

Coronavirus disease 2019 (COVID-19) messenger RNA vaccination and myocarditis—beauty and the beast

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Prior to the 20th century, several communities and nations were ravished with epidemics and pandemics from infectious diseases that often left in their wake devastation of livelihood and high mortality.¹ With improvements in sanitation and advances in medicine leading to the development of antimicrobials and vaccines, the mortality from infectious diseases waned and was replaced by mortality from chronic diseases.¹ This epidemiologic transition led many to believe that infectious diseases were going to be a thing of the past. But the emergence and re-emergence of new pathogens, such as human immunodeficiency virus and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have caused pandemics that reminded the world of the devastation that infectious diseases can cause and of the need for vaccines.

Globally, there have been about 239 million confirmed cases, and 4.9 million deaths attributed to coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2.² In the United States, about 44.5 million confirmed cases and 716,370 deaths due to COVID-19 have been reported.³ Vaccination has been a major component of public health efforts to reduce the spread, hospitalization, and mortality associated with the COVID-19 pandemic. National data show that 187.8 million Americans have been fully vaccinated and 404.4 million doses of vaccines have been administered.³ Despite the demonstrated success of the COVID-19 vaccines in reducing the rates of hospitalizations and deaths,^{4,5} emerging reports show that some messenger ribonucleic acid (mRNA) vaccines, namely the BNT162b2 vaccine (Pfizer–BioNTech) and

mRNA-1273 (Moderna), have adverse side effects.^{6–8} Overall, mRNA vaccines are reported to be associated with higher incidence of systemic and local side effects than viral vector-based vaccines, but these side effects often have milder symptoms and occur at frequencies lower than those reported in most Phase 3 trials.^{4,5,9} Recently, public discussion on adverse effects of mRNA vaccines has primarily focused on acute myocarditis, especially in adolescents and young adults.

Indeed, the sudden occurrence of myocarditis after vaccination, although rare, has been observed for other diseases. Studies based on passive surveillance databases have often reported cases of myocarditis and pericarditis that ranged in severity from mild and without symptoms to severe and sometimes resulting in mortality.^{10,11} Using data from the United States's Vaccine Adverse Event Reporting System (VAERS) from 1990 to 2018, Su et al. identified 708 cases of myocarditis or pericarditis (0.1% of all adverse events reported) after vaccination, with smallpox and anthrax vaccines being the most commonly reported vaccine.¹⁰ A greater proportion of this adverse event was reported in men (79%) with 72% having symptom onset ≤ 2 weeks postvaccination. Another review of the VAERS from 2011–2015 coupled with a systematic review reported 199 cases of myocarditis/pericarditis.¹¹ Of this number, 149 reported having received smallpox vaccination.¹¹ Among the 15 persons aged <18 years who had myocarditis/pericarditis in the VAERS database, five died compared to two deaths in the 35 persons with myocarditis/pericarditis who were ≥ 18 years old at the time of vaccination. These findings should be interpreted in the light of limitations of VAERS. VAERS is a passive surveillance system that relies on voluntary reporting. Therefore, it is subject to either underreporting of adverse events, especially those that have mild symptoms or expected events, or it is subject to over-ascertainment of events due to the open access system.^{10,11}

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Myocarditis has been reported to occur rapidly in young people, usually after the second dose of mRNA vaccinations for COVID-19.¹² Using the VAERS database, the Centers for Disease Control and Prevention (CDC) in June 2021 reported rates of myocarditis/pericarditis (confirmed and unconfirmed cases) that were higher among children, ranging from 37 cases per million doses among persons aged 12–17 years to 1.3 cases per million doses among adults aged ≥ 65 years.^{7,8} In confirmed cases, the rate of myocarditis/pericarditis occurring 21 days after vaccination in persons aged 12 to 39 years was 8 cases per million doses of mRNA vaccines administered.⁷ This rate was higher after the second dose than the first dose (12.6 vs. 4.4 cases per million doses).⁷ Comparing the rates of myocarditis/pericarditis after the second dose of the mRNA vaccines, Moderna vaccines had higher rates of postvaccination myocarditis/pericarditis than Pfizer-BioNTech (19.8 vs. 8.0 cases per million doses), with men having rates that were approximately eight-fold higher than women (32 vs. 4.7 cases per million doses).⁷ Some reports have noted that vaccination-associated myocarditis in children, especially boys, was underreported by the CDC.⁶ A recent study of vaccination-associated myocarditis in children aged 12–17 years using the VAERS database reported rates of 94.0 cases per million doses, an estimate that was 31.5% higher than the rate reported by the CDC (66.7 cases per million doses) despite using the same case definition of myocarditis that the CDC used.⁶ Regardless of the discrepancies in rates reported, it is important to recognize that all these studies were based on a passive surveillance system that lacked a control group to provide suitable denominators for vaccine exposures, and to determine any potential associations between COVID-19 vaccination and myocarditis.

The Phase 3 trials of Pfizer–BioNTech and Moderna did not report any excess vaccine-associated myocarditis.^{13,14} The reasons for this are many, but the majority of them pertain to the limitations of clinical trials. For instance, Phase 3 trials often recruit relatively smaller numbers of healthier-than-average subjects compared to individuals in the general population who are the target for the interventions. Hence, they are

often underpowered to detect significant differences in rare adverse events like myocarditis. This highlights the importance of post-marketing surveillance to monitor the safety of vaccines in real-world settings.¹⁵ Since COVID-19 vaccines have been administered in the United States for less than a year, it is not surprising that evidence for mRNA vaccine-associated myocarditis among Americans from active surveillance systems with control groups is sparse in the literature. An analysis of the Optum healthcare claims database by the United States Food and Drug Administration reported an excess risk of myocarditis/pericarditis of approximately 200 cases per million vaccinated males aged 16–17 years.¹⁶ Diaz et al. compared vaccine related cases occurring from February to May 2021 to myocarditis occurring from 2019 through to January 2021 using data from individuals who were part of the Providence healthcare system that includes 40 hospitals in Washington, Oregon, Montana, and Los Angeles County, California.¹² Among the two million individuals who received at least one COVID-19 vaccination, 20 adjudicated vaccine-related myocarditis (incidence of 1.0 case per 100,000 persons) occurred after a median of 3.5 days from vaccination.¹² The median age of persons with myocarditis was 36 years, 75% were men, and 80% developed symptoms after the second vaccination.¹² The occurrence of adverse events was similar among persons who received the Pfizer/BioNTech (11 cases) or the Moderna (9 cases) vaccine.

Another study of 2.4 million adults aged 18 years or older who were in the Kaiser Permanente Southern California integrated healthcare system and received at least one dose of the mRNA vaccine between December 14, 2020, and July 20, 2021, reported 15 cases of confirmed myocarditis over a 10-day observation window.^{17,18} All 15 cases were men who were ≤ 40 years of age with no prior cardiac history.^{17,18} The incidence of vaccine-associated myocarditis was 0.8 cases per 1 million persons after the first dose and 5.8 cases per 1 million persons after the second dose of vaccine.¹⁷ Compared to the 75 cases (52% men) of myocarditis that occurred during the study period among individuals who were not vaccinated, the risk ratio (RR) for myocarditis was 0.38 (95% confidence interval [CI]: 0.05–1.40)

for the first dose and 2.7 (95% CI: 1.4–4.8) for the second dose.¹⁷ Taken together, these results parallel prior studies that showed that vaccine-associated myocarditis primarily occurs in young men who have recently received their second vaccine dose,¹⁷ and also suggest that there is no statistically significant difference in the incidence of myocarditis after the first dose of the mRNA vaccine. However, there is an elevated risk of myocarditis after the second dose of the vaccine when compared to unvaccinated individuals without COVID-19.

Ideally, to place the risk of vaccine-associated myocarditis in context of the ongoing pandemic will require comparing these rates with the rate of myocarditis in patients with COVID-19 versus those without COVID-19. However, implementation of such studies have been a challenge since the pandemic itself has affected healthcare operations in various parts of the world.¹⁹ During the early days of the pandemic, cardiovascular complications, including myocarditis secondary to SARS-CoV-2 cardiotropism, were reported in patients with COVID-19.^{20,21} To date, the only available study with large samples that compared the incidence of myocarditis among mRNA vaccinated persons and persons with COVID-19 was based on information from 1,736,832 persons who are part of the largest healthcare organization in Israel.¹⁵ This study reported 21 cases of vaccine-associated myocarditis in persons with median age of 25 years of whom 91% were male. Compared to persons without vaccination, the mRNA vaccines were associated with elevated risk of myocarditis (RR: 3.24; 95% CI: 1.55–12.44; risk difference, 2.7 events per 100,000 persons), a result similar to those reported in the Kaiser Permanente Southern California integrated health care system.¹⁷ Furthermore, a substantial risk of myocarditis was observed among COVID-19 patients without prior vaccination (RR: 18.28; 95% CI, 3.95–25.12; risk difference, 11.0 events per 100,000 persons) compared to persons without COVID-19.¹⁵ Serious adverse events, such as pericarditis, arrhythmia, deep vein thrombosis, pulmonary embolism, myocardial infarction and intracranial hemorrhage were observed among COVID-19 patients compared to milder conditions, such as lymphadenopathy, appendicitis, and herpes zoster infection, that were reported in vaccinated persons.¹⁵

Despite milder adverse events reported in individuals who received the mRNA vaccine, it is worth noting that myocarditis could be potentially serious and require intensive care support.¹⁵ So far, most short-term follow-up studies on vaccine-associated myocarditis have reported favorable outcomes among vaccinated persons who develop this condition. The CDC reported that 68% (218 of the 323) of persons aged 12–29 years with vaccine-associated myocarditis had their symptoms resolve after a few days.^{6,7} This estimate is similar to the 70% cardiac symptom resolution within 1 week of onset that was reported by a case series of 23 (22 previously healthy) male members of the United States military who developed myocarditis within 4 days of receiving the mRNA vaccine.²² Others have reported 100% resolution of symptoms with conservative management among persons who developed vaccine associated myocarditis.²³

In conclusion, COVID-19 is associated with substantial risk for myocarditis and other serious conditions associated with mortality. Vaccine-associated myocarditis is rare; the risk of myocarditis is higher among persons who received two doses of the mRNA vaccines compared to individuals who did not receive the vaccine. Although these observational studies do not provide evidence of causality, the short duration between vaccination and the development of myocarditis in healthy individuals without prior cardiac conditions lend strong support to a possible relationship that warrants further investigation. The long-term sequelae of vaccine-associated myocarditis are currently unknown. With the greatest burden of vaccine-associated myocarditis observed among adolescents and young adults, real-time vaccine safety surveillance and active follow-up of persons with vaccine-associated myocarditis are of utmost importance. Discussions and decisions about vaccine-associated myocarditis ought to be balanced with the benefits of vaccines in preventing serious adverse events, hospitalizations, and mortality due to COVID-19 in spite of emerging variants of the SARS-CoV-2.

Keywords: COVID-19, vaccines, mRNA, myocarditis, adverse effects

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