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

Kylie Hall, MPH

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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.

World Health Organization

Vaccine Hesitancy

Ten threats to global health in 2019

Vaccine Safety is a TOP PRIORITY

- We all want safe vaccines.
- Maintaining public confidence in vaccines is critical.
- A higher standard of safety is generally **expecte** of vaccines than of other medical interventions because, in contrast to most pharmaceutical products that are administered to ill persons for treatment purposes, **vaccines are generally administered to healthy persons** to prevent disease.

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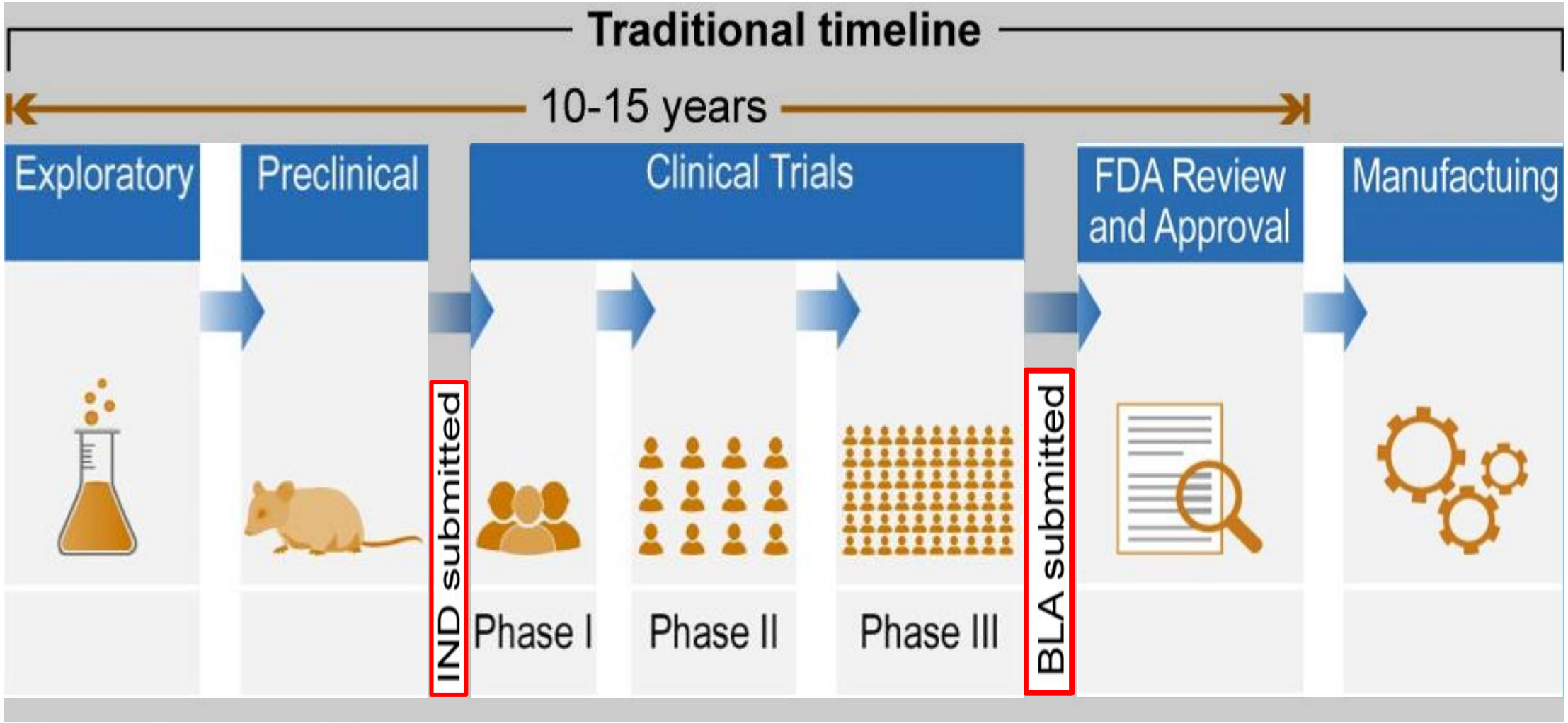
What does “safe” mean?

- It does not mean “zero” risk.

- When making a decision about whether to take a vaccine, one must weigh the risks and benefits of vaccination vs. the disease.

The Journey of a Vaccine:
From Development to Public Availability

Vaccine Development Timeline



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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	4,413
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	Subunit	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

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

- May not detect very rare adverse events
- May not detect delayed adverse events
- Expensive and difficult
- Take a very long time
- Pediatric populations and pregnant women often studied much later

*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

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

Example:

Phase III trial for Pfizer mRNA COVID-19 vaccine - N = 22,000 in vaccine arm

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

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

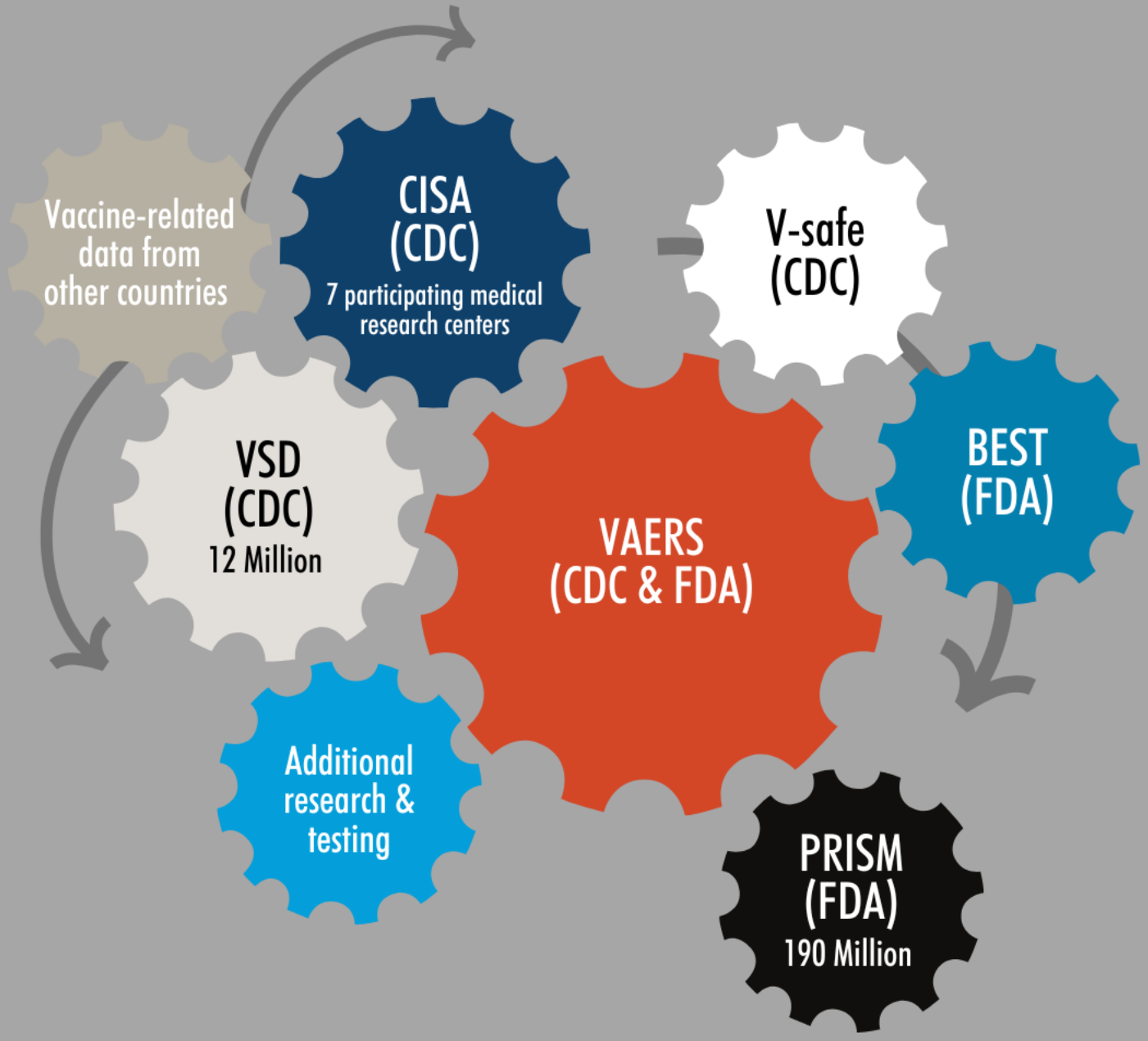
In addition, one must then statistically compare the event rate in the vaccine arm with same event rate in the non-vaccine arm

Adverse Events Associated with Vaccination

Vaccine	Event	Risk
Any	Anaphylaxis	1 : 1,000,000
Influenza (Inactivated)	Guillain Barre Syndrome (GBS)	1 : 1,000,000
MMR	Immune Thrombocytopenia (ITP)	1 : 40,000
MMR MMRV	Febrile Seizures 12-47 months old	1 : 2,500 1 : 1,250
RRV-TV (Rotashield)	Intussusception	1 : 11,000
RV1 (Rotarix) and RV5 (Rotateq)	Intussusception	1:20,000-1:100,000

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.

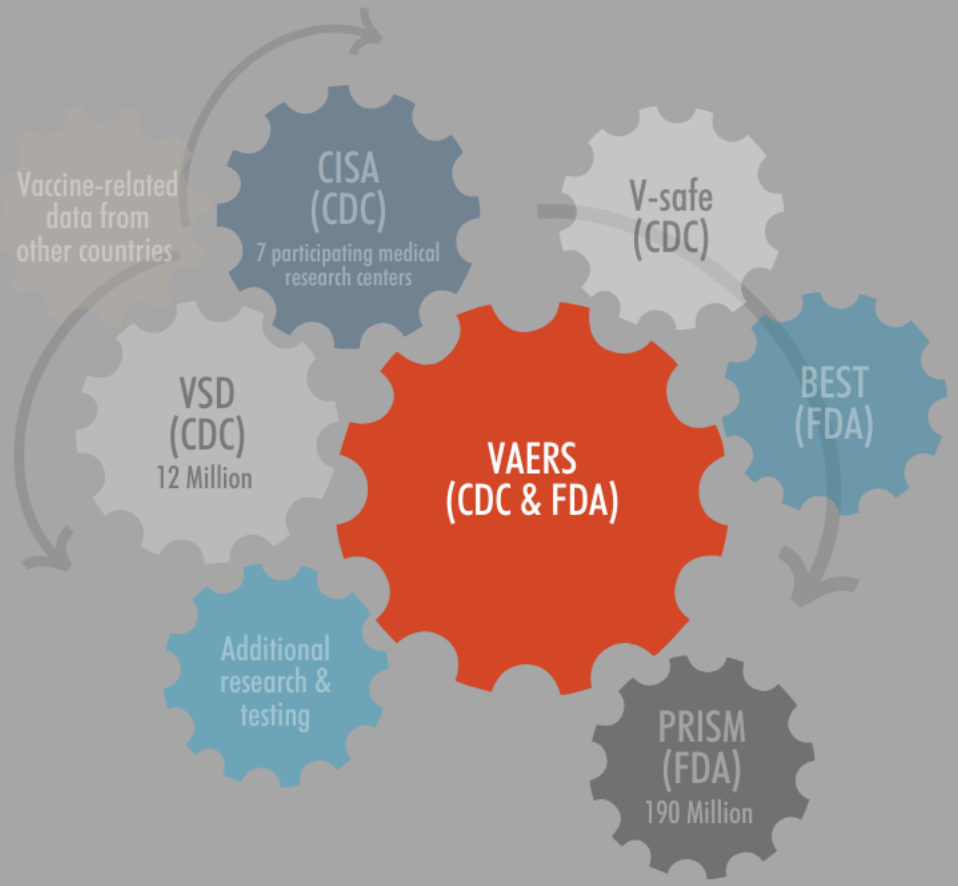


Passive Surveillance

- 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

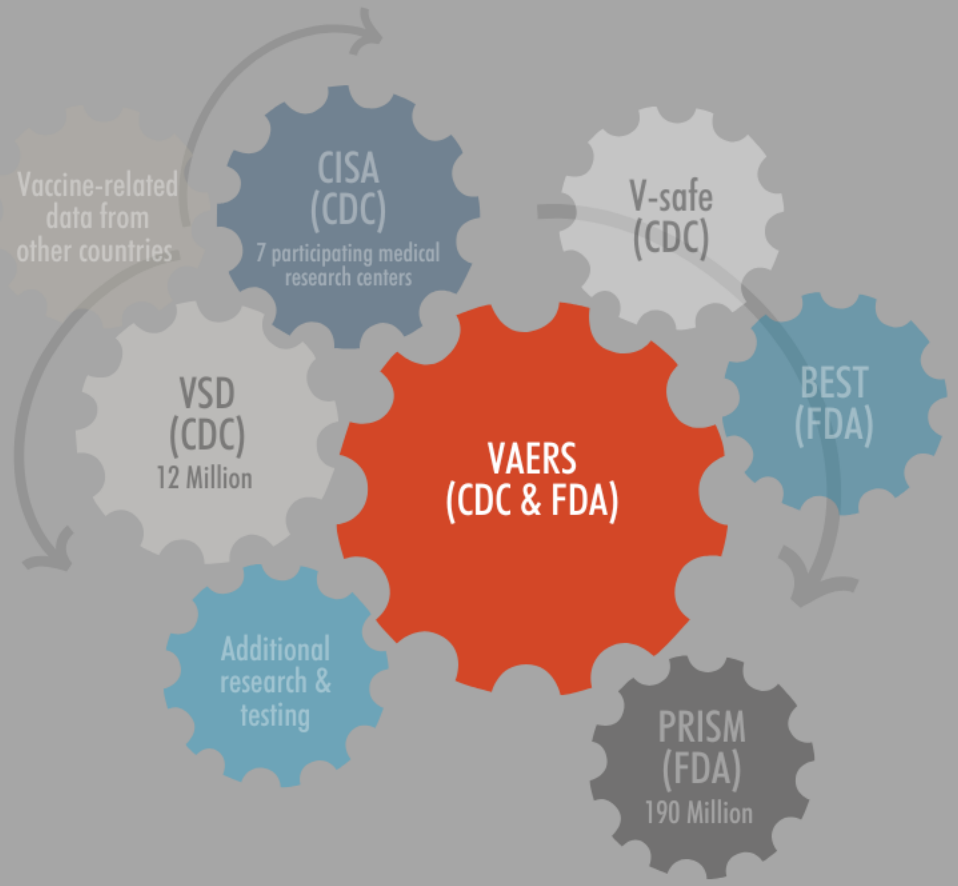
Active Surveillance

- 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



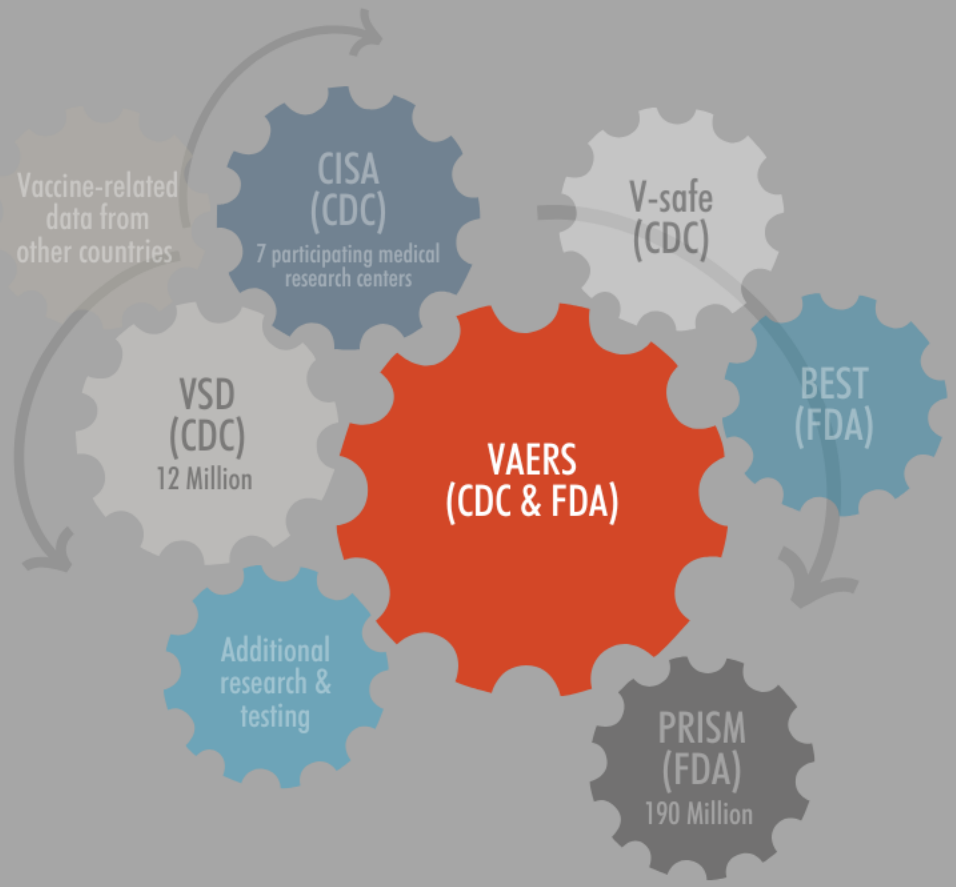
Vaccine Adverse Event Reporting System (VAERS)

VAERS: What is it?



- 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
  - Have unusual patterns

VAERS: Strengths & Limitations



STRENGTHS

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

LIMITATIONS

- Cannot determine if a vaccine caused the reported adverse event
- There is no control group to compare rates of adverse events in those who did and did not receive a vaccine (VAERS cannot determine if an adverse event is occurring more often following vaccination than what would be expected in the general population)
- Reports may lack details or contain errors

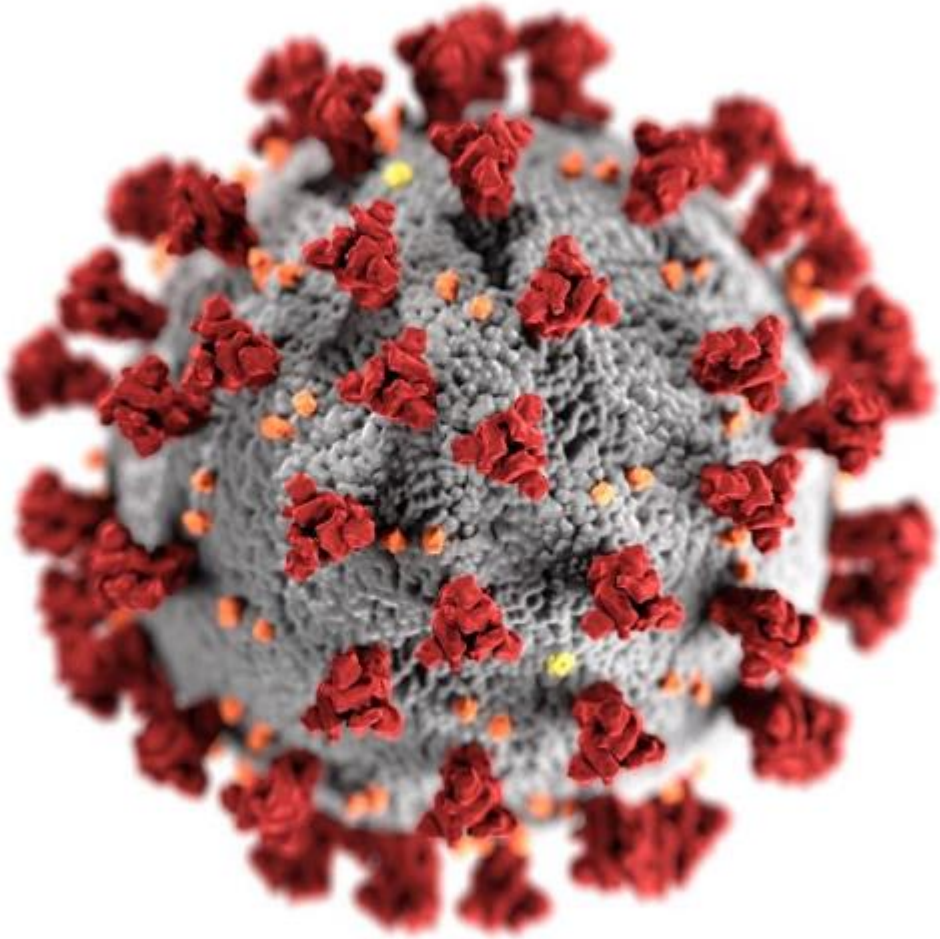
EXAMPLE of using VAERS data:

COVID-19 vaccine safety update: Primary series in young children and booster doses in older children and adults

Advisory Committee on Immunization Practices (ACIP)

September 1, 2022

Tom Shimabukuro, MD, MPH, MBA
CDC COVID-19 Immunization Safety Unit



cdc.gov/coronavirus

U.S. reports to VAERS among children after primary series Pfizer-BioNTech (ages 6 months–4 years) or Moderna (ages 6 months–5 years) vaccination* (as of August 21, 2022)

Manufacturer	Doses admin†	Total reports	Median age	Male‡ n (%)	Female‡ n (%)	Non-serious n (%)	Serious§ n (%)	Myocarditis reports (n)
Pfizer-BioNTech	890,378	496	3 years	249 (50)	245 (49)	486 (98)	10 (2)	0
Moderna	664,484	521	2 years	272 (52)	240 (46)	512 (98)	9 (2)	0
Total	**1,554,862**	**1,017**	**3 years**	**521 (51)**	**485 (48)**	**998 (98)**	**19 (2)**	**0**

CDC + FDA VAERS

* Among children ages 6 months–4 years after Pfizer-BioNTech, and among children ages 6 months–5 years after Moderna, vaccinated during June 18–August 21, 2022; reports received and processed as of August 23, 2022

† Dose 1 and dose 2 administered among children described in previous footnote during June 16–August 18, 2022.

‡ 2 reports after Pfizer-BioNTech and 9 reports after Moderna did not have sex reported

§ Based on the Code of Federal Regulations if one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization, permanent disability, congenital anomaly or birth defect

UNITED STATES

How a CDC Database Is Fueling Global Anti-Vaccination Sentiment

By Corbin Duncan April 6, 2021

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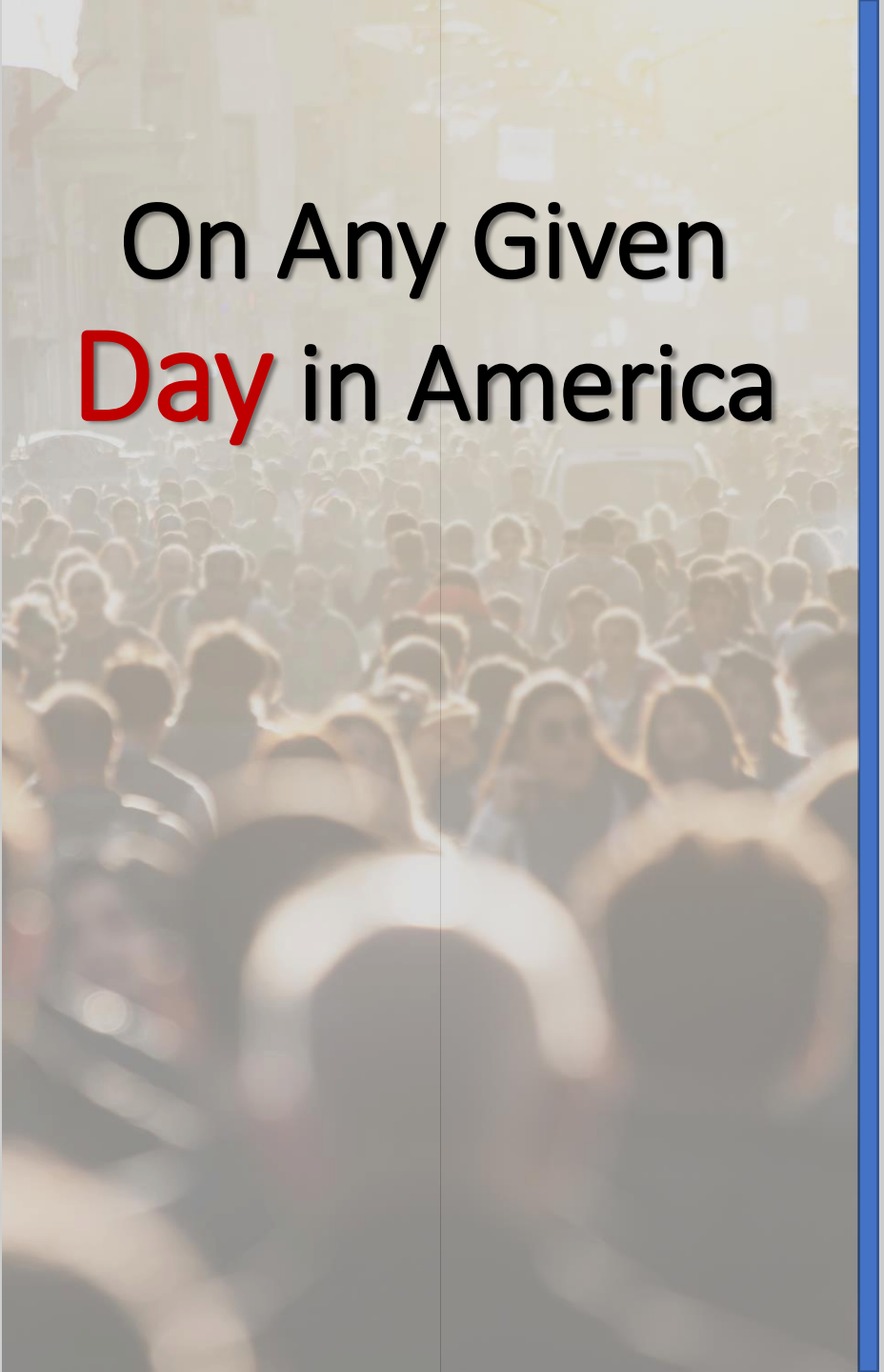
HARVARD POLITICAL REVIEW

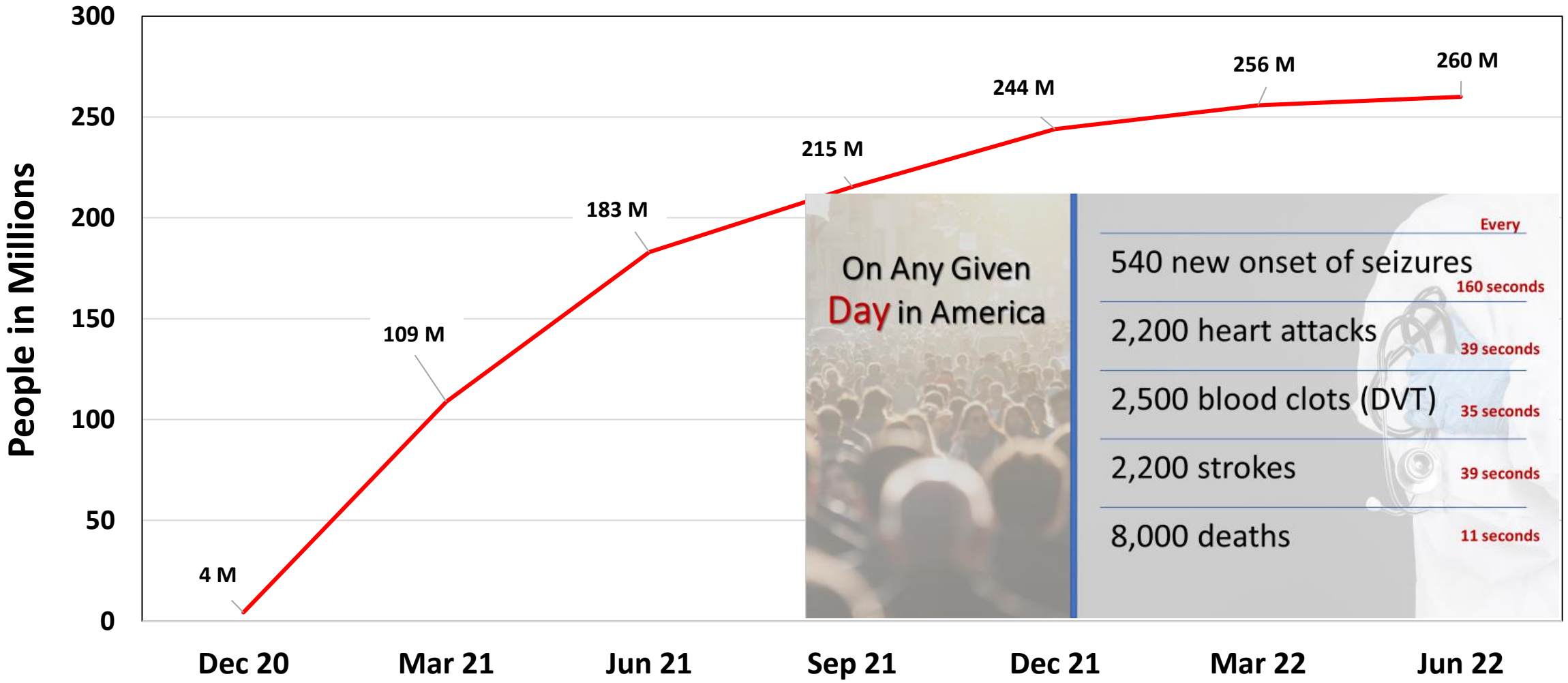
Tuesday, June 15, 2021



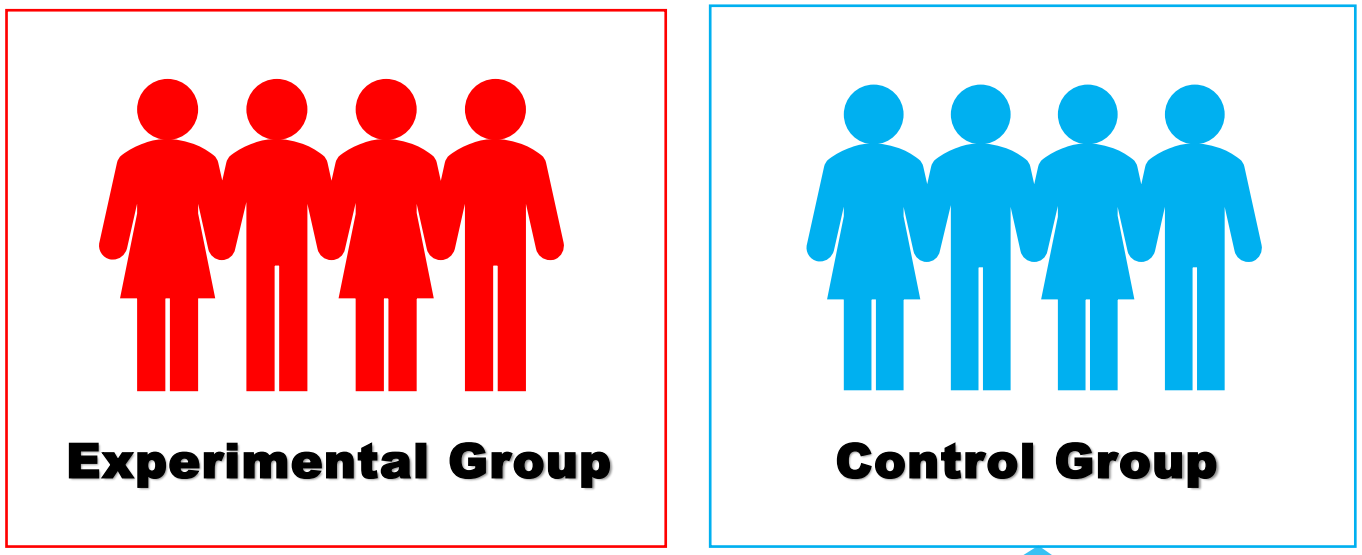
On Any Given Day in America

	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

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

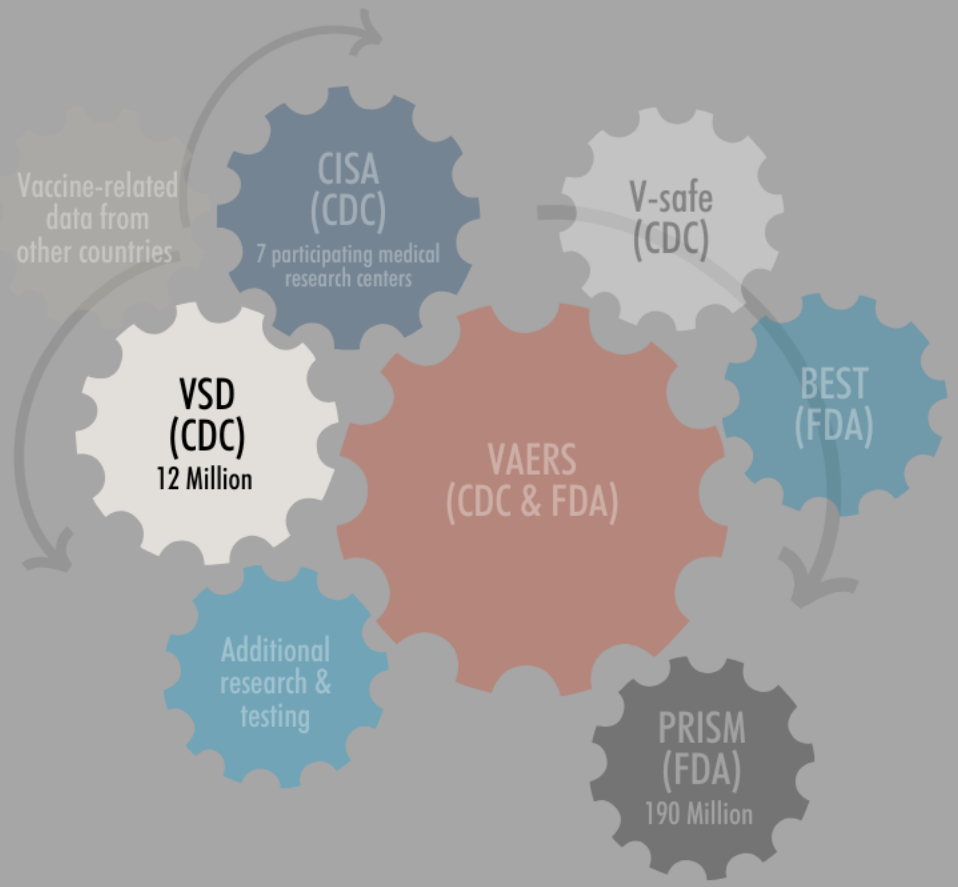


THE IMPORTANCE OF A CONTROL GROUP



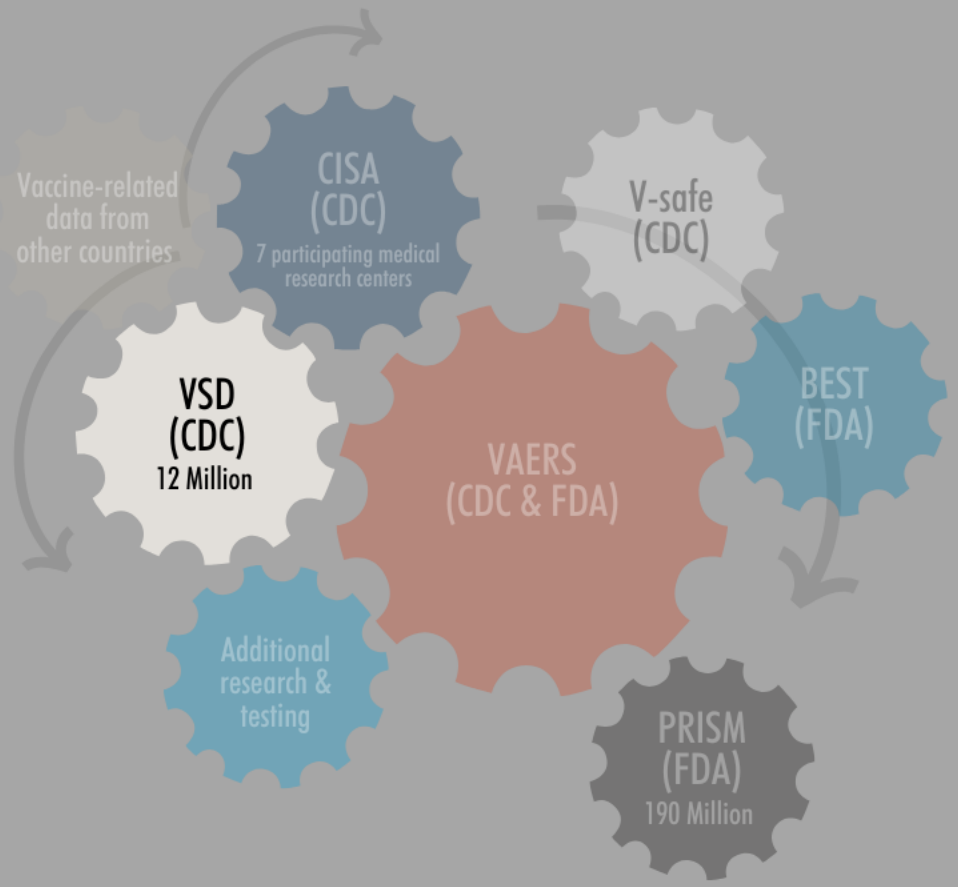
A control group is a group in an experiment that doesn't include the variable being tested. It is used as a benchmark against which other test results are measured.

Without a unvaccinated control group, you cannot determine if an adverse event is occurring more often following vaccination than what would be expected in the general population. You are unable to establish if an association exists.



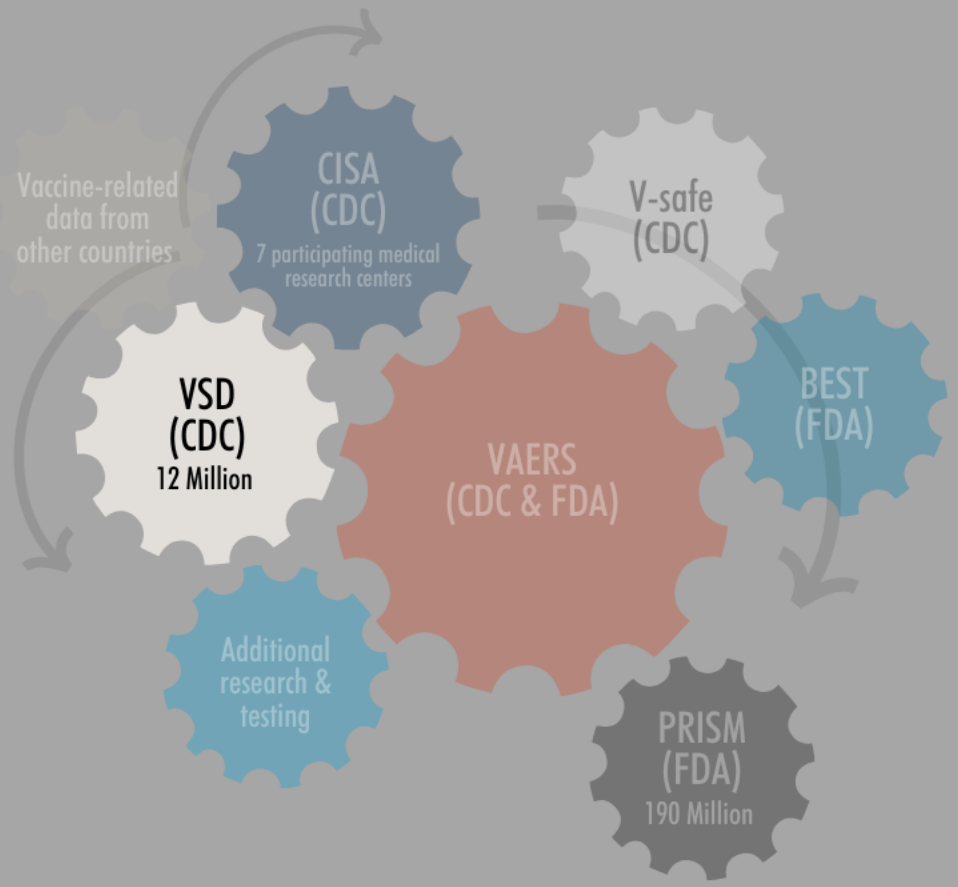
Vaccine Safety Datalink (VSD)

VSD: What is it?



- A network of 13 managed care sites across the U.S. with a combined patient population of more than 12 million people
- Used to determine if possible side effects identified using VAERS may be associated with vaccination
- Can identify safety signals using nearly real-time monitoring
- Evaluates particular health-related outcomes that may be associated with vaccination and compares it to the expected number of outcomes in a comparison group

VSD: Strengths & Limitations



STRENGTHS

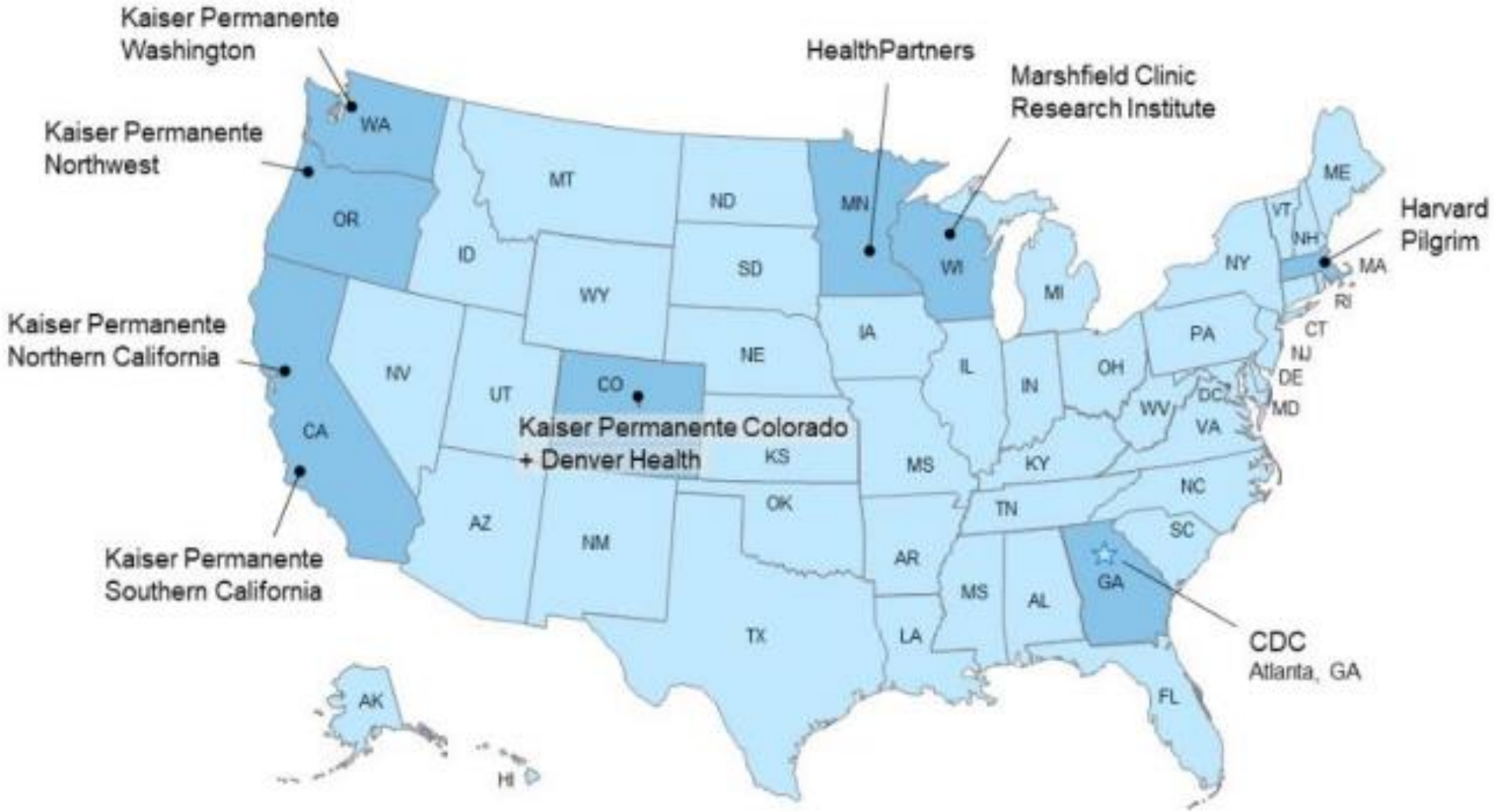
- Conduct timely vaccine safety studies
- Use of a control group – allowing for the comparison of adverse events in those who did and did not receive a vaccine

LIMITATIONS

- May not have enough patients to detect extremely rare adverse events
- May not capture vaccine administration data outside of the health system
- Cannot determine if an association between an adverse event and vaccination is causal

VSD

Vaccine Safety Datalink



9 participating integrated healthcare organizations

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

EXAMPLE of using VSD data:

COVID-19 vaccine safety update: Primary series in young children and booster doses in older children and adults

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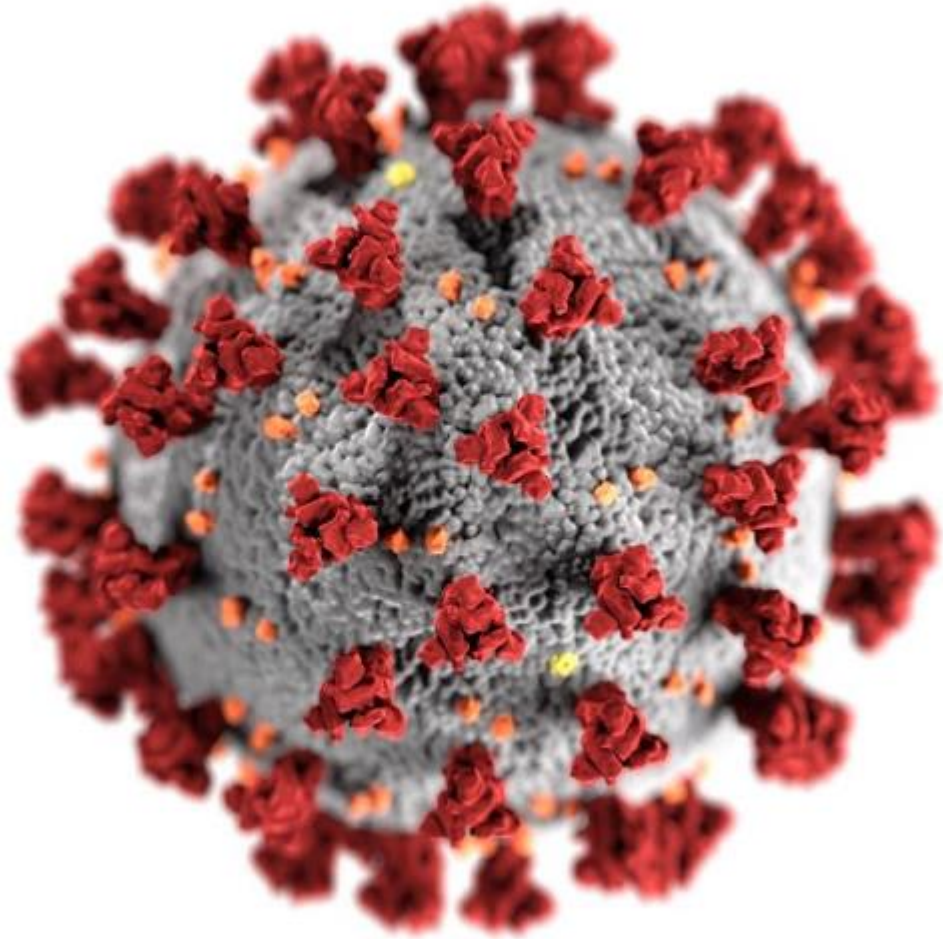

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VSD COVID-19 vaccine RCA prespecified surveillance outcomes

EHR = Electronic health record

Prespecified outcomes	Settings
Acute disseminated encephalomyelitis	Emergency dept, Inpatient
Acute myocardial infarction – **First ever in EHR in ICD-10 era**	Emergency dept, Inpatient
Acute respiratory distress syndrome	Emergency dept, Inpatient
Anaphylaxis – **First in 7 days in EHR in ICD-10 era**	Emergency dept, Inpatient
Appendicitis	Emergency dept, Inpatient
Bell's palsy – **First ever in EHR in ICD-10 era**	Emergency dept, Inpatient, Outpatient
Cerebral venous sinus thrombosis	Emergency dept, Inpatient
Disseminated intravascular coagulation	Emergency dept, Inpatient
Encephalitis / myelitis / encephalomyelitis	Emergency dept, Inpatient
Guillain-Barré syndrome	Emergency dept, Inpatient
Immune thrombocytopenia	Emergency dept, Inpatient, Outpatient
Kawasaki disease	Emergency dept, Inpatient
Multisystem inflammatory syndrome in children/adults (MIS-C/MIS-A)	Emergency dept, Inpatient
Myocarditis / pericarditis – **First in 60 days in EHR in ICD-10 era**	Emergency dept, Inpatient
Narcolepsy / cataplexy	Emergency dept, Inpatient, Outpatient
Pulmonary embolism – **First ever in EHR in ICD-10 era**	Emergency dept, Inpatient
Seizures (including 0-7 days for youngest ages)	Emergency dept, Inpatient
Stroke, hemorrhagic	Emergency dept, Inpatient
Stroke, ischemic	Emergency dept, Inpatient
Thrombosis with thrombocytopenia syndrome – **First ever in EHR in ICD-10 era**	Emergency dept, Inpatient
Thrombotic thrombocytopenic purpura	Emergency dept, Inpatient
Transverse myelitis	Emergency dept, Inpatient
Venous thromboembolism – **First ever in EHR in ICD-10 era**	Emergency dept, Inpatient, Outpatient

VSD
vaccine safety datalink

VSD RCA results in children ages 6 months–4 years (Pfizer-BioNTech) and 6 months–5 years (Moderna) for primary series mRNA COVID-19 vaccination

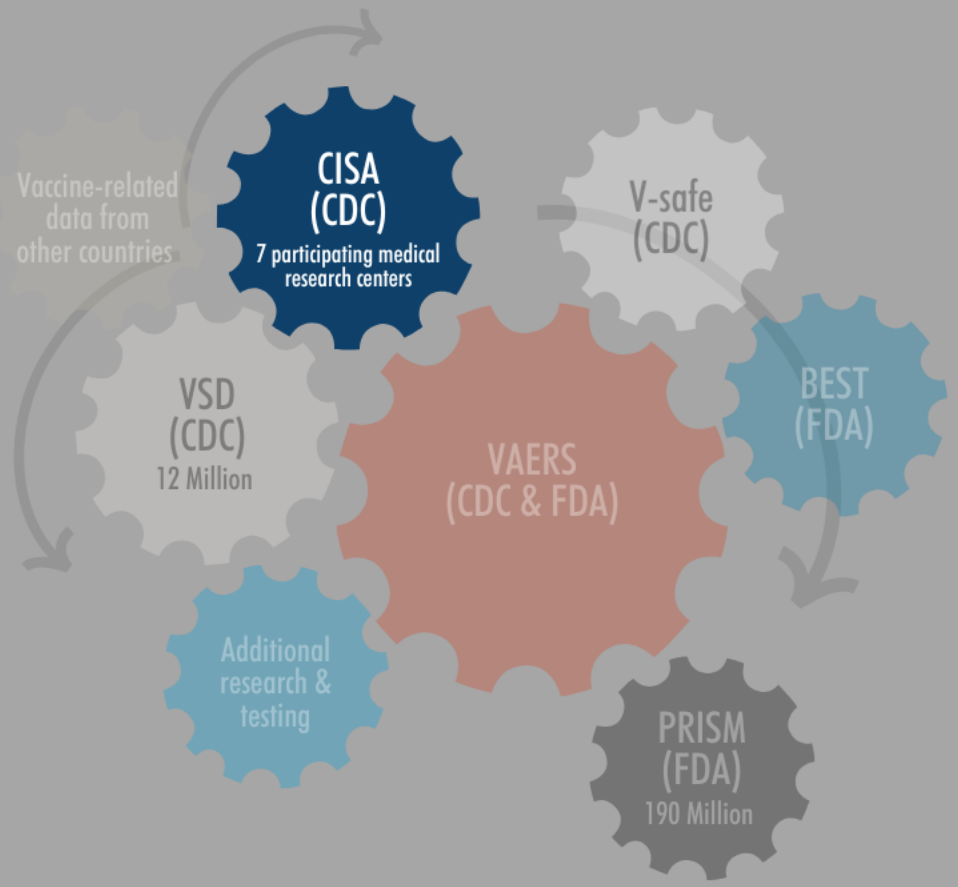
- Doses administered:

Doses	Pfizer-BioNTech	Moderna	Total
Dose 1	31,784	34,466	66,250
Dose 2	18,729	17,940	36,669
Total	**50,513**	**52,406**	**102,919**

- No statistical signals to date* for any pre-specified surveillance outcomes for either mRNA COVID-19 vaccine

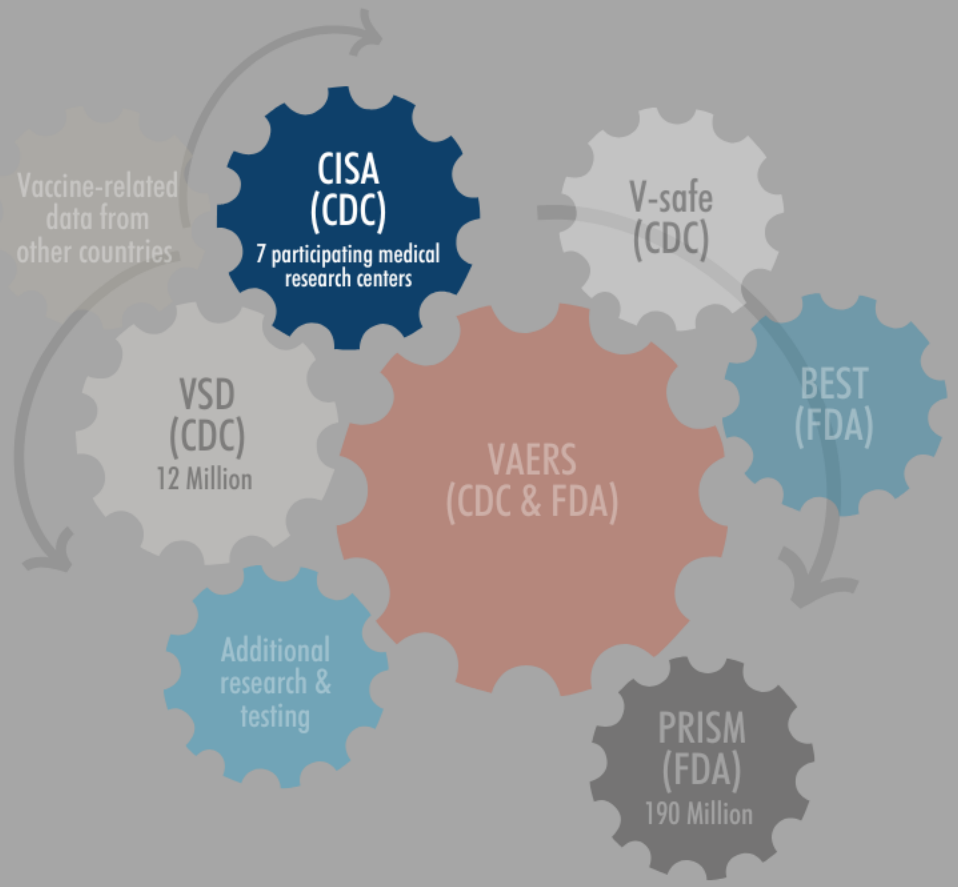
VSD vaccine safety datalink

* Data through Aug 13, 2022



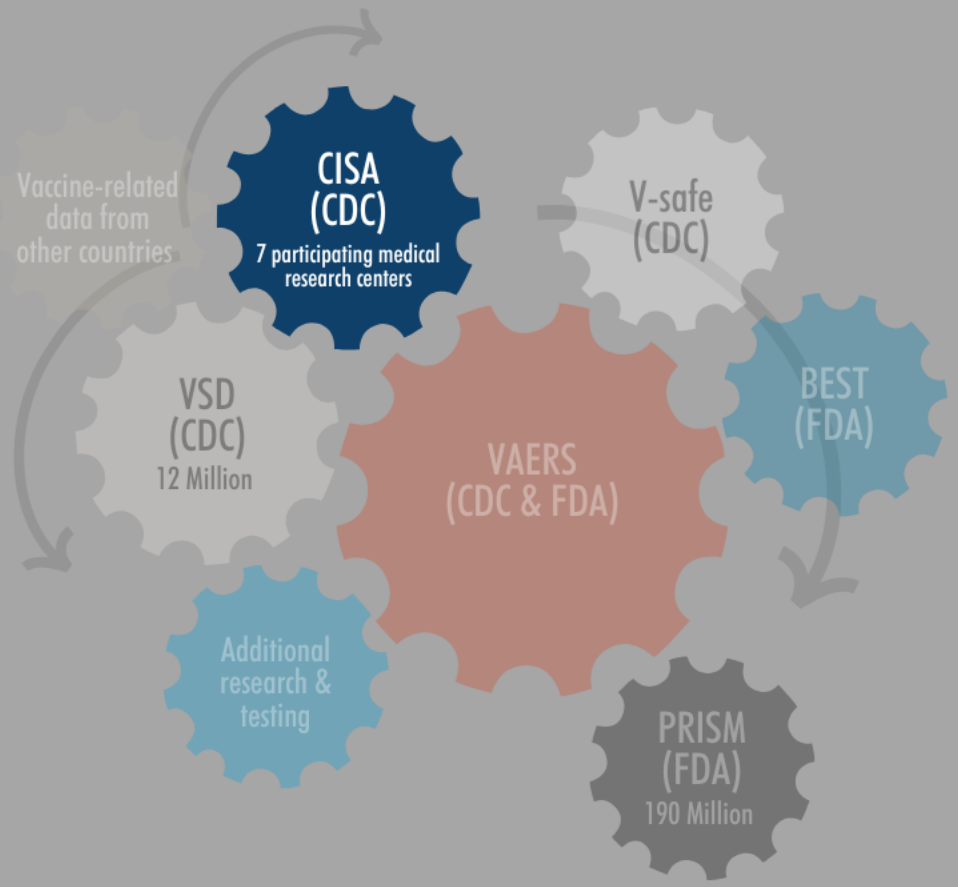
Clinical Immunization Safety Assessment Project (CISA)

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

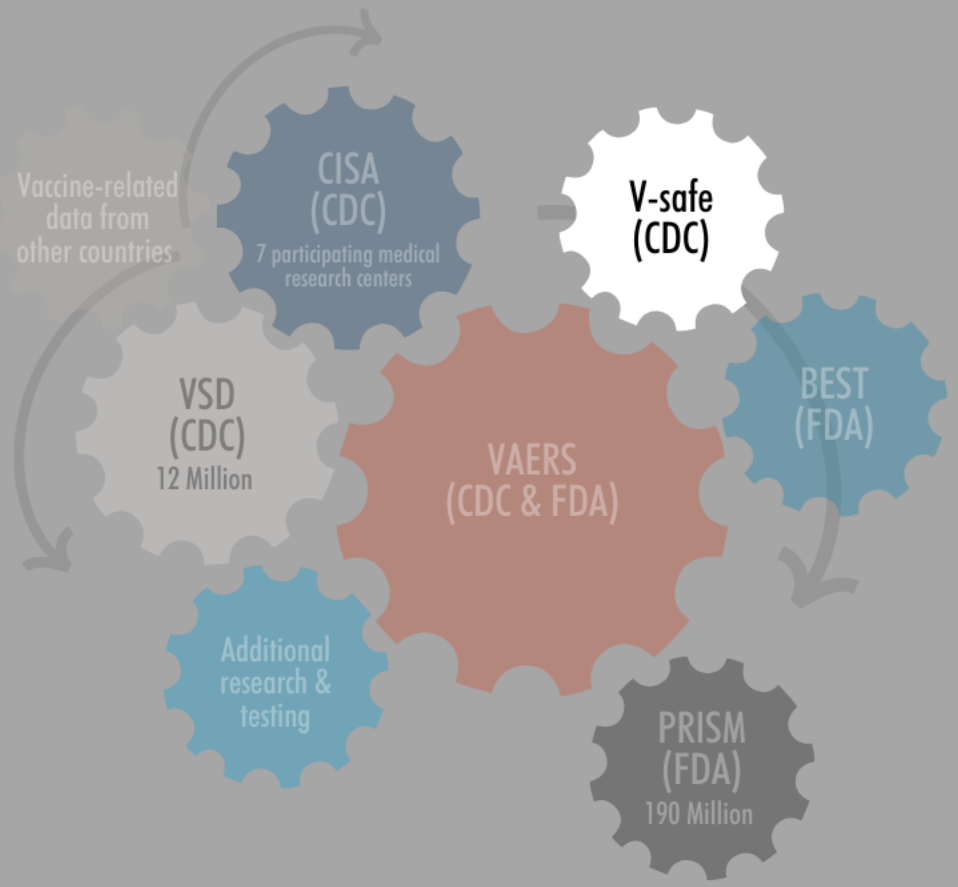


STRENGTHS

- 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

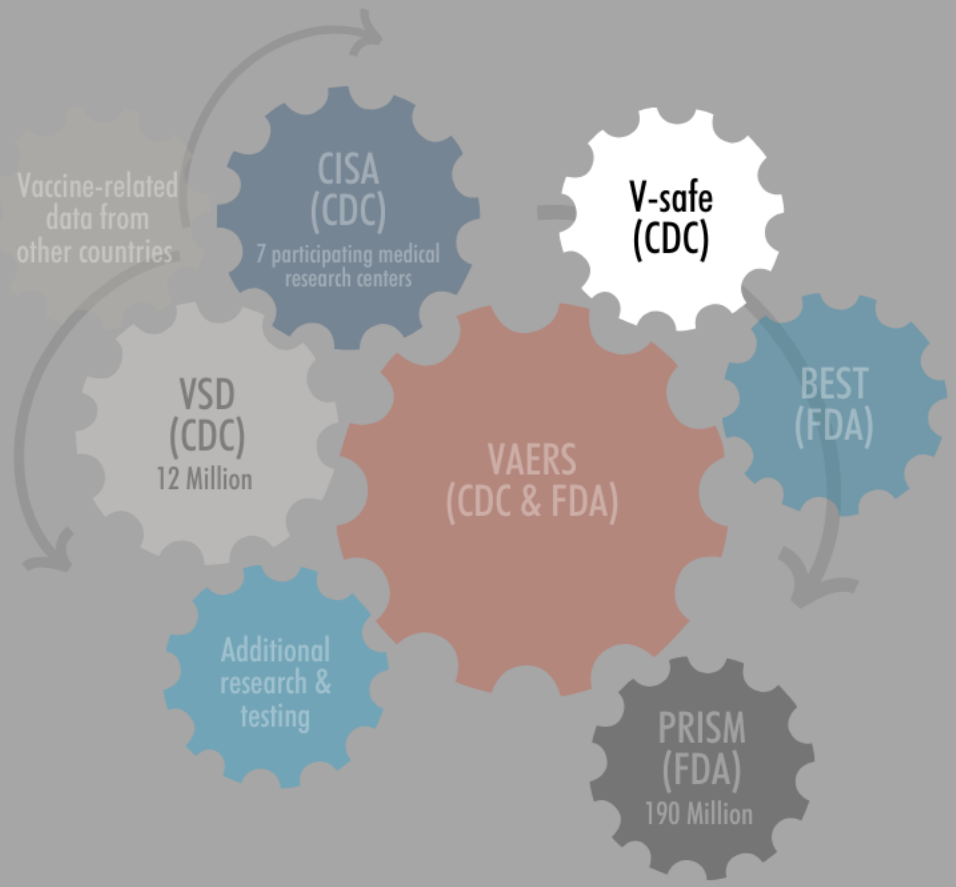
LIMITATIONS

- 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-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

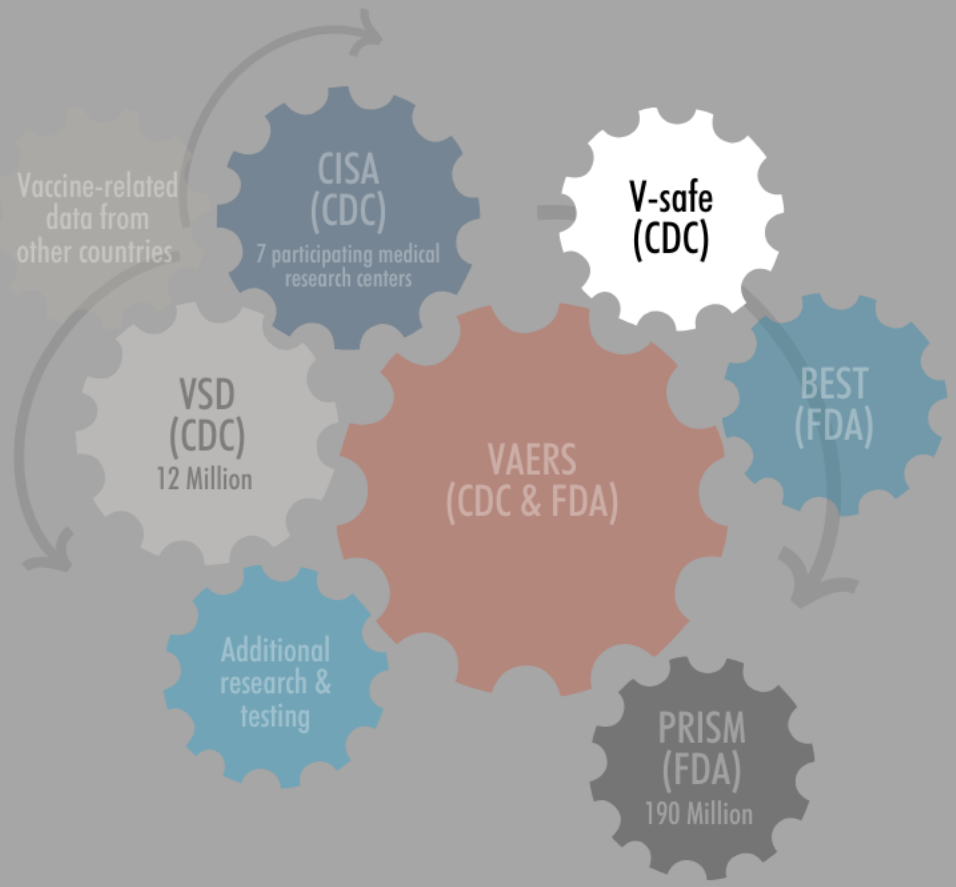
V-safe

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

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

EXAMPLE of using V-safe data:

COVID-19 vaccine safety update: Primary series in young children and booster doses in older children and adults

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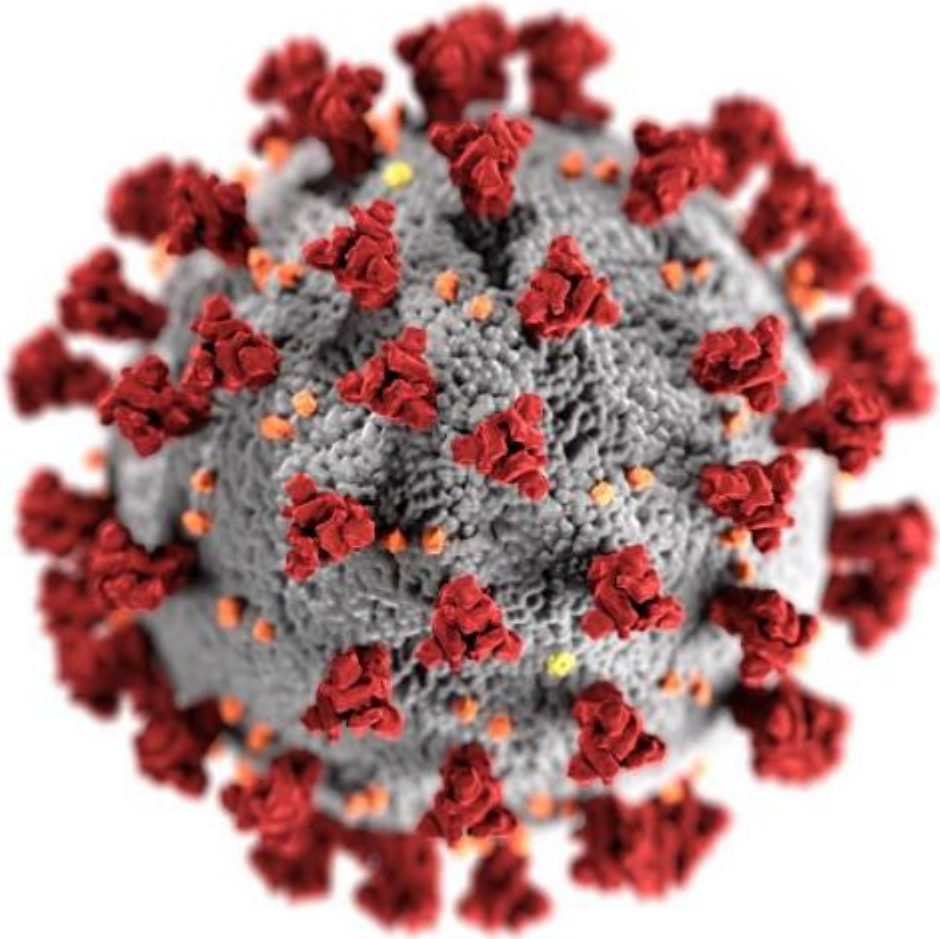

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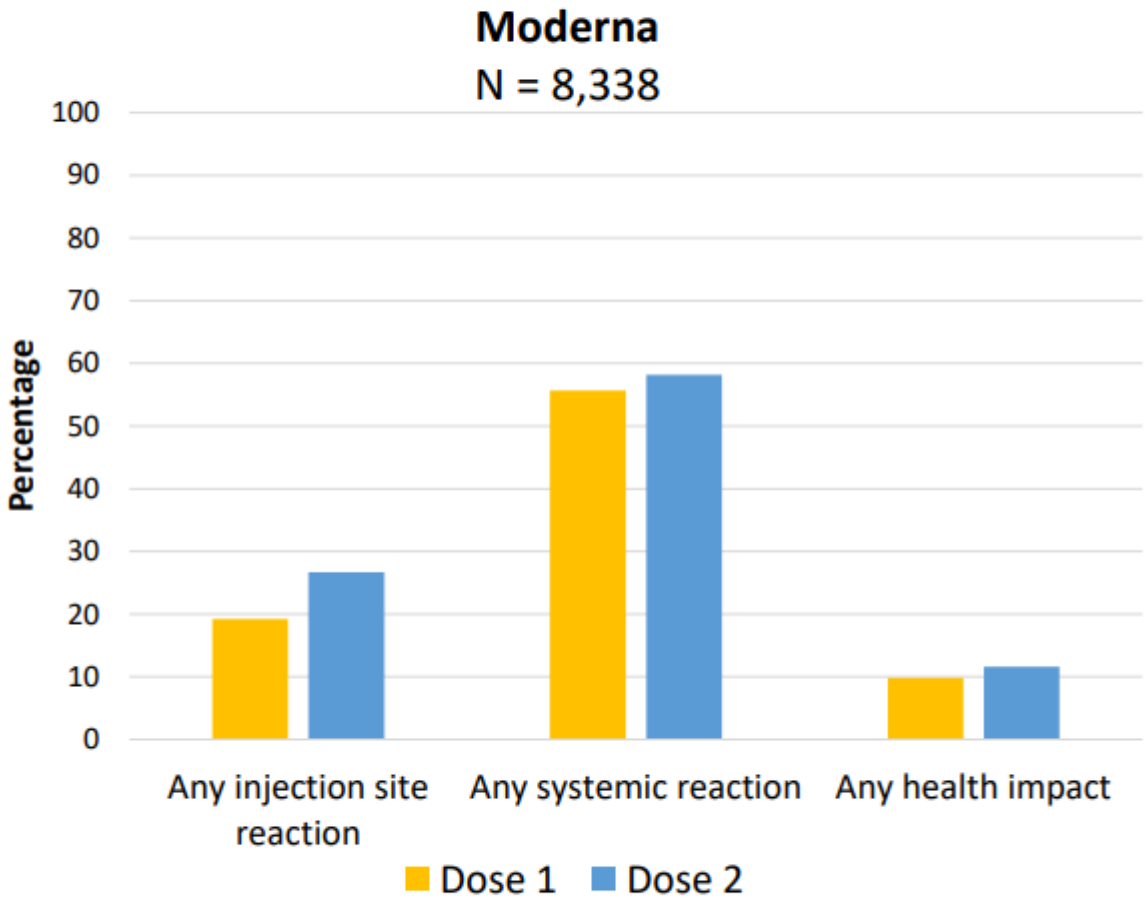
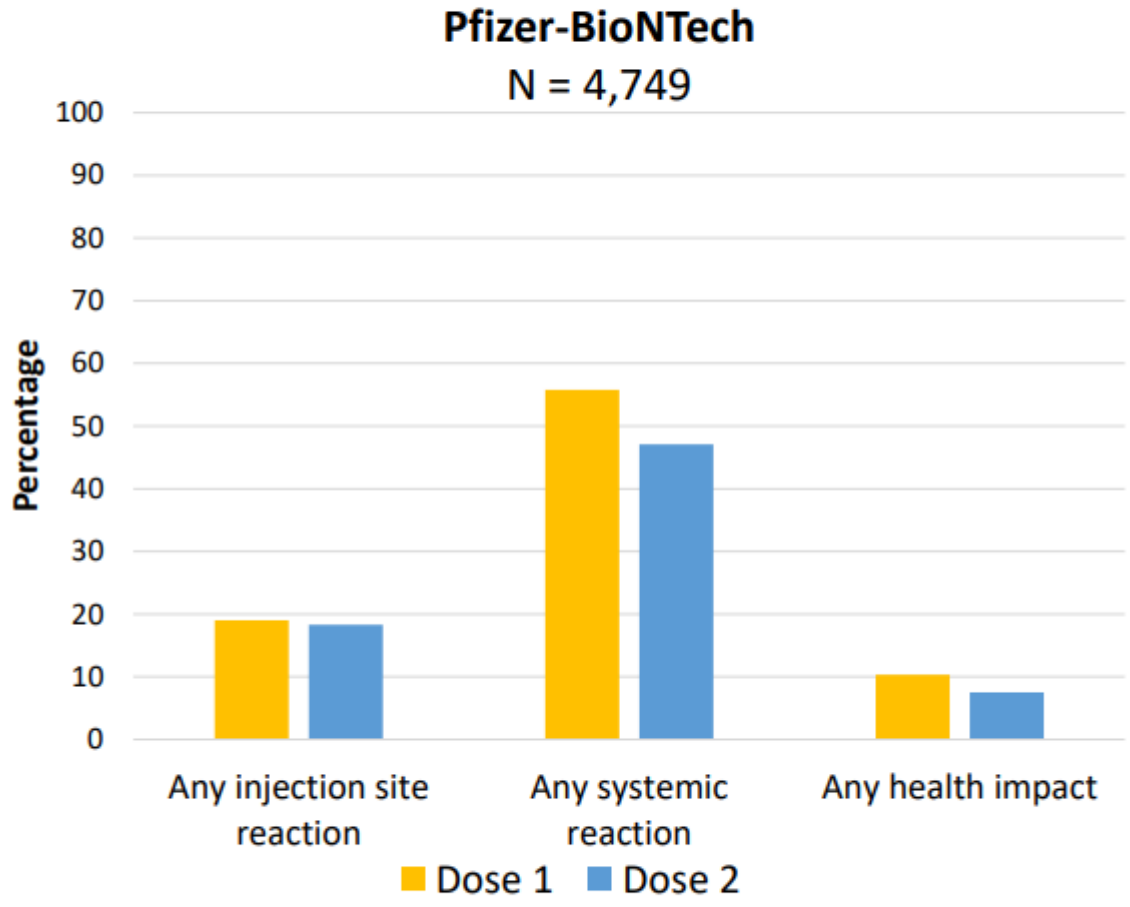
Reactions and health impacts reported for children aged 6 months–≤2 years at least once in days 0–7 following COVID-19 vaccination, by dose

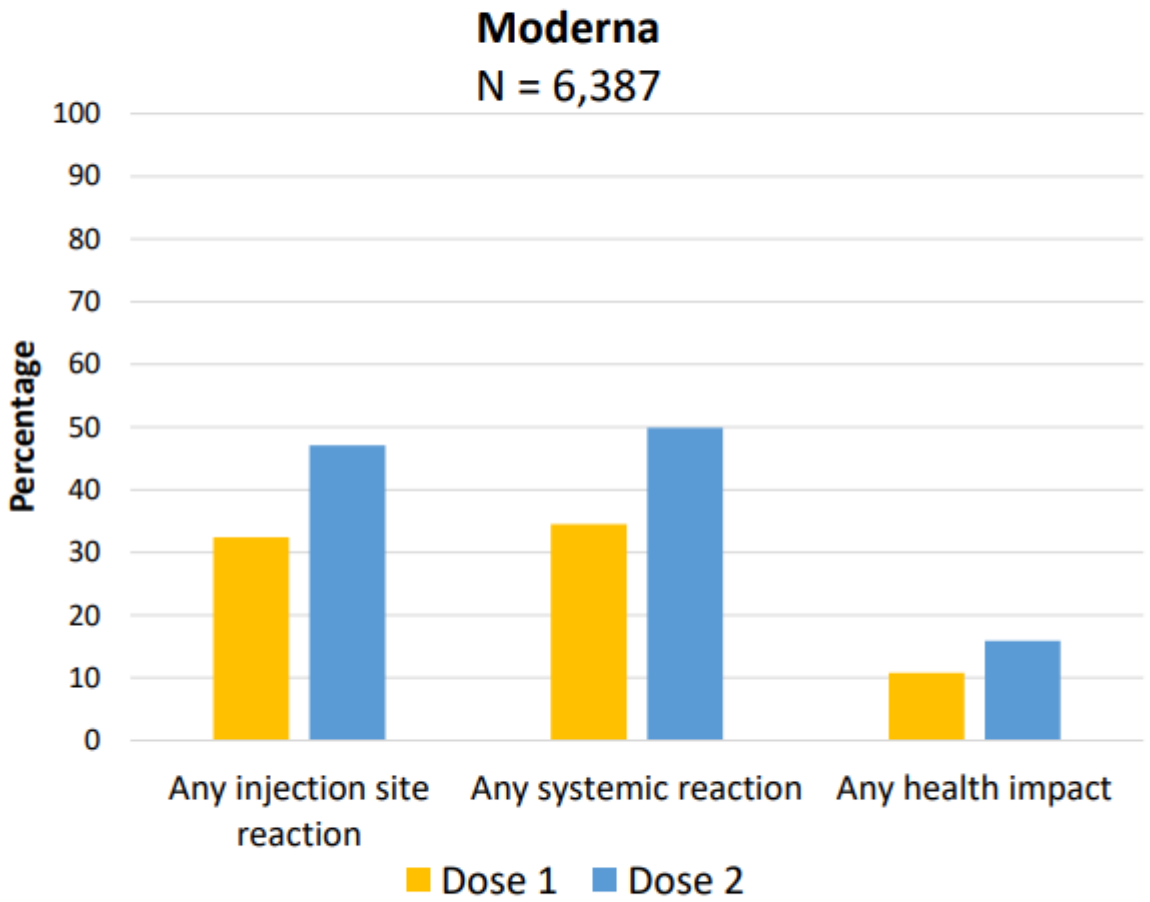


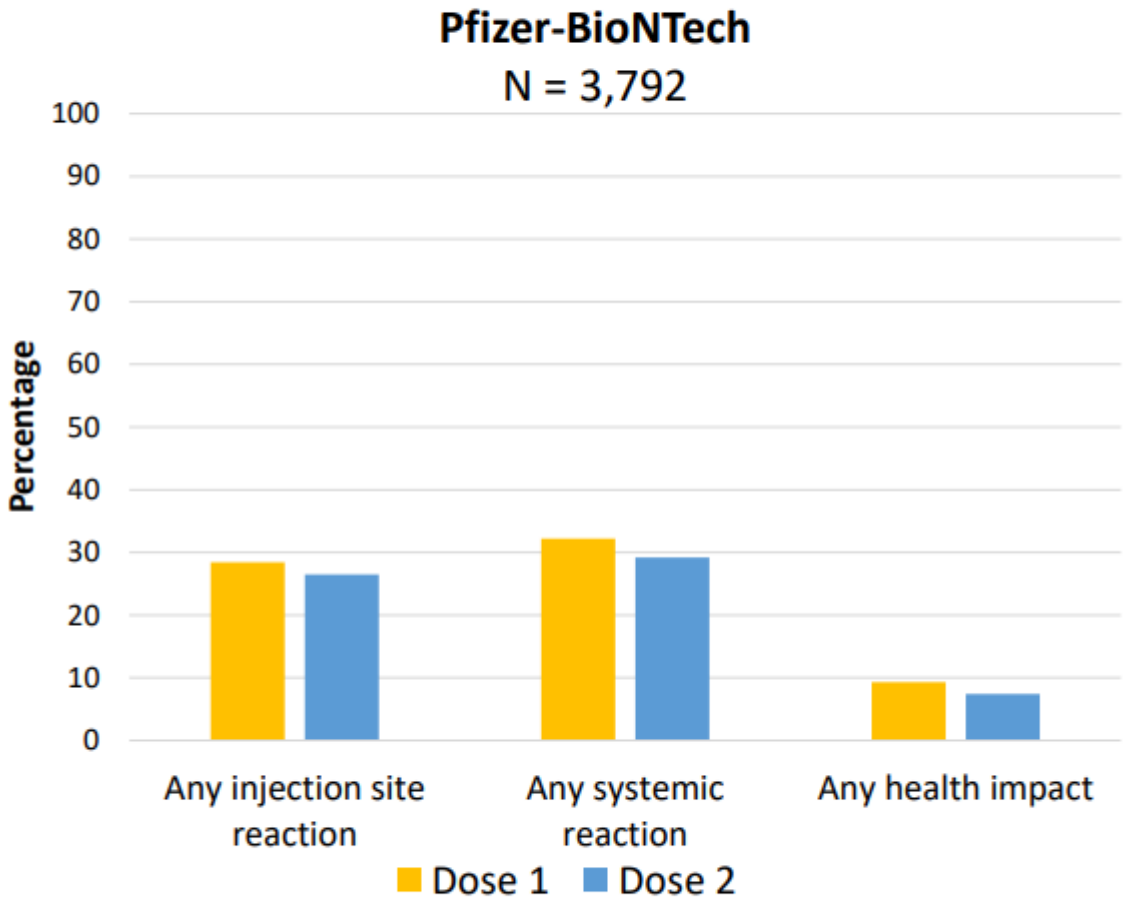


v-safe after vaccination health checker

Data as of August 21, 2022. Includes 4,749 children (aged 6 months–2 years) who received Pfizer-BioNTech and 8,338 who received Moderna.

Reactions and health impacts reported for children aged 3–5 years at least once in days 0–7 following COVID-19 vaccination, by dose



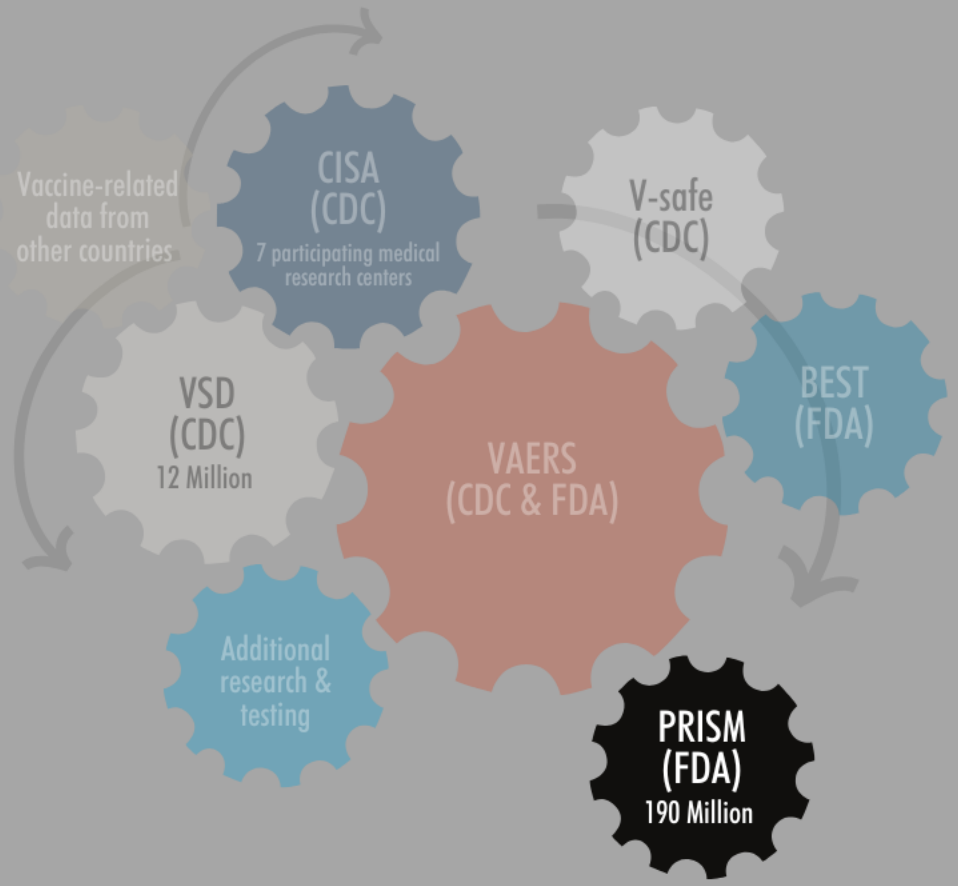


v-safe after vaccination health checker

Data as of August 21, 2022. Includes 3,792 children (aged 3–4 years) who received Pfizer-BioNTech and 6,387 who received Moderna (aged 3–5 years) .

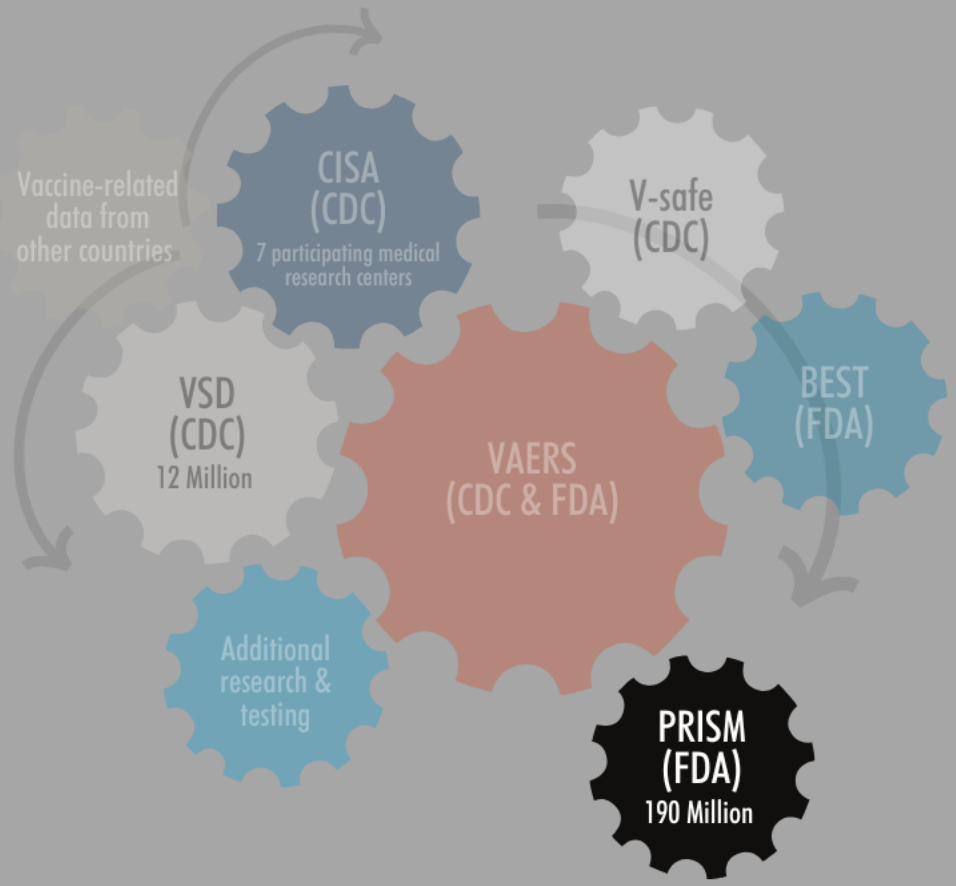
Summary: mRNA COVID-19 vaccine safety of primary series vaccination in children ages 6 months–5 years

- Initial safety findings of both mRNA COVID-19 vaccines (Pfizer-BioNTech and Moderna) are consistent with those observed in the clinical trials
- Systemic and local reactions are commonly reported adverse events
- Vaccination errors are also being reported to VAERS
- No unexpected safety findings to date
- No evidence of an increased risk for myocarditis following mRNA COVID-19 vaccination in children ages 6 months–5 years



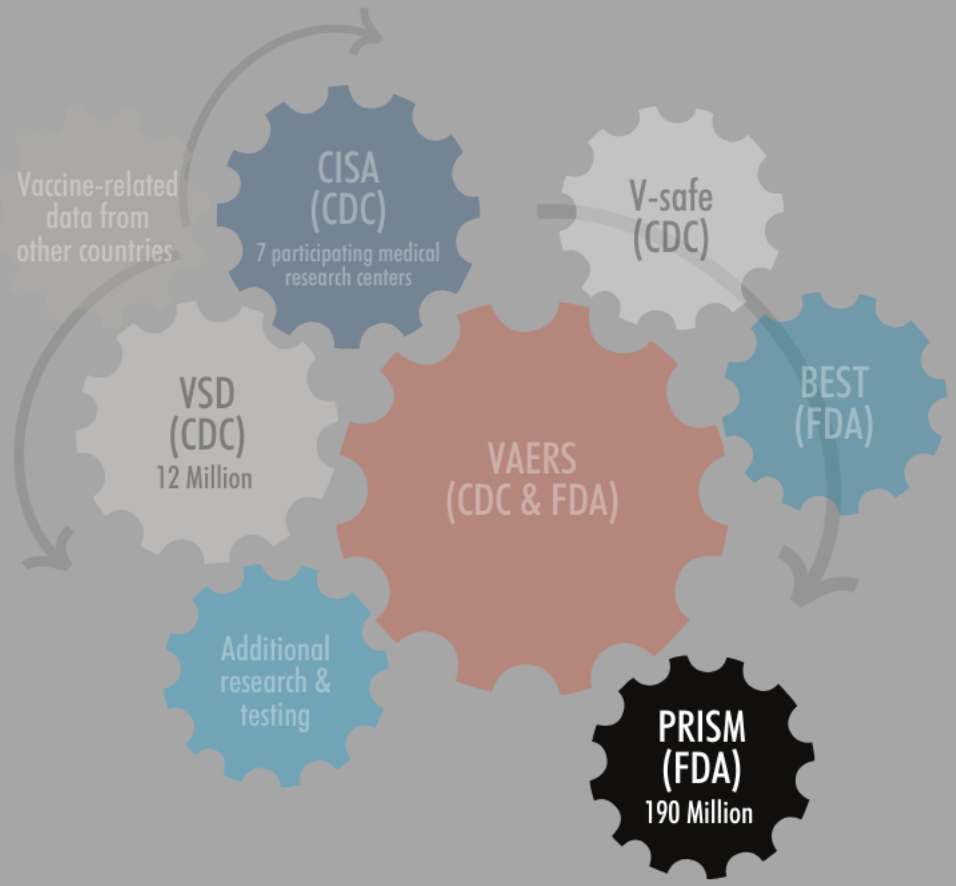
Post-licensure Rapid Immunization Safety Monitoring System (PRISM)

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

PRISM: Strengths & Limitations

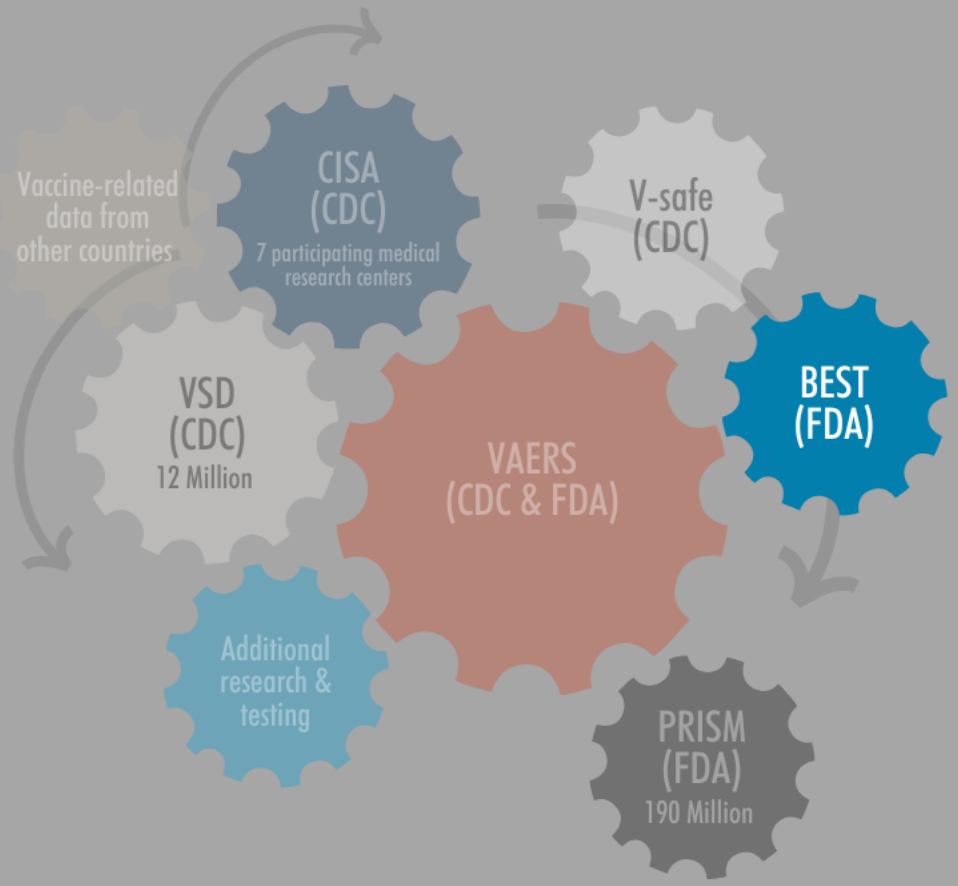


STRENGTHS

- Covers 190 million people
- PRISM uses a database of health insurance claims to identify and evaluate possible safety issues for licensed vaccine
- Linked to some state-wide registries and birth registries - allowing for more complete vaccine exposure data
- Access to denominator data for vaccine exposure, which allows the FDA to estimate a measure of association between a vaccine and adverse events

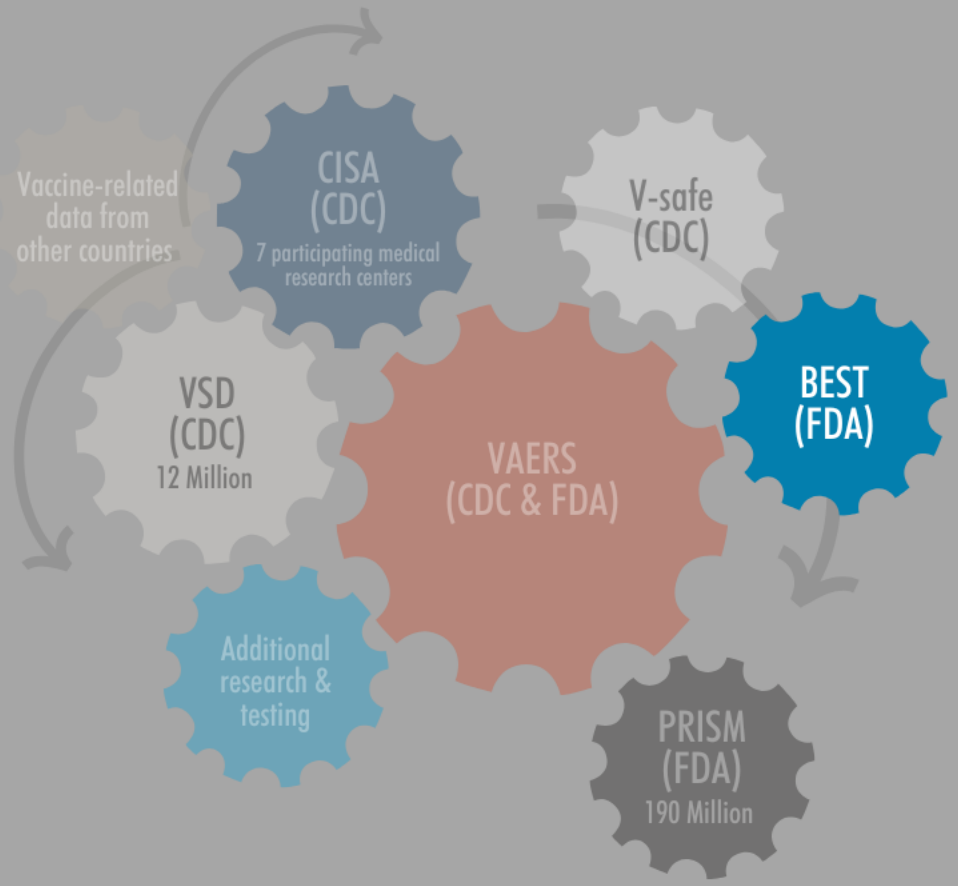
LIMITATIONS

- 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



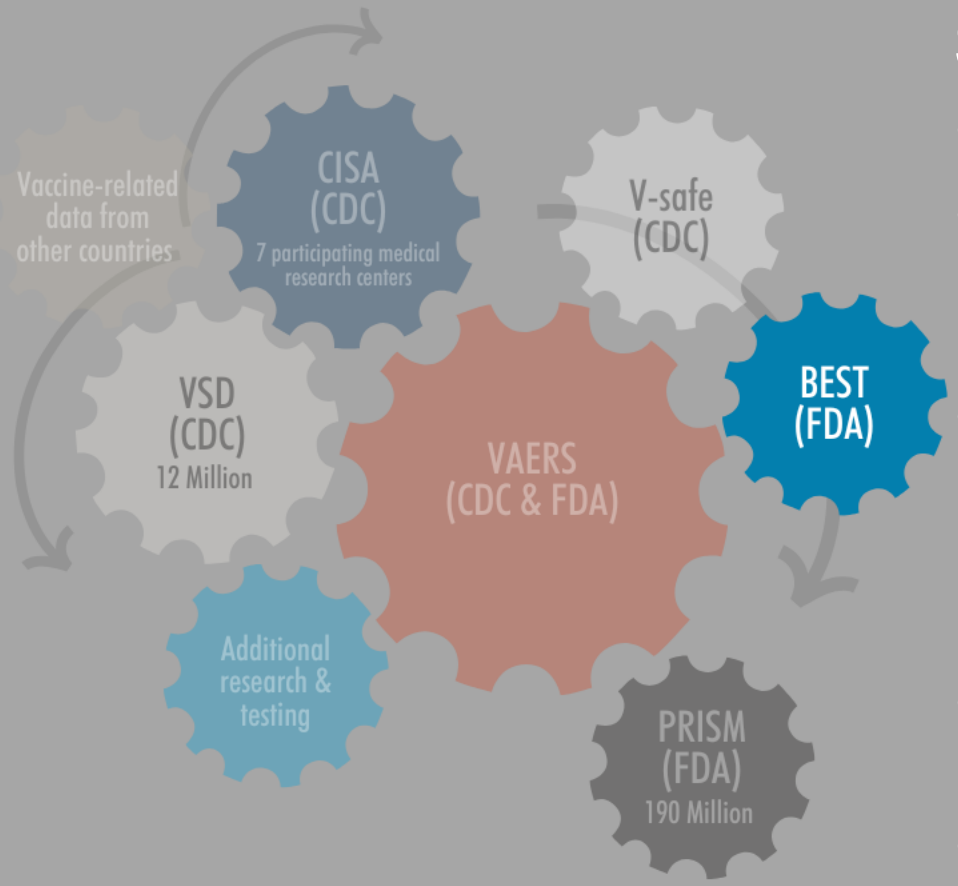
The Biologics Effectiveness and Safety (BEST) Initiative

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

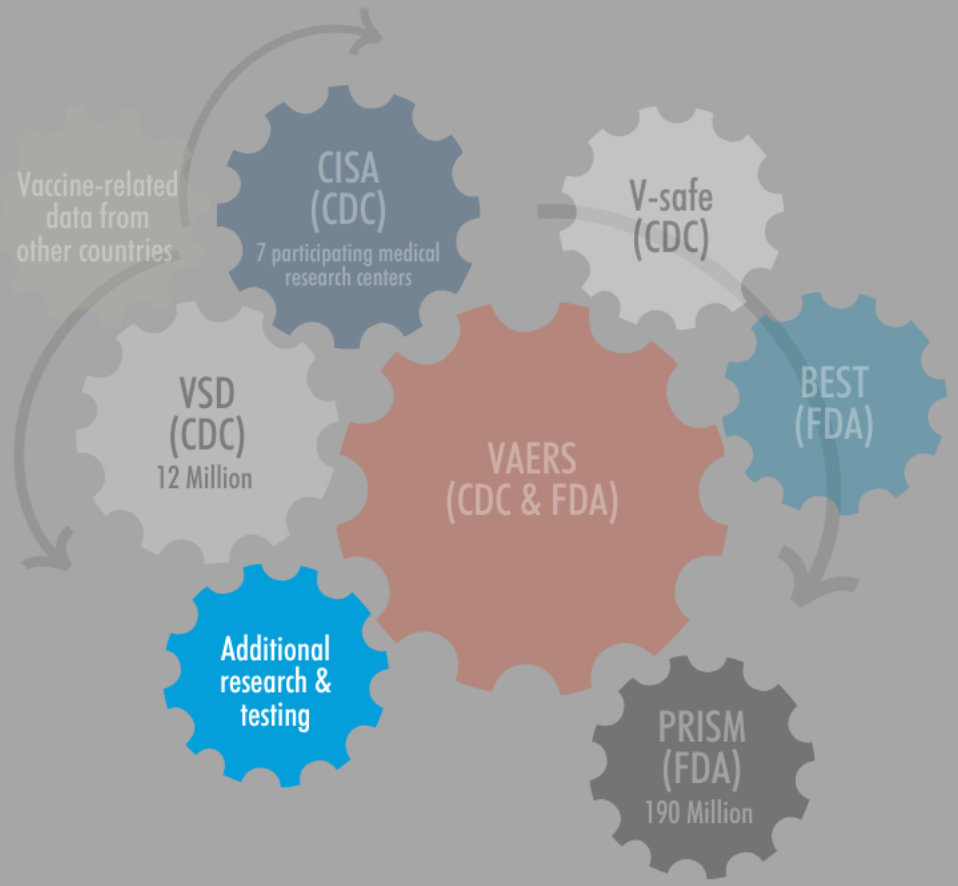
- Near real-time analysis with available data
- Use of a control group, allowing for the comparison of adverse events in those who did and did not receive a vaccine (can compare vaccinated to unvaccinated)
- Ability to assess safety of vaccine in sub-populations (ex. those with pre-existing conditions,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

LIMITATIONS

- May not be representative of those without insurance coverage
- Potential lag time in accessing some data
- Cannot determine if an association between an adverse event and vaccination is causal

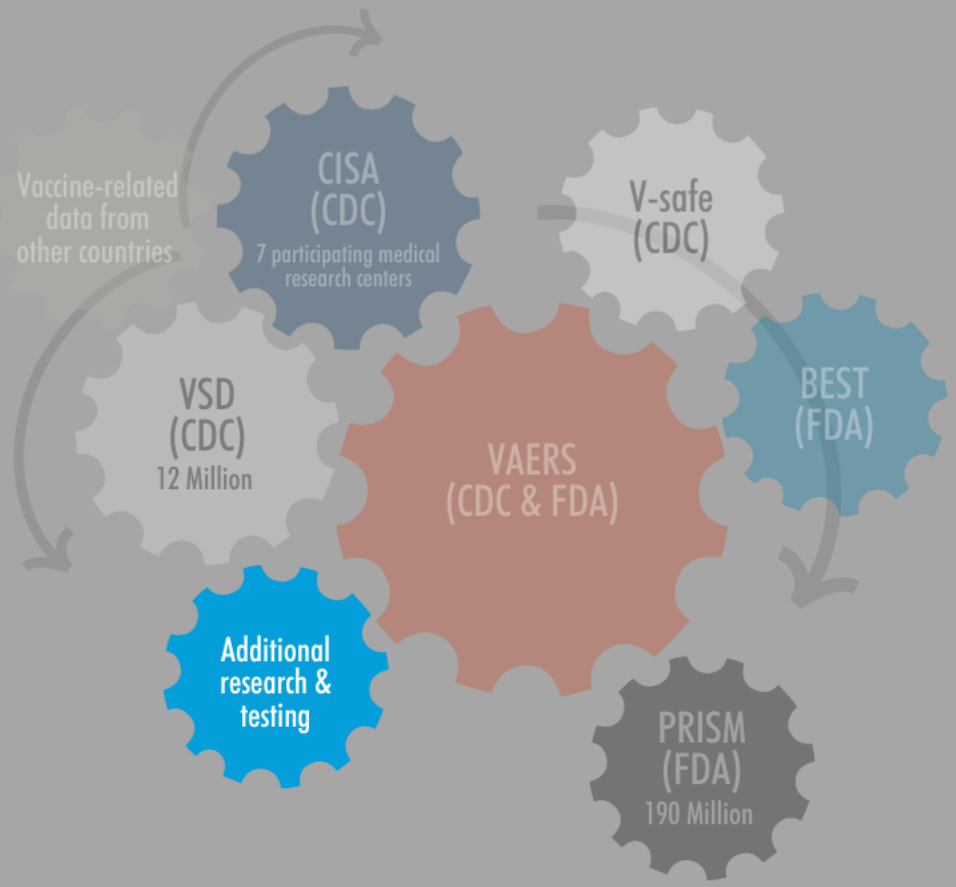
Safety Monitoring System Populations

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+ years of age in US, including 650K long-term care facility residents)	~50M beneficiaries 65+ years old
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



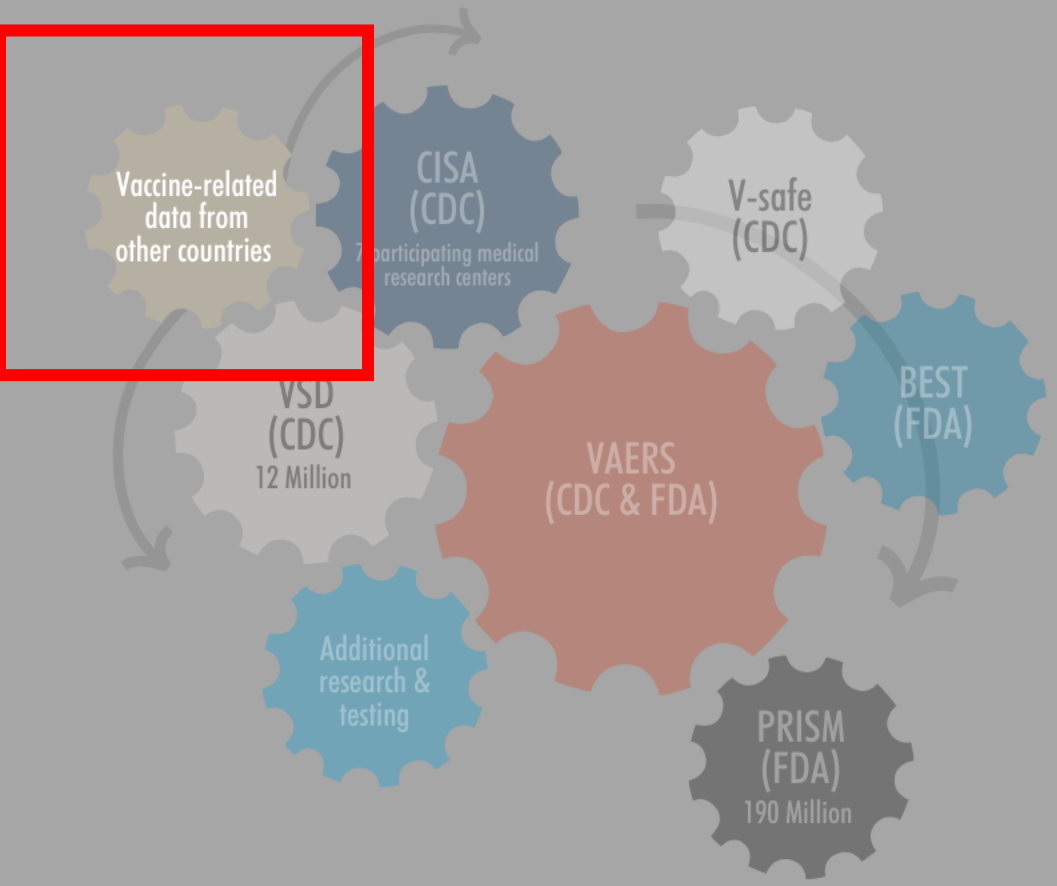
Additional research & testing conducted in the U.S.

Additional Research & Testing



There are a number of other organizations involved in assessing the safety of vaccines, including:

- The Department of Defense (DoD)
- The U.S. Department of Veterans Affairs (VA)
- The Indian Health Service (IHS)
- The National Institutes of Health (NIH)
- The Office of Infectious Disease and HIV/AIDS Policy (OIDP)



Vaccine-related Data from Other Countries

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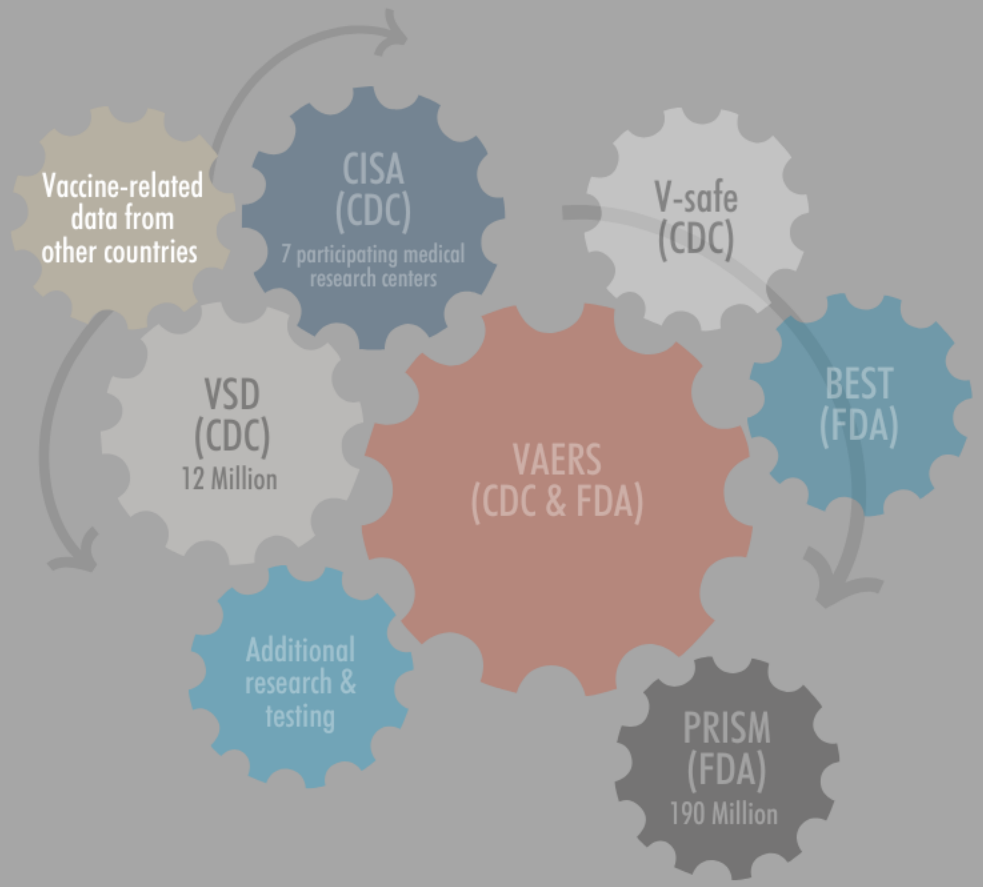
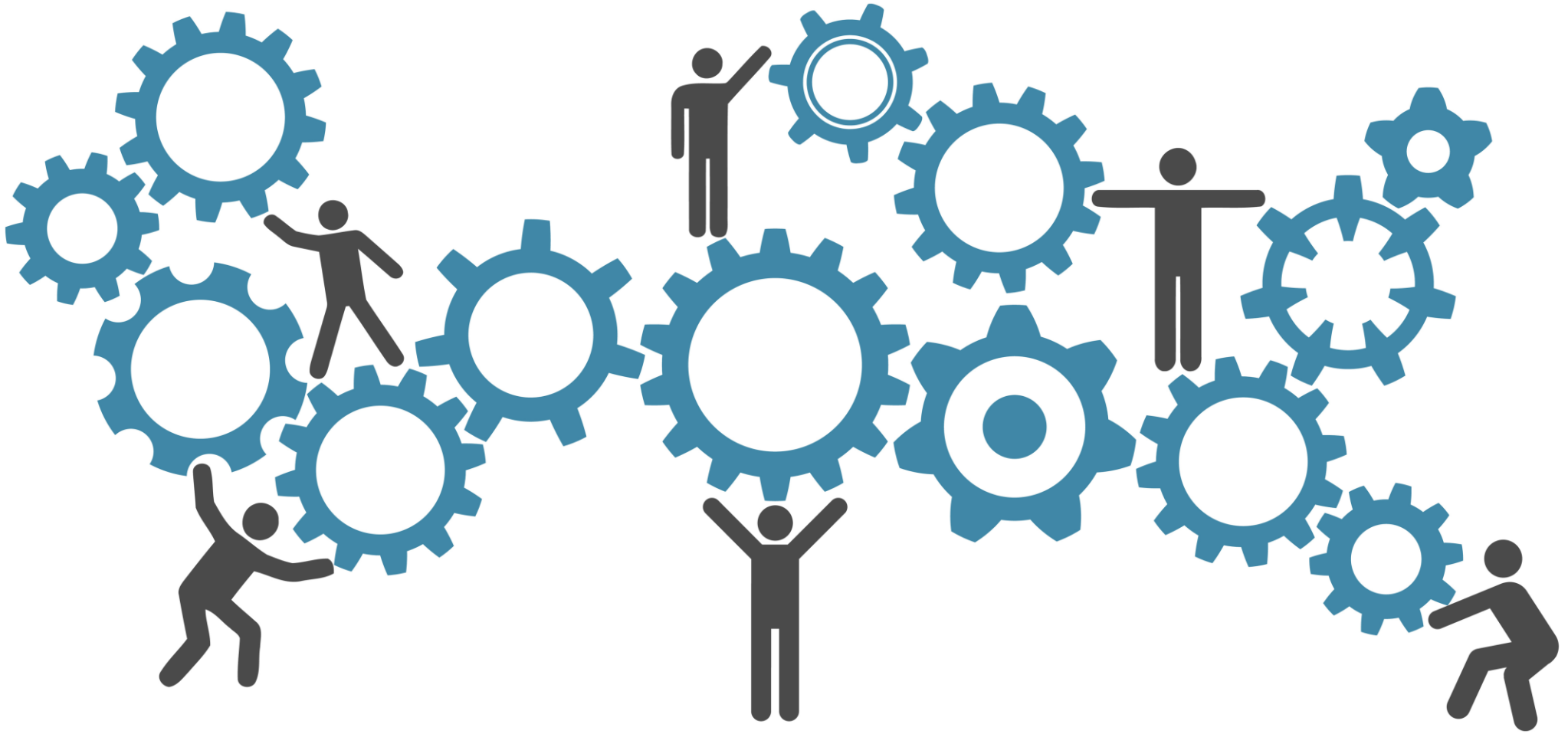


- The U.S. also monitors/assesses high-quality data on vaccine safety and effectiveness from other countries:
  - Countries with large, national healthcare-related datasets
  - Ability to compare large groups and control for various factors/health outcomes
  - Examples: Israel, the U.K. and Qatar
- These data can provide insight on what signals should be assessed/monitored in the U.S.

Let’s look at how these systems work together to find and manage potential safety issues



The face of rotavirus

Diarrhea
Vomiting
Dehydration
Shock
Death

Pre-Vaccine

- 3 million cases / year
- 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

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 (2006)

68,000 subjects

Monovalent Rotarix (2008)

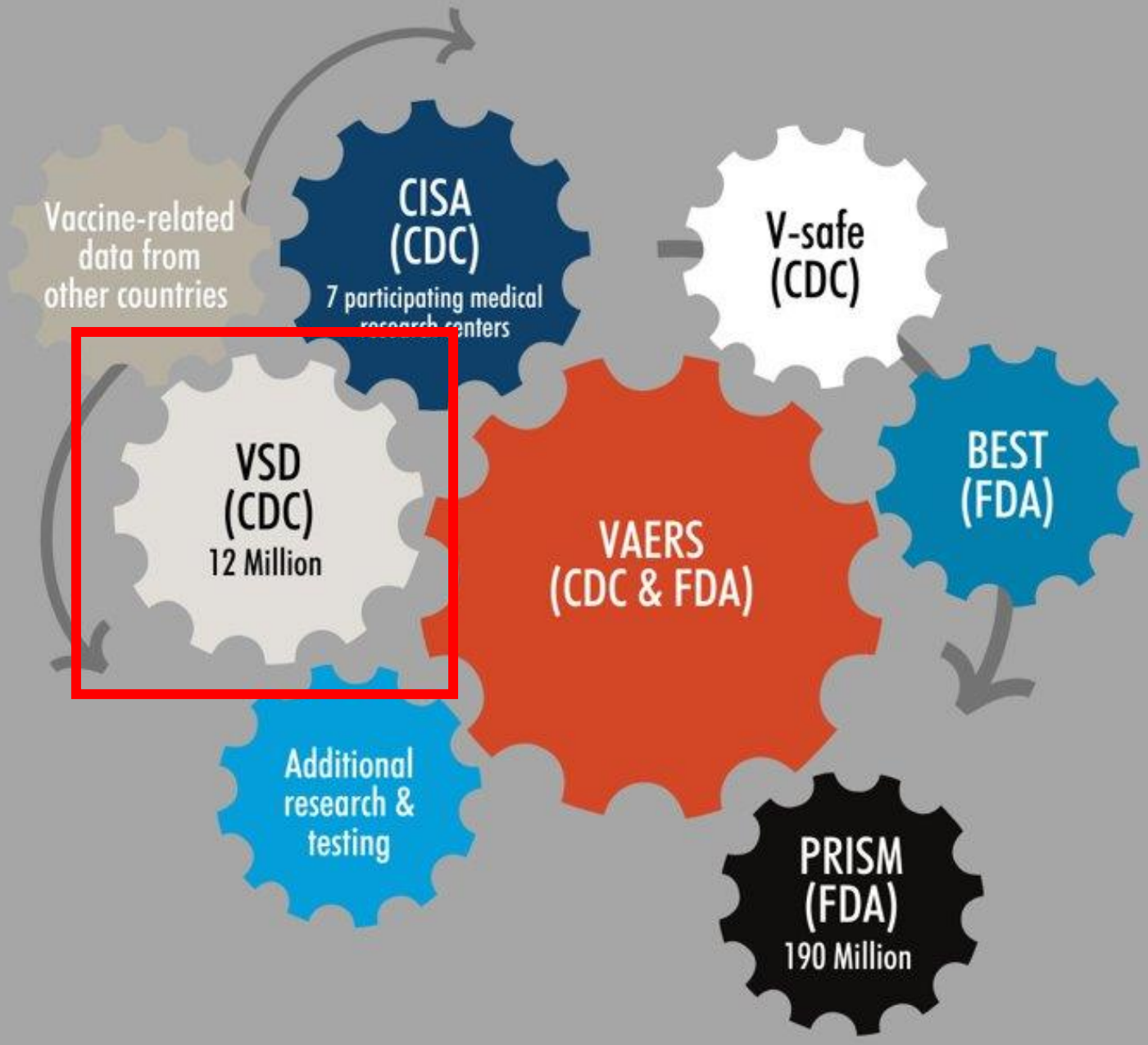
80,000 subjects

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 (RotaTeq) ~ 1.5 additional intussusceptions per 100,00 1st dose recipients.



Pathogen
Vaccine

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	Association? / 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	Association? / 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+ years old	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+ years old
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

Find NDSU CIRE online:

www.ndsu.edu/centers/immunize/

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https://www.youtube.com/c/NDSUCenterforImmunizationResearchEducation/featured

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Vaccine Safety Monitoring Resource from NDHHS and NDSU CIRE

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How is Vaccine Safety Monitored in the U.S.?

Vaccine safety monitoring systems in the U.S.

The success of vaccination programs depends not only on vaccines' effectiveness, but also on their safety. Because vaccines are given to millions of healthy people each year, they are held to a very high standard and are continuously monitored for safety.

The U.S. has one of the most advanced systems in the world for assessing vaccine safety. This includes a coordinated and overlapping approach using state-of-the-art technologies and systems working together. Each of the "gears", or systems, supplies a different type of data for researchers to analyze. Together, they work as a well-oiled machine to help provide a comprehensive picture of vaccine safety in the U.S. Each of these systems is detailed below.

Why is it important to monitor vaccines post-licensure?

Monitoring a vaccine after it is licensed or authorized helps ensure that vaccines continue to be safe and effective and the benefits continue to outweigh the risks.

Clinical trials typically involve thousands of participants. However, even large clinical trials may lack adequate sample sizes to identify rare adverse events - an event that may occur after one in 100,000 or one in 1,000,000 doses administered. Post-licensure safety studies help validate safety data from clinical trials and may detect adverse events that were not picked up in clinical trials.

Clinical trials may exclude specific vulnerable sub-populations, such as pregnant women or immunocompromised adults, for whom a vaccine may be indicated. Studies done post-licensure monitor the safety, effectiveness and benefits of vaccination in these populations.

Vaccine Adverse Event Reporting System (VAERS)

VAERS is used by the FDA and the CDC to collect reports of adverse events (possible side effects) that happen after vaccination. The system relies on individuals to send in reports of adverse health events following vaccination – meaning anyone can and should report adverse events to VAERS.

Scientists monitor VAERS reports, looking for adverse events that are unexpected, appear to happen more often than expected, or have unusual patterns. If a safety signal is identified, it is analyzed further using other safety monitoring systems (like VSD) to determine whether a vaccine is associated with a certain outcome and the rate at which it occurs.

What are the strengths of VAERS?

- Anyone can submit reports to VAERS (passive surveillance system)
- Serves as an early warning/hypothesis-generating system for vaccine safety issues. For example, in early 2021, reports to VAERS indicated a possible increased risk of severe allergic reactions following mRNA COVID-19 vaccination. Additional investigation concluded that these reactions are quite rare, happening in less than one in 200,000 doses administered.

What are the limitations of VAERS?

- Cannot determine if a vaccine caused the reported adverse event
- There is no control group to compare rates of adverse events in those who did and did not receive a vaccine (VAERS cannot determine if an adverse event is occurring more often following vaccination than what would be expected in the general population)
- Reports may lack details or contain errors

Vaccine Safety Datalink (VSD)

The VSD is a network of thirteen managed care sites across the U.S. with a combined patient population of more than 24 million people. The VSD can be used to determine if safety signals identified using VAERS are related to vaccination. It can also identify safety signals through real-time monitoring; for example, VSD evaluates particular health-related outcomes that may be associated with vaccination and compares it to the expected number of outcomes in a comparison group.

What are the benefits of VSD?

- Conduct timely vaccine safety studies, including assessments of rare adverse events and longitudinal studies involving prolonged follow-up of individual patients
- 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)

What are the limitations of VSD?

- May not have enough patients to detect extremely rare adverse events
- May not capture vaccine administration data outside of the health system
- Cannot determine if an association between an adverse event and vaccination is causal

Acknowledgements

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NDSU CENTER FOR IMMUNIZATION RESEARCH AND EDUCATION

Any questions?

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