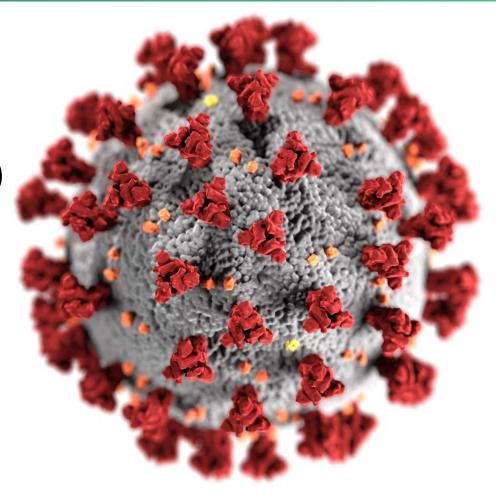
COVID-19 Vaccine Safety Updates

Advisory Committee on Immunization Practices (ACIP) Oct 21, 2021

Tom Shimabukuro, MD, MPH, MBA Vaccine Safety Team CDC COVID-19 Vaccine Task Force





cdc.gov/coronavirus

Topics

- Overview of myocarditis following COVID-19 vaccination
- Update on the safety of Janssen COVID-19 Vaccine
- Safety of a Janssen COVID-19 primary vaccination followed by an additional mRNA COVID-19 vaccination



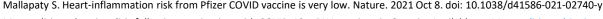
Myocarditis and Myocarditis with Pericarditis (Myopericarditis) Following COVID-19 Vaccination



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.



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 (publishealthontario ca).



Myocarditis and myopericarditis following mRNA COVID-19 vaccination – presentation topics

- Highlights from:
 - U.S. Food and Drug Administration (FDA) monitoring
 - U.S. Department of Defense (DoD) monitoring
 - Department of Veterans Affairs (VA)
 - International surveillance
 - CDC investigation of long-term effects of myocarditis
- Vaccine Adverse Event Reporting System (VAERS) and Vaccine Safety
 Datalink (VSD) updates on myocarditis and myopericarditis following mRNA
 COVID-19 vaccination will be provided separately during this safety session



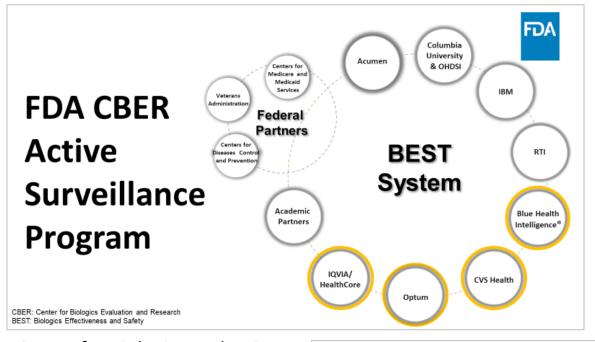


Surveillance Updates of Myocarditis/Pericarditis and mRNA COVID-19 Vaccination in the FDA BEST System

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





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



Incidence rates for mRNA COVID-19 vaccines

Incidence rate ratios for Moderna versus Pfizer-BioNTech

Center for Biologics Evaluation and Research (CBER)

Biologics Effectiveness and Safety (BEST) Initiative

Limitations



- 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



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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- Military Health System continues to identify and follow patients with myocarditis following COVID-19 vaccination
- Overall rate of myocarditis within 7 days of vaccination is 10 cases per million doses, but risk is strongly dependent on patient age and sex, and vaccine dose and type; rate of myocarditis in younger (under age 20) males after 2nd dose mRNA vaccine is >100 cases per million doses
- Approximately two-thirds of patients report feeling fully recovered within 6 weeks of diagnosis; standard American College of Cardiology recommendations limit strenuous activity for 3-6 months; follow-up within Military Health System is ongoing

June 29, 2021

Myocarditis Following Immunization With mRNA COVID-19 Vaccines in Members of the US Military

Jay Montgomery, MD^{1,2}; Margaret Ryan, MD, MPH^{1,3}; Renata Engler, MD⁴; Donna Hoffman, MSN^{1,2}; Bruce McClenathan, MD^{1,5}; Limone Collins, MD¹; David Loran, DNP^{1,3}; David Hrncir, MD^{1,6}; Kelsie Herring, MD⁷; Michael Platzer, MD⁸; Nehkonti Adams, MD^{4,8}; Aliye Sanou, MD⁸; Leslie T. Cooper Jr, MD⁹

» Author Affiliations | Article Information

JAMA Cardiol. 2021;6(10):1202-1206. doi:10.1001/jamacardio.2021.2833





- Weekly analysis comparing observed to expected number of prespecified outcomes from historical rates adjusting for sequential tests
- Near-real time chart reviews for assessment of specific incident events
 - Initial chart review to assess presumptive events
 - Detailed chart review:
 - Subject matter experts confirm outcomes through defined criteria
 - Evaluates the timeframe of onset (i.e., within risk period)

Collaborators/Federal Partners – CDC, FDA, DOD

Summary of VA RCA for myocarditis/pericarditis

- Vaccinated population
 - 3.5 million Moderna doses administered (1.84 million dose 1, 1.70 million dose 2)
 - 3.1 million <u>Pfizer-BioNTech</u> doses administered (1.64 million dose 1, 1.46 million dose 2)
 - Limited use of the <u>Janssen</u> vaccine in VA population (~270 thousand doses)
 - 89% male; 60% aged 65+ years old, with Janssen vaccinated cohort younger
- No statistical signals for myocarditis/pericarditis with any COVID-19 vaccine, although limited data available for Janssen vaccine
- 7 chart confirmed myocarditis/myopericarditis cases
 - 6 in males and 1 in a female
 - Median age 37 years (range 24-66 years)
 - Median onset 3 days (range 1-18 days)
 - Most after dose 2: Pfizer-BioNTech dose 2 (n=4) and dose 1 (n=1), Moderna dose 2 (n=2)
 - Highest rate in 18-39-year-olds
 - All cases clinically resolved
- Absence of myocarditis signal in VA data likely due to age differences in VA population

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel

D. Mevorach, E. Anis, N. Cedar, M. Bromberg, E.J. Haas, E. Nadir, S. Olsha-Castell, D. Arad, T. Hasin, N. Levi, R. Asleh, O. Amir, K. Meir, D. Cohen, R. Dichtiar, D. Novick, Y. Hershkovitz, R. Dagan, I. Leitersdorf, R. Ben-Ami, I. Miskin, W. Saliba, K. Muhsen, Y. Levi, M.S. Green, L. Keinan-Boker, and S. Alroy-Preis

Mevorach et al. Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel. N Engl J Med. 2021 Oct 6. doi: 10.1056/NEJMoa2109730.

Public Santé publique Ontario



Myocarditis and Pericarditis Following Vaccination with COVID-19 mRNA Vaccines in Ontario: December 13, 2020 to August 7, 2021

https://www.publichealthontario.ca/-/media/documents/ncov/epi/covid-19-myocarditis-pericarditis-vaccines-epi.pdf?sc lang=en



ORIGINAL ARTICLE

Myocarditis after Covid-19 Vaccination in a Large Health Care Organization

Guy Witberg, M.D., Noam Barda, M.D., Ph.D., Sara Hoss, M.D., Ilan Richter, M.D., M.P.H., Maya Wiessman, M.D., Yaron Aviv, M.D., Tzlil Grinberg, M.D., Oren Auster, M.Sc., Noa Dagan, M.D., Ph.D., M.P.H., Ran D. Balicer, M.D., Ph.D., M.P.H., and Ran Kornowski, M.D.

Witberg et al. Myocarditis after Covid-19 Vaccination in a Large Health Care Organization. N Engl J Med. 2021 Oct 6. doi: 10.1056/NEJMoa2110737



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.





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)

CDC

^{* &}lt;a href="https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myo-outcomes.html">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



^{* &}lt;a href="https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myo-outcomes.html">https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myo-outcomes.html

Update on the Safety of Janssen COVID-19 Vaccine





Review of Post Authorization Safety Data for Janssen COVID-19 Vaccine

Narayan Nair, MD

Division Director

Division of Epidemiology,

Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, FDA

October 15, 2021



Adverse Event Reporting under EUA



Vaccine Recipients

Vaccination Providers Vaccine EUA Sponsor





- Spontaneous reports
- Solicited reports from v-safe program

Mandatory Reporting

- Vaccination administration errors (providers only)
- Serious adverse events (SAEs)
- Multisystem Inflammatory Syndrome
- Cases of COVID-19 that result in hospitalization or death

Monthly Periodic Safety Reports

- Analysis of aggregate AE data
- Newly identified safety concerns



- Review of all Adverse Events of Special Interest (AESI)
- Data Abstraction

VAERS





- Screening of all incoming SAEs
- Literature review
- Data Mining
- Potential safety signals will be further evaluated





Most Commonly Reported Adverse Events to VAERS after Janssen COVID-19 Vaccine - 14,688,615 doses of vaccine administered (data as of 10/7/21)



N (%)
16,408 (26.1)
13,939 (22.2)
11,717 (18.6)
11,202 (17.8)
10,553 (16.8)
8,495 (13.5)
8,469 (13.5)
6,265 (10.0)
4,931 (7.8)
4,230 (6.7)

^{*}Terms are not mutually exclusive





Summary of Post-authorization Safety Data following the Janssen Vaccine



Existing safety concerns

FDA and CDC continue to follow cases of GBS, and TTS reported to VAERS following Janssen COVID-19 vaccination

Emerging potential safety

Information regarding these adverse events are currently communicated in EUA Fact Sheets

safety
concerns

FDA and CDC continue to assess cases of myocarditis, pericarditis, ITP, TEE reported to VAERS following Janssen COVID-19 vaccination

https://www.bestinitiat ive.org/wpcontent/uploads/2021/ 01/C19-Vaccine-Safety-AESI-Background-Rate-Protocol-2020.pdf Preliminary analysis of unadjudicated cases in VAERS reveal an increased observed to expected ratio of myocarditis/pericarditis, and ITP

FDA Near Real-Time Surveillance of 16 potential outcomes does not reveal safety signals for these adverse events at this time



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Vaccine Safety Datalink (VSD) Rapid Cycle Analysis (RCA) findings for Janssen COVID-19 vaccine



- VSD conducts RCA, which is near real-time sequential monitoring for prespecified surveillance outcomes of interest
- A relatively small number of Janssen COVID-19 vaccinations (~440 thousand) administered compared to mRNA COVID-19 vaccinations (~14 million)
- No statistical signals detected for any VSD RCA prespecified surveillance outcomes following Janssen COVID-19 vaccination in the 1–21-day risk interval
- Descriptive analysis indicates an imbalance of Guillain-Barré syndrome (GBS) cases following Janssen COVID-19 vaccination compared to mRNA COVID-19 vaccination with proportionally more GBS cases being observed after Janssen COVID-19 vaccination



Thrombosis with thrombocytopenia syndrome (TTS)

This is an official CDC HEALTH ALERT

Distributed via the CDC Health Alert Network April 13, 2021, 1:00 PM ET CDCHAN-00442

Cases of Cerebral Venous Sinus Thrombosis with Thrombocytopenia after Receipt of the Johnson & Johnson COVID-19 Vaccine

Summary

As of April 12, 2021, approximately 6.85 million doses of the Johnson & Johnson (J&J) COVID-19 vaccine (Janssen) have been administered in the United States. The Centers for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA) are reviewing data involving six U.S. cases of a rare type of blood clot in individuals after receiving the J&J COVID-19 vaccine that were reported to the Vaccine Adverse Events Reporting System (VAERS). In these cases, a type of blood clot called cerebral venous sinus thrombosis (CVST) was seen in combination with low levels of blood platelets (thrombocytopenia). All six cases occurred among women aged 18–48 years. The interval from vaccine receipt to symptom onset ranged from 6–13 days. One patient died. Providers should maintain a high index of suspension for symptoms that might represent serious thrombotic events or thrombocytopenia in patients who have recently received the J&J COVID-19 vaccine. When these specific type of blood clots are observed following J&J COVID-19 vaccination, treatment is different from the treatment that might typically be administered for blood clots. Based on studies conducted among the patients diagnosed with immune thrombotic thrombocytopenia after the AstraZeneca COVID-19 vaccine in Europe, the pathogenesis of these rare and unusual adverse events after vaccination may be associated with platelet-activating antibodies against platelet factor-4 (PF4), a type of protein. Usually, the anticoagulant drug called heparin is used to treat blood clots. In this setting, the use of heparin may be harmful, and alternative treatments need to be given.

CDC will convene an emergency meeting of the Advisory Committee on Immunization Practices (ACIP) on Wednesday, April 14, 2021, to further review these cases and assess potential implications on vaccine policy. FDA will review that analysis as it also investigates these cases. Until that process is complete, CDC and FDA are recommending a pause in the use of the J&J COVID-19 vaccine out of an abundance of caution. The purpose of this Health Alert is, in part, to ensure that the healthcare provider community is aware of the potential for these adverse events and can provide proper management due to the unique treatment required with this type of blood clot.

Background

VAERS is a national passive surveillance system jointly managed by CDC and FDA that monitors adverse events after vaccinations. The six patients (after 6.85 million vaccine doses administered) described in these VAERS reports came to attention in the latter half of March and early April of 2021 and developed symptoms a median of 9 days (range = 6–13 days) after receiving the J&J COVID-19 vaccine. Initial presenting symptoms were notable for headache in five of six patients, and back pain in the sixth who subsequently developed a headache. One patient also had abdominal pain, nausea, and vomiting. Four developed focal neurological symptoms (focal weakness, aphasia, visual disturbance) prompting presentation for emergency care. The median days from vaccination to hospital admission was 15 days (range = 10–17 days). All were eventually diagnosed with



Reporting rates of confirmed TTS cases (N=47) in VAERS after Janssen COVID-19 vaccination (15.3 million doses administered as of Oct 13, 2021†)

	Females (n=34)				Males (n:	=13)
Age group	TTS cases	Doses admin.	Reporting rate [‡] (per million)	TTS cases	Dose admin.	Reporting rate [‡] (per million)
18–29 yrs	4	1,130,467	3.5	3	1,640,147	1.8
30–39 yrs	11	1,079,231	10.2	2	1,517,490	1.3
40–49 yrs	9	1,145,500	7.9	4	1,450,634	2.8
50–64 yrs	8	2,053,566	3.9	4	2,405,659	1.7
65+ yrs	2	1,115,936	1.8	0	1,023,268	0

- Cases include 5 deaths related to complications from TTS following Janssen COVID-19 vaccination
 - Median age 37 years (range 29–52 years); 4 of 5 female; all 5 had cerebral venous sinus thrombosis
 - None received heparin; median platelet count nadir 15,000/μL (range 9,000-31,000/μL)
 - Anti-PF4 antibody ELISA testing performed for 4 decedents, all positive with optical density values >2.0



^{*} Source of doses administered: https://covid.cdc.gov/covid-data-tracker/#vaccinations

[†] Reporting rate = TTS cases per 1 million Janssen COVID-19 vaccine doses administered

Summary of Janssen COVID-19 safety monitoring

- Existing safety concerns for Janssen COVID-19 vaccine
 - Current evidence suggests a causal association for TTS, though the condition is rare (47 confirmed cases after 15.3 million Janssen COVID-19 vaccinations administered)
 - Most cases are in women, with most aged 18-49 years old
 - Monitoring in VAERS and VSD suggest a possible association between Guillain-Barré syndrome and Janssen COVID-19 vaccination
- CDC, FDA, and federal partners will continue to assess emerging potential safety concerns (myocarditis/pericarditis, immune thrombocytopenia, thromboembolic events)



Safety of Janssen COVID-19 Primary Vaccination Followed by an Additional mRNA COVID-19 Vaccine Dose: Vaccine Safety Datalink (VSD)



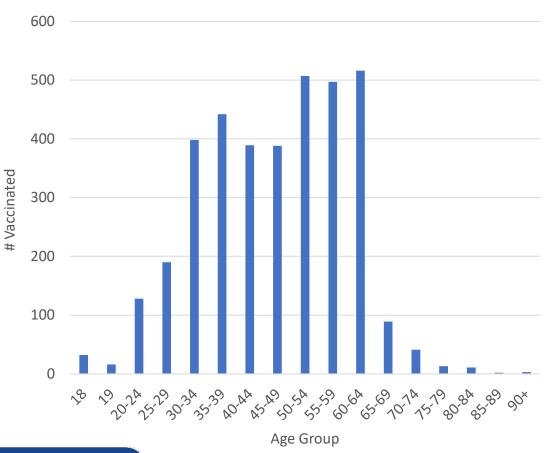
VSD Rapid Cycle Analysis (RCA)

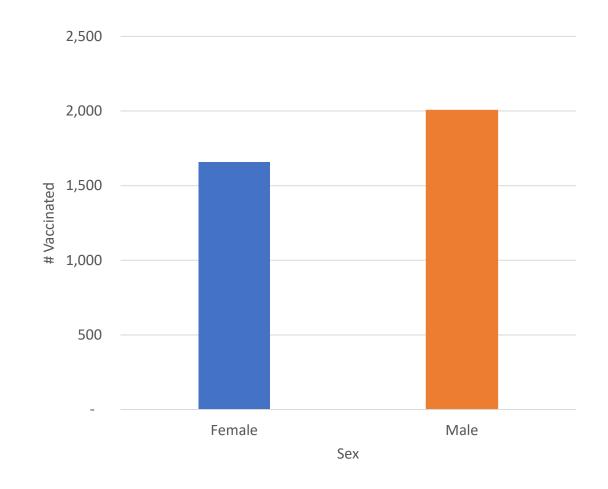
- VSD is monitoring the safety of COVID-19 vaccines weekly for prespecified outcomes of interest
- As of October 16, 2021, approximately 14.3 million doses have been administered and around 7.2 million members are fully vaccinated

COVID-19 vaccine combination	# of people fully vaccinated
Moderna + Moderna	2,711,487
Pfizer-BioNTech + Pfizer-BioNTech	4,026,967
Janssen one dose only	442,299
Janssen + mRNA dose	5,463
Janssen + mRNA dose (with a minimum of 60 days between doses)	3,662



VSD demographics in persons with Janssen primary + additional mRNA vaccine dose with a minimum of 60 days between doses







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		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

VSD Rapid Cycle Analysis (RCA)

 Among the 3,662 persons who received a Janssen primary vaccination and a subsequent mRNA vaccination at a minimum interval of 60 days after the Janssen primary dose, 2 prespecified surveillance outcomes* were detected in the 1–42-day risk interval

Prespecified outcome (n=2)	Patient sex	Patient age in years	Interval b/w Janssen primary dose & subsequent mRNA vaccination
Acute myocardial infarction	Male	50–64	125 days
Seizure	Female	25–29	142 days



^{*} Both were following a Pfizer-BioNTech vaccine dose

VSD summary of heterologous dose safety

- Limited data are available on a Janssen primary vaccination followed by an additional mRNA COVID-19 vaccination at a minimum interval of 60 days after the Janssen primary vaccination
 - There is a lack of evidence to date of a safety problem with respect to any of the prespecified VSD surveillance outcomes for this vaccination practice



What can you do for vaccine safety?

 Report adverse events following vaccination to VAERS even if you aren't sure if the vaccination caused the adverse event



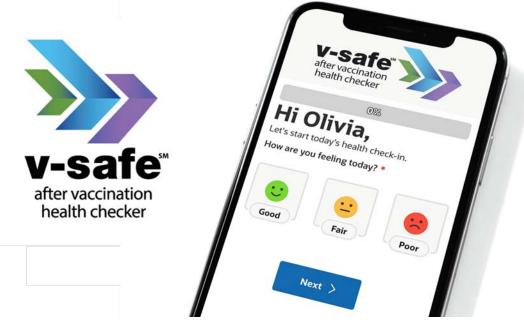


Vaccine Adverse Event Reporting System

http://vaers.hhs.gov



- Enroll yourself in v-safe
- Healthcare providers, encourage your patients to enroll in v-safe
- Parents and guardians, you can enroll your children in v-safe







Please get involved, your participation matters

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
- U.S. Department of Defense
- U.S. Department of Veterans Affairs



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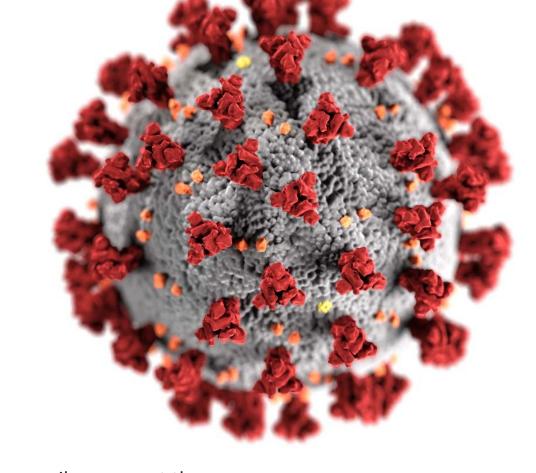
- The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC)
- Mention of a product or company name is for identification purposes only and does not constitute endorsement by CDC



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.

