COVID-19 vaccine safety surveillance for the 2023-2024 season

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CDC surveillance systems monitoring COVID-19 vaccine safety

- **Vaccine Adverse Event Reporting System (VAERS)**
- **V-safe**
- **Vaccine Safety Datalink (VSD)**

Key points up front

- The Vaccine Safety Datalink (VSD) identified two statistical signals for mRNA COVID-19 vaccines during the 2023-2024 season
  - Guillain-Barré syndrome (GBS) following Pfizer COVID-19 vaccine among people aged ≥65 years
    - An association between mRNA COVID-19 vaccines and GBS had not been observed prior to this season in VSD or other systems
    - The increased rate ratio observed during the 2023-2024 season may or may not represent a true risk
    - If there is a true risk, it is estimated to be similar to what is considered acceptable for other adult vaccines
  - Ischemic stroke following Moderna (aged ≥65 years) and Pfizer (aged 50-64 years) COVID-19 vaccines
    - The VSD previously observed a statistical signal for ischemic stroke during 2022-2023 for bivalent Pfizer COVID-19 vaccine (aged ≥65 years)
    - Available data do not provide clear and consistent evidence of a safety problem for ischemic stroke with mRNA COVID-19 vaccines
- No other new or unexpected safety concerns were identified for the 2023-2024 COVID-19 vaccines
- Any real or theoretical risks of vaccine adverse events need to be placed in the context of the benefits of COVID-19 vaccines in preventing COVID-19 and its potentially serious complications

Vaccine Adverse Event Reporting System (VAERS)

VAERS

Vaccine Adverse Event Reporting System

CDC + FDA

Co-Managed by CDC and FDA

http://vaers.hhs.gov

VAERS: U.S. reports following COVID-19 vaccination[1]

Manufacturer	Reports N	Age, years Median (IQR)	Sex, female N (%)	Non-serious N (%)	Serious[2] N (%)	Onset interval, days Median (IQR)
Pfizer	7,215	57 (33–70)	4,129 (57)	6,781 (94)	434 (6)	0 (0–3)
Moderna	5,954	60 (31–72)	3,474 (58)	5,502 (92)	457 (8)	0 (0–1)
Novavax	153	51 (35–70)	86 (56)	140 (92)	13 (8)	1 (0–2)
Unknown	176	58.5 (34–71)	95 (54)	152 (86)	24 (14)	0 (0–1)
Total	**13,491**	**59 (32–71)**	**7,780 (58)**	**12,568 (93)**	**923 (7)**	**0 (0–2)**

1. Reports received during September 12, 2023 – April 19, 2024; reported date of vaccination during September 12, 2023 – April 19, 2024 or missing
2. Based on the U. S. Code of Federal Regulations (21 CFR 600.80), classification of a serious adverse event includes a report of one of the following: death, life-threatening illness, hospitalization or prolongation of hospitalization, permanent disability, congenital anomaly, or birth defect.

VAERS: most frequent MedDRA Preferred Terms following COVID-19 vaccination by manufacturer

Pfizer		Moderna		Novavax	
MedDRA PT	N=7,215 n (%)	MedDRA PT	N=5,954 n (%)	MedDRA PT	N=153 n (%)
COVID-19	1899 (26)	Fever	743 (13)	Headache	21 (13)
Headache	485 (7)	Fatigue	729 (12)	Fever	19 (12)
Fatigue	465 (6)	Headache	712 (12)	Pain	18 (11)
Fever	407 (6)	Pain	546 (9)	Pain in extremity	18 (11)
Pain	365 (5)	Pain in extremity	502 (8)	Fatigue	15 (9)

Reports received during September 12, 2023 – April 19, 2024; reported date of vaccination during September 12, 2023 – April 19, 2024 or missing.

MedDRA PT = Medical Dictionary for Regulatory Activities Preferred Terms (https://www.meddra.org). More than one MedDRA Preferred Term may be assigned to a single report.

Percents represent the number of reports divided by the total number of reports for each vaccine.

V-safe

V-safe methods

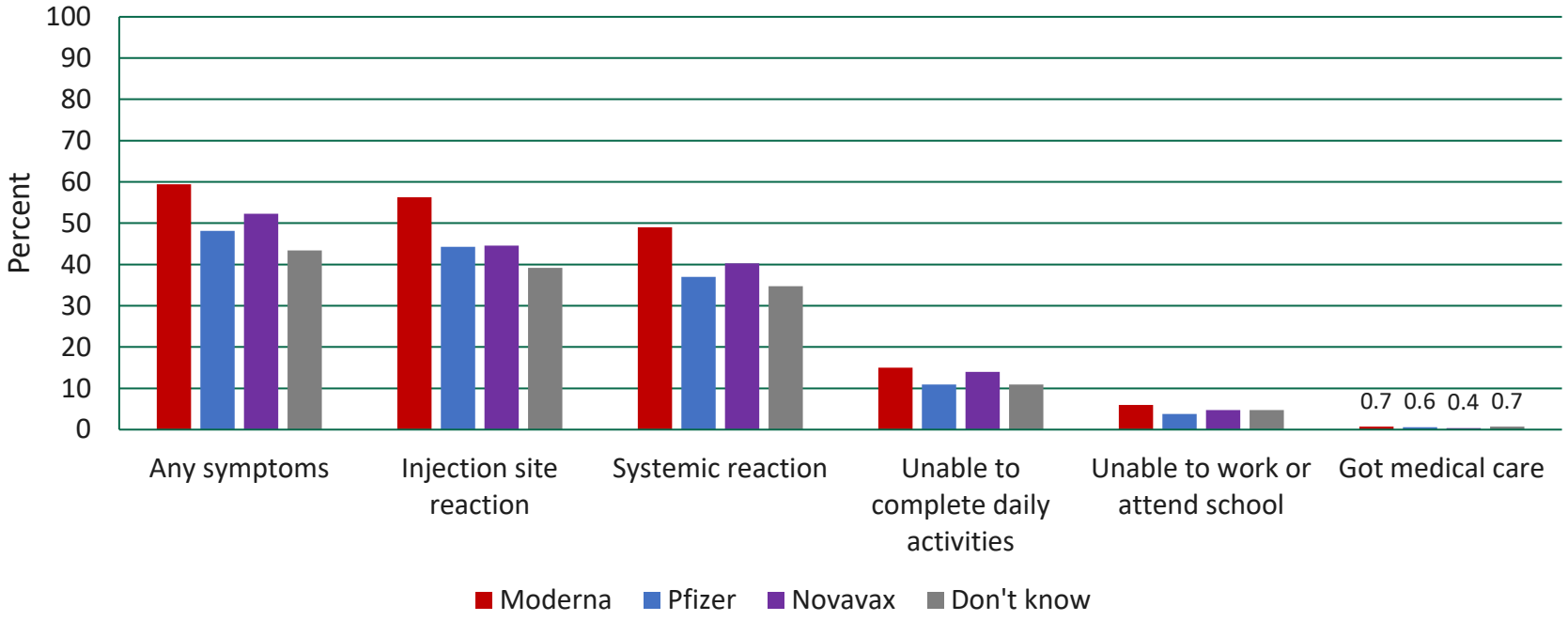
- Participants self-enroll at https://vsafe.cdc.gov
- Post-vaccination surveys
  - Daily during the first week
  - Weekly through week 6
- Daily surveys solicit adverse events and health impacts after vaccination
  - Local reactions (e.g., pain, redness, swelling)
  - Systemic reactions (e.g., fatigue, headache, muscle pain)
  - Health impacts (e.g., unable to perform normal daily activities, missed school or work, or received medical care)

V-safe: characteristics of participants with reported COVID-19 vaccination[1]

Characteristic	Vaccine manufacturer, %				
	Moderna N=4,828	Pfizer N=4,481	Novavax N=258	Do not know N=576	Total N=10,143
Female sex assigned at birth	61.5	61.2	69.4	63.7	61.7
Age group, years					
3-17	0.2	0.6	0.8	-	0.4
18-59	26.5	30.8	41.9	34.6	29.3
≥60	73.3	68.6	57.4	65.5	70.4
Immunocompromised	**7.7**	**7.0**	**8.5**	**5.0**	**7.2**
Vaccine(s) co-administered	**18.3**	**21.0**	**14.0**	**33.0**	**20.2**
Influenza	8.1	9.9	7.8	17.0	9.4
RSV	3.5	3.5	2.3	4.9	3.5
Other	6.7	7.6	3.9	11.1	7.3

1. For 10,143 V-safe participants aged ≥3 years enrolled in the COVID-19 protocol with ≥1 completed daily survey during September 11, 2023-May 27, 2024.

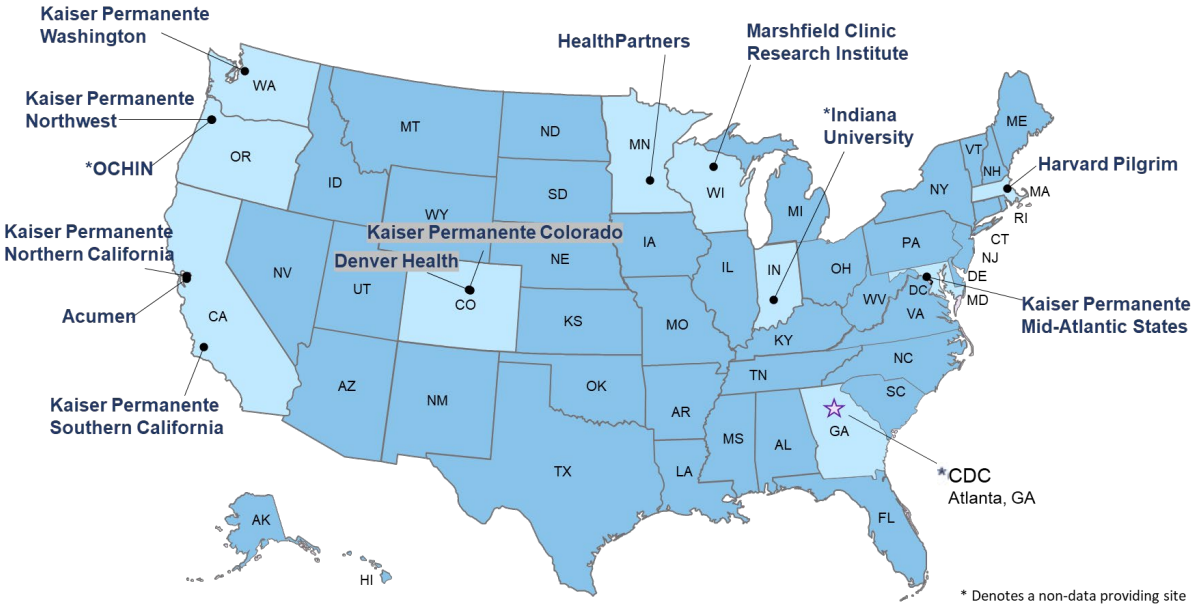
V-safe: percent of people aged ≥3 years who reported reactions and health impacts at least once in days 0-7 following COVID-19 vaccination, by manufacturer



Vaccine Safety Datalink (VSD)

Vaccine Safety Datalink (VSD)

- Collaborative project between CDC and 13 integrated healthcare organizations
- Population of ~13.5 million people annually



VSD Rapid Cycle Analysis (RCA) surveillance

- Sequential monitoring as data become available
- Monitors a limited set of prespecified outcomes of special interest
- Designed to detect statistical signals (values above specified statistical thresholds)
- **Statistical signals are potential associations and further investigation is required before concluding that a safety concern exists**

VSD RCA methods for the 2023-2024 COVID-19 vaccine

- Time period: September 10, 2023 – April 27, 2024
- Evaluated the first COVID-19 vaccine dose received during this period
- Design: analysis using COVID-19 vaccinated concurrent comparators
  - Compares the outcome incidence among vaccinees in a risk interval with outcome incidence on the same day among vaccinees in a comparison interval
  - Adjusted for outcome calendar date, age group, sex, race/ethnicity, VSD site
- Statistical signal criteria:
  - The signal threshold is determined from an alpha-spending plan that keeps the overall chance of a Type 1 error <0.05 during the surveillance period
  - Supplemental rate ratios with exact 95% confidence intervals

VSD pre-specified outcomes

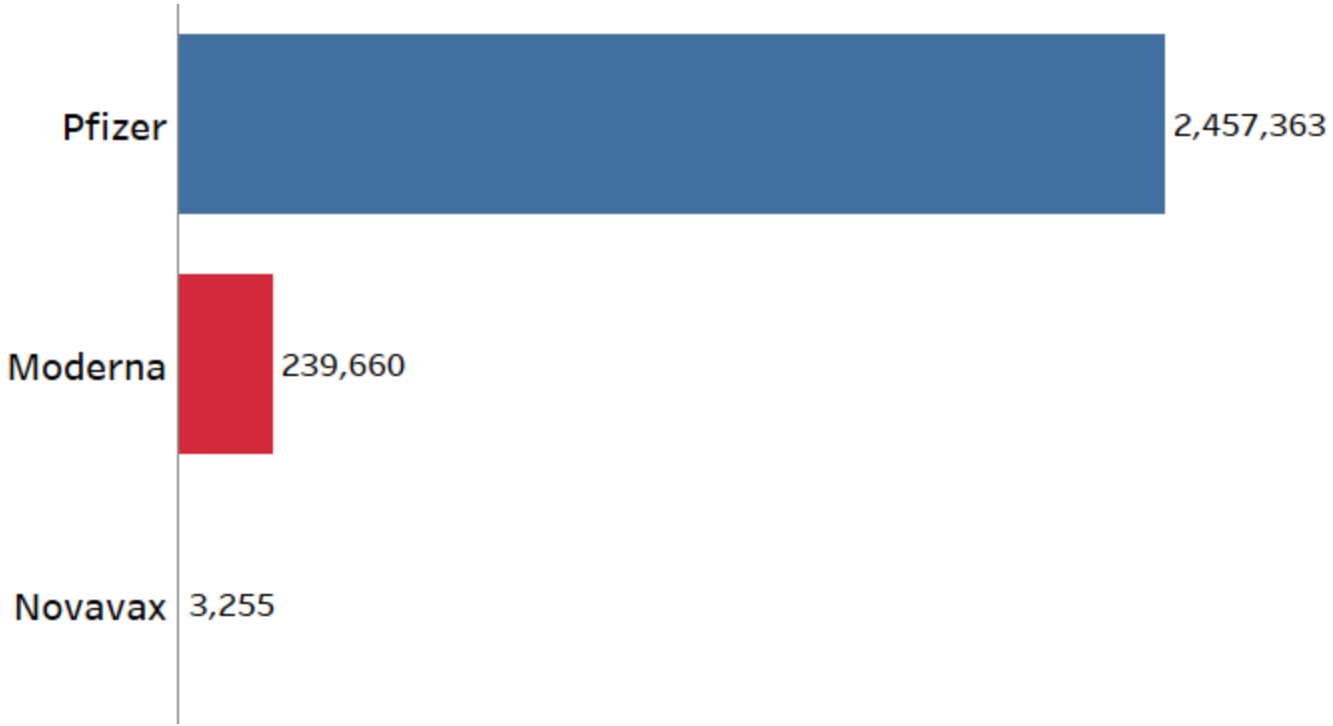
Acute disseminated encephalomyelitis (ADEM)
Acute myocardial infarction
Encephalitis / myelitis / encephalomyelitis (not ADEM or TM)
Guillain-Barré syndrome (GBS)
Hemorrhagic stroke
Ischemic stroke
Immune thrombocytopenia
Myocarditis / pericarditis
Pulmonary embolism
Seizure
Transverse myelitis (TM)

RCA COVID-19 Primary and Supplemental Analyses

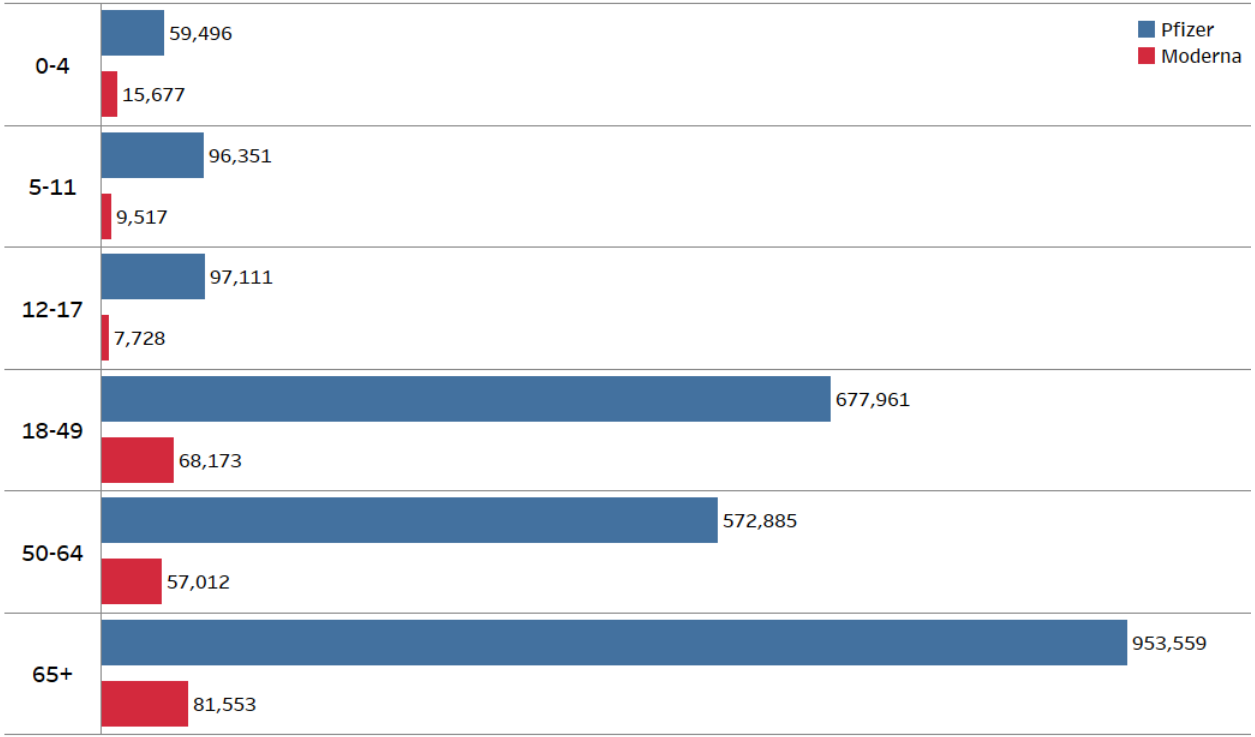
Parameters	Primary Analyses	Supplemental Analyses
Vaccine Types	Moderna Novavax Pfizer	Pfizer & Moderna combined Pfizer with flu Pfizer with flu high dose/adjuvant Moderna with flu Moderna with flu high dose/adjuvant Pfizer without same day vaccines Moderna without same day vaccines
Risk vs. Comparison Intervals	1-21 days vs 43-63 days 1-42 days vs 43-84 days	For myocarditis/pericarditis: 1-21 days vs 22-42 days
Age Groups	0-4 y 5-11 y 12-17 y 18-64 y ≥65 y	All ages (≥ 6 months) 18-49 y 50-64 y 60-74 y ≥75 y For myocarditis/pericarditis: 12-39 y

VSD Results

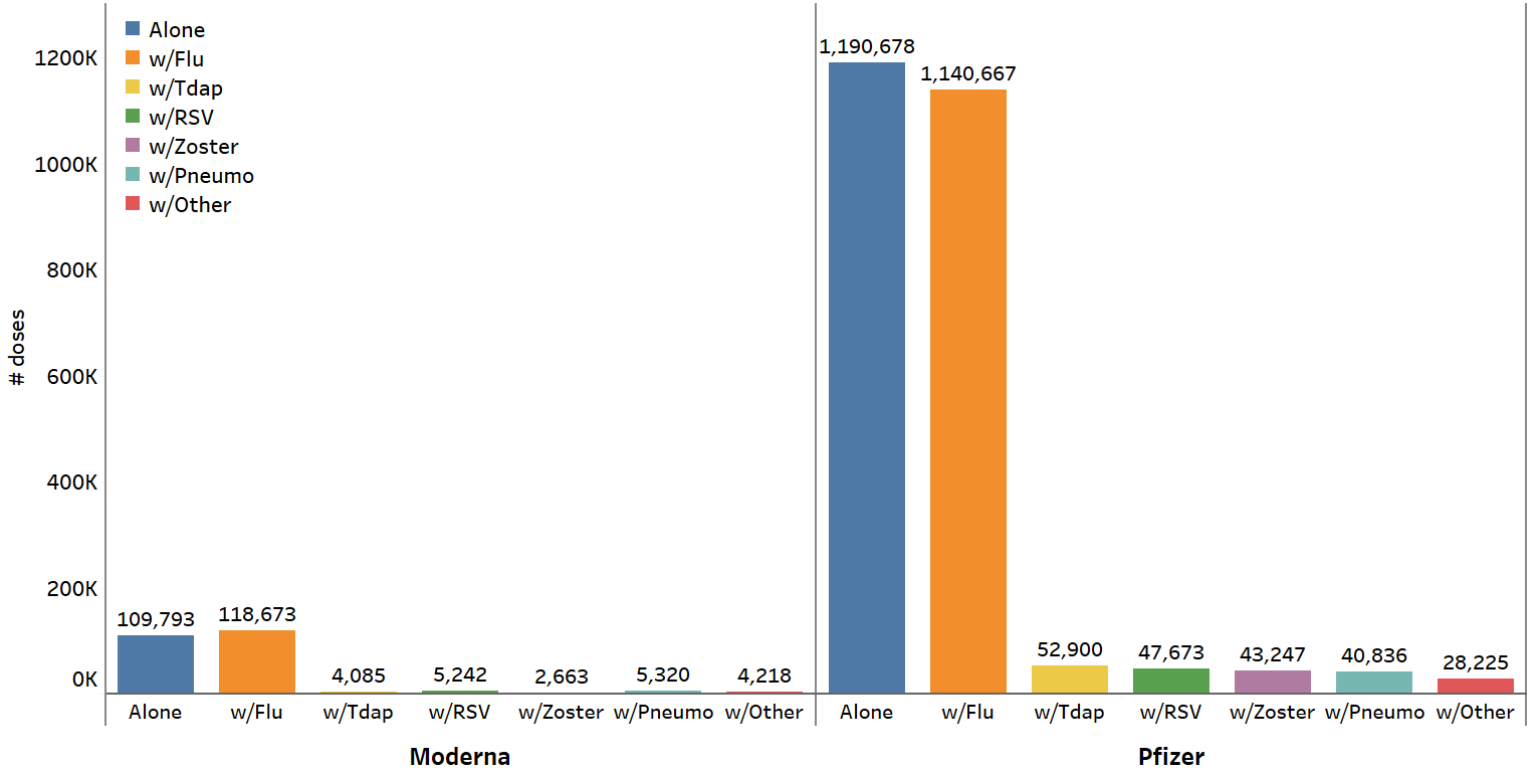
COVID-19 vaccine doses administered in VSD by manufacturer



COVID-19 vaccine doses administered in VSD by age group



COVID-19 vaccine doses administered in VSD with other vaccines on the same day[1]



[1] Some people received more than two vaccines on the same day. Not all categories are mutually exclusive.
Flu=Influenza vaccine; Tdap=Tetanus, Diphtheria, Pertussis vaccine; RSV=Respiratory syncytial virus vaccine; Zoster=Zoster recombinant vaccine; Pneumo=Pneumococcal vaccine

VSD RCA statistical signals

Outcome	Moderna	Pfizer
Acute disseminated encephalomyelitis (ADEM)	No	No
Acute myocardial infarction	No	No
Encephalitis / myelitis / encephalomyelitis (not ADEM or TM)	No	No
Guillain-Barré syndrome (GBS)	No	Yes
Hemorrhagic stroke	No	No
Ischemic stroke	Yes	Yes
Immune thrombocytopenia	No	No
Myocarditis / pericarditis	No	No
Pulmonary embolism	No	No
Seizure	No	No
Transverse myelitis (TM)	No	No

Guillain-Barré syndrome (GBS)

Guillain-Barré syndrome (GBS)
VSD statistical signals

Vaccine	Moderna		Pfizer	
Risk Interval (days)	**1 - 21**	**1 - 42**	**1 - 21**	**1 - 42**
Age Group (years)				
0 – 4	No	No	No	No
5 – 11	No	No	No	No
12 – 17	No	No	No	No
18 – 64	No	No	No	No
≥65	No	No	Yes	Yes

Characteristics of chart-confirmed GBS cases after Pfizer COVID-19 vaccine among people aged ≥65 years

Characteristic	Risk Interval cases Days 1-42 (n = 7)	Comparison Interval cases Days 43-84 (n = 3)
Brighton Level[1]		
1	2	0
2	5	3
3	0	0
Age Group (years)		
65 – 74	4	1
75 – 84	3	2
≥85	0	0
Same day vaccines		
None	5	2
Any	2	1
Influenza	1	1
Influenza + PCV	1	0

[1] Sejvar et al. Guillain-Barré syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. Vaccine. 2011;29(3):599-612

Chart-confirmed GBS concurrent comparator analysis for Pfizer COVID-19 vaccine among people aged ≥65 years

Analysis	Cases in Risk Interval (Days 1-42)	Cases in Comparison Interval (Days 43-84)	Adjusted Rate Ratio[1] (95% Confidence Interval)
Pfizer, all doses	7	3	4.45 (1.07– 22.62)
Pfizer without same day vaccines	5	2	4.86 (0.88 – 38.52)

Estimated excess GBS cases: 4.1 per million doses

[1] Adjusted for outcome calendar date, age group, sex, race/ethnicity, VSD site

VSD summary and interpretation for GBS

- VSD identified a statistical signal for GBS after Pfizer COVID-19 vaccine in adults aged ≥65 years during the 2023-2024 season
  - The VSD had not identified any signals for GBS with previous mRNA COVID-19 vaccine formulations (i.e., original primary series, original booster, or 2022-2023 bivalent)
  - The analysis did not suggest that other vaccines administered on the same day accounted for the increased rate
- The increased rate ratio observed for Pfizer COVID-19 vaccine during the 2023-2024 season may or may not represent a true risk, because a large number of analyses may find some associations by chance alone, and surveillance analyses may have residual confounding
- There were insufficient doses of Moderna or Novavax vaccines administered in the VSD to assess the rate of GBS with those vaccines
  - There is not necessarily a difference in GBS rate following Pfizer COVID-19 vaccine and the other COVID-19 vaccines

Ischemic stroke

Ischemic stroke
VSD statistical signals

Vaccine	Moderna		Pfizer	
Risk Interval (days)	**1 - 21**	**1 - 42**	**1 - 21**	**1 - 42**
Age Group (years)				
0 – 4	No	No	No	No
5 – 11	No	No	No	No
12 – 17	No	No	No	No
18 – 64	No	No	Yes	No
≥65	No	Yes	No	No

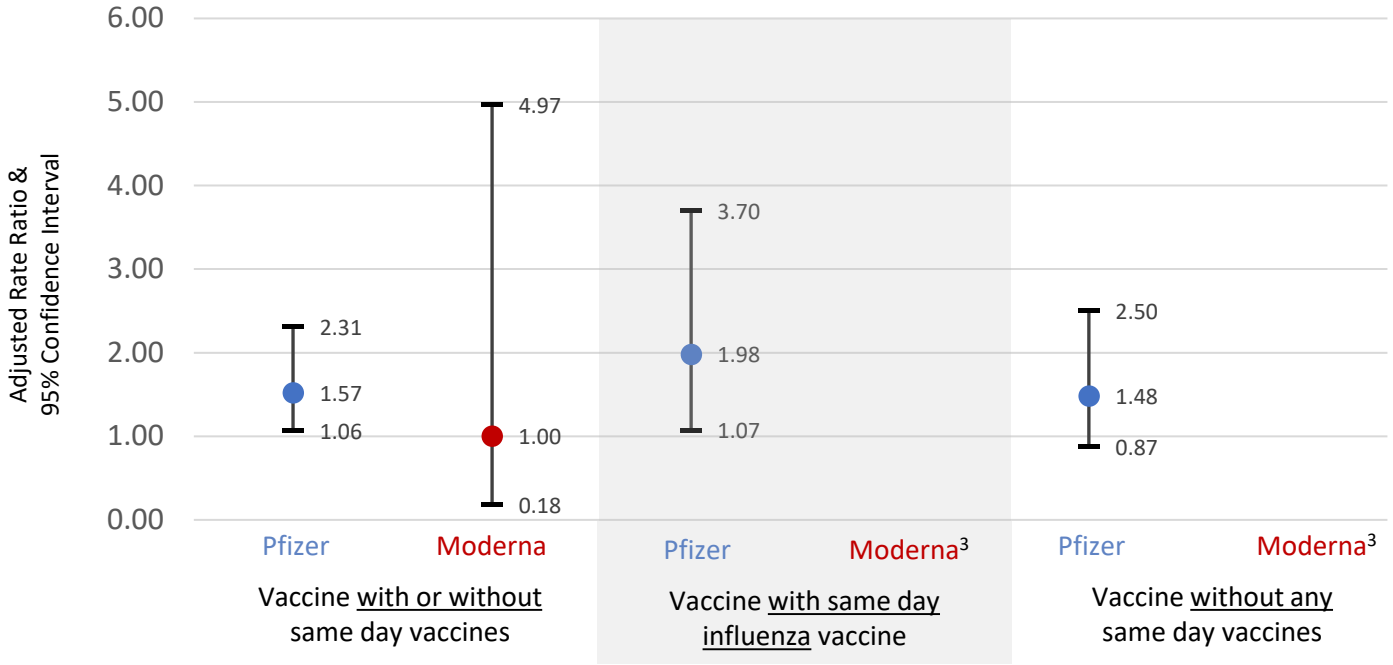
Ischemic stroke concurrent comparator analysis for Pfizer COVID-19 vaccine among people aged 18-64 years

Analysis	Cases in Risk Interval (Days 1-21)	Cases in Comparison Interval (Days 43-63)	Adjusted Rate Ratio[1] (95% Confidence Interval)
Ages 18-49	13	13	1.12 (0.46 – 2.67)
Ages 50-64	69	57	1.57 (1.06 – 2.31)

[1] Adjusted for outcome calendar date, age group, sex, race/ethnicity, VSD site

Ischemic stroke supplemental analyses to evaluate statistical signal for Pfizer COVID-19 vaccine among people aged 50-64 years

Exact Analysis 1-21 days vs 43-63 days
Adjusted Rate Ratios and 95% Confidence Intervals[1,2]



[1] Dose totals for age group: Pfizer = 572,885; Moderna = 57,012
[2] Rate ratios adjusted for outcome calendar date, age group, sex, race/ethnicity, VSD site
[3] This analysis not done for Moderna due to small sample size

Ischemic stroke concurrent comparator analysis for Moderna COVID-19 vaccine among people aged ≥65 years

Vaccine	Cases in Risk Interval (Days 1-42)	Cases in Comparison Interval (Days 43-84)	Adjusted Rate Ratio[1] (95% Confidence Interval)
Moderna	53	51	1.53 (0.96 – 2.42)

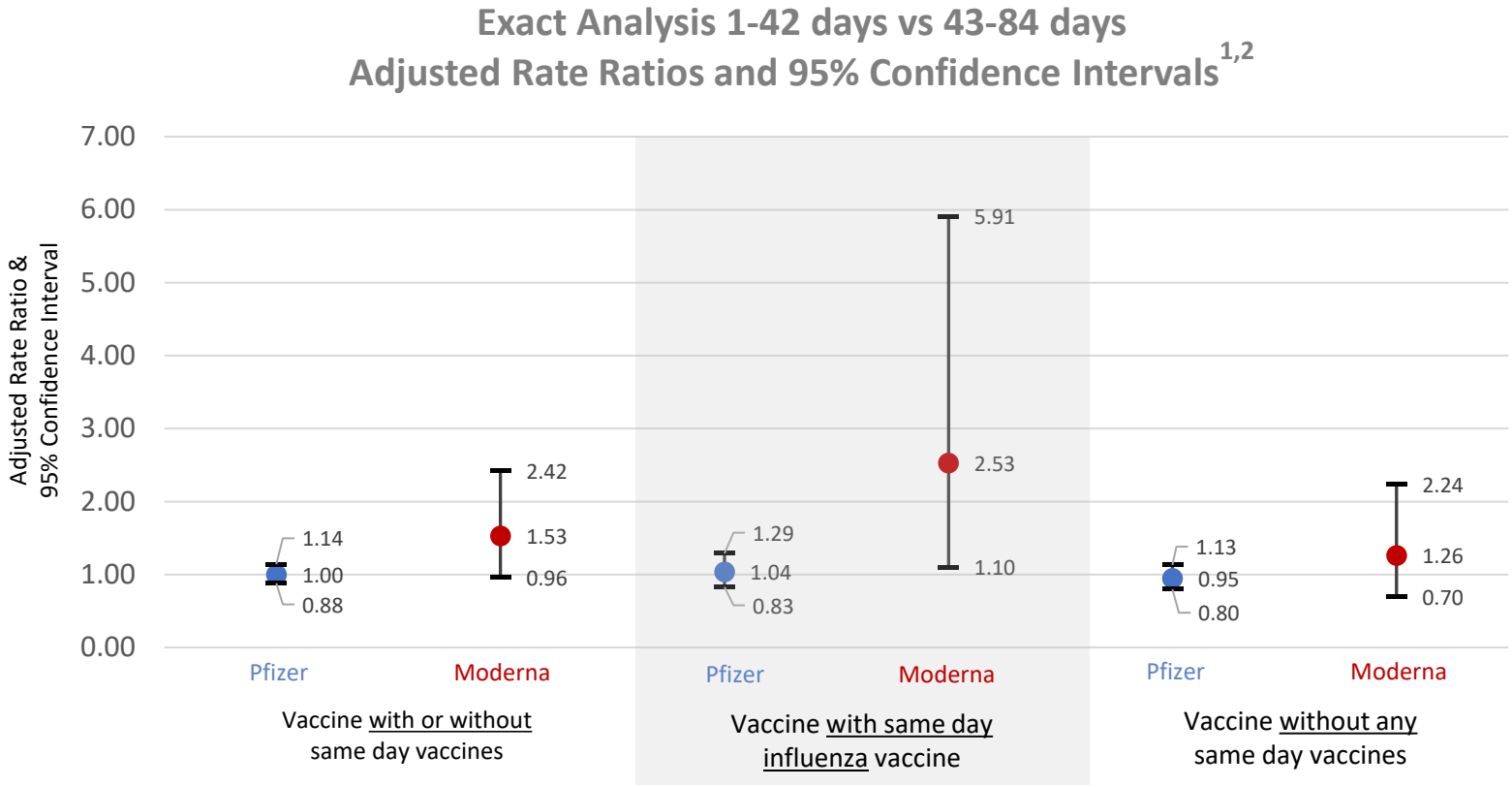
[1] Adjusted for outcome calendar date, age group, sex, race/ethnicity, VSD site

Ischemic stroke concurrent comparator analysis for mRNA COVID-19 vaccines among people aged ≥65 years

Vaccine	Cases in Risk Interval (Days 1-42)	Cases in Comparison Interval (Days 43-84)	Adjusted Rate Ratio[1] (95% Confidence Interval)
Moderna	53	51	1.53 (0.96 – 2.42)
Pfizer	574	714	1.00 (0.88 – 1.14)

[1] Adjusted for outcome calendar date, age group, sex, race/ethnicity, VSD site

Ischemic stroke supplemental analyses to evaluate statistical signal for Moderna COVID-19 vaccine among people aged ≥65 years



[1] Dose totals for age group: Pfizer = 953,559; Moderna = 81,553

[2] Rate ratios adjusted for outcome calendar date, age group, sex, race/ethnicity, VSD site

VSD summary and interpretation for ischemic stroke

- VSD detected statistical signals for ischemic stroke for Pfizer and Moderna COVID-19 vaccines during the 2023-2024 season
  - There was a lack of consistent findings across age groups or risk intervals
  - There was not a significantly different risk associated with receipt of simultaneous influenza vaccine
- The VSD previously identified a statistical signal for ischemic stroke for the 2022-2023 bivalent formulation of Pfizer vaccine in the ≥65 years age group using the 1-21 day risk interval
- **This season's findings are consistent with CDC Immunization Safety Office's prior interpretation based on data review in October 2023 that stated: "Available data do not provide clear and consistent evidence of a safety problem for ischemic stroke with bivalent mRNA COVID-19 vaccines when given alone or given simultaneously with influenza vaccines"[1]**
- The statistical signals during the 2022-2023[2] and the 2023-2024 seasons require further evaluation
  - The VSD has a follow-up retrospective study in progress to further assess the risk of ischemic stroke

[1] Shimabukuro TS, presentation to ACIP, October 25, 2023. Available at: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-10-25-26/01-VaxSafety-Shimabukuro-508.pdf
[2] Klein NK, presentation to ACIP, September 12, 2023. Available at: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-09-12/07-COVID-Klein-508.pdf

Conclusions

Conclusions

- Rates of local and/or systemic reactions reported by V-safe participants during the first week after receiving a dose of the 2023-2024 COVID-19 vaccine were similar to last season
- VSD identified statistical signals for GBS and ischemic stroke
- No other new or unexpected safety concerns were identified for the 2023-2024 COVID-19 vaccines by VAERS, V-safe, or VSD

Conclusions

- The increased rate ratio of GBS following Pfizer COVID-19 vaccine among people aged ≥65 years observed during the 2023-2024 season may or may not represent a true risk
  - If there is a true risk, then the estimated excess GBS cases of 4.1 per million doses is similar to previous estimates for other vaccines for adults
    - Influenza: 1 - 2 cases per million doses[1]
    - Recombinant Zoster Vaccine: 3 - 6 cases per million doses[2]
- The VSD statistical signals for ischemic stroke after mRNA COVID-19 vaccines during the 2023-2024 season do not provide sufficient evidence to conclude that there is a safety concern. A follow-up VSD study is in progress to further examine the risk of ischemic stroke after mRNA COVID-19 vaccines
- FDA's 2023-2024 COVID-19 vaccine safety surveillance using commercial health plans and Medicare claims databases results are expected later this year, which will provide additional information about GBS, stroke, and other outcomes

[1] Perez-Vilar S, et al. Guillain-Barré Syndrome After High-Dose Influenza Vaccine Administration in the United States, 2018-2019 Season. J Infect Dis. 2021 Feb 13;223(3):416-425.
[2] Janusz CB, et al. Projected risks and health benefits of vaccination against herpes zoster and related complications in US adults. Human Vaccines & Immunotherapeutics, 18(5), 2022.

Conclusions

- Any real or theoretical risks of vaccine adverse events need to be placed in the context of the benefits of COVID-19 vaccines in preventing COVID-19 and its potentially serious complications
- CDC and FDA will continue to monitor the safety of COVID-19 vaccines

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- **VSD Sites**
  - Denver Health, Denver, Colorado
  - HealthPartners Institute, Minneapolis, Minnesota
  - Kaiser Permanente Colorado, Denver, Colorado
  - Kaiser Permanente Mid Atlantic, Rockville Maryland
  - Kaiser Permanente Northern California, Oakland, California
  - Kaiser Permanente Northwest, Portland, Oregon
  - Kaiser Permanente Southern California, Los Angeles, California
  - Kaiser Permanente Washington, Seattle, Washington
  - Marshfield Clinic Research Institute, Marshfield, Wisconsin
- **FDA Center for Biologics Evaluation and Research, Office of Biostatistics and Pharmacovigilance**

For more information, contact CDC
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