Vaccine Safety Updates:
Myocarditis Following mRNA COVID-19 Vaccination

WHO COVID-19 Vaccines Research R&D Blueprint

Oct 25, 2021

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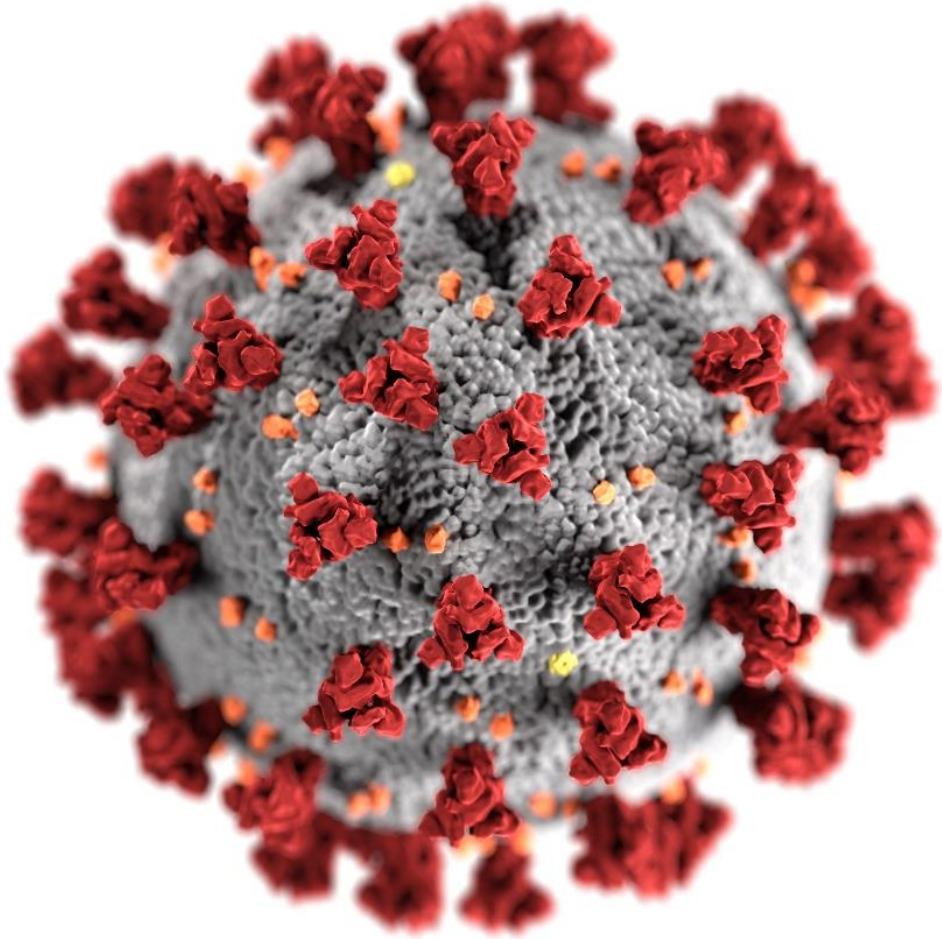


cdc.gov/coronavirus

Disclaimer

- 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) and 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

References

- All information included in this presentation is available at the websites for the Advisory Committee on Immunization Practices (ACIP) and the Vaccines and Related Biological Products Advisory Committee (VRBPAC)
  - https://www.cdc.gov/vaccines/acip/meetings/slides-2021-10-20-21.html
  - https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-october-14-15-2021-meeting-announcement

CDC vaccine safety monitoring

- COVID-19 vaccines are being administered under **the most intensive vaccine safety monitoring effort in U.S. history**
- Strong, complementary systems are in place—both new and established

v-safe

VAERS

VSD

CISA Project

Full list of U.S. COVID-19 vaccine safety monitoring systems

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

Myocarditis and myopericarditis following mRNA COVID-19 vaccination

- Evidence from multiple safety monitoring systems in multiple countries supports the finding of an increased risk of myocarditis and myopericarditis following mRNA COVID-19 vaccination*
  - Risk:
    - Highest in adolescents and young adults
    - Males > females
    - Following dose 2 > dose 1
  - Onset clusters within a few days of vaccination, mostly within a week
  - Cases have tended to be clinically mild

* Gargano et al. Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices — United States, June 2021. MMWR Morb Mortal Wkly Rep 2021;70:977–982.

Mallapaty S. Heart-inflammation risk from Pfizer COVID vaccine is very low. Nature. 2021 Oct 8. doi: 10.1038/d41586-021-02740-y.

Myocarditis and pericarditis following vaccination with COVID-19 mRNA vaccines in Ontario. Available at: Myocarditis and Pericarditis Following Vaccination with COVID-19 mRNA Vaccines in Ontario: December 13, 2020 to August 7, 2021 (publichealthontario.ca).

Comirnaty and Spikevax: possible link to very rare cases of myocarditis and pericarditis. Available at Comirnaty and Spikevax: possible link to very rare cases of myocarditis and pericarditis | European Medicines Agency (europa.eu).

Paterlini M. Covid-19: Sweden, Norway, and Finland suspend use of Moderna vaccine in young people "as a precaution". BMJ. 2021 Oct 11;375:n2477.

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

CDC + FDA

VAERS

Vaccine Adverse Event Reporting System

http://vaers.hhs.gov

Reporting rates (per 1 million doses administered) of myocarditis among males after mRNA COVID-19 vaccines, 7-day risk period (N=797)*

- **169,740,953** doses of mRNA vaccine administered to males (dose 1 and dose 2) *
- Reporting rates exceed background incidence**
  - After dose 1 of Pfizer (12–24 yrs) and Moderna (18–39 yrs)
  - After dose 2 of Pfizer (12–39 yrs) and Moderna (18–49 yrs)

	Pfizer		Moderna	
	(Males)		(Males)	
Ages	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**
12-15	**4.2**	**39.9**	0.0	not calculated
16-17	**5.7**	**69.1**	0.0	not calculated
18-24	**2.3**	**36.8**	**6.1**	**38.5**
25-29	1.3	**10.8**	**3.4**	**17.2**
30-39	0.5	**5.2**	**2.3**	**6.7**
40-49	0.3	2.0	0.2	**2.9**
50-64	0.2	0.3	0.5	0.6
65+	0.2	0.1	0.1	0.3

* As of Oct 6, 2021; 797 of 935 reports after doses 1 and 2 of mRNA vaccines occurred during Days 0–6 after vaccination among males; reports verified to meet case definition by provider interview or medical record review

** 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 the 7-day risk period, this estimated background is **0.2 to 1.9 per 1 million person 7-day risk period**

Reporting rates (per 1 million doses administered) of myocarditis among females after mRNA COVID-19 vaccines, 7-day risk period (N=138)*

- **193,215,313** doses of mRNA vaccine administered to females (dose 1 and dose 2)*
- Reporting rates exceed background incidence**
  - After dose 2 of Pfizer (12–24 yrs) and dose 2 Moderna (18–29 yrs)

	Pfizer		Moderna	
	(Females)		(Females)	
Ages	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**
12-15	0.4	**3.9**	0.0	0.0
16-17	0.0	**7.9**	0.0	0.0
18-24	0.2	**2.5**	0.6	**5.3**
25-29	0.2	1.2	0.4	**5.7**
30-39	0.6	0.7	0.5	0.4
40-49	0.1	1.1	0.2	1.4
50-64	0.3	0.5	0.5	0.4
65+	0.1	0.3	0.0	0.3

* As of Oct 6, 2021; 138 of 935 reports after doses 1 and 2 of mRNA vaccines occurred during Days 0–6 after vaccination among females; reports verified to meet case definition by provider interview or medical record review

** 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 the 7-day risk period, this estimated background is **0.2 to 1.9 per 1 million person 7-day risk period**

Care and outcomes of preliminary myopericarditis cases reported to VAERS after COVID-19 vaccination in persons ≤29 years old (N=1,640)

(data thru Oct 6, 2021)

1,640 total preliminary reports

- **877** met CDC case definition* of myocarditis or myopericarditis
- 637 under review

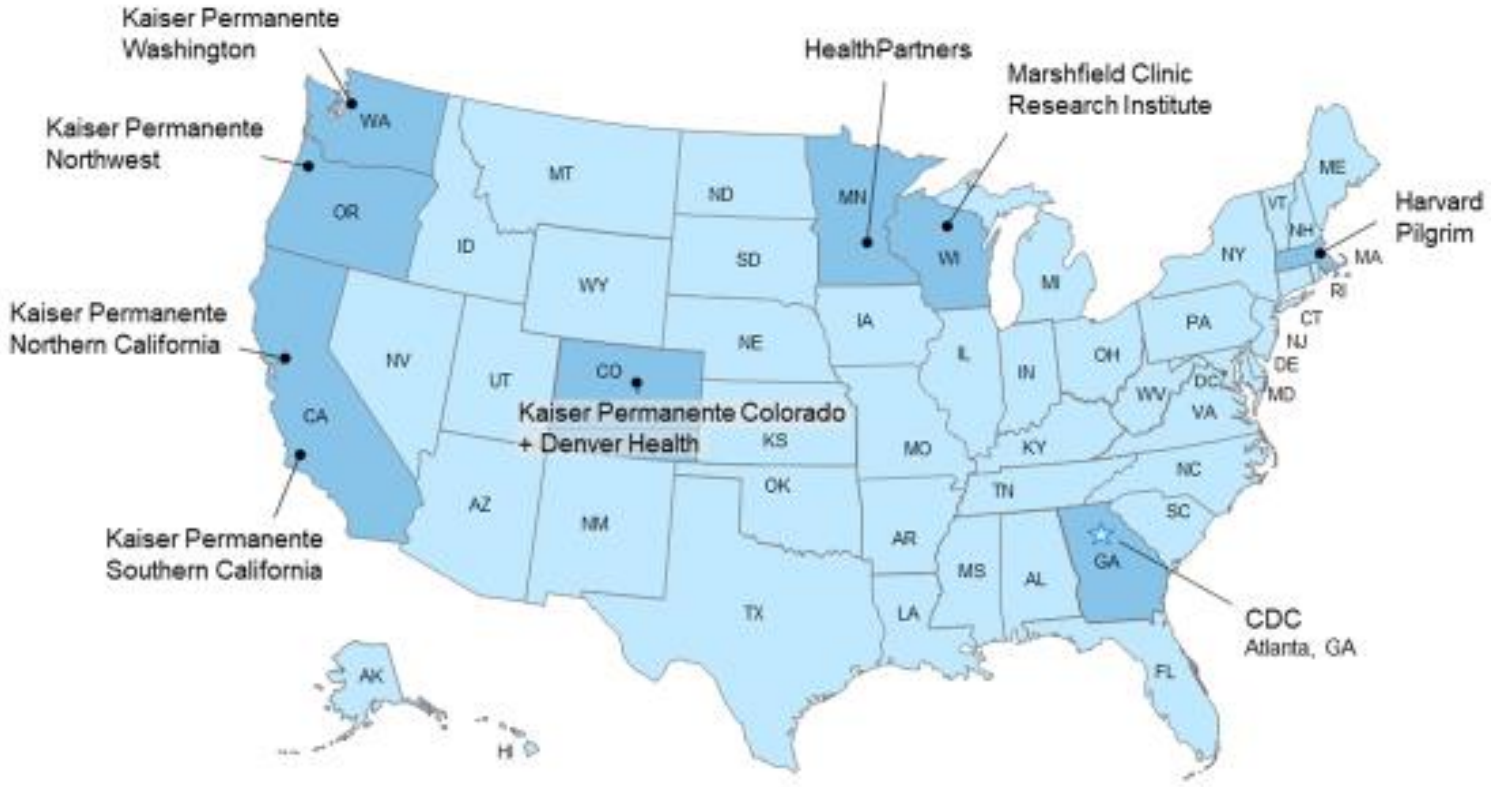
Of 877 meeting case definition:

- 829 were hospitalized
  - 789 discharged
    - **607 (77%) known to have recovered from symptoms at time of report**
  - 19 still hospitalized (5 in ICU)
  - 21 with unknown disposition
- 34 were not hospitalized (seen in emergency dept., urgent care, outpatient clinic, not specified)

* Gargano JW, Wallace M, Hadler SC, et al. Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices — United States, June 2021. MMWR Morb Mortal Wkly Rep 2021;70:977–982.

https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7027e2-H.pdf

The Vaccine Safety Datalink (VSD)



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

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https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/08-COVID-Klein-508.pdf

VSD Rapid Cycle Analysis (RCA)

Aims:

1. To monitor the safety of COVID-19 vaccines weekly using pre-specified outcomes of interest among VSD members.

2. To describe the uptake of COVID-19 vaccines over time among eligible VSD members overall and in strata by age, site, and race/ethnicity.

Surveillance began in December 2020.

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https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/08-COVID-Klein-508.pdf

Confirmed Myocarditis/Pericarditis, among 12–17-year-olds (Pfizer only) in the 0-7 and 0-21 Day Risk Interval by Dose

Compared with Outcome Events in Vaccinated Comparators on the Same Calendar Days

				Analysis			
Risk Interval	Dose	Events in Risk Interval	Events in Comparison Interval[1]	Adjusted Rate Ratio[2,3]	95% Confidence Interval	2-Sided P-value	Excess Cases in Risk Period per 1 Million Doses
Days 0-21	**Both Doses**	30	0	**very high**	**5.68 - ∞**	**<0.001**	**29.6**
	Dose 1	2	0	very high	0.31 - ∞	0.198	3.8
	Dose 2	24	0	**very high**	**9.09 - ∞**	**<0.001**	**56.7**
Days 0-7	**Both Doses**	27	0	**very high**	**16.88 - ∞**	**<0.001**	**25.9**
	Dose 1	0	0	NE	NE	NE	NE
	Dose 2	23	0	**very high**	**28.83 - ∞**	**<0.001**	**54.0**

NE= not estimable; indicates that vaccine effect cannot be estimated.
[1]Comparison interval is 22–42 days after either dose.
[2]Adjusted for VSD site, 5-year age group, sex, race/ethnicity, and calendar date.
[3]The focus should be on the lower bound of the confidence interval.

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https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/08-COVID-Klein-508.pdf

Confirmed Myocarditis/Pericarditis in the 0-7 Day Risk Interval, among 18–39-year-olds 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[1]	Adjusted Rate Ratio[2]	95% Confidence Interval	2-Sided P-value	Excess Cases in Risk Period per 1 Million Doses
Both mRNA	Both Doses	39	6	12.61	5.27 - 34.47	<0.001	8.4
	Dose 1	10	6	9.69	2.90 - 34.22	<0.001	4.1
	Dose 2	29	5	14.33	5.50 - 43.88	<0.001	13.1
Pfizer	Both Doses	17	5	7.98	2.72 - 26.50	<0.001	5.7
	Dose 1	5	5	8.05	1.89 - 33.89	0.006	3.3
	Dose 2	12	4	8.77	2.56 - 35.34	<0.001	8.5
Moderna	Both Doses	22	1	37.42	6.68 - 801.33	<0.001	12.8
	Dose 1	5	1	10.47	1.38 - 258.35	0.020	5.2
	Dose 2	17	0	very high[3]	11.70 - ∞	<0.001	21.0

[1]Comparison interval is 22–42 days after either dose.
[2]Adjusted for VSD site, 5-year age group, sex, race/ethnicity, and calendar date.
[3]The focus should be on the lower bound of the confidence interval.

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https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/08-COVID-Klein-508.pdf

Myocarditis/Pericarditis: Moderna vs Pfizer

- Analyses with vaccinated concurrent comparators indicate that both Pfizer and Moderna are associated with increased risk of myocarditis/pericarditis in 12–39-year-olds.
  - Pfizer results include 12–39-year-olds while Moderna only includes 18–39-year-olds.
- Analyses with vaccinated concurrent comparators indirectly suggest that Moderna is associated with more risk of myocarditis/pericarditis than Pfizer.
- To directly test whether the risk of myocarditis/pericarditis after Moderna differs from that after Pfizer, we conducted head-to-head comparisons among 18–39-year-olds.

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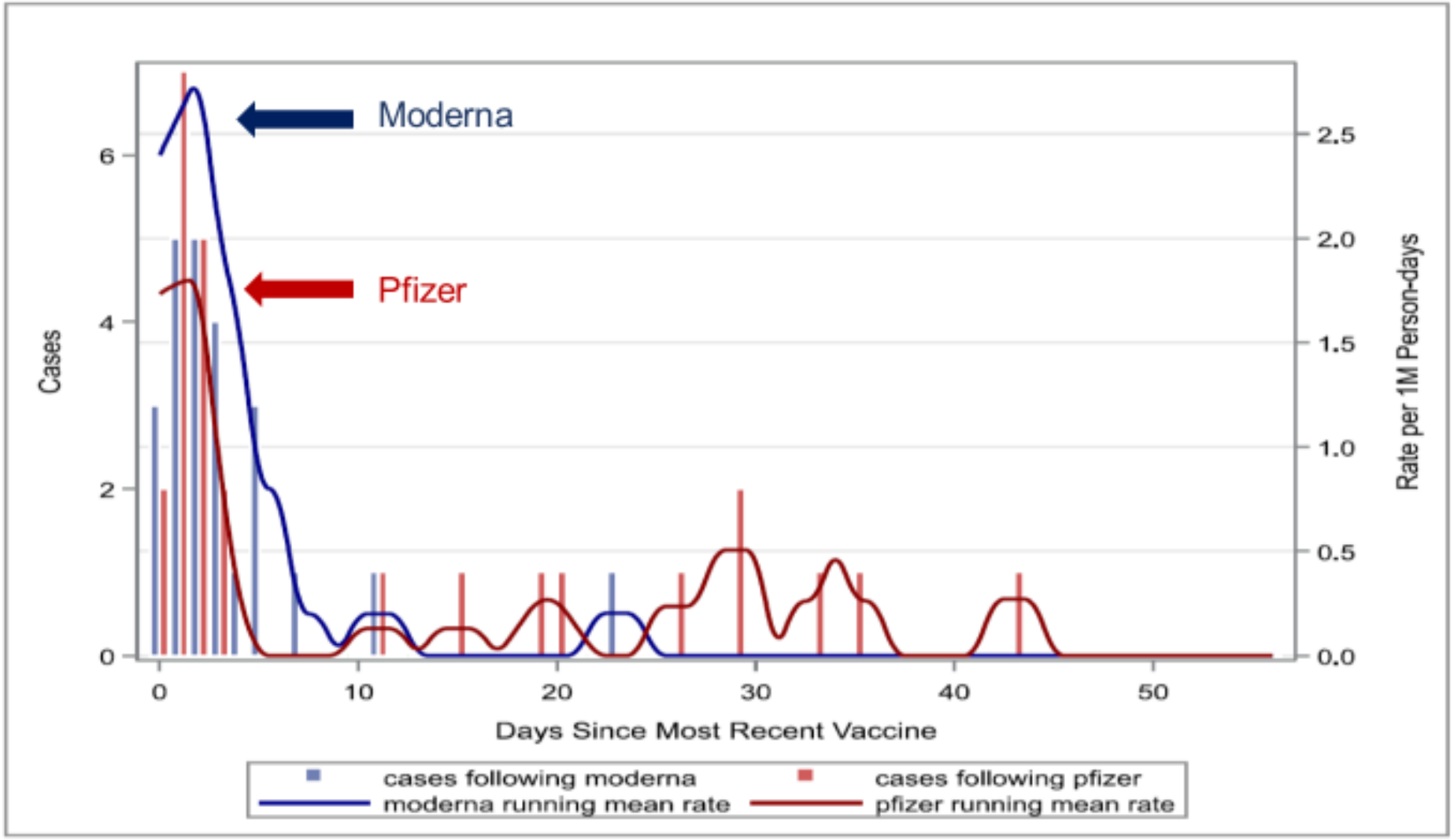
https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/08-COVID-Klein-508.pdf

Incidence of Confirmed Myocarditis/Pericarditis in 18-39 Year-Olds: Moderna vs Pfizer



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https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/08-COVID-Klein-508.pdf

Summary of Myocarditis/Pericarditis Analyses Days 0-7 after Dose 2 among 18-39 Year Olds: Moderna vs Pfizer

Includes Pericarditis	Sex	Adjusted Rate Ratio[1]	95% Confidence Interval	2-sided P-value	Excess Cases in Risk Period per 1M Doses of Moderna vs Pfizer [2]
Yes	Both Sex	2.72	1.25 - 6.05	0.012	13.3
	Male	2.26	1.00 - 5.19	0.051	21.5
No	Both Sex	2.28	1.00 - 5.22	0.049	9.7
	Male	2.14	0.93 - 4.98	0.074	19.1

[1]Adjusted for VSD site, age, sex, race/ethnicity, and calendar date. Adjusted rate ratio is an estimate of the Moderna rate divided by Pfizer rate.
[2]Excess cases is an estimate of the Moderna rate minus the Pfizer rate.

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https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/08-COVID-Klein-508.pdf

Surveillance Updates of Myocarditis/Pericarditis and mRNA COVID-19 Vaccination in the FDA BEST System

Vaccines and Related Biological Products Advisory Committee
October 14, 2021

Hui-Lee Wong, PhD, MSc
Associate Director for Innovation and Development
Office of Biostatistics and Epidemiology
Center for Biologics Evaluation and Research
US Food and Drug Administration

https://www.fda.gov/media/153090/download

Myocarditis/pericarditis in first 1-7 days of receipt of mRNA COVID-19 vaccines in FDA BEST System

FDA

- Incidence rates for mRNA COVID-19 vaccines
- Incidence rate ratios for Moderna versus Pfizer-BioNTech

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Center for Biologics Evaluation and Research (CBER)

Biologics Effectiveness and Safety (BEST) Initiative

Limitations

FDA

- Events were not chart-confirmed
- Partial adjustment for potential confounders
  - Cannot rule out biased estimates
- Large uncertainty of incidence rates and incidence rate ratios
  - Small number of events, wide confidence intervals
- Relies on the assumption that the claims delay for Pfizer is similar to Moderna.
  - Claims delay: the time between the day of service and the day of observation in the database
- Heterogeneity results across databases are under review

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https://www.fda.gov/media/153090/download

Summary

- Incidence rates estimates of myocarditis/pericarditis after mRNA COVID-19 vaccination
  - Highest in males ages 18 to 25 years
  - More events were observed post-Dose 2 than in post-Dose 1
  - Wide range of incidence rates among four BEST databases with wide confidence intervals
- Incidence rate ratio estimates comparing Moderna and Pfizer-BioNTech vaccines
  - Preliminary results do not support a significant difference for males 18-25 years
  - Estimates had large uncertainty
    - Small numbers of observed events
    - Partial adjustment for some potential confounders

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https://www.fda.gov/media/153090/download

CDC COVID-19 Vaccine Safety Technical (VaST) Work Group

Moderna COVID-19 vaccination: Overview of post-authorization safety – myocarditis/pericarditis

- Data available to date show association of myocarditis with both mRNA vaccines in adolescents and young adults, males > females
  - Some systems show greater risk after Moderna than Pfizer vaccination
    - United States (VSD), Canada, Scandinavian countries
  - Other U.S. safety monitoring systems do not show a difference between the two mRNA vaccines
    - VAERS, FDA BEST Systems, VA
- Further data are being compiled to understand
  - Differences between safety systems
  - Optimal management strategies
  - Long-term outcomes

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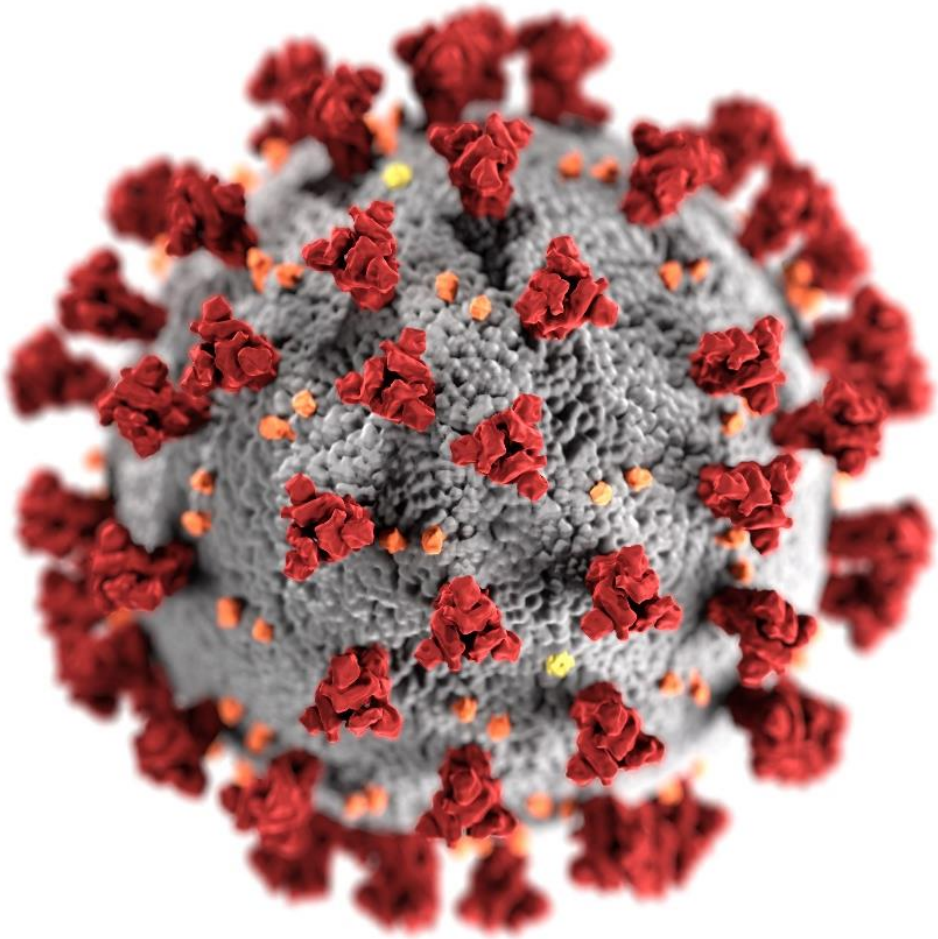
https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/09-COVID-Talbot-508.pdf

Acknowledgments

Thanks to the many people who made analysis of these data possible:

- **VAERS Team**
  - VAERS TTS abstraction team
  - VAERS Myopericarditis abstraction team
  - VAERS data team
- **Clinical Immunization Safety Assessment Project**
- **CDC team investigating long-term effects of myocarditis**
- **VSD Team, VSD participating sites, and investigators from Kaiser Permanente Northern California and the Marshfield Clinic Research Institute**
- **CDC COVID-19 Data Monitoring and Reporting Group**
- **FDA/Center for Biologics Evaluation and Research**

Thank you!



For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

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 enhanced surveillance for myocarditis outcomes after mRNA COVID-19 vaccination in VAERS case reports*

- 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: Ascertains 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
- Timeline: data collection August 2021–November 2021 (anticipated)

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

CDC enhanced surveillance for myocarditis outcomes after mRNA COVID-19 vaccination in VAERS case reports* (cont.)

- As of August 2021, VAERS had received 826 reports of myocarditis or myopericarditis after COVID-19 vaccination that met case definition
- To date, around 680 patients have reached 90 days post-myocarditis diagnosis
  - Of these, 282 (41%) have received at least one phone call
    - Of the 282 patients who have received a call, 168 (60%) completed the survey and 67 (24%) were unreachable or declined to participate
      - Of the 168 patients surveyed, 132 (79%) provided cardiologist or healthcare provider contact information
        - Of the 132 cardiologist or healthcare providers, 26 have completed the survey
        - Remaining 106 in the process of being contacted

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

VSD COVID-19 vaccine prespecified surveillance outcomes	Settings	Risk window (days)	Exclude if COVID-19 in the prior X days
Acute disseminated encephalomyelitis	E, I	1-21, 1-42	
Acute myocardial infarction – **First Ever**	E, I	1-21, 1-42	30 days
Acute respiratory distress syndrome	E, I	0-84	42 days
Anaphylaxis – **First in 7 days**	E, I	0-1	
Appendicitis	E, I	1-21, 1-42	
Bell's palsy – **First Ever**	E, I, O	1-21, 1-42	30 days
Cerebral venous sinus thrombosis	E, I	1-21, 1-42	30 days
Disseminated intravascular coagulation	E, I	1-21, 1-42	42 days
Encephalitis / myelitis / encephalomyelitis	E, I	1-21, 1-42	30 days
Guillain-Barré syndrome	E, I	1-21, 1-42	
Immune thrombocytopenia	E, I, O	1-21, 1-42	30 days
Kawasaki disease	E, I	1-21, 1-42	
Multisystem inflammatory syndrome in children/adults	E, I	0-84	
Myocarditis / pericarditis – **First in 60 Days**	E, I	1-21, 1-42	30 days
Narcolepsy / cataplexy	E, I, O	0-84	
Pulmonary embolism – **First Ever**	E, I	1-21, 1-42	30 days
Seizures	E, I	1-21, 1-42	30 days
Stroke, hemorrhagic	E, I	1-21, 1-42	30 days
Stroke, ischemic	E, I	1-21, 1-42	30 days
Thrombosis with thrombocytopenia syndrome – **First Ever**	E, I	1-21, 1-42	30 days
Thrombotic thrombocytopenic purpura	E, I	1-21, 1-42	30 days
Transverse myelitis	E, I	1-21, 1-42	
Venous thromboembolism – **First Ever**	E, I, O	1-21, 1-42	30 days

Abbreviations: E=ED, I=Inpatient, O=Outpatient