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EDITORIAL COMMENTARY

Weighing the Risks of Perimyocarditis With the Benefits of SARS-CoV-2 mRNA Vaccination in Adolescents

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The overwhelming burden of the COVID-19 pandemic persists in many parts of the world [1]. In the United States, efforts to vaccinate adults, and more recently adolescents, against SARS-CoV-2 have brought hope for a return to pre-pandemic work and school life. With widespread vaccination have come rare reports of perimyocarditis, predominantly occurring in adolescents and young adults [2–4]. Understandably, these reports, identified through well-established systems designed to detect rare vaccine side effects, have raised concerns and are being carefully assessed.

In this issue of the *Journal of the Pediatric Infectious Diseases Society*, Tano and colleagues [5] summarize their experience with 8 adolescents who developed perimyocarditis after receiving either 1 or 2 doses of the Pfizer-BioNTech SARS-CoV-2 messenger RNA (mRNA) vaccine. The report describes the onset of chest pain, fatigue, and other characteristic symptoms of myocarditis; elevated troponin levels; recent history of COVID-19 vaccination; and absence of an infectious diagnosis [5]. Symptoms resolved quickly with supportive care and the occasional use of anti-inflammatory agents or intravenous gamma globulin (IVIG).

As we consider the individual, regulatory, and public health implications of perimyocarditis occurring after COVID-19 vaccination, we offer several observations to contextualize these findings [3, 5–7]. First, virtually all case reports of perimyocarditis to date describe temporary symptoms and good outcomes; in fact, and in contrast to many causes of fulminant myocarditis, many affected children improved rapidly with no intervention at all [4]. (And while some children received IVIG, it is not clear whether this was for suspicion of multisystem inflammatory syndrome in children (MIS-C) or for myocarditis associated with COVID-19 vaccination.) However, long-term outcomes data are imperative to determine if even mild perimyocarditis after COVID-19 vaccination has long-term effects.

Second, because of the apparent mild and temporary nature of the symptoms in reported cases, it is possible—and even likely—that the unparalleled scrutiny of COVID-19 vaccination may have contributed to the frequency of detection of these cases. Many of the affected children's clinical case descriptions echo those observed in adolescents with symptomatic influenza and other viral illnesses. In the pre-COVID age, it is possible that these children may have stayed home in bed for a few days, taken over-the-counter antipyretics and anti-inflammatories, and eventually recovered without incident. Furthermore, due to heightened awareness of MIS-C, children presenting with vague symptoms are more often evaluated with a broad panel of tests that increase the sensitivity of detecting episodes of perimyocarditis that might not require intervention. While it is important to document any adverse events associated with vaccination, we must recognize these ascertainment biases. It falls upon healthcare workers and public health authorities to contextualize these findings and communicate them to the public in a manner that captures this nuance without undermining the value of surveillance efforts.

Third, any potential adverse events following vaccination must be weighed against the individual and societal risks of withholding vaccination. The original

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Pfizer/BioNTech phase 3 study that led to the vaccine's initial emergency use authorization included over 37 000 adults and demonstrated an estimated 95% efficacy against severe infections or hospitalization [8]. After widespread administration, the estimated effectiveness continues to be well over 90%. The smaller phase 3 Pfizer study of 2300 US 12- to 15-year olds reported 100% efficacy [2]. Despite frequent local reactions and transient systemic symptoms, more often after the second dose, there were no reported serious adverse events in either the adult or adolescent study cohorts. As of June 22, 2021, over 318 million doses of COVID-19 vaccine have been administered in the United States, with over 150 million people now fully vaccinated [9]. Of these, over 8 million children aged 12–17 years have received 1 dose of vaccine and almost 6 million have received 2 doses. As the reported cases of mild and self-limited perimyocarditis temporally associated with the receipt of an mRNA SARS-CoV-2 vaccine in children and young adults currently number between 250 and 300, this represents an estimated rate of 1–4 per 100 000 vaccinated.

To put this risk in perspective, in the United States as of June 22, 2021, there have been over 33 000 000 infections and over 600 000 deaths due to COVID-19 disease, including more than 4 million cases in children [9]. SARS-CoV-2 infection in children may result in severe manifestations, including myocarditis at a rate higher than that observed following COVID-19 vaccination [10–12]. At the time of this writing, over 450 children have died from COVID-19-associated complications in the United States (more than twice the number of pediatric deaths than seen in a severe influenza season) [9, 13]. MIS-C following asymptomatic or mild SARS-CoV-2 infection occurs at rates 10-fold higher than the rates of perimyocarditis potentially associated with vaccination [14]; in cohorts of affected children who underwent echocardiography, MIS-C was associated with left ventricular systolic dysfunction in 31%–100%, myocarditis in > 40%, pericarditis in around 25%, and coronary artery aneurysms in > 10% [15]. To date, more than 4000 children in the United States have met diagnostic criteria for MIS-C, with 36 attributed deaths [16]. And we are just beginning to understand the longer-term post-infectious complications including "long COVID-19" and MIS-C as well as possibly diabetes [17–19]. Furthermore, the social and mental health consequences of the pandemic continue to plague our youth. One in 10 children has sought mental health treatment as a result of school closures and social isolation, including large numbers of adolescents needing inpatient treatment for mental health emergencies and/or suicidality that far exceeds the availability of openings [20].

We have made calculations on the tolerability of risk before and to the benefit of public health. It is helpful to reflect upon the smallpox vaccine, which is still widely considered the most effective vaccine in history and was responsible for the global eradication of that illness. With one dose, the smallpox vaccine led to robust and incredibly durable immune responses in virtually all populations. However, this high level of immunogenicity had side effects: myocarditis associated with smallpox vaccination occurred at a frequency of between 12 and 400 cases per 100 000 vaccinated [21–23]. It is worth noting that many of these cases were subclinical or mild in nature, and often only found because of increased surveillance—similar to the current SARS-CoV-2 experience [3–5]. Ultimately, the benefit to society was deemed great enough to outweigh the low risk of mild illness for all but those at highest risk for severe perimyocarditis, and the Advisory Committee on Immunization Practices (ACIP) currently recommends the administration of smallpox vaccine to individuals with risk of exposure to orthopoxviruses who do not have evidence of preexisting cardiac disease [24].

SARS-CoV-2 mRNA vaccines have been remarkably effective in protecting against COVID-19, and these observations of perimyocarditis associated with adolescent COVID-19 mRNA vaccination should not distract us from this fact. Weighing the pandemic's physical and social-emotional harms to our children against the rare, typically mild episodes of perimyocarditis potentially associated with the vaccine, we agree with public health authorities and major medical societies that the benefit remains strongly on the side of vaccination [25]. Recommendations to vaccinate everyone who is age-eligible should not change based on current data. However, it is imperative that pediatricians, immunization providers, and public health officials continue to evaluate the data arising from these events, in order to ensure that, should the balance someday become less favorable, we apply knowledge to practice and recommendations. A successful long-term, population-wide strategy to control SARS-CoV-2 infection worldwide continues to center on vaccinating as many people as possible.

Note

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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