EDITORIAL

Myocarditis Occurring After Immunization With mRNA-Based COVID-19 Vaccines

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Two reports in the current issue of *JAMA Cardiology* describe cases of acute myocarditis that occurred among persons who received the BNT162b2-mRNA (Pfizer-BioNTech) or mRNA-1273 (Moderna) messenger RNA (mRNA)-based COVID-19 vaccines authorized for use in the US.[1,2] During the clinical evaluations of these patients, alternative etiologies for myocarditis were not detected.

The first report describes 4 cases of myocarditis with symptom onset 1 to 5 days after receipt of a second dose of mRNA-based COVID-19 vaccine (2 receiving the BNT162b2-mRNA vaccine and 2 receiving the mRNA-1273 vaccine) who were evaluated in a single tertiary care medical center (Duke University Medical Center) that attempted to define its catchment population.[1] Three cases occurred in men aged 23 to 36 years and the fourth in a 70-year-old woman; details about the medical history of the fourth patient were not provided, but she received coronary angiography during her evaluation and no atherosclerosis was found. All presented with severe acute chest pain, had abnormal electrocardiogram results, and had evidence of myocardial injury demonstrated by elevated troponin levels. Cardiac magnetic resonance imaging was performed in these 4 patients on days 3 through 5 after vaccine receipt, and the findings were consistent with acute myocarditis as defined by recent expert consensus guidelines.[3]

The second, larger case report comes from the US Military Health System and describes 23 individuals with acute myocarditis who presented within 4 days after mRNA-based COVID-19 vaccination.[2] All patients were male, 22 of 23 were on active duty, and the median (range) age was 25 (20-51) years; 20 cases occurred after receipt of a second dose of an mRNA-based COVID-19 vaccine. Clinical presentations and laboratory findings were similar to those described in the smaller case series[1]; 8 of 23 patients in this series received cardiac magnetic resonance imaging, and all 8 demonstrated findings again consistent with acute myocarditis.[2]

A separate case report published by Marshall et al[4] provides additional context in a younger population. They report 7 US male adolescents aged 14 to 19 years who presented with myocarditis or myopericarditis within 4 days after receipt of a second dose of the BNT162b2-mRNA COVID-19 vaccine.[4] These adolescents were found to have elevated troponin levels, abnormal electrocardiogram results, and findings on cardiac magnetic resonance imaging consistent with acute myocarditis.

Although the extent of the search for alternative etiologies for acute myocarditis varied for each patient in these 3 reports,[1,2,4] no evidence of common causes of acute myocardial injury in healthy persons was found, and findings of tests for enterovirus and adenovirus infection were negative. The striking clinical similarities in the presentations of these patients, their recent vaccination with an mRNA-based COVID-19 vaccine, and the lack of any alternative etiologies for acute myocarditis suggest an association with immunization. Myocarditis or pericarditis were not detected in the clinical trials for these vaccines; however, it is possible that any association is too rare for recognition in a clinical trial enrolling less than several hundred thousand participants. The patients described in these US-based case series had resolution of symptoms or are recovering after receipt of brief supportive care and continue to be monitored during recovery from the acute illness.

What do we know about this possible association between myocarditis and immunization with mRNA-based COVID-19 vaccines, and what remains unclear? Acute onset of chest pain 3 to 5 days after vaccine administration, usually after a second dose, is a typical feature of reported cases and suggests an immune-mediated mechanism.[5] Myocarditis following receipt of other vaccines is rare and is recognized as causally linked only with smallpox immunization.[6] For example, myopericarditis has been reported in healthy adults after receipt of replication-competent live vaccinia virus vaccines.[7] These highly reactogenic smallpox vaccines differ dramatically by composition and by immunologic responses compared with the mRNA-based lipid nanoparticle vaccines currently in use for prevention of COVID-19. We do not know the specific mechanisms by which immunologic responses to mRNA-based COVID-19 vaccines could lead to myocarditis. Further investigation is critical and should be informed by the fact that most cases occurred following the second dose of a 2-dose series, some in patients with a history of prior COVID-19 infection. We know that infection with SARS-CoV-2 can result in acute cardiac compromise in substantial proportions of hospitalized patients and that it might lead to cardiac magnetic imaging findings suggestive of myocarditis in competitive college athletes with evidence of COVID-19, although the mechanisms that could lead to either direct SARS-CoV-2 viral injury or immunopathologic injury of myocardial tissues are unclear and under active investigation.[8]

None of the US case series reports are population based,[1,2,4] and therefore, estimating rates of myocarditis following COVID-19 vaccination is problematic. However, based on data available to date, we can say that myocarditis occurring after

COVID-19 immunization is rare. Kim et al[1] estimated that more than 560 000 persons in the 6 counties surrounding their tertiary care institution had received 2 doses of an mRNA-based COVID-19 vaccine by April 30, 2021; they detected 4 myocarditis cases by that date.[1] The Military Health System administered more than 2.8 million doses of mRNA-based vaccines through April 30, 2021, and detected 23 myocarditis cases.[2] Based on the military's extensive experience with vaccinia-associated myocarditis,[9] it is possible that the military system may be more likely to detect mild myocarditis cases than most civilian medical centers. Among the 436 000 male active-duty military who have received 2 mRNA vaccine doses, Montgomery et al[2] estimated that 0 to 8 cases of myocarditis might be expected based on US data on the background incidence rate of myocarditis, whereas they detected 19 myocarditis cases in that group.[2] The most comprehensive data about the risk of myocarditis following immunization with mRNA vaccines comes from Israel. The Israeli Ministry of Health recently posted data describing 121 myocarditis cases occurring within 30 days of a second dose of mRNA vaccine among 5 049 424 persons, suggesting a crude incidence rate of approximately 24 cases per million following a second dose in this subset of their vaccinated population.[10]

While more definitive data on the incidence of myocarditis following immunization with mRNA COVID-19 vaccines and associated risk will eventually be provided by large population-based vaccine adverse event monitoring systems, including the US Centers for Disease Control and Prevention Vaccine Safety Datalink,[11] several interim conclusions can be offered. Cardiac injury after SARS-CoV-2 infection occurs and may result in severe outcomes.[8] Based on currently available data, myocarditis following immunization with current mRNA-based vaccines is rare. All possible myocarditis cases should be reported to the US Vaccine Adverse Events Reporting System to help better define the characteristics of this syndrome and its relationship to receipt of mRNA-based COVID-19 vaccines authorized for use in the US. At present, the benefits of immunization in preventing severe morbidity favors continued COVID-19 vaccination, particularly considering the increasing COVID-19 hospitalization rates among adolescents reported during spring 2021.[12] Many questions remain. What modifications to the vaccine schedule, if any, should be considered among persons with a history of possible or confirmed myocarditis after a first dose of COVID-19 vaccine? How should postvaccine myocarditis be managed, particularly given the apparently benign outcomes described thus far and the success of supportive or conservative management alone? How often should follow-up assessments, including repeated cardiac imaging, be performed in these patients, and how might follow-up assessments affect recommendations to avoid vigorous physical activity following the diagnosis of myocarditis? Do all likely cases of acute myocarditis that appear to be uncomplicated require cardiac magnetic resonance imaging for more definitive diagnosis? While the data needed to answer such questions are being collected, there is an opportunity for researchers with expertise in myocarditis to develop a comprehensive, national assessment of the natural history, pathogenesis, and treatment of acute myocarditis associated with receipt of mRNA-based COVID-19 vaccines.

Finally, the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices held a public meeting from June 23 to 25, 2021. On June 23, the committee heard presentations about the epidemiology of myocarditis and pericarditis, an update on COVID-19 vaccine safety, including myocarditis following receipt of mRNA-based COVID-19 vaccines, and a benefit-risk assessment of COVID-19 mRNA vaccination programs in adolescents and young adults. Advisory Committee on Immunization Practices discussions and recommendations are summarized on the Centers for Disease Control and Prevention website.[13]

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Published Online: June 29, 2021. doi:10.1001/jamacardio.2021.2821

Conflict of Interest Disclosures: None reported.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US 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 the CDC.

Additional Contributions: We thank C. Buddy Creech, MD (Vanderbilt Vaccine Research Program, Department of Pediatrics, Vanderbilt University, School of Medicine, Nashville, Tennessee), and Matthew E. Oster, MD (National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia). Neither were compensated for their reviews.

REFERENCES

1. Kim HW, Jenista ER, Wendell DC, et al. Patients with acute myocarditis following mRNA COVID-19 vaccination. *JAMA Cardiol*. Published online June 29, 2021. doi:10.1001/jamacardio.2021.2828

2. Montgomery J, Ryan M, Engler R, et al. Myocarditis following immunization with mRNA COVID-19 vaccines in members of the US military. *JAMA Cardiol*. Published online June 29, 2021. doi:10.1001/jamacardio.2021.2833

3. Ferreira VM, Schulz-Menger J, Holmvang G, et al. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. *J Am Coll Cardiol*. 2018;72(24):3158-3176. doi:10.1016/j.jacc.2018.09.072

4. Marshall M, Ferguson ID, Lewis P, et al. Symptomatic acute myocarditis in seven adolescents following Pfizer-BioNTech COVID-19 vaccination. *Pediatrics*. Published online June 4, 2021. doi:10.1542/peds.2021-052478

5. Stone CA Jr, Rukasin CRF, Beachkofsky TM, Phillips EJ. Immune-mediated adverse reactions to vaccines. *Br J Clin Pharmacol*. 2019;85(12):2694-2706. doi:10.1111/bcp.14112

6. Dudley MZ, Halsey NA, Omer SB, et al. The state of vaccine safety science: systematic reviews of the evidence. *Lancet Infect Dis*. 2020;20(5):e80-e89. doi:10.1016/S1473-3099(20)30130-4

7. Petersen BW, Damon IK, Pertowski CA, et al. Clinical guidance for smallpox vaccine use in a postevent vaccination program. *MMWR Recomm Rep*. 2015;64(RR-02):1-26.

8. Chung MK, Zidar DA, Bristow MR, et al. COVID-19 and cardiovascular disease: from bench to bedside. *Circ Res*. 2021;128(8):1214-1236. doi:10.1161/CIRCRESAHA.121.317997

9. 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(3):e0118283. doi:10.1371/journal.pone.0118283

10. Surveillance of myocarditis (inflammation of the heart muscle) cases between December 2020 and May 2021. News release. Israeli Ministry of Health; June 6, 2021. Accessed June 22, 2021. https://www.gov.il/en/departments/news/01062021-03

11. McNeil MM, Gee J, Weintraub ES, et al. The Vaccine Safety Datalink: successes and challenges monitoring vaccine safety. *Vaccine*. 2014;32(42):5390-5398. doi:10.1016/j.vaccine.2014.07.073

12. Havers FP, Whitaker M, Self JL, et al; COVID-NET Surveillance Team. Hospitalization of adolescents aged 12–17 years with laboratory-confirmed COVID-19—COVID-NET, 14 states, March 1, 2020–April 24, 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(23):851-857. doi:10.15585/mmwr.mm7023e1

13. US Centers for Disease Control and Prevention. COVID-19 ACIP vaccine recommendations. Accessed June 22, 2021. https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19.html

Temporal Associations Between Immunization With the COVID-19 mRNA Vaccines and Myocarditis

The Vaccine Safety Surveillance System Is Working

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Prior reports of adverse events following immunization for measles, mumps, and rubella, later deemed unsubstantiated, raised significant public alarm and led to vaccine resistance—an effect that lingers to this day. In light of this legacy, as well as ongoing fears related to vaccination leading to variable uptake, especially in populations at higher risk for COVID-19, the editorial decision to publish 2 articles reporting the association of myocarditis following COVID-19 messenger RNA (mRNA) vaccination was not taken lightly.[1,2]

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The 2 case series by Montgomery and coworkers[1] and Kim and coworkers[2] in the current issue of *JAMA Cardiology* describe a temporal association between myocarditis and vaccination against SARS-CoV-2 with the Pfizer-BioNTech and Moderna mRNA vaccines. This temporal association does not establish causality, especially because a myocarditis-like syndrome has been seen following SARS-CoV-2 infection. Rather, these case series highlight the need for additional surveillance and investigation.

The editors recognize that publication of these data may contribute to additional public concern regarding immunization because reports of myocarditis following COVID-19 mRNA vaccination have already been reported in the news[3] and in peer-reviewed publications.[4] Furthermore, concerns regarding vaccine safety are the most common reason cited for lack of vaccination.[5] However, as highlighted in the accompanying Editorial from immunization safety experts at the US Centers for Disease Control and Prevention (CDC),[6] clinicians discussing immunization with patients should recognize that these case series suggest that the symptomatic events consistent with myocarditis are still very rare and appear to be self-limiting. Given the risks of COVID-19, including the risk of myocarditis from COVID-19 infection, the editors do not believe these case reports are sufficient to interrupt the march toward maximal vaccination against SARS-CoV-2 as expeditiously as possible.

Importantly, we endorse a different perspective: these data are exemplary of a successful formal and informal vaccine surveillance system, a system about which most of our readers may be unaware. Phase 3 clinical trials of vaccine efficacy and safety are able to detect common adverse effects but are not powered to detect more rare events, and it is noteworthy that myocarditis was not reported in the trials of the mRNA vaccines.[7-9] A well-developed multipronged postmarketing surveillance system monitors vaccine safety after approval and is designed to detect extremely rare events that occur in less than 1 in 1 million vaccinees. This system includes the Vaccine Adverse Events Reporting System, a voluntary and easily accessible reporting system that archives possible vaccine adverse effects[10]; the Vaccine Safety Datalink, a hospital network designed to evaluate for increases in background rates of certain possible events[11]; and the Clinical Immunization Safety Assessment Project, in which the CDC partners with 7 medical research centers to leverage expertise in vaccine safety.[12] For COVID-19 vaccines, the CDC also set up the v-safe system, which is offered to vaccine recipients and uses a smartphone app to collect symptoms following immunization.[13] In addition, medical researchers across the country, including those highlighted in the Brief Reports published in *JAMA Cardiology*,[1,2] form an informal network of vaccine safety surveillance capable of detecting potential clusters of events for further investigation. Increased engagement with this system by the public will help provide continued critical data for vaccine safety monitoring. In short, a web of safety and surveillance supports vaccine administration, and based on these case reports, that system is working.

Persons with cardiovascular disease are at high risk of complications from COVID-19, and physicians caring for these patients should encourage immunization and help guide patients in their decision-making. In one study, 66% of older adults reported that they would talk to their health care professional first before making a decision regarding immunization.[14] In addition to discussing the risks of COVID-19 infection and the efficacy of vaccines, physicians should identify patient concerns regarding vaccine safety and be prepared to discuss these risks with patients.

The rarity of these events, including the identified link between the even rarer cerebral venous sinus thrombosis