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Sean T. O'Leary, MD, MPH, Yvonne A. Maldonado, MD

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Myocarditis after SARS-CoV-2 Vaccination: True, True, and…Related?

Sean T. O'Leary, MD, MPH[1,2], Yvonne A. Maldonado, MD[3]

Affiliations:

[1]Adult and Child Consortium for Health Outcomes Research and Delivery Science, University of Colorado Anschutz Medical Campus and Children's Hospital Colorado, Aurora, CO;
[2]Department of Pediatrics, University of Colorado Anschutz Medical Campus, Aurora, CO;
[3]Department of Pediatrics, Stanford University School of Medicine, Stanford, California

Corresponding Author:
Sean T. O'Leary, MD, MPH
University of Colorado, Department of Pediatrics
Mail Stop F443
13199 E Montview Blvd, Suite 300
Aurora CO 80045
Office phone: 303-724-1582; Office fax: 303-724-1934
Email: sean.oleary@cuanschutz.edu

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Dr. Maldonado is the site Principal Investigator for a Pfizer COVID-19 vaccine clinical trial in children and a Pfizer RSV vaccine clinical trial in pregnant women. She is a member of a Data Safety Monitoring Board for a Pfizer non-COVID-19 vaccine clinical trial. Dr. O'Leary has no relevant conflicts of interest to disclose.

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Abbreviations: COVID-19, Coronavirus Disease 2019; SARS-CoV-2, Serious Acute Respiratory Syndrome Coronavirus 2; FDA, Food and Drug Administration; CDC, Centers for Disease Control and Prevention; VAERS, Vaccine Adverse Event Reporting System; VSD, Vaccine Safety Datalink.

In this month's issue of *Pediatrics*, Marshall et al. report a case series describing seven 14- to 19-year-old males who developed symptomatic myocarditis after the second dose of the Pfizer-BioNTech COVID-19 vaccine.[1] The authors report that the symptoms began between two and four days after the second dose, and that all seven patients experienced rapid resolution of symptoms. This case series is published in the context of other media reports of myocarditis in young adults, mostly males, from the United States military and from Israel[2] as well as a recent increase in reports of myocarditis following SARS-CoV-2 vaccines to the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) Vaccine Adverse Event Reporting System (VAERS).[3] As such, this case series offers useful preliminary information on clinical and therapeutic details regarding myocarditis among adolescents.

While the authors are quick to point out that a causal relationship between vaccination and myocarditis has not been established, the temporal association of these cases with vaccination as well as the striking similarity in the clinical and laboratory presentations raise the possibility for such a relationship. However, the authors also acknowledge that a significant limitation in their report is that they compiled cases through personal communication rather than through a systematic surveillance system. Clearly, this approach could introduce reporting bias, and a case series cannot establish causality. Another critical point to consider is that the reported cases mirror the seasonal prevalence, sex, and age profile of background cases of myocarditis, thereby complicating an assessment of a potential association with SARS-CoV-2 vaccines. The authors themselves note in their discussion the high background rate of myocarditis in adolescent and young adult males,[4] precisely the population in this case series. Thus, a causal relationship between the Pfizer/BioNTech vaccine and myocarditis based on sporadic clinical reports must be

promptly investigated further using a robust and structured surveillance platform, such as that provided by CDC VAERS.

Due to the severity of the pandemic and the urgent need for suppression and control, vaccines against SARS-CoV-2 have been delivered to the US population with unprecedented speed and scale, undoubtedly saving many thousands of lives as a result. Although there was consensus among the scientific and public health communities that rapid dissemination of SARS-CoV-2 vaccines was necessary following Emergency Use Authorization by the FDA, there were potential risks in doing so. Specifically, clinical trials for vaccines — or any biological product — are highly unlikely to detect rare adverse events. The clinical trials for SARS-CoV-2 vaccines were actually larger than for most vaccines and certainly most medications, with roughly 30,000 to 45,000 participants for each of the three vaccines currently authorized in the US. Safety profiles in those trials were very favorable, which is reassuring, but the sample sizes of the trials were not large enough to detect possible adverse events with an incidence of, for example, one case in 100,000 doses. Thus, the risk of such rare adverse events must be outweighed by the benefits of the proposed intervention. With over 4 million COVID-19 cases diagnosed in children under 18 in the US that resulted in over 15,000 hospitalizations and between 300 and 600 deaths, the benefits of vaccination in this population far exceed the risks of rare adverse events.[5]

Because vaccines are generally administered to healthy populations, they are held to a much higher safety standard than most other biological products that might be given as therapeutics.

However, recognizing that rare side effects of vaccines may only be detected after administration to large numbers of individuals, over the last several decades the US FDA and the CDC have in concert developed robust post-licensure vaccine safety surveillance systems, continuously monitoring potential adverse events to assure the safety of vaccines.[6] These systems were especially valuable when rapid and extensive safety monitoring was called for with the advent of SARS-CoV-2 vaccines. Surveillance for these vaccines depended on the expertise developed with existing systems like VAERS and the Vaccine Safety Datalink (VSD), as well as new systems such as V-Safe that added further surveillance capacity. Indeed, the identification of a rare risk of anaphylaxis after the Pfizer BioNTech and Moderna vaccines[7,8] and of cerebral venous sinus thrombosis after the Janssen vaccine[9] within literally a matter of days after rollout validate the efficacy of the US safety surveillance systems.

Both VAERS and VSD have rapidly provided information to the general US population about specific potential adverse events consequent to SARS-CoV-2 vaccines (known as "pre-specified outcomes" in the vaccine safety system).[6] Among these outcomes are myocarditis and pericarditis. According to the CDC, as of May 28, 2021, over 166 million doses of COVID-19 vaccines have been administered in the US, with 2.5 million doses of the Pfizer/BioNTech delivered to adolescents 12 to 15 years of age in just the two weeks since it was approved for use in this age group and 4 million doses given to 16 to 18 years since FDA EUA approval in December 2020. Despite this widespread and rapid vaccine uptake especially among children less than 18 years of age, based on their surveillance data, FDA and CDC have not judged that myocarditis is causally related to SARS-CoV-2 vaccination, suggesting that a causal association, if it exists, is likely extraordinarily rare and may exist only in a subset of the population, for

example among young adult and adolescent males, in which the majority of current cases appear to be reported, mirroring the background prevalence of myocarditis.

The authors state "Post-immunization myocarditis is a known rare adverse event following other vaccinations, particularly following smallpox vaccination." In fact, although myocarditis has been reported as an adverse event following other vaccinations, smallpox vaccination is the *only* vaccine that has ever been conclusively linked to myocarditis based on a significantly higher relative risk.[10] It is worth noting that smallpox is a live vaccine and is associated with more adverse events than vaccines in the routine schedule.[11] Thus, if myocarditis following vaccination were confirmed to be a causally related rare adverse event after SARS-CoV-2 vaccination, it would be unique among non-live vaccines, so that gaining an understanding of the underlying biologic mechanism would be important. Typically, the pathogenesis of viral myocarditis involves direct viral infection of the myocardium, which could not be invoked as a cause in these reported cases. In vaccinia-associated myopericarditis, an autoimmune phenomenon is suspected,[12] but the time to onset of symptoms after vaccination is typically greater than one week,[13,14] much longer than the current case series. If a causal relationship between myocarditis and SARS-CoV-2 vaccination is identified, a different biologic mechanism is likely responsible and will need investigation.

While we await more definitive data regarding the nature of the relationship between the Pfizer/BioNTech vaccine and myocarditis, there are some concerns regarding this case series that might suggest a causal relationship and therefore warrant further analysis through established

surveillance systems. First, the consistent timing of symptoms in these seven cases after the second vaccination suggests a uniform biological process. Second, the similarities in clinical findings and laboratory characteristics in this series suggest a common etiology. Finally, these cases occurred in the context of a dearth of circulation of common respiratory viruses known to be associated with myocarditis, and thorough diagnostic evaluations did not identify infectious etiologies. While the number of cases in this series is small and subject to reporting bias, scientists should rapidly address any possible association of myocarditis and COVID-19 vaccinations through continuing analyses within our national surveillance systems. Investigators should also consider the timing of the *first* dose of the vaccine relative to reported cases of myocarditis, which the authors do not report in this case series. Although these patients did not meet criteria for the Multisystem Inflammatory Syndrome in Children (MIS-C), the unusual cardiac manifestations and generally quick resolution of symptoms in both this case series and in many children with MIS-C suggests a possible common pathogenesis. Given that MIS-C typically happens 3-5 weeks after a SARS-CoV-2 infection, we must also consider the possibility that the first dose is the initiating factor.

Despite the current lack of a definitive association between myocarditis and SARS-CoV-2 vaccines, a few key points can be communicated to pediatricians and to the public at large. First, the reported cases of myocarditis appear to be mild in nature and respond rapidly to minimally invasive therapy. Second, any potential association between myocarditis and SARS-CoV-2 vaccination will likely be quite rare given that our national safety surveillance systems have not yet identified a signal despite large numbers of vaccines administered to individuals 12 years of age and older. Third, the benefits of vaccination against this deadly and highly transmissible

disease clearly far outweigh any potential risks. Finally, rapid and robust real-time analysis of existing surveillance data should be reported as quickly as possible through the VAERS system and other national surveillance in order to provide confidence in the nature of the safety profile of SARS-CoV-2 vaccines in the pediatric population.

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