Clinical Infectious Diseases

MAJOR ARTICLE

Myocarditis Following Coronavirus Disease 2019 mRNA Vaccine: A Case Series and Incidence Rate Determination

Yalile Perez,[1] Emily R. Levy,[2,3] Avni Y. Joshi,[4] Abinash Virk,[2] Martin Rodriguez-Porcel,[5] Matthew Johnson,[6] Daniel Roellinger,[6] Greg Vanichkachorn,[7] W. Charles Huskins,[2] and Melanie D. Swift[7]

[1]Department of Pediatric and Adolescent Medicine, Division of Pediatric Cardiology, Mayo Clinic, Rochester, Minnesota, USA; [2]Department of Pediatric and Adolescent Medicine, Division of Pediatric Infectious Diseases, Mayo Clinic, Rochester, Minnesota, USA; [3]Department of Pediatric and Adolescent Medicine, Division of Pediatric Critical Care Medicine, Mayo Clinic, Rochester, Minnesota, USA; [4]Department of Pediatric and Adolescent Medicine, Division of Pediatric Allergy and Immunology, Mayo Clinic, Rochester, Minnesota, USA; [5]Department of Cardiovascular Medicine, Division of Ischemic Heart Disease and Critical Care, Mayo Clinic, Rochester, Minnesota, USA; [6]Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA; and [7]Division of Preventive, Occupational, and Aerospace Medicine, Mayo Clinic, Rochester, Minnesota, USA.

Background. Myocarditis following coronavirus disease 2019 (COVID-19) mRNA vaccines (Pfizer-BioNTech and Moderna) has been increasingly reported. Incidence rates in the general population are lacking, with pericarditis rather than myocarditis diagnostic codes being used to estimate background rates. This comparison is critical for balancing the risk of vaccination with the risk of no vaccination.

Methods. A retrospective case series was performed using the Mayo Clinic COVID-19 Vaccine Registry. We measured the incidence rate ratio (IRR) for myocarditis temporally related to COVID-19 mRNA vaccination compared with myocarditis in a comparable population from 2016 through 2020. Clinical characteristics and outcomes of the affected patients were collected. A total of 21 individuals were identified, but ultimately 7 patients met the inclusion criteria for vaccine-associated myocarditis.

Results. The overall IRR of COVID-19–related myocarditis was 4.18 (95% confidence interval [CI], 1.63–8.98), which was entirely attributable to an increased IRR among adult males (IRR, 6.69; 95% CI, 2.35–15.52) compared with females (IRR 1.41; 95% CI, .03–8.45). All cases occurred within 2 weeks of a dose of the COVID-19 mRNA vaccine, with the majority occurring within 3 days (range, 1–13) following the second dose (6 of 7 patients, 86%). Overall, cases were mild, and all patients survived.

Conclusions. Myocarditis is a rare adverse event associated with COVID-19 mRNA vaccines. It occurs in adult males with significantly higher incidence than in the background population. Recurrence of myocarditis after a subsequent mRNA vaccine dose is not known at this time.

Keywords. COVID-19; vaccine-associated myocarditis.

The coronavirus disease-2019 (COVID-19) outbreak was declared a pandemic by the World Health Organization on 11 March 2020, and development of a safe, effective COVID-19 vaccine rapidly became a global priority. In the United States, the BNT162b2 mRNA (Pfizer-BioNTech) and mRNA-1273 (Moderna) COVID-19 vaccines were granted emergency use authorization by the US Food and Drug Administration in December 2020 following interim results of phase 3 clinical trials [1, 2]. These clinical trials and real-world data have demonstrated more than 95% effectiveness of the mRNA vaccines, preventing 164 900 cases of COVID-19, 25 000 hospitalizations, and 3628 deaths per million doses of mRNA vaccines given in the United States [1]. With more than 216 million people having received at least 1 dose of the COVID-19 mRNA vaccine to date in the United States, recognition and understanding of the potential adverse events of these novel vaccines are essential [3].

Myocarditis has been reported in association with immunizations, most notably the live attenuated smallpox vaccine [4]. Recently, cases of myocarditis following receipt of the COVID-19 mRNA vaccine in adolescents and young adults have been published [5–8]. The Centers for Disease Control and Prevention (CDC) has issued clinical guidance alerting providers to this potential association, noting that the reported cases have been predominantly in male adolescents and young adults [9]. Available incidence rates in the general population for comparison are lacking, with pericarditis rather than myocarditis diagnostic codes being used to estimate background rates in the population [10].

Here, we present a series of 7 patients (aged 22 to 71 years) with myocarditis presenting shortly after receipt of a dose of the COVID-19 mRNA vaccine (Pfizer-BioNTech or Moderna) from a registry designed to capture outcomes for a defined population of vaccinated individuals. We also calculated the incidence rate of myocarditis following COVID-19 mRNA vaccination and compared this to the background incidence rate of myocarditis in a comparable population.

Received 28 August 2021; editorial decision 20 October 2021; published online 3 November 2021.
Correspondence: M. D. Swift, Mayo Clinic, 200 1st Street Southwest, Rochester, MN 55905 (Swift.Melanie@mayo.edu).

Clinical Infectious Diseases® 2022;75(1):e749–54

https://doi.org/10.1093/cid/ciab926

METHODS

Study Population and Study Design

A retrospective case series study was performed using the Mayo Clinic COVID-19 Vaccine Registry, which tracks recipients of COVID-19 vaccines administered at the Mayo Clinic main campus in Rochester, Minnesota, and the Mayo Clinic Health System in the upper Midwest states (Minnesota and Wisconsin). It also contains demographic information and clinical outcomes for vaccinated individuals. To be included in the vaccine registry, an individual had to meet the following criteria: received at least 1 dose of any COVID-19 vaccine including the mRNA vaccines and the Johnson & Johnson/Janssen vaccine and was a primary care patient of the Mayo Clinic (Minnesota and Wisconsin) at the time of the first vaccination dose. At the time of this analysis, there were 175 472 individuals (aged 12 to 106 years) in the vaccine registry. The COVID-19 registry contained 718 (0.4%) adolescents aged 12 to 15 years.

The registry was queried for individuals with a clinical diagnosis of myocarditis (*International Classification of Diseases, Tenth Revision, Clinical Modification* [ICD-10] codes: I40.0 [infective myocarditis], I40.1 [isolated myocarditis], I40.8 [other acute myocarditis], I40.9 [acute myocarditis], I41 [myocarditis in diseases classified elsewhere], I51.4 [myocarditis unspecified], or B33.22 [viral myocarditis]) following any dose of a COVID-19 mRNA vaccine from 17 December 2020 through 13 May 2021. To ensure that we captured all the adverse events from the vaccine, this query was limited to the COVID-19 vaccine registry population. We did not exclude individuals with a mixed series of COVID-19 mRNA vaccines. For instance, there were 365 individuals (0.2%) who received different vaccines, of whom 14 received 1 dose of the Johnson & Johnson/Janssen vaccine.

The Rochester Epidemiology Project (REP) is a collaboration of clinics, hospitals, and other medical facilities in Minnesota and Wisconsin linking medical records for research purposes. Since 1996, the REP has enrolled hundreds of thousands of individuals who agreed to share their medical records and provided a comparable population for this study [11]. We conducted a query of the REP database using the ICD-10 codes listed above for the years 2016 through 2020 to identify the incidence of myocarditis among the REP population aged ≥16 years.

The observation window for vaccinated individuals in the vaccine registry varied from 6 weeks to 5 months. Because all cases of post-immunization myocarditis in the vaccine registry population presented within 13 days of receiving a dose of a mRNA vaccine, we assigned each vaccination dose an observation time of 14 days when calculating person-years of observation. In total, there were 12 648 person-years of observation in the vaccine registry cohort. Most individuals (145 876; 83%) had more than 30 days of follow-up since their last vaccination date.

Clinical presentation, diagnostic test results, comorbidities, treatment, and outcomes were extracted retrospectively from the electronic medical record. The American Heart Association and European Society of Cardiology have published guidelines for the diagnosis and management of myocarditis [12]. Recently, the CDC provided guidance regarding the diagnosis and management of COVID-19 vaccine–related myocarditis [13, 14]. The Mayo Clinic Institutional Review Board approved the study.

Statistical Analyses

Frequencies and percentages are reported for categorical variables. Data are presented as median (interquartile range [IQR]) for nonnormally distributed data and mean ± standard deviation for normally distributed data. Differences between groups were tested using the χ^2 test or a Fisher exact test for categorical variables as appropriate. Incidence rates and incidence rate ratios (IRRs) were calculated. Statistical analyses were performed using OpenEpi (version 3) [1, 15].

RESULTS

A total of 21 individuals were identified as having a clinical diagnosis of myocarditis via the Mayo Clinic COVID-19 Vaccine Registry after receiving at least 1 dose of a COVID-19 mRNA vaccine on or before 13 May 2021; records were screened by 2 physicians (M. D. S. and A. Y. J.). However, only 7 individuals had new onset myocarditis following vaccination. The remaining 14 patients were excluded since they did not have evidence of COVID-19 vaccine–related myocarditis; however, the diagnosis was used during a post-immunization clinical encounter due to a prior history of myocarditis. No cases of myocarditis were found following a dose of the Johnson & Johnson/Janssen vaccine.

Summary of Cases

Table 1 summarizes the demographic characteristics of the cohort. The median age at the time of diagnosis was 44 years (range, 22–71), and most patients were male (6 of 7, 86%). All patients self-identified as non-Hispanic White. The most common comorbidities were hypertension (5 of 7, 72%), obesity (4 of 7, 57%), obstructive sleep apnea (4 of 7, 57%), tobacco use (3 of 7, 42%), and dyslipidemia (3 of 7, 42%). One patient (14%) had a history of myocarditis, and another patient (14%) had a history of pericarditis. One patient (14%) was previously infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Three patients (42%) received the Pfizer-BioNTech vaccine and 4 (57%) received the Moderna vaccine. All cases occurred within 2 weeks of a dose of the COVID-19 mRNA vaccine, with the majority occurring within 3 days (range, 1–13). All except 1 case occurred after the second dose of the vaccine.

The clinical characteristics of the patients with COVID-19 vaccine–related myocarditis are shown in the Supplementary

Table 1. Demographics of Cases

Variable	Frequency
Sex, male	6 (86)
Age, years	44.8 (31.8–64.2)
Ethnicity	
White/Non-Hispanic White	7 (100)
Body mass index, kg/m^2	30 (28–31)
Comorbidities	
Obesity	4 (57)
Obstructive sleep apnea	4 (57)
Tobacco use	3 (42)
Hypertension	5 (72)
Dyslipidemia	3 (42)
Prior history of myocarditis	1 (14)
Prior history of pericarditis	1 (14)
Previous COVID-19 infection	1 (14)
Type of COVID-19 mRNA vaccine	
mRNA-1273 (Moderna)	4 (57)
BNT162b2 (Pfizer-BioNTech)	3 (42)
Time interval between first vaccine and onset of symptoms (range), days	31 (24–42)
Time interval between second vaccine and onset of symptoms (range), days	3 (3–15)
Hospitalization	6 (86)
Duration (range), days	2 (2–4)
Survival to hospital discharge	7 (100)

n is the number of patients; % is the percentage of the total number of patients (N = 7). Values are n (%) or median (interquartile range) unless otherwise indicated.

Abbreviation: COVID-19, coronavirus disease 2019.

Table. The most common presenting symptoms were chest pain, dyspnea, and fatigue. COVID-19 polymerase chain reaction tests at the time of diagnosis were negative in most of the cases (6 of 7, 86%), except in 1 patient who had COVID-19 infection 22 days prior to the diagnosis of myocarditis. Serology testing for COVID-19 was not obtained in any of the patients. Elevations in inflammatory (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and cardiac (troponin T) markers were typical. For instance, the median CRP was 38.3 mg/L (IQR, 4.4–63.5; reference range, <8.0 mg/L), ESR was 18 mm/h (IQR, 10.5–29.25; reference range, 2–20 mm/h), and baseline fifth-generation troponin T was 486.5 (IQR, 222.5–965; reference range, ≤15 μg/L). N-terminal prohormone B type natriuretic peptide (NT-proBNP) levels were also elevated in 4 of 5 patients (80%).

Five of 7 patients (71%) had abnormalities noted in the electrocardiogram (ECG), with ST-segment changes being the predominant finding. ECG changes in combination with elevated troponin T levels triggered further evaluation for acute coronary syndrome in 3 patients (43%). In this subgroup, 1 patient underwent a dedicated computerized tomography coronary angiogram that revealed normal coronary arteries, and 2 patients underwent cardiac catheterization that showed angiographically normal coronary arteries.

An echocardiogram was performed in 5 patients (71%). Although it is not indicated to make the diagnosis of myocarditis, it is helpful for the assessment of ventricular function and to look for regional wall motion abnormalities, valve regurgitation, or pericardial effusion. Three patients (60%) were noted to have reduced left ventricular ejection fraction; right ventricular dysfunction, albeit mild, was seen in 3 patients. Cardiac magnetic resonance imaging (MRI) was obtained in 6 patients (86%). Myocardial delayed enhancement was universal. Pericardial involvement was seen in 3 (50%) patients.

Treatment consisted of a combination of steroids (2 of 7, 29%), nonsteroidal antiinflammatory drugs (NSAIDs; 2 of 7, 29%), and colchicine (5 of 7, 71%), which is known to modulate multiple antiinflammatory pathways [16]. None of the patients received intravenous immunoglobulin. Angiotensin-converting enzyme (ACE) inhibitors and beta blockers were also prescribed for patients with left ventricular dysfunction. Overall, cases were mild, and there were no deaths.

Incidence Rate of Myocarditis Following COVID-19 Vaccination

The overall incidence rate of myocarditis among individuals in the COVID-19 vaccine registry was 55.35 (95% confidence interval [CI], 22.25–114.00) per 100 000 person-years during the 2 weeks following a dose of a COVID-19 mRNA vaccine (Table 2). In the REP population over the prior 5 years, the overall incidence rate of myocarditis was 13.25 (95% CI, 10.60–16.36) per 100 000 person-years. In both populations, incidence rates were higher in males. The IRR for myocarditis following COVID-19 mRNA vaccination was increased for males at 6.69 (95% CI, 2.35–15.52), but it was not statistically significant for females at 1.41 (95% CI, .03–8.45).

Table 2. Myocarditis Incidence Rates and Incidence Rate Ratios

	Coronavirus Disease 2019 Vaccine Registry Population			Rochester Epidemiology Project Population			IRRs		
Gender	Incidence Rate per 100 000 Person-Years	$LoCI_{95}$	$UpCI_{95}$	Incidence Rate per 100 000 Person-Years	$LoCI_{95}$	$UpCI_{95}$	IRR	$LoCI_{95}$	$UpCI_{95}$
Males	109.52	40.19	238.4	16.37	12.33	21.3	6.69	2.35	15.52
Females	13.95	3.53	77.72	9.9	6.73	14.05	1.41	0.03	8.45
All	55.35	22.25	114	13.25	10.6	16.36	4.18	1.63	8.98

Abbreviations: IRR, incidence rate ratio; $LoCI_{95}$, lower limit of the 95th confidence interval; $UpCI_{95}$, upper limit of the 95th confidence interval.

DISCUSSION

Clinical studies have shown an association between SARS-CoV-2 infection and cardiovascular disease such as myocardial injury, acute coronary syndrome, and arrhythmias [17–19]. Since the emergence of the SARS-CoV-2 virus, the genomic sequence and protein structure of the virus have been extensively studied [20, 21]. However, the exact mechanism by which SARS-CoV-2 leads to myocardial damage has not been elucidated. Some theories include direct damage to the cardiac myocytes, systemic inflammation, and interferon-mediated immune response, among others [22]. Another postulated mechanism is molecular mimicry, whereby a foreign antigen, in this case moieties or proteins in the SARS-CoV-2 virus, share sequence or structural similarities to cardiac proteins, leading to cross-reaction and inflammation [23–25].

Myocarditis is a consequence of myocardial damage that can be diagnosed histologically or clinically using a combination of clinical findings and diagnostic criteria [12, 26]. Most often, it results from infection caused by viruses; enterovirus and adenovirus are classically associated with myocarditis [27]. However, there is considerable geographic and temporal variation in the prevalence of these viral infections. Thus, a specific viral etiology for myocarditis may not be identified during the evaluation, and other causes such as bacteria, fungi, drug-induced hypersensitivity reactions, or autoimmune disorders need to be considered [28]. There is also a preponderance of males affected, and children may have a more fulminant course [29].

Myocarditis after vaccination was reported following the live attenuated smallpox vaccine [4]. Recently, myocarditis has been reported after mRNA COVID-19 vaccination [5–8]. For instance, a case series noted similar clinical presentations of post-immunization myocardial and pericardial inflammation in adolescents after receipt of the Pfizer-BioNTech vaccine [6]. Most of the affected patients were male, as in our case series. An important distinction in our study is that individuals of all ages, particularly adults, appeared to be at risk for this rare complication. Additionally, we found that myocarditis occurred within several days of COVID-19 vaccination and more often after receipt of the second dose of the vaccine, either the Pfizer-BioNTech or Moderna vaccine. Myocarditis has also been associated with the post-infection hyperinflammatory syndrome, multisystem inflammatory syndrome in children and adults [30, 31]. Similar to the lack of clarity for the pathogenesis of myocarditis caused by SARS-CoV-2, the mechanism of myocarditis after COVID-19 mRNA vaccination has not been elucidated.

The incidence of myocarditis in the general population remains unknown. For instance, one study found a background rate of 17 cases per 100 000 person-years among Finnish military recruits, which is very similar to our findings in the adult male population [32]. For purposes of comparing vaccine adverse events to background rates, pericarditis is commonly reported with or without myocarditis [10]. The incidence rates we observed following COVID-19 mRNA vaccination are significantly higher than those previously reported following smallpox vaccination [32–35]. Montgomery et al recently reported the incidence of post-immunization myocarditis in a cohort of US military members [36]. They identified 23 military recruits who presented with acute chest pain within 4 days after receipt of a COVID-19 mRNA vaccine. They found that the observed number of male military members with post-vaccination myocarditis was higher than the expected number using an estimated incidence of 1 to 10 cases per 100 000 person-years in the United States. Simone et al also evaluated the incidence rate of myocarditis following COVID-19 mRNA vaccination and found that the observed incidence was 5.8 cases per 1 million second doses over a 10-day observation period [37]. The IRR was 3.3 (95% CI, 1.0–13.7) for the second dose compared with our IRR of 4.18 (95% CI, 1.63–8.98). Overall, the findings of both studies are consistent with ours in that males are disproportionally affected, most cases occur after receipt of the second vaccine dose, and cases are generally mild.

To our knowledge, this is the first case series to estimate a post-immunization incidence rate of myocarditis in a defined population of COVID-19 mRNA vaccine recipients, along with a background rate in a comparable population. This comparison is relevant as it is critical to balance the risk of vaccination with the risk of no vaccination.

In summary, physicians should consider myocarditis if patients present with chest pain shortly following a COVID-19 mRNA vaccine. The initial evaluation should include an ECG and laboratory testing for inflammatory markers and cardiac enzymes. If these biomarkers are elevated, point-of-care ultrasound and/or cardiac MRI in addition to early cardiology consultation should be considered. In patients at risk for atherosclerotic disease or those with preexisting cardiovascular disease, further evaluation for acute coronary syndrome is warranted. In addition to supportive care and NSAIDs, colchicine may constitute a low-cost and effective treatment for myocarditis. In the absence of left ventricular dysfunction, beta-blockers and ACE inhibitors are unlikely to be beneficial. The clinical course of this condition tends to be mild; although some patients in our study were hospitalized, they responded well to medical therapy. All patients survived to hospital discharge. The long-term sequelae, if any, of post-immunization myocarditis in this population remains to be determined.

Our study is subject to some limitations. The vaccine registry that was used contains patients vaccinated in a single health system in the upper Midwest, which may limit generalizability. All reported cases were non-Hispanic Caucasian patients, which may reflect selection bias due to regional population demographics. Because cases were identified using diagnostic codes associated with clinical care, there is a potential bias for most severe cases who present for clinical care and, therefore,

the rates may be underestimated. However, this limitation also applies to the comparison REP population, so the increased IRR would remain valid. Additionally, the vaccination dates were chosen to coincide with vaccine availability in individuals aged >16 years. Thus, this cohort does not include younger adolescents who may experience different incidence rates of post-immunization myocarditis.

CONCLUSIONS

Myocarditis is a rare adverse event associated with COVID-19 mRNA vaccines; in adult males, it occurs with significantly higher incidence than in the background population. Patients with preexisting cardiovascular disease or prior history of myocarditis may be at increased risk for COVID-19 vaccine–related myocarditis, but more data are needed. The condition is more often seen after the second dose of the COVID-19 mRNA vaccine. Post-immunization myocarditis is relatively straightforward to diagnose and treat, and the clinical course tends to be mild in most patients.

As COVID-19 vaccination continues and expands to younger populations, physicians should remain vigilant and report suspected vaccine adverse events to the CDC through the Vaccine Adverse Event Reporting System, which has detected safety signals for this and other vaccine-associated adverse events. Despite the increased frequency of this rare condition following COVID-19 vaccination, the benefits of COVID-19 vaccination far exceed the risk, and vaccination is strongly recommended by the authors. Vaccination is an effective means to prevent COVID-19 infection, transmission, and related complications.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. The authors thank Barbara Abbott and colleagues from the Rochester Epidemiology Project for their assistance with this research.

Potential conflicts of interest. M. D. S. received grant funding for a vaccine side effect registry from Pfizer via Duke University (research funding for the Healthcare Worker Exposure Response & Outcomes [HERO] Together registry). E. R. L. receives support from the Centers for Disease Control and Prevention (CDC; subcontract of federal contract 75D30120C07725) and from the National Institute of Allergy and Infectious Diseases (federal contract AI144301) as grants to the institution for coronavirus disease (COVID)–related studies, neither of which had any impact on this work; reports receiving the following grants/contracts: National Institutes of Health (NIH) AI 154470-01; Immunobiology of Influenza Virus-related Critical Illness in Young Hosts, CDC 75D30120C07725-01; Understanding COVID-19 Among Critically Ill Children in the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network, AI 144301-01; An Observational Cohort Study to Determine Late Outcomes and Immunological Responses after Infection with SARS-CoV-2 in Children With and Without MIS-C (multisystem inflammatory syndrome in children, Clinical and Translational Science (CCaTS) Center for Biomedical Discovery (CBD) (intramural institutional grant; Mayo Clinic); Understanding the Connection Between Mother and Infant in Breast Milk Driver Protection of Neonatal sepsis; and reports honoraria for presentation from Shanghai Childrens Hospital; Sinounited. W. C. H. serves as a paid member of an outcome adjudication committee for Pfizer, owns common stock in Pfizer, has served as a paid advisory board member for ADMA Biologics, and has personal stock with Bristol Meyers Squibb and Zimmer Biomet. M. R.-P. reports receiving support from NIH and Regenerative Medicine Minnesota and travel support from Mayo Clinic to attend scientific meetings. A. V. reports royalties/licenses as an inventor for the Mayo Clinic Travel App Interaction with Smart Medical Kit and Medical Kit for Pilgrims. G. V. reports receipt of fees as a paid consultant with BrainFx and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, and educational events from American Occupational Health Professionals for Minnesota Association of Cardiac and Physical Rehab, Mid Atlantic Region of Occupational and Environmental Medicine, and State of Montana. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Polack FP, Thomas SJ, Kitchin N, et al; C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med **2020**; 383:2603–15.
2. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med **2020**; 384:403–16. doi:10.1056/NEJMOA2035389.
3. Centers for Disease Control and Prevention COVID Data Tracker. Available at: https://covid.cdc.gov/covid-data-tracker/#vaccinations. Accessed 4 August 2021.
4. Engler RJ, Nelson MR, Collins LC Jr, et al. A prospective study of the incidence of myocarditis/pericarditis and new onset cardiac symptoms following smallpox and influenza vaccination. PLoS One **2015**; 10:e0118283.
5. Albert E, Aurigemma G, Saucedo J, Gerson DS. Myocarditis following COVID-19 vaccination. Radiol Case Rep **2021**; 16:2142–5.
6. Marshall M, Ferguson I, Lewis P, et al. Symptomatic acute myocarditis in seven adolescents following Pfizer-BioNTech COVID-19 vaccination. Pediatrics **2021**:e2021052478. doi:10.1542/PEDS.2021-052478.
7. Abu Mouch S, Roguin A, Hellou E, et al. Myocarditis following COVID-19 mRNA vaccination. Vaccine **2021**; 39:3790–3.
8. Diaz GA, Parsons GT, Gering SK, Meier AR, Hutchinson IV, Robicsek A. Myocarditis and pericarditis after vaccination for COVID-19. JAMA **2021**; 326:1210–2.
9. Centers for Disease Control and Prevention. Clinical Considerations: Myocarditis after mRNA COVID-19 Vaccines. Available at: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html. Accessed 4 August 2021.
10. Gubernot D, Jazwa A, Niu M, et al. U.S. population-based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines. Vaccine **2021**; 39:3666–77.
11. Rocca WA, Grossardt BR, Brue SM, et al. Data resource profile: expansion of the Rochester epidemiology project medical records-linkage system (E-REP). Int J Epidemiol **2018**; 47:368–368j.
12. Caforio AL, Pankuweit S, Arbustini E, et al; European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J **2013**; 34:2636–48, 2648a–2648d.
13. 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**; 70:977–82.
14. Centers for Disease Control and Prevention. Clinical Considerations: Myocarditis after mRNA COVID-19 Vaccines. Available at: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html. Accessed 4 August 2021.
15. Dean A, Sullivan KSM. OpenEpi Menu. OpenEpi: Open Source Epidemiologic Statistics for Public Health. Published **2014**. Available at: https://www.openepi.com/Menu/OE_Menu.htm. Accessed 4 August 2021.

16. Leung YY, Yao Hui LL, Kraus VB. Colchicine—Update on mechanisms of action and therapeutic uses. Semin Arthritis Rheum **2015**; 45:341–50.
17. He XW, Lai JS, Cheng J, et al. Impact of complicated myocardial injury on the clinical outcome of severe or critically ill COVID-19 patients. Zhonghua Xin Xue Guan Bing Za Zhi **2020**; 48:456–60.
18. Wu CI, Postema PG, Arbelo E, et al. SARS-CoV-2, COVID-19, and inherited arrhythmia syndromes. Heart Rhythm **2020**; 17:1456–62.
19. Long J, Luo Y, Wei Y, Xie C, Yuan J. The effect of cardiovascular disease and acute cardiac injury on fatal COVID-19: a meta-analysis. Am J Emerg Med **2021**; 48:128–39.
20. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell **2020**; 181:281–292.e6.
21. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell **2020**; 181:271–280.e8.
22. Babapoor-Farrokhran S, Gill D, Walker J, Rasekhi RT, Bozorgnia B, Amanullah A. Myocardial injury and COVID-19: possible mechanisms. Life Sci **2020**; 253:117723.
23. Cusick MF, Libbey JE, Fujinami RS. Molecular mimicry as a mechanism of autoimmune disease. Clin Rev Allergy Immunol **2012**; 42:102–11.
24. Li Y, Heuser JS, Cunningham LC, Kosanke SD, Cunningham MW. Mimicry and antibody-mediated cell signaling in autoimmune myocarditis. J Immunol **2006**; 177:8234–40.
25. Vojdani A, Kharrazian D. Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases. Clin Immunol **2020**; 217:108480.
26. Kociol RD, Cooper LT, Fang JC, et al. Recognition and initial management of fulminant myocarditis. Circulation **2020**; 141:E69–E92.
27. Kühl U, Pauschinger M, Noutsias M, et al. High prevalence of viral genomes and multiple viral infections in the myocardium of adults with "idiopathic" left ventricular dysfunction. Circulation **2005**; 111:887–93.
28. Tschöpe C, Cooper LT, Torre-Amione G, Van Linthout S. Management of myocarditis-related cardiomyopathy in adults. Circ Res **2019**; 124:1568–83.
29. Ghelani SJ, Spaeder MC, Pastor W, Spurney CF, Klugman D. Demographics, trends, and outcomes in pediatric acute myocarditis in the United States, 2006 to 2011. Circ Cardiovasc Qual Outcomes **2012**; 5:622–7.
30. McMurray JC, May JW, Cunningham MW, Jones OY. Multisystem inflammatory syndrome in children (MIS-C), a post-viral myocarditis and systemic vasculitis—a critical review of its pathogenesis and treatment. Front Pediatr **2020**; 8:626182.
31. Multisystem Inflammatory Syndrome (SIS). Centers for Disease Control and Prevention. Updated June 25, **2021**. Available at: https://www.cdc.gov/mis/. Accessed 7 August 2021.
32. Karjalainen J, Heikkilä J. Incidence of three presentations of acute myocarditis in young men in military service. A 20-year experience. Eur Heart J **1999**; 20:1120–5.
33. Halsell J, Riddle J, Atwood J, et al. Myopericarditis following smallpox vaccination among vaccinia-naive US military personnel. JAMA **2003**; 289:3283–9.
34. Arness MK, Eckart RE, Love SS, et al. Myopericarditis following smallpox vaccination. Am J Epidemiol **2004**; 160:642–51.
35. Morgan J, Roper M, Sperling L, et al. Myocarditis, pericarditis, and dilated cardiomyopathy after smallpox vaccination among civilians in the United States, January-October 2003. Clin Infect Dis **2008**; 46(Suppl 3). doi:10.1086/524747
36. Montgomery J, Ryan M, Engler R, et al. Myocarditis following immunization with mRNA COVID-19 vaccines in members of the US military. JAMA Cardiol **2021**. doi:10.1001/JAMACARDIO.2021.2833
37. Simone A, Herald J, Chen A, et al. Acute myocarditis following COVID-19 mRNA vaccination in adults aged 18 years or older. JAMA Intern Med **2021**. doi:10.1001/JAMAINTERNMED.2021.5511