COVID-19 mRNA bivalent booster vaccine safety

Advisory Committee on Immunization Practices (ACIP) meeting

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Tom T. Shimabukuro, MD, MPH, MBA
Director, Immunization Safety Office
Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention (CDC)

Topics

- Describe CDC's Vaccine Safety Datalink (VSD) Rapid Cycle Analysis (RCA) monitoring methods and assessment processes for statistical signals
- Describe VSD RCA signal detection and signal assessment for ischemic stroke after Pfizer-BioNTech COVID-19 mRNA bivalent booster dose vaccination in the age group 65 years and older
- Describe rates of myocarditis/pericarditis following COVID-19 mRNA vaccination

Background: COVID-19 mRNA bivalent booster vaccination in the United States

- Bivalent COVID-19 mRNA booster vaccinations first became available in the United States in September 2022
- As of February 8, 2023, 52.5 million COVID-19 mRNA bivalent booster doses administered in people ages 5 years and older in the United States*
  - Includes 22.3 million doses in people ages 65 years and older*
- CDC and partners monitor the safety of licensed and authorized U.S. vaccines using multiple complementary systems (Vaccine Information and Safety Studies | Vaccine Safety | CDC)
- Safety data support CDC recommendations that everyone eligible for a COVID-19 mRNA bivalent booster get vaccinated

* CDC COVID Data Tracker: Vaccinations in the US

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

Prepared by:
Kaiser Permanente Northern California Vaccine Study Center

Presented by Tom Shimabukuro, MD, MPH, MBA
Centers for Disease Control and Prevention

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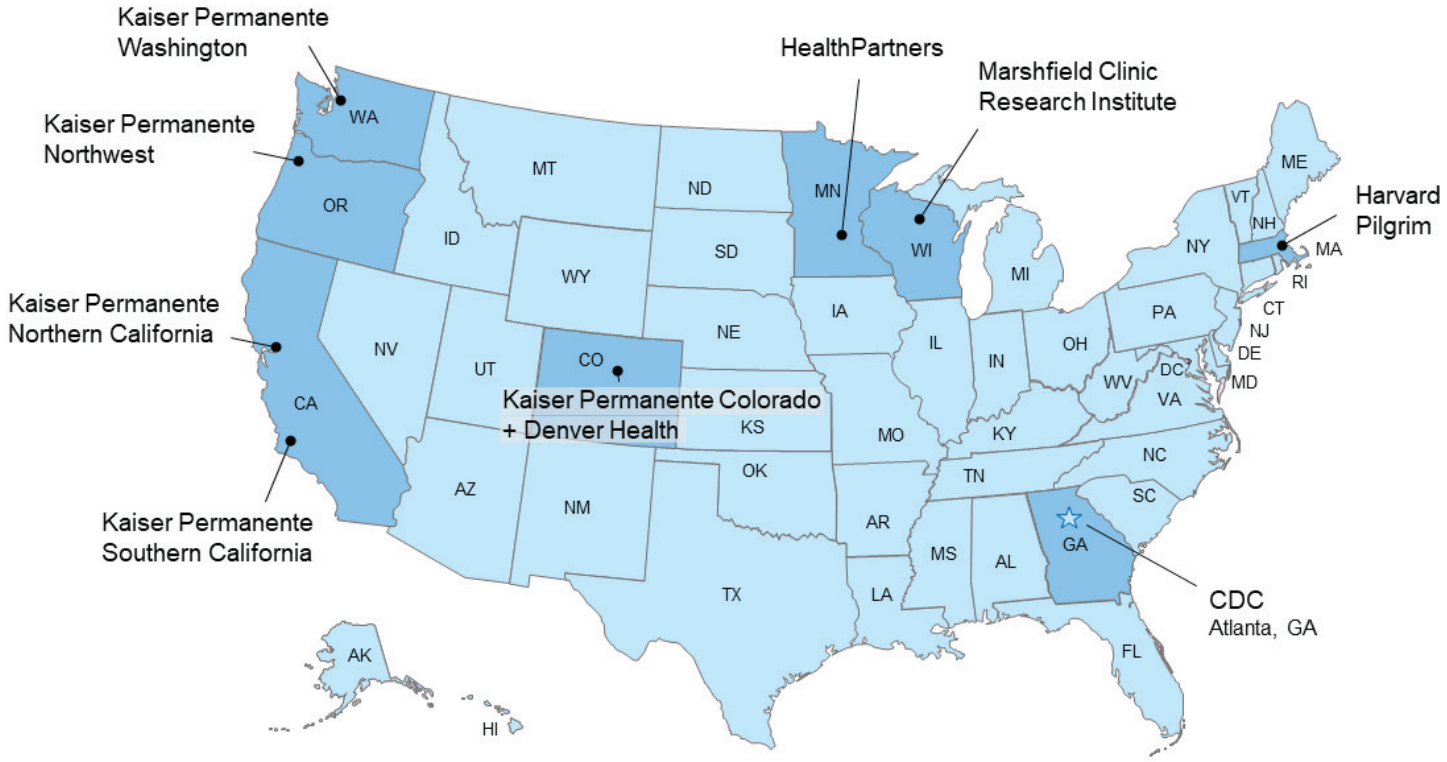
Vaccine Safety Datalink (VSD)



- 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

Strengths of VSD Rapid Cycle Analysis (RCA)

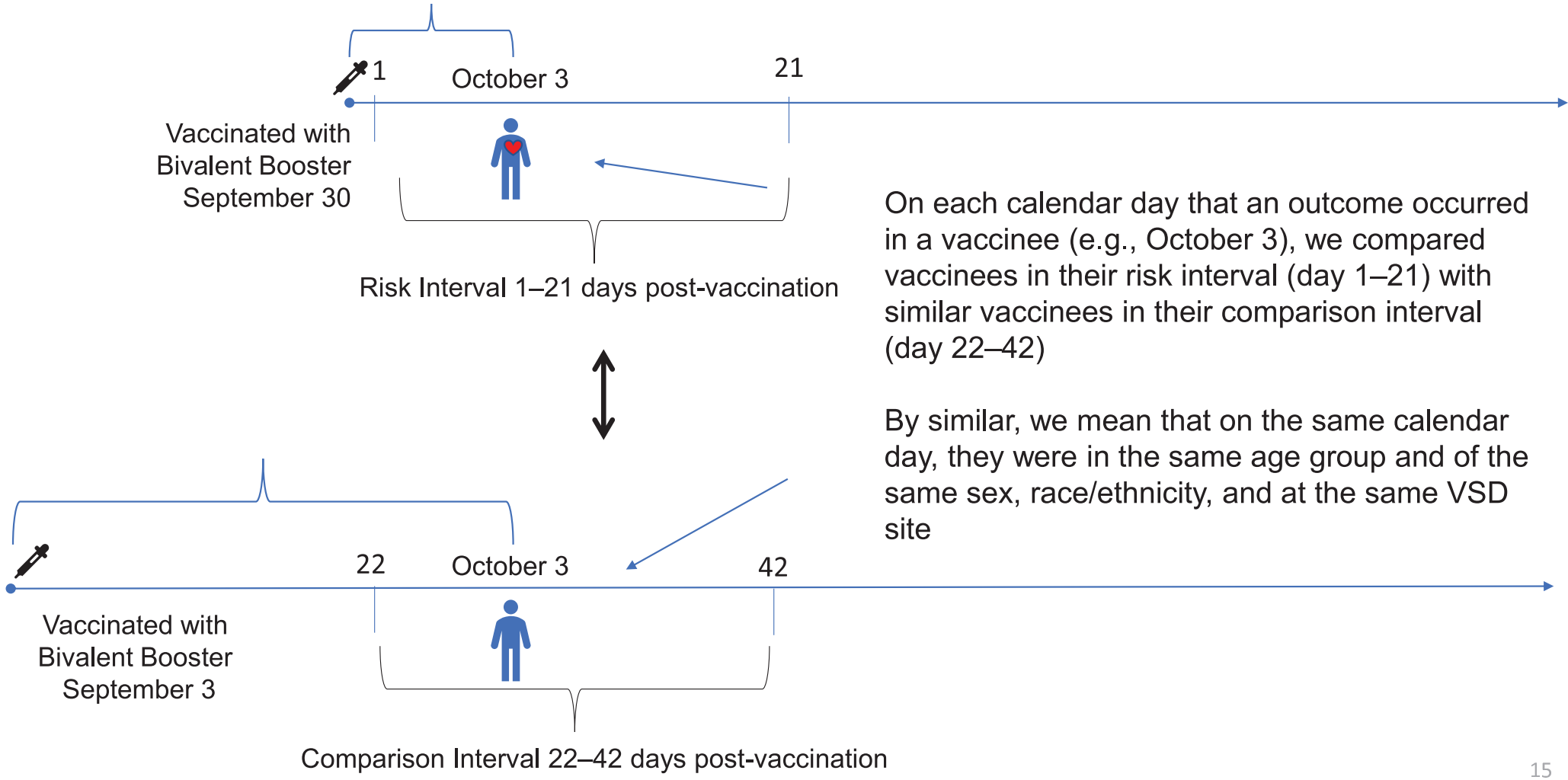
- **Population**
  - ~12.5 million people (equal to ~4% of the U.S. population) across VSD data sites are geographically and racially/ethnically diverse
- **Data**
  - Near real-time data, with analyses updated weekly
  - Access to comprehensive medical records, including exposures (vaccination) and outcomes, allowing rapid chart reviews to obtain additional clinical information as needed
- **Innovative Methods**
  - *Vaccinated concurrent comparators:* Recent vaccinees as comparators are expected to be more similar to current vaccinees than unvaccinated individuals with the following advantages
    - Careful adjustment for potential biases associated with calendar time, site, and demographic factors
    - Analyses can begin sooner than alternative methods
  - *Supplemental analyses conducted weekly:* Unvaccinated/un-boosted comparators would also be available to provide context in real time
  - Using vaccinated concurrent comparators with supplemental analyses offers substantial benefits compared with either unvaccinated or historical comparators

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
  - 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)

Vaccinee with outcome in the risk interval and a concurrent comparator "bivalent vaccinated individuals only"



On each calendar day that an outcome occurred in a vaccinee (e.g., October 3), we compared vaccinees in their risk interval (day 1–21) with similar vaccinees in their comparison interval (day 22–42)

By similar, we mean that on the same calendar day, they were in the same age group and of the same sex, race/ethnicity, and at the same VSD site

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

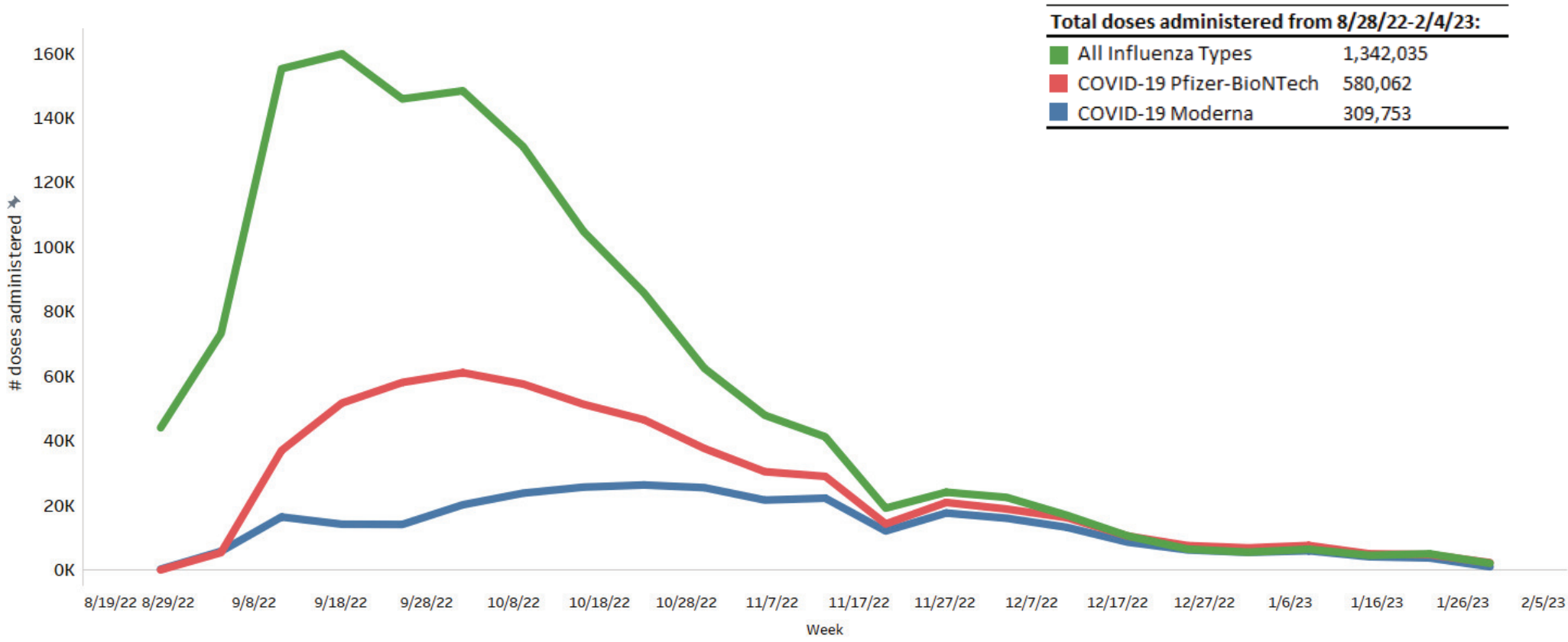
VSD investigations of an RCA signal to assess whether it reflects a real effect of vaccination on an outcome

- 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 preliminary analyses: Ischemic stroke after Pfizer-BioNTech bivalent booster among people ≥65 years of age

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



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*

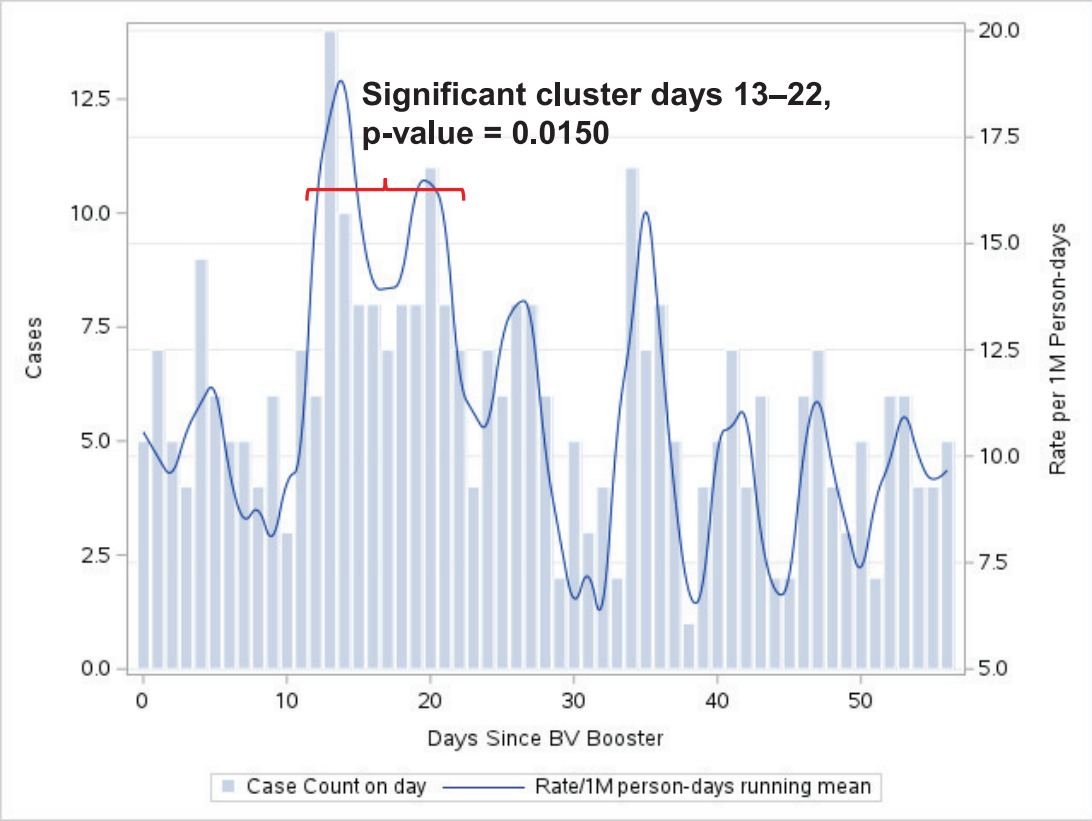
				Nominal analysis		Sequential analysis	
Age group (years)	**Vaccine**	**Risk events (N)**	**Comp events (N)**	**Adjusted Rate Ratio**	**95% Confidence Interval**	**1-sided p-value**	**Signal? 1-sided p <0.01**
18–64	Pfizer	39	38	1.09	0.68 – 1.75	0.398	No
	Moderna	14	26	0.49	0.24 – 0.95	0.990	No
65+	**Pfizer**	**143**	**117**	**1.36**	**1.05 – 1.76**	**0.011**	**No**
	Moderna	68	63	1.17	0.82 – 1.67	0.224	No

* Data through Feb 4, 2023

Ischemic stroke after Pfizer-BioNTech bivalent booster, age ≥65 years, counts and adjusted rate ratios (Oct 16, 2022 – Feb 4, 2023)

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

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



* Data cutoff 3 weeks prior

Ischemic stroke *preliminary* chart review: Cases ≥65 years old during days 11–21 post-Pfizer-BioNTech bivalent booster vaccination

- Review of a subset of cases at one site (N=24); 22 of 24 were incident stroke/TIA (pos. pred. value 92%)
  - None had any history of stroke or transient ischemic attack (TIA)
  - Median age of verified cases was 77.5 years
  - Symptom onset date rarely shifted from electronic date
  - 5 (23%) with known history of SARS-CoV-2 infection, only 1 within last 6 months
  - 0 with mention of recent exposure to SARS-CoV-2 in chart notes
  - 14 (64%) had simultaneous flu vaccination on the same day (13 high-dose flu vaccines and 1 adjuvanted flu vaccine)
- Outcomes
  - 13 of 22 (59%) discharged home
  - 4 of 22 (18%) discharged home with home health
  - 2 of 22 (9%) discharged to a skilled nursing facility
  - 3 of 22 (14%) died
    - One death in a 75–79-year-old male ~1 month after stroke; death was likely related to the stroke
    - One stroke in a 65–69-year-old female noted after craniotomy, though relationship with surgery unclear; death due to cardiac arrest ~2.5 months later
    - One stroke in a 70–74-year-old male during hospitalization for metastatic cancer, with subsequent death due to cancer-related complications during hospitalization
- Currently reviewing a random sample of risk and comparison interval cases across VSD sites

Supplemental 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	134	1510	1.07	0.89–1.28	0.483

* Analyses only included outcomes through December 10, 2022.

Supplemental analyses:
Ischemic strokes during the 1–21 and *22–42*-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	134	1510	1.07	0.89–1.28	0.483
	22–42	Not bivalent boosted	Pfizer	83	1081	**0.76**	0.60–0.95	**0.018**

* Analyses only included outcomes through December 10, 2022.

- **Findings suggest reduced rate of stroke in comparison interval**

Post-signal analyses: Simultaneous high-dose or adjuvanted influenza vaccines

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	26	**1.65 (1.02 – 2.72)**	**0.04**
Bivalent Pfizer + same day standard dose flu vaccine	8	8	1.00 (0.36 – 2.76)	1.00
Bivalent Pfizer without any same day flu vaccine	88	74	1.19 (0.87 – 1.62)	0.27

* Analyses only include vaccination data through December 3, 2022, and stroke outcome data through January 14, 2023
** Adjusted by 5-year age groups

Post-signal analyses*:
Expected cases after bivalent booster + high-dose or adjuvanted flu vaccine, based on ischemic stroke incidence in un-boosted people eligible for a booster

Age at vaccination	Expected cases in a 3-week interval (Risk or Comparison)	Observed cases in a 1–21-day Risk Interval (N)	Observed cases in 22–42-day Comparison Interval (N)
65–69 years	7.3	8	6
70–74 years	8.5	8	7
75–79 years	9.8	11	6
80–84 years	6.3	8	3
85–89 years	4.2	5	4
90+ years	2.5	3	0
Total	**38.7**	**43**	**26**

* Analyses only include vaccination data through December 3, 2022, and stroke outcome data through January 14, 2023

- **Findings also suggest reduced rate of stroke in comparison interval**

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

- **Statistical signal persistent for 8 weeks**
  - Rate ratio has slowly attenuated from 1.92 to 1.36 and intermittently met signaling criteria
- **Additional signal investigation analyses**
  - Temporal clustering evaluation found a significant cluster 13–22 days after vaccination
  - Supplemental analyses using un-boosted concurrent comparators showed a rate ratio RR=1.07 (95% CI 0.89–1.28)
  - Of small subset of charts reviewed, most confirmed cases had simultaneous high-dose or adjuvanted flu vaccine
  - Analyses evaluating simultaneous high-dose or adjuvanted flu vaccine showed a rate ratio RR=1.65 (95% CI 1.02–2.72; p-value 0.04)
    - 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

Additional considerations

- **Small numbers of strokes and imprecise rate ratios limit some analyses**
  - Reduced follow-up time after Moderna booster due to distribution delays
  - Simultaneous flu vaccine analyses limited by small numbers
- **Difficult to interpret temporal clustering during risk and comparison intervals**
- **Possible unmeasured confounding**
  - Results may be influenced by confounders that vary over time
  - Do early adopters of bivalent booster vaccine have greater risk of near-term cardiovascular events?
    - Same trend has not been observed for acute myocardial infarctions
    - Potential impact of differential vaccine availability after EUA (Pfizer-BioNTech > Moderna)
- **Possible role of SARS-CoV-2 infection before booster?**
  - Background incidence of SARS-CoV-2 infection was rapidly changing during bivalent booster uptake
    - Analysis excluded cases with COVID-19 diagnosis or positive test in prior 30 days, although asymptomatic infections and home antigen tests are not consistently documented in EHR; however, KPNC chart reviews did not find recent SARS-CoV-2 infection or exposure

Further evaluation and key next steps

Further evaluation

- Continue to monitor weekly and explore potential data-related explanations for the statistical signal in VSD
- In the process of chart reviewing a random sample of 100 cases across VSD sites
- 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 in the 3–6 weeks following vaccination

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 of COVID-19 mRNA bivalent booster and flu vaccines

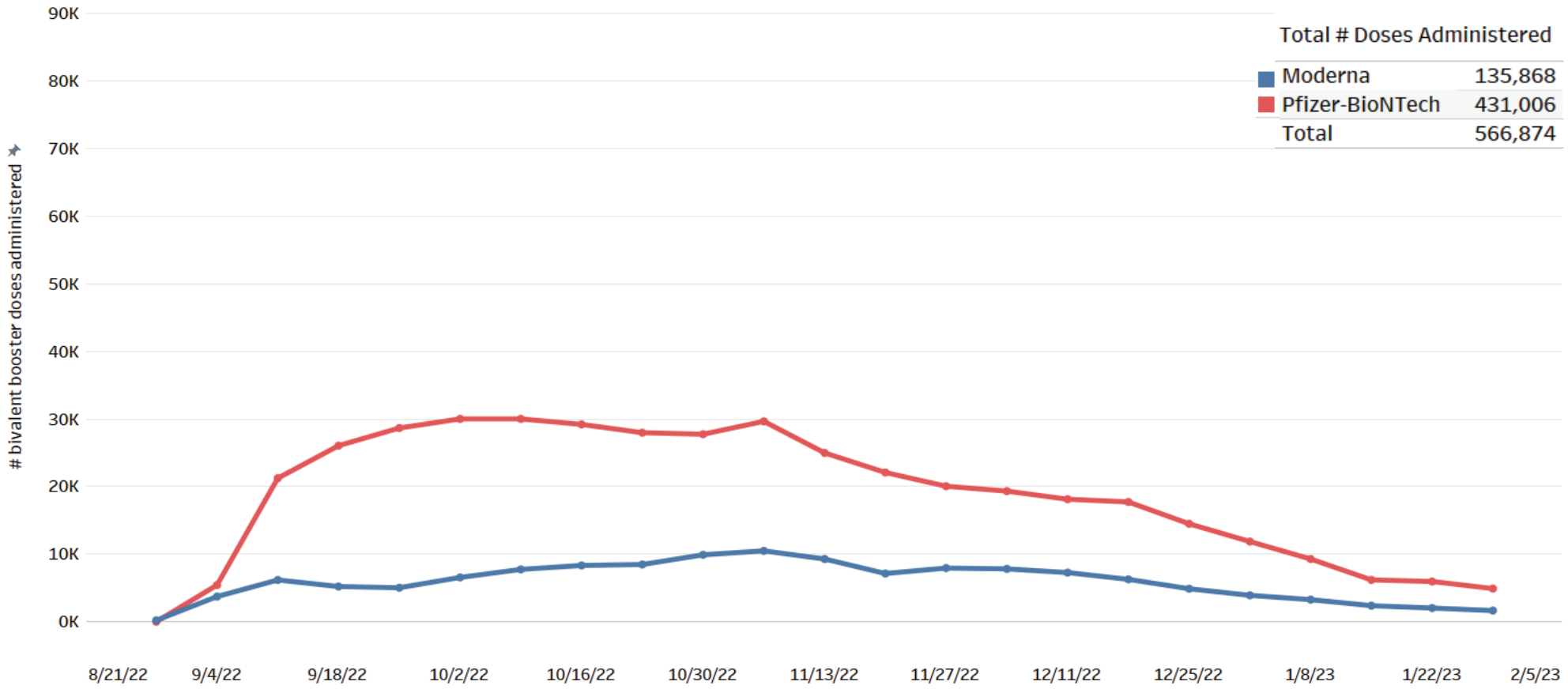
COVID-19 mRNA bivalent booster vaccination safety – data from other monitoring systems and programs*

- No unusual or unexpected reporting patterns observed, and no evidence of a safety concern detected for ischemic stroke with either COVID-19 mRNA bivalent boosters in Vaccine Adverse Event Reporting System (VAERS) monitoring (see supplemental slides)
- 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

Myocarditis/pericarditis following COVID-19 mRNA vaccination in VSD

Number of COVID-19 bivalent booster doses administered over time among persons aged 12-39 years, by vaccine type in VSD



* Bivalent booster data through January 29, 2023

VSD incidence rates of verified myocarditis or pericarditis in the 0–7 days after Pfizer-BioNTech vaccination in people ages 12–39 years*

	Dose 2 primary series Pfizer-BioNTech			1st monovalent booster dose Pfizer-BioNTech			Bivalent booster dose Pfizer-BioNTech		
Age/sex	Cases	Dose 2 total	Incidence rate/ million doses (95% CI)	Cases	1st booster total	Incidence rate/ million doses (95% CI)	Cases	Bivalent booster total	Incidence rate/ million doses (95% CI)
12–17 years									
Males	45	308,046	146.1 (106.6–195.5)	14	129,487	108.1 (59.1–181.4)	0	48,066	0.0 (0.0–62.3)
Females	6	311,247	19.3 (7.1–42.0)	2	139,118	14.4 (1.7–51.9)	0	49,725	0.0 (0.0–60.2)
18–29 years									
Males	27	331,889	81.4 (53.6–118.4)	7	166,973	41.9 (16.9–86.4)	1	50,687	19.7 (0.5–53.1)
Females	2	400,321	5.0 (0.6–18.0)	1	240,226	4.2 (0.1–23.2)	0	80,211	0.0 (0.0–37.3)
30–39 years									
Males	5	341,527	14.6 (4.8–34.2)	3	197,554	15.2 (3.1–44.4)	0	82,191	0.0 (0.0–36.4)
Females	3	410,713	7.3 (1.5–21.3)	1	268,412	3.7 (0.1–20.8)	0	115,014	0.0 (0.0–26.0)

* Primary series and 1st monovalent booster data through August 20, 2022, bivalent booster data through January 29, 2023; Source: Goddard K, et al. Incidence of Myocarditis/Pericarditis Following mRNA COVID-19 Vaccination Among Children and Younger Adults in the United States. Ann Intern Med. 2022;175:1169-1771.

VSD incidence rates of verified myocarditis or pericarditis in the 0–7 days after Moderna vaccination in people ages 18–39 years*

	Dose 2 primary series Moderna			1st monovalent booster dose Moderna			Bivalent booster dose Moderna		
Age/sex	Cases	Dose 2 total	Incidence rate/ million doses (95% CI)	Cases	1st booster total	Incidence rate/ million doses (95% CI)	Cases	Bivalent booster total	Incidence rate/ million doses (95% CI)
18–29 years									
Males	19	195,809	97.0 (58.4 – 151.5)	7	109,337	64.0 (25.7 – 131.9)	0	18,499	0.0 (0.0–161.9)
Females	0	243,560	0.0 (0.0 – 12.3)	1	156,707	6.4 (0.2 – 35.6)	0	29,561	0.0 (0.0–101.3)
30–39 years									
Males	8	216,583	36.9 (15.9 – 72.8)	1	149,468	6.7 (0.2 – 37.3)	0	35,318	0.0 (0.0–84.8)
Females	1	259,780	3.9 (0.1 – 21.4)	2	191,765	10.4 (1.3 – 37.7)	0	47,620	0.0 (0.0–62.9)

* Primary series and 1st monovalent booster data through August 20, 2022, bivalent booster data through January 29, 2023; source: Goddard K, et al. Incidence of Myocarditis/Pericarditis Following mRNA COVID-19 Vaccination Among Children and Younger Adults in the United States. Ann Intern Med. 2022;175:1169-1771.

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Disclaimer/disclosures

- 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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VAERS and v-safe supplemental slides

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

CDC + FDA

VAERS

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 February 6, 2023) (N=23,395)

Manufacturer	Median Age (IQR), years	Male† N (%)	Female† N (%)	Non-serious N (%)	Serious N (%)	Doses admin‡
Pfizer-BioNTech	54 (33–69)	5,450 (38)	8,750 (61)	13,496 (93)	944 (7)	33,676,379
Moderna	61 (44–71)	3,378 (38)	5,457 (61)	8,460 (94)	495 (6)	19,076,635
Total	**58 (37–70)**	**8,828 (38)**	**14,207 (61)**	**21,956 (94)**	**1,439 (6)**	**52,753,014**

- **Distribution by age, sex, and serious status similar regardless of manufacturer**
  - Most reports (94%) were non-serious
  - Race, ethnicity distribution comparable to monovalent COVID-19 mRNA vaccines (49% race and/or ethnicity unknown; 39% non-Hispanic white)

* Includes reports after Moderna bivalent booster among ages ≥6 years; † Excludes 360 (2%) reports where sex was not reported

‡ Doses administered among children ages 5–11 years vaccinated during October 18, 2022–February 8, 2023

Most frequent MedDRA Preferred Terms* to VAERS following *Pfizer-BioNTech* bivalent booster vaccination among people ages ≥5 years (as of February 6, 2023)

Non-serious reports (N=13,496)†

Rank	MedDRA PT (not mutually exclusive)	n (%)
1	COVID-19	1,785 (13)
2	Fatigue	1,091 (8)
3	Headache	1,067 (8)
4	Pyrexia/fever	1,016 (8)
5	SARS-CoV-2 test positive	974 (7)
6	Pain	969 (7)
7	Cough	779 (6)
8	Chills	677 (5)
9	Dizziness	571 (4)
10	Pain in extremity	554 (4)

Serious reports (N=944)

Rank	MedDRA PT (not mutually exclusive)	n (%)
1	COVID-19	274 (29)
2	SARS-CoV-2 test positive	238 (25)
3	Dyspoena	138 (15)
4	Asthenia	109 (12)
5	Condition aggravated	93 (10)
6	Pyrexia/fever	87 (9)
7	Death‡	83 (9)
8	Cerebrovascular accident	72 (8)
9	Cough	71 (8)
10	Fatigue	69 (7)

* Medical Dictionary for Regulatory Activities Preferred Terms (https://www.meddra.org/how-to-use/basics/hierarchy)
† Clinical outcomes only, as determined by subject matter expert consensus
‡ Median age 80 years (IQR: 72–88)

Most frequent MedDRA Preferred Terms* to VAERS following *Moderna* bivalent booster vaccination among people ages ≥6 years (as of February 6, 2023)

Non-serious reports (N=8,460)†

Rank	MedDRA PT (not mutually exclusive)	n (%)
1	COVID-19	877 (10)
2	Headache	863 (10)
3	Pyrexia/fever	858 (10)
4	Fatigue	837 (10)
5	SARS-CoV-2 test positive	792 (9)
6	Pain	751 (9)
7	Cough	604 (7)
8	Chills	536 (6)
9	Pain in extremity	440 (5)
10	Oropharyngeal pain	404 (5)

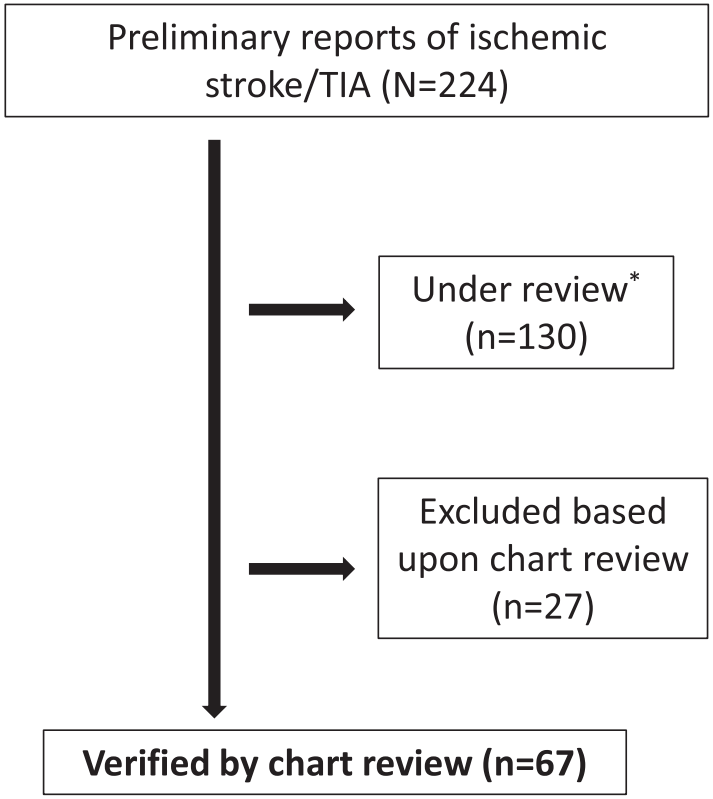
Serious reports (N=495)

Rank	MedDRA PT (not mutually exclusive)	n (%)
1	COVID-19	146 (30)
2	SARS-CoV-2 test positive	134 (27)
3	Dyspnoea	86 (17)
4	Condition aggravated	50 (10)
5	Death‡	47 (9)
6	Asthenia	46 (9)
7	Pyrexia/fever	45 (9)
8	Cough	44 (9)
9	Anticoagulant therapy	42 (8)
10	Dizziness	38 (8)

* Medical Dictionary for Regulatory Activities Preferred Terms (https://www.meddra.org/how-to-use/basics/hierarchy)
† Clinical outcomes only, as determined by subject matter expert consensus
‡ Median age 75 years (IQR: 66–84)

Reports to VAERS of ischemic stroke/transient ischemic attack (TIA) after bivalent COVID-19 mRNA vaccination (as of February 6, 2023)

- 67 verified reports of ischemic stroke/TIA
  - Median age: 73 years (IQR: 67–79 years)
  - Median time to onset: 8 days (IQR: 3–24 days)
  - 28 males, 39 females
  - 47 after Pfizer-BioNTech bivalent
  - 20 after Moderna bivalent



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

Reporting rate to VAERS of ischemic stroke/transient ischemic attack after bivalent COVID-19 mRNA vaccine in people ages ≥65 years

(as of February 6, 2023)

	Chart-verified reports			Chart-verified reports + reports under review		
Manufacturer	**Reports**	**Doses administered***	**Reporting rate (per million doses administered)**	**Reports**	**Doses administered***	**Reporting rate (per million doses administered)**
Pfizer-BioNTech	47	13,217,119	**2.9**	139	13,217,119	**8.4**
Moderna	20	9,268,318	**1.9**	58	9,268,318	**4.8**

- Incidence of ischemic stroke among people ages ≥65 years = 670–970 per 100,000 person years[†]

* Doses administered as of Feb 9, 2023; [†] Roger et al. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. Circulation 2011;123:e18–e209

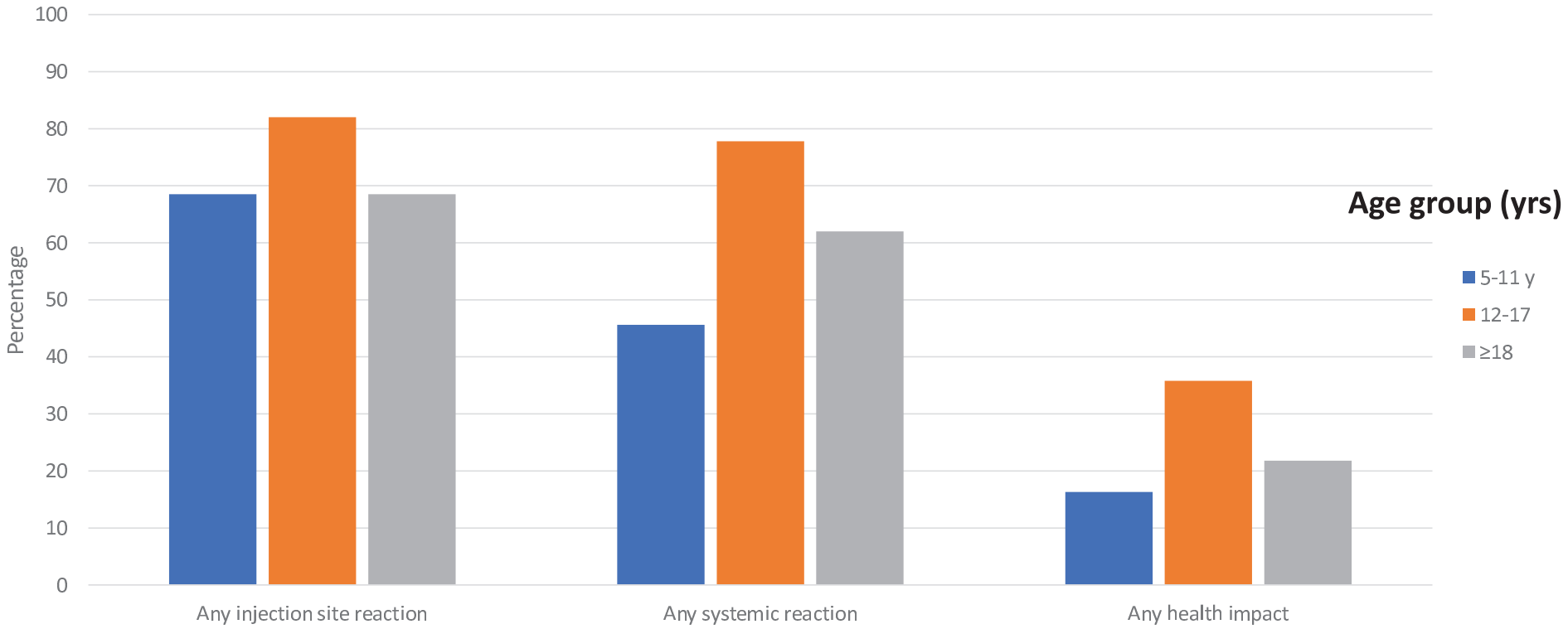
V-safe: Smartphone-based active safety monitoring

v-safe[SM]
after vaccination
health checker

https://vsafe.cdc.gov

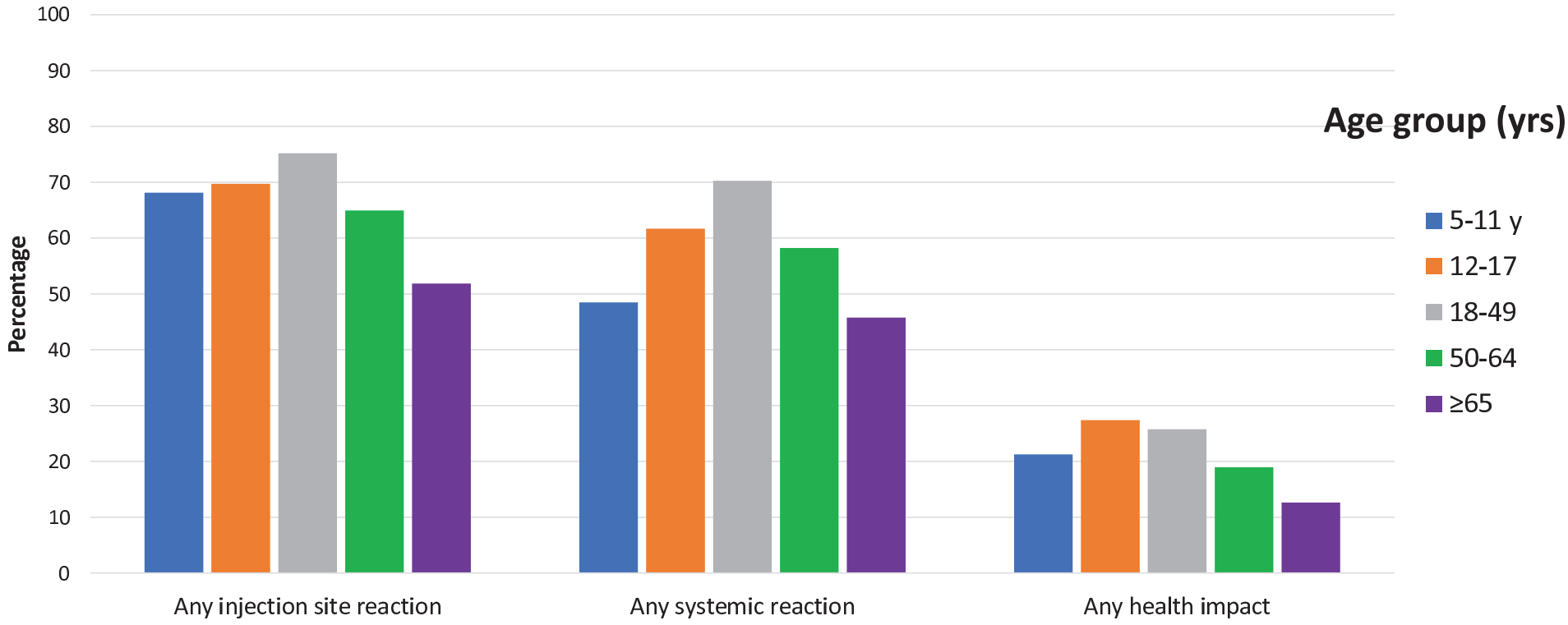
Enroll yourself or your dependent after any dose!

Reactions and health impacts reported by v-safe participants aged ≥5 years at least once 0-7 days after *first monovalent booster* dose, by age group



Data for participants aged ≥18 years as of October 23, 2022. Includes 677,009 participants who completed at least 1 survey in the first week after mRNA booster dose.
Data for participants aged 12-17 years as of February 20, 2022. Includes 3,418 participants who completed at least 1 survey in the first week after homologous booster dose.
Data for participants aged 5-11 years as of July 31, 2022. Includes 3,249 participants who completed at least 1 survey in the first week after homologous booster dose.

Reactions and health impacts reported by v-safe participants aged ≥5 years at least once 0-7 days after *bivalent booster dose*, by age group



Data for participants aged ≥12 years as of October 23, 2022. Includes 311,205 participants who completed at least 1 survey in the first week after booster dose.
Data for participants aged 5-11 years as of February 5, 2023. Includes 3,588 participants who completed at least 1 survey in the first week after booster dose.