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Myopericarditis and COVID-19 Vaccination

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Abbreviations: COVID-19: Coronavirus disease of 2019, SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2, EKG: Electrocardiogram, CDC: Centers for Disease Control and Prevention, cMRI: Cardiac Magnetic Resonance Imaging, US: United States, mRNA: Messenger Ribonucleic Acid, Pfizer: Pfizer-BioNTech's BNT162B2, Moderna: Moderna's mRNA-1273, S: Viral Spike Glycoprotein, AZ: Oxford/Astrazeneca: Vaxzevria, VAM: Vaccination Associated Myopericarditis, VAERS: Vaccine Adverse Event Reporting System

Coronavirus disease of 2019, colloquially known as COVID-19, is a multisystemic infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The most common symptoms of COVID-19 include fever, myalgia, chills, cough, shortness of breath, fatigue, along with anosmia and dysgeusia. SARS-CoV-2 infection can result in simultaneous inflammation in multiple tissues including, and not limited to, pulmonary, renal, central nervous and cardiac organ systems. Cardiac involvement in COVID-19 may be asymptomatic with cardiac biomarker changes and/or electrocardiogram (EKG) changes; or symptomatic.

Symptomatic disease may involve one or more functional elements of cardiac tissue e.g., pericardium, myocardium and the conduction system. There are numerous reports of COVID-19 associated myocarditis in the literature **[1-3]**.

The Centers for Disease Control and Prevention's (CDC) definition of a confirmed case of myocarditis is the presence of new or worsening clinical symptoms as listed in **Table 1** along with new findings on cardiac magnetic resonance imaging (cMRI) or histopathology and no other identifiable cause of the symptoms and findings **[4]**. Definitions of acute pericarditis and myopericarditis are also listed in **Table 1**.

For simplicity, the remainder of the manuscript refers to these conditions collectively as myopericarditis. The etiologies of myopericarditis include non infectious causes, such as medication-induced, autoimmune, physical trauma, and infectious causes. Those attributable to infectious agents may be incited by common viruses including influenza and SARS-CoV-2. Myopericarditis may also occur after vaccination against viral diseases such as smallpox **[5]**. Among viral causes, at the molecular level, whether the virus itself infects cardiac cells resulting in a direct viral insult on cellular machinery or whether an immunologic cascade leads to cellular damage remains elusive. While chest pain is the most common symptom of myopericarditis, other symptoms include fever, sore throat, dyspnea, palpitations, and fatigue.

Table 1. CDC case definitions of probable and confirmed myocarditis, pericarditis, and myopericarditis **[4]**.

Condition	**Definition**	
Acute myocarditis	Probable case	Confirmed case
	Presence of ≥1 new or worsening of the following clinical symptoms:	Presence of ≥1 new or worsening of the following clinical symptoms:
	• chest pain, pressure, or discomfort	• chest pain, pressure, or discomfort
	• dyspnea, shortness of breath, or pain with breathing	• dyspnea, shortness of breath, or pain with breathing
	• palpitations	• palpitations
	• syncope	• syncope
	AND	AND
	≥1 new finding of	≥1 new finding of
	• troponin level above upper limit of normal (any type of troponin)	• Histopathologic confirmation of myocarditis
	• abnormal EKG or rhythm monitoring findings consistent with myocarditis	
	• abnormal cardiac function or wall motion abnormalities on echocardiogram	• cMRI findings consistent with myocarditis in the presence of troponin level above upper limit of normal (any type of troponin)
	• cMRI findings consistent with myocarditis	
	AND	AND
	• No other identifiable cause of the symptoms and findings	• No other identifiable cause of the symptoms and findings
Acute pericarditis	Presence of ≥2 new or worsening of the following clinical features:	
	• acute chest pain	
	• pericardial rub on exam	
	• new ST-elevation or PR-depression on EKG	
	• new or worsening pericardial effusion on echocardiogram or MRI	
Myopericarditis	Verbiage for cases that meet criteria for both myocarditis and pericarditis.	

The diagnostic evaluation of suspected myopericarditis should include initial laboratory testing and cardiac imaging. Initial testing should include a complete blood count, chemistries, EKG, cardiac biomarkers including serum troponin levels, chest X-ray, and nonspecific inflammatory markers such as erythrocyte sedimentation rate and C reactive protein. Cardiac imaging for myopericarditis includes an echocardiogram to evaluate for global ventricular function, valvular function, and other potential causes of cardiac dysfunction. Coronary angiography is indicated in selected patients with presentation identical to that of acute coronary syndrome. cMRI and endomyocardial biopsy are reserved for

complex clinical scenarios. Following the diagnosis of viral myopericarditis, some patients experience spontaneous, gradual improvement while others require more focused care. Mild cases may be managed by conservative therapy including rest and medications, such as non steroidal anti inflammatory drugs and/or corticosteroids. Moderate to severe cases may require drugs such as, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, beta blockers, diuretics and cardiac inotropes. Lastly, intensive care is reserved for the most severe clinical presentations and treatment for these cases may need intra aortic balloon pump, extra corporeal membrane oxygenation and ventricular assist devices or heart transplant.

Vaccines against COVID-19 have been available for use in the United States (US) population since December 2020 **[6]**. Currently, there are four types of COVID-19 vaccines that have been listed for emergency use by the World Health Organization **[7]**. The first type uses messenger ribonucleic acid (mRNA) technology and includes Pfizer-BioNTech's BNT162B2 also called Comirnaty® (Pfizer) and Moderna's mRNA-1273 (Moderna). Nucleoside-modified mRNA encoding the viral spike glycoprotein (S) is delivered to the vaccine recipient and this ultimately results in antibody production. The second type are vector vaccines and notable manufacturers are Janssen and Oxford/AstraZeneca: Vaxzevria (AZ). S protein of SARS-CoV-2 is placed in an altered version of a viral vector and when the immune system is challenged with vaccination, robust antibody production occurs. The third type of COVID-19 vaccination consists of protein subunit vaccines, manufactured by Novavax and Serum Institute of India, the active ingredient being SARS-CoV-2 S protein. The fourth type of COVID-19 vaccine contains inactivated virus and prominent manufacturers include Bharat Biotech, Sinopharm and Sinovac. While COVID-19 vaccines have demonstrated potency and efficacy in reducing COVID-19 related hospitalizations and severe disease, they have also been implicated in vaccination associated myopericarditis (VAM).

A surveillance system in the US called 'Vaccine Adverse Event Reporting System'

(VAERS) records instances of adverse events following immunization, including COVID-19 VAM. More than 192 million people received an mRNA vaccine from December 2020 through August 2021. Recent reports indicate that COVID-19 VAM could occur following mRNA vaccination, including Pfizer and Moderna. COVID-19 VAM cases have been observed primarily in adolescent and young adult males. The second dose of mRNA vaccines notably confer a higher risk. Oster et al reported that 1626 cases met the definition of myocarditis following COVID-19 vaccination; the majority of these cases occurred following the second dose of vaccination with 82% occurring in males whose median age was 21 years. The breakdown per age group of males is listed in **Table 2 [8]**.

Table 2. Age groups and incidence of VAM among males following receipt of second dose of COVID-19 vaccine **[8]**.

Age	Vaccine	Incidence
12 - 16 years	Pfizer	70.7 cases per million
16 - 17 years	Pfizer	105.9 per million
18 - 24 years	Pfizer and Moderna	52.4-56.3 per million

Choi et al reported a singular case of myocarditis induced sudden death after receipt of the Pfizer vaccination **[9]**.

Tables 3 and 4 contain summaries of population studies and case series on COVID-19 VAM.

Table 3. Summary of population studies on COVID-19 VAM.

Authors	Study region	Study period	COVID-19 vaccine(s) evaluated	Ages studied	Age finding	Gender predilection	Myopericarditis incidence (Cumulative)	Additional findings
Oster et al **[8]**.	US	December 2020 - August 2021	Pfizer and Moderna	>12 years	12-29 years	Males	8.45 per million vaccine doses	
Witberg et al **[10]**.	Israel	December 2020 - May 2021	Pfizer	>12 years	16 to 29 years	Males	2.13*	Subgroup incidence: 10.69
Mevorach et al **[11]**.	Israel	December 2020 - May 2021	Pfizer	>16 years	16 to 19 years	Males	Standardized incidence ratio: 5.34	Largely on account of myocarditis in younger male recipients
Patone et al **[12]**.	England	December 2020 - August 2021	Pfizer, Moderna and AZ	>16 years	<40 years	Males	Incidence rate ratios highest after second dose of mRNA COVID-19 vaccination	
Fleming Nouri et al **[13]**.	Connecti cut, US	January 2021 - May 2021	Pfizer, Moderna	16 to 25 years	16 to 24 years	Males	0.03% of the individuals studied who received two doses of an mRNA vaccine	All 8 cases of myopericarditis were among Pfizer recipients
Chua et al **[14]**.	Hong Kong	June 2021 - September 2021	Pfizer	12 to 17 years	Median age: 15.25 years	Males	18.52*	Among male adolescents, incidence after the first dose: 5.57 After the second dose: 37.32
Husby et al **[15]**.	Denmark	October 2020 - October 2021	Pfizer, Modern a, AZ, Janssen	>12 years	12-39 years	Males	1.7*	Incidence rate for Pfizer: 1.4 Modern a: 4.2

* Incidence rates are reported per 100,000 vaccinated individuals in the studied groups/subgroups.

Table 4. Synopsis of non population studies (case series reports) of COVID-19 VAM.

Authors	Study region	Study period	COVID-19 vaccine(s) evaluated	Age findings	Number of cases	Time from vaccination to symptom onset (days)
Truong et al **[16]**.	US and Canada	December 2020 - July 2021	Pfizer, Moderna, Janssen	Age range: 12-20 years (median age: 15.8 years)	Males:126 Females: 14	0-22
Montgomery et al **[17]**.	US	January 2021 - April 2021	Pfizer, Moderna	Age range: 20-51 years	Males: 23	0-4
Marshall et al **[18]**.	US	December 2020 - May 2021	Pfizer	Median age: 14 years, age range: 14-19 years	Males: 7	0-4
Rosner et al **[19]**.	US	December 2020 - June 2021	Moderna, Pfizer, Janssen	<40 years	Males: 7	2-7
Larson et al **[20]**.	US and Italy	December 2020 - June 2021	Pfizer, Moderna	Age Range: 22-40 years	Males: 8	2-4
Mouch et al **[21]**.	Israel	January 2021 - February 2021	Pfizer	Median age: 23 years	Males: 6	1-16
Kim et al **[22]**.	US	February 2021 - April 2021	Pfizer, Moderna	Age range: 23-36 years, 1 outlier: 70 years	Males: 3 Female: 1	0-5

As seen above, numerous studies have linked COVID-19 vaccines, especially mRNA vaccines including Pfizer and Moderna with myopericarditis. Despite these observations, the overall incidence of myopercaridits following COVID-19 vaccination including mRNA vaccination has been deemed low among all age groups and genders **[23]**. Further, myopericarditis has rarely been observed thus far following COVID-19 vaccination with adenoviral vector vaccines (Janssen and AZ). Majority of cases reported in the literature occurred among young males, within 30 days after vaccination, most often within 7 days of vaccine receipt.

Future possible areas of research include long term sequelae of COVID-19 VAM, its impact on future athletic pursuits, and the ability to seek COVID-19 vaccines in the future including booster doses. Lastly, the advent of childhood vaccination (for those <5 years of age) against COVID-19 poses many questions about vaccination related adverse events including COVID-19 VAM in this age group. Despite such speculation, and all the information quoted in the literature to date, protection conferred by COVID-19 vaccines against severe disease and death has shown significant promise, building the case for greater benefits than risks of vaccine receipt.

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