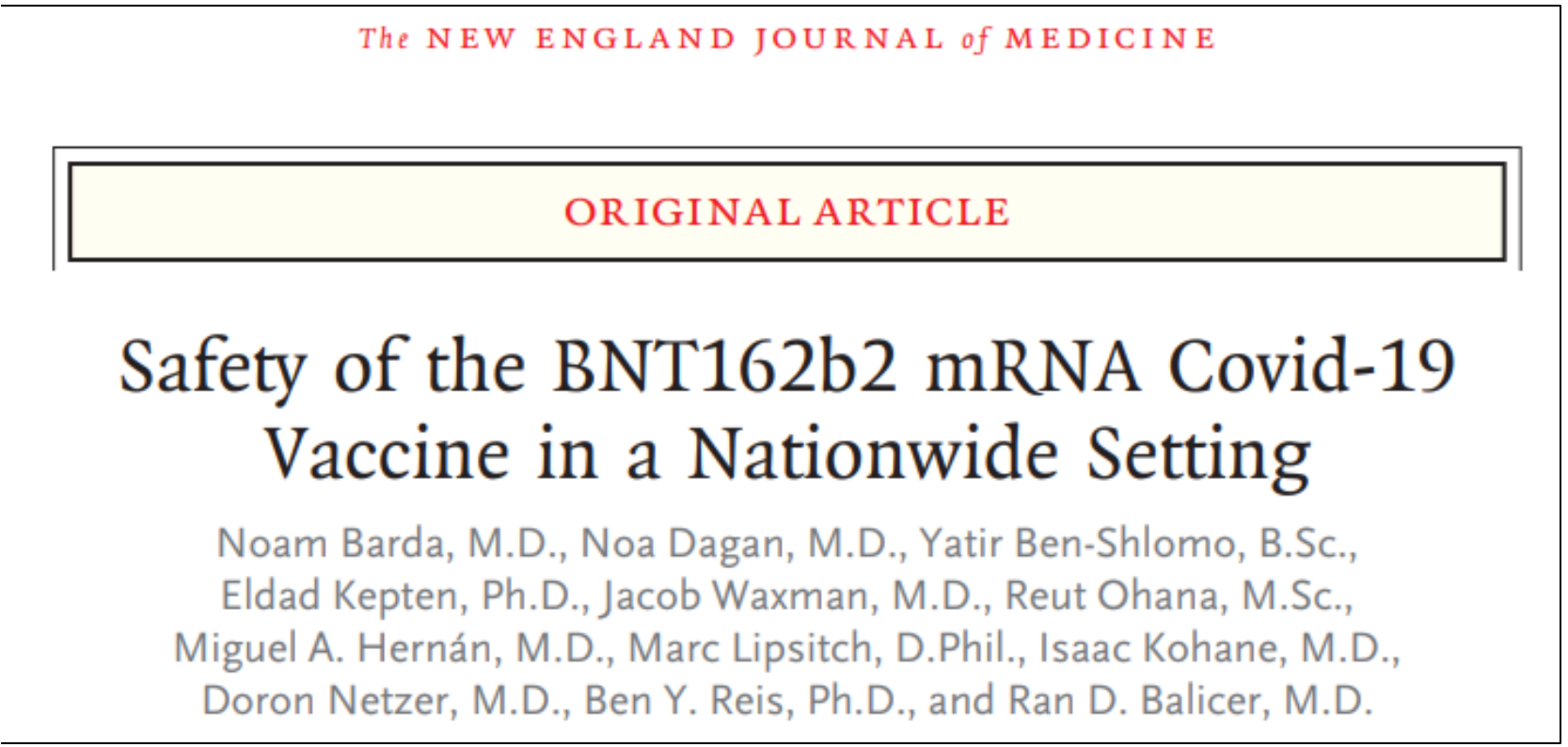
(L-G Bekker PhD, L Fairall PhD);

Eric J Haas, Frederick J Angulo, John M McLaughlin, Emilia Anis, Shepherd R Singer, Farid Khan, Nati Brooks, Meir Smaja, Gabriel Mircus, Kaijie Pan, Jo Southern, David L Swerdlow, Luis Jodar, Yeheskel Levy, Sharon Alroy-Preis

Vaccine Efficacy or Effectiveness (VE) Against Variants

Vaccine	Study type	VE	
Pfizer	Post-EUA	• 90% against B.1.1.7 in Qatar* • 75% against B.1.351 in Qatar	100% for severe/ critical disease
Janssen	Pre-EUA	• 74% in U.S. • 66% in Brazil • 52% in S. Africa	73-82% for severe/critical disease in each country
Novavax	Pre-EUA Pre-EUA	• 96% against non-B.1.1.7 in UK • 86% against B.1.1.7 in UK • 51% against B.1.351 in S. Africa	
AstraZeneca	Pre-EUA Pre-EUA	• 84% against non-B.1.1.7 in UK • 75% against B.1.1.7 in UK • 10% against B.1.351 in South Africa*	

*>85% in UK & Israel (predominate B.1.1.7): https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html
Abu-Radad and Butt. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants | NEJM
https://www.fda.gov/media/146217/download
Novavax.: https://ir.novavax.com/news-releases/news-release-details/novavax-covid-19-vaccine-demonstrates-893-efficacy-uk-phase-3
Shinde et al. Efficacy of NVX-CoV2373 Covid-19 Vaccine against the B.1.351 Variant | NEJM
Madhi et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant | NEJM
Emary et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): The Lancet. **mild/moderate illness



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

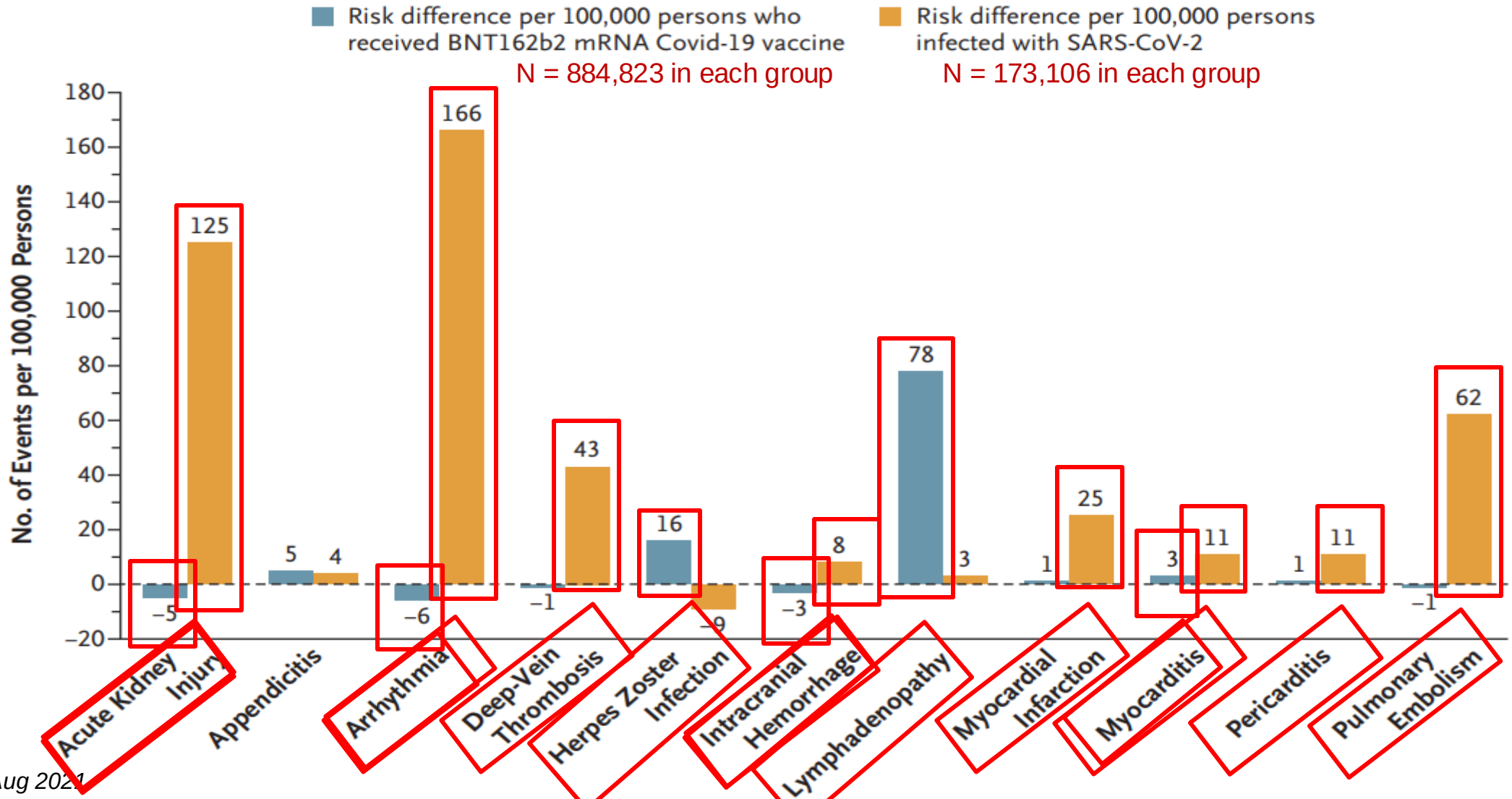
Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting

Noam Barda, M.D., Noa Dagan, M.D., Yatir Ben-Shlomo, B.Sc., Eldad Kepten, Ph.D., Jacob Waxman, M.D., Reut Ohana, M.Sc., Miguel A. Hernán, M.D., Marc Lipsitch, D.Phil., Isaac Kohane, M.D., Doron Netzer, M.D., Ben Y. Reis, Ph.D., and Ran D. Balicer, M.D.

https://www.nejm.org/doi/full/10.1056/NEJMoa2110475#

Acute kidney injury
Anemia
Appendicitis
Arrhythmia
Arthritis or arthropathy
Bell's palsy
Cerebrovascular accident
Deep-vein thrombosis
Herpes simplex infection
Herpes zoster infection
Intracranial hemorrhage
Lymphadenopathy
Lymphopenia
Myocardial infarction
Myocarditis
Neutropenia
Other thrombosis
Paresthesia
Pericarditis
Pulmonary embolism
Seizure
Syncope
Thrombocytopenia
Uveitis
Vertigo

Absolute Excess Risk of Various Adverse Events after Vaccination or SARS-CoV-2 Infection



Barda N. NEJM Aug 2021

Question

Which vaccine was suspended after safety surveillance detected a rare but serious adverse event related to intestinal blockage in infants?

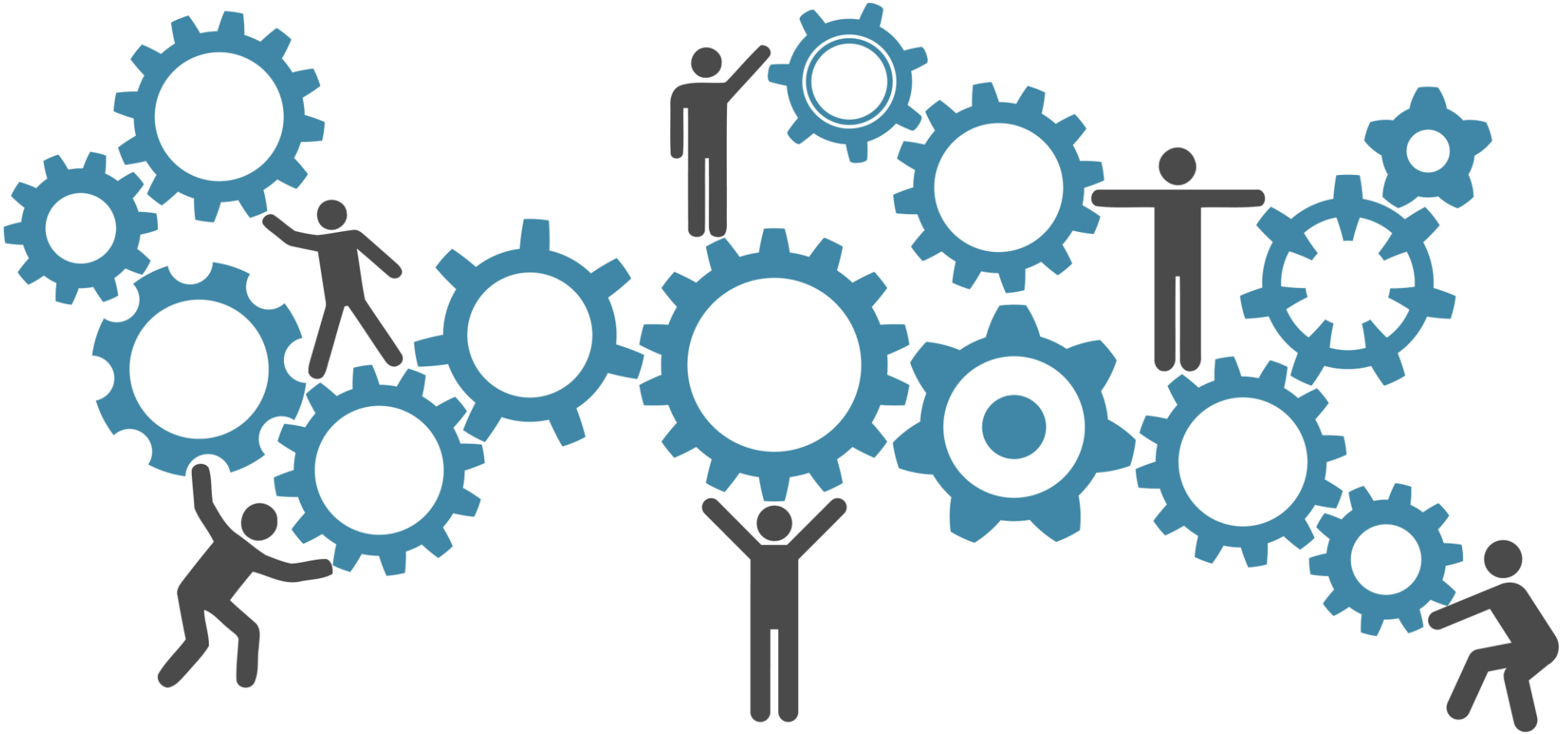
A) Measles, Mumps, and Rubella (MMR) vaccine

B) Rotavirus vaccine

C) Influenza vaccine

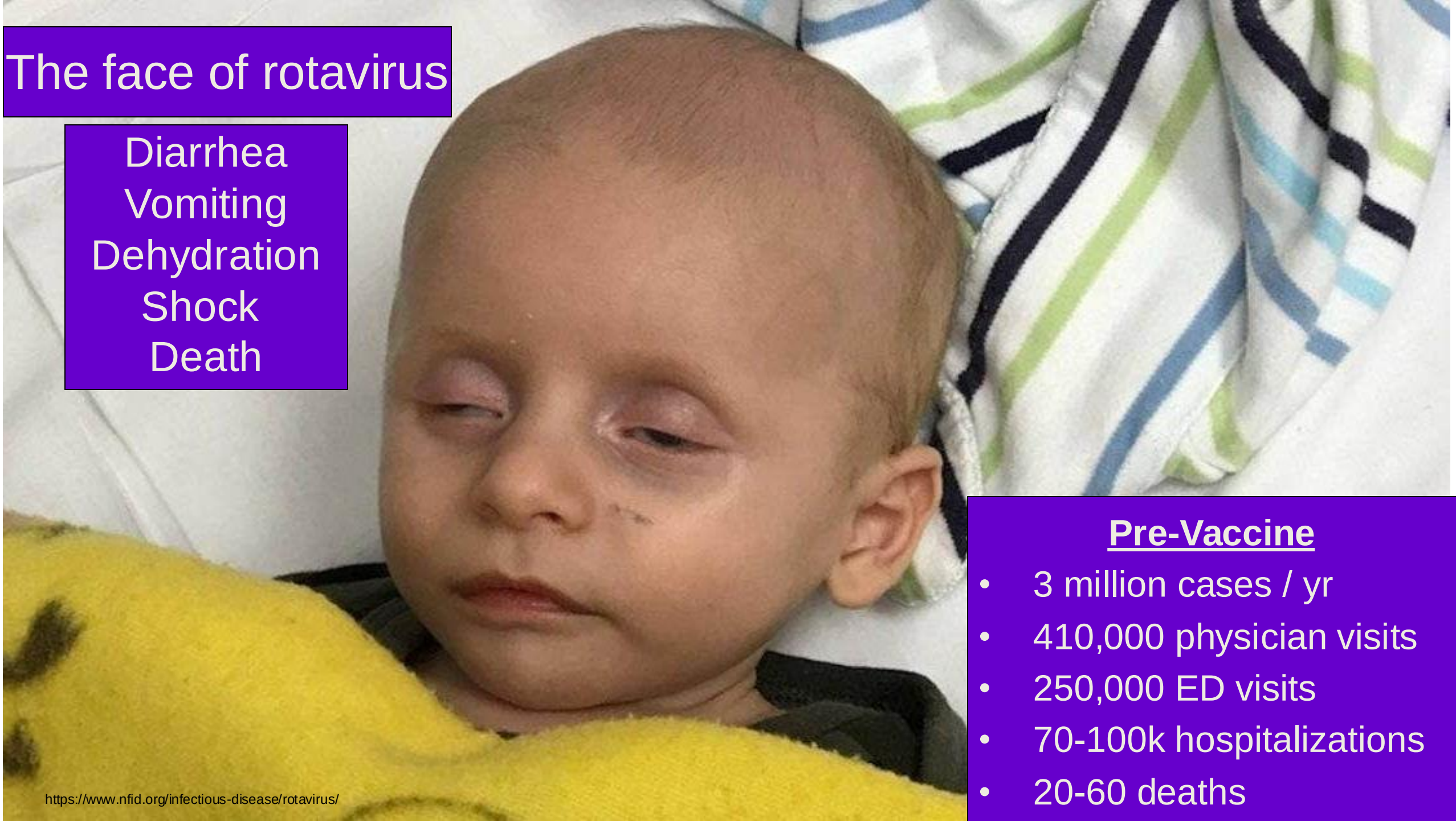
D) Hepatitis B vaccine

Let’s look at how these systems work together to find and manage potential safety issues using the Rotavirus disease and vaccine as an example



The face of rotavirus

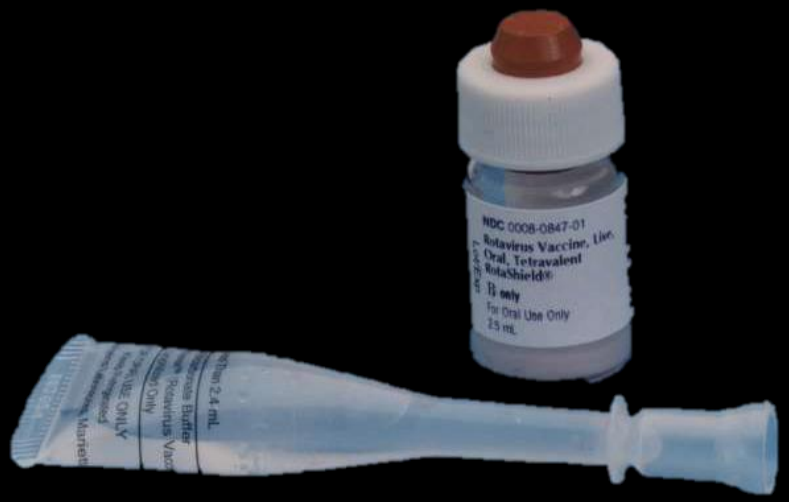
Diarrhea
Vomiting
Dehydration
Shock
Death



https://www.nfid.org/infectious-disease/rotavirus/

Pre-Vaccine

- 3 million cases / yr
- 410,000 physician visits
- 250,000 ED visits
- 70-100k hospitalizations
- 20-60 deaths



Rotashield: Timeline of Events

FDA approves Rotashield N=4,413

August 1998

VAERS identifies 15 cases of intussusception – CDC suspends vaccine

July 1999

CDC uses CISA, VSD and other sources to conduct a case-series analysis, case-control study, and retrospective cohort study - confirmed association in 1:11,000 children. Vaccine withdrawn from market.

October 1999


Pathogen
Vaccine

Finding Rare Events: Rule of 3

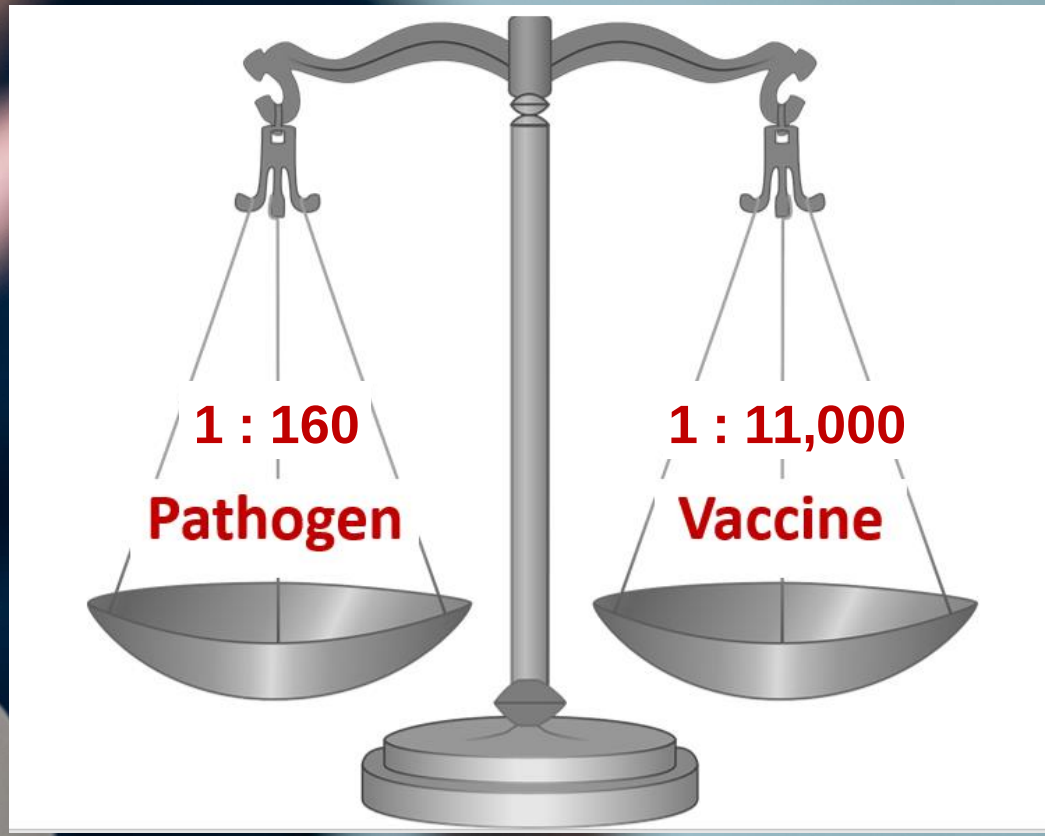
You can be 95% confident that your sample size (N) can detect events at a rate of 3/N or greater

<u>Original Rotashield Example</u>:

Cumulative incidence of Rotavirus hospitalization for children up to 5 y.o. - 1:160

Phase III trial for Rotashield vaccine - N = 2,200 in vaccine arm - 3 / 2,200 = 0.136% = 1:733 (not enough to detect the rare 1:11,000 risk of IS found later, but much better than the 1:160 risk from the virus!)

Rotavirus



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Efficacy of a Pentavalent Human–Bovine (WC3) Reassortant Rotavirus Vaccine

ABSTRACT

N ENGL J MED 354;1 WWW.NEJM.ORG JANUARY 5, 2006

BACKGROUND

Rotavirus is a leading cause of childhood gastroenteritis and death worldwide.

METHODS

We studied healthy infants approximately 6 to 12 weeks old who were randomly assigned to receive three oral doses of live pentavalent human–bovine (WC3 strain) reassortant rotavirus vaccine containing human serotypes G1, G2, G3, G4, and P[8] or placebo at 4-to-10-week intervals in a blinded fashion. Active surveillance was used to identify subjects with serious adverse and other events.

RESULTS

The 34,035 infants in the vaccine group and 34,003 in the placebo group were monitored for serious adverse events. Intussusception occurred in 12 vaccine recipients and 15 placebo recipients within one year after the first dose including six vaccine recipients and five placebo recipients within 42 days after any dose (relative risk, 1.6; 95 percent confidence interval, 0.4 to 6.4). The vaccine reduced hospital-

Pentavalent
Rotateq
68,000 subjects

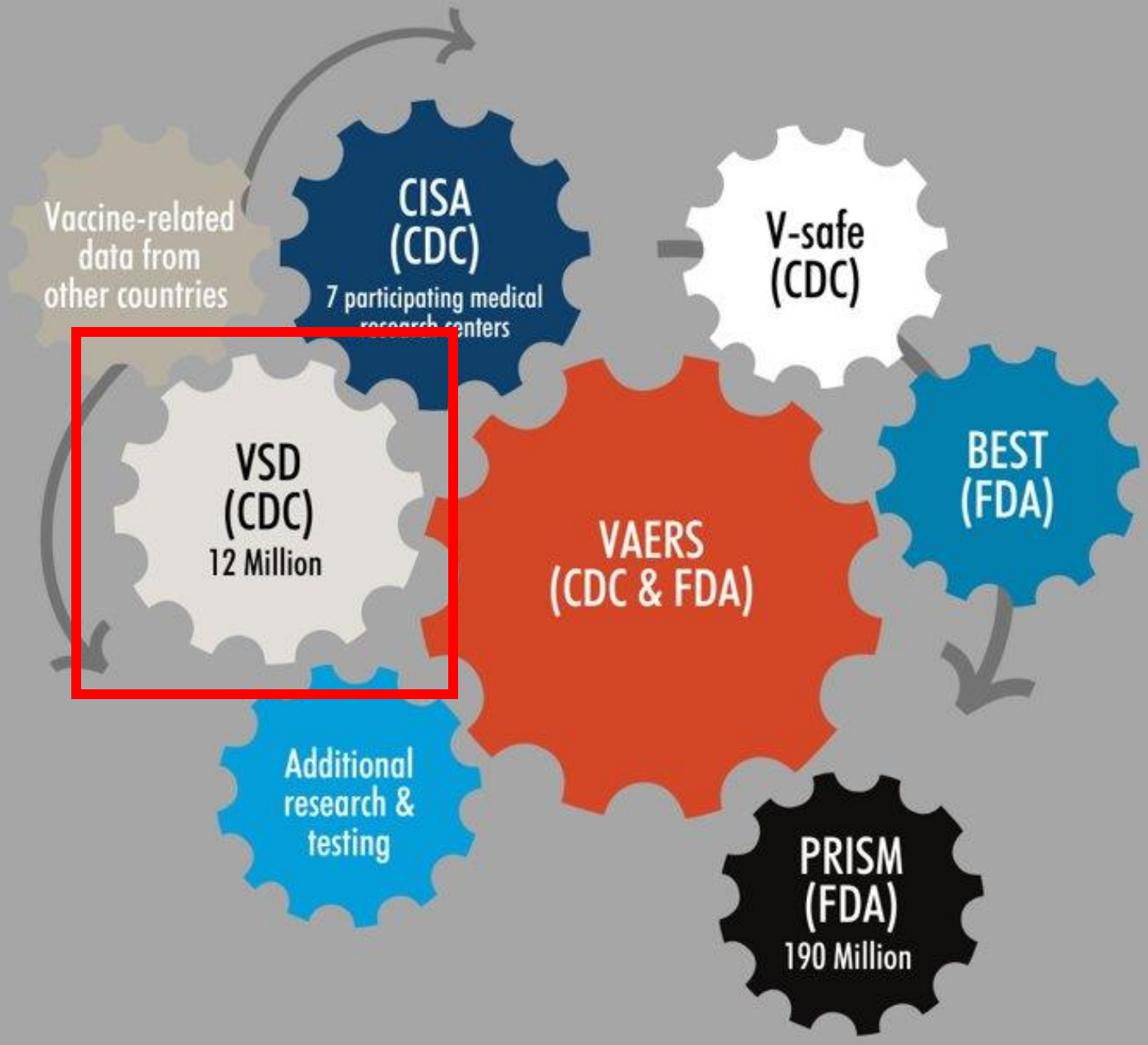
Monovalent
Rotarix
80,000 subjects

No additional risk found

Monitoring continued after licensure due to ongoing safety concerns. Data from other countries suggested slight increased risk.

CDC initiated a cohort study through VSD involving 0.5 million 1st doses and 1.27 million 2nd doses of RV5.

RV5 ~ 1.5 additional intussusceptions per 100,00 1st dose recipients.



Benefits and Risks: Summary of Estimates of One Rotavirus Vaccinated Birth Cohort to age 5

Annual Outcomes in Birth Cohort[1]	Caused by Vaccination[2]	Prevented by Vaccination	Prevented RV Outcome per 1 excess IS outcome
Hospitalization	45	53,444	1093 : 1
ED Visit	13	169,949	12,115 : 1
Death	0.2	14	71 : 1

1. ~ 4.3 million infants in 2000 and 2007 birth cohorts followed over 5 yrs
2. Vaccine-associated intussusception

Tate et al. Pediatrics Sept 2016

Examples of Assessing Safety Signals

	Concern	How was it detected?	Follow up assessment	Ass'n? / Action?
1996	Vaccine-associated paralytic polio (VAPP) & OPV	VAERS	VSD; Data from other countries & PAHO; NIS; IOM review	YES / YES Transition from oral polio vaccine to inactivated polio vaccine in U.S.
2008-2011	DVT from HPV vaccination	VAERS & VSD	VSD, Denmark, Sweden, Canada: Cohort studies	NO / NO No change to vaccination schedules
2021	Johnson & Johnson COVID-19 vaccine & VITT (rare form of blood clot)	VAERS & data from Europe	Additional data out of Europe; CISA; VSD; VA Data	YES / YES Vaccine use limited and FDA eventually rescinded EUA.
2021	mRNA COVID-19 vaccines & myo/pericarditis	Data from Israel	VAERS; V-safe; CISA; VSD; Military Health System & PCORnet data; DoD; Data from other countries	YES / Partial No change to vaccination schedules. HOWEVER, an optional 8-week interval between 1st & 2nd dose was added to recommendations.

Examples of Assessing Safety Signals

	Concern	How was it detected?	Follow up assessment	Ass'n? / Action?
2001	Use of thimerosal in vaccines & autism	NONE (Public Concern)	VAERS; VSD; CISA; IOM; Data from other countries	NO / YES Data doesn't support association. HOWEVER, thimerosal removed from childhood vaccines in U.S.
2012	HPV vaccine & primary ovarian insufficiency (POI)	NONE (Public Concern)	VAERS; CISA; VSD; Data from other countries; WHO	NO / NO Data doesn't support association between HPV vaccination & POI.
2023	Pfizer's bivalent COVID-19 vaccine & stroke in 65+ yoa	VSD	VAERS; CMS & VA data; BEST; Data from other countries	NO / NO Data doesn't support association between Pfizer's COVID-19 vaccination and stroke in 65+ yoa.
2022-23	Aluminum in vaccines & asthma	NONE (Public Concern)	VSD; Data from other countries	MAYBE / YES Majority of data doesn't support association, however this will continue to be studied.

“I never breathe a sigh of relief until the first 3 million doses are out there.”

Dr. Maurice Hilleman


CONFIDENCE