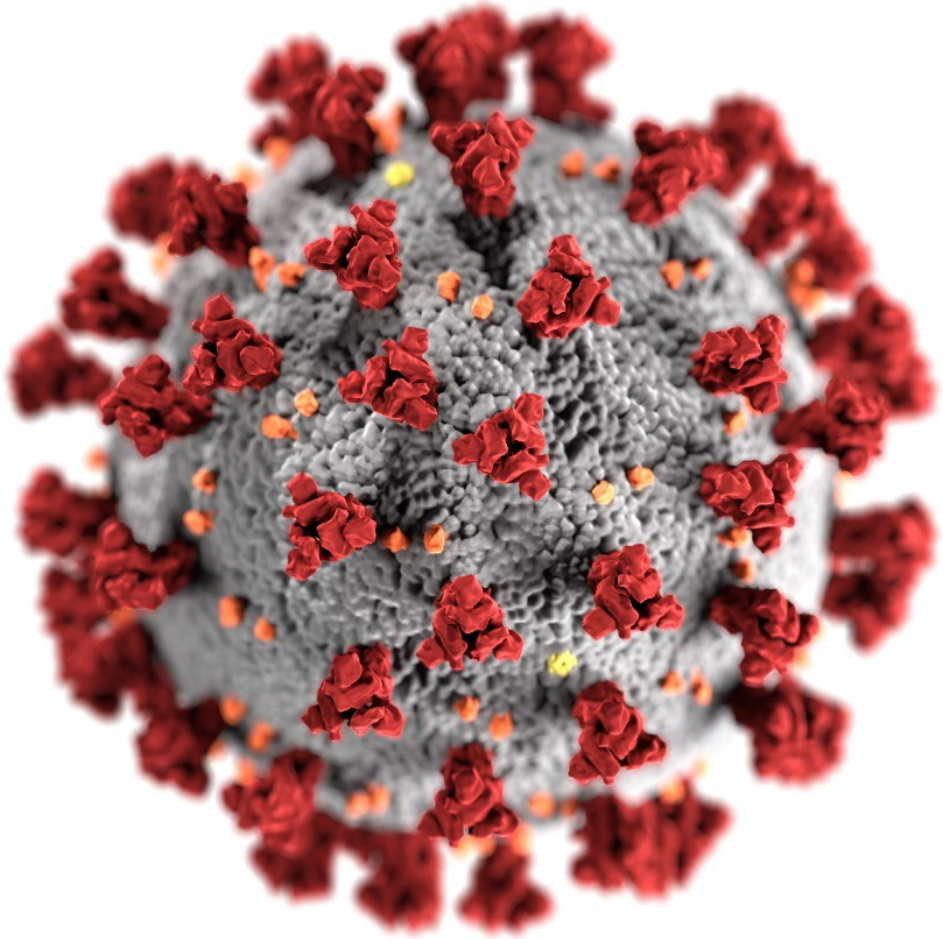
Update on myocarditis following mRNA COVID-19 vaccination

Vaccines and Related Biological Products Advisory Committee (VRBPAC)

June 7, 2022



Tom Shimabukuro, MD, MPH, MBA
CDC COVID-19 Vaccine Coordination Unit

cdc.gov/coronavirus

Topics

- Background on classic myocarditis and myocarditis associated with mRNA COVID-19 vaccination
- Update on myocarditis following mRNA COVID-19 vaccination with a focus on people ages 18 years and older
  - Vaccine Adverse Event Reporting System (VAERS)
  - Vaccine Safety Datalink (VSD)

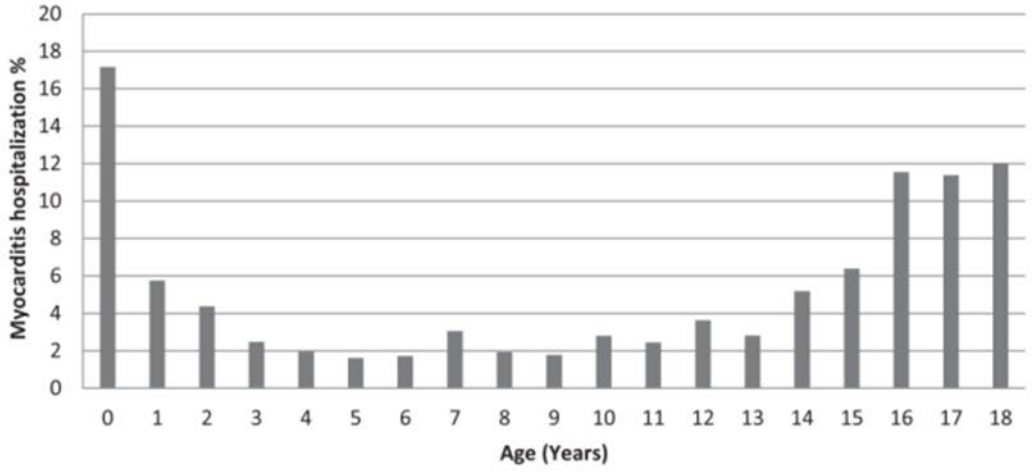
Epidemiology of classic myocarditis (excluding infants)

- Usually has an infectious cause, typically viral or presumed to be viral, although infection with a pathogen is frequently not identified (only ~40% of time a pathogen is identified)[1,2,3]
- Can be due to direct microbial infection of myocardial cells and/or ongoing inflammatory response, with or without clearance of pathogen[4,5,6]
  - Can also be toxin-mediated or in setting of systemic infection or infection of non-cardiac tissue
- Rarer causes include autoimmune, hypersensitivity, and giant cell myocarditis
- Incidence in males > females starting after age 5 years[7]
- It is common to not identify a pathogen or possible infectious etiology for myocarditis
  - Based on case series, where autopsy tissues were examined and tissue-based infectious disease testing was performed, a specific infectious cause was only identified in 13%–36% of cases across age groups[6,8,9]
  - For a case series where endomyocardial biopsy tissues were tested, viral nucleic acids were detected in heart tissues in ~38% (adults and children combined)[1]

[1]Bowles et al. J Am Coll Cardiol. 2003;42:466-72. [2]Simpson et al. J Am Coll Cardiol. 2013;61:(10_Supplement) E1264. [3]Park et al. J Korean Med Sci. 2021;36:e232. [4]Caforio et al. Eur Heart J. 2013;34:2636-48, 2648a-2648d. [5]Feldman et al. N Engl J Med. 2000;343:1388-98. [6]Guarner et al. Hum Pathol. 2007;38:1412-9. [7]Arola et al. J Am Heart Assoc. 2017;6:e005306. [8]Weber et al. Arch Dis Child. 2008;93:594-8. [9]Ilina et al. Pediatrics. 2011;128:e513-20.

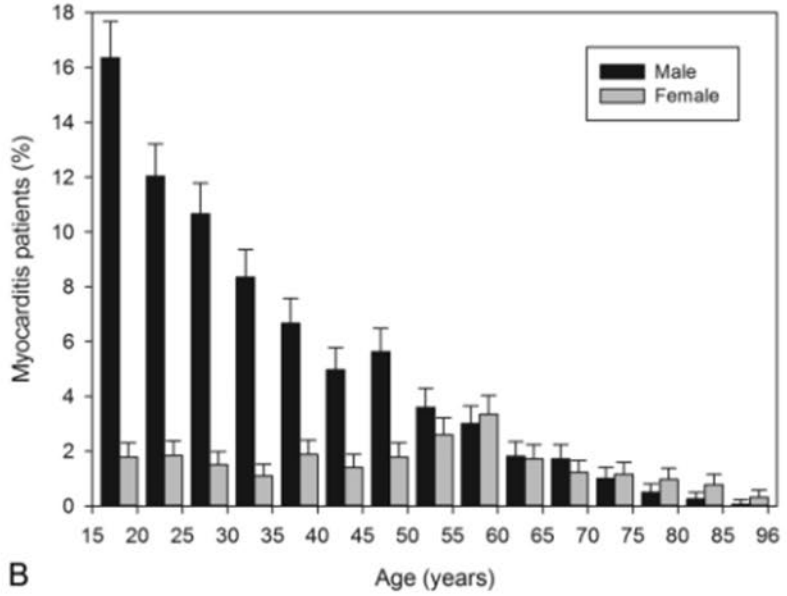
Epidemiology of myocarditis

- Children
  - Annual incidence 0.8 per 100,000
    - In 15-18yo, 1.8 per 100,000 in 2015-2016
  - 66% male
  - Median LOS 6.1 days



Vasudeva et al. *American J Cardiology.* 2021.

- Adults
  - Gradual decrease in incidence with age
  - 76% male



Kyto et al. *Heart*. 2013.

Previously presented: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-06/02-COVID-Oster-508.pdf

LOS = Length of hospital stay Previously presented:

Characteristic	Myocarditis associated with mRNA COVID-19 vaccination*,†	Viral myocarditis‡
Inciting exposure	mRNA COVID-19 vaccination • Dose 2 > Dose 1	Viral illness • 30–60% with asymptomatic viral course
Demographics	Most cases in adolescents and young adults, males > females	Males > females, male incidence peaks in adolescence and gradually declines
Symptom onset	A few days after vaccination, most within a week	1–4 weeks after viral illness
Fulminant course	Rare¶	23%
ICU level support	~2%	~50%
Mortality/transplant	Rare¶	11–22%
Cardiac dysfunction	12%	60%
Recovery of cardiac function	Nearly all	~75%
Time to recovery of cardiac function (ejection fraction on cardiac echo), if initially poor	Hours to days	Days to weeks to months

* https://www.cdc.gov/vaccines/acip/meetings/index.html, https://www.cdc.gov/vaccinesafety/research/publications/index.html

† Oster et al. JAMA. 2022;327:331-340.

‡ Law et al. Circulation. 2021;144:e123-e135. Ghelani et al. Circ Cardiovasc Qual Outcomes. 2012;5:622-7. Kim et al. Korean Circ J. 2020;50:1013-1022. Messroghli et al. Am Heart J. 2017;187:133-144. Patel et al. J Am Heart Assoc. 2022;11:e024393.

¶ There are rare reports in the literature, especially from other countries, but it is unclear to what extent such cases were investigated

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

CDC + FDA

VAERS

Vaccine Adverse Event Reporting System

http://vaers.hhs.gov

VAERS

VAERS accepts reports from everyone (healthcare professionals, patients, parents, caregivers, manufacturers, etc.) regardless of the plausibility of the vaccine causing the event or the clinical seriousness of the event

Key strengths

- Rapidly detects potential safety problems
- Can detect rare adverse events

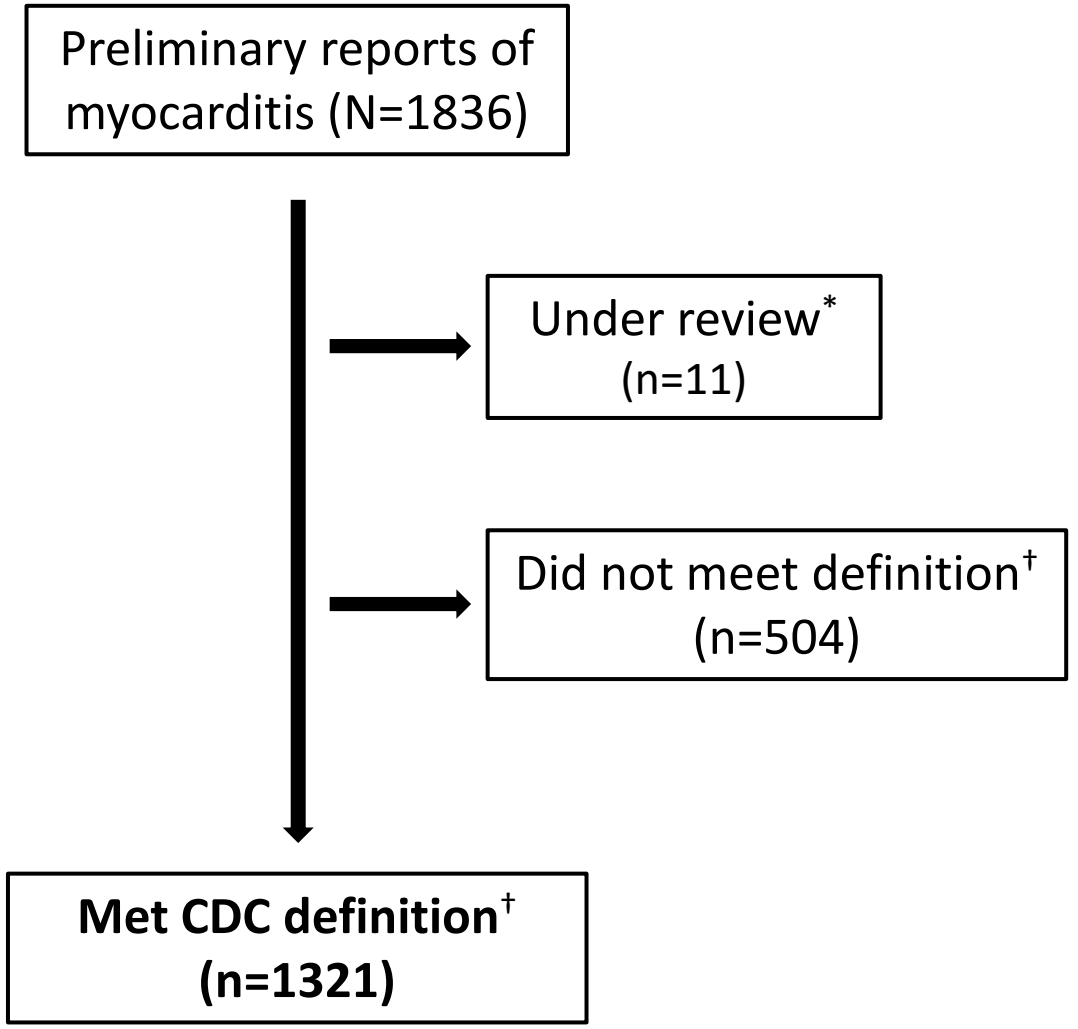
Key limitations

- Passive surveillance system
- Inconsistent quality and completeness of information
- Reporting biases
- Generally, cannot determine cause and effect

U.S. reports to VAERS of myocarditis after mRNA COVID-19 vaccination among people ages 18 years and older following primary series and 1st booster

(as of May 26, 2022)

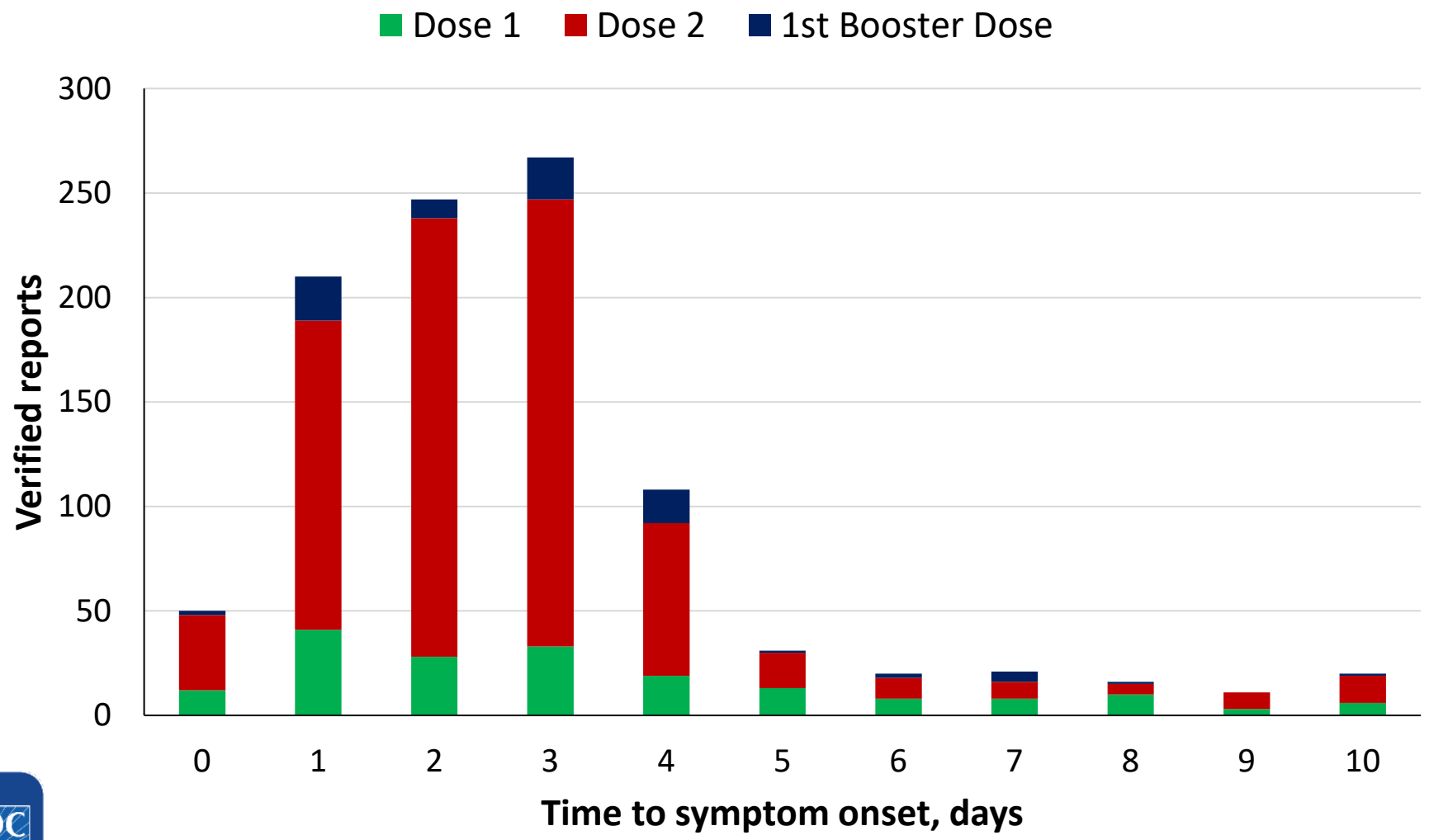
- Estimated **491.9 million** primary series and 1st booster mRNA COVID-19 vaccine doses administered in the Unites States among people ages 18 years and older
  - 213.3 million dose 1
  - 185.1 million dose 2
  - 93.4 million 1st booster dose



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

† Adjudicated after healthcare provider interview and/or medical record review, or vaccine received before authorized for use; CDC myocarditis case definition available at: https://www.cdc.gov/mmwr/volumes/70/wr/mm7027e2.htm

Verified* U.S. reports to VAERS of myocarditis after mRNA COVID-19 vaccination among people ages 18 years and older following primary series and 1st booster, by time to symptom onset† and dose number (N=1184; as of May 26, 2022)



† 1184 of 1321 (90%) with known time to symptom onset; 183 (15%) reports with time to symptom onset >10 days

*Verified according to CDC myocarditis case definition available at: https://www.cdc.gov/mmwr/volumes/70/wr/mm7027e2.htm

Verified U.S. reports to VAERS of myocarditis after mRNA COVID-19 vaccination among people ages 18 years and older following primary series and 1st booster (as of May 26, 2022, 491.9 million primary series and 1st booster doses administered)

- 1321 reports verified using CDC case definition
  - Median age: 28 years (IQR: ages 21–42 years)
  - Median time to symptom onset after vaccination: 3 days (IQR: 2–5 days)
    - 229/1184 (19%) reports with known symptom onset >7 days after vaccination
  - After dose 2 (n=962), dose 1 (n=257), 1st booster dose (n=102)
  - Male cases (n=960), female cases (n=361)

VAERS reporting rates of myocarditis (per 1 million doses administered) after mRNA COVID-19 vaccination, days 0–7 and 8–21 post-vaccination*,†

		0–7 days			8–21 days			0–7 days			8–21 days		
		Males			Males			Females			Females		
	Age (yrs)	Dose 1	Dose 2	Booster	Dose 1	Dose 2	Booster	Dose 1	Dose 2	Booster	Dose 1	Dose 2	Booster
Pfizer-BioNTech	5–11	0.2	2.6	0.0	0.6	0.0	0.0	0.2	0.7	0.0	0.2	0.0	0.0
	12–15	5.3	46.4	15.3	1.2	1.2	0.9	0.7	4.1	0.0	0.4	0.2	0.9
	16–17	7.2	75.9	24.1	1.7	3.2	1.3	0.0	7.5	0.0	0.7	0.4	0.0
Pfizer-BioNTech and Moderna	18–24	4.2	38.9	9.9	1.1	2.2	0.4	0.6	4.0	0.6	0.2	0.7	0.0
	25–29	1.8	15.2	4.8	0.4	1.1	0.5	0.4	3.5	2.0	0.2	0.0	0.8
	30–39	1.9	7.5	1.8	0.4	0.8	0.2	0.6	0.9	0.6	0.3	0.2	0.0
	40–49	0.5	3.3	0.4	0.2	0.5	0.0	0.4	1.6	0.6	0.2	0.2	0.0
	50–64	0.5	0.7	0.4	0.2	0.3	0.1	0.6	0.5	0.1	0.2	0.5	0.1
	65+	0.2	0.3	0.6	0.3	0.2	0.1	0.1	0.5	0.1	0.1	0.2	0.1

* As of May 26, 2022; reports verified to meet case definition by provider interview or medical record review; primary series and 1st booster doses only

† An estimated 1–10 cases of myocarditis per 100,000 person years occurs among people in the United States, regardless of vaccination status; adjusted for days 0–7 and 8–21 risk intervals, this estimated background is **0.2 to 2.2 per 1 million person-day 0–7 risk interval and 0.4 to 3.8 per 1 million person-day 8–21 risk interval** (peach shaded cells indicate that reporting rate exceeded estimated background incidence for the period)

Verified U.S. reports to VAERS of myocarditis after mRNA COVID-19 vaccination among people ages 18 years and older following primary series and 1st booster (as of May 26, 2022, 491.9 million primary series and 1st booster doses administered)

- 1321 reports verified using CDC case definition
  - 1201/1314 hospitalized*
    - 990 with known outcome at time of report*
    - 719/990 (73%) recovered from symptoms at time of last follow-up
  - 21 reports of death involving myocarditis (median age=38 years, IQR 27–70)
    - After dose 2 (n=13), dose 1 (n=6), 1st booster dose (n=2)
    - Myocarditis was attributed to causes other than a vaccination (n=1)
    - Potential alternate etiology was present (n=4)
    - Cause of death was not attributed to myocarditis (n=15)
    - Adequate information was not available to fully evaluate (n=1)

* Of 1,321 reports, 1,314 (>99%) had known (yes/no) hospitalization status; of 1,202 reports of hospitalized patients, 990 had known outcome

CDC enhanced surveillance for myocarditis outcomes following mRNA COVID-19 vaccination in VAERS case reports among people ages 12–29 years*,†

- **Purpose**: Assess functional status and clinical outcomes among individuals reported to have developed myocarditis after mRNA COVID-19 vaccination
- **Methods**: A two-component survey conducted at least 90 days after the onset of myocarditis symptoms
  - Patient survey: Focused on ascertaining functional status, clinical symptoms, quality of life, and need for medication or other medical treatment
  - Healthcare provider (e.g., cardiologist): Gather data on cardiac health and functional status

* https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myo-outcomes.html

† Previous presentation available at: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-02-04/04-COVID-Kracalic-508.pdf

CDC enhanced surveillance for myocarditis outcomes following mRNA COVID-19 vaccination in VAERS case reports among people ages 12–29 years

- As of Nov 2021, VAERS had received 852 reports of myocarditis or myopericarditis after mRNA COVID-19 vaccination in patients ages 12–29 years that met CDC case definition* and were at least 90 days post-myocarditis diagnosis
  - **360 completed the patient survey**, 270 were unreachable on multiple attempts, 204 had no telephone contact information in the report, and 18 declined to participate
    - For the 360 patients interviewed, time from myocarditis onset to interview was 143 days (IQR: 131–162 days)
  - **398 cardiologists or other healthcare providers (HCP) completed a survey**, 268 were unreachable on multiple attempts, and 186 had no telephone contact information in the report
    - For the 398 HCP interviewed, time from myocarditis onset to interview was 191 days (IQR: 170–216 days)

* https://www.cdc.gov/mmwr/volumes/70/wr/mm7027e2.htm

CDC enhanced surveillance for myocarditis outcomes following mRNA COVID-19 vaccination in VAERS case reports among people ages 12–29 years

Results of cardiologist/healthcare provider survey

- Based on the cardiologists or healthcare provider assessment, most patients appear to have fully or probably fully recovered from their myocarditis
  - 398 patients received a follow-up assessment by a cardiologist or other healthcare provider regarding their myocarditis recovery

81.7% fully recovered or probably fully recovered

- **265 (66.6%) fully recovered**
- **60 (15.1%) probably fully recovered but awaiting more information**
- 61 (15.3%) improved but not fully recovered
- 8 (2.0%) recovery status unsure
- 4 (1.0%) same cardiac status as at initial myocarditis diagnosis

CDC enhanced surveillance for myocarditis outcomes following mRNA COVID-19 vaccination in VAERS case reports among people ages 12–29 years

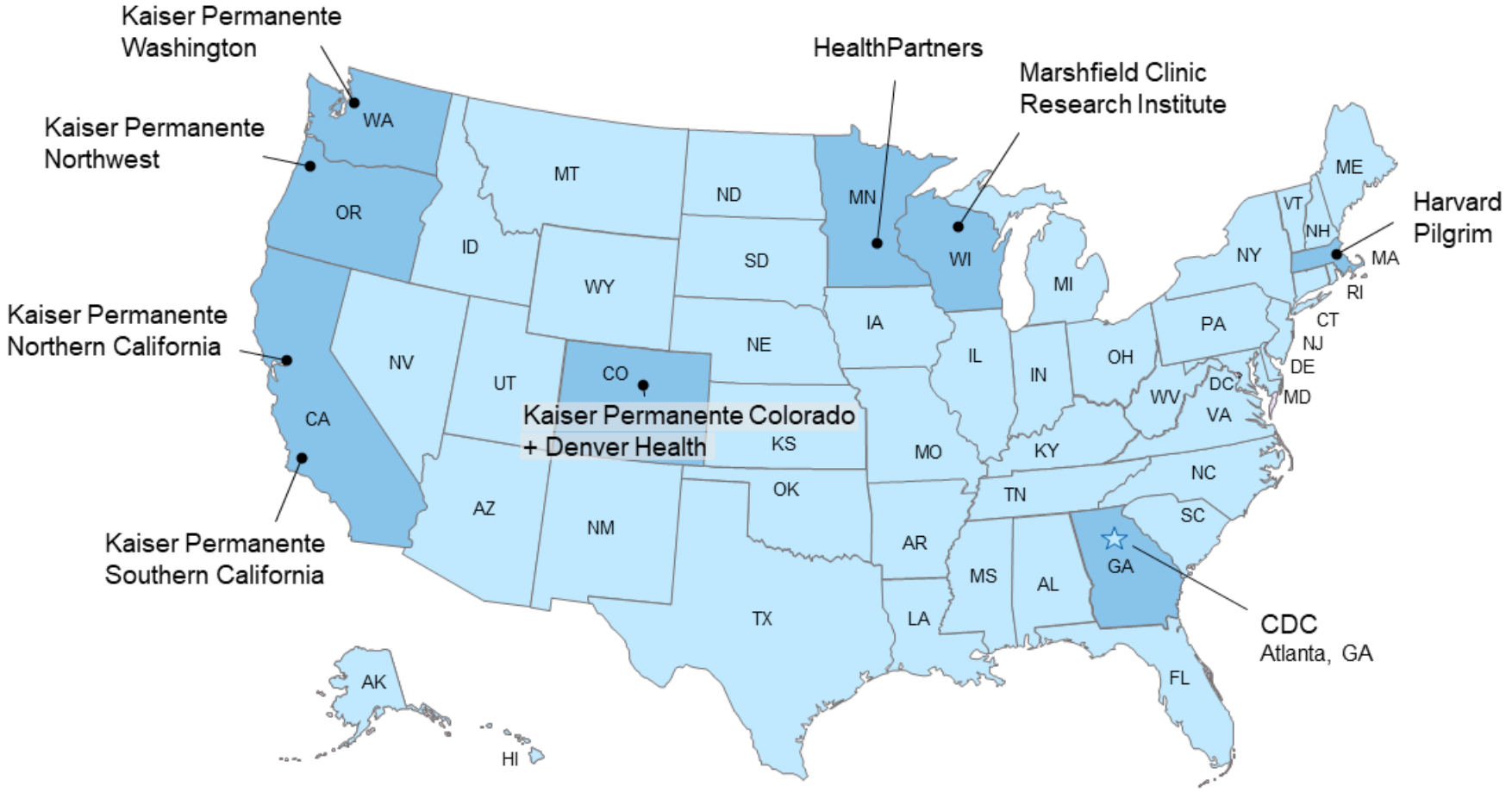
Key findings

- At least 90 days after myocarditis diagnosis, most patients who were reached reported no impact on their quality of life, and most did not report missing school or work
- Most (81.7%) healthcare providers who completed surveys indicated the patient was fully recovered or probably fully recovered
  - There was substantial heterogeneity in initial and follow-up treatment and testing
  - There did not appear to be a single test that was indicative of recovery

Next steps

- Additional follow-up with patients who were not yet recovered at time of the 90+ day survey (and their healthcare providers) to further assess recovery status at 12+ months
- Follow-up and evaluation of myocarditis cases in children ages 5–11 years is ongoing

Vaccine Safety Datalink (VSD)



- Established in 1990
- Collaborative project between CDC and 9 integrated healthcare organizations

VSD Rapid Cycle Analysis (RCA)

Aims

- To monitor the safety of COVID-19 vaccines weekly using pre-specified outcomes of interest among VSD members
- To describe the uptake of COVID-19 vaccines over time among eligible VSD members overall and in strata by age, site, and race/ethnicity

VSD COVID-19 vaccine RCA prespecified surveillance outcomes

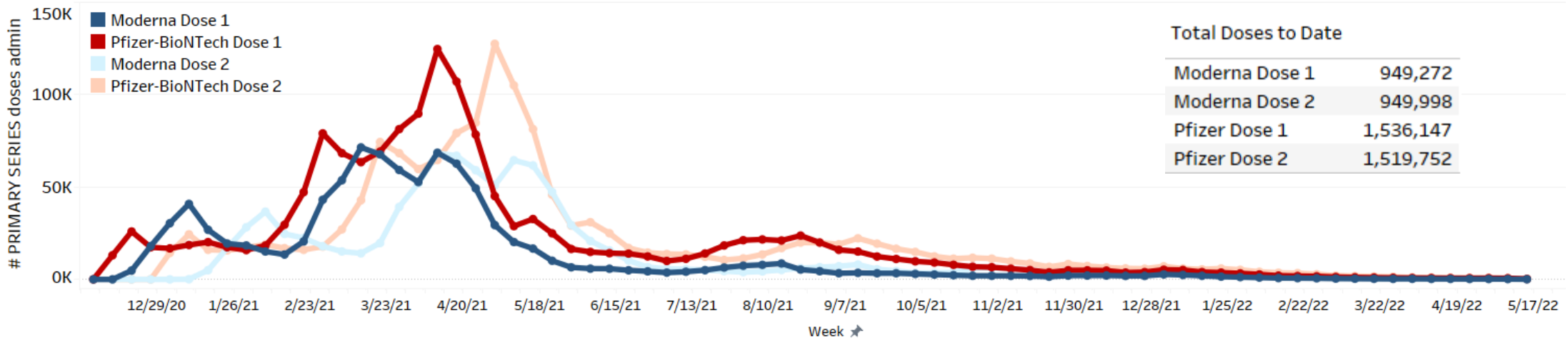
Prespecified outcomes	Settings
Acute disseminated encephalomyelitis	Emergency dept, Inpatient
Acute myocardial infarction – **First ever in EHR in ICD-10 era**	Emergency dept, Inpatient
Acute respiratory distress syndrome	Emergency dept, Inpatient
Anaphylaxis – **First in 7 days in EHR in ICD-10 era**	Emergency dept, Inpatient
Appendicitis	Emergency dept, Inpatient
Bell's palsy – **First ever in EHR in ICD-10 era**	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 – **First in 60 days in EHR in ICD-10 era**	Emergency dept, Inpatient
Narcolepsy / cataplexy	Emergency dept, Inpatient, Outpatient
Pulmonary embolism – **First ever in EHR in ICD-10 era**	Emergency dept, Inpatient
Seizures	Emergency dept, Inpatient
Stroke, hemorrhagic	Emergency dept, Inpatient
Stroke, ischemic	Emergency dept, Inpatient
Thrombosis with thrombocytopenia syndrome – **First ever in EHR in ICD-10 era**	Emergency dept, Inpatient
Thrombotic thrombocytopenic purpura	Emergency dept, Inpatient
Transverse myelitis	Emergency dept, Inpatient
Venous thromboembolism – **First ever in EHR in ICD-10 era**	Emergency dept, Inpatient, Outpatient

VSD Rapid Cycle Analysis (RCA) analytic strategy

- For the primary analysis, the number of outcomes observed in the risk interval after COVID-19 vaccination were compared to the number expected
- The expected was derived from “vaccinated concurrent comparators” who were in a comparison interval after COVID-19 vaccination
- On each day that an outcome occurred, vaccinees who were in their risk interval were compared with similar vaccinees who were concurrently in their comparison interval
  - Comparisons were adjusted for age group, sex, race/ethnicity, VSD site, as well as calendar date
- For the pre-specified outcome myocarditis/pericarditis, cases were verified using the CDC case definition (https://www.cdc.gov/mmwr/volumes/70/wr/mm7027e2.htm)

mRNA COVID-19 vaccine doses administered in VSD in 18–39-year-olds by week

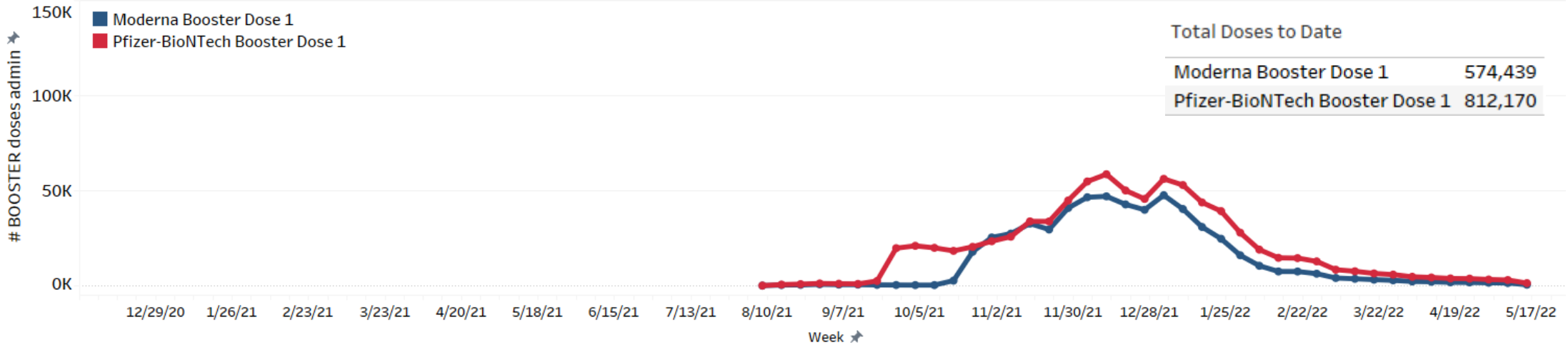
PRIMARY SERIES doses administered to 18-39-year-olds by week



Total Doses to Date

Moderna Dose 1	949,272
Moderna Dose 2	949,998
Pfizer Dose 1	1,536,147
Pfizer Dose 2	1,519,752

BOOSTER doses administered to 18-39-year-olds by week

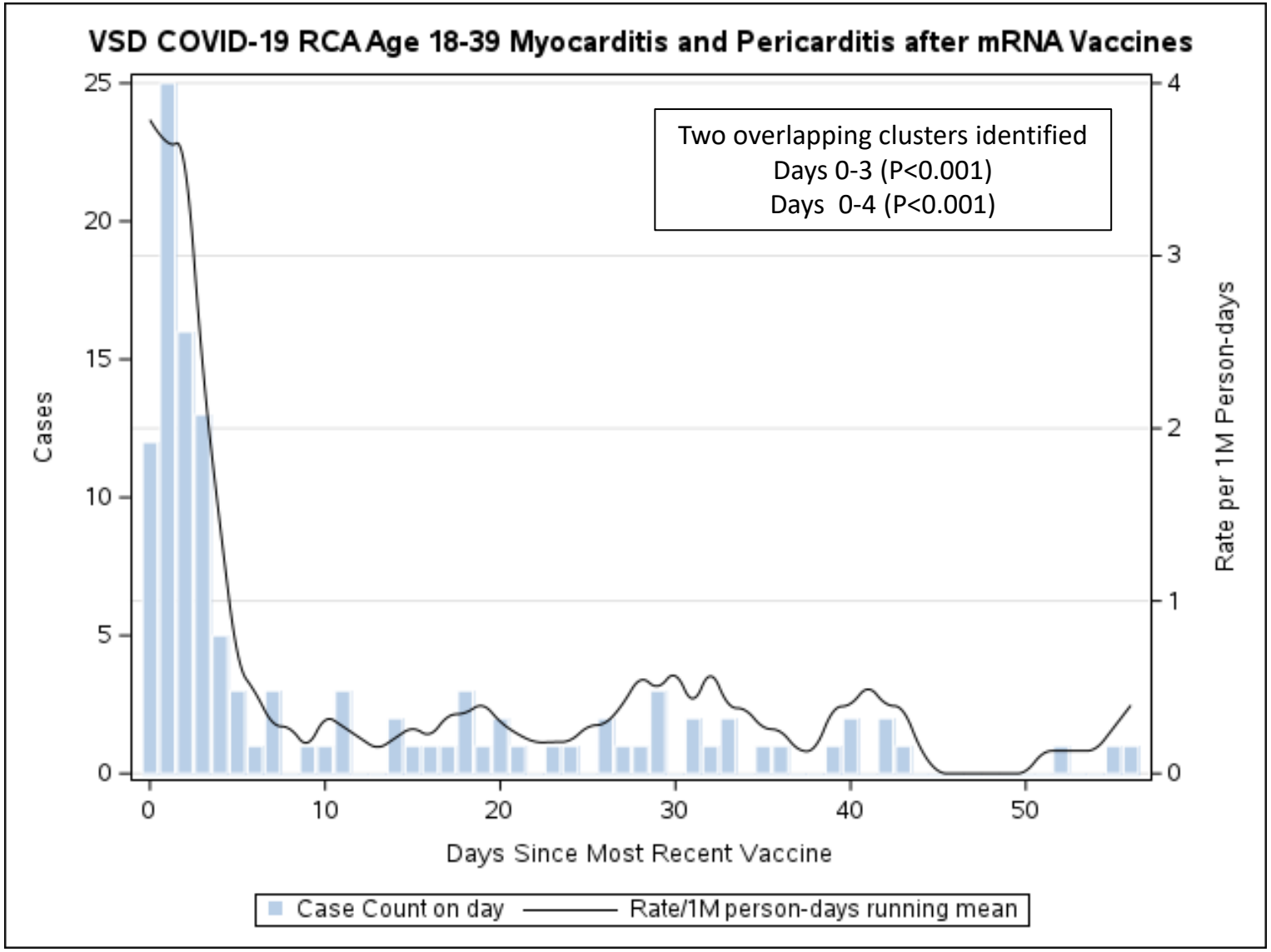


Total Doses to Date

Moderna Booster Dose 1	574,439
Pfizer-BioNTech Booster Dose 1	812,170

Note: Data shown on slide are from December 14, 2020 – May 21, 2022

Day of onset of verified myocarditis/pericarditis among 18–39-year-olds after either primary series dose of a mRNA COVID-19 vaccine



Verified myocarditis and pericarditis in the 0–7-day Risk Interval among 18–39-year-old MALES by product and dose

(compared with outcome events in vaccinated comparators on the same calendar days)

		Analysis					
Vaccine	Dose	Events in Risk Interval	Events in Comparison Interval*	Adjusted Rate Ratio†	95% Confidence Interval	2-sided P-value	Excess cases in Risk Period per million doses
Either mRNA COVID-19 Vaccine**	Dose 1	11	18	2.10	0.86 – 4.97	0.101	5.1
	Dose 2	59	11	**14.51**	**7.54 – 29.88**	**<0.001**	50.6
	Booster	18	5	**7.53**	**2.66 – 24.53**	**<0.001**	29.5
Pfizer-BioNTech (primary)	Dose 1	5	12	1.91	0.56 – 5.87	0.279	3.4
	Dose 2	32	7	**13.98**	**6.01 – 36.14**	**<0.001**	44.1
Pfizer-BioNTech (booster)	Booster	10	2	**13.72**	**2.86 – 104.20**	**<0.001**	32.3
Moderna (primary)	Dose 1	6	6	2.41	0.63 – 9.24	0.193	8.2
	Dose 2	27	3	**23.46**	**7.49 – 100.76**	**<0.001**	62.7
Moderna (booster)	Booster	5	2	4.56	0.82 – 36.56	0.085	21.5

* Comparison interval is 22–42 days after either dose

† Adjusted for VSD site, 5-year age group, sex, race/ethnicity, and calendar date

** Individual product events may not sum to "Either mRNA COVID-19 Vaccine" total due to heterologous series and/or noninformative events.

Verified myocarditis and pericarditis in the 0–7-day Risk Interval among 18–39-year-old FEMALES by product and dose

(compared with outcome events in vaccinated comparators on the same calendar days)

		Analysis					
Vaccine	Dose	Events in Risk Interval	Events in Comparison Interval*	Adjusted Rate Ratio†	95% Confidence Interval	2-sided P-value	Excess cases in Risk Period per million doses
Either mRNA COVID-19 Vaccine**	Dose 1	3	2	5.36	0.70 – 50.71	0.105	1.8
	Dose 2	6	1	**22.08**	**3.10 – 530.11**	**<0.001**	4.4
	Booster	4	3	2.68	0.54 – 14.85	0.227	3.4
Pfizer-BioNTech (primary)	Dose 1	1	1	5.44	0.14 – 213.88	0.312	1.0
	Dose 2	5	1	**19.85**	**2.59 – 495.35**	**0.002**	5.9
Pfizer-BioNTech (booster)	Booster	1	2	0.98	0.03 – 12.91	0.976	-0.05
Moderna (primary)	Dose 1	2	1	3.86	0.27 – 120.68	0.325	2.9
	Dose 2	1	0	NE	0.33 - ∞	0.136	2.0
Moderna (booster)	Booster	1	1	2.48	0.06 – 105.24	0.591	6.9

NE= not estimable

* Comparison interval is 22–42 days after either dose

** Individual product events may not sum to "Either mRNA COVID-19 Vaccine" total due to heterologous series and/or noninformative events.

† Adjusted for VSD site, 5-year age group, sex, race/ethnicity, and calendar date

Verified myocarditis and pericarditis 0-7 days after any primary series dose of mRNA COVID-19 vaccine: Level of care and status by age group/product

Level of care and status	18–39-year-olds (Pfizer-BioNTech) N=43	18-39–year-olds (Moderna) N=35
Highest level of care		
Emergency department	5 (12%)	6 (17%)
Admitted to hospital	37 (86%)	29 (83%)
Admitted to ICU	1 (2%)	0 (0%)
Length of hospital stay, median (range)	1 day (0 – 2 days)	1 day (0 – 13 days)
0 – 1 days	24 (56%)	23 (66%)
2 – 3 days	19 (44%)	11 (31%)
4+ days	0 (0%)	1 (3%)
Discharged to home	43 (100%)	35 (100%)

Verified myocarditis and pericarditis 0-7 days after 1st booster dose of mRNA COVID-19 vaccine: Level of care and status by age group/product

Level of Care and Status	18–39-year-olds (Pfizer-BioNTech) N=23	18-39–year-olds (Moderna) N=12
Highest level of care		
Emergency department	4 (17%)	2 (17%)
Admitted to hospital	18 (78%)	9 (75%)
Admitted to ICU	1 (4%)	1 (8%)
Length of hospital stay, median (range)	1 day (0 – 3 days)	1 days (0 – 2 days)
0 – 1 days	17 (74%)	9 (75%)
2 – 3 days	6 (26%)	3 (25%)
4+ days	0 (0%)	0 (0%)
Discharged to home	23 (100%)	12 (100%)

Summary: Myocarditis and pericarditis following mRNA COVID-19 vaccination

- Current evidence supports a causal association between mRNA COVID-19 vaccination and myocarditis and pericarditis
- Cases following mRNA COVID-19 vaccination cluster within the first week of vaccination
- Risk is greatest in adolescents and young adults, higher after dose 2 compared to dose 1 of the primary series, and higher in males compared to females
  - Some risk estimates for females in VSD are comparable to males but case counts are small and excess risk in females is substantially lower than for males
- Risk appears to decrease with age and the male to female predominance of cases attenuates with age
- Reporting rates in VAERS are highest following dose 2; reporting rates following dose 1 and 1st booster dose tend to be lower
- Incidence rates in VSD of verified myocarditis/pericarditis 0–7 days following mRNA COVID-19 vaccination are generally highest following dose 2
  - In a minority of age and sex strata (e.g., males ages 16–17 years), incidence is highest following booster dose
- Available information suggests that most persons with myocarditis after mRNA COVID-19 vaccination recover from myocarditis by 3–8 months after diagnosis

Acknowledgments

- VAERS Team
- Clinical Immunization Safety Assessment (CISA) Project
- Vaccine Safety Datalink (VSD) Team
- CDC MOVING Team
- CDC Immunization Safety Office
- CDC Infectious Diseases Pathology Branch
- COVID-19 Vaccine Task Force Data Monitoring and Reporting Group
- FDA/Center for Biologics Evaluation and Research
- 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 report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC) or the U.S. Food and Drug Administration (FDA)
- Mention of a product or company name is for identification purposes only and does not constitute endorsement by CDC or FDA

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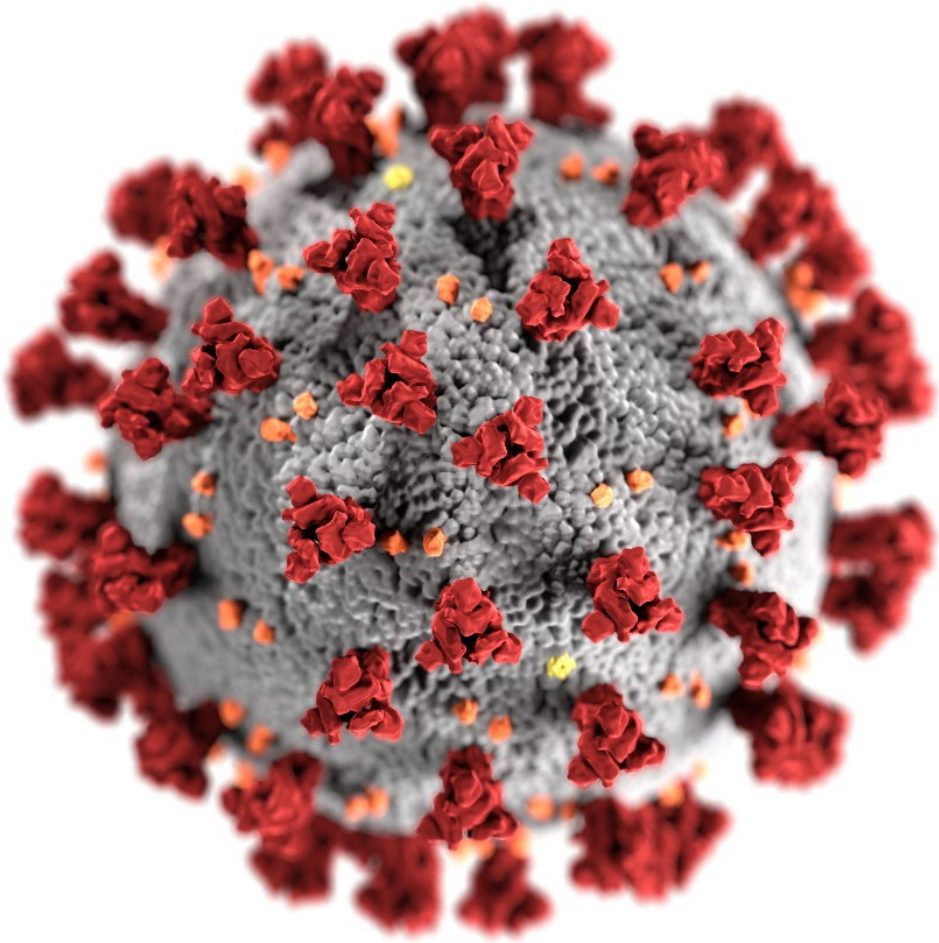

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TTY: 1-888-232-6348 www.cdc.gov

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