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COVID-19 mRNA bivalent booster vaccine safety

Vaccines and Related Biological Products Advisory Committee meeting

January 26, 2023

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Objectives

- 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
- Describe further evaluation and key next steps

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 January 11, 2023, 49.5 million COVID-19 mRNA bivalent booster doses administered in people ages 5 years and older in the United States*
  - Includes 21.3 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 continue to 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 RCA: Preliminary Analyses of Ischemic Stroke after Pfizer Bivalent Booster Dose

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VACCINE STUDY CENTER

CDC

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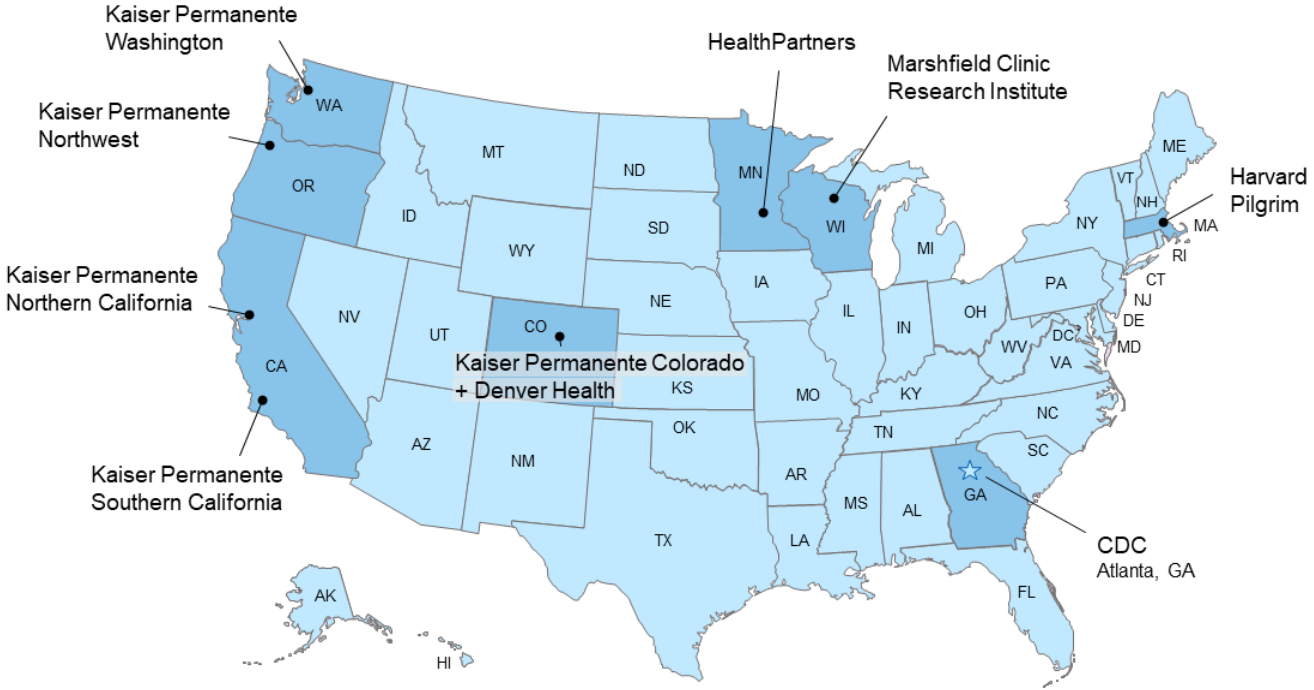
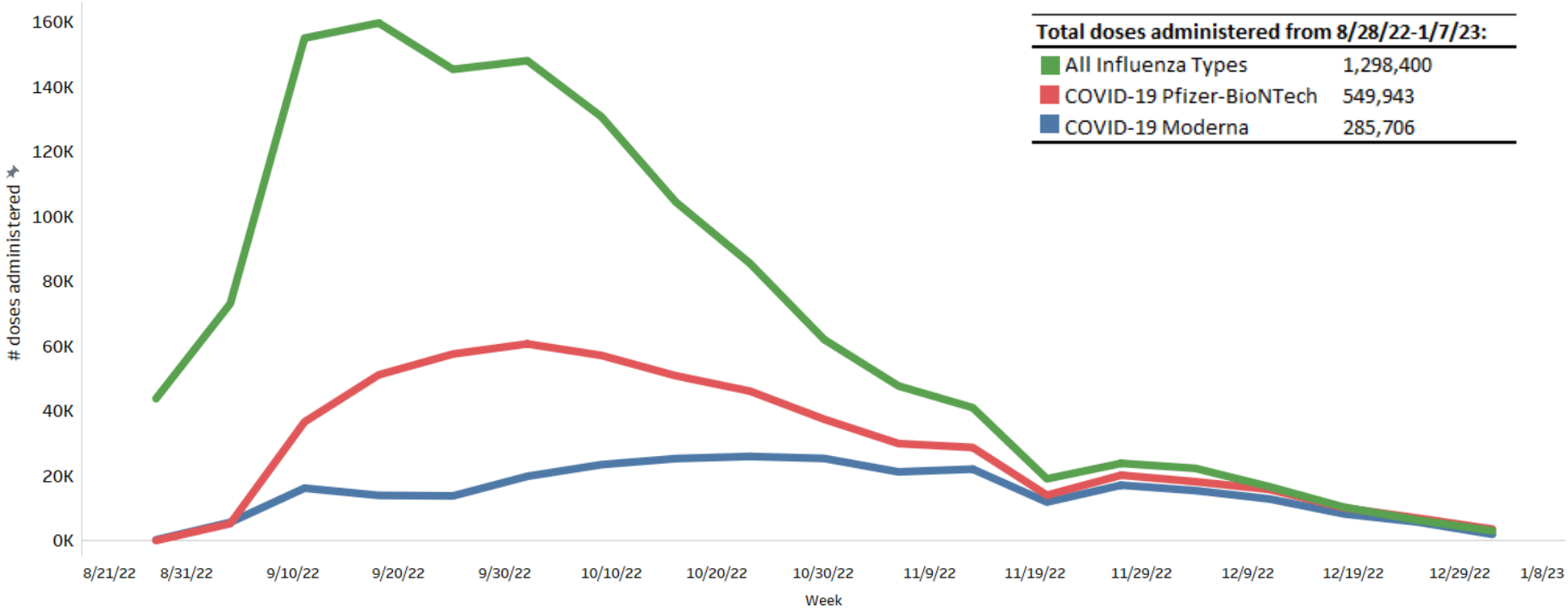
Research Institute

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

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



Strengths of VSD Rapid Cycle Analysis

- **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

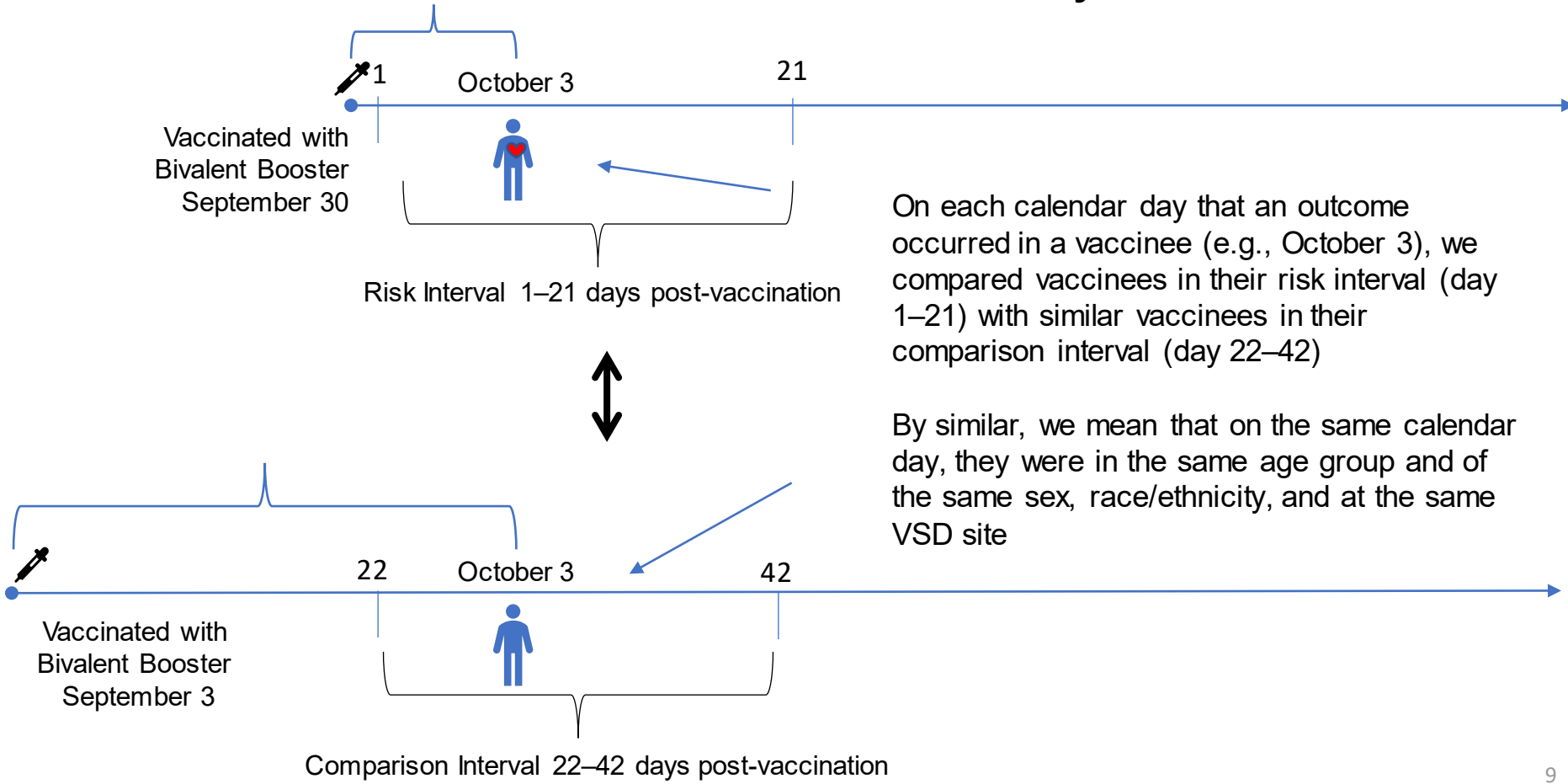
- **Innovative Methods**
  - *Vaccinated concurrent comparators:* Recent vaccinees as comparators are expected to be more similar to current vaccinees than unvaccinated individuals with the following advantages
    - Careful adjustment for potential biases associated with calendar time, site, and demographic 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
  - We believe using vaccinated concurrent comparators with supplemental analyses offered substantial benefits when compared with either unvaccinated or historical comparators

VSD Rapid Cycle Analysis (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 https://www.cdc.gov/vaccinesafety/pdf/COVID19-RCA-Protocol-1342-508.pdf

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 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 1–21-day Risk Interval versus 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	33	23	1.34	0.77–2.36	0.183	no
	Moderna	11	13	0.65	0.27–1.52	0.89	no
65+	**Pfizer**	**130**	**92**	**1.47**	**1.11–1.95**	**0.005**	**yes**
	Moderna	57	49	1.12	0.75–1.67	0.323	no

* Data through Jan 8, 2023

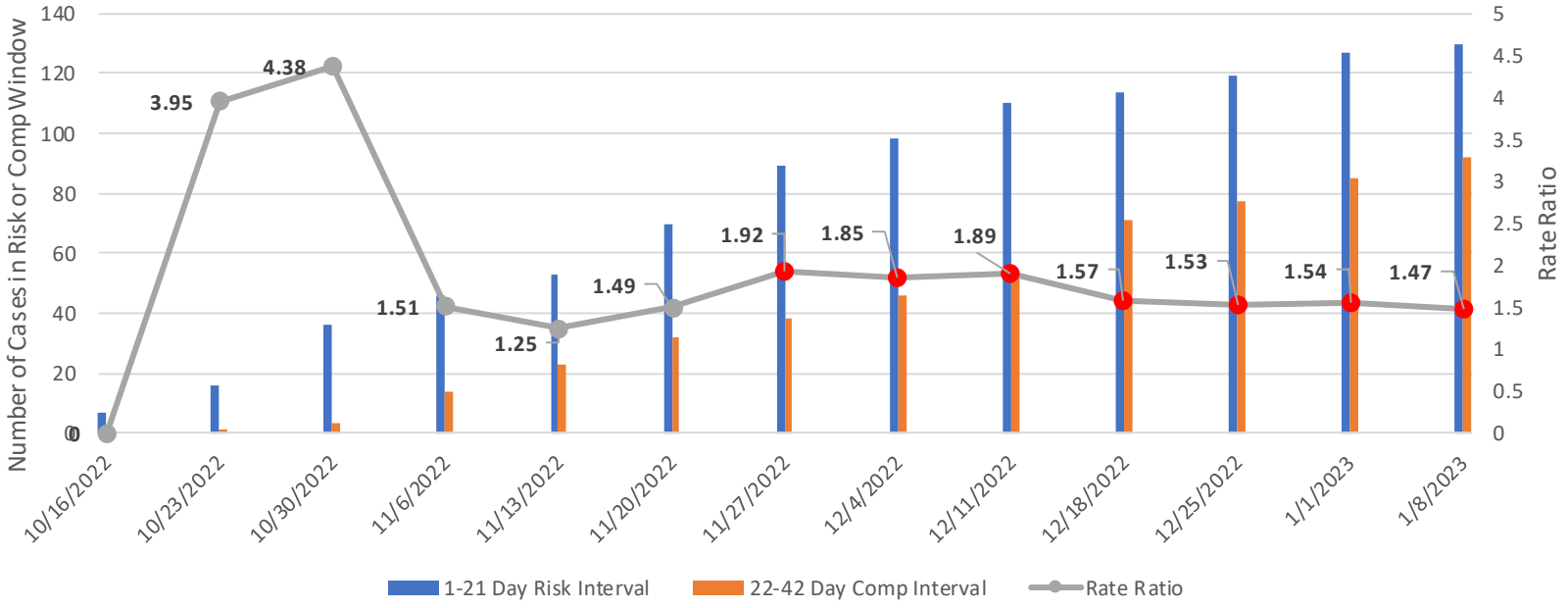
VSD investigations of an RCA signal to assess whether it reflects a real effect of vaccination on an outcome

- 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 concomitant 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 epidemiolocal studies to further investigate surveillance findings

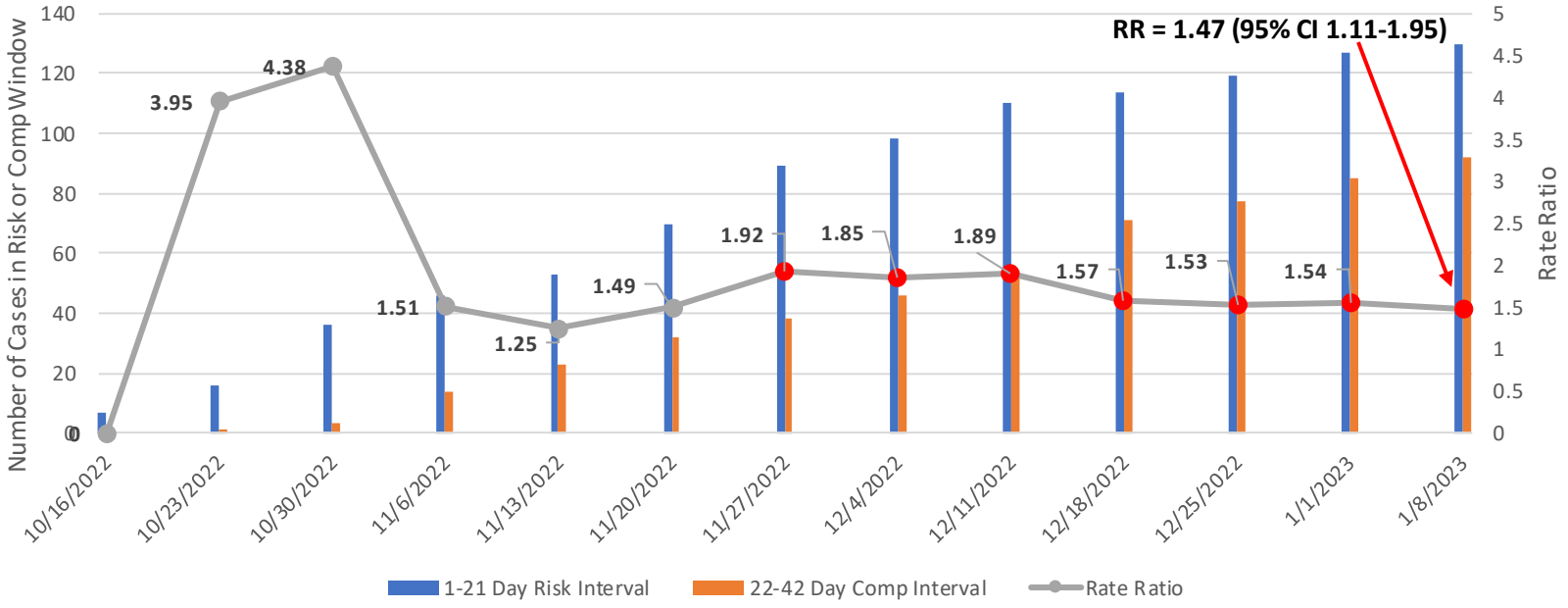
Rapid Cycle Analysis (RCA) to monitor the safety of COVID-19 vaccines in near real-time within the Vaccine Safety Datalink. Available at https://www.cdc.gov/vaccinesafety/pdf/COVID19-RCA-Protocol-1342-508.pdf

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

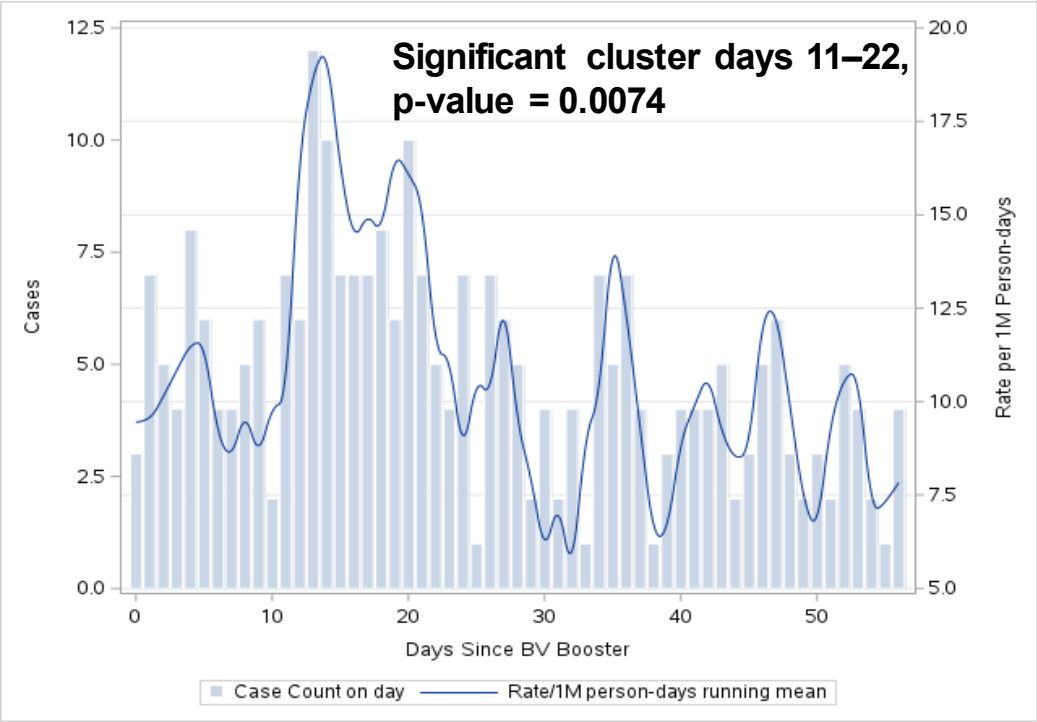
Ischemic stroke after Pfizer bivalent booster, age ≥65 years, counts and adjusted rate ratios (Oct 16, 2022 – Jan 8, 2023)



Ischemic stroke after Pfizer bivalent booster, age ≥65 years, counts and adjusted rate ratios (Oct 16, 2022 – Jan 8, 2023)



Ischemic stroke by day after Pfizer 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 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 flu vaccine co-administered 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

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:
Concomitant 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=103)	Cases in 22–42-day Comparison Interval (N=82)	Adjusted Rate Ratio** (95% CI)	P-value
Bivalent Pfizer + same-day high-dose or adjuvanted flu vaccine	40	20	**2.00 (1.18–3.48)**	**0.010**
Bivalent Pfizer + same day standard dose flu vaccine	3	4	0.75 (0.14–3.63)	0.727
Bivalent Pfizer without any same day flu vaccine	60	58	1.03 (0.72–1.49)	0.855

* Analyses only include vaccination data through November 5, 2022, and stroke outcome data through December 17, 2022
** 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	6.7	6	5
70–74 years	7.6	7	6
75–79 years	8.7	11	5
80–84 years	5.8	8	1
85–89 years	3.7	5	3
90+ years	2.0	3	0
Total	**34.5**	**40**	**20**

* Analyses only include vaccination data through November 5, 2022, and stroke outcome data through December 17, 2022.

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

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

- **Statistical signal persistent for 7 weeks**
  - Rate ratio has slowly attenuated from 1.92 to 1.47 but has continued to meet signaling criteria
- **Additional signal investigation analyses**
  - Temporal clustering evaluation found a significant cluster 11–22 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 co-administered high-dose or adjuvanted flu vaccine
  - Analyses evaluating concomitant high-dose or adjuvanted flu vaccine showed a rate ratio RR=2.00 (95% CI 1.18–3.48; p-value 0.010)
    - 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
  - Concomitant 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 > 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

Summary

Further evaluation

- Continue to monitor weekly and explore potential data-related explanations for the statistical signal in VSD
- Consider expanding chart review to all VSD sites
- Consult with other surveillance systems to better understand:
  - Possible role of concomitant 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 co-administration of 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
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  - 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

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

For more information, contact CDC
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Photo credit: James Gathany (https://phil.cdc.gov/Details.aspx?pid=8876)

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Extra 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 Jan 8, 2023) (N=17,843)

Manufacturer	Median Age (IQR), years	Male† N (%)	Female† N (%)	Non-serious N (%)	Serious N (%)	Doses admin‡
Pfizer-BioNTech	56 (33–69)	3,756 (37)	6,238 (61)	9,501 (93)	663 (7)	31,768,902
Moderna	61 (44–71)	2,928 (38)	4,652 (61)	7,308 (95)	371 (5)	18,016,805
Total	**58 (38–70)**	**6,684 (37)**	**10,890 (61)**	**16,809 (94)**	**1,034 (6)**	**49,785,707**

- **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 (45% race and/or ethnicity unknown; 42% non-Hispanic white)

* Includes reports after Moderna bivalent booster among ages ≥6 years; † Excludes 269 (2%) reports where sex was not reported;
‡ Doses of administered among children ages 5–11 years vaccinated during Oct 18–Nov 17, 2022

Most frequent MedDRA Preferred Terms* to VAERS following *Pfizer-BioNTech* bivalent booster vaccination among people ages ≥5 years† (as of January 8, 2023)

Non-serious reports (N=9,501)†

Rank	MedDRA PT (not mutually exclusive)	n (%)
1	COVID-19	1,316 (14)
2	Fatigue	927 (10)
3	Headache	905 (10)
4	Pyrexia/fever	864 (9)
5	Pain	840 (9)
6	SARS-CoV-2 test positive	749 (8)
7	Cough	615 (6)
8	Chills	594 (6)
9	Dizziness	512 (5)
10	Pain in extremity	497 (5)

Serious reports (N=663)

Rank	MedDRA PT (not mutually exclusive)	n (%)
1	COVID-19	181 (27)
2	SARS-CoV-2 test positive	158 (24)
3	Dyspoena	100 (15)
4	Asthenia	71 (11)
5	Pyrexia/fever	67 (10)
6	Condition aggravated	62 (9)
7	Death‡	59 (9)
8	Vaccine breakthrough infection	51 (8)
9	Pain	50 (8)
10	Fatigue	48 (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 79 years (IQR: 71–78)

Most frequent MedDRA Preferred Terms* to VAERS following *Moderna* bivalent booster vaccination among people ages ≥6 years (as of January 8, 2023)

Non-serious reports (N=7,308)†

Rank	MedDRA PT (not mutually exclusive)	n (%)
1	Headache	730 (10)
2	Pyrexia/fever	725 (10)
3	Fatigue	692 (9)
4	COVID-19	634 (9)
5	Pain	625 (9)
6	SARS-CoV-2 test positive	571 (8)
7	Chills	477 (7)
8	Cough	440 (6)
9	Pain in extremity	386 (5)
10	Dizziness	336 (5)

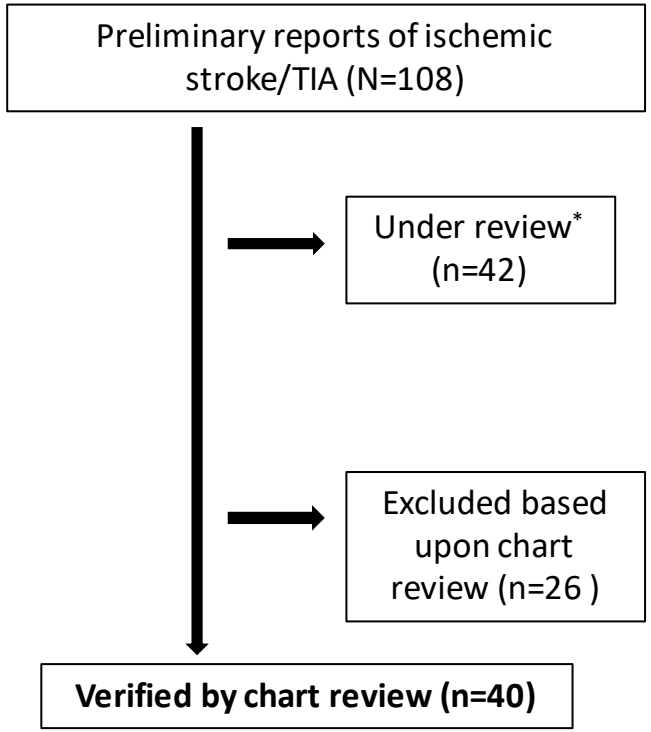
Serious reports (N=371)

Rank	MedDRA PT (not mutually exclusive)	n (%)
1	COVID-19	99 (27)
2	SARS-CoV-2 test positive	85 (23)
3	Dyspnoea	68 (18)
4	Condition aggravated	37 (10)
5	Asthenia	36 (10)
6	Cough	35 (9)
7	Anticoagulant therapy	34 (9)
8	Death‡	34 (9)
9	Pyrexia/fever	32 (9)
10	Dizziness	31 (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 78 years (IQR: 66–85)

Reports to VAERS of ischemic stroke/transient ischemic attack (TIA) after bivalent COVID-19 mRNA vaccination (as of January 8, 2023)

- 40 verified reports of ischemic stroke/TIA
  - Median age: 74 years (IQR: 70–80 years)
  - Median time to onset: 4 days (IQR: 3–15 days)
  - 19 males, 21 females
  - 25 after Pfizer-BioNTech bivalent
  - 15 after Moderna bivalent



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

† Doses administered as of January 11, 2023

Reporting rate to VAERS of ischemic stroke/transient ischemic attack after bivalent COVID-19 mRNA vaccine (as of Jan 8, 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	25	31,768,902	**0.8**	51	31,768,902	**1.6**
Moderna	15	18,016,805	**0.8**	31	18,016,805	**1.7**

- **Reporting rate among people ages ≥50 years (per million doses administered)**
  - Chart verified reports = 1.1 per million (Pfizer-BioNTech) and 1.1 per million (Moderna)
  - Including reports under review = 2.3 per million (Pfizer-BioNTech) and 2.1 per million (Moderna)
  - Incidence of ischemic stroke among ages ≥ 65 years = 670–970 per 100,000 person years†

* Doses administered as of Jan 11, 2023; † Roger et al. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. Circulation 2011;123:e18–e209

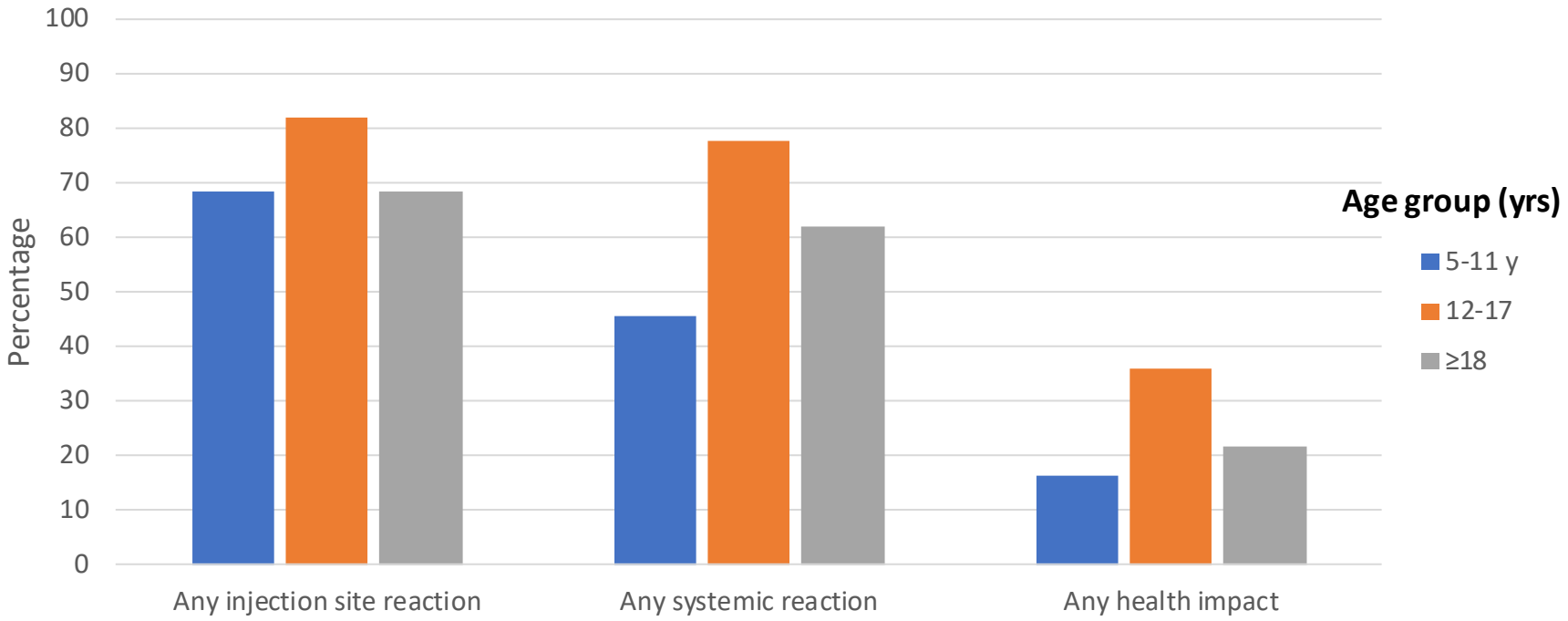
V-safe: Smartphone-based active safety monitoring

v-safe[SM]
after vaccination
health checker

Enroll yourself or your dependent after any dose!

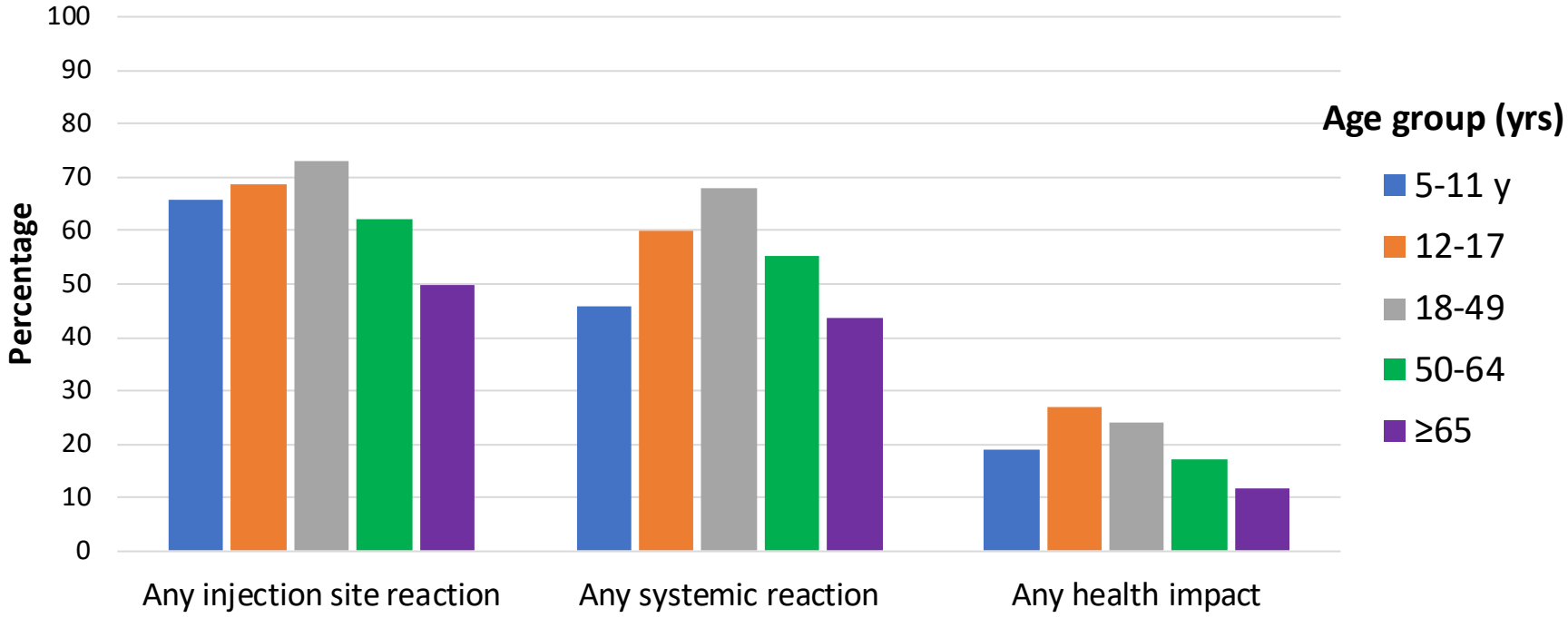
https://vsafe.cdc.gov

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 211,959 participants who completed at least 1 survey in the first week after booster dose.
Data for participants aged 5-11 years as of January 1, 2023. Includes 3,259 participants who completed at least 1 survey in the first week after booster dose.

VSD COVID-19 vaccine RCA prespecified surveillance outcomes

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.