Myocarditis Following COVID-19 Vaccination: A Systematic Review (October 2020–October 2021)

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Introduction	Reports of SARS-CoV-2 coronavirus (COVID-19) vaccine-related myocarditis, particularly after mRNA vaccines, have raised concerns amongst the general public. This review examined the literature regarding myocarditis post COVID-19 vaccination, drawing from vaccine safety surveillance databases and case reports.
Methods	Combinations of search terms were used in PubMed and COVID-19-specific repositories – LitCovid and the Cochrane COVID-19 Study Register – between 1 October 2020 and 31 October 2021. Manual searches of GoogleScholar and screening of article bibliographies were also performed.
Results	Information was obtained from five vaccine safety surveillance databases. Fifty-two (52) case reports totalling 200 cases of possible COVID-19 vaccine-related myocarditis were summarised. Vaccine surveillance databases differed in reporting formats and vaccination rates; however, gross estimates suggested low overall incidence rates of 2–5 per million mRNA vaccines. The incidence appeared to be higher in younger male populations, with onset of symptoms within a few days, usually after the second dose. Some with prior COVID-19 infections had onset after the first dose. Cases with prior unrelated myocarditis were also noted. Almost all presented with chest pain (98.0%). Troponin elevation was universally described and cardiac magnetic resonance imaging was commonly reported based on the updated Lake Louise criteria. Clinical course was mild in the majority, with response to anti-inflammatory treatment.
Conclusion	COVID-19 vaccine-related myocarditis is an important but rare adverse event. More research is needed into its pathogenesis and reasons for its predominance in young males, while gaps in data exist in those aged <16 years, as well as those with prior COVID-19 infections and prior myocarditis.
Keywords	COVID-19 vaccine • Myocarditis • mRNA vaccine

Introduction

As the pandemic caused by the SARS-CoV-2 coronavirus (COVID-19) continues, global efforts driving vaccinations are pivotal to restoring health and attempting economic and social recovery. In December 2020, the USA Food and Drug Administration (FDA) granted emergency authorisation for the Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273) COVID-19 vaccines. In recent months, reports of myocarditis following COVID-19 vaccination, particularly

after the messenger RNA (mRNA) vaccines, have received media publicity and raised concerns amongst the general public.

There is a pressing need for a better understanding of the available data, especially as several countries debate vaccination of adolescents in light of the concerns from the Omicron variant. This report reviews the current literature regarding myocarditis post COVID-19 vaccination, summarising both publicly available information from vaccine safety surveillance databases and published case reports, with particular attention to reporting rates, patient and disease characteristics, as well as investigation and treatment outcomes.

Methods

This review performed systematic searches of online databases, including PubMed and two COVID-19-specific databases (LitCovid [1] and the Cochrane COVID-19 Study Register) between 1 October 2020 and 31 October 2021. LitCovid was selected as a curated literature repository for articles on COVID-19 from PubMed [2]. The Cochrane COVID-19 Study Register was selected for comprehensiveness and accuracy, with multiple data sources cited, including PubMed and Embase.com [3]. The medical subjects heading (MeSH) terms "myocarditis", "pericarditis" in combination with "COVID 19 vaccines" were used. The MeSH term "COVID 19 vaccines" includes both mRNA and non-mRNA vaccines. Manual searches of Google Scholar were also performed. All bibliographies of papers were screened for relevant references.

All articles – including case series, case reports, and letters to the editor in peer-reviewed journals – describing myocarditis associated with COVID-19 vaccinations were included. Letters to the editor were included due to the early burgeoning nature of literature at a time when understanding of the condition was still limited. Reports in paediatric cases were included.

Papers that were excluded were those describing myocarditis or cardiac complications after COVID-19 infection rather than vaccination, as well as papers and guidelines referring to general safety of the vaccines, without particular reference to myocarditis. Pooled analyses were also omitted to avoid repetition of source data.

Publicly available statements and publications from vaccine safety surveillance databases were screened for relevant details up to 30 December 2021, with focus on reporting rates of myocarditis adverse events following the vaccine and disease characteristics.

Two (2) authors independently screened the abstracts found for inclusion. A third author was available for consult in case of conflict of opinion. Case reports and series were summarised to include the following data, where available: patient demographics, vaccine type and dose, time to symptom onset, common symptomatology, investigation findings, and treatment and clinical outcomes.

Supplementary material was accessed, where available, to identify any missing fields or clarify any unclear findings, otherwise these fields were left as unreported without further assumptions made about the data.

Results

Vaccine Safety Surveillance Databases

The most commonly referenced vaccine safety surveillance databases were selected, these were: the World Health Organization (WHO) global database VigiBase [4], the USA Vaccine Adverse Event Reporting System (VAERS) [5], the UK Medicines and Healthcare Regulatory Agency (MHRA), and information from the Israeli Ministry of Health. These countries are amongst those that had relatively early and large-scale vaccination drives. Data from the Health Sciences Authority (HSA) of Singapore from the Southeast Asian region were also included.

A disproportionality analysis of the international pharmacovigilance database VigiBase was performed to evaluate drug adverse event reports from inception (1967) to 7 May 2021 [6]. This analysis identified 1,251 reports of myocarditis involving a suspected culprit vaccine of any type; 214 (17.1%) of these were associated with COVID-19 vaccines, while only the mRNA vaccines of mRNA-1273 (n=51 IC_{025}=1.1) and BNT162b2 (n=105 IC_{025}=0.05) were significantly associated with myocarditis. Disproportional analysis also showed over-reporting in males for both vaccines and in the younger 18–44-years age group for the mRNA-1273 vaccine. The median time to onset between the prior vaccine dose was 3 days (n=202 interquartile range 1–6 days).

This analysis was limited by inherent difficulties posed by passive reporting. In particular, it was not possible for incidence rates to be estimated, as the underlying base population serviced by this global database is not well understood; under-reporting was also likely. Nevertheless, this is the only disproportionality analysis available with comparators of other vaccines within a large established database. The important insight of mRNA vaccines rather than other COVID vaccine types being associated with myocarditis seems to correspond with overall data from other databases and case reports. The commonalities of younger males with short time to onset also seem to apply.

A search of the VAERS database in the Centre for Disease Control (CDC) website completed as early as 30 March 2021 resulted in 37 cases of reported myocarditis following mRNA COVID-19 vaccination [7]. The base population here was not described and variable amounts of clinical detail were reported in the supplementary material, again highlighting the difficulties inherent in searches of passive reporting databases. However, the summary information again highlighted a young male preponderance. One death was reported with "apparent acute myocarditis" requiring extracorporeal membrane oxygenation (ECMO) support; however, this is difficult to interpret in isolation and without further clinical detail.

Table 1 Centre for Disease Control (CDC) case definition of probable and confirmed myocarditis, pericarditis, and myopericarditis (modified to exclude criteria in those aged <12 years) [8].

Condition	Definition	
Acute Myocarditis	Probable Case	Confirmed Case
	Presence of ≥1 new or worsening of the following clinical symptoms:	Presence of ≥1 new or worsening of the following clinical symptoms:
	- chest pain, pressure, or discomfort	- chest pain, pressure, or discomfort
	- dyspnoea, shortness of breath, or pain with breathing	- dyspnoea, shortness of breath, or pain with breathing
	- palpitations	- palpitations
	- syncope	- syncope
	AND ≥1 new finding of	AND ≥1 new finding of
	- troponin level above upper limit of normal (any type of troponin)	- histopathologic confirmation of myocarditis
	- abnormal ECG or rhythm monitoring findings consistent with myocarditis*	- cMRI findings consistent with myocarditis in the presence of troponin level above upper limit of normal (any type of troponin)
	- abnormal cardiac function or wall motion abnormalities on echocardiogram	AND
	- cMRI findings consistent with myocarditis using either original or revised Lake Louise criteria	- no other identifiable cause of the symptoms and findings
	AND	
	- no other identifiable cause of the symptoms and findings	
Acute Pericarditis	Presence of ≥2 new or worsening of the following clinical features:	
	- acute chest pain	
	- pericardial rub on exam	
	- new ST-elevation or PR-depression on ECG	
	- new or worsening pericardial effusion on echocardiogram or MRI	
Myopericarditis	This term may be used for patients who meet criteria for both myocarditis and pericarditis.	

Abbreviations: ECG, electrocardiogram; cMRI, cardiac magnetic resonance imaging.
*To meet ECG or rhythm monitoring criteria, a probable case must include at least one of 1) ST-segment or T-wave abnormalities; 2) paroxysmal or sustained atrial, supraventricular or ventricular arrhythmias; or 3) atrioventricular nodal conduction delays or intraventricular conduction defects.

A clearer overview was obtained from the CDC's Advisory Committee on Immunisation Practices (ACIP) report from June 2021 [8]. From VAERS, this described 1,226 reports of myocarditis after mRNA vaccination between 29 December 2020 and 11 June 2021. The median age was 26 years (n=1,194 range 12–94), and 1,212 (76%) were male. The median time to symptom onset from prior vaccine dose was 3 days, although the range was between 0–179 days. The extreme of the time range brings into question how the diagnoses of vaccine-related myocarditis were made in such cases, as causality is difficult to establish, except for close temporal associations with the vaccines, in most described cases. Nevertheless, the median suggests that such cases are in the minority.

Importantly, the CDC also convened a rapid review of 484 cases of such myocarditis in young adults aged <30 years. These benefited from patient record reviews or provider interviews by independent CDC clinicians, with 323 patients meeting the CDC criteria for myocarditis, pericarditis and/or myopericarditis (Table 1); 297 (92%) had symptom onset within 7 days from the prior vaccination dose and 310 (96%) were hospitalised. Treatment data were incomplete, but the authors suggested that most had non-severe clinical courses with resolution with non-steroidal anti-inflammatory drugs (NSAID), with 304 (95%) of hospitalised patients with known clinical outcomes discharged at the time of writing. No deaths were reported in this subgroup.

The CDC published crude reporting rates of myocarditis cases in VAERS (defining these as cases with onset within 7 days after a second dose of an mRNA vaccine) using national COVID-19 vaccine administration data up to 8 July 2021 [9]. In males aged 18–29 years, myocarditis reporting rates were calculated at 24.3 cases per million *second* doses of mRNA COVID-19 vaccines. In females aged 18–29 years, the rate was 3–4 cases per million second doses. The reports in this younger age group had been individually reviewed and confirmed. The unconfirmed reporting rates in males aged 30–49 was 5–6 per million second doses and in females 1–2 per million second doses; this was 1 per million second doses in the older age groups.

As of 15 December 2021, the MHRA had recorded 543 cases of myocarditis and 378 of pericarditis following the BNT162b2 vaccine, as well as 122 of myocarditis and 69 of pericarditis following the mRNA-1273 vaccine [10]. It also recorded 178 reports of myocarditis and 201 pericarditis after the AstraZeneca (AZD1222) vaccine, a non-replicating viral vector vaccine. Although there were six mortalities recorded, the MHRA reported underlying illnesses in these patients that could have provided alternative explanations. The estimated background incidence of myocarditis in the UK was 60 per million patients per year. The MHRA estimated the overall reporting rate as being 12 per million doses of BNT162b2, 42 per million doses of mRNA-1273, and 4 per million doses of AZD1222. It cautioned that many factors can influence passive reporting and that the different reporting rates between the different vaccines should not be compared (e.g., there is more limited experience with the mRNA-1273 vaccine in the UK). In their earlier review of the evidence, the independent advisory body advised that while reports after AZD1222 had been received, there was insufficient evidence to recommend warnings of vaccine-related myocarditis with it [11].

A press release from the Israeli Ministry of Health [12] reported 148 cases of myocarditis within 30 days from vaccination doses, including 27 cases of 5,401,150 vaccinated individuals after the first dose, and 121 cases of 5,049,424 vaccinated individuals after the second dose. Their review suggested that cases were mostly in younger men aged 16–19 years and 95% were considered to be clinically mild. Further details do not appear to be available in the public domain, although the rates appear to be similarly low, and the patient and disease characteristics appear similar to other database conclusions.

Lastly from Singapore's HSA, as of 31 August 2021, a total of 8.5 million doses of mRNA vaccines had been administered, with 65 reports of suspected vaccine-related myocarditis and/or pericarditis [13]; 36 of these were in young males aged <30 years, putting the incidence rate above the expected background rates for this age group. The local overall background incidence of myocarditis leading to hospitalisation was estimated at 5–7 cases in 100,000 persons per year. HSA estimated the overall local incidence rate at 1.06 cases per 100,000 vaccine doses administered and in particular, 4.84 per 100,000 of *second* doses administered in males aged <30 years. The majority of the cases in the younger age group were reported to have recovered, without further clinical details available.

Summary of Case Reports

Fifty-one (51) papers were identified from the LitCovid database and 11 were excluded as being irrelevant to the inclusion topic criteria. Twenty-nine (29) papers were identified from the Cochrane COVID-19 Study Register, with nine excluded. Fifty-six (56) papers were identified from PubMed, with seven excluded. After removing repeat findings, 52 papers detailing a total of 200 cases of myocarditis or peri-myocarditis following COVID-19 vaccination were summarised (Supplemental Table 1). An additional three papers describing cases of isolated pericarditis were also noted [14–16].

The majority of papers originated from the USA, with other reports from Israel, Spain, Italy, Germany, France, Poland, Turkey, Korea, Qatar, and Canada. One hundred and eighty-three (183; 91.5%) of patients were male. The median age reported was <30 years in the majority of papers, with an age range of 12–70 years. Of note, several papers had a paediatric or adolescent focus [17–20], while two papers may have had a skewed population representation due to cases being obtained from military populations [21,22].

The mean time to presentation was 3 days (range, 1–25) when an outlier case of late presentation (90 days post vaccination [23]) was excluded. Although this case was included in the summaries, it was noted that the establishment of causality was not straightforward and may have represented an idiopathic case of myocarditis with such a late presentation. Of the 200 cases, three were after receipt of the Janssen (Ad26.COV2.S) non-replicating viral vector vaccine [24–26] and one after the AZD1222 vaccine [27]. All other cases were after mRNA vaccines, with the majority occurring after the second vaccine doses (87.0%). In 21 cases (10.5%), the symptoms occurred after the first vaccine dose; of these, nine had documented prior COVID-19 infections. One case was after a third booster BNT162b2 dose, reflecting the beginning of booster drives in certain countries. The predominant symptoms were chest pain (98.0% n=200), fever (37.3% n=177), dyspnoea (20.9% n=177), and also variable reports of viral prodromes such as chills, malaise, myalgia, and headache. More cardiac-specific symptoms, although uncommon, included palpitations and syncope.

Where reported, troponin levels were elevated in all cases, in keeping with myocardial injury. C-reactive protein elevation was common when performed (88.7% n=133). Some institutions had the capability of detailed SARS-CoV-2 PCR and serology testing, usually showing negative PCR, absent nucleocapsid antibodies, but presence of spike protein antibodies, which was in keeping with a vaccinated status without active disease. In one particular series [24], the authors hypothesised that spike antibodies were negative in two patients because they had only received one vaccine dose. Further investigations into the aetiology of myocarditis were not universally performed, but if they were they included variations of autoimmune (antinuclear antibody, rheumatoid factor) and serological testing (hepatitis B, C, Epstein-Barr, cytomegalovirus, *Coxiella burnetii*, parvovirus B-19, mycoplasma, HIV, adenovirus, coxsackie A, coxsackie B1, and/or human herpes 1 and 2), as well as respiratory viral panels such as for influenza.

Cardiac-specific investigations included electrocardiography (ECG), echocardiography, coronary imaging either via computed tomography or catheter-based coronary angiography, cardiac magnetic resonance imaging (MRI), and cardiac biopsy. ST elevation was commonly described (63.8%

n=185), in keeping with a degree of peri-myocarditis. Other ECG findings included T-wave changes (18.6% n=172) and non-sustained ventricular tachycardia (4.1% n=195). Echocardiography was within normal limits in the majority of cases (64.5% n=186), while other findings included segmental wall motion abnormalities (21.1% n=180), ejection fraction <50% (17.7% n=186), pericardial effusions (8.9% n=180), and global hypokinesia (8.3% n=180). Where coronary imaging was performed (n=67), one case was abnormal, albeit with only non-obstructive coronary artery disease not requiring intervention; all other cases described normal coronaries. Cardiac MRI was performed in the majority of cases (n=149), with detailed imaging-focussed descriptions of protocols and findings in some reports [28,29]. Findings generally focussed on fulfilment of the revised Lake Louise criteria [30], describing oedema from T2-weighted images (73.4% n=143) and subepicardial and/or mid-myocardial late gadolinium enhancement in a non-coronary distribution (96.0% n=149).

Lastly, histological descriptions were uncommon: in the seven cases where they were reported, normal myocardial tissue was found in two [24,31]. Two (2) cases were autopsies performed after mortalities from cardiogenic shock and sudden cardiac death, respectively [32,33]. Biventricular involvement with a mixed inflammatory infiltrate, predominantly T-cells and macrophages, was noted in the former, while the latter described a more unusual pattern of isolated atrial myocarditis with neutrophilic predominance. The other abnormal histological findings obtained from biopsies were also heterogenous, describing acute lymphocytic myocarditis [34] in one case and healing myocarditis [35] in another, where the biopsy sample had been taken after clinical recovery of cardiac function.

Treatment was predominantly with NSAIDs (67.2% n=128), followed by colchicine (25.8% n=128). Some cases received corticosteroids (16.1% n=143) and beta blockade therapy (16.1% n=143), the latter more so where initial tachycardia, arrhythmias, or impaired ejection fraction were described. Some received only supportive therapy (12.5% n=128). Other heart failure-specific therapies were not routinely described. Of note, intravenous immunoglobulin (IVIG) was used in some, predominantly in paediatric populations or in two critically ill adult patients (13.3% n=143) [18–20,35,36]. The most commonly cited reason for using IVIG in the paediatric population was decrease in left ventricular function, though authors also acknowledged that use of IVIG was often based on clinical judgment alone. The critically ill adult patients described by Abbate et al. also received tocilizumab and ECMO support.

While most cases occurred in previously healthy patients, a few warrant special mention. Some patients with previous episodes of recovered myocarditis prior to COVID-19 vaccination were described; these patients had idiopathic myocarditis [22,37,38] and one had smallpox vaccine-related myocarditis [39]. One case described a patient with known arrhythmogenic left ventricular cardiomyopathy [40].

A few cases highlighted the difficulties in teasing out true vaccine-related myocarditis, as opposed to patients coincidentally presenting with myocardial infarction, congestive cardiac failure or severe sepsis. Deb et al. [7] described an older 67-year-old patient with previous ischaemic heart disease, presenting with fluid overload requiring positive pressure ventilation hours after receiving the COVID-19 vaccine; this patient was also treated with antibiotics. Although the team treated the patient for possible vaccine-related myocarditis, there was no coronary evaluation or cardiac MRI. Nassar et al. [25] described a 70-year-old patient with multiple sclerosis presenting with both cardiogenic and vasoplegic shock 2 days after receiving the Ad26.COV2.S vaccine, who was treated with vasopressors and antibiotics. While a temporal association was suggestive, diagnostic certainty of vaccine-related myocarditis was difficult. Gautam et al. [23] described the possibility of a late presentation of myocarditis 90 days after the vaccine dose; however, causality is difficult to establish when the intervening period is so prolonged.

Other reports of note applied different methodologies. Kim et al. [39] and Snapiri et al. [41] performed comparisons of incidence rates of peri-myocarditis in the same patient populations at comparable time periods in past years, noting higher incidence in the periods with COVID-19 vaccine administration, although not in sufficient numbers to identify statistical significance. Muthukumar et al. [42] performed extensive exploratory studies in their patient, with genetic testing for cardiomyopathy-associated variant genes, cytokine response, autoantibodies, and autoimmune cell subsets, although their findings in one case must be considered strictly hypothesis-generating.

Lastly, most cases had a benign clinical course with full recovery (90.0% n=180). Where cases described incomplete recovery, there were either lingering symptoms of chest discomfort or residual subclinical imaging findings such as impaired ejection fraction or signs of inflammation on repeat MRI. Fulminant myocarditis and mortalities were only described in a few cases [25,32,33,35].

Discussion

The reports of myocarditis post COVID-19 vaccines, particularly with mRNA vaccines, are a public safety concern. Myocarditis itself is usually idiopathic. If an identified cause is found, it is usually viral in aetiology [43]. Vaccine-related myocarditis is rare, with previous cases associated with the smallpox [44,45] and influenza [46,47] vaccines. The original clinical trials for these mRNA vaccines did not detect myocarditis [48,49], although there was one case of paroxysmal ventricular arrhythmia in the BNT162b2 vaccine trial. However, given the rarity of occurrence, it is likely that the relatively low number of trial participants (n=21,720 with BNT162b2 vaccine; n=15,210 with mRNA-1273 vaccine) would have limited the ability of the trials to detect this.

While vaccine safety surveillance databases are limited by inherent biases in passive reporting, they remain an important source of information in safety signal generation. The

overall reported trends are consistent in reflecting an increased risk of myocarditis following mRNA COVID-19 vaccines, particularly among younger males. However, the overall incidence rates are low and considered to be rare. Continued surveillance remains important as vaccination drives continue, especially with the adolescent groups where parental anxieties contribute to vaccine hesitancy and anti-vaccination sentiments [50].

Although there were cases of myocarditis following non-mRNA COVID-19 vaccines, there was no data suggesting an increased incidence with these vaccines above background incidence rates. Amongst the mRNA vaccines, the onset of myocarditis appears to commonly be after the second dose. There are cases reported after the first, with note of prior COVID-19 infection in some [21,28,31,51]. Cases of prior unrelated myocarditis were also reported [22,37,39] and one case of arrhythmogenic left ventricular cardiomyopathy [40]. The numbers are too small to draw conclusions, but it is reasonable to hypothesise that a prior COVID-19 infection alters the immunological response to vaccination, or that prior myocardial injury such as with myocarditis or cardiomyopathies could indicate or result in susceptibility. COVID-19 infection itself has also been associated with myocardial injury with an unknown mechanism, with theories related to the mechanism of entry via angiotensin-converting enzyme 2 (ACE2) proteins and high expression of ACE2 in the myocardium [52].

This raises questions regarding the pathogenesis of myocarditis following the mRNA vaccines. As pointed out by Shay et al. [53], the composition and mechanism of action of the mRNA vaccines greatly differ from the smallpox and influenza vaccines. A commonly cited theory is that of "molecular mimicry", where the viral antigen resembles myocardial proteins, triggering an immune cross-reactivity in genetically susceptible individuals [54]. An immune-mediated mechanism is perhaps also supported by systemic reactogenicity events being more regularly reported in younger (16–55 years) than older (>55 years) vaccine recipients and after the second dose in the original BNT162b2 trial [48]. This corresponds with the preponderance of young patients with myocarditis after the second vaccine dose, although it does not explain the male predominance. Research must be directed towards this area to help answer practical questions such as whether dose regimens should be altered in young males, those with prior COVID-19 infections, prior myocarditis, or underlying cardiomyopathies.

The clinical diagnosis of vaccine-related myocarditis is so far largely dependent on temporal association. A close temporal association between onset of symptoms and prior vaccine dose has been seen, with most cases occurring within a few days to a week. The CDC included cases within 7 days of prior vaccine dose [8], while the Israeli Ministry of Health included cases up to 30 days [12]. There is no current consensus defining either a time period or diagnostic criteria specifically for vaccine-related myocarditis, with most centres in the case reports relying on absence of other identified aetiology and temporal association to make this diagnosis. A

few cases were reported with longer time intervals; however, this makes it more difficult to establish causality.

The case reports provide clinical detail and serve as an indicator of generally accepted current clinical practice; the majority performed SARS-CoV-2 viral PCR to rule out active infection. This may be important in children where multisystem inflammatory syndrome (MIS-C) from COVID-19 infection can present with overlapping symptomatology and disease processes such as myocarditis [55]. Where available, serology for nucleocapsid and spike protein antibodies can be indicative of vaccine status, although one case report elaborated on a lack of spike protein antibodies after the first vaccine dose [24]. While serological status can be supportive of vaccine status, it is not diagnostic of the vaccine causing myocarditis. Infectious panels to exclude other aetiology were variably performed, with stronger indication to screen for viruses where prodromal or infective symptoms were reported. Although some screened for autoimmune markers, other authors pointed out that systemic autoimmune diseases were unlikely in the absence of other clinical signs.

The clinical presentation is important to note and forms part of the European Society of Cardiology [43] and CDC case definitions for myocarditis (Table 1). Chest pain was the common complaint, with or without typical pericarditic descriptions of pain worse on lying down and relieved on sitting up. While viral prodromal symptoms were also reported, these are commonly noted adverse effects which in isolation may not warrant urgent clinical attention. Public advisories should hence highlight seeking medical attention should chest pain, palpitations, or syncope occur post vaccination.

Cardiac-specific investigations should include cardiac enzymes, baseline ECG, and echocardiogram. These are important as part of diagnostic criteria and also in clinical management. Troponin elevation is a sensitive marker for myocardial injury; in the absence of a cardiac biopsy, troponin elevation and suggestive cardiac MRI findings are required for the CDC diagnosis of confirmed myocarditis (Table 1). Conversely, normal troponin levels would make the diagnosis of myocarditis unlikely, although isolated pericarditis is possible in the presence of suggestive symptoms and ECG findings. Echocardiogram findings of wall motion abnormalities, impaired left ventricular ejection fraction, and pericardial effusion are supportive of the diagnosis and affect treatment decisions, although echocardiogram can frequently be normal. In cases with preserved ejection fraction, strain imaging may be useful to detect left ventricular dysfunction [56]. Coronary evaluation should also be considered to rule out ischaemic heart disease as the cause of myocardial injury, where reasonable suspicion for an acute coronary syndrome exists, more commonly in the older age groups or those with pre-existing risk factors.

The roles of cardiac MRI and biopsy in myocarditis have been debated. Previous Dallas criteria relied on histological findings, but the ability of cardiac MRI to detect changes of myocarditis and lack of expertise to perform cardiac biopsies have perhaps resulted in reduced reliance on this invasive

procedure [57], as was reflected in the low numbers performed in the case reports. The majority of cases also had a benign clinical course, where an invasive procedure may not have been warranted. Conversely, in rare cases where patients are critically ill with multiorgan failure, the presence of ECMO or renal replacement machinery may make biopsies logistically difficult. The normal histology in two cases also highlighted that this is subject to sampling difficulties, given that myocardial involvement can be patchy. However, cardiac biopsy remains an important tool for those with severe cases of myocarditis where treatment decisions such as immunosuppressive therapies may be considered.

Cardiac MRI was commonly performed in the case reports, with reference to the updated Lake Louise criteria to diagnose myocarditis [30]. Although not all cases described both classical myocarditis findings, the intervening time from presentation to imaging was not always reported, with a possible explanation being resource limitation resulting in delays and resolution of changes before MRI imaging could be performed. MRI imaging was also mentioned as a potential differentiator in children and adolescents with MIS-C rather than myocarditis, as the cardiac MRI in the former is characterised by diffuse myocardial oedema without late gadolinium enhancement [58].

Finally, treatment options include supportive management, NSAIDs, colchicine, and immunomodulators. In both the vaccine safety surveillance databases and case reports, clinical courses were mild with low mortality rates. Most patients recovered fully with conservative treatment, although some cases reported persistent chest pain symptoms or had subclinical residual imaging abnormalities after discharge. For cases with residual impaired ejection fraction, conventional heart failure therapies should be considered.

Corticosteroids were the most commonly used immunomodulator, although its role in treating myocarditis is debated [59] and its use in pericarditis is mainly recommended for recurrent episodes [60]. IVIG use was mainly reported in paediatric cases; it has been analysed in predominantly paediatric populations (aged <18 years) with myocarditis to potentially improve ejection fraction and decrease death or heart transplantation rates [61]. As vaccination programs extend to adolescents, this may be a potential treatment in paediatric cases with haemodynamic instability or impaired ejection fraction. While IVIG and tocilizumab were used in two critically ill adult cases, the authors acknowledged the combination as being used across a variety of systemic autoimmune diseases with inappropriate macrophage activation, rather than as specific evidence-based treatment for myocarditis [35]. Mechanical cardiac support should be considered in cases of fulminant myocarditis with haemodynamic instability [35].

Where mentioned, patients were advised to avoid strenuous exertion for 6 months post recovery, due to incidences of sudden cardiac death in athletes with possible myocarditis as the underlying cause [62]. In Singapore, advice has been given to the general public to avoid exertion for 1 week after either dose of the vaccine, perhaps out of an abundance of caution.

In all cases, the authors tended to come to a similar conclusion that the risks of occurrence, as well as serious morbidity or mortality from COVID-19 mRNA vaccine-related myocarditis, are low. Incidence rate estimates are subject to inherent reporting biases in vaccine surveillance databases. Databases also vary in the format of reporting incidence rates, such as by first or second vaccine doses, or categorised per age and sex. Nevertheless, a gross estimated overall incidence rate of between 2–5 per million mRNA vaccine doses seems reasonable as the range presented from larger population estimates in Europe, Canada, and the USA [63]. The CDC estimate of the more susceptible young male age group between 18–29 years of 24.3 cases per million mRNA second doses administered is likely a best estimate, given that these cases were individually reviewed and confirmed [9]. The benefits of 94–95% efficacies in prevention of serious disease from COVID-19 infection and potential return to social norms appear to outweigh the risks, although continued surveillance and awareness of the condition are important.

This review focussed on larger vaccine safety surveillance databases and was unable to perform searches of other countries' reporting systems. The countries in these databases and the case reports had more widespread use of the mRNA vaccines instead of other vaccine types. In particular, vaccine-related adverse events in developing countries, where use of other vaccine types is more prevalent, are likely to be more difficult to monitor, given the overwhelmed health services and lack of resources. There is therefore an inherent likelihood of reporting bias within the articles found in this review. Pharmaceutical companies with more global resources may be able to perform more thorough phase IV post-marketing surveillance.

There are also limited available data in those aged 12–15 years, as BNT162b2 vaccinations have only begun to be available in this group in a few countries (USA, Canada, Singapore, and United Arab Emirates), starting at the end of May 2021. The trial in 12–15 year-olds did not detect any cases of myocarditis in the 1,131 recipients [64]. These numbers are small to detect rare adverse events, hence continued surveillance is important. Thought should be given to active surveillance studies to avoid under-reporting and biases in vaccine safety surveillance databases. It is also important to continue to survey adverse events in adults, as the need for more booster doses appears in the face of new variants such as Omicron, with one case report of myocarditis after the third vaccine dose [65].

Further research into pathogenesis and diagnostic criteria specifically for vaccine-related myocarditis should be prioritised. Further knowledge gaps are also noted in subgroups, such as whether patients with prior COVID-19 infections or prior history of myocarditis should have altered vaccine regimens. In addition, there is no current consensus whether patients diagnosed with COVID-19 vaccine-related myocarditis are suitable for second or booster doses.

Conclusion

As countries debate vaccination of younger adolescents and children, the public and health care professionals should be aware of the symptoms associated with COVID-19 vaccine-related myocarditis, but also that the overall risk appears low. However, further research into this condition is warranted, particularly regarding the pathogenesis and higher prevalence in younger males. There is also a current gap in understanding in a few population groups, including those aged <16 years, those with prior COVID-19 infections, and those with previous episodes of myocarditis. Current vaccination guidance does not differ for these groups and further information must be obtained over time.

Declarations of Interest

None.

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Appendices. Supplementary Data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.hlc.2022.02.002.

References

[1] Chen Q, Allot A, Lu Z. Keep up with the latest coronavirus research. Nature. 2020;579:193.

[2] Chen Q, Allot A, Lu Z. LitCovid: An open database of COVID-19 literature. Nucleic Acids Res. 2021;49(D1):D1534–40.

[3] Metzendorf MI, Featherstone RM. Evaluation of the comprehensiveness, accuracy and currency of the Cochrane COVID-19 Study Register for supporting rapid evidence synthesis production. Res Synth Methods. 2021;12(5):607–17.

[4] Lindquist M. VigiBase, the WHO Global ICSR Database System: Basic facts. Drug Inf J. 2008;42(5):409–19.

[5] Shimabukuro TT, Nguyen M, Martin D, DeStefano F. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). Vaccine. 2015;33(36):4398–405.

[6] Kerneis M, Bihan K, Salem J-E. COVID-19 vaccines and myocarditis. Arch Cardiovasc Dis. 2021:2019–21.

[7] Deb A, Abdelmalek J, Iwuji K, Nugent K. Acute Myocardial Injury Following COVID-19 Vaccination : A Case Report and Review of Current Evidence from Vaccine Adverse Events Reporting System Database 2021; 12:21501327211029230.

[8] Gargano Julia W, Wallace Megan, Hadler Stephen C, Langley Gayle, Su John R, Oster Matthew E, M, 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(27):977–82.

[9] Rosenblum HG, Hadler SC, Moulia D, Shimabukuro TT, Su JR, Tepper NK, et al. Use of COVID-19 Vaccines After Reports of Adverse Events Among Adult Recipients of Janssen (Johnson & Johnson) and mRNA COVID-19 Vaccines (Pfizer-BioNTech and Moderna): Update from the Advisory Committee on Immunization Practices - United States, July 2021. MMWR Morb Mortal Wkly Rep. 2021;70(32):1094–9.

[10] Coronavirus vaccine - weekly summary of Yellow Card reporting. Med Healthc Prod Regul Agency. https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting.

[11] COVID-19 vaccines: updates for July 2021. Med Healthc Prod Regul Agency. https://www.gov.uk/drug-safety-update/covid-19-vaccines-updates-for-july-2021. [accessed 29.12.21].

[12] Surveillance of Myocarditis (Inflammation of the Heart Muscle) Cases Between December 2020 and May 2021 (Including). https://www.gov.il/en/departments/news/01062021-03.

[13] Health Sciences Authority S. HSA's Safety Update #5 COVID-19 Vaccines (30 Dec 2020-31 Aug 2021). https://www.hsa.gov.sg/docs/default-source/hprg-vcb/safety-update-on-covid19-vaccines/hsa-safety-update-no-5-on-covid-19-vaccines-(31-august-2021).pdf.

[14] Ramírez-García A, Jiménez SL, Ximénez ID, Cacho AG, Aguado-Noya R, Cubero JS. Pericarditis tras la administración de la vacuna de ARNm BNT162b2 contra la COVID-19. Rev Española Cardiol. 2021;74(12):1121–3.

[15] Vidula MK, Ambrose M, Glassberg H, Chokshi N, Chen T, Ferrari VA, et al. Myocarditis and Other Cardiovascular Complications of the mRNA-Based COVID-19 Vaccines. Cureus. 2021;74(12):1120–2.

[16] Ashaari S, Sohaib HA, Bolger K. A case report: symptomatic pericarditis post-COVID-19 vaccination. Eur Hear J Case Rep. 2021;5(10):ytab375.

[17] Ambati S, Colon M, Mihic M, Sanchez J, Bakar A. Acute Myopericarditis after COVID-19 Vaccine in Teenagers. Case Rep Cardiol. 2021:8268755.

[18] Schauer J, Buddhe S, Colyer J, Sagiv E, Law Y, Mallenahalli Chikkabyrappa S, et al. Myopericarditis After the Pfizer Messenger Ribonucleic Acid Coronavirus Disease Vaccine in Adolescents. J Pediatr. 2021;238:317–20.

[19] Dionne A, Sperotto F, Chamberlain S, Baker AL, Powell AJ, Prakash A, et al. Association of Myocarditis With BNT162b2 Messenger RNA COVID-19 Vaccine in a Case Series of Children. JAMA Cardiol. 2021;6(12):1446–50.

[20] Das BB, Moskowitz WB, Taylor MB, Palmer A. Myocarditis and Pericarditis Following mRNA COVID-19 Vaccination: What Do We Know So Far? Child. 2021;8(7):607.

[21] Montgomery J, Ryan M, Engler R, Hoffman D, McClenathan B, Collins L, et al. Myocarditis Following Immunization With mRNA COVID-19 Vaccines in Members of the US Military. JAMA Cardiol. 2021;92134:1–5.

[22] Levin D, Shimon G, Fadlon-Derai M, Gershovitz L, Shovali A, Sebbag A, et al. Myocarditis following COVID-19 vaccination – A case series. Vaccine. 2021;39(42):6195–200.

[23] Gautam N, Saluja P, Fudim M, Jambhekar K, Pandey T, Al'Aref S. A Late Presentation of COVID-19 Vaccine-Induced Myocarditis. Cureus. 2021;13(9):e17890.

[24] Rosner CM, Genovese L, Tehrani BN, Atkins M, Bakhshi H, Chaudhri S, et al. Myocarditis Temporally Associated with COVID-19 Vaccination. Circulation. 2021;144(6):502–5.

[25] Nassar M, Nso N, Gonzalez C, Lakhdar S, Alshamam M, Elshafey M, et al. COVID-19 vaccine-induced myocarditis: Case report with literature review. Diabetes Metab Syndr. 2021;15(5):102205.

[26] Sulemankhil I, Abdelrahman M, Negi SI. Temporal association between the COVID-19 Ad26.COV2.S vaccine and acute myocarditis: A case report and literature review. Cardiovasc Revasc Med. 2021. S1553-8389(21)00578-00579.

[27] Chamling B, Vehof V, Drakos S, Weil M, Stalling P, Vahlhaus C, et al. Occurrence of acute infarct-like myocarditis following COVID-19 vaccination: just an accidental co-incidence or rather vaccination-associated autoimmune myocarditis? Clin Res Cardiol. 2021;110(11):1850–4.

[28] Shaw KE, Cavalcante JL, Han BK, Gössl M. Possible Association Between COVID-19 Vaccine and Myocarditis: Clinical and CMR Findings. JACC Cardiovasc Imaging. 2021;14(9):186–1861.

[29] Dickey JB, Albert E, Badr M, Laraja KM, Sena LM, Gerson DS, et al. A Series of Patients with Myocarditis Following SARS-CoV-2 Vaccination with mRNA-1279 and BNT162b2. JACC Cardiovasc Imaging. 2021;14(9):1862–3.

[30] Ferreira VM, Schulz-Menger J, Holmvang G, Kramer CM, Carbone I, Sechtem U, et al. Cardiovascular Magnetic Resonance in Nonischemic Myocardial Inflammation: Expert Recommendations. J Am Coll Cardiol. 2018;72:3158–76.

[31] Larson KF, Ammirati E, Adler ED, Cooper LT, Hong KN, Saponara G, et al. Myocarditis after BNT162b2 and mRNA-1273 Vaccination. Circulation. 2021;144(6):506–8.

[32] Verma AK, Lavine KJ, Lin C-Y. Myocarditis after Covid-19 mRNA Vaccination. N Engl J Med. 2021;385(14):1332–4.

[33] Choi S, Lee S, Seo J-W, Kim M-J, Jeon YH, Park JH, et al. Myocarditis-induced Sudden Death after BNT162b2 mRNA COVID-19 Vaccination in

Korea: Case Report Focusing on Histopathological Findings. J Korean Med Sci. 2021;36. e286–e286.

[34] Ehrlich P, Klingel K, Ohlmann-Knafo S, Hüttinger S, Sood N, Pickuth D, et al. Biopsy-proven lymphocytic myocarditis following first mRNA COVID-19 vaccination in a 40-year-old male: case report. Clin Res Cardiol. 2021;110(11):1855–9.

[35] Abbate A, Gavin J, Madanchi N, Kim C, Shah PR, Klein K, et al. Fulminant myocarditis and systemic hyperinflammation temporally associated with BNT162b2 mRNA COVID-19 vaccination in two patients. Int J Cardiol. 2021;340:119–21.

[36] Marshall M, Ferguson ID, Lewis P, Jaggi P, Gagliardo C, Collins JS, et al. Symptomatic Acute Myocarditis in Seven Adolescents Following Pfizer-BioNTech COVID-19 Vaccination. Pediatrics. 2021;148(3): e2021052478.

[37] Minocha PK, Better D, Singh RK, Hoque T. Recurrence of Acute Myocarditis Temporally Associated With Receipt of the mRNA COVID-19 Vaccine in an Adolescent Male. J Pediatr. 2021;238:321–3.

[38] Viskin D, Topilsky Y, Aviram G, Mann T, Sadon S, Hadad Y, et al. Myocarditis Associated with COVID-19 Vaccination: Echocardiography, Cardiac Tomography, and Magnetic Resonance Imaging Findings. Circ Cardiovasc Imaging. 2021;14(9):e013236.

[39] Kim HW, Jenista ER, Wendell DC, Azevedo CF, Campbell MJ, Darty SN, et al. Patients With Acute Myocarditis Following mRNA COVID-19 Vaccination. JAMA Cardiol. 2021;6(10):1196–201.

[40] Alania-Torres E, Morillas-Climent H, Garcia-Escriva A, Vinueza-Buitron P, Poquet-Catala I, Zorio E, et al. Case Report: Probable Myocarditis After Covid-19 mRNA Vaccine in a Patient With Arrhythmogenic Left Ventricular Cardiomyopathy. Front Cardiovasc Med. 2021;8:759119.

[41] Snapiri O, Rosenberg Danziger C, Shirman N, Weissbach A, Lowenthal A, Ayalon I, et al. Transient Cardiac Injury in Adolescents Receiving the BNT162b2 mRNA COVID-19 Vaccine. Pediatr Infect Dis J. 2021;40(10):e360–3.

[42] Muthukumar A, Narasimhan M, Li Q-Z, Mahimainathan L, Hitto I, Fuda F, et al. In Depth Evaluation of a Case of Presumed Myocarditis Following the Second Dose of COVID-19 mRNA Vaccine. Circulation. 2021;144(6):487–98.

[43] Caforio ALP, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2013;34(33):2636–48. 2648a-2648.

[44] Eckart RE, Love SS, Atwood JE, Arness MK, Cassimatis DC, Campbell CL, et al. Incidence and follow-up of inflammatory cardiac complications after smallpox vaccination. J Am Coll Cardiol. 2004;44(1):201–5.

[45] Cassimatis DC, Atwood JE, Engler RM, Linz PE, Grabenstein JD, Vernalis MN. Smallpox vaccination and myopericarditis: A clinical review. J Am Coll Cardiol. 2004;43(9):1503–10.

[46] Engler RJM, Nelson MR, Collins LC, Spooner C, Hemann BA, Gibbs BT, et al. A prospective study of the incidence of myocarditis/pericarditis and new onset cardiac symptoms following smallpox and influenza vaccination. PLoS One. 2015;10(3):e0118283.

[47] Nagano N, Yano T, Fujita Y, Koyama M, Hasegawa R, Nakata J, et al. Hemodynamic Collapse After Influenza Vaccination: A Vaccine-Induced Fulminant Myocarditis? Can J Cardiol. 2020;36(9):1554.e5–7.

[48] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020;383:2603–15.

[49] Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021;384:403–16.

[50] Burki T. The online anti-vaccine movement in the age of COVID-19. Lancet Digit Heal. 2020;2(10):e504–5.

[51] Abu Mouch S, Roguin A, Hellou E, Ishai A, Shoshan U, Mahamid L, et al. Myocarditis following COVID-19 mRNA vaccination. Vaccine. 2021;39(29):3790–3.

[52] Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. Nat Rev Cardiol. 2020;17(9):543–58.

[53] Shay DK, Shimabukuro TT, DeStefano F. Myocarditis Occurring After Immunization With mRNA-Based COVID-19 Vaccines. JAMA Cardiol. 2021;6(10):1115–7.

[54] Segal Y, Shoenfeld Y. Vaccine-induced autoimmunity: the role of molecular mimicry and immune crossreaction. Cell Mol Immunol. 2018;15(6):586–94.

[55] Rubens JH, Akindele NP, Tschudy MM, Sick-Samuels AC. Acute covid-19 and multisystem inflammatory syndrome in children. BMJ. 2021;372:n385.

[56] Patel YR, Louis DW, Atalay M, Agarwal S, Shah NR. Cardiovascular magnetic resonance findings in young adult patients with acute myocarditis following mRNA COVID-19 vaccination: a case series. J Cardiovasc Magn Reson. 2021;23. 101.

[57] Baughman KL. Diagnosis of myocarditis death of Dallas criteria. Circulation. 2006;113(4):593–5.

[58] Blondiaux E, Parisot P, Redheuil A, Tzaroukian L, Levy Y, Sileo C, et al. Cardiac MRI in children with multisystem inflammatory syndrome associated with COVID-19. Radiology. 2020;297(3):E283–8.

[59] Chen HS, Wang W, Wu SN, Liu JP. Corticosteroids for viral myocarditis. Cochrane Database Syst Rev. 2013;2013(10):CD004471.

[60] Imazio M, Brucato A, Cumetti D, Brambilla G, Demichelis B, Ferro S, et al. Corticosteroids for Recurrent Pericarditis: High Versus Low Doses: A Nonrandomized Observation. Circulation. 2008;118(6):667–71.

[61] Li Y, Yu Y, Chen S, Liao Y, Du J. Corticosteroids and Intravenous Immunoglobulin in Pediatric Myocarditis: A Meta-Analysis. Front Pediatr. 2019;7:342.

[62] Maron BJ, Doerer JJ, Haas TS, Tierney DM, Mueller FO. Sudden Deaths in Young Competitive Athletes. Circulation. 2009;119(8):1085–92.

[63] Pepe S, Gregory AT, Denniss AR. Myocarditis, Pericarditis and Cardiomyopathy After COVID-19 Vaccination. Hear Lung Circ. 2021;30(10): 1425–9.

[64] Frenck RW, Klein NP, Kitchin N, Gurtman A, Absalon J, Lockhart S, et al. Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. N Engl J Med. 2021;385(3):239–50.

[65] Schmitt P, Demoulin R, Poyet R, Capilla E, Rohel G, Pons F, et al. Acute Myocarditis after COVID-19 vaccination: A case report. Rev Med Interne. 2021;42(11):797–800.