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## *Weekly Journal Scan*

# Myocarditis after BNT162b2 mRNA SARS-CoV-2 vaccine: low incidence and mild severity

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Comment on 'Myocarditis after Covid-19 Vaccination in a Large Health Care Organization' published in *N Engl J Med* (doi:10.1056/NEJMoa2110737) and on 'Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel' published in *N Engl J Med* (doi:10.1056/NEJMoa2109730).

## Key Points

- Two papers reported retrospective data on cases of presumed myocarditis that were detected after receipt of the BNT162b2 messenger RNA (mRNA) vaccine (Pfizer–BioNTech) in Israel.[1,2] Witberg *et al.*[1] searched the database of Clalit Health Services, the largest Healthcare Organization (HCO) in Israel, for diagnoses of myocarditis in patients who had received at least one dose of the BNT162b2 mRNA vaccine, from December 2020 to May 2021. Mevorach *et al.*[2] reviewed data from medical records obtained from the Israeli Ministry of Health regarding hospitalized patients with suspected myocarditis among vaccinated persons, when compared with unvaccinated controls, from December 2020 to May 2021.
- Witberg *et al.*[1] identified 54 cases that fulfilled the definition of myocarditis used by the Centers for Disease Control and Prevention (CDC) among >2.5 million vaccinated persons listed in the database of HCO. Among the patients with myocarditis, 37 (69%) were diagnosed ∼3–5 days after the second vaccine dose. The overall estimated incidence of myocarditis up to 42 days after at least one dose of vaccine was 2.13 cases per 100 000 persons [95% confidence interval (CI): 1.6–2.7]. The highest incidence was among male patients aged between 16 and 29 years (10.7 cases per 100 000 persons; 95% CI: 6.9–14.5). Most cases of myocarditis were mild (76%) or moderate (22%) in severity; one case was fulminant. Patients who showed left ventricular dysfunction on admission (29%) had normalized left ventricular function at follow-up (median 83 days).
- According to Mevorach *et al.*, there were 136 definite or probable cases of myocarditis, based on the Brighton Collaboration definition, reported during the surveillance of ∼5.1 million persons receiving two doses of the BNT162b2 mRNA vaccine. Of these, 117 (86%) presented after the second dose and 81% of them were hospitalized within 7 days from vaccination. These findings were mostly referred to the first week after the second vaccine dose as the main risk window. In males, myocarditis had an incidence of 0.6 cases per 100 000 people within 21 days after the first dose and 3.8 cases per 100 000 people within 21 days after the second dose. The incidence increased to 1.3 and 15.1 per 100 000 people after the first and second doses, respectively, in teenager/boys aged 16–19 years. When compared with the incidence expected on historical data (2017–19), the standardized incidence ratio was 5.3 (95% CI: 4.5–6.4) and was the highest after the second dose in male recipients aged between 16 and 19 years (13.6; 95% CI: 9.3–19.2). The rate ratio for myocarditis 30 days after the second vaccine dose when compared with unvaccinated persons was 2.4 (95% CI: 1.1–5.0), and the highest rate was again among male recipients between 16 and 19 years (8.9; 95% CI: 4.5–17.83), with a ratio of 1 in 6637. Among these presumed cases, 95% of the patients had a benign, self-resolving course, but one patient died.

## Comment

The risks of acute myocarditis associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccination, especially in male teenagers, have raised great concern and garnered intense media attention.

Historically, myocarditis has been reported as a rare adverse event after vaccinations, especially smallpox, influenza, and hepatitis B vaccinations.[3] In the pre-COVID-19 era, among 620 195 reports filed at the United States (US)-Vaccine Adverse Event Reporting System (VAERS) between 1990 and 2018, 0.1% were attributable to myopericarditis. Of those myopericarditis reports, 79% were in

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young males.[3] Myocarditis in general practice, independent of vaccination, is most common in young men and resolves spontaneously in at least half of patients, while leads to dilated cardiomyopathy, heart transplantation, or death in up to a quarter of cases.

By July 2021, the CDC reported a likely association between the SARS-CoV-2 mRNA vaccines and cases of myocarditis and pericarditis; the reported CDC myocarditis/pericarditis rate was low ≈12.6 cases per million second-dose mRNA vaccine among individuals aged 12–39 years.[4,5] Almost all confirmed cases with follow-up showed resolution of symptoms; and among those who had follow-up electrocardiogram/echocardiography and laboratory testing, most had returned to normal status.[5]

The two retrospective studies from Israel[1,2] showed a slightly different incidence of post-vaccine myocarditis, and an increased incidence compared with the available data from the CDC, probably because of the different data collection methods and differences in criteria for diagnosing myocarditis. Indeed, the diagnosis of myocarditis is challenging and often hard to establish in the absence of endomyocardial biopsy.[6] Both groups reported clinically suspected myocarditis of unspecified cause, as only three patients in one study[1] and two in the other[2] underwent endomyocardial biopsy. Cardiac magnetic resonance imaging was also performed in about one-third[1,2] of patients. Both studies could not exclude confounders that might also contribute to the incidence of myocarditis, and the Witberg study lacked a simultaneously enrolled comparator group. As for other case reports and case series on myopericarditis following SARS-CoV-2 mRNA vaccination existing in the literature,[7,8] the Israeli studies[1,2] can only establish a temporal relationship between vaccine administration and development of myocarditis, whereas they cannot demonstrate a conclusive causality. Still, these data highlight the need for further investigation and longer follow-up.

Myocarditis associated with SARS-CoV-2 mRNA vaccination mainly occurs in young male adults within 1 week of viral antigen-induced immune activation but can sometimes occur in vaccine recipients with immune and genetic susceptibility to myocarditis. The mechanisms are not known but they may be related to mRNA sequence that encodes for the spike protein of SARS-CoV-2, or to the immune response that follows vaccination.[9] The propensity of young adults to develop myocarditis following the second dose of vaccine supports the hypothesis of the vaccine-associated maladaptive immune response, related to sex hormone differences, causing cardiac injury.[9]

Most of the reported cases that occurred after vaccination had an uneventful course, recovering cardiac function within 1–5 weeks after an initial hospitalization of 3–5 days.[1,2] By contrast, the incidence of COVID-19-associated cardiac injury or myocarditis is estimated to be 100 times higher (1000–1400 per 100 000 people with COVID-19) than that of SARS-CoV-2 mRNA-vaccine-related myocarditis. Moreover, in contrast to the overall mild presentation and good outcome of vaccine-associated myocarditis, COVID-19 is associated with a higher risk of cardiovascular complications.[10] Although symptoms resolved rapidly in almost all patients, the potential development of myocardial fibrosis and the unknown long-term effects on the heart recommend long-term cardiac surveillance with follow-up visits and cardiac imaging for all patients with mRNA vaccine-related myocarditis.

In conclusion, clinically suspected myocarditis is temporally associated with the BNT162b2 mRNA vaccine. This association does not imply causation. The risk is very low, although more common in young male patients. Vaccine-related myocarditis is self-limiting in most cases. The results of these two studies may contribute to reassure physicians, patients, general population, and media, as the benefit–risk assessment for SARS-CoV-2 mRNA vaccination shows a highly favourable balance for all age and sex groups.

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