

## REVIEW ARTICLE

# COVID-19 VACCINE-INDUCED CARDIAC CONCERNS

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Myocarditis has been increasingly recognized as a rare complication of COVID-19 mRNA vaccinations, especially in young adolescent males. According to the US Centers for Disease Control and Prevention, the incidence of myocarditis in males 16–29 years of age is approximately 10.7 cases per 100,000. Of those diagnosed with myocarditis, roughly 69% were diagnosed 3–5 days after their second vaccination. Most recent reports have shown clinical presentations consistent with chest pain, elevated cardiac enzymes, ST elevations on ECG, and further echocardiogram or cardiac MRI findings displaying mild to moderate left systolic dysfunction. Although mechanisms in the development of myocarditis are still not clear, a promising hypothesis is that myocarditis is exacerbated by a hyperimmune response to the second dose of the vaccine. Children have a robust immune response to COVID-19, which has been exemplified by increasing cases of multisystem inflammatory syndrome in children. This report will review trends seen in patients with vaccine-induced myocarditis and highlight the benefit to risk assessment of cardiovascular complications associated with COVID-19.

## INTRODUCTION

Myocarditis is an inflammatory cardiomyopathy, most frequently caused by viral infections, affecting about 10–20 individuals per 100,000 each year in the general population.<sup>1,2</sup> Myocarditis following vaccine administration has been traditionally reported as a rare event, accounting for 0.1% of more than 620,000 reports recorded at the Vaccine Adverse Event Reporting System (VAERS) over a period of 18 years.<sup>2,3</sup> Most events occurred after administration of live-attenuated smallpox vaccine and less commonly after other vaccines such as diphtheria, tetanus, polio, and influenza. In late December of 2020, initiation of COVID-19 vaccination efforts began in the United States in hopes of flattening the epidemiology curve and reducing COVID-19 hospitalizations.<sup>1</sup>

In phase 3 studies on the COVID-19 mRNA vaccines, no safety issues concerning post-vaccine myocarditis were reported.<sup>2</sup> It was found that the incidence of serious adverse events with BNT162b2 vaccine (Pfizer-BioNTech) and mRNA-1273 vaccine (Moderna) was comparable in the vaccine and placebo groups by 0.6% and 0.5% respectively.<sup>1,2</sup> As of June 2021, a total of 1,226 reports of probable myocarditis or pericarditis were filed in the VAERS after the administration of approximately 300 million COVID-19 mRNA vaccine doses, resulting in a prevalence of 4.8 cases per 1 million doses administered.<sup>2,4</sup> This complication was most reported in

young men between the ages of 15 and 30 years, 72–96 hours after receiving the second dose of Pfizer and Moderna vaccines. The Moderna, mRNA-1273, vaccine was associated with a higher incidence of cases of myocarditis. Clinical findings included chest pain (>85%), ST elevation or T-wave changes and elevated cardiac enzymes (>70% for both).<sup>3</sup> Most patients were admitted for hospitalization and fully recovered with no underlying cardiac damage by further follow-up studies.

Serious adverse events associated with receipt of vaccinations targeting COVID-19 are of great interest to the public, public health officials, and vaccine safety surveillance organizations. There is now increasing evidence of myocarditis as a rare complication of COVID-19 vaccination, especially in young adolescent males. Using the most up-to-date data, we will explore this complication to aid in the risk-benefit assessment of COVID-19 mRNA vaccines in regard to short- and long-term cardiovascular outcomes.

## EPIDEMIOLOGY

Analysis of the US Centers for Disease Control and Prevention (CDC) Vaccine Safety Datalink revealed an increased risk of myocarditis or pericarditis among male individuals 12–39 years of age in a 7-day risk interval post-vaccination period with mRNA COVID-19 vaccines when compared with unvaccinated individuals [95% CI, 3.2–49.0].<sup>2,5,6</sup> Additionally, no patients were found to have a history of COVID-19 comorbidities, and all had good vaccine efficacy by protective spike protein antibody levels.<sup>2</sup> The Israeli Ministry of Health also reported a similar finding, reporting 148 cases of myocarditis among 10.4 million vaccinated individuals within 30 days of receipt of second BNT162b2 vaccine (Pfizer-BioNTech) mRNA vaccination.<sup>7</sup> The prevalence of myocarditis was

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1/20,000 for the 16–30-year-old group, compared with 1/100,000 in the general population receiving the Pfizer BioNTech mRNA vaccine.<sup>6</sup> Overall, individuals receiving Moderna vaccination were deemed to have a higher prevalence of myocarditis after the second dose.<sup>8</sup> Finally, of 2.8 million COVID-19 vaccinations administered by the Israeli Military Health System, 23 previously healthy male military members, with a median age of 25, were identified as having myocarditis approximately 4 days after administration of the second dose.<sup>9</sup>

## CLINICAL PRESENTATION

Acute myocarditis was classified as probable or confirmed from the CDC working case definition. Probable acute myocarditis was based on presence of one or more symptoms of chest pain, discomfort, pressure, dyspnea, palpitations, syncope and one new finding of elevated troponins above the upper limit of normal, abnormal electrocardiogram (ECG), abnormal echocardiogram, or cardiac MRI.<sup>10</sup> Confirmed cases of acute myocarditis were classified as the probable criteria plus histopathologic confirmation of myocarditis or elevated troponin above upper limits of normal and cardiac MRI findings consistent with myocarditis.<sup>10</sup> A large study conducted in Israel, in which 54 vaccinated patients who met criteria for myocarditis, revealed chest pain to be the most common presenting symptom, found in 82% of cases.<sup>12</sup> Similarly, the CDC Advisory Committee on Immunization Practices found that in 484 probable cases of myocarditis, 86% reported chest pain on presentation.<sup>11</sup> ECG findings showed ST-segment or T-wave changes in greater than 57% of cases.<sup>11</sup> Vital signs associated with myocarditis/pericarditis were generally normal, with only a select few cases that reported hemodynamic instability as a result of cardiogenic shock. Vaccine-induced myocardial injury has been considered a prevalent finding in patients who met criteria for myocarditis. Out of 323 confirmed myocarditis or pericarditis cases, 64% displayed elevated troponins.<sup>8,11</sup> A study of 23 male military patients, with a median age of 25, revealed elevated troponin levels of 10-fold to 400-fold of their upper limits in all patients after the second dose of mRNA COVID-19 vaccination.<sup>8</sup> Patients who underwent further cardiac imaging, including an echocardiogram and cardiac MRI, displayed mostly normal systolic function and normal chamber size. These findings were further reinforced in a recent study published in *Pediatrics* in which 14% of patients had mildly decreased left ventricular function (ejection fraction 45%–54%) by echocardiography.<sup>12</sup> More concerning, however, were cardiac MRI findings of late gadolinium enhancement in the inferolateral and lateral walls of the left ventricle, a pattern consistent with nonischemic myocardial injury and necrosis.<sup>7</sup>

## POTENTIAL MECHANISM OF COVID-19 VACCINE-INDUCED MYOCARDITIS

COVID-19 mRNA vaccines contain nucleoside-modified mRNA encoding the viral spike protein of the SARS-CoV-2, but not the live virus or DNA.<sup>13,14</sup> Once integrated within host cells, an adaptive immune response occurs to identify and destroy the virus expressing the spike protein. Although mRNA modifications have been shown to reduce innate immunogenicity, studies

have suggested that some individuals may have a genetic predisposition in which the immune response to mRNA may not be turned down. Instead, aberrant persistent cytokine activation via toll-like receptors detect the mRNA in the vaccine as antigen, which results in a downstream cascade of pro-inflammatory modulator pathways in the heart that may play a role in the development of myocarditis as part of a systemic reaction.<sup>13</sup> Another proposed mechanism of vaccine-induced myocarditis includes cross-reactivity between mRNA vaccine spike protein antibodies and myocardial contractile proteins. Molecular mimicry can occur when a foreign antigen shares a sequence or structural similarity with a self-antigen. Antibodies directed to mRNA viral spike proteins may have a structural similarity to protein sequences of alpha-myosin heavy chain, an important myocardial contractile protein.<sup>13,14</sup> Essentially the autoantibodies generated will therefore target self-myocardial tissues, resulting in myocardial inflammation injury and myocyte cell death.<sup>6</sup> Finally, given that vaccine-induced myocarditis was vastly seen in male patients, this suggests a hormonal component hyperimmune response.<sup>14</sup> Testosterone is known to inhibit anti-inflammatory immune cells, which result in a potent T-cell-mediated response, whereas estrogen has pro-inflammatory signaling and properties which gives rise to a decreased cell-mediated immune response.<sup>14</sup>

## RISK

A recent analysis has contrasted the risk of developing myocarditis following COVID-19 mRNA vaccines with the baseline. While myocarditis can be life-threatening, most vaccine-associated myocarditis events have been mild and self-limiting.<sup>9,11</sup> Most patients required minimal intervention and were discharged from the hospital within 2–3 days with full resolution of cardiac symptoms and normal echocardiogram findings. Given that the myocarditis risk in unvaccinated individuals with COVID-19 is 16–18 times higher than that of the general population, and the known complications with COVID-19 infections in younger adults have a known mortality rate of roughly 1%, the risk-benefit ratio remains significantly favorable for vaccination.<sup>8,12</sup> Vaccination not only prevents COVID-19-related hospitalizations, and deaths, but also decreases the risk of developing multisystem inflammatory syndrome in children (MIS-C), and post-COVID-19 infection sequelae.<sup>8,10</sup>

## MANAGEMENT

Although vaccine-induced myocarditis is a rare phenomenon, clinicians should be aware of its presentation and clinical management. Initial evaluation with an ECG and troponin-T levels should be obtained upon admission. Further imaging, such as echocardiograms and cardiac MRIs based on clinical presentation, is generally warranted given abnormal cardiac markers or ECG findings. Treatment is primarily supportive. In published case reports, nonsteroidal anti-inflammatory drugs, steroids, and colchicine were used for management of selective patients with myocarditis after COVID-19 vaccination, in addition to supportive care.<sup>15</sup> Some patients were initiated on  $\beta$ -blocker and angiotensin-converting enzyme inhibitor therapy due to left ventricular systolic dysfunction.<sup>8,10</sup> Although most reported cases of vaccine-

induced myocarditis fully recover with minimal underlying cardiac damage, it is imperative to restrict strenuous physical activity and sports competition pending complete resolution of symptoms, further diagnostic imaging, normalization of cardiac biomarkers, and clearance from a cardiologist.<sup>5,6</sup>

## CONCLUSION

Vaccines against COVID-19 have proved to be highly effective at preventing symptomatic disease. Vaccination flattens the case count per capita curve and significantly reduces the risk of COVID-19-related hospitalization, intensive care admission, and death in both young and elderly individuals.<sup>16,17</sup> COVID-19 vaccination also reduces the risk of COVID-19-associated acute kidney injury, arrhythmia, and thrombosis.<sup>9,15</sup> The prevalence of vaccine-induced myocarditis is approximately 1 out of every 100,000 individuals in the general population receiving the same mRNA vaccine.<sup>6</sup> In most cases of vaccine-induced myocarditis, individuals recovered without symptoms or long-term sequelae.<sup>17</sup> Therefore, COVID-19 vaccination retains a favorable benefit-risk ratio in spite of post-mRNA-vaccine-induced myocarditis and should be recommended in adolescent and adult populations. Strategies to reduce the risk of vaccine-associated myocarditis, in at-risk individuals, continue to be studied.

## COVID-19 VACCINE UPDATES

On June 18, 2022, the Advisory Committee on Immunization Practices (ACIP) and the US Food and Drug Administration updated the emergency use authorization for the Moderna COVID-19 vaccine mRNA-1273 for the prevention of symptomatic COVID-19 in children from ages 6 months old to 5 years old. Soon thereafter, the Pfizer-BioNTech COVID-19 vaccine was also authorized. Studies have shown that children who have received COVID-19 vaccines during testing developed high levels of antibodies to protect against COVID-19.<sup>18</sup> A great benefit of COVID-19 vaccinations in this population, is the potential to prevent multisystem inflammatory syndrome in children, and hospitalization. Side effect profiles of both the Pfizer BioNTech and Moderna vaccines in children 6 months to 5 years were relatively benign, with the most common symptoms being pain at injection site, swelling, fever, headache, chills, and irritability, which lasted roughly 2–4 days.<sup>18</sup> Vaccine-induced myocarditis in this population has not been well studied at this time. However, the benefit-risk ratio is favorable for the vaccine and its known efficacy to decrease severe illness and hospitalizations.

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