Vaccine safety signal detection and evaluation

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Advisory Committee on Immunization Practices meeting
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Outline

- **Definitions**
- **Approach to signal detection and evaluation**
- **Example**
  - Previous statistical signals for ischemic stroke in the Vaccine Safety Datalink (VSD)

Definition: adverse event following immunization (AEFI)

- **Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom, or disease.**

Notes: "Immunization" as used in these definitions means the usage of a vaccine for the purpose of immunizing individuals. "Usage" includes all processes that occur after a vaccine product has left the manufacturing/packaging site, i.e. handling, prescribing and administration of the vaccine.

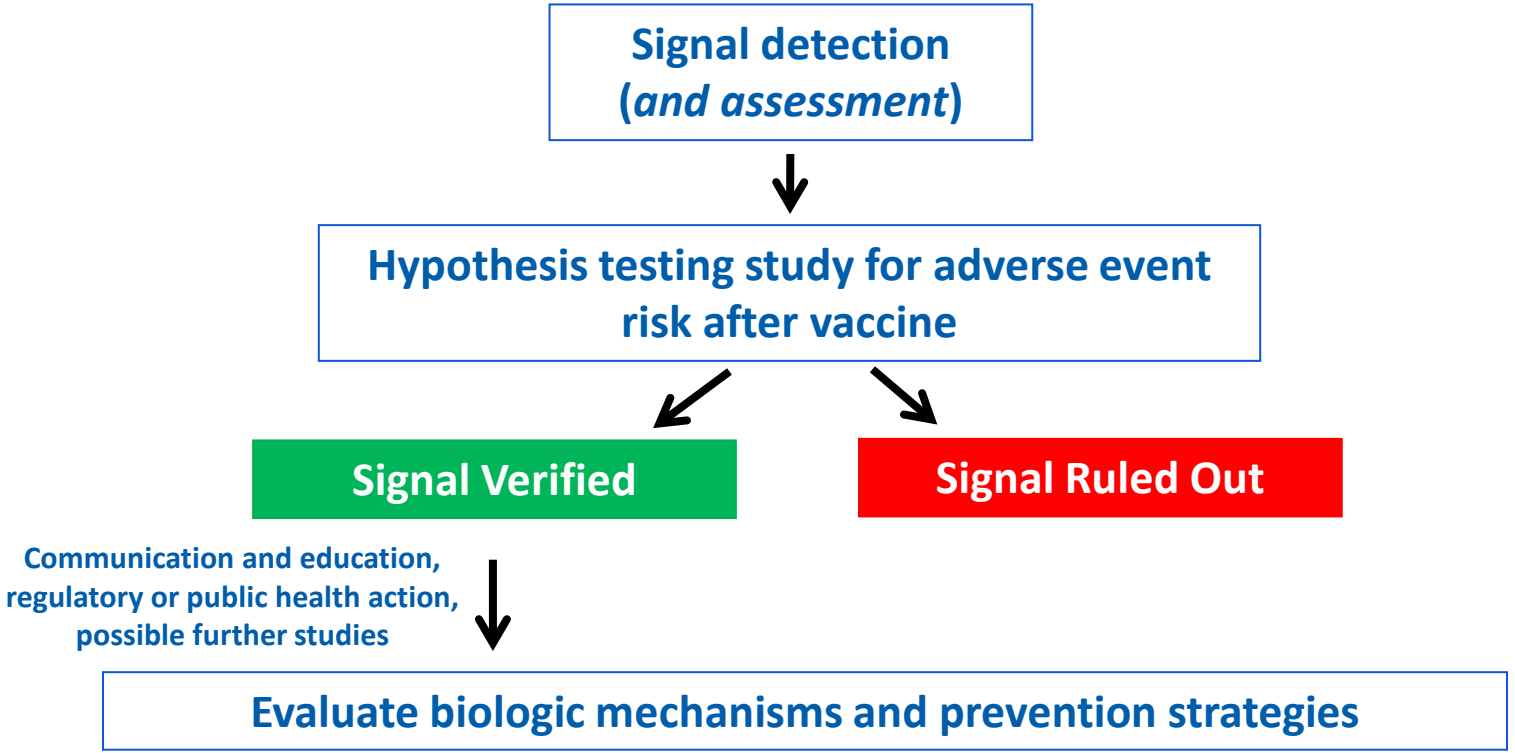
Source: Council for International Organizations of Medical Sciences. Definition and application of terms for vaccine pharmacovigilance: report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance. Geneva: CIOMS, 2012.

Definition: signal

- **Information that arises from one or multiple sources (including observations and experiments) which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.**

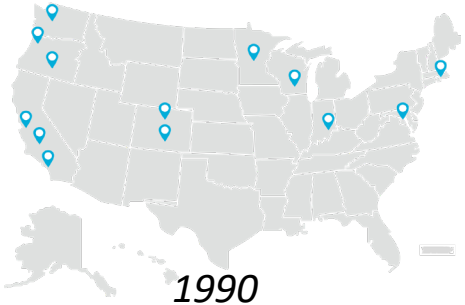
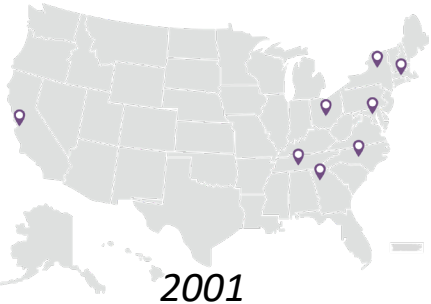
Source: Council for International Organizations of Medical Sciences. Definition and application of terms for vaccine pharmacovigilance: report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance. Geneva: CIOMS, 2012

Vaccine safety signal pathway



*Adapted from: Practical Aspects of Signal Detection in Pharmacovigilance: Report of CIOMS Working Group VIII – CIOMS. (2010)

CDC's Immunization Safety Office Monitors Vaccine Safety Through Strong, Complementary Systems

VAERS	VSD	CISA Project	V-safe
			
1990	*1990*	*2001*	*2020*

Systems work together to rapidly detect and assess potential safety concerns to help inform public health actions

Evaluation following previous statistical signals for ischemic stroke in the Vaccine Safety Datalink (VSD)

Vaccine Safety Datalink (VSD)

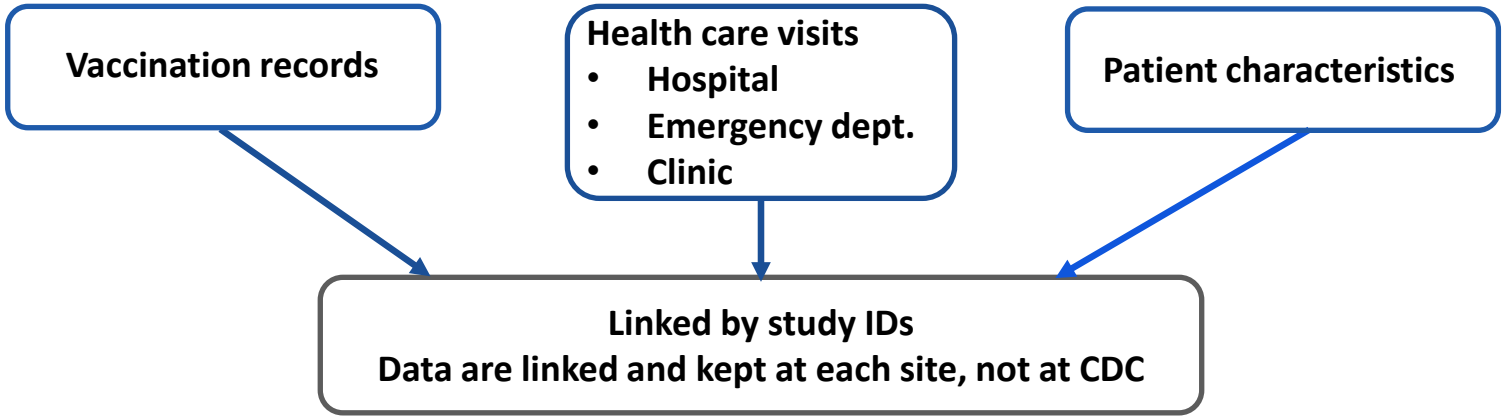
Collaborative Model for High-Quality Vaccine Safety Data

VSD

- 13 integrated healthcare organizations, covering >15.5 million people per year
- Active monitoring using electronic medical records (EMR) and chart reviews
- Rapid monitoring for pre-specified events as well as monitoring for unexpected events
- Can detect and assess safety signals
- Develops innovative methods for monitoring safety

Vaccine Safety Datalink (VSD)

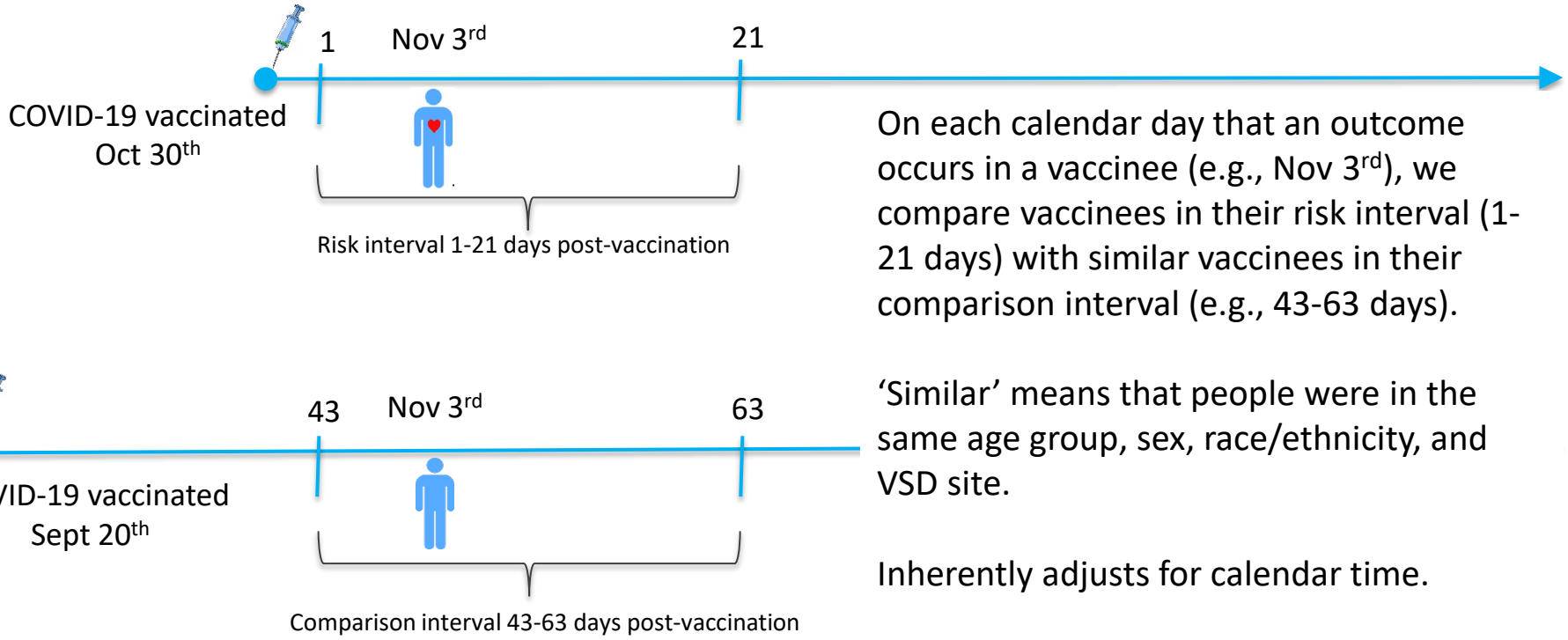
- **Links vaccination data to health outcomes**



Vaccine Safety Datalink (VSD)
Rapid Cycle Analysis (RCA) surveillance

- Weekly sequential monitoring as data accrue
- Monitors a limited set of prespecified adverse events of special interest
  - Potential cases identified using ICD-10 codes for healthcare encounters
- Designed to detect statistical signals
  - A statistical signal is a finding from an analysis where a calculated value (i.e., the test statistic) exceeds a specified statistical threshold
  - A statistical signal does not necessarily represent a vaccine safety problem and requires further assessment before conclusions can be drawn.
- Since 2020, VSD has utilized a vaccinated concurrent comparator method

Vaccinated Concurrent Comparator Method



On each calendar day that an outcome occurs in a vaccinee (e.g., Nov 3rd), we compare vaccinees in their risk interval (1-21 days) with similar vaccinees in their comparison interval (e.g., 43-63 days).

'Similar' means that people were in the same age group, sex, race/ethnicity, and VSD site.

Inherently adjusts for calendar time.

Ref: Klein N, et al. Kaiser Permanente Northern California –
https://jamanetwork.com/journals/jama/fullarticle/2784015

Vaccine Safety Datalink (VSD)
Statistical signal detection and evaluation

- Statistical signal detection: RCA concurrent comparator analysis
  - Intended to be rapid
  - Might have residual bias
- Statistical signal evaluation: self-controlled case-series (SCCS) analysis
  - Requires waiting for complete accrual of follow-up time
  - Less prone to bias

Core list of adverse events of special interest monitored by U.S. federal agencies, 2020-2023

Outcome	VAERS	VSD	VA	DMSS	DHA IHD	CMS	BEST
Acute myocardial infarction	x	x	x	x	–	x	x
Anaphylaxis	x	x	x	x	x	x	x
Appendicitis	x	x	x	x	x	x	x
Bell's palsy	x	x	x	x	x	x	x
Disseminated intravascular coagulation	x	x	x	x	–	x	x
Encephalomyelitis/Encephalitis	–	–	–	x	–	x	x
Encephalitis	x	x	x	–	x	–	–
Encephalomyelitis	x	x	x	–	x	–	–
Guillain-Barré syndrome	x	x	x	x	x	x	x
Immune thrombocytopenic purpura	–	x	x	x	x	x	x
Multisystem Inflammatory Syndrome in Adults	x	x	x	x	–	x	x
Multisystem Inflammatory Syndrome in Children	x	x	–	–	–	–	x
Myocarditis / pericarditis	x	x	x	x	x	x	x
Narcolepsy / cataplexy	x	x	x	x	x	x	x
Stroke	x	–	x	–	x	–	–
Non-hemorrhagic stroke	–	x	x	–	–	x	x
Hemorrhagic stroke	–	x	x	–	–	x	x
Thrombosis with thrombocytopenia syndrome and/or cerebral venous sinus thrombosis	x	x	–	x	–	x	x
Transverse myelitis	x	x	x	x	x	x	x
Venous thromboembolism	x	x	x	x	x	x	x
Pulmonary embolism	–	x	x	x	x	x	x
Deep vein thrombosis	–	–	x	x	–	x	x

Note: "x" indicates a health outcome that was monitored in the vaccine safety system; health outcomes in each system varied depending on age group and vaccine. The Indian Health Service is not included in this table, as no pre-specified outcomes in the monitoring systems.

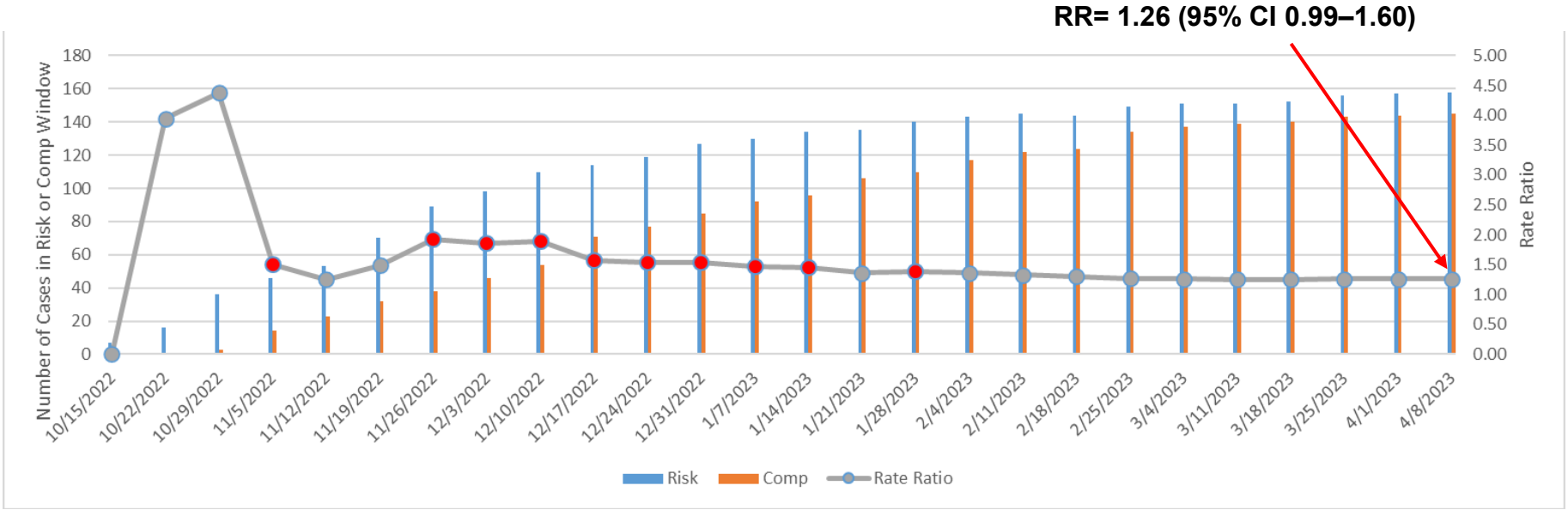
Abbreviations: VAERS, Vaccine Adverse Event Reporting System; VSD, Vaccine Safety Datalink; VA, Department of Veterans Affairs Warehouse; DMSS, Defense Medical Surveillance System; DHA IHD, Defense Health Agency Immunization Health Division; CMS, Centers for Medicare & Medicaid Services; BEST, Biologics Effectiveness and Safety System.

https://www.sciencedirect.com/science/article/pii/S0264410X2400224X?via%3Dihub

History of VSD RCA statistical signals for ischemic stroke following mRNA COVID-19 vaccines

	mRNA vaccine formula	VSD RCA statistical signal for ischemic stroke
2020-21	original, primary series	No
2021-22	original, booster dose	No
2022-23	bivalent (original and BA.4/BA.5)	Yes
2023-24	XBB.1.5	Yes
2024-25	KP.2	No

VSD RCA ischemic stroke after Pfizer-BioNTech bivalent booster, age ≥65 years, counts and adjusted rate ratios, Oct 16, 2022–April 8, 2023



● Red dot represents sequential signal: p-value <0.01 (1-sided)

This information was previously presented to the Advisory Committee on Immunization Practices (ACIP) meeting on April 19, 2023

Initial VSD statistical signal for ischemic stroke

January 13, 2023

May 31, 2023 update

- **"Other safety monitoring systems have not observed similar findings."**
- **"As time has passed and more safety data have accumulated, the initial finding has decreased, and scientists believe factors other than vaccination might have contributed to the initial finding."**
- **"The current evidence does not support the existence of a safety issue."**

CDC and FDA Identify Preliminary COVID-19 Vaccine Safety Signal for Persons Aged 65 Years and Older | FDA

History of VSD RCA statistical signals for ischemic stroke following mRNA COVID-19 vaccines

- 2022-2023 (bivalent vaccine)
  - Pfizer COVID-19 vaccine, age ≥65 years
    - Question about effect of same day administration with influenza vaccine
- 2023-2024 (XBB.1.5 vaccine)
  - Moderna COVID-19 vaccine, age ≥65 years
  - Pfizer COVID-19 vaccine, age 50-64 years
- Additional information that was previously pending
  - A follow-up VSD analysis using self-controlled case-series (SCCS) analysis
  - FDA's 2023-2024 COVID-19 vaccine safety surveillance using Medicare claims database results

VSD SCCS analysis of ischemic stroke after Pfizer COVID-19 vaccine with or without influenza vaccine, 2022-2023

		IRR (95% Confidence Interval)			
		21-day risk interval		42-day risk interval	
	Age group	COVID-19 vaccination without influenza vaccination	Same-day coadministration of COVID-19 and influenza vaccinations	COVID-19 vaccination without influenza vaccination	Same-day coadministration of COVID-19 and influenza vaccinations
Pfizer	Overall	0.87 (0.58–1.29)	1.14 (0.88–1.47)	0.83 (0.58–1.19)	1.12 (0.91–1.37)
	12 - 64 years	0.92 (0.45–1.90)	0.88 (0.50–1.54)	0.93 (0.51–1.70)	1.06 (0.71–1.60)
	65+ years	0.85 (0.53–1.37)	1.25 (0.94–1.68)	0.79 (0.51–1.23)	1.15 (0.91–1.45)

No statistically significant increased risks found for either separate or same day administration

VSD SCCS analysis of ischemic stroke after mRNA COVID-19 vaccine with or without influenza vaccine, 2023-2024

		IRR (95% Confidence Interval)			
		21-day risk interval		42-day risk interval	
	Age group	COVID-19 vaccination without influenza vaccination	Same-day coadministration of COVID-19 and influenza vaccinations	COVID-19 vaccination without influenza vaccination	Same-day coadministration of COVID-19 and influenza vaccinations
Pfizer	Overall	1.19 (0.65-2.17)	0.90 (0.64-1.28)	1.12 (0.67-1.89)	1.08 (0.79-1.46)
	12 - 64 years	0.60 (0.08-4.64)	1.17 (0.62-2.21)	0.89 (0.24-3.41)	1.23 (0.69-2.17)
	65+ years	1.34 (0.71-2.53)	0.83 (0.55-1.26)	1.20 (0.68-2.11)	1.06 (0.73-1.53)
Moderna	Overall	2.11 (0.81-5.53)	1.41 (0.35-5.76)	1.29 (0.48-3.46)	1.13 (0.33-3.93)
	12 - 64 years	2.73 (0.51-14.52)	0.70 (0.05-10.67)	1.53 (0.30-7.80)	0.39 (0.01-10.17)
	65+ years	1.94 (0.60-6.30)	1.96 (0.43-9.03)	1.22 (0.36-4.16)	1.56 (0.46-5.24)

No statistically significant increased risks found for either separate or same day administration

FDA surveillance: Safety Monitoring of Multiple Health Outcomes Following 2023–2024 COVID-19 Vaccination among Medicare Beneficiaries Aged 65 Years and Older in the United States

- **Methods:**
  - Medicare Fee-for-Service (FFS) claims database from September 2023 to April 2024
  - Self-controlled case series design
- **Results:**
  - Approximately 7.6 million Medicare FFS beneficiaries received a 2023–2024 COVID-19 vaccination
  - Non-hemorrhagic stroke or transient ischemic attack
    - Pfizer: IRR: 1.03 [99% CI: 0.91, 1.17]
    - Moderna: IRR: 0.96 [99% CI: 0.85, 1.10]
    - Novavax: IRR: 0.98 [99% CI: 0.19, 5.13]
- **Interpretation: "we did not find evidence for an elevation in non-hemorrhagic stroke risk following vaccination with any of the vaccine brands"**

https://www.medrxiv.org/content/10.1101/2025.01.03.25319975v1

Summary

- **The Vaccine Safety Datalink (VSD) rapid cycle analysis (RCA) surveillance monitored a list of pre-specified adverse events of special interest after COVID-19 vaccines, including ischemic stroke**
- **The VSD detected statistical signals for ischemic stroke during 2022-2023 and 2023-2024**
- **Signal evaluation using self-controlled case-series analyses in the VSD and in other data sources have not confirmed an increased risk of ischemic stroke**

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