mRNA COVID-19 bivalent booster vaccine safety update

Advisory Committee on Immunization Practices (ACIP) meeting

April 19, 2023

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Topics

- Describe current data on ischemic stroke following mRNA COVID-19 bivalent booster vaccination
  - CDC's Vaccine Safety Datalink (VSD) Rapid Cycle Analysis (RCA) signal assessment for ischemic stroke after Pfizer-BioNTech COVID-19 mRNA bivalent booster dose vaccination in the age group ≥65 years old
  - Vaccine Adverse Event Reporting System (VAERS) data on ischemic stroke following mRNA COVID-19 bivalent booster dose vaccination

VSD COVID-19 Rapid Cycle Analysis: Analyses of Ischemic Stroke after Pfizer-BioNTech Bivalent Booster Dose

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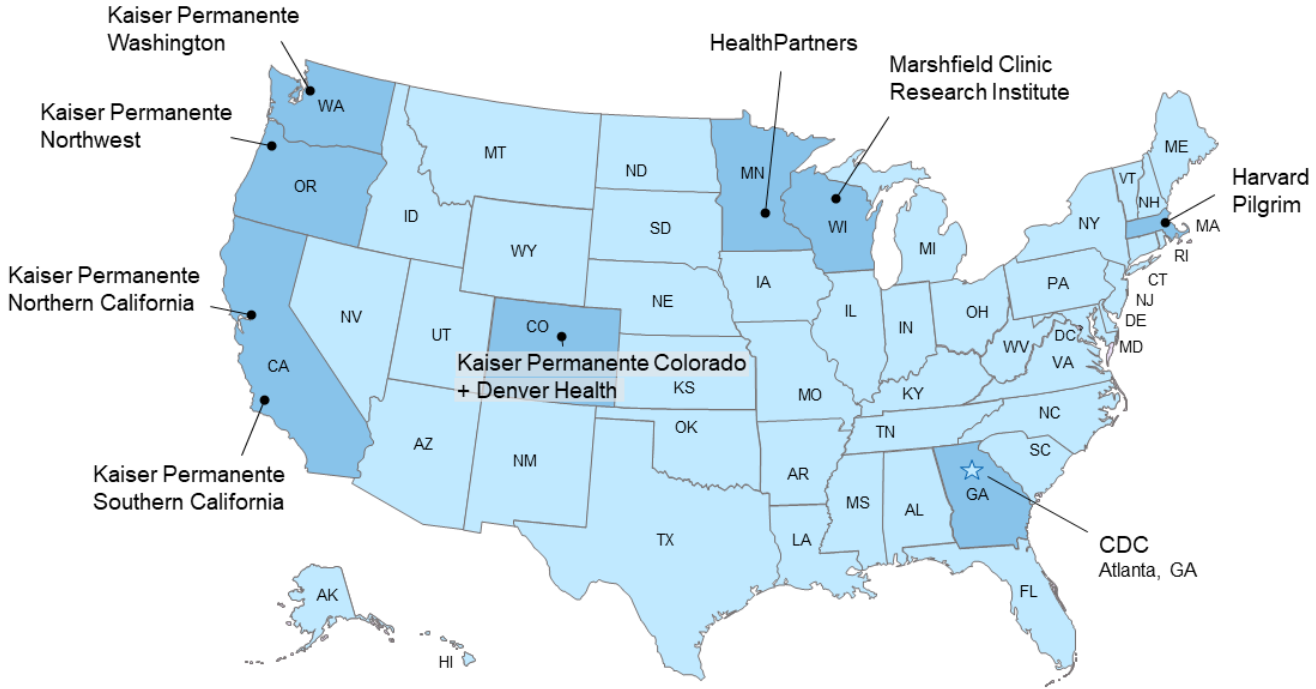
Vaccine Safety Datalink (VSD)



- Established in 1990
- Collaborative project between CDC and 9 integrated healthcare organizations
- Includes electronic health record data on ~12.5 million individuals across all sites

VSD RCA for bivalent boosters

- Pre-specified outcomes were assessed during weekly sequential monitoring after COVID-19 bivalent booster vaccination*
  - Risk of pre-specified outcomes 1–21 days following a bivalent vaccination compared with bivalent vaccinated individuals who were 22–42 days following the bivalent dose (vaccinated concurrent comparator method)
  - All analyses adjusted for age, sex, race/ethnicity, VSD site, calendar time (days) and seasonality (time)
  - Signal if p-value <0.01 (1-sided)

* Rapid Cycle Analysis (RCA) to monitor the safety of COVID-19 vaccines in near real-time within the Vaccine Safety Datalink. Available at: Rapid Cycle Analysis (RCA) to monitor the safety of COVID-19 vaccines in near real-time within the Vaccine Safety Datalink (cdc.gov)

VSD COVID-19 vaccine RCA prespecified surveillance outcomes

- In COVID-19 bivalent booster vaccine monitoring, VSD RCA detected a statistical signal for ischemic stroke after Pfizer-BioNTech bivalent booster vaccination in the age group 65 years and older
- No other VSD RCA pre-specified surveillance outcomes have signaled in any age groups for either of the mRNA COVID-19 bivalent booster vaccines or when data for the two mRNA vaccine types are combined/pooled

Prespecified outcomes	Settings
Acute disseminated encephalomyelitis	Emergency dept, Inpatient
Acute myocardial infarction	Emergency dept, Inpatient
Acute respiratory distress syndrome	Emergency dept, Inpatient
Anaphylaxis*	Emergency dept, Inpatient
Appendicitis	Emergency dept, Inpatient
Bell's palsy	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*	Emergency dept, Inpatient
Narcolepsy / cataplexy	Emergency dept, Inpatient, Outpatient
Pulmonary embolism	Emergency dept, Inpatient
Seizures/Convulsions (including 0-7 days for youngest ages)	Emergency dept, Inpatient
Stroke, hemorrhagic	Emergency dept, Inpatient
Stroke, ischemic	Emergency dept, Inpatient
Thrombosis with thrombocytopenia syndrome	Emergency dept, Inpatient
Thrombotic thrombocytopenic purpura	Emergency dept, Inpatient
Transverse myelitis	Emergency dept, Inpatient
Venous thromboembolism	Emergency dept, Inpatient, Outpatient

*All outcomes are first ever in the ICD-10 era, except anaphylaxis which is first in 7 days, and myocarditis/pericarditis which is first in 60 days

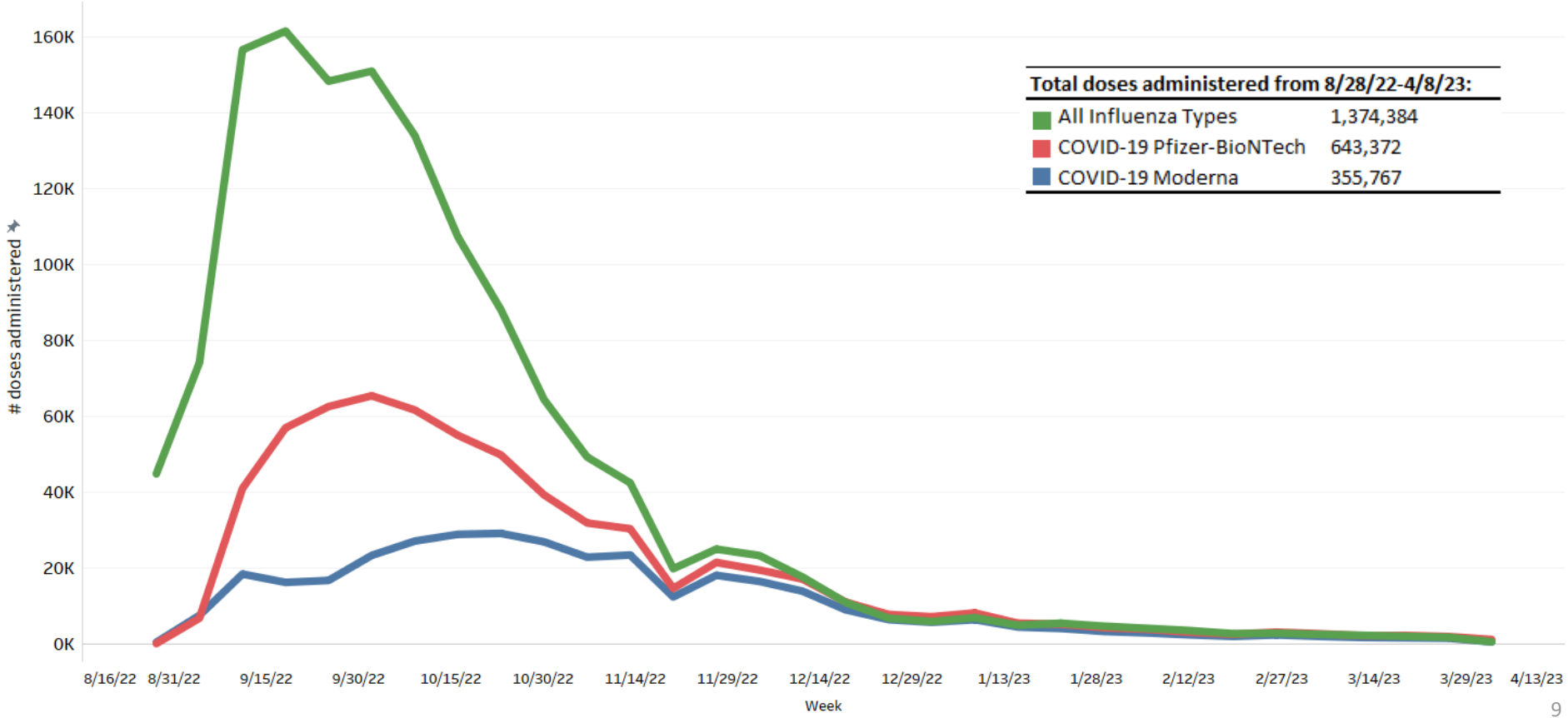
VSD investigations of an RCA signal to assess whether it reflects a real effect of vaccination on an outcome

- Data quality assessment for errors, anomalies, or missing/late-arriving data
- Analyses using different comparators than primary concurrent (e.g., un-boosted, unvaccinated or “historical” comparators) to supplement our primary analyses
- Additional investigations to provide context (e.g., background rates, etc.)
- Graphic displays of outcome incidence day by day after vaccination, using temporal scan statistics to assess apparent clustering
  - Examine the temporal clustering of outcome events in subgroups defined by demographics, site or simultaneous exposure (e.g., flu vaccine)
- If the signal is driven by a strong association in one subgroup or VSD site, further analyses by site or subgroup as appropriate
- Chart review to confirm cases and collect additional data (e.g., date of symptom onset).
- Consider epidemiologic studies to further investigate surveillance findings

Rapid Cycle Analysis (RCA) to monitor the safety of COVID-19 vaccines in near real-time within the Vaccine Safety Datalink. Available at: Rapid Cycle Analysis (RCA) to monitor the safety of COVID-19 vaccines in near real-time within the Vaccine Safety Datalink (cdc.gov)

VSD COVID-19 RCA analyses: Ischemic stroke after Pfizer-BioNTech bivalent booster among people ≥65 years of age

COVID-19 bivalent booster doses and influenza vaccine doses administered over time among persons aged ≥65 years, by vaccine type



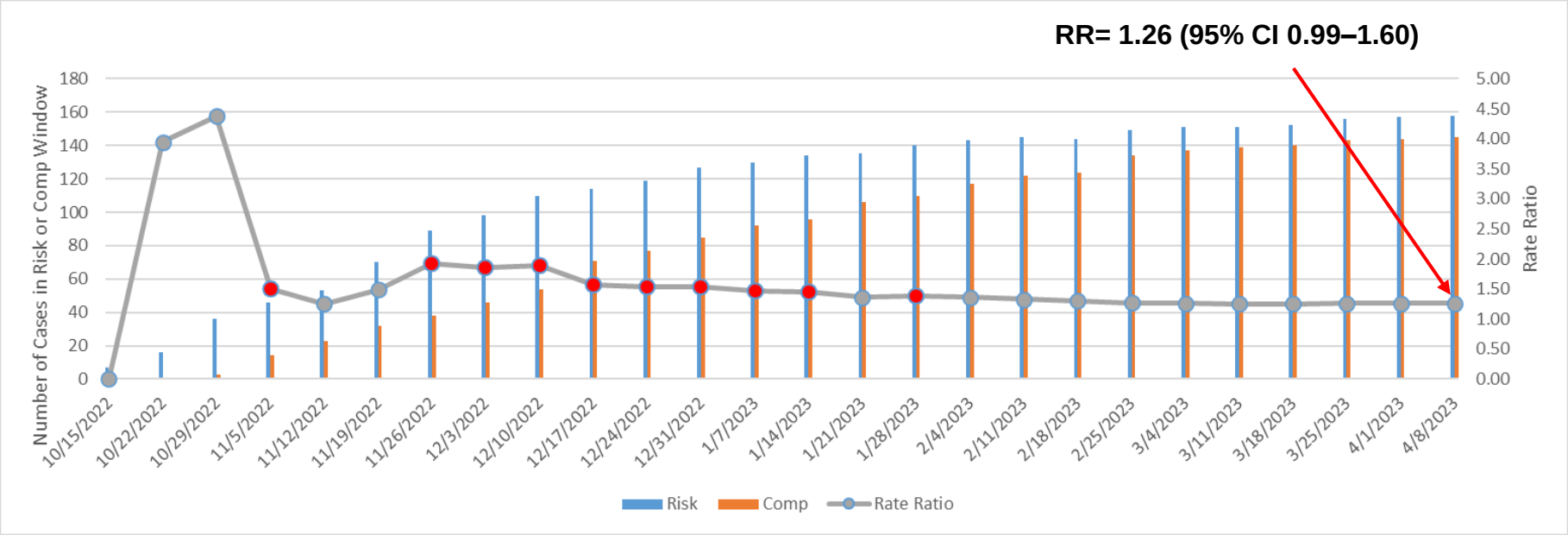
VSD RCA ischemic stroke definition

ICD-10 CODES TO FIND INCIDENT CASES	ICD-10 CODES FOR LOOKBACK TO ADJUST ONSET DATE (in all settings)	ICD-10 CODES - TO DETECT PREVALENCE (history of, in all settings)	ICD-10 CODES - OTHER CAUSE EXCLUSIONS (in all settings)
Stroke, ischemic (settings = Emergency, Inpatient)	**Codes to adjust Stroke, ischemic onset (if seen within 1 day before case)**	**Stroke, ischemic - Review for Prevalence - 1ST EVER**	**Other possible causes of Stroke, ischemic**
G45.8 Other transient cerebral ischemic attacks and related syndromes G45.9 Transient cerebral ischemic attack, unspecified I63.* Cerebral infarction	**Adjust onset date if occurs in the 1 day prior to incident case:** Z92.82 Status post administration of tPA (rtPA) in a different facility within the last 24 hours prior to admission to current facility R51.* Headache R47.* Speech disturbances, not elsewhere classified R29.810 Facial weakness R53.1 Weakness R42.* Dizziness and giddiness R41.82 Altered mental status, unspecified R40.4 Transient alternation of awareness G81.9* Hemiplegia, unspecified H53.9 Unspecified visual disturbance H53.13* Sudden visual loss	**Exclude if occurs EVER prior to incident case:** Z86.73 Personal history of transient ischemic attack (TIA), and cerebral infarction without residual deficits I69.* Sequelae of cerebrovascular disease	**Exclude if COVID-19 in the last 30 days prior to incident case (not including same day):** COVID-19 DIAGNOSIS **OR** COVID-19 POSITIVE LAB TEST **Exclude if occurs in the time period noted prior to incident case (not including same day):** I48.* Atrial fibrillation and flutter (if seen EVER prior to incident case) I21.* Acute myocardial infarction (if seen within 28 days prior to incident case) S15.* Injury of blood vessels at neck level (if seen within 1 day prior to incident case) I74.* Arterial embolism and thrombosis (if seen within 1 day prior to incident case) D57.* Sickle-cell disorders (if seen EVER prior to incident case) D68.5* Primary thrombophilia (if seen EVER prior to incident case)

Bivalent RCA concurrent comparator analyses of ischemic strokes during a 1–21-day Risk Interval versus a 22–42-day Comparison Interval (data through April 8, 2023)

				Nominal analysis		Sequential analysis	
Age group (years)	Vaccine	Risk events (N)	Comp events (N)	Adjusted Rate Ratio	95% Confidence Interval	1-sided p-value	Signal this week? 1-sided p <0.01
18–64	Pfizer	49	52	1.09	0.73–1.63	0.372	No
	Moderna	18	32	0.56	0.30–1.01	0.981	No
65+	Pfizer	158	145	1.26	0.99–1.60	0.032	No
	Moderna	80	77	1.21	0.87–1.68	0.142	No

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)

Supplemental RCA analyses: Ischemic strokes during the *1–21*-day interval comparing *bivalent boosted vs. un-boosted* concurrent comparators (but eligible for bivalent booster)*

Age group (years)	Interval (days)	Comparators	Vaccine	Risk events (N)	Comp events (N)	Adjusted Rate Ratio	95% Confidence Interval	P-value (2-sided)
65+	1–21	Not bivalent boosted	Pfizer	168	2536	1.01	0.86–1.19	0.907

* Analyses only included outcomes through April 8, 2023.

Post-signal analyses*: Ischemic stroke incidence during days 1–21 compared with days 22–42, among ≥65 years with and without simultaneous influenza vaccination

Analytic population	Cases in 1–21-day Risk Interval (N=139)	Cases in 22–42-day Comparison Interval (N=108)	Adjusted Rate Ratio** (95% CI)	P-value
Bivalent Pfizer + same-day high-dose or adjuvanted flu vaccine	43	27	1.59 (0.99–2.61)	0.06
Bivalent Pfizer + same day standard dose flu vaccine	8	11	0.73 (0.28–1.83)	0.50
Bivalent Pfizer without any same day flu vaccine	107	99	1.08 (0.82– 1.42)	0.58

* Analyses only include vaccination data through January 14, 2023, and stroke outcome data through Feb 25, 2023
** Adjusted by 5-year age groups

Ischemic stroke following bivalent Pfizer-BioNTech mRNA COVID-19 booster vaccination in people ages 65+ years

- **Statistical signal**
  - The statistical signal persisted during the November 2022–January 2023 timeframe
  - The rate ratio has slowly attenuated from 1.92 to 1.26 and has not met signaling criteria during the past 10 weekly analyses
- **Additional signal investigation analyses**
  - Supplemental analyses using un-boosted concurrent comparators showed a rate ratio RR=1.01 (95% CI 0.86–1.19; p-value 0.907)
  - Analyses evaluating simultaneous high-dose or adjuvanted flu vaccine showed a rate ratio RR=1.59 (95% CI 0.99–2.61; p-value 0.06)
    - Separate analyses did not detect an elevated RR for stroke after flu vaccine alone (data not shown)
  - Supplemental analyses suggest comparison interval (22–42 days) rates were lower than expected (data previously presented to ACIP February 24, 2023*)

* ACIP Meeting COVID-19 mRNA bivalent booster vaccine safety--February 24, 2023 (cdc.gov)

Vaccine Adverse Event Reporting System (VAERS)

VAERS is the nation's early warning system for vaccine safety

Vaccine Adverse Event Reporting System

http://vaers.hhs.gov

U.S. reports to VAERS following bivalent booster COVID-19 mRNA vaccination among ages ≥5 years* (as of April 2, 2023) (N=28,363)

Manufacturer	Median Age (IQR), years	Male† N (%)	Female† N (%)	Non-serious N (%)£	Serious N (%)	Doses admin‡
Pfizer-BioNTech	56 (35–69)	6,599 (38)	10,580 (61)	16,124 (93)	1,307 (8)	35,256,444
Moderna	62 (45–71)	4,159 (38)	6,620 (61)	10,209 (93)	725 (7)	19,900,255
Total	**59 (39–70)**	**10,758 (38)**	**17,198 (61)**	**26,331 (93)**	**2,032 (7)**	**55,156,699**

- **Distribution by age, sex, and serious status similar regardless of manufacturer**
  - Most reports (93%) were non-serious

* Includes reports after Moderna bivalent booster among ages ≥6 years

† Excludes 407 (1%) reports where sex was not reported

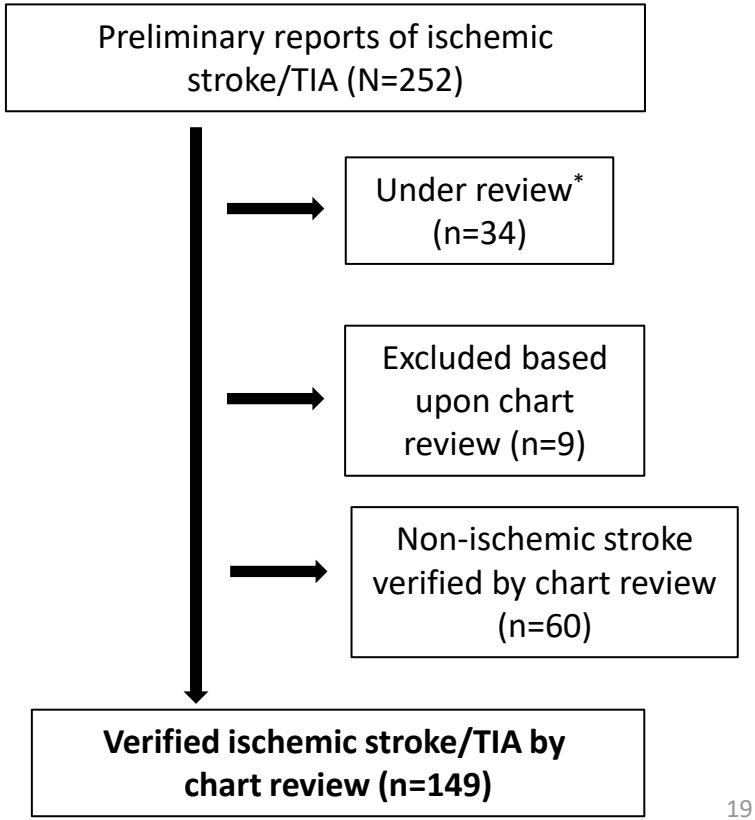
£ 2 reports documented receipt of Moderna and Pfizer Bivalent, they are counted in each group but only counted once total

‡ Doses administered among children ages 5–11 years vaccinated during October 18, 2022–March 29, 2023

Reports to VAERS of ischemic stroke/transient ischemic attack (TIA) after bivalent COVID-19 mRNA vaccination in people ages ≥18 years

(as of April 2, 2023)

- 149 verified reports of ischemic stroke/TIA
  - Ischemic stroke (110), TIA (35), ischemic stroke + TIA (4)
  - Pfizer-BioNTech bivalent (112), Moderna bivalent (37)
  - Median age: 72 years (IQR: 66–79 years)
  - Median time to onset: 13 days (IQR: 4–29 days)
  - 68 males, 81 females
  - All verified reports (149, 100%) had at least one risk factor for ischemic stroke
    - The most common was hypertension (89, 60%)
  - Simultaneous influenza vaccination
    - 18–64 years: standard dose (6)
    - ≥65 years: high-dose (10), adjuvanted (3), standard dose (2), unknown type (1)



* Awaiting medical records and/or healthcare provider interview; some still processing

VAERS reports and reporting rates of ischemic stroke/TIA in the 3 weeks after mRNA COVID-19 bivalent vaccination in people ages 18–39, 40–64, and ≥65 years

(as of April 2, 2023)

		Chart-verified reports			Chart-verified reports + reports under review			Background
Age group (years)	Vaccine	Obs reports	Doses admin*	Reporting rate (per million doses admin)	Obs reports	Doses admin*	Reporting rate (per million doses admin)	Exp cases†
18–39	Pfizer-BioNTech	3	6,334,671	0.5	3	6,334,671	0.5	88
18–39	Moderna	0	3,048,913	0	1	3,048,913	0.3	42
40–64	Pfizer-BioNTech	13	12,419,399	1.0	17	12,419,399	1.4	1,168
40–64	Moderna	4	7,028,873	0.6	5	7,028,873	0.7	661
≥65	Pfizer-BioNTech	51	13,693,161	3.7	60	13,693,161	4.4	4,993
≥65	Moderna	19	9,622,716	2.0	23	9,622,716	2.4	3,509

* Doses administered as of April 5, 2023

† Ramirez et al. Trends in Transient Ischemic Attack Hospitalizations in the United States. *J Am Heart Assoc*. 2016;5(9):e004026. (Estimated expected cases based upon observed annual incidence in 2010 for ages 25–44, 45–54, and 65–84 years, adjusted for period corresponding to 3 weeks after vaccination).

VAERS monitoring: COVID-19 mRNA bivalent booster vaccination and ischemic stroke

- No unusual or unexpected reporting patterns observed, and no evidence of a safety concern detected for ischemic stroke with either mRNA COVID-19 bivalent boosters in VAERS monitoring

Summary

COVID-19 mRNA bivalent booster vaccination safety – data from other monitoring systems and programs*

- FDA monitoring in the CMS data and Department of Veterans Affairs monitoring in the VA system have not detected any safety signals for ischemic stroke following COVID-19 mRNA bivalent boosters using historical comparator designs
- Surveillance conducted by international regulatory and public health partners has not detected a safety concern for ischemic stroke following bivalent COVID-19 mRNA booster vaccination
- No evidence of a safety signal for ischemic stroke in Pfizer's global monitoring of bivalent COVID-19 mRNA booster vaccination
- No safety signals were detected for ischemic stroke for ***primary series*** or ***monovalent boosters*** for Pfizer-BioNTech or Moderna COVID-19 vaccines in U.S. and global monitoring

* These surveillance activities did not include analyses to evaluate the effect of simultaneous flu vaccination; different formulations of COVID-19 mRNA bivalent booster vaccinations were used globally

Further evaluation and key next steps

Further evaluation

- Consult with other surveillance systems to better understand:
  - Possible role of simultaneous high-dose or adjuvanted flu vaccination with COVID-19 vaccination
  - Possible decreased rate of stroke observed in VSD in the 3–6 weeks following vaccination
- In the process of chart reviewing a random sample of 100 cases across VSD sites
- Continue monitoring in VAERS

Key next steps

- CDC continues to recommend that everyone eligible for a COVID-19 mRNA bivalent booster or a flu vaccine get vaccinated
- CDC and FDA are engaged in epidemiologic analyses regarding simultaneous vaccination with COVID-19 mRNA bivalent booster and flu vaccines

Acknowledgements

- CDC Immunization Safety Office
  - VAERS Team
  - V-safe Team
  - Clinical Immunization Safety Assessment (CISA) Project
  - Vaccine Safety Datalink (VSD) Team
- COVID-19 Vaccine Task Force Data Monitoring and Reporting Group
- Kaiser Permanente Northern California (VSD)
- Marshfield Clinic Research Institute (VSD)
- VSD sites
  - HealthPartners Institute, Minneapolis, MN
  - Kaiser Permanente Colorado, Denver, CO
  - Kaiser Permanente Northwest, Portland, OR
  - Kaiser Permanente Southern California, Los Angeles, CA
  - Kaiser Permanente Washington, Seattle, WA
  - Denver Health, Denver, CO

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- The findings and conclusions in this presentation are those of the presenters and do not necessarily represent the official position of the CDC
- Mention of a product or company name is for identification purposes only and does not constitute endorsement by CDC
- Dr. Nicola Klein reports research support from Pfizer for COVID-19 vaccine clinical trials and from Pfizer, GlaxoSmithKline, Merck and Sanofi Pasteur for unrelated studies

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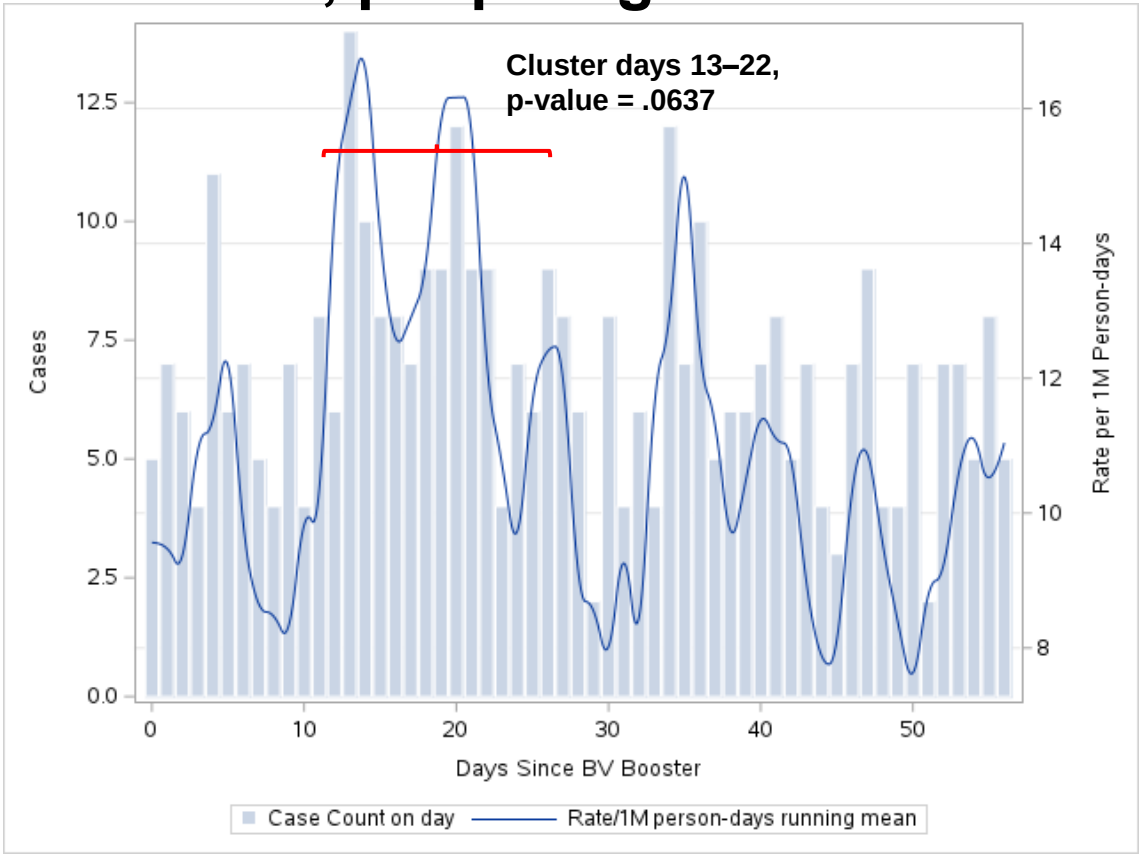
Extra Slides

Ischemic stroke by day after Pfizer-BioNTech bivalent boosters, people ages ≥65 Years*



* Data cutoff 2/28/2023