

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

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I have no financial conflicts to disclose

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Objectives

01. Understand how safety is prioritized in the vaccine development and approval process.
02. Evaluate differences between vaccine safety surveillance systems in the U.S. and how they work together manage potential safety signals
03. Review historical examples of how vaccine surveillance systems have successfully identified safety concerns and the corresponding actions taken


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

Disease	20 th Century Annual Morbidity ¹	2023 Reported Cases ^{1 1}	Percent Decrease
Smallpox	29,005	0	100%
Diphtheria	21,053	2	> 99%
Measles	530,217	47	> 99%
Mumps	162,344	429	> 99%
Pertussis	200,752	5,611	97%
Polio (paralytic)	16,316	0	100%
Rubella	47,745	3	> 99%
Congenital Rubella Syndrome	152	0	100%
Tetanus	580	15	97%
<i>Haemophilus influenzae</i>	20,000	27*	> 99%

1. JAMA. 2007;298(18):2165-2163
^{1 1} CDC. National Notifiable Diseases Surveillance System, Weekly Tables of Infectious Disease Data. Atlanta, GA: CDC Division of Health Informatics and Surveillance. Available at: <https://www.cdc.gov/nndss/>.
 Data submitted through Dec 31, 2023; accessed on Jan 24, 2024. diphtheria and polio case counts reported by CDC Program.
 * *Haemophilus influenzae* type b (Hib) < 5 years of age. An additional 12 cases of Hib are estimated to have occurred among the 257 notifications of *Haemophilus influenzae* (< 5 years of age) with unknown serotype.


National Center for Immunization & Respiratory Diseases
 Historical Comparisons of Vaccine-Preventable Disease Morbidity in the U.S.
 2/14/2024



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Some (Not So) Fun Facts in U.S.

- Growing minority (20%) believe vaccines are more dangerous than diseases they prevent
 - Up to 31% if lean or vote Republican
- 64% are unsure, or think vaccines may cause autism
 - (80%) if lean or vote Republican
- Minority believe vaccines are extremely important for their children (63% Democrats, 26% Republicans)
- Up to 10% of PCPs in U.S. have doubts about vaccine necessity, safety, and efficacy



GALLUP 2024 Vaccine 40 (2022) 2588-2603

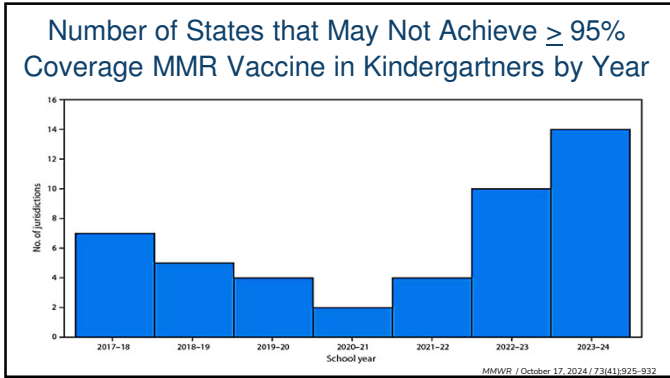
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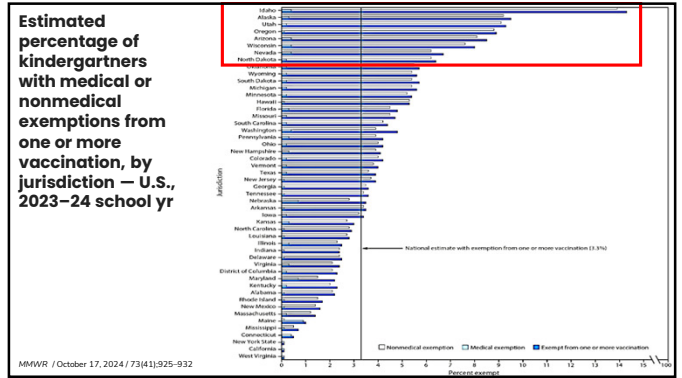

Vaccine Hesitancy

Ten threats to global health in 2019

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9 million children to be vaccinated against polio in Africa after outbreak in Malawi
Published March 22, 2022 at 7:41 a.m. ET

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.

Israel's current polio outbreak is tip of the iceberg - Health Min. D-G
Health Ministry director-general Nachman Ash stressed that polio can be eradicated through the use of vaccines.

Polio makes a comeback in the Philippines 19 years after the country was declared free of the disease
Published 10/19/2023

Measles cases across Europe continue to surge, putting millions of children at risk
Rapid response to measles outbreak is critical; all cases this year predicted to soon exceed total number reported in 2023

US measles cases hit 1,234 as Brooklyn outbreak called over
Published 09/20/2023

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SAFETY + EFFICACY

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What does "Safe" Mean?

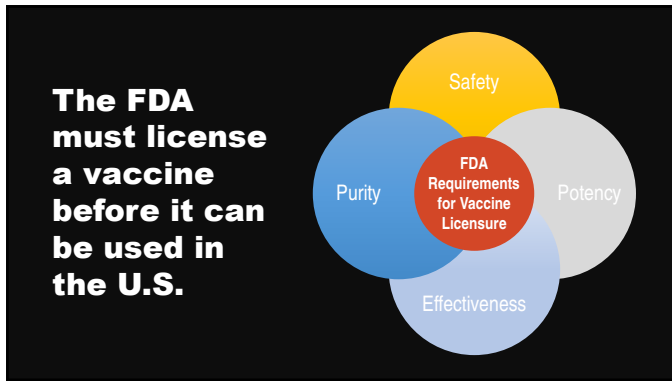
It Does Not Mean "Zero" Risk

Pathogen **Vaccine**

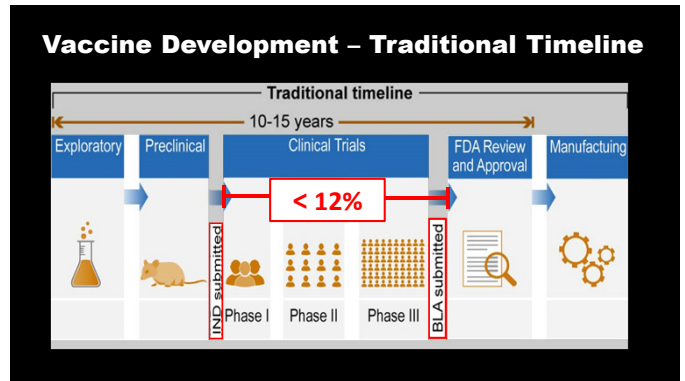
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The Journey of a Vaccine: From Development to Public Availability

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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	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
Pprevnar 13 - pediatric	Inactivated	Pneumococcal Disease	2010	Saline placebo-controlled trial	49,296
Spikevax (Moderna)	mRNA	COVID-19	2022	Saline placebo-controlled trial	30,420
Cominaty (Pfizer)	mRNA	COVID-19	2021	Saline placebo-controlled trial	43,998
Jcovden (J&J)	Viral Vector	COVID-19		Saline placebo-controlled trial	44,325

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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

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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

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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 $\geq 1:7333$

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

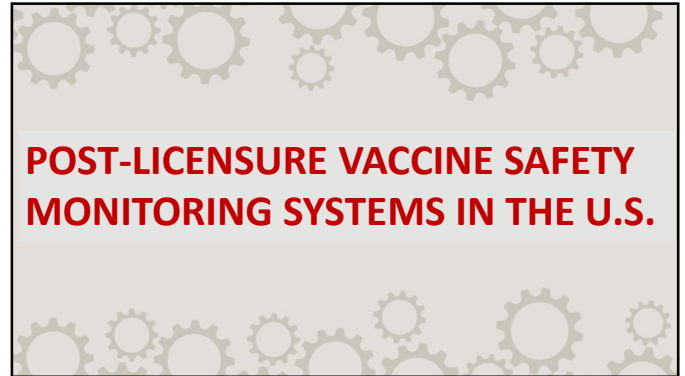
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Adverse Events Associated with Vaccination

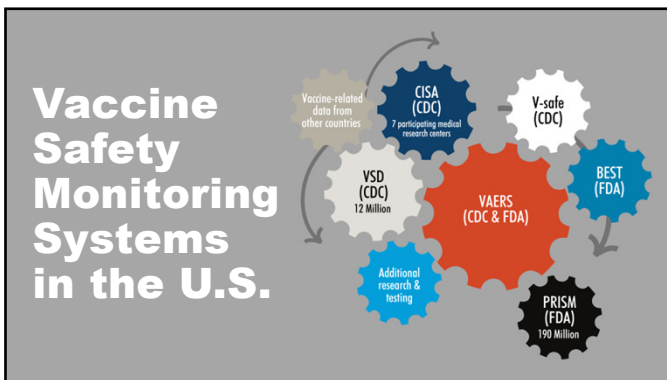
Vaccine	Event	Risk
Any	Anaphylaxis	1 : 1,000,000
Influenza (Inactivated)	G-B Syndrome	1-10 : million
MMR	ITP	1 : 40,000
MMR	Febrile Seizures	1 : 2,500
MMRV	12-47 mos old	1 : 1,250
RRV-TV (Rotashield)	Intussusception	1 : 11,000
RV1 and RV5 (Rotateq)	Intussusception	1 : 100,000

Bonhke, Pediatrics 2003;112:815; Mandakovic, J Pediatr 2010;156:623; Peter, Pediatrics 2002;110:e67; Klein, Pediatrics 2010;126:ACIP Meeting, June 2013

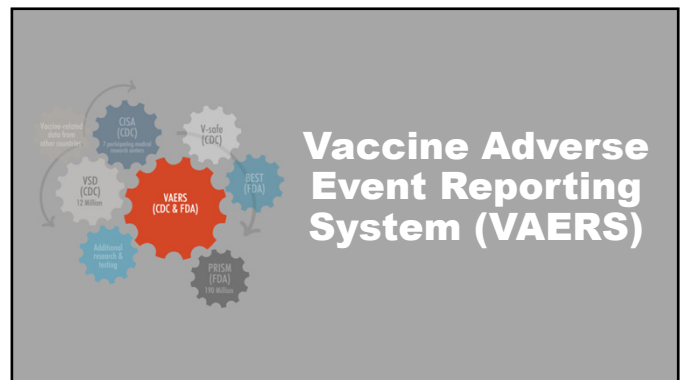
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VAERS

- 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

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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

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Misinformation and Confusion around VAERS

VAXX DEATHS	
UK	1 470
US	11 000
EU	18 000
	x 10 ?

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Our Brains Are Hardwired to Make Causal Inferences

"He was vaccinated, and something changed. My son is my science"

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

NO!

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

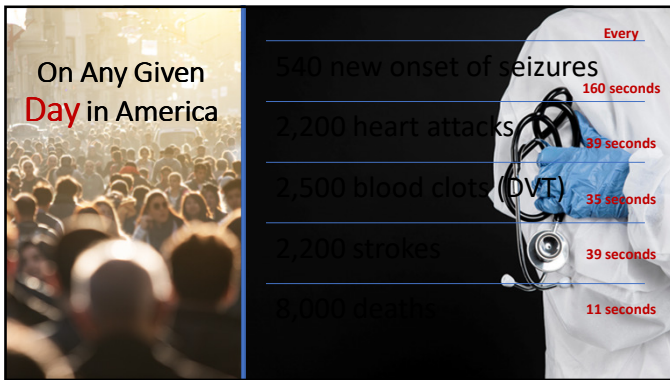
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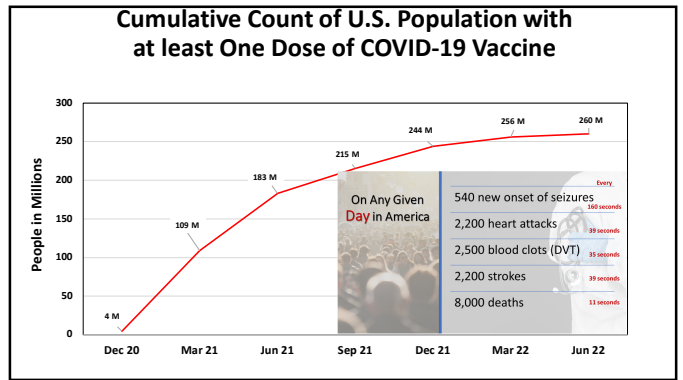
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Expected Coincidental Bad Events Randomly Following Vaccination in U.S.

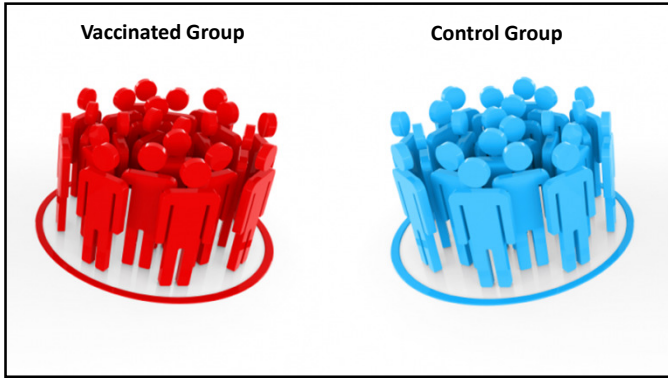
Event	Rate per 1,000	Births / Yr	Number of Events Randomly Happening		
			Month after Immunization	Week after Immunization	Day after Immunization
Epilepsy in 1 st year of life	1.3	4,000,000	1560	360	52
Autism dx in 5 th year of life	15	"	4,500	1,038	148
Death before 1 st birthday	5.9	"	7,080	1634	232
Guillain-Barre' Syndrome	.02	9,830,000 flu vaccinated adults	16	4	0.5

Assumptions: ~ 4 vaccines in 1st year of life. 1 set of shots between 4-5 years of life. 90% of children vaccinated.

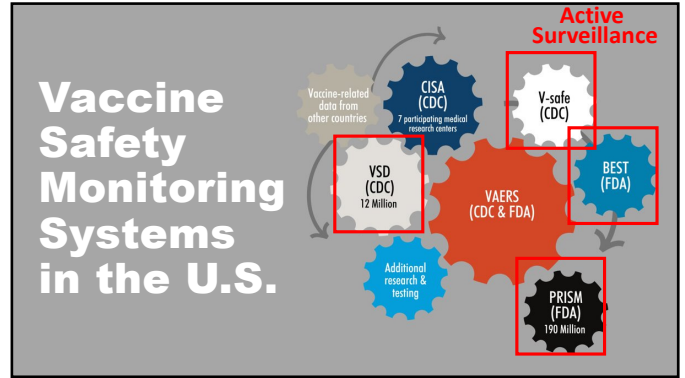
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Passive Surveillance	Active Surveillance
<ul style="list-style-type: none"> • Unsolicited reports of adverse events sent to a central database or health authority • In the U.S., these are received and entered into the Vaccine Adverse Event Reporting System (VAERS) that is co-managed by FDA and CDC 	<ul style="list-style-type: none"> • 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

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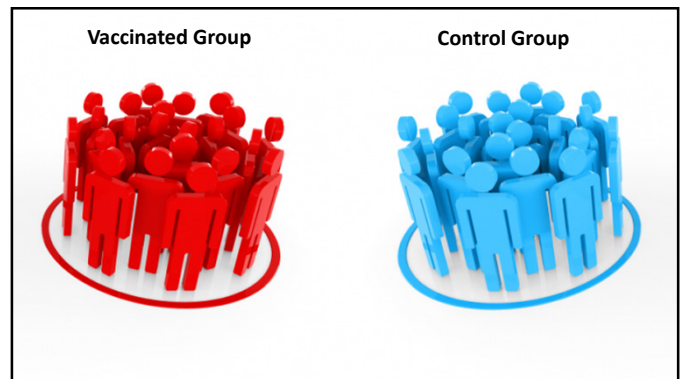
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CDC

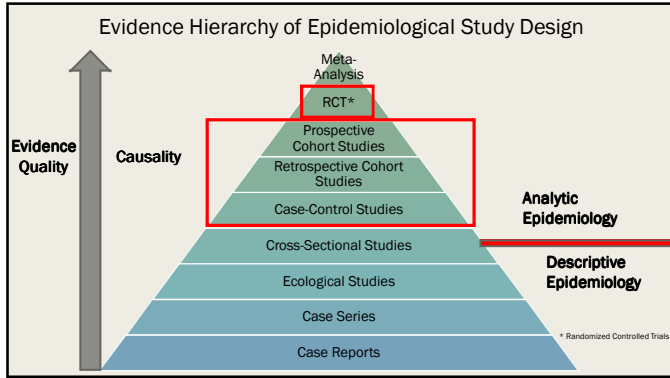
VSD Vaccine Safety Datalink

9 participating integrated healthcare organizations
data on over 12 million persons per year

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JAMA | Original Investigation

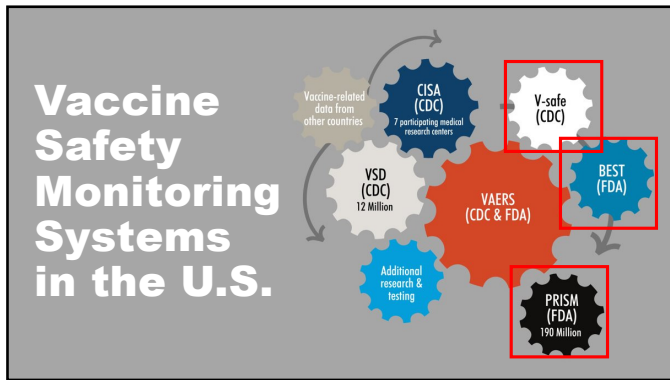
Surveillance for Adverse Events After COVID-19 mRNA Vaccination

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.

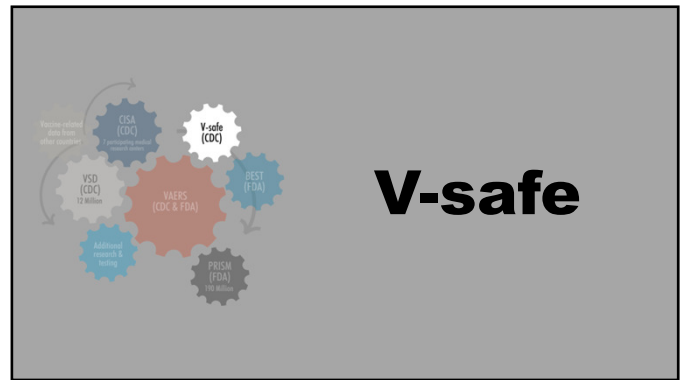
Key Findings:

- 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)

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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

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V-safe Strengths & Limitation

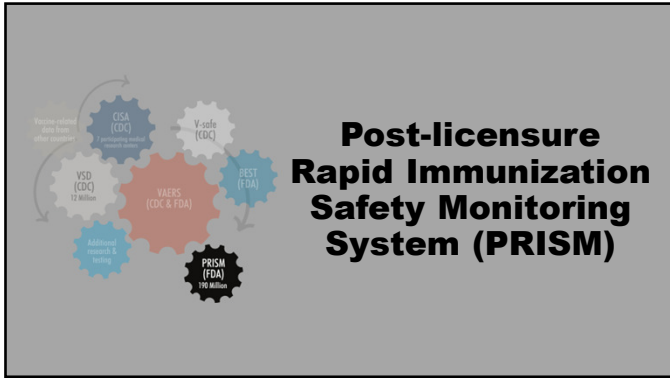
STRENGTHS

- 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

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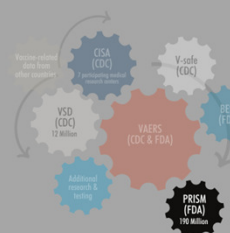
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PRISM: What is it?

- 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

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PRISM: Strengths & Limitations



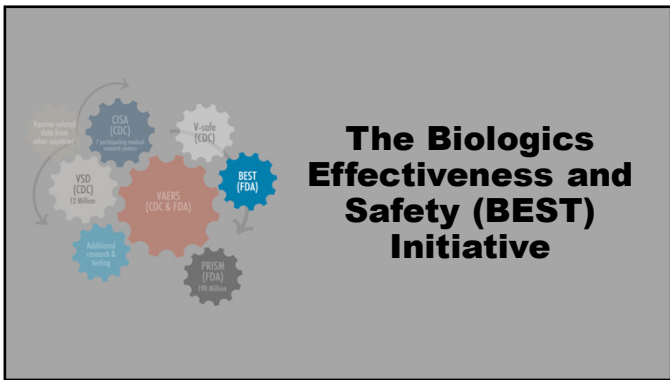
STRENGTHS

- 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

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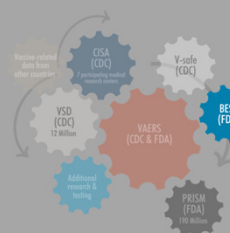
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BEST Initiative: What is it?

- 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

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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

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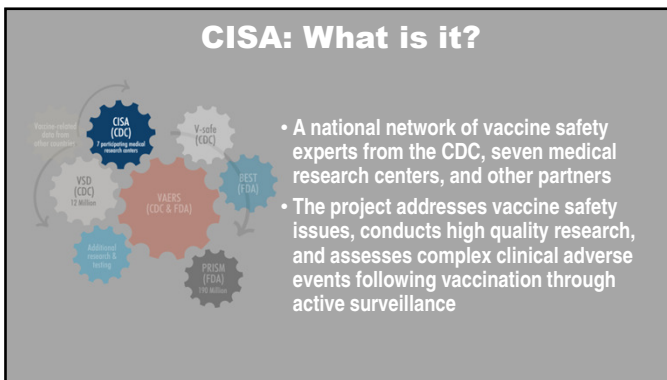
Safety Monitoring System Populations

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
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

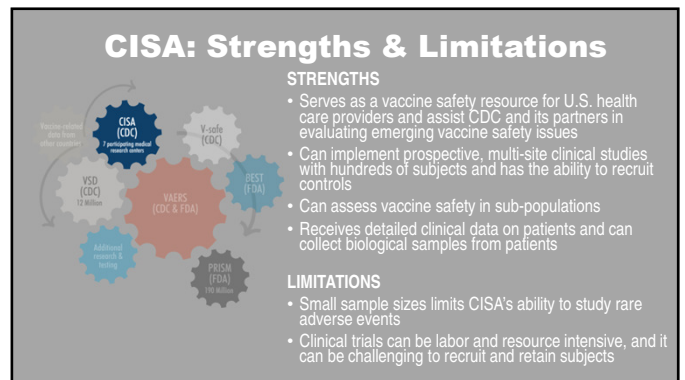
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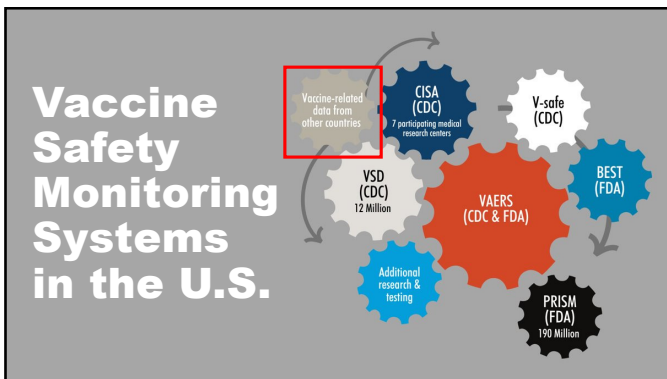
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Vaccine-related Data from Other Countries: Examples

THE LANCET

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

Vaccine Efficacy or Effectiveness (VE) Against Variants

Vaccine	Study type	VE
Pfizer	Post-EUA	• 90% against B.1.1.7 in Qatar*
	Pre-EUA	• 75% against B.1.1.7 in Qatar
Janssen	Pre-EUA	• 74% in U.S.
	Pre-EUA	• 60% in Israel
Novavax	Pre-EUA	• 74.82% for severe/critical disease†
	Pre-EUA	• 52% in S. Africa
AstraZeneca	Pre-EUA	• 90% against non-B.1.1.7 in UK
	Pre-EUA	• 80% against B.1.1.7 in UK
AstraZeneca	Pre-EUA	• 51% against B.1.351 in S. Africa
	Pre-EUA	• 44% against non-B.1.1.7 in UK
AstraZeneca	Pre-EUA	• 75% against B.1.1.7 in UK
	Pre-EUA	• 100% against B.1.351 in South Africa*

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THE NEW ENGLAND JOURNAL OF MEDICINE

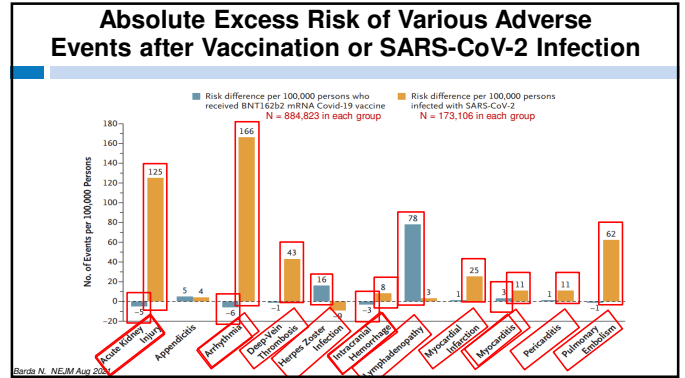
ORIGINAL ARTICLE

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

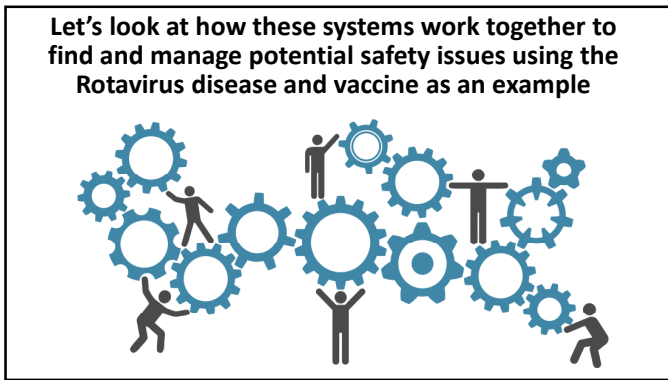
Noam Barda, M.D., Noa Dagan, M.D., Yotir Ben-Shlomo, B.Sc., Eldad Kepten, Ph.D., Jacob Waxman, M.D., Reut Ohana, M.Sc., Miguel A. Hernán, M.D., Marc Lipsitch, D.Phil., Isaac Kohane, M.D., Doron Netzer, M.D., Ben Y. Reis, Ph.D., and Ran D. Balicer, M.D.

- 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
- Mycocardial infarction
- Mycocarditis
- Neutropenia
- Other thrombosis
- Paresthesia
- Pericarditis
- Pulmonary embolism
- Seizure
- Syncope
- Thrombocytopenia
- Uveitis
- Vertigo

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The face of rotavirus

- Diarrhea
- Vomiting
- Dehydration
- Shock
- Death

Pre-Vaccine

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

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Rotashield: Timeline of Events

August 1998: FDA approves Rotashield (N=4,413)

July 1999: VAERS identifies 15 cases of intussusception - CDC suspends vaccine

October 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.

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Pathogen vs **Vaccine**

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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

Original Rotashield Example:

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!)



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Rotavirus

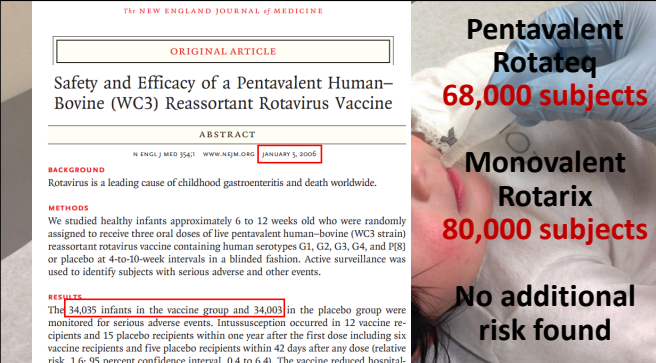


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Pentavalent Rotateq
68,000 subjects

Monovalent Rotarix
80,000 subjects

No additional risk found

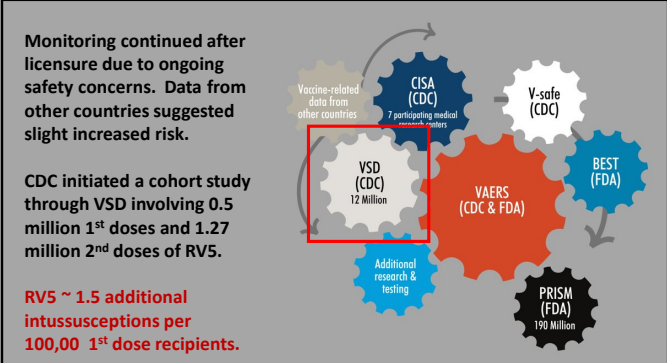


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Monitoring continued after licensure due to ongoing safety concerns. Data from other countries suggested slight increased risk.

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 100,000 1st dose recipients.



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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

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Examples of Assessing Safety Signals

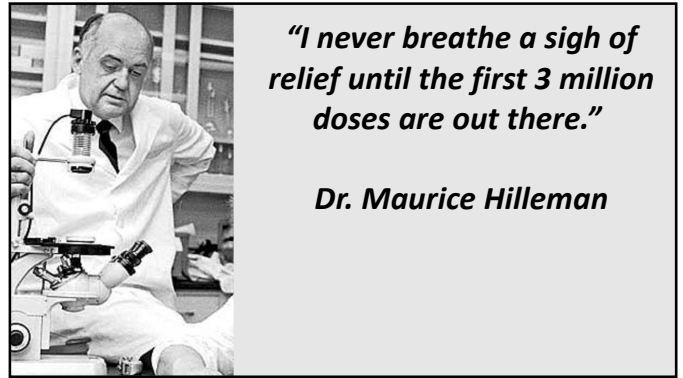
Concern	How was it detected?	Follow up assessment	Ass'n? / Action?
Vaccine-associated paralytic polio (VAPP) & OPV	VAERS	VSD; Data from other countries & PAHO; NIS; IOM review	YES / YES Transition from oral polio vaccine to inactivated polio vaccine in U.S.
DVT from HPV vaccination	VAERS & VSD	VSD, Denmark, Sweden, Canada; Cohort studies	NO / NO No change to vaccination schedules
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.
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 1 st & 2 nd dose was added to recommendations.

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Examples of Assessing Safety Signals

Concern	How was it detected?	Follow up assessment	Ass'n? / Action?
2003 Use of thimerosal in vaccines & autism	NONE (Public Concern)	VAERS; VSD; CISA; IOM; Data from other countries	NO / YES Data doesn't support association. HOWD-09, 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.

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