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REVIEW

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

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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.

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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.

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Article highlights

- The incidence of myocarditis in association with COVID-19 vaccines is estimated to be 20-30 per million patients
- Myocarditis incidence is higher with COVID-19 vaccines that use mRNA technology than those that use a traditional viral vector approach.
- Myocarditis is believed to affect males more than females due to differential effects of sex hormones on cytokine production.
- Even in at-risk populations, vaccine-associated myocarditis leads to far fewer hospitalizations than COVID-19 and causes much less morbidity and mortality.
- The risk of vaccine-associated myocarditis should only delay vaccination in patients with pre-existing unresolved myocarditis or pericarditis; all other patients are recommended to proceed with vaccination.
- Mechanisms for myocarditis are unclear but may include molecular mimicry as suggested by the high number of shared epitopes between SARS-CoV-2 spike protein and human self-antigens. Myocarditis may be triggered by cross-reactivity between COVID-19 vaccine mRNA components and RNA receptors of the innate immune system.
- General guidelines for managing myocarditis should be applied to vaccine-associated myocarditis with prompt immunosuppression for symptomatic patients, heart failure management if necessary, and standard precautions in the recovery phase

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 subpopulation, 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

Table 1. ~TC~

Incidence of Myocarditis after COVID-19 Vaccination

	Klein et al., 2021[36]	Witberg et al., 2021[37]	Mevorach et al., 2021[38]	Simone et al., 2021[39]	Montgomery et al., 2021[40]	Diaz et al., 2021[41]	Perez et al., 2021[42]
Total population, N	Approx. 6,200,000	2,558,421	9,289,765	2,392,924	Approx. 1,745,000	2,000,287	175,472
Total doses, N	11,845,128		-	-	2,810,000	-	-
Proportion completing 2nd dose (%)	-	94	55.2	93.5	-	76.5	-
Cases of myocarditis, N	34	54	136	15	23	20	7
Proportion of cases after 2nd dose (%)	-	-	86.0	86.7	87.0	80.0	-
Incidence overall	13.2 cases per 100,000 person-years	2.13 cases per 100,000 persons	5.34 (Incidence Ratio)	0.08 cases per 100,000 first doses; 0.58 cases per 100,000 second doses	0.82 cases per 100,000 doses	1.0 cases per 100,000 persons	55.4 cases per 100,000 person-years
Proportion of cases, male (%)	85	94.4	86.8	100	100	75	86
Age of cases (years)	12–39 (range)	27 (median)	16–19 (most freq. range)	25 (median)	25 (median)	36 (median)	44 (median)
Incubation period after vaccine (days; range)	0–7	3–5	-	0–10	0–4	3.5 (median)	1–13
Cohort Demographics							
Male (%)	46	49	-	46	-	41	-
Age (years)	49 (mean)	44 (median)	-	49 (median)	-	57 (median)	12–106 (range)
Study Details							
Vaccine (type)	57.0% BNT 162b2 43.0% MRNA-1273	100% BNT 162b2	100% BNT 162b2	50.0% BNT 162b2 50.2% MRNA-1273	BNT 162b2, MRNA-1273	52.6% BNT 162b2, 44.1% MRNA-1273, 3.1% Ad26.COV2.S	BNT 162b2, MRNA-1273
Inclusion criteria	All ages, at least 1 dose of BNT 162b2 or MRNA-1273 vaccine	Age 16+, at least 1 dose of BNT 162b2 vaccine	Age 16+, at least 1 dose of BNT 162b2 vaccine	Age 18+, at least 1 dose of BNT 162b2 or MRNA-1273 vaccine	At least 1 dose of BNT 162b2 or MRNA-1273 vaccine	At least 1 dose of BNT 162b2, MRNA-1273 or Ad26.COV2.S	Any age, at least 1 dose of BNT 162b2 or MRNA-1273 vaccine
Setting	8 healthcare systems, USA	Clalit Health Services, Israel	Ministry of Health Database, Israel	Kaiser Permanente Southern California, USA	Military Health System, USA	Providence Health and Services, USA	Mayo Clinic, Minnesota and Wisconsin, USA
Enrollment period	12/14/2020 – 6/26/2021	12/20/2020 – 5/24/2021	12/20/2020 – 5/31/2021	12/14/2020 – 7/20/2021	1/1/2021 – 4/30/2021	– 5/25/2021	12/17/2020 – 5/13/2021

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 involved 6.2 million subjects and 11.8 million vaccines (57% BNT 162b2, 43% mRNA-1273) at 9 health care organizations primarily located in the Western 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 post-vaccine 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 inflammasome 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 cytokines 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 IFNγ-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.

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