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Acute myocarditis caused by COVID-19 disease and following COVID-19 vaccination

Ran Kornowski ,[1] Guy Witberg [2]

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[1]Department of Cardiology, Rabin Medical Center, Beilinson Hospital & Faculty of Medicine, Tel Aviv University, Tel Aviv, Petah Tikva, Israel
[2]Department of Cardiology, Rabin Medical Center, Beilinson Hospital & Faculty of Medicine, Tel Aviv University, Tel Aviv, Petach Tikva, Israel

Correspondence to
Dr Ran Kornowski; ran.kornowski@gmail.com

ABSTRACT

Myocarditis and pericarditis are inflammatory conditions of the heart that present a range of symptoms, often including chest pain, fatigue, breathlessness and palpitations that may be irregular due to cardiac rhythm disturbances. Myocarditis has been proposed to account for a fraction of cardiac injury among patients infected with SARS-CoV-2 and associated systemic inflammation; and it might be one of the reasons for the high mortality seen in COVID-19 patients. Furthermore, following vaccination with mRNA COVID-19 vaccines (ie, Comirnaty and Spikevax), myocarditis and pericarditis can develop within a few days of vaccination, particularly following the second dose. Based on recent reviewed data, the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have determined that the risk for both of these conditions is overall 'very rare' (~1 in 10 000 vaccinated people may be clinically affected), with the highest risk among younger males. Both EMA and FDA agree that the benefits of all authorised COVID-19 vaccines continue to outweigh their risks, given the threat of serious COVID-19 illness and related complications. Since myocarditis has a very wide clinical spectrum, ranging from mild to fulminant life-threatening disease, we present in this review a sum of the latest findings and considerations for the proper diagnosis and management of affected patients.

INTRODUCTION

COVID-19: from subclinical myocardial injury to fulminant lethal myocarditis

SARS-CoV-2 gains entry into human cells by binding its cleaved spike protein (S1/S2 and S2′ sites) to the ACE2 membrane protein,[1] which, can be found on ciliated columnar epithelial cells of the respiratory tract, type II pneumocytes and also cardiomyocytes.[2] Since, failed human hearts have a higher percentage of ACE2-expressing cardiomyocytes, patients with heart failure are at a higher risk and are more susceptible to severe infection.[2]

Furthermore, viral infections are a known common cause of myocarditis, due to a combination of direct cellular injury and T-cell cytotoxicity pointed at the myocardium,[3] which can be augmented by the cytokine storm syndrome.[4] Interleukin 6 (IL-6) appears to be the central mediator of the cytokine storm,[5] which causes T-lymphocyte activation and a further release of inflammatory cytokines, stimulating more T lymphocytes into a positive feedback loop of immune activation and myocardial damage.[4] As such, myocarditis has been proposed to account for a fraction of cardiac injury patients infected with SARS-CoV-2 and associated systemic inflammation.[6]

This inflammatory disease of the myocardium is classified as acute, chronic or fulminant; with the latter being a sudden, severe manifestation associated with acute heart failure, cardiogenic shock and life-threatening arrhythmias.[7] The gold standard for diagnosis is the Dallas criteria, based on endomyocardial biopsy (EMB) histopathology.[3 8 9] Since 2009, a cardiac MRI (CMRI)-based diagnosis of myocarditis has been supported by the Lake Louise criteria (LLC), targeting three aspects of myocardial inflammation: oedema, hyperaemia and necrosis and/or fibrosis.[10] Most of the cases of COVID-19-related myocarditis were diagnosed based on CMRI findings, with biopsy performed in very few cases.[11]

Patients with myocarditis often present with chest pain, fatigue and dyspnoea, similar to viral infections such as COVID-19 with or without myocarditis; but others, report symptoms such as myalgia, diarrhoea, nausea, vomiting and headaches.[7] According to a systematic review by Kariyanna *et al*,[12] the most consistent findings in suspected COVID-19-related myocarditis were cardiac biomarkers elevation; bilateral ground glass opacities on chest CT; and late gadolinium enhancement (LGE) from CMRI, both of which findings were observed in all patients in the study.[12 13] Myocardial oedema was reported in more than half of these patients, and tissue characterisation through the use of LGE and T1/T2 mapping was more useful at detecting myocardial injury than assessing ventricular function according to the authors.[12–15] Laboratory tests

revealed leukocytosis with increased C reactive protein, and arterial blood gas analysis showed respiratory acidosis.[12] Also, electrocardiography demonstrated ST-segment elevation or inverted T waves; and, echocardiography revealed reduced left ventricular ejection fraction (LVEF) with cardiomegaly or increased wall thickness.[12]

As for EMB findings, an initial case report of a clinically suspected acute myocarditis, SARS-CoV-2 was shown not in cardiomyocytes but within macrophages.[16] Later, reports found viral invasion and necrosis of myocytes.[17 18] Italia *et al*[11] have recently published a table summarising the latest conclusions from different reported studies, showing different degrees of myocardial inflammation; and, limited or absent myocardial necrosis.[11] Also, Basso *et al*[19] did a multicentric postmortem study in COVID-19-diseased patients, and found that in 86% of the cases, the most common cardiac autoptic evidence was non-specific interstitial macrophage infiltration, with 14% of the patients presenting a multifocal lymphocytic myocarditis.[19] The high mortality in COVID-19 is very likely due to cytokine storm destroying the lungs architecture and fulminant myocarditis.[20]

COVID-19 induced myocarditis

Despite the growing understanding of COVID-19 myocardial involvement, cases of COVID-19 myocarditis are likely under-reported.[13] One recent study showed the prevalence of clinically confirmed COVID-19 myocarditis across a large multinational registry to be 0.01% (256 patients), with an associated increased mortality, underscoring the importance of diagnosing patients with myocarditis early in the process.[21] Current patient management is mainly supportive with the potential addition of interventions recommended for severe COVID-19 disease, such as remdesivir, dexamethasone with or without convalescent plasma.[22] In the setting of cardiogenic shock and refractory life-threatening arrhythmias, advanced mechanical circulatory support procedures should be considered. The history and clinical features of myocarditis are often nonspecific, as such early recognition and aggressive intervention are key factors in reducing morbidity and mortality. Furthermore, ventricular arrhythmias and sudden cardiac death secondary to myocarditis are also a concern in COVID-19 patients.[13]

Subclinical myocardial involvement is also a common finding among COVID-19 patients. In fact, Li *et al*[23] reported 28 out of 40 COVID-19 patients with myocardial dysfunction based on reduced left ventricular 2D-global longitudinal strain, when compared with healthy controls.[13 23] Twenty-four of the 40 patients exhibited elevated extracellular volume fraction in comparison with healthy controls, denoting diffuse interstitial fibrosis in a majority of these patients.[13 23] These findings indicate the extensive incidence of subclinical cardiac abnormalities, only recognised months after COVID-19 recovery. The distinction between COVID-19 associated myocardial injury and overt myocarditis syndrome remains in some cases challenging; and, CMRI with or without myocardial biopsy is needed to validate the precise diagnosis.

COVID-19 postvaccination myocarditis

To end the COVID-19 pandemic, vaccination is an essential component of the public health strategy. Large, randomised controlled trials of COVID-19 vaccines were found safe and effective in preventing laboratory-confirmed symptomatic COVID-19[24–26]; even though, adverse effects have been reported. In the specific group population of young adults and adolescent males, myocarditis is considered a rare complication of mRNA vaccination[27] (ie, BNT162b2-Comirnaty by BioNTech/Pfizer, New York City, New York and Spikevax- mRNA-1273 by Moderna, Cambridge, Massachusetts, USA).

Within the US Vaccine Adverse Event Reporting System: 1226 reports of myocarditis after mRNA vaccination were received during 29 December 2020–11 June 2021; with a median age of 26 years (range 12–94 years); and, median symptom onset interval of 3 days after vaccination (range=0–179).[27] Among 1094 patients with number of vaccine doses received reported, 76% occurred after receipt of the second-dose of mRNA vaccine; and, cases were reported after both Comirnaty and Spikevax.[27] One of the initial reports was a retrospective case series within the US Military Health System[28] that showed unexpected incidence of male military members diagnosed with clinical myocarditis following vaccination.

Our group have studied this topic extensively. In a cohort of ~2.5 million members of the largest Israeli healthcare system (ie, Clalit Health Fund) who received at least one dose of Comirnaty, we found that the estimated incidence of myocarditis was 2.13 cases per 100 000 persons; with the highest incidence among young male patients (16–29 years, 10.7 per 100 000 persons).[29] Most cases of myocarditis were mild in relevance to clinical severity.

In another Israeli study that included ~5.4 million vaccinated people, second-dose vaccination-related myocarditis had a standardised incidence ratio of 5.34 per 100 000 persons—driven mostly by diagnosis in younger males.[30] The risk ratio for myocarditis compared with unvaccinated people was 1.8.[30] Among the aged <30 years old, the standardised incidence ratio was 12.2 per 100 000 vaccinated. From 136 adjudicated cases, only one fulminant case was reported. Patients with myocarditis consistently presented chest pain 2–3 days after second dose; and, showed elevated cardiac troponin levels, abnormal ECG with ST elevations in most, and CMRI suggestive of myocarditis in all (when performed), with no evidence of acute COVID-19 or other viral infections.[31]

In a series of 15 male patients with clinically adjudicated myocarditis within 42 days of first-Comirnaty vaccination who underwent CMRI, imaging findings were consistent with 'classical myocarditis'.[32] LGE was found among 13/15 patients with a median of 2% (range 0%–15%), with inferolateral wall being the most common location (8/13). The patterns of the LGE were: mid-wall in six patients; epicardial in five patients; and mid-wall and

epicardial in two patients. The short-term clinical course and outcomes were favourable in all cases.

Another report from 26 US medical centres identified 139 adolescents and young adults with suspected myocarditis.[33] Most patients were male (90.6%) with median age of 15.8 years. Suspected myocarditis occurred in 131 (94.2%) following Comirnaty, with 128 (91.4%) after the second dose. Median symptom on-set was 2 days after vaccination. Twenty-six patients (18.7%) were admitted to intensive care unit (ICU), two were treated with inotropic/vasopressor support, but none required mechanical support or died. Of 97 patients who underwent CMRI, 75 (77.3%) had abnormal findings: 74 (76.3%) had LGE, 54 (55.7%) had myocardial oedema. Among 26 patients with LVEF <55% on echocardiogram, follow-up showed normalised function (N=25).[33]

The Centers for Disease Control (CDC) has estimated an incidence of myocarditis after any COVID-19 vaccination as 0.48 cases per 100 000 overall, and 1.2 cases per 100 000 among vaccine recipients between the ages of 18–29 years.[34] This estimate can vary according to the patient population, accuracy of case identification and definition of myocarditis events (eg, suspected vs confirmed cases). Importantly, per million second doses of mRNA COVID-19 vaccine administered to this group: 11 000 COVID-19 infections, 560 hospitalisations, 138 ICU admissions and 6 deaths due to COVID-19 could be prevented, compared with 39–47 expected myocarditis cases after COVID-19 vaccination.[34] As such, the benefits (prevention of COVID-19 disease and associated hospitalisations, ICU admissions, mechanical support of the cardiorespiratory system and deaths) clearly outweigh the risks (expected myocarditis cases after vaccination) in this group population, as in all populations for which vaccination has been recommended.[34]

Most recently, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency has reviewed two large European epidemiological studies, one conducted using data from the French national health system (Epi-phare) and the other based on Nordic registry data.[35] Both studies provide estimates of the number of extra cases of myocarditis in younger males following the second dose, compared with unexposed persons of the same age and gender. For Comirnaty, the French study showed that, in a period of 7 days after the second dose, there were about 0.26 extra cases of myocarditis in 12–29 years old males per 10 000 compared with unexposed. In the Nordic study, in a period of 28 days after the second dose, there were 0.57 extra cases of myocarditis in 16–24 years old males per 10 000 compared with unexposed. In the case of Spikevax, the French study showed that in a period of 7 days after the second dose there were about 1.3 extra cases of myocarditis in 12–29 year old males per 10 000 compared with unexposed. The Nordic study showed that in a period of 28 days after the second dose of Spikevax there were ≈1.9 extra cases of myocarditis in 16–24 years old males per 10 000 compared with unexposed. Based on the reviewed data, PRAC confirmed the overall 'very rare' risk, higher among younger males; but concluded that vaccination benefits clearly outweigh the risks.

Gaps of knowledge

How to best diagnose and manage affected cases?

Patients should be tested for baseline cardiac biomarkers/enzymes on hospital admission (eg, troponin and N-terminal pro-B-type natriuretic peptide (NT-pro-BNP)); because, cardiac troponin I, cardiac troponin T, NT-pro-BNP and BNP levels are usually elevated in myocarditis due to acute myocardial injury and possible ventricular dilation.[4] In patients with suspected acute myocarditis, cardiac echocardiography should be performed repeatedly and CMRI should advance the diagnosis according to the revised Lake LLC.[17] Nonetheless, CMRI is limited in many centres with the requisite for some breath-holding manoeuvres; and given the high contagiousness of COVID-19, requires comprehensive disinfection measures after use.[4] Usually, echocardiogram is more readily available, and the cardinal signs of myocarditis are increased wall thickness, chamber dilation and pericardial effusion in the background of ventricular systolic dysfunction.[4] If coronary angiography is performed, it is reasonable to perform this procedure concomitantly with EMB in experienced centres, in order to obtain samples for immunohistochemistry of inflammatory infiltrates and RNA/DNA extraction for the presence of viral genomes. EMB collection also serves as an opportunity for accurate confirmed diagnosis, and analysis of possible biomarkers of SARS-CoV-2 myocarditis.

Because inflammation is a substrate for atrial arrhythmias, such as atrial fibrillation, these tend to be more frequent in COVID-19 cardiomyopathies, occurring in up to half of patients admitted to an ICU.[17] As such, cardiac monitoring is advisable to enable appropriate therapy. Ventricular arrhythmias are also observed and may accompany cardiac arrest in these patients.[17] QT prolongation will need to be monitored.[17] The appropriate use of anticoagulants evaluating risk vs benefit is also important.[17]

What are the long-term effects?

The immune activation and dysfunction can lead to target tissue fibrosis and microangiopathy, causing long-term effects in the affected patients. Owing to concerns about myocardial injury caused by COVID-19, investigators started imaging survivors of COVID-19 using CMRI and found a concerningly high frequency (up to 78%) of patients with abnormalities: elevated T1 values (a marker of fibrosis or inflammation) in up to 73% of patients, increased T2 values (a marker of oedema) in up to 60% of patients and myocarditis-like LGE patterns in 32%–45% of patients when CMRI was performed within 37–71 days after COVID-19 diagnosis.[13] A German study suggested that 2 months after SARS-CoV-2 positivity, 78% of survivors had persistent cardiac involvement, of which 60% presented ongoing signs of myocarditis.[14] These findings

raised the spectre of ongoing myocarditis, and give an alert of an eventual epidemic of long-term heart failure. As such, early identification of patients with cardiac involvement is vital, so they can benefit from cardioprotective therapy and appropriate follow-up strategies. It is important to emphasise that these persistent CMRI findings were not identified among myocarditis cases induced by vaccination against COVID-19. It is probable that since most affected people were not hospitalised for a very long period of time and most had good functional and clinical recovery, the overall long-term prognosis should be favourable as well among vaccinated patients with myocarditis.

Repeat vaccination for those who already had myocarditis?

Although vaccine-associated myocarditis has received widespread attention in the media, this adverse effect is quite rare; and, the severity of the complication tends to be mild to moderate with an early clinical diagnose with CMRI.[36] Also, vaccine-associated myocarditis responds well to conservative treatment (eg, rest, supportive treatment, pain management, anti-inflammatory drugs, haemodynamic support as needed); but follow-up should be ongoing to determine long term outcomes and cardiac function.

The long-term implications in these patients are not yet known, but still the benefit of vaccination against COVID-19 far outweighs the risk.[36]

If a person develops myocarditis after the first or second dose of an mRNA vaccine, the CDC recommends that their subsequent dose be delayed and that the next dose could be reconsidered on resolution of symptoms, signs and findings, under certain circumstances.[34] There is evolving evidence that even a double-dose mRNA vaccine does not offer adequate long-term protection in the general population against new SARS-COV-2 variants, and further studies are needed to determine efficacy of a third-dose 'booster' in different age groups.[35] Most recent data from Israel indicates that among 758 118 people who received a booster third dose of Comirnaty at least 5 months after a second dose, there was 90% lower mortality due to COVID-19 compared with participants who did not receive a booster (adjusted HR for death due to COVID-19 in the booster group vs the non-booster group was 0.10 with 95% CI 0.07 to 0.14; p<0.001).[37] Nonetheless, the incidence of myocarditis following the third (or even 4th) booster mRNA vaccination dose remains to be determined.

How to identify patients at risk?

Although rare, clinicians should be aware of the myocarditis risk, which should be considered in individuals, presenting with chest pain within a week after vaccination, especially in the younger male population. The reasons for male predominance especially at younger age in myocarditis cases remain unknown. It is possible that genetic predisposition and/or sex hormone differences in immune response might contribute to the onset of myocarditis; and also, that women are underdiagnosed for their cardiac symptoms. The risk of COVID-19-associated myocarditis and COVID-19 vaccine related myocarditis among adolescents and children (age <16 years) has to be studied in multiple countries. A recent Israeli national study by Mevorach D et al. (DOI: 10.1056/NEJMc2116999) showed that among 404,407 adolescents (12 to 15 years of age, 195,579 of whom are male) who received the first dose of the Comirnaty\BNT162b2 vaccine and 326,463 adolescents (157,153 male) who received the second dose, the risk estimates of myocarditis among adolescents male recipients in the 21 days after the first and second doses were 0.56 cases per 100,000 after the first dose and 8.09 cases per 100,000 after the second dose; the risk estimates among female recipients were 0 cases per 100,000 after the first dose and 0.69 cases per 100,000 after the second dose. Thus, based on this preliminary resport, it seems that adolescents are not at augmented risk for myocarditis post vaccination compared to adults. For initial evaluation, ECG and cardiac troponin level should be obtained, and inflammatory markers such as C reactive protein and erythrocyte sedimentation rate can be helpful.[31] Clinical examination combined with ECG and echocardiography testing should be undertaken in suspected cases regardless of age, sex or ethnicity.

Comparative risks of different vaccines

Finally, the comparative risk of the diverse vaccines has been a matter of uncertainly until recently. A large study (N=38 615 491) undertook in England assessed an extra 2, 1 and 6 myocarditis events per 1 million people vaccinated with adenovirus-based (ChAdOx1), Comirnaty and Spikevax mRNA vaccines, respectively, in the 28 days following a first dose and an extra 10 myocarditis events per 1 million vaccinated in the 28 days after a second dose of Spikevax.[38] This compares with an extra 40 myocarditis events per 1 million patients in the 28 days following a SARS-CoV-2 positive test. Subgroup analyses by age showed the increased risk of myocarditis associated with the two mRNA vaccines was present only in those younger than 40.[38]

CONCLUSIONS

Although nucleoside modifications of mRNA used in these vaccines reduce their innate immunogenicity; it might be that in certain individuals with genetic predisposition, the immune response to mRNA may linger and drive the activation of an abnormal innate/acquired immune response against the myocardium.[39] Even though, despite the rare cases of myocarditis, the benefit–risk assessment shows a strong positive balance for all age and sex groups; therefore, COVID-19 vaccination is currently strongly recommended.

As suggested by Bozkurt *et al*,[31] a collaborative registry of myocarditis related to COVID-19 vaccination as well as COVID-19 disease with data collected on patient demographics, clinical presentation, biomarkers including cardiac troponin, diagnostic findings of ECG, echocardiography and CMRI, biomarkers, together with a paired

bioregistry with blood and cardiac tissue samples, would be quite valuable to answer many of the open questions we still have as cardiologists and medical community at large.

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ORCID iDs
Ran Kornowski http://orcid.org/0000-0002-7708-8253
Guy Witberg http://orcid.org/0000-0003-2110-0484

REFERENCES

1 Hoffmann M, Kleine-Weber H, Schroeder S, *et al*. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;181:271–80.
2 Guo J, Wei X, Li Q, *et al*. Single-cell RNA analysis on ACE2 expression provides insights into SARS-CoV-2 potential entry into the bloodstream and heart injury. *J Cell Physiol* 2020;235:9884–94.
3 Yajima T, Knowlton KU. Viral myocarditis. *Circulation* 2009;119:2615–24.
4 Siripanthong B, Nazarian S, Muser D, *et al*. Recognizing COVID-19-related myocarditis: the possible pathophysiology and proposed guideline for diagnosis and management. *Heart Rhythm* 2020;17:1463–71.
5 Lee DW, Gardner R, Porter DL, *et al*. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood* 2014;124:188–95.
6 Guo T, Fan Y, Chen M, *et al*. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020;5:811–8.
7 Ho JS, Sia C-H, Chan MY, *et al*. Coronavirus-Induced myocarditis: a meta-summary of cases. *Heart Lung* 2020;49:681–5.
8 Aretz HT, Billingham ME, Edwards WD, *et al*. Myocarditis. A histopathologic definition and classification. *Am J Cardiovasc Pathol* 1987;1:3–14.
9 Baughman KL. Diagnosis of myocarditis: death of Dallas criteria. *Circulation* 2006;113:593–5.
10 Luetkens JA, Faron A, Isaak A, *et al*. Comparison of original and 2018 lake Louise criteria for diagnosis of acute myocarditis: results of a validation cohort. *Radiol Cardiothorac Imaging* 2019;1:e190010.
11 Italia L, Tomasoni D, Bisegna S, *et al*. COVID-19 and heart failure: from epidemiology during the pandemic to myocardial injury, myocarditis, and heart failure sequelae. *Front Cardiovasc Med* 2021;8:713560.
12 Kariyanna PT, Sutarjono B, Grewal E, *et al*. A systematic review of COVID-19 and myocarditis. *Am J Med Case Rep* 2020;8:299–305.
13 Atri L, Morgan M, Harrell S, *et al*. Role of cardiac magnetic resonance imaging in the diagnosis and management of COVID-19 related myocarditis: clinical and imaging considerations. *World J Radiol* 2021;13:283–93.
14 Puntmann VO, Carerj ML, Wieters I, *et al*. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020;5:1265–73.
15 Huang L, Zhao P, Tang D, *et al*. Cardiac involvement in patients recovered from COVID-2019 identified using magnetic resonance imaging. *JACC Cardiovasc Imaging* 2020;13:2330–9.
16 Tavazzi G, Pellegrini C, Maurelli M, *et al*. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. *Eur J Heart Fail* 2020;22:911–5.
17 Liu PP, Blet A, Smyth D, *et al*. The science underlying COVID-19: implications for the cardiovascular system. *Circulation* 2020;142:68–78.
18 Dolhnikoff M, Ferreira Ferranti J, de Almeida Monteiro RA, *et al*. SARS-CoV-2 in cardiac tissue of a child with COVID-19-related multisystem inflammatory syndrome. *Lancet Child Adolesc Health* 2020;4:790–4.
19 Basso C, Leone O, Rizzo S, *et al*. Pathological features of COVID-19-associated myocardial injury: a multicentre cardiovascular pathology study. *Eur Heart J* 2020;41:3827–35.
20 Santoso A, Pranata R, Wibowo A, *et al*. Cardiac injury is associated with mortality and critically ill pneumonia in COVID-19: a meta-analysis. *Am J Emerg Med* 2021;44:352–7.
21 Annie FH, Alkhaimy H, Nanjundappa A, *et al*. Association between myocarditis and mortality in COVID-19 patients in a large registry. *Mayo Clin Proc Innov Qual Outcomes* 2022;6:3037:114–9.
22 Agdamag ACC, Edmiston JB, Charpentier V, *et al*. Update on COVID-19 myocarditis. *Medicina* 2020;56. doi:10.3390/medicina56120678. [Epub ahead of print: 09 Dec 2020].
23 Li X, Wang H, Zhao R, *et al*. Elevated extracellular volume fraction and reduced global longitudinal strains in participants recovered from COVID-19 without clinical cardiac findings. *Radiology* 2021;299:E230–40.
24 Dagan N, Barda N, Kepten E, *et al*. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med Overseas Ed* 2021;384:1412–23.
25 Polack FP, Thomas SJ, Kitchin N, *et al*. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *New England Journal of Medicine* 2020;383:2603–15.
26 Baden LR, El Sahly HM, Essink B, *et al*. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021;384:403–16.
27 Gargano JW, Wallace M, Hadler SC, *et al*. Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices - United States, June 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:977–82.
28 Montgomery J, Ryan M, Engler R, *et al*. Myocarditis following immunization with mRNA COVID-19 vaccines in members of the US military. *JAMA Cardiol* 2021;6:1202–6.
29 Witberg G, Barda N, Hoss S, *et al*. Myocarditis after Covid-19 vaccination in a large health care organization. *N Engl J Med* 2021;385:2132–9.
30 Mevorach D, Anis E, Cedar N, *et al*. Myocarditis after BNT162b2 mRNA vaccine against Covid-19 in Israel. *N Engl J Med* 2021;385:2140–9.
31 Bozkurt B, Kamat I, Hotez PJ. Myocarditis with COVID-19 mRNA vaccines. *Circulation* 2021;144:471–84.
32 Shiyovich A, Witberg G, Aviv Y, *et al*. Myocarditis following COVID-19 vaccination: magnetic resonance imaging study. *Eur Heart J Cardiovasc Imaging* 2021. doi:10.1093/ehjci/jeab230. [Epub ahead of print: 05 Nov 2021].
33 Truong DT, Dionne A, Muniz JC, *et al*. Clinically suspected myocarditis temporally related to COVID-19 vaccination in adolescents and young adults: suspected myocarditis after COVID-19 vaccination. *Circulation* 2022;145:345-356.
34 Wallace M, Oliver S. *COVID-19 mRNA vaccines in adolescents and young adults: benefit-risk discussion*. CDC, 2021.
35 EMA. Pharmacovigilance Risk Assessment Committee (PRAC), Draft agenda for the meeting on 29 November-02 December, 2021. Available: https://www.ema.europa.eu/en/documents/agenda/agenda-prac-draft-agenda-meeting-29-november-02-december-2021_en.pdf
36 Satterfield BA, Bhatt DL, Gersh BJ. Cardiac involvement in the long-term implications of COVID-19. *Nat Rev Cardiol* 2021;9.
37 Arbel R, Hammerman A, Sergienko R, *et al*. BNT162b2 vaccine booster and mortality due to Covid-19. *N Engl J Med* 2021;385:2413–20.
38 Patone M, Mei XW, Handunnetthi L, *et al*. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. *Nat Med* 2021. doi:10.1038/s41591-021-01630-0. [Epub ahead of print: 14 Dec 2021].
39 Karikó K, Buckstein M, Ni H, *et al*. Suppression of RNA recognition by Toll-like receptors: the impact of nucleoside modification and the evolutionary origin of RNA. *Immunity* 2005;23:165–75.