Myocarditis following COVID-19 vaccination: incidence, mechanisms, and clinical considerations

John R. Power, Lucas K. Keyt and Eric D. Adler

Division of Cardiovascular Medicine, University of California San Diego, San Diego, California, United States

ABSTRACT

Introduction: Vaccines have demonstrated protection against the morbidity and mortality of COVID-19, but concerns regarding the rare side effect of acute myocarditis have stymied immunization efforts. This review aims to describe the incidence and theorized mechanisms of COVID vaccine-associated myocarditis and review relevant principles for management of vaccine-associated myocarditis.

Areas covered: Epidemiologic studies of myocarditis after COVID vaccination are reviewed, which show an incidence of approximately 20–30 per million patients. The vast majority of these cases are seen with mRNA vaccines especially in male patients under 30 years of age. Mechanisms are largely theoretical, but molecular mimicry and dysregulated innate immune reactions have been proposed. While studies suggest that this subtype of myocarditis is mild and self-limited, long-term evidence is lacking. Principles of myocarditis treatment and surveillance are outlined as they apply to COVID vaccine-associated myocarditis.

Expert Opinion: COVID vaccine-associated myocarditis is rare but well described in certain at-risk groups. Better understanding of its pathogenesis is key to mitigating this complication and advancing vaccination efforts. Risk-benefit analyses demonstrate that individual- and population-level benefits of vaccination exceed the risks of this rare and mild form of myocarditis.

1. Introduction

The concept of introducing substrate resembling infectious organisms to initiate the adaptive immune system was first developed in the 1700s after the observation that milk maids who had been infected with cowpox were protected against smallpox infection [1]. In the subsequent 250 years, vaccinations have been unequivocally demonstrated to provide improved quality of life, increased life expectancy, and in some cases, the eradication of certain diseases entirely [2,3]. Since the original inoculation with inactivated bacterial or viral material, more advanced forms of vaccination have been developed. Delivery of genetic material using tissue-tropic viral vectors and augmentation of purified protein or polysaccharide vaccines with adjuvant nanoparticles are examples of vaccine platforms that prepare the host immune system for unencountered pathogens [4]. The development of vaccines utilizing messenger RNA (mRNA) to initiate host cell synthesis of antigens is only the most recent example of such progress. In the midst of the ongoing COVID-19 pandemic, novel mRNA vaccines remain the most effective means for curbing the spread of SARS-CoV-2 infection. Efficacy of COVID-19 vaccinations has been demonstrated internationally in numerous large populations, reducing the spread of infection, severe symptoms, and death [5–10]. However, while COVID-19 vaccines offer reduced burden of disease, if not full immunity, they may be associated with adverse events of their own.

2. Incidence

2.1. Base incidence of myocarditis

The overall incidence of acute myocarditis (AM) from any cause is uniquely challenging to describe and somewhat disputed, as the clinical presentation often varies in severity and definitive diagnosis requires invasive investigation, such as endomyocardial biopsy or postmortem autopsy, with limited sensitivity [11]. Best estimates provided by the 2019 Global Burden of Cardiovascular Disease suggest an annual incidence of 6.1 cases in men and 4.4 cases in women per 100,000 subjects aged 35–39 years with mortality rates of 0.2 and 0.1 per 100,000 subjects, respectively [12]. Other studies indicate that incidence may be as high as 10 to 20 cases per 100,000 subjects [13,14]. These data may be an underestimation in part due to many cases of myocarditis remaining undiagnosed due to relatively mild or asymptomatic subclinical disease. Autopsy-derived estimates produce rates ranging from 0.1% to as high as 12%, often in association with sudden cardiac death [15–22]. AM remains an important cause of cardiac adverse events in the pediatric population and appears to be significantly more fatal in subjects aged 1–4, demonstrating a mortality rate 56-fold greater than the comparative geriatric population [16]. Ultimately, it can be determined that AM is a relatively rare cardiac disease with potentially severe outcomes that has preponderance toward young males.
Regardless of etiology, AM is generally self-limiting with most patients achieving full recovery with only supportive care. However, a small portion of AM can cause pronounced cardiac damage with significant long-term morbidity and increased risk for cardiac adverse events. In certain cases, cardiac inflammation may persist over extended periods long after the cessation of initial insult and can progress into clinical cardiomyopathy with systolic dysfunction [23]. Additionally, AM has been associated with ventricular arrhythmias, with heightened risk for fatal rhythms such as ventricular tachycardia [24–26]. Because of such risks, detection and management of AM is of utmost importance in at-risk populations.

### 2.2. Myocarditis in other vaccines

Myocarditis occurring in association with vaccination is generally uncommon but has been well-documented historically. The live-attenuated smallpox vaccine (vaccinia virus), most often administered to U.S. service members, is one such vaccine that has been linked to clinical myocarditis. In a prospective analysis of service members receiving the smallpox vaccine, 10.6% of subjects developed new cardiac symptoms with a concomitant rise in troponin as compared to 2.6% in patients receiving the trivalent influenza vaccine (p < 0.001), resulting in an overall 200-fold increase in incidence of clinical myocarditis to 16.1 cases per 100,000 vaccine recipients [27]. In a similar analysis of 37,901 civilian first responders voluntarily receiving the smallpox vaccine, 5 probable and 16 suspected cases of myocarditis occurred, suggesting approximately 5.5 cases per 10,000 vaccine recipients (1.3 cases per 10,000 recipients if suspected cases are excluded) [28]. Interestingly, this series found 3 cases of dilated cardiomyopathy that developed over several months after vaccination. Following these studies, a number of case reports have demonstrated biopsy-proven myocarditis after smallpox vaccination, including a case of eosinophilic-lymphocytic myocarditis [29]; however, it should be noted that no large population studies have confirmed cases of postsmallpox vaccine myocarditis with endomyocardial biopsy.

### 2.3. COVID-19 vaccine

Due to the unprecedented efforts of Operation Warp Speed, Emergency Use Authorization of several COVID-19 vaccines allowed for expanded immunity of the general population. Although several clinical trials demonstrated the novel mRNA vaccines to be generally safe and well-tolerated, they have been linked with a number of rare adverse events, such as AM [30,31]. An association between COVID-19 vaccination and AM was reported by the CDC through analysis of the Vaccine Adverse Event Reporting System (VAERS) [32], a network that encourages voluntary reporting of side effects observed with vaccine administration. Since the VAERS relies on passive reporting without extensive quality controls, it may underestimate true prevalence [33,34]. Nevertheless, the VAERS can produce immediate results, which allowed the CDC to be the first organization to estimate an incidence of post-COVID-19 vaccination myocarditis with 0.48 per 100,000 in the general population and 1.2 per 100,000 in recipients aged 18–29 [35]. This analysis found that the adolescent males are the most-affected subgroup, typically presenting with symptoms of chest pain, shortness of breath, and/or palpitations approximately one week after the second vaccine dose.

Since these early VAERS reports, several large population studies have further characterized the incidence of AM following COVID-19 vaccination (Table 1) [36–42]. One such study using an administrative data set from a large Israeli healthcare organization identified patients who met CDC case definition of myocarditis within 42 days of COVID-19 vaccination [37]. This report found 54 cases of myocarditis among 2,558,421 vaccine (100% BNT 162b2) recipients, resulting in an incidence of 2.13 cases per 100,000 person years and a median age of 27. The highest incidence of myocarditis was reported in male patients between the ages of 16 and 29 years (10.69 cases per 100,000 persons; 95% CI, 6.93 to 14.46). Interestingly, of those who received echocardiograms, 29% demonstrated acute left ventricular dysfunction; all cases demonstrated normalization of function at the time of follow-up; however, long-term follow-up data were not reported. One of the largest studies assessing postvaccination outcomes involved nearly the entire population of Israel (100% BNT 162b2) and demonstrated a postvaccination myocarditis incidence ratio of 5.34, with the vast majority of cases occurring after the second dose [38]. Interestingly, 87% of AM cases occurred in male subjects with the most affected age group being 16–19 years. Estimates from this study suggest that AM occurred in 1 per 6,637 fully vaccinated Israeli men (15.1 per 100,000). Finally, a retrospective analysis of hospital admissions among approximately 138,000 Israeli Defense Forces personnel, a population generally consisting of young individuals meeting military fitness criteria, who received both doses of BNT 162b2 vaccine, found that the estimated incidence of myocarditis the week
| Study Details | Vaccine (type) | Inclusion criteria | Setting | Enrollment period |
|---------------|----------------|--------------------|---------|------------------|
|               | 57.0% BNT 162b2 | All ages, at least 1 dose of BNT 162b2 or MRNA-1273 vaccine | 8 healthcare systems, USA | 12/14/2020 – 6/26/2021 |
|               | 43.0% MRNA-1273 |                     |         |                  |
|               | 100% BNT 162b2 | Age 16+, at least 1 dose of BNT 162b2 vaccine | Clalit Health Services, Israel | 12/20/2020 – 5/24/2021 |
|               | 100% BNT 162b2 | Age 16+, at least 1 dose of BNT 162b2 vaccine | Ministry of Health Database, Israel | 12/20/2020 – 5/31/2021 |
|               | 100% BNT 162b2 | Age 18+, at least 1 dose of BNT 162b2 or MRNA-1273 vaccine | Kaiser Permanente Southern California, USA | 12/14/2020 – 7/20/2021 |
|               | 50.0% BNT 162b2 | At least 1 dose of BNT 162b2 or MRNA-1273 vaccine | Military Health System, USA | 1/1/2021 – 4/30/2021 |
|               | 50.2% MRNA-1273 |                     |         |                  |
|               | BNT 162b2,   | At least 1 dose of BNT 162b2 or MRNA-1273 vaccine | Providence Health and Services, USA | – 5/25/2021 |
|               | MRNA-1273    |                     |         |                  |
|               | 52.6% BNT 162b2 | At least 1 dose of BNT 162b2 or MRNA-1273 vaccine | Mayo Clinic, Minnesota and Wisconsin, USA | 12/17/2020 – 5/13/2021 |
|               | 44.1% MRNA-1273 |                     |         |                  |
|               | 3.1% Ad26.COV2.S |                     |         |                  |
|               | BNT 162b2,   | Any age, at least 1 dose of BNT 162b2 or MRNA-1273 vaccine |                  |                  |
|               | MRNA-1273    |                     |         |                  |
|               | –            |                     |         |                  |
|               | –            |                     |         |                  |
following a second dose was 5.07/100,000 people vaccinated [43].

Similar findings have been demonstrated in American populations with analogous investigations involving U.S. military or large healthcare networks. One of the larger American studies included 6.2 million subjects and 11.8 million vaccines (57% BNT 162b2, 43% mRNA-1273) at 9 health care organizations primarily located in the United States participating in the Vaccine Safety Datalink registry [36]. This retrospective analysis found that vaccinated patients 1–21 days after either dose of COVID-19 vaccine had an incidence of myocarditis of 13.2 per 100,000 person-years. While this was not significantly different from patients 22–42 days after vaccine, it was notably higher than unvaccinated comparators with a RR of 1.39. Subgroup analysis of age 12–39 at 0–7 days after vaccination had an incidence of 32.1 per 100,000 person-years, with a relative risk for myocarditis/pericarditis of 9.83 corresponding to 6.3 cases of AM per million doses of COVID-19 vaccine. Among the 34 cases in this subgroup, 85% were male and patients tended to present within 5 days of vaccination. Separate analyses of postvaccine myocarditis in a pediatric population aged 12–17 demonstrated similar presenting symptoms as adults [44], with an incidence of 4.2 cases of myopericarditis per 32.4 million doses [45], although overall incidence in this subpopulation remains unclear due to the relative delay in vaccination of youth populations.

Of the large population studies reviewed, follow-up data after COVID-19 vaccine were generally limited to several months. Across all studies, the vast majority of individuals who developed AM after vaccination did not experience further adverse events within the follow-up period and appeared to have either improving symptoms or complete recovery. However, a number of individuals had adverse outcomes; specifically, one patient died from fulminant myocarditis [38], several patients had persistent severely reduced ejection fractions [38], and one patient died from unknown cause during the follow-up period [37]. While rare instances of life-threatening myocarditis after COVID vaccine have been reported, these events are exceedingly rare and atypical for this subtype of myocarditis [46].

While fewer studies have described myocarditis incidence after viral vector COVID-19 vaccines, evidence suggests that this vaccine type is not associated with myocarditis risk. A study of the VAERS by Li et al. showed that over December 2020 to August 2021, Ad26.COV2.S vaccine did not have significant association with the composite of myocarditis or pericarditis with a reporting odds ratio of 1.39 (95% CI = 0.99–1.97) [47]. A separate study by Diaz et al. of over 60,000 Ad26.COV2.S vaccine recipients across 40 US hospitals over February through May 2021 showed zero cases of myocarditis and two cases of pericarditis. While isolated cases of myocarditis have been described after viral vector COVID-19 vaccines, this association is not well established and causation is not clear [48].

While COVID-19 vaccination is associated with an increased risk for AM, this risk may be lower than the risk for AM caused by direct infection with SARS-CoV-2. Histologically proven associations between AM and COVID-19 are typically limited to case reports [49,50]; however, a number of studies report incidence of clinical myocarditis. The CDC has reported an incidence of approximately 150 cases of AM per 100,000 patients with COVID-19. However, subgroup analysis shows that COVID-19-associated AM may occur less often in younger patients [51,52]. A recent study that is yet to be peer-reviewed measured rates of myocarditis in individuals younger than 20 after testing positive for COVID-19 and demonstrated an incidence of 56–88 cases per 100,000 males and 21–71 cases per 100,000 females depending on age stratification [53]. Additionally, an analysis of 1,597 Big Ten college athletes who tested positive for COVID-19 and underwent cardiac evaluation, including ECG, echocardiogram, troponin, and CMR imaging, demonstrated myocarditis in 2.1% (95% CI, 1.1%-4.4%) of athletes, with males accounting for 73% of cases [54]. In general, the likelihood of developing AM appears to be higher in those infected with COVID-19 than those who receive COVID-19 vaccinations although comparative studies remain limited.

### 2.3.1. Limitations to incidence estimates

Several key limitations are inherent in determining the overall incidence of AM following COVID-19 vaccines. One notable limitation to many of the above population studies is that they rely on passive surveillance, which only detects cases that are both recognized and reported, thus underestimating the true incidence of myocarditis. Similarly, detection of myocarditis in these studies relies on subjects seeking medical care, which may fail to identify subclinical myocarditis. It is also unclear how the heightened media attention, political influence, and varying public opinion surrounding COVID-19 vaccines may affect detection and reporting. Additionally, although impractical to achieve on the population scale, diagnosis was rarely supported with myocardial biopsy, potentially limiting the diagnostic confidence of confirmed cases. Another notable limitation is the lack of long-term follow-up in publications to date. Due to the relative novelty and evolving nature of the COVID-19 pandemic, follow-up was restricted to several months or less in most studies, which might have blunted the detection of any delayed presentations of myocarditis or long-term outcomes in established cases.

### 2.4. Differences across vaccine types

It remains largely unknown if there are significant differences in AM incidence across different COVID-19 vaccine types. Most of the large population studies are limited to incidence associated with BNT 162b2 and MRNA-1273 mRNA vaccines, in part because these were the first vaccines to achieve widespread approval and availability. Initial findings from the CDC VAERS analysis suggested higher rates of myocarditis associated with the MRNA-1273 vaccine as compared to the BNT 162b2 vaccine, with roughly 2.8-fold and 2.5-fold higher rates of myocarditis after the first and second doses, respectively [55]. However, the statistical significance of this comparison is unclear and any notable difference is yet to be validated in other studies. Of the large population studies reviewed, three studies had relatively equal numbers of BNT 162b2 and MRNA-1273 vaccination rates among the studied populations, and no
significant difference in myocarditis rates was appreciated [36,39,41].

3. Mechanisms
3.1. Histopathological insights

The pathophysiology of COVID-19 vaccine-associated myocarditis remains unknown, and mechanistic insights from case reports are limited. Few published cases have undergone extensive immunologic testing, and reports including histopathological analysis are few, perhaps due to the generally low severity of COVID-19 vaccine-associated myocarditis [56]. Of the few autopsy reports published, most cases demonstrate a lymphocyte predominance, with some cases also describing an accompanying neutrophil population [46,56,57]. This finding is mirrored by the lymphocyte-predominant immune infiltrates seen in cases where endomyocardial biopsy is used [58–62]. While some reports describe eosinophilic myocarditis in patients with severe vaccine-associated myocarditis, this is a very rare finding with unclear implications [57,63]. In contrast to vaccine-associated myocarditis, the multifactorial cardiac inflammation seen with SARS-CoV-2 infection is believed to be indirectly driven by circulating cytokines, with true myocarditis being uncommon [64,65]. However, when COVID-19 does cause myocarditis, it is typically a monocyte-predominant infiltrate, which is believed to be recruited via CCL2 and other cytokines released with direct viral infection of cardiomyocytes [66,67].

3.2. Proposed mechanisms
3.2.1. Molecular mimicry

While the mechanisms of COVID-19 vaccine-associated myocarditis remain speculative, a leading theory is that of molecular mimicry between the vaccine product and self-antigens [68]. Viral infections have long been associated with the subsequent development of autoimmune disease in general [69]. Respiratory viruses including coronaviruses have been associated with acute lymphocytic myocarditis without direct viral infection of myocytes [70]. Cross-reactivity of pathogen-directed antibodies with human proteins through molecular mimicry is the leading theory for the rare but statistically significant association of autoimmune diseases such as guillain-barre syndrome and multiple sclerosis with influenza and hepatitis B vaccines, respectively [71]. These observations raise the possibility that molecular mimicry drives autoimmune myocarditis after COVID-19 vaccines.

Recently, Kanduc et al. found polypeptide sequences in the COVID-19 spike glycoprotein to have a high degree of commonality with sequences in the human proteasome [72,73]. Furthermore, antibodies against the S1 spike protein have been shown to react with multiple tissue antigens including f-actin and α-myosin [68,74]. The number of shared molecular patterns between SARS-CoV-2 viral proteins and self-antigens exceeds that of other coronaviruses and has been proposed as a central mechanism by which the characteristic inflammatory effects of COVID-19 occur [75]. Although all COVID-19 vaccines contain spike protein, it is theoretically possible that subtle differences in antigen presentation may cause molecular mimicry to occur with higher incidence in mRNA vaccines as compared to traditional vaccine platforms [76]. While these studies would suggest that cross-reaction of cardiac antigens with antibodies generated by COVID vaccination is possible, the clinical implications of this are unclear, especially given the lack of evidence for durable autoimmune response after COVID vaccination.

3.2.2. Adaptive immune response

The second leading theory for vaccine-associated myocarditis is that unique properties of the mRNA vaccines drive innate immune overactivation. Understanding the basic mechanisms of COVID mRNA vaccines is important to draw these connections. Among COVID-19 vaccines, BNT 162b2 and MRNA-1273 vaccines are unique in that they use lipid nanoparticles to deliver synthetic in vitro transcribed (IVT) mRNA that encodes SARS-CoV-2 spike protein [43]. This mRNA is then translated in the host cytoplasm into SARS-CoV-2 spike protein at sufficient quantities to mount an adaptive immune response via CD8 + and Th1-type CD4 + T-cells [77,78]. When exposed to COVID-19 virus, vaccine-induced antibodies bind the viral envelope spike protein, which both inhibits viral binding to the host cell surface protein angiotensin-converting enzyme 2 (ACE2) – a necessary step for cell entry and infection – and targets virus for destruction [79].

This unique mechanism of vaccine-induced immunity has generated the hypothesis that excessive innate immune activation by both lipid nanoparticle and RNA components of COVID-19 vaccines can cause vaccine-associated myocarditis. COVID-19 mRNA vaccines mark one of the first clinical applications of in vitro transcribed (IVT) mRNA, a technology that has been under development since 1990 [80]. The rollout of IVT mRNA was initially hampered by inherent immunogenicity and instability of mRNA molecules. Endosomal toll-like receptors TLR3, TLR7, and TLR8 in immune cells and cytosolic receptors RIG-I and MDA5 in nonimmune cells act as a natural defense to foreign RNA but can cross-react with IVT RNA [81]. Activation of these receptors triggers an inflammatory cascade, resulting in the assembly of inflamasome platforms, production of type I interferons, and nuclear translocation of NF-kB [82]. Similarly, lipid nanoparticles have been used in these vaccines to prevent IVT mRNA degradation and to facilitate mRNA delivery but have been linked with TLR-mediated release of proinflammatory cytokines as well as complement activation-related hypersensitivity reactions [83–85]. Thus, perturbed adaptive immune response, which is believed to be at the root of many autoimmune diseases, may also drive myocarditis with mRNA vaccines [86].

Every component of IVT mRNA has been re-engineered to minimize inflammatory reactions. The use of naturally occurring modified nucleosides has been shown to decrease cytokine response and innate immune response to mRNA but has to be balanced against their association with decreased protein expression [87,88]. Furthermore, careful vaccine purification is necessary to remove abortive RNA transcripts and dsRNA byproducts that can have immunogenic effects [89,90]. While some experimental therapies have combined
IVT RNA therapies with innate immune inhibitors, this strategy was not used in either MRNA-1273 or BNT 162b2 vaccines [91–93]. Finally, lipid nanoparticles have been resized and redesigned to incorporate ionizable lipids and lipid-like material to minimize immunogenicity [94]. These measures have reduced but not eliminated innate immune activation with COVID-19 vaccines. In fact, mRNA vaccines rely on their inherent activation of the innate immune since they do not include the addition of an adjuvant, a component that is included in most traditional vaccines to promote a sufficient immune response to antigen. Therefore, pathological autoimmunity could potentially happen secondary to innate immune activation in susceptible individuals or in the setting of excessively activating batches of vaccines, which could occur with production flaws [95].

3.3. Male gender as a risk factor for myocarditis

The observation that vaccine-associated myocarditis occurs at higher frequency in males mirrors epidemiological trends in myocarditis generally. Unlike most autoimmune diseases that have a female predilection, myocarditis occurs with a male to female ratio of approximately 1.7:1 [96,97]. It is theorized that sex hormones mediate this difference through their receptors in both immune cells and host cardiac tissues. Sex differences in myocarditis have been studied extensively in mouse models of coxsackievirus infection and show that testosterone promotes a pro-inflammatory Th1 pathway, while estradiol favors an IL-4-associated Th2-type response [98]. Mouse models have also shown that the testosterone-mediated IFN-γ/Th1 response has unique mechanisms in cardiomyocytes; testosterone promotes TLR4 and IL-18 signaling in myocarditis rather than the traditional IL-12/STAT4 pathway that induces IFN-γ production in other tissues [99,100]. Thus, sex hormone and tissue-dependent TLR4 and IL-18 pathways could potentially explain both male preference and cardioselective nature of COVID-19 vaccinerelated autoimmunity.

3.4. Other vaccine-associated side effects

It is worth noting that while much attention has been paid to the association between COVID-19 vaccines and vaccine-induced immune thrombotic thrombocytopenia (VITT) and Guillain-Barre syndrome, these rare side effects have been described in viral vector vaccines ChAdOx1 nCoV-19 and Ad26.COV2.S but not in the mRNA vaccines that have highest risk for myocarditis [101,102]. While mechanisms of these reactions are unclear, a study showing no cross-reactivity between anti-PF4 antibodies in affected patients and the COVID-19 spike protein suggests that alternate mechanisms are at play [103].

4. Clinical considerations

4.1. Policy implications

The association between COVID-19 mRNA vaccines and AM fuels vaccine hesitancy and forces a reconsideration of COVID-19 vaccination programs. Attention has been focused on young male patients who are at the highest risk for vaccine-associated AM yet have low rates of COVID-19 infection-related comorbidity and mortality. In response to these reports, Finland and Sweden have restricted use of mRNA-1273 vaccine in patients under 30, while Denmark did so in patients under 18 [104]. Since these restrictions, several policy analyses have been published, which further inform vaccination policy.

4.2. Risk-Benefit Analysis

A CDC analysis published in June 2021 determined that for every million males age 12–29 who underwent a 2-dose regimen of mRNA COVID-19 vaccine, “11,000 COVID-19 cases, 560 hospitalizations, 138 ICU admissions, and six deaths due to COVID-19 could be prevented, compared with 39–47 expected myocarditis cases after COVID-19 vaccination.” [105] This analysis was based on May 2021 rates of COVID-19 prevalence, morbidity, and mortality and served as the basis for CDC recommendations to vaccinate children age 12–15 [106]. In a more flexible risk-benefit model, Gurdasani et al. estimated that in children age 12–17, the number of prevented COVID-related hospitalizations exceeds the incidence of mRNA vaccine-associated myocarditis as long as the incidence of COVID-19 is greater than 30/100,000 teenagers per week, a level unseen in England throughout 2021 [107].

These models provide a useful guide for health authorities but belie the fact that while more than 95% of vaccine-associated myocarditis cases result in inpatient admission, more than 80% of COVID-19 cases are never admitted although these infections can also have long-term effects [107,108]. Furthermore, while the vast majority of vaccine-associated myocarditis hospitalizations are mild and self-limited, hospitalization with COVID-19 is often highly morbid, can cause long-term health consequences, and does result in mortality even in young patients. Finally, these analyses do not account for secondary effects of vaccination in young patients, particularly decreased education disruption and, most importantly, decreased infections in the general population.

4.3. Clinical considerations

4.3.1. Impact of myocarditis risk on vaccine candidacy

Medical history has little influence on the risk-benefit profile of COVID-19 vaccination except in the case of prior myocarditis or pericarditis. There is no evidence that patients are at higher risk for myocarditis if they have recovered from COVID-19 previously or if they have chronic heart disease. The CDC recommends vaccination for patients with a history of myocarditis as long as their “heart has recovered” [35]. Separately, in patients who experience myocarditis with their first dose of COVID-19 vaccine, the CDC suggests deferring the second dose pending further data [109]. The same CDC guidance states that pericarditis is not a barrier to vaccination as long as symptoms have resolved.
4.3.2. Proposed strategies to mitigate myocarditis risk

While the data on vaccine-associated myocarditis strongly favor vaccination in terms of both patient- and population-level benefits, further work is needed to minimize this adverse event. Some have suggested that mRNA vaccine dose reduction, a strategy that implemented vaccines for children under 12, may decrease risk for myocarditis in vulnerable populations without sacrificing immune response [110,111]. Recent VAERS surveillance data showing fewer reports of myocarditis in children 5–11 compared to teenagers further support a dose-reduction strategy [112]. Alternatively, a longer interval between doses could theoretically decrease IFN-γ-associated Th1-type inflammatory response [113]. Others have suggested that addressing shortcomings in production or maintenance of cold chain could minimize the rate of myocarditis [114]. Ultimately, more research into the mechanisms of vaccine-associated myocarditis is needed to reduce myocarditis with mRNA vaccines. Further work is also needed to identify patients at highest risk for vaccine-associated myocarditis.

4.3.3. Diagnosis

When managing COVID-19 vaccine-associated myocarditis, clinicians should largely follow guidelines for general myocarditis. Screening strategies are unlikely to prove to be fruitful given the rare occurrence and low morbidity associated with this syndrome. Vaccine-associated myocarditis should be considered in young, especially male, patients with cardiopulmonary symptoms within several weeks of COVID mRNA vaccine. Myocarditis is unlikely in patients with normal ECG, troponin, ESR, and CRP [105]. Since there is no standard diagnostic approach to AM, clinician judgment is often the deciding factor when test results are discrepant. Hospital admission is indicated in patients with significant symptoms, ECG changes, elevated cardiac biomarkers, and/or abnormalities on cardiac imaging [115]. In these cases, diagnostic workup should include confirmation with cardiac MRI when available and patients should be hospitalized until they clinically improve [116].

4.3.4. Treatment

In mild cases with immediate improvement, patients can be conservatively managed without anti-inflammatory treatment. Since most trials of AM therapies use ejection fraction and survival as primary end points, their findings are less applicable in vaccine-associated myocarditis where severe outcomes are uncommon [115]. Case reports of COVID-19 vaccine-associated myocarditis describe a range of anti-inflammatory treatments including corticosteroids, colchicine, and nonsteroidal anti-inflammatory drugs with severe cases treated with IVIG [117–119]. While little evidence base exists to support treatment decisions, the centrality of IFN-γ to myocarditis led Hajjo et al. to propose corticosteroids as a preferred treatment for vaccine-associated myocarditis [113]. Until further evidence emerges, standard AM treatment with early corticosteroids in symptomatic cases with abnormal cardiac studies may be best to prevent progression or lasting sequelae [120,121]. In rare cases of fulminant myocarditis, inotropic therapy and mechanical support can be considered, as they would be with other causes of fulminant AM.

4.3.5. Recovery and surveillance

The management of patients after recovery from COVID-19 vaccine-associated myocarditis presents several dilemmas. Other forms of AM have been shown to cause persistent cardiomyopathy; the largest registry of children with AM showed that over a 3-year period, 48% had persistent systolic dysfunction, 7% died, and 19% required transplant [122]. Results in adults are quite different, analysis of the Lombardy registry shows that among 429 patients with AM who survived their hospitalization, only 2.8% experienced MACE at the 5-year follow-up, and residual LV dysfunction was seen in 4.5% of patients at a median follow-up of 200 days [123]. Because of potential for long-term consequences, postacute care of myocarditis generally includes electrocardiography, echocardiography, and laboratory testing at annual or semiannual frequency with a low threshold to obtain cardiac MRI if symptoms or testing suggest recurrence [116]. In patients with persistent cardiac dysfunction, guideline-directed medical therapy should be started. With little known about the long-term outcomes after vaccine-associated myocarditis, it is reasonable to adopt these surveillance measures at least for now. Also unknown is whether restricting exercise for 3–6 months after vaccine-associated myocarditis enables recovery and sudden cardiac death prevention as in general myocarditis [124]. Until vaccine-associated myocarditis is better understood, this remains the safest strategy, perhaps with a shorter 3-month exercise restriction.

5. Conclusion

Early reports linking myocarditis with COVID-19 vaccines have coalesced in a clear association that deserves awareness and further investigation. Estimating the prevalence of myocarditis has always been challenging but is especially difficult for the COVID-19 vaccine-associated subtype of AM. While 95% of vaccine-associated myocarditis cases are reported from inpatient hospitalizations, a substantial number of cases are certainly unrecognized in the outpatient population. Additionally, since myocarditis is diagnostically challenging and cardiac MRI can often be inaccessible, many cases likely go unconfirmed. Furthermore, incidence estimates are largely based on adverse event reporting and administrative registries, which have well-known methodological limitations. These limitations, however, are not unique to vaccine-associated myocarditis and reflect challenges faced by population studies of myocarditis generally.

A trove of recent publications have led to the estimate that COVID vaccine-associated myocarditis occurs with an incidence of around 20–30 per 1,000,000 patients vaccinated. Cases most often occur days after the second vaccine dose and are usually mild and self-limited; long-term morbidity and mortality with myocarditis have been extremely rare. Young and male patients are at highest risk for myocarditis after COVID-19 vaccination, a demographic trend that has been demonstrated in myocarditis generally. While
young patients are at low risk for morbidity and mortality with COVID-19 infection, the risk benefit ratio, even at an individual level, still strongly favors vaccination for this demographic. Nevertheless, mitigating this risk remains a high priority for the field and will require a concrete understanding of the mechanisms of disease. Molecular mimicry has long been cited as a cause of vaccine-associated autoimmune phenomena and may contribute to myocarditis in these patients. However, the higher rates of myocarditis with mRNA vaccines suggest that this technology may be the culprit, perhaps through unique activation of innate immune pathways.

By all reports, COVID-19 vaccine-associated myocarditis has very low severity compared to myocarditis of other etiologies. However, long-term effects have not yet been studied. Clinicians should heed general myocarditis guidelines regarding the diagnosis, treatment, and surveillance of vaccine-associated myocarditis. While awareness of vaccine-associated myocarditis should prompt careful consideration when vaccinating patients with a history of myocarditis or pericarditis, it should not delay the vaccination programs among the general population in whom vaccine benefits strongly outweigh risks.

6. Expert opinion

Myocarditis associated with COVID-19 mRNA vaccines is a rare albeit increasingly recognized adverse event with wide-ranging implications. Case reports starting in the spring of 2021 describe myocarditis onset within one week of the second vaccine dose with a short length of stay and self-limited symptoms. Several recent population-based studies estimate the prevalence of vaccine-associated myocarditis to be between 2 and 32 cases per 100,000 person years. For unknown reasons, adult males in the third decade of life have emerged as the highest-risk subgroup with a COVID-19 vaccine-associated myocarditis incidence 5–6 times higher than the general population. These studies likely underestimate the true incidence of COVID-19 vaccine myocarditis given the challenges in postmarketing adverse event reporting and the relatively complex diagnostic workup required to identify myocarditis. The incidence in younger patients is uncertain but may become clearer as vaccines are expanded to this population.

While the exact mechanisms by which COVID-19 mRNA vaccines cause myocarditis are unknown, leading theories are that 1) antibodies to spike protein cross react with cardiac antigens through molecular mimicry or 2) mRNA vaccines are recognized by RNA receptors that trigger innate immune response. Further investigation into these mechanisms is warranted given that the critical role mRNA vaccines will continue to play in combating the global COVID-19 epidemic as well the potential to apply mRNA technology to a host of other disease states.

Most COVID-19 vaccine-associated myocarditis cases are mild and self-limiting and do not require intensive treatment. Nevertheless, clinicians should exercise caution as long-term implications of COVID-19 vaccine-associated myocarditis are unknown. The recommendations of limiting vigorous exercise for 3 months and surveilling of late onset heart failure after myocarditis still apply at least until more evidence emerges. Given these uncertainties, several countries have modified vaccine recommendations for subgroups at high risk for vaccine-associated myocarditis. While this may be a valid consideration, the low incidence of vaccine-associated myocarditis is far outweighed by the potential health consequences of COVID-19. Alternative approaches of achieving immunity to COVID-19 with either a dose-reduced mRNA vaccine or extended interval vaccination schedule are worth considering in select patients at high risk for vaccine-associated myocarditis.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers of this manuscript have no relevant financial or other relationships to disclose.

Funding

This article was not funded.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Huth E. Quantitative evidence for judgments on the efficacy of inoculation for the prevention of smallpox: england and New England in the 1700s. J R Soc Med. 2006;99(5):262–266.
2. Greenwood B. The contribution of vaccination to global health: past, present and future. Philos Trans R Soc Lond B Biol Sci. 2014;369(1645):20130433.
3. Plotkin S. History of vaccination. Proc Natl Acad Sci U S A. 2014;111 (34):12283–12287.
4. Draper SJ, Heeney JL. Viruses as vaccine vectors for infectious diseases and cancer. Nat Rev Microbiol. 2010;8(1):62–73.
5. Thompson MG, Stenehjem E, Grannis S, et al. Effectiveness of Covid-19 vaccines in ambulatory and inpatient care settings. N Engl J Med. 2021;385(15):1355–1371.
6. Hall VJ, Foulkes S, Saei A, et al. COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study. Lancet. 2021;397(10286):1725–1735.
7. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. N Engl J Med. 2021;384(15):1412–1423.
8. Rinott E, Youngster I, Lewis YE. Reduction in COVID-19 patients requiring mechanical ventilation following implementation of a national COVID-19 vaccination program - Israel, December 2020-February 2021. MMWR Morb Mortal Wkly Rep. 2021;70(9):326–328.
9. Benenson S, Oster Y, Cohen MJ, et al. BNT162b2 mRNA covid-19 vaccine effectiveness among health care workers. N Engl J Med. 2021;384(18):1775–1777.
10. Butt AA, Omer SB, Yan P, et al. SARS-CoV-2 vaccine effectiveness in a high-risk national population in a real-world setting. Ann Intern Med. 2021;174(10):1404–1408.
11. Angelini A, Calzolari V, Calabrese F, et al. Myocarditis mimicking acute myocardial infarction: role of endomyocardial biopsy in the differential diagnosis. Heart. 2000;84(3):245–250.
12. Roth GA, Mensah GA, Johnson CO, et al. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 Study. J Am Coll Cardiol. 2020;76(25):2982–3021. 

13. Tschöpe C, Ammirati E, Bozkurt B, et al. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. Nat Rev Cardiol. 2021;18(3):169–193.

14. Bozkurt B, Kamat I, Hotze PJ. Myocarditis with COVID-19 mRNA vaccines. Circulation. 2021;144(6):471–484.

15. Gravanis MB, Sternby NH. Incidence of myocarditis. A 10-year autopsy study from Malmö, Sweden. Arch Pathol Lab Med. 1991;115(4):390–392.

16. Kytö V, Saraste A, Voipio-Pulkki L-M, et al. Incidence of fatal myocarditis: a population-based study in Finland. Am J Epidemiol. 2007;165(5):570–574.

17. Wakafugi S, Okada R. Twenty year autopsy statistics of myocarditis incidence in Japan. Jpn Circ J. 1986;50(12):1288–1293.

18. Blauwet LA, Cooper LT. Myocarditis. Prog Cardiovasc Dis. 2010;52(4):274–281.

19. Carniel E, Sinagra G, Bussani R, et al. Fatal myocarditis: morphologic and clinical features. Ital Heart J. 2004;5(4):702–706.

20. Diaz FJ, Loewe C, Jackson A. Death caused by myocarditis in Wayne County, Michigan: a 9-year retrospective study. Am J Forensic Med Pathol. 2006;27(4):300–303.

21. Doolan A, Langlois N, Semsarian C. Causes of sudden cardiac death in young Australians. Med J Aust. 2004;180(3):110–112.

22. Okada R, Kawai S, Kasuya H. Nonspecific myocarditis: a statistical and clinicopathological study of autopsy cases. Jpn Circ J. 1989;53(1):40–48.

23. Kearney MT, Cotton JM, Richardson PJ, et al. Viral myocarditis and dilated cardiomyopathy: mechanisms, manifestations, and management. Postgrad Med J. 2001;77(903):4–10.

24. Liu PP, Mason JW. Advances in the understanding of myocarditis. Circulation. 2001;104(9):1076–1082.

25. Peretto G, Sala S, Rizzo S, et al. Ventricular arrhythmias in myocarditis: characterization and relationships with myocardial inflammation. J Am Coll Cardiol. 2020;75(9):1046–1057.

26. Power JR, Alexandre J, Choudhary A, et al. Electrocardiographic manifestations of immune checkpoint inhibitor myocarditis. Circulation. 2021;144(18):1521–1523.

27. Engler RJM, Nelson MR, Collins LC Jr, 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.

28. Casey CG, Iskander JK, Roper MH, et al. Adverse events associated with smallpox vaccination in the United States. JAMA. 2003 [January-October]; 294(21): 2734–2743.

29. Murphy JG, Wright RS, Bruce GK, et al. Eosinophilic-lymphocytic myocarditis after smallpox vaccination. Lancet. 2003;362(9393):1378–1380.

30. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. N Engl J Med. 2020;383(27):2603–2615. • This trial establishes the efficacy of the BNT162b2 mRNA 19-covid-19 vaccine.

31. 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(5):403–416. • This trial establishes the efficacy of the mRNA-1273 mRNA covid-19 vaccine.

32. CDC. Myocarditis and pericarditis after mRNA COVID-19 vaccination [Internet]. 2021 cited 2021 Nov 14]. Available from 2021 Nov 14: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myocarditis.html.

33. Shimabukuro TT, Nguyen M, Martin D, et al. Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS). Vaccine. 2015;33(36):4398.

34. Munro C. Covid-19: study that claimed boys are at increased risk of myocarditis after vaccination is deeply flawed, say critics. BMJ. 2021;2251:n2251. DOI:10.1136/bmj.n2251

35. Wallace M, Oliver S, Meeting A. cdc.gov/coronavirus COVID-19 mRNA vaccines in adolescents and young adults: benefit-risk discussion. 2021. [cited 2021 Nov 14]. Available from: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-06-05-COVID-Wallace-508.pdf. The first description of incidence of COVID-19 vaccine associated myocarditis came from this CDC analysis of data from the Vaccine Adverse Event Reporting System (VAERS).

36. Klein NP, Lewis N, Goddard K, et al. Surveillance for adverse events after COVID-19 mRNA vaccination. JAMA. 2021;326(14):1390–1399.

37. 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(23):2123–2139.

38. Mevorach D, Anis E, Cedar N, et al. Myocarditis after BNT162b2 mRNA vaccine against Covid-19 in Israel. N Engl J Med. 2021;385(23):2140–2149. • This claims data analysis from a large Israeli healthcare organization demonstrated at-risk groups and characterized most cases as mild-moderate severity. See Table 1 for a comparison of similar studies. This report also demonstrates how severe outcomes from COVID vaccine-associated myocarditis are exceedingly rare.

39. Simone A, Herald J, Chen A, et al. Acute Myocarditis following COVID-19 mRNA vaccination in adults aged 18 years or older. JAMA Intern Med. 2021;181(12):1668.

40. 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(10):1202–1206.

41. Diaz GA, Parsons GT, Gering SK, et al. Myocarditis and pericarditis after vaccination for COVID-19. JAMA. 2021;326(12):1210–1212.

42. Perez Y, Levy ER, Joshi AV, et al. Myocarditis following COVID-19 mRNA vaccine: a case series and incidence rate determination. Clin Infect Dis. 2021. DOI:10.1093/cid/ciaa926.

43. Levin D, Shimon G, Fadlon-Derali M, et al. Myocarditis following COVID-19 vaccination - A case series. Vaccine. 2021;39(42):6195–6200.

44. Das BB, Kohli U, Ramachandran P, et al. Myopericarditis after messenger RNA Coronavirus disease 2019 vaccination in adolescents 12 to 18 years of age. J Pediatr. 2021;238:26–32.e1.

45. Kohli U, Desai L, Chowdhury D, et al. MRNA Coronavirus-19 vaccine-associated myopericarditis in adolescents: a survey study. J Pediatr Internet. 2021 cited 2022 Feb 8. Available from: https://www.jpeds.com/article/S0022-3476(21)01231-2/fulltext.

46. Verma AK, Lavine KJ, Lin C-Y. Myocarditis after Covid-19 mRNA vaccination. N Engl J Med. 2021;385(14):1332–1334.

47. Li M, Yuan J, Lv G, et al. Myocarditis and pericarditis following COVID-19 vaccination: inequalities in age and vaccine types. J Pers Med. 2021;12(1):11. • This analysis of the VAERS database showed no association of the Ad26.COV2.S vaccine with acute myocarditis or pericarditis.

48. 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. DOI:10.1016/j.carrev.2021.08.012.

49. Escher F, Pietsch H, Aleschcheva G, et al. Detection of viral SARS-CoV-2 genomes and histopathological changes in endomyocardial biopsies. ESC Heart Failure. 2020;7(5):2440–2447.

50. Nicol M, Capouib L, Baudet M, et al. Delayed acute myocarditis and COVID-19-related multisystem inflammatory syndrome. ESC Heart Failure. 2020;7(6):4371–4376.

51. Boehmer TK, Kompanjeyts L, Lavery AM, et al. Association between COVID-19 and myocarditis using hospital-based administrative data - United States, March 2020-January 2021. MMWR Morb Mortal Wkly Rep. 2021;70(35):1228–1233. • CDC analysis of a large healthcare administrative database reporting system shows that while patients with COVID-19 are at approximately 16 times elevated risk for acute myocarditis, this is still a rare complication. Incidence varies by age and gender.
52. Lala A, Johnson KW, Januzzi JL, et al. Prevalence and impact of myocardial injury in patients hospitalized with COVID-19 infection. J Am Coll Cardiol. 2020;76(5):533–546.

53. Singer ME, Taub IB, Kaelber DC. Risk of myocarditis from COVID-19 infection in people under age 20: a population-based analysis. medRxiv. 2021. DOI: 10.1101/2021.07.23.21260998

54. Daniels CJ, Rajpal S, Greenshields JT, et al. Prevalence of clinical and subclinical myocarditis in competitive athletes with recent SARS-CoV-2 infection: results from the big ten COVID-19 cardiac registry. JAMA Cardiol. 2021;6(9):1078–1087.

55. ACIP June 2021 Presentation slides [Internet]. [cited 2021 Nov 18]. Available from: https://www.cdc.gov/vaccines/acip/meetings/slides-2021-06.html. VAERS data suggests 2.5-2.8 times higher incidence of vaccine-associated myocarditis with MRNA-1273 as compared to BNT 162b2 vaccines.

56. Sessa F, Salerno M, Esposito M, et al. Autopsy findings and causality relationship between death and COVID-19 vaccination: a systematic review. J Clin Med Res. 2021;10(1). DOI: 10.3390/jcm10245876.

57. Ameratunga R, Woon S-T, Sheppard MN, et al. First identified case of fatal fulminant necrotizing eosinophilic myocarditis following the initial dose of the Pfizer-BioNTech mRNA COVID-19 vaccine (BNT162b2, Comirnaty): an extremely rare idiosyncratic hypersensitivity reaction. J Clin Immunol. 2022. DOI:10.1007/s10875-021-01187-0

58. Ehrlich P, Klingel K, Olhmann-Knafo S, 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):1855–1859.

59. Abbate A, Gavin J, Madanchi N, et al. Fulminant myocarditis and systemic hyperinflammation temporally associated with BNT162b2 mRNA COVID-19 vaccination in two patients. Int J Cardiol. 2021;340:119–121.

60. Almeida F, Azimi P, Lozier MR, et al. Lymphohistiocytic myocarditis after Ad26.COV2.S viral vector COVID-19 vaccination. Int J Cardiol Heart Vasc. 2021;36:100869.

61. Maki H, Ikawa T, Ibe T, et al. Biventricular systolic dysfunction in acute myocarditis after SARS-CoV-2 mRNA-1273 vaccination. Eur Heart J Cardiovasc Imaging. 2022;23(2):e87.

62. Nguyen TD, Mall G, Westphal JG, et al. Acute myocarditis after COVID-19 vaccination with mRNA-1273 in a patient with former SARS-CoV-2 infection. ESC Heart Failure. 2021;8(6):4710–4714.**

63. While many endomyocardial biopsies of COVID vaccine-associated myocarditis are non-diagnostic, those that do result positive show lymphocytic myocarditis as in this case report.

64. Sokolska JM, Kurcz J, Kosmala W. Every rose has its thorns - acute myocarditis following COVID-19 vaccination. Kardiol Pol. 2021;79(10):1153–1154.

65. Deng Q, Hu B, Zhang Y, et al. Suspected myocardial injury in patients with COVID-19: evidence from front-line clinical observation in Wuhan, China. Int J Cardiol. 2020;311:116–121.

66. Bradley BT, Maioli H, Johnston R, et al. Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington state: a case series. Lancet. 2020;396(10247):320–322.

67. Wenzel P, Kopp S, Göbel S, et al. Evidence of SARS-CoV-2 mRNA in endomyocardial biopsies of patients with clinically suspected myocarditis tested negative for COVID-19 in nasopharyngeal swab. Cardiovasc Res. 2020;116(10):1661–1663.

68. Yang L, Nilsson-Payant BE, Han Y, et al. Cardiomyocytes recruit monocytes upon SARS-CoV-2 infection by secreting CCL2. Stem Cell Reports. 2021;16(9):2274–2288.

69. Fujinami RS, von Herrath MG, Christen U, et al. Molecular mimicry, bystander activation, or viral persistence: infections and autoimmune disease. Clin Microbiol Rev. 2006;19(1):80–94.

70. Veronese G, Cipriani M, Bottirolli M, et al. Fulminant myocarditis triggered by OC43 subtype coronavirus: a disease deserving evidence-based care bundles. Journal of Cardiovascular Medicine. 2020;21(7):529–531.

71. Segal Y, Shoenfeld Y. Vaccine-induced autoimmunity: the role of molecular mimicry and immune crossreaction. Cell Mol Immunol. 2018;15(6):586–594.

72. Kunduc D, Shoenfeld Y. Molecular mimicry between SARS-CoV-2 spike glycoprotein and mammalian proteomes: implications for the vaccine. Immunol Res. 2020;68(5):310–313.

73. Kunduc D, Shoenfeld Y. On the molecular determinants of the SARS-CoV-2 attack. Clin Immunol. 2020;215:108426.

74. Vojdani A, Vojdani E, Kharrazian D. Reaction of human monoclonal antibodies to SARS-CoV-2 proteins with tissue antigens: implications for autoimmune diseases. Front Immunol. 2020;11:617089.

75. Kunduc D. From Anti-SARS-CoV-2 immune responses to COVID-19 via molecular mimicry. Antibodies (Basel). 2020;9(3). Internet. Available from: doi:10.3390/antib9030033

76. Heinz FX, Stiasny K. Distinguishing features of current COVID-19 vaccines: knowns and unknowns of antigen presentation and modes of action. NPJ Vaccines. 2021;6(1):104.

77. Verbeke R, Lentacker I, Smelt SC, et al. The dawn of mRNA vaccines: the COVID-19 case. J Control Release. 2021;333:511.

78. Dr B, Hm ES, E B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384(5):403–416.

79. Fp P, Sj T, K N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383(27):2603–2615.

80. Hs H, Mh D, B B, et al. Description and proposed management of the acute COVID-19 cardiovascular syndrome. Circulation. 2020;141(23):1903–1914.

81. Ja W, Rw M, W P, et al. Direct gene transfer into mouse muscle in vivo. Science. 1990;247(4949):1465–1468.

82. S U, K K, Türeci Ö, Ö T. mRNA-based therapeutics—developing a new class of drugs. Nat Rev Drug Discov. 2014;13(10):759–780.**

This review describes the development of mRNA technology with a focus on immunogenicity.

83. Kaufman KI, Mir FF, Jhunjhunwala S, et al. Efficacy and immunogenicity of unmodified and pseudouridine-modified mRNA delivered systemically with lipid nanoparticles in vivo. Biomaterials. 2016;109:78–87.

84. Halamoda-Kenzouai B, Bremer-Hoffmann S. Main trends of immune effects triggered by nanomedicines in preclinical studies. Int J Nanomedicine. 2018;13:5419–5431.

85. Samaridou E, Heyes J, Lutwyche P. Lipid nanoparticles for nucleic acid delivery: current perspectives. Adv Drug Deliv Rev. 2020;154–155:37–63.

86. R S, Jb N, M Y. Pattern recognition and signaling mechanisms of RIG-I and MDAS. Front Immunol. Internet. 2014;5. [cited2022 Jan 15]. Available from: https://pubmed.ncbi.nlm.nih.gov/25101084/.

87. P K, S T, M K, et al. Nucleic acid-sensing TLRs and autoimmunity: novel insights from structural and cell biology. Immunol Rev. 2016;269(1):60–75.

88. 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(2):165–175.

89. Thess A, Grund S, Mui BL, et al. Sequence-engineered mRNA without chemical nucleoside modifications enables an effective protein therapy in large animals. Mol Ther. 2015;23(9):1456–1464.

90. Baisersdörfer M, Boros G, Muramatsu H, et al. A facile method for the removal of dsRNA contaminant from in vitro-transcribed mRNA. Mol Ther Nucleic Acids. 2019;15:26–35.

91. Martin CT, Muller DK, Coleman JE. Processivity in early stages of transcription by T7 RNA polymerase. Biochemistry. 2002;27(11):3966–3974.

92. Zhong Z, Mc Cafferty S, Combes F, et al. mRNA therapeutics deliver a hopeful message. Nano Today. 2018;23:16–39.
93. Liu Y, Krishnan MN, Phua KKL. Suppression of mRNA nanoparticle transfection in human fibroblasts by selected interferon inhibiting small molecule compounds. Biomolecules. 2017;7(4):56.

94. Reichmuth AM, Oberli MA, Jaklenec A, et al. mRNA vaccine delivery using lipid nanoparticles. Ther Deliv. 2016;7(5):319–334.

95. Tinari S. The EMA covid-19 data leak, and what it tells us about mRNA instability. BMJ. 2021;372(627). DOI:10.1136/bmj.n627-• Flaws in production and distribution have been proposed as sources of mRNA vaccine immunogenicity.

96. Mason JW, O’Connell JB, Herskowitz A, et al. A clinical trial of immunosuppressive therapy for myocarditis, the myocarditis treatment trial investigators. N Engl J Med. 1995;333:269–275.

97. Caforio ALP, Calabrese F, Angeliini A, et al. A prospective study of biopsy-proven myocarditis: prognostic relevance of clinical and aetiopathogenetic features at diagnosis. Eur Heart J. 2007;28(11):1326–1333.

98. Huber SA, Pfaffie B. Differential Th1 and Th2 cell responses in male and female BALB/c mice infected with coxsackievirus group B type 3. J Virol. 1994;68(8):5126–5132. • Mouse models of acute viral myocarditis show that sex hormones modulate key inflammatory pathways.

99. Coronado MJ, Brandt JE, Kim E, et al. Testosterone and interleukin-1β increase cardiac remodeling due coxsackievirus B3 myocarditis via serpin A 3n. Am J Physiol Heart Circ Physiol. 2012;302(8):H1726–36.

100. Fairweather D, Yusung S, Frisancho S, et al. IL-12 receptor beta 1 and Toll-like receptor 4 increase IL-1 beta- and IL-18-associated myocarditis and coxsackievirus replication. J Immunol. 2003;170(9):4731–4737.

101. Elrashdy F, Tambuwalama MM, Hassan SS, et al. Autoimmune roots of the thrombotic events after COVID-19 vaccination. Autoimmun Rev. 2021;20(11):102941.

102. Maramattom BV, Krishnan P, Paul R, et al. Guillain-Barré syndrome following ChAdOx1/S - nCoV –19 vaccine. Ann Neurol. 2021;90(2):312–314.

103. Greinacher A, Sellenk K, Mayerle J, et al. Anti-platelet factor 4 antibodies causing VITT do not cross-react with SARS-CoV-2 spike protein. Blood. 2021;138(14):1269–1277.

104. Finland joins other Nordic nations in curbing moderna shots [Internet]. Associated Press. 2021, [cited 2021 Nov 13]. Available from: https://apnews.com/article/coronavirus-pandemic-business-finland-coronavirus-vaccine-public-health-34db41c3b115f385153adfc5b4cafee.

105. 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. MMWR Morb Mortal Wkly Rep. 2021;Jun (27):977–982.

106. CDC recommends pediatric COVID-19 vaccine for children 5 to 11 years [Internet]. 2021, [cited 2021 Nov 13]. Available from: https://www.cdc.gov/media/releases/2021/s1102-PediatricCOVID-19Vaccine.html.

107. Gurdasani D, Bhatt S, Costello A, et al. Vaccinating adolescents against SARS-CoV-2 in England: a risk–benefit analysis. J R Soc Med. 2021;114(11):01410768211052589. • This risk benefit analysis compares the mortality and hospitalization rate of vaccine-associated myocarditis to that of COVID infection, and aims to determine how this calculation changes as incidence fluctuates.

108. Stokes EK, Zambrano LD, Anderson KN, et al. Coronavirus disease 2019 case surveillance - United States. MMWR Morb Mortal Wkly Rep. 2020;69 (24):759–765.

109. Wallace M, Meeting SOA. COVID-19 mRNA vaccines in adolescents and young adults: benefit-risk discussion [Internet]. [cited 2021 Nov 14]. Available from: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-06-05-COVID-Wallace-508.pdf

110. Walter EB, Talata KR, Sabharwal C, et al. Evaluation of the BNT162b2 Covid-19 vaccine in children 5 to 11 years of age. N Engl J Med. 2021. DOI:10.1056/NEJMoa2116298.

111. Albano L, Ferrara P. Could fractional mRNA COVID-19 vaccines reduce myocarditis in adolescents? Travel Med Infect Dis. 2021;44:102164. Internet]; Available from: 02-covid-su-508.pdf. [cited2022 Jan 25]. Available from: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-01-05/02-covid-su-508.pdf

112. Hajjo R, Sabbah DA, Bardaweel SK, et al. Shedding the light on post-vaccine myocarditis and pericarditis in COVID-19 and non-COVID-19 vaccine recipients. Vaccines (Basel). 2021;9(10). DOI:10.3390/vaccines9101186. • A systems biology approach suggests MAPK and JAK-STAT pathways may be central to vaccine-associated myocarditis. Accordingly, authors propose increasing the interval between vaccine doses may decrease inflammatory side effects such as acute myocarditis.

113. Lazaros G, Klein AL, Hatziantoniou S, et al. The novel platform of mRNA COVID-19 vaccines and myocarditis: clues into the potential underlying mechanism. Vaccine. 2021;39(35):4925–4927.

114. Caforio ALP, Pankuvweit S, Arbustini E, 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. 2021;34(33):2636–2648, 2648a–2648b. • ESC guidelines on acute myocarditis recommend thresholds for hospital admission in suspected cases.

115. Law YM, Lal AK, Chen S, et al. Diagnosis and management of myocarditis in children: a scientific statement from the american heart association. Circulation. 2021;144(16)e123–e135. • This review outlines expert opinion on monitoring approach to patients who have recovered from acute myocarditis.

116. Tano E, San Martin S, Girgis S, et al. Perimyocarditis in adolescents after Pfizer-BioNTech COVID-19 vaccine. J Pediatric Infect Dis Soc. 2021;10(10):962–966.

117. Marshall M, Ferguson ID, Lewis P, et al. Symptomatic acute myocarditis in 7 adolescents after Pfizer-BioNTech COVID-19 vaccination. Pediatrics. Internet]. 2021;148(3). DOI:10.1542/peds.2021-052478.

118. Dickey JB, Albert E, Badr M, et al. A series of patients with myocarditis following SARS-CoV-2 vaccination with mRNA-1279 and BNT162b2. JACC: Cardiovascular Imaging. 2021;14(9):1862–1863.

119. Zhang L, Zlotoff DA, Awadalla M, et al. Major adverse cardiovascular events and the timing and dose of corticosteroids in immune checkpoint inhibitor-associated myocarditis. Circulation. 2020;141 (24):2031–2034.

120. Larson KF, Ammirati E, Adler ED, et al. Myocarditis after BNT162b2 and mRNA-1273 vaccination. Circulation. 2021;144(6):506–508.

121. Foerster SR, Canter CE, Cinar A, et al. Ventricular remodeling and survival are more favorable for myocarditis than for idiopathic dilated cardiomyopathy in childhood. Circ Heart Fail. 2010;3 (6):689–697.

122. Ammirati E, Cipriani M, Moro C, et al. Clinical presentation and outcome in a contemporary cohort of patients with acute myocarditis. Circulation. 2018;138(11):1088–1099.

123. Pelliccia A, Solberg EE, Papadakis M, et al. Recommendations for participation in competitive and leisure time sport in athletes with cardiomyopathies, myocarditis, and pericarditis: position statement of the sport cardiology section of the European Association of Preventive Cardiology (EAPC). Eur Heart J. 2019;40(1):19–33.