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Myocarditis with COVID-19 mRNA Vaccines

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Abstract

Myocarditis has been recognized as a rare complication of coronavirus 2019 (COVID-19) mRNA vaccinations, especially in young adult and adolescent males. According to the U.S. Centers for Disease Control (CDC), myocarditis/pericarditis rates are approximately 12.6 cases per million doses of second dose mRNA vaccine among 12–39-year-olds. In reported cases, patients with myocarditis invariably presented with chest pain, usually 2-3 days after a second dose of mRNA vaccination and had elevated cardiac troponin levels. ECG was abnormal with ST elevations in most, and cardiac MRI was suggestive of myocarditis in all tested patients. There was no evidence of acute COVID-19 or other viral infections. In one case, a cardiomyopathy gene panel was negative, but autoantibody levels against certain self-antigens and frequency of natural killer cells were increased. Although the mechanisms for development of myocarditis are not clear, molecular mimicry between the spike protein of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and self-antigens, trigger of preexisting dysregulated immune pathways in certain individuals, immune response to mRNA and activation of immunological pathways, and dysregulated cytokine expression have been proposed. The reasons for male predominance in myocarditis cases are unknown, but possible explanations relate to sex hormone differences in immune response and myocarditis, and also under-diagnosis of cardiac disease in women. Almost all patients had resolution of symptoms and signs, and improvement in diagnostic markers and imaging with or without treatment. Despite rare cases of myocarditis, the benefit-risk assessment for COVID-19 vaccination shows a favorable balance for all age and sex groups; therefore COVID-19 vaccination is recommended for everyone 12 years of age and older.

Key words: myocarditis; pericarditis; COVID-19; SARS-CoV-2; vaccination; COVID-19 vaccine; mRNA vaccines; COVID

Non-standard Abbreviations and Acronyms:
ACE: Angiotensin converting enzyme
COVID-19: Coronavirus disease 2019
CDC: Centers for Disease Control and Prevention
FDA: Food and Drug Administration
IL: Interleukin
IVIG: Intravenous immunoglobulin
MIS: Multisystem inflammatory syndrome (MIS) in children (MIS-C) and younger adults (MIS-A)
MIS-C: Multisystem inflammatory syndrome in children
MIS-A: Multisystem inflammatory syndrome in adults
mRNA: Messenger ribonucleic acid
VAERS: Vaccine Adverse Event Reporting System
SARS: severe acute respiratory syndrome
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

Introduction

There is now increasing evidence for myocarditis and myopericarditis as rare complications of coronavirus 2019 (COVID-19) mRNA vaccinations, especially in young adult and adolescent males. Here we provide further details about this phenomenon and its potential underlying mechanisms. We also discuss the balance of risk of myocarditis with vaccination vs cardiac and other risks from COVID-19 viral infection.

Epidemiology and Clinical Presentation of Myocarditis post COVID-19 Vaccination

Historically, post-vaccination myocarditis has been reported as a rare adverse event following vaccinations, especially smallpox vaccination, influenza, hepatitis B, or other vaccinations. [1] In the general population, myocarditis is diagnosed in approximately 10-20 individuals per 100,000 per year, [2] and occurs more commonly and at younger ages in males compared with females. [3] In the pre- COVID-19 era, among 620,195 reports filed at the Vaccine Adverse Event Reporting System (VAERS) between 1990 and 2018, 0.1% were due to myopericarditis. [1] 79% of those myopericarditis reports were in males. [1] However, VAERS is primarily a safety signal detection and hypothesis generating system; and cannot be used to determine if a vaccine caused an adverse event. [4] Through this passive reporting, the Centers for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA) conduct post-licensure vaccine safety monitoring. [4] This approach is not specific and a majority of VAERS events are typically not actually linked to vaccinations. Instead, various methods and statistical techniques are used to analyze VAERS data, which CDC and FDA use to guide further safety evaluations, such as Vaccine Safety Datalink, and inform decisions around vaccine recommendations and regulatory action. Therefore, VAERS data must be interpreted with caution due to the inherent limitations of passive surveillance. [4] VAERS is subject to reporting bias, including both under- and over-

reporting of adverse events or stimulated reporting that might occur in response to intense media attention and increased public awareness. [4]

Recently, a CDC Advisory Committee on Immunization Practices (ACIP) identified a "likely association" between the two Covid-19 mRNA vaccines from Pfizer-BioNTech and Moderna and cases of myocarditis and pericarditis.[5] Patient reports in VAERS were categorized according to CDC work case definitions as probable myocarditis, confirmed myocarditis or acute pericarditis. [5] (Figure 1) According to the Advisory Committee on Immunization Practices (ACIP), after ~300 million COVID-19 mRNA vaccine doses administered through Jun 11, 2021, there were 1,226 reports of probable myocarditis/pericarditis cases in VAERS, 67% of which followed the second dose. [5] 79% were in males, with the majority in individuals younger than 30 years with a median age of 24. Time to onset of symptoms was a median of 3 days, with the highest rate at day 2 after vaccination, and among ages 16-18. In 484 probable myocarditis/pericarditis cases among age ≤29 that were reviewed and characterized by the CDC, [5] 86% had reports of chest pain on presentation, 61% ST or T wave changes on electrocardiogram (ECG), 64% elevated cardiac enzymes and 17% abnormal cardiac imaging . [5] In 323 of the reports that met the CDC definition of confirmed myocarditis/pericarditis, 96% were hospitalized, but the majority were discharged with resolution of symptoms. [5] The observed myocarditis/pericarditis reports were higher than expected case rates for males compared with females, and higher at younger ages compared with older ages. (Table 1) [5]

Additional analyses of CDC Vaccine Safety Datalink (VSD) with data from 9 participating integrated healthcare organizations revealed an increased risk of myocarditis/pericarditis events among 12–39-year-olds in the 7-day risk interval post vaccination with mRNA Covid-19 vaccines compared with unvaccinated individuals or

individuals vaccinated with non-mRNA COVID-19 vaccines on the same calendar days (Rate ratio of 10.8, 95 % CI: 3.2–49.0, adjusted for site, age, sex, race/ethnicity, and calendar date). [5] The estimated myocarditis/pericarditis chart-confirmed rate was 12.6 cases per million doses with second dose mRNA vaccine among 12–39-year-olds. [5] The rates based on ICD-10 coded cases were also higher in males compared with females. [5] (Table 1) All chart-confirmed cases with follow-up had resolution of symptoms; and among those who had follow-up ECG/echo and lab testing, most had returned to normal or baseline.[5] On this basis, the FDA will add a warning to the product label of both mRNA vaccines regarding the risk of myocarditis. [6]

A number of myocarditis cases after COVID-19 vaccination have been published in peer reviewed journals, [7-16] [17, 18] with reports predominantly after the second dose of mRNA COVID-19 vaccines (BNT162b2 mRNA-Pfizer-BioNTech and the mRNA-1273-Moderna). (Table 2) Patients in these reports invariably presented with chest pain, usually 2-3 days after a second dose of mRNA vaccination, some preceded with fever and myalgia one day after vaccination. These were predominantly young males requiring hospitalization for myocarditis and without prior history of COVID-19 or comorbidities. All tested negative for current COVID-19 by PCR testing. A majority had spike antibody levels for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) suggesting effective immunization. All had elevated cardiac troponin, the highest-level peaking usually 3 days post vaccination. (Table 2) ECG was abnormal with ST elevations in most presentations. An echocardiogram was abnormal only in 40%, with only a small percentage having an LVEF< 50% on presentation. Cardiac MRI was abnormal in all tested patients, with findings suggestive of myocarditis such as late gadolinium enhancement and myocardial edema. BNP or NT-proBNP levels were only mildly elevated in approximately 2/3 of the patients when measured. CRP levels were elevated in most and decreased along with

troponin through the hospital stay. Almost all patients had resolution of symptoms and signs and improvement in diagnostic markers and imaging with or without treatment. (Table 2)

The Israeli Ministry of Health also reported 148 myocarditis cases among 10.4 million vaccinated individuals occurring within 30 days of mRNA vaccination, a majority after a second dose, mostly in men aged 16-30. [19] Most cases required hospitalization up to 4 days but were considered mild. The report suggested a probable link between the second dose mRNA vaccine and myocarditis among men aged 16 to 30, [19] with a stronger link for age 16 to 19, and decreasing association with older age. [15,19] The prevalence of myocarditis was 1/20 000 for the 16-30 year old group compared with 1/100 000 in the general population receiving the same vaccine. Similarly, the U.S. Department of Defense reported 23 male military personnel diagnosed with myocarditis following 2.8 million doses of COVID-19 vaccinations administered in the Military Health System, mostly after the second dose of mRNA COVID-19 vaccination, reflecting higher than expected numbers of myocarditis cases. [17]

COVID-19-associated Myocarditis

With the emergence of COVID-19 in Hubei Province, China, there was an expectation that the SARS-CoV-2 would cause predominantly respiratory illness, similar to that seen with severe acute respiratory syndrome (SARS) in 2002-2003. [20] However, with the next phase of the COVID-19 epidemic in Southern Europe and later New York City, it became apparent that there was cardiovascular involvement and thromboembolic complications. [21] Therefore, COVID-19 emerged as a virus pathogen affecting the vasculature and resulting in myocardial injury, requiring far different therapeutic approaches compared with SARS. [21, 22] Historically, pre-COVID-19, coronaviruses have not been commonly associated with significant myocardial damage. SARS infected more than 8,000 individuals without significant incidence of

myocarditis. In one autopsy series, SARS-CoV-1 was PCR amplifiable in 7 of 20 (35%) hearts, but was not associated with lymphocytic myocarditis, the hallmark of classic viral myocarditis. [23] Similarly, Middle east respiratory syndrome coronavirus (MERS-CoV) infected over 2,000 individuals, with only one case report of MRI-diagnosed MERS-CoV myocarditis. [24] On the other hand, epidemiological data suggest that approximately 12-20% of hospitalized patients with COVID-19 have evidence of cardiac injury as indicated by elevated levels of cardiac troponin. [22, 25] Furthermore in young athletes recovering from COVID-19 infection, [26] cardiac MRI abnormalities consistent with myocarditis have been reported at a higher prevalence than expected, in approximately in 1-3% of the athletes. [27] [28-31] It was also recognized that COVID-19 can also result in a multisystem inflammatory syndrome (MIS) in children (MIS-C) and younger adults (MIS-A). This rare but serious condition is defined by an excessive hyperinflammatory response that can affect multiple organs including the lungs, kidneys, brain, skin, eyes, gastrointestinal and the cardiovascular system resulting in ventricular dysfunction, coronary aneurysms and shock.[32, 33]

While some investigators have proposed direct virus invasion as the most likely mechanism, others focus more on host inflammatory cell responses. Emerging data indicate that a maladaptive host immune response fueled by excessive activation of innate immune pathways along with pro-inflammatory cytokine surge, deregulated thromboinflammation, thrombotic microangiopathy and endothelial dysfunction may play a role in pathogenesis of cardiac injury related to COVID-19.[34, 35] Other hypothesized mechanisms include demand ischemia, and stress and hypoxia induced myocardial injury. [22] Baseline comorbidities including metabolic syndrome, hypertension and cardiovascular disease likely also play a role.

Though SARS-CoV-2 can enter the cardiomyocyte through an ACE2-mediated entry and SARSCoV-2 copies have been detected in heart tissue, [36-38] cardiac histopathology studies have reported the absence of diffuse lymphocytic myocarditis traditionally seen in viral myocarditis or confluent myocyte necrosis expected in fulminant myocarditis. [37, 39-42] Hearts of patients who died from COVID-19 have revealed greater number and diffuse distribution of CD68+ cells compared with matched control or other myocarditis hearts, indicating cells of monocyte/macrophage lineage rather than lymphocytes may be dominant in this setting. [34] Other studies revealed that interstitial cells, pericytes and macrophages in the myocardium contain SARS-COV-2 RNA by in-situ hybridization, and that pericytes infected by SARS-CoV-2 may play a role in capillary endothelial cell or microvascular dysfunction and individual cell necrosis. [38 41, 43] It is important to note that macrophages can mediate both local and systemic responses to viral infection, and are also capable of fixing complement and therefore could cause the direct death of nearby myocytes through the activation of apoptotic attack complexes. [34] These findings suggest that COVID-19 may incite a form of myocarditis that is different from the typical lymphocytic myocarditis associated with other viral myocarditis presentations and may instead be associated with diffusely infiltrative cells of monocytes/macrophage lineage. [34, 40, 43]

Potential Mechanisms of COVID-19 Vaccine Myocarditis

SARS-CoV-2 mRNA vaccines contain nucleoside-modified mRNA, encoding the viral spike glycoprotein of SARS-CoV-2, but not live virus or DNA. They are encapsulated in lipid nanoparticles that act as delivery vehicles to transport mRNA into the cells and may include inactive ingredients such as buffer and salts. Once inside the host cells, the vaccine's mRNA causes the cells to build the spike protein which then stimulates an adaptive immune response to identify and destroy a virus expressing spike protein. Vaccine induced spike protein IgG

antibodies prevent attachment of SARS-COV-2 to its host cell via spike protein binding to the ACE2 receptor, and thereby neutralizes the virus.

Selected RNA molecules can be immunogenic and stimulate the mammalian innate immune system, destroying the mRNA before it reaches target cells, preventing the spike protein and neutralizing antibody production. Nucleoside modifications of mRNA have been groundbreaking, shown to reduce innate immunogenicity and result in less activation of cytokines; paving the path for mRNA vaccine development. [44] Covid-19 mRNA vaccines have been shown to be highly effective and safe in large-scale trials. [45, 46] Systemic reactions to the vaccine, which are usually mild and transient, were reported more commonly among the younger population and more often after the second dose. Adverse cardiovascular effects in these trials were isolated, with incidences less than 0.05%, and did not include myocarditis. [45, 46]

Though nucleoside modifications of mRNA have been shown to reduce their innate immunogenicity; [44] in certain individuals with genetic predisposition, [47] the immune response to mRNA may not be turned-down and may drive the activation of an aberrant innate and acquired immune response. The dendritic cells or Toll-like receptor expressing cells exposed to RNA may still have the capacity to express cytokines and activation markers in certain individuals, though this may be markedly less when exposed to mRNA with nucleoside modifications than when treated with unmodified RNA. [44] The immune system may therefore detect the mRNA in the vaccine as an antigen, result in activation of pro-inflammatory cascades and immunological pathways, which may play a role in development of myocarditis as part of a systemic reaction in certain individuals. [44, 47] It will be important to monitor possibility of such complications as the revolutionary use of mRNA is being considered for other vaccinations and therapies.

In published reports of myocarditis following COVID-19 vaccination, cardiac biopsy was reported only in two cases, and did not demonstrate myocardial infiltrate [10] or any evidence of myocarditis. [8] This could be due to sampling error in these few cases, or a different mechanism causing myocardial injury detected by cardiac biomarkers and MRI not manifest as traditional lymphocytic or eosinophilic myocarditis or myonecrosis on cardiac histopathology. SARS-COV-2 PCR and viral serology for other etiologies including hepatitis, Epstein-Barr virus, Cytomegalovirus, Parvovirus, Mycoplasma, HIV, Influenza A/B, Respiratory Syncytial Virus, Rhinovirus, Enterovirus (Coxsackie A, Coxsackie B), Adenovirus and other etiologies were negative for acute or active infection, when tested, arguing against myocarditis caused by COVID-19 or other infections. [9 13-16 17] Serology for autoimmune disorders with ANA and RF were negative, with no evidence of predilection to individuals with preexisting autoimmune disorders. [9] There was also no evidence of leukocytosis, eosinophilia, anemia, or thrombocytopenia, or transaminase elevation. [9, 11] D dimer was slightly elevated in two patients without an evidence of pulmonary embolus or venous thromboembolic events, [11, 13] and ESR was mildly elevated in some cases.[13] In one case report, a panel testing for variants in 121 genes potentially linked to cardiomyopathy was negative [16], arguing against an existing predisposition to cardiomyopathy due to known gene variants in that case.

By one case report, SARS-CoV-2 spike IgM and IgG neutralizing antibody levels were not significantly different in the patient with myocarditis compared to individuals without myocarditis post COVID-19 mRNA vaccination [16] arguing against a hyperimmune response. [16] In the same report, the patient with myocarditis had elevated levels of IL-1 receptor antagonist, IL-5, IL-16, but not pro-inflammatory cytokines such as IL-6 , TNF, IL-1B, IL-2 or interferon-γ levels. On the other hand, the patient had diminished levels of leukemia inhibitory factor,

varying bidirectional profiles for IL-10, macrophage migration inhibitory factor, and vascular endothelial growth factor relative to an unvaccinated individual or a vaccinated individual without myocarditis. [16] Interestingly, this patient also had higher levels of antibodies against some self-antigens such as aquaporin 4, endothelial cells antigen, and proteolipid protein 1. [16] Historically, circulating heart-reactive autoantibodies have been reported at a higher frequency in myocarditis patients and have been implicated in pathogenesis. [48] These autoantibodies are usually directed against multiple antigens, some of which may have functional effects on cardiac myocytes. [48] Thus, autoantibody generation could be one of the mechanisms whereby myocarditis may develop in susceptible individuals after vaccination. However, it should be noted that in the studied patient, autoantibody levels peaked on day 2 along with symptoms, but they did not recede as expected, as the clinical condition improved, though the follow-up was rather short. Autoantibodies are found more frequently in first-degree relatives of patients with cardiomyopathy than in the normal population raising the possibility that myocarditis may develop in a subgroup of patients with the appropriate genetic background. Also, the autoantibodies may not be pathogenic and could also be seen as a result of myocardial inflammation. Additionally, this case patient had a 2-fold increase in the frequency of natural killer (NK) cells, which are the classical population of innate lymphoid cells, expressing a heterogeneous repertoire of germline-encoded receptors that allows them to destroy cells that are infected by viruses, cancer cells, or cells that are rejected. The surge in NK cells may have either contributed to the pathology or the disease resolution process. It is not clear whether the differences seen in this patient regarding relative increases in NK cells, autoantibodies and dysregulated cytokine profile reflect a causal pathologic immune response or reactive adaptive responses to myocardial inflammation, and await validation by further studies.

Another important potential mechanism for myocarditis is molecular mimicry between the spike protein of SARS-CoV-2 and self-antigens. [49] Antibodies against SARS-CoV-2 spike glycoproteins have been experimentally shown to cross-react with structurally similar human peptide protein sequences, including alpha-myosin. [49] However, severe adverse events or autoimmune reactions have been very rare. [45, 46] Though COVID-19 vaccination does not appear to provoke de-novo immune mediated adverse events, it is possible that it may trigger preexisting dysregulated pathways in certain individuals with predisposition, resulting in a polyclonal B-cell expansion, immune complex formation and inflammation. [47]

Earlier animal studies of vaccines for SARS-CoV-1 and MERS-CoV had raised concerns for enhanced disease with re-exposure to wild-type virus after vaccination. [50, 51] These were triggered by different mechanisms, including neutrophilic and eosinophilic cellular infiltrates, possibly linked to Th17 responses, or non-neutralizing antibodies resulting in enhancement of antibody-induced cellular cytotoxicity, complement-dependent pathways, and aberrant activation of the innate and acquired immune system. [52 53 54, 55] Antibody-dependent enhancement of immunity (ADE), was initially observed in the 1960s with RSV and measles vaccines, [56] and characterized by non-neutralizing antibodies generated by past infection or vaccination failing to shut down the pathogen upon re-exposure and acting as a gateway by allowing the virus to gain entry and replicate and lead to wider dissemination of illness, and over-reactive immune responses causing more severe illness. However, no evidence of either cellular immune enhancement or ADE was observed in non-human primate studies following SARS-CoV-2 virus challenge, either after vaccination or previous infection. [57] These findings led an NIH ACTIV Study panel to conclude that the risk of immune enhancement following COVID-19 immunizations was low, but required ongoing pharmacovigilance and monitoring. [57] To date,

neither COVID-19 disease nor the new COVID-19 vaccines have shown evidence of causing ADE or other forms of immune enhancement with re-exposure. People infected with SARS-CoV-2 have not been reported to develop ADE upon repeat exposure and vaccine break-through COVID-19 cases are rare and mild. Furthermore, there is no evidence of acute COVID-19 infection during presentation with myocarditis cases following COVID-19 vaccination, arguing against a breakthrough infection as a cause. (Table 2)

Reports to date also do not suggest a delayed hypersensitivity reaction, such as serum sickness–like reaction, or eosinophilic myocarditis as a cause for myocarditis following mRNA COVID-19 vaccination. [14] Though rare, delayed localized skin hypersensitivity reactions have been described with mRNA COVID-19 vaccination with a median latency of 7 days, [58] unlike myocarditis emerging earlier within 3-4 days after vaccination. None of the case reports published to date had evidence of eosinophilia in peripheral blood or immune complex deposition or eosinophilic infiltrates in endomyocardial biopsy samples arguing against hypersensitivity, allergic or eosinophilic myocarditis. [7-16] Lipid nanoparticles or adjuvants used in mRNA vaccines have not been shown to result in an immune or inflammatory response and have not been associated with myocarditis either.

Rare occurrences of vaccine-induced immune thrombotic thrombocytopenia have been reported after vaccination with the recombinant adenoviral vector encoding the spike protein antigen of SARS-COV-2. [59] Though very rare thrombotic complications have been reported following mRNA COVID-19 vaccinations, these patients did not have thrombocytopenia or antiplatelet antibodies. [60, 61]None of the myocarditis cases reported following mRNA vaccination had evidence of thrombotic events, thrombocytopenia or disseminated intravascular coagulation. (Table 2) These patients also did not have persistent fever beyond first few days,

lymphadenopathy, hepatosplenomegaly, cytopenias (anemia, leukopenia, thrombocytopenia), hypofibrinogenemia, transaminitis, extreme elevation in ferritin or multiorgan impairment to suggest a cytokine storm, hemophagocytic lymphohistiocytosis or macrophage activation syndrome that results from over-activation of T lymphocytes and macrophages.[62, 63]

Male predominance in myocarditis/ pericarditis cases has been described in clinical and experimental studies before and the reasons are unknown. An important possible explanation relates to sex hormone differences. [3, 64, 65] Testosterone is thought to play a role, by a combined mechanism of inhibition of anti-inflammatory cells, [3, 64-66] and commitment to a Th1-type immune response. [67] Estrogen has inhibitory effects on proinflammatory T cells, resulting in a decrease in cell-mediated immune responses; and pericarditis incidence is higher in women during the postmenopausal period.[68] Another contributing factor could be under-diagnosis in women. Interestingly, by our analysis of the VAERS database, as of 6/6/2021, there were 6235 reported cases of chest pain, 69 % of which were in females, versus 30% in males. [69] Despite a higher prevalence of chest pain in women, diagnostic evaluation, including ECG, laboratory biomarkers, echocardiography and MRI was performed and reported more often in males compared with female patients presenting with chest pain after COVID vaccination. (Unpublished data)

Assessing the Risk

Most importantly, despite these rare cases of myocarditis, the benefit-risk assessment for COVID-19 vaccination shows a favorable balance for all age and sex groups. [5] (Figures 2 and 3) Given the known potential risk of complications with COVID-19 infection including hospitalizations and death even in younger adults (mortality remains 0.1-1 per 100,000 for persons aged 12-29 years), the risk-benefit decision remains overwhelmingly favorable for

vaccination; therefore COVID-19 vaccination is currently recommended for everyone 12 years of age and older. [5] (Figure 3) COVID-19 vaccination not only prevents COVID-19 related hospitalizations and death, but also COVID-19 related complications such as myocarditis, multisystem inflammatory syndrome (MIS), [32] and post-acute sequelae of SARS-CoV-2 infection (PASC) or long COVID-19. [70]

Management Strategies

Though rare, clinicians should be aware of the myocarditis and pericarditis risk, which should be considered in individuals presenting with chest pain within a week post vaccination, especially in the younger population. For initial evaluation, ECG, cardiac troponin level should be obtained, and inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate can be helpful.[5] For suspected cases, cardiology consultation and evaluation with echocardiography and cardiac MRI should be considered. An evaluation for acute COVID-19 infection (via PCR of respiratory tract sample) and past disease (via SARS-CoV-2 nucleocapsid and spike protein antibodies) would be helpful. Evaluation and management may vary depending on the patient's age, clinical presentation, potential other causes and comorbidities, hemodynamic and rhythm stability and clinical course. Patients with chest pain, evidence of myocardial injury, ECG changes, cardiac imaging abnormality, arrhythmia, hemodynamic instability following COVID-19 vaccination likely will require hospitalization and close follow-up.

In published case reports, in addition to supportive care, nonsteroidal anti-inflammatory drugs, steroids, and colchicine were used for management of some of the patients with myocarditis following COVID-19 vaccination. A few patients were treated with intravenous immunoglobulin and aspirin and some were initiated on beta-blocker and angiotensin converting enzyme inhibitor therapy due to left ventricular systolic dysfunction. Though there are no

prospective or randomized studies, it is reasonable to consider these therapies, especially in patients with significant symptoms and findings. Among patients with rapid resolution of symptoms, with preserved cardiac function and normal biomarkers or resolving cardiac biomarker abnormality; therapy may be deferred. In patients with persistent mild symptoms without hemodynamic instability, arrhythmia, significant LV dysfunction or heart failure; colchicine, nonsteroidal anti-inflammatory drugs and or steroids may be considered. In patients with left ventricular dysfunction, heart failure, new onset arrhythmia, or hemodynamic instability; intravenous steroids and intravenous immunoglobulin along with other cardiac or circulatory supportive measures can be considered. In patients with left ventricular systolic dysfunction, guideline directed therapy including beta-blockers and angiotensin converting enzyme inhibitors should be initiated. Management should include a cardiologist for initial assessment, evaluation, treatment and follow-up, and an infection disease specialist for guidance on subsequent immunization strategies.

Though the clinical course appears mild with likely resolution of symptoms and signs, it is reasonable to restrict or defer strenuous physical activity and competitive sports until after complete resolution of symptoms, signs, hemodynamic, rhythm, diagnostic and biomarker abnormalities. If a person develops myocarditis or pericarditis after the first dose of an mRNA vaccine, CDC recommends that their second dose be delayed and that the second dose could be reconsidered upon resolution of symptoms, signs and findings, under certain circumstances. [71] There is evolving evidence that a single dose mRNA vaccine does not offer adequate protection in the general population against new SARS-COV-2 variants, and further studies are needed to determine efficacy of a single versus two doses of mRNA vaccination in different age groups. [71]

CDC recommends all cases of myocarditis and pericarditis post-COVID-19 vaccination be reported to VAERS. [5]

Future Direction and Research Priorities

Studies are needed to elucidate the incidence, risk factors including genetic predisposition, prognosis, potential mechanisms, reasons for sex differences, clinical course, treatment strategies, and long-term impact of myocarditis following COVID-19 vaccination. [5]

Future research studies should be designed and supported, specifically: 1) to characterize the role of specific immune cell populations; their similarities and differences in the development of COVID-19, immunity post COVID-19 vaccinations, myocardial injury and MIS-C related to COVID-19, and myocarditis related to COVID-19 vaccines; 2) to characterize histopathology, immunohistochemistry, ultrastructural and functional changes of the myocardium in the setting of myocardial injury related to COVID-19, and myocarditis related to COVID-19 vaccines; and their correlation with cardiac imaging and cardiac biomarker findings; 3) to prospectively screen for development of myocarditis and or myocardial injury following COVID-19 vaccinations in different populations with specific emphasis on sex and age related differences; 4) to explore predisposing factors for development of myocardial injury with COVID-19 or myocarditis with COVID-19 vaccines (e.g. genetic factors, comorbidities, immunity or autoimmunity profile); 5) to explore the mechanisms for development of myocarditis related to COVID-19 mRNA vaccination; including but not limited to molecular mimicry, autoantibody formation, mRNA immune reactivity, trigger of preexisting dysregulated immune processed - it is also important to determine whether these factors are specific for spike delivery through the mRNA technology or possibly a rare event from mRNA vaccinations; 6) to prospectively characterize the clinical course and short- and long-term outcomes of myocardial

injury related to COVID-19, and myocarditis related to COVID-19 vaccines 7) to explore appropriate treatment and management strategies for myocardial injury related to COVID-19, and myocarditis related to COVID-19 vaccines; 8) to characterize cardiac biomarkers, cardiac function and structure in patients with prolonged symptoms following COVID-19 or myocarditis related to COVID-19 vaccine, if any; 9) to determine risk benefit ratio for different age and sex groups with different doses of COVID-19 vaccination; and 10) to provide guidance on return to play and return to activity for patients with evidence of myocardial injury related to COVID-19, and myocarditis related to COVID-19 vaccines.

A collaborative registry of myocarditis related to COVID-19 vaccination with data collected on patient demographics, clinical presentation, biomarkers including cardiac troponin, diagnostic findings of ECG, echocardiography and cardiac MRI, biomarkers, with a paired bioregistry with blood and cardiac tissue samples would be quite valuable and help answer some of these questions.

Conclusions

In summary, more than 177 million people have received at least one dose of COVID-19 vaccine (more than 300 million doses) in the United States, and CDC and other international organizations continue to monitor the safety of COVID-19 vaccines for any health problems including rare cases of myocarditis after vaccination. [71] Despite rare cases of self-limited myocarditis, the benefit-risk assessment for COVID-19 vaccination shows a favorable balance for all age and sex groups; therefore COVID-19 vaccination is currently recommended for everyone 12 years of age and older.

Disclosures

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PH: Inventor on a COVID-19 vaccine technology owned by Baylor College of Medicine that was licensed non-exclusively to vaccine companies in India (Biological E) and elsewhere.

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Table 1. Expected / Observed Number, Crude Reporting Rates in Vaccine Adverse Event Reporting System (VAERS) and ICD-10 Coding Rates of Myocarditis/Pericarditis following mRNA COVID-19 Vaccination

Expected versus Observed Number of Myocarditis/Pericarditis Cases in 7-day Risk Window Following Dose 2 of mRNA Covid-19 Vaccination [*]						
Age groups	**Females**			**Males**		
	Doses administered	**Expected**[*,†]	**Observed**[*]	**Doses administered**	**Expected**[*,†]	**Observed**[*]
12–17 years	2,189,726	0–2	19	2,039,871	0–4	128
18–24 years	5,237,262	1–6	23	4,337,287	1–8	219
25–29 years	4,151,975	0–5	7	3,625,574	1–7	59
30–39 years	9,356,296	2–18	11	8,311,301	2–16	61
40–49 years	9,927,773	2–19	18	8,577,766	2–16	34
50–64 years	18,696,450	4–36	18	16,255,927	3–31	18
65+ years	21,708,975	4–42	10	18,041,547	3–35	11
Crude Reporting Rates of Myocarditis/Pericarditis Cases per Million Doses following mRNA COVID-19 Vaccination[‡]						
	Female rates per million doses			**Male rates per million doses**		
Age groups	**All doses**	**Dose 1**	**Dose 2**	**All doses**	**Dose 1**	**Dose 2**
12-17 years	4.2	1.1	9.1	32.4	9.8	66.7
18-24 years	3.6	1.5	5.5	30.7	8.7	56.3
25-29 years	2.0	0.8	2.6	12.2	4.5	20.4
30-39 years	1.8	1.4	1.8	6.9	2.0	10.0
40-49 years	2.0	0.9	2.8	3.5	1.0	5.1
50-64 years	1.6	1.0	1.8	1.9	1.0	2.3
65+ years	1.1	0.6	1.2	1.2	0.7	1.4
Myocarditis/Pericarditis Rates based on ICD-10 Codes [§]						
Age group 12-39 years	**Female cases**	**Female rates per million doses (95 % CI)**		**Male cases**	**Male rates per million doses (95 % CI)**	
Any mRNA both doses	6	3.2 (1.2–6.9)		26	16.9 (11.0–24.8)	

Any mRNA dose 1	2	1.9 (0.2–7.0)	4	4.7 (1.3–12.0)
Any mRNA dose 2	4	4.7 (1.3–12.0)	22	32.0 (20.1–48.5)

* Preliminary myocarditis/pericarditis reports to US Vaccine Adverse Event Reporting System (VAERS) following dose-2 mRNA vaccination, expected versus observed number of cases using 7-day risk window with data thru Jun 11, 2021. Includes total preliminary reports identified by CDC Advisory Committee on Immunization Practices through VAERS database searches for reports with myocarditis/pericarditis codes and pre-screened VAERS reports with signs and symptoms consistent with myocarditis/pericarditis. Observed cases may include probable and confirmed cases by CDC. .Adapted from [5].

† Based on [75] U.S. Population-Based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines and expected counts among females 12–29 years adjusted for lower prevalence relative to males by factor of 1.7 [3] Adapted from [5].

‡ Preliminary myocarditis/pericarditis crude reporting rates per million mRNA vaccine doses administered by sex and dose number to US Vaccine Adverse Event Reporting System (VAERS) following mRNA COVID-19 vaccination with no restrictions on post-vaccination observation time, data thru Jun 11, 2021. Adapted from [5].

§ Myocarditis/pericarditis rates based on ICD-10 coded cases in CDC Vaccine Safety Datalink (VSD) in 21-day risk interval, ages 12–39 years old, data through June 5, 2021. Adapted from [5].

Table 2. Case Reports and Case Series of Myocarditis after COVID-19 Vaccination

Case series							Case Report							Summary
Author	Marshall M et al. [7]	Rosner DM et al [8]	Larson K et al [10]	Abu M et al [9]	Kim H et al. [18]	Montgomery J et al [17]	**Author**	Ammirati E et al [11]	Bautista Garcia J et al [12]	McLean L et al (US) [13]	D'Angelo T et al [14]	Albert E et al [15]	Muthukumar A et al [16]	
Cases, n	7	7	8	6	4	23	**Case, n**	1	1	1	1	1	1	61 patients
Case source	Hospitalized patients different centers in US	Hospitalized patients in 2 US centers	Hospitalized patients in Italy and US	Hospitalized patients in Israel	Hospitalized patients in 1 US center	Case series from US Military Health System	**Case source**	Hospitalized patient in Italy	Hospitalized patient in Spain	Hospitalized patient in US	Hospitalized patient in Italy	Hospitalized patient in US	Hospitalized patient in US	All hospitalized
Male Sex (%)	100%	100%	100%	100%	75%	100%	**Gender**	male	male	male	male	male	male	98% males
Median age (range), years	17 (14-19)	24 (19-30)	29 (21-56)	22 (16-45)	30 (23-70)	25 (20-51)	**Age, years**	56	39	16	30	24	52	Mean age 26 years
Vaccine Type	All BNT 162b2 (Pfizer)	5 BNT162b2 (Pfizer),1 mRNA-1273 (Moderna), 1 J&J	5 BNT 162b2 (Pfizer), 3 mRNA-1273 (Moderna)	BNT 162b2 (Pfizer)	2 BNT 162b2 (Pfizer), 2 mRNA-1273 (Moderna)	7 BNT 162b2 (Pfizer), 16 mRNA-1273 (Moderna)	**Vaccine Type**	BNT162b2 (Pfizer)	BNT162b2 (Pfizer)	BNT162b2 (Pfizer)	BNT162b2 (Pfizer)	mRNA-1273 (Moderna)	mRNA-1273 (Moderna)	All mRNA vaccines except for one
% Patients presenting after second vaccination	100%	71%	88%	83%	100%	87%	**Presentation after 2nd vaccine**	Yes	Yes	Yes	Yes	Yes	Yes	89%
% Patients with prior COVID-19 history	0%	14%	25%	0%	0%	13%	**Prior history of Covid-19?**	Yes, 9 months ago	no	no	no	no	no	11%
% Patients COVID-19 PCR positive	0% (all tested)	0% (6/7 tested)	0% (all tested)	0% (all 6 tested)	0%	0% (19/23 tested)	**Is the patient Covid-19 PCR positive?**	no	no	no	no	no	no	0%
% Patients with COVID nucleocapsid antibody present (% of tested)	0% (6 tested, all negative)	0% (4/7 patients tested, all negative)	n/r	0% (6 tested, all negative)	n/r	n/r	**Does the patient have a nucleocapsid antibody?**	yes	no	n/r	no	n/r	no	5%
% Patients with SARS-CoV-2 spike antibody	100%	67% (4of 6 tested patients, 2 presented after first vaccination)	n/r	100% (all 6 tested)	n/r	n/r	**Does the patient have SARS-CoV-2 spike antibody?**	yes	yes	n/r	yes	n/r	yes	91%
Presentation														
Time between last vaccine and symptom onset, median days, (range)	2 (2-4)	3 (2-7)	3 (1-4)	2.5 (1-16), (5 pts 1-3 days, 1 patient 16 days post first dose)	2.5 (1-5)	2 (1-4)	**Time between last vaccination and symptom onset (days)**	3	1	1	3	4	1	2.4 days
% Patients with chest pain on presentation	100%	100%	100%	100%	100%	100%	**Did the patient have chest pain?**	yes	yes	yes	yes	yes	yes	100%
% Patients with other symptoms (e.g. myalgia, fatigue, fever)	86%	42%	63%	33%	75%	n/r	**Did the patient have other symptoms (e.g. myalgia, fatigue, fever)**	no	yes	yes	yes	yes	Yes	63%

Diagnostic Evaluation														
% Patients with troponin elevation (of tested)	100%	100%	100%	100% (6/6)	100%	100% (23/23)	**Did the patient have troponin elevation?**	yes	yes	yes	yes	yes	yes	100%
Median time to troponin peak after vaccination, days	3	n/r	3	n/r	n/r	n/r	**Median day to troponin peak after vaccination**	4	2	3	3	4	4	3
% Patients with BNP or NT-proBNP elevation (among tested)	83% (5 of 6 tested)	50% (6 tested)	n/r	n/a	50% (2 of 4 tested)	n/r	**Did the patient have a BNP or NT-proBNP elevation?**	n/r	n/r	yes	n/r	n/r	no	61%
% Patients with CRP elevation (among tested)	86% (6 of 7 tested)	71%	88%	100%	100% (3 of 3 tested)	n/r	**Did the patient have CRP elevation?**	yes	n/r	yes	yes	yes	yes	89%
% patients with eosinophilia (among tested)	n/r	n/r	0%	0%	n/r	n/r	**Did the patient have eosinophilia?**	no	n/r	no	mild	no	no	0%
% Patients with abnormal ECG (among tested)	100 % abnormal (86% with ST elevation, 1 with AV dissociation and junctional rhythm)	71% (4 patients with ST elevations, 1 patient with nonspecific ST/T changes)	88% (6 patients with ST elevation, 1 patient peaked T waves, 1 patient normal)	100% (all 6 with ST elevation)	100% (all with ST elevation, 2 with PR depression)	83% (19/23 with ST-segment elevations, T-wave inversions, and nonspecific ST changes)	**Did the patient have an abnormal ECG?**	Yes (ST elevation)	Yes (ST elevation)	Yes (ST elevation)	Yes (ST elevation)	No ischemic changes	Yes (incomplete RBBB and left axis deviation)	87 %
% Patients with abnormal cardiac MRI (among tested)	100% (all with myocardial edema, LGE, hyperemia)	100 % (all with LGE, 1 with wall motion abnormality, 3 with myocardial edema in T2)	100% (all with LGE, 6 with edema)	100% (all with mild subepicardial edema and LGE)	100% (all with LGE, increased T1 and T2 intensity)	100% (8/8 with subepicardial late gadolinium enhancement and/or focal myocardial edema)	**Did the patient have an abnormal cardiac MRI?**	Yes (LGE and myocardial edema in T2 imaging)	Yes (subepicardial enhancement)	Yes (signs of myocardial fibrosis, myocardial hyperemia, and a small pericardial effusion)	Yes (subepicardial LGE of the myocardium)	Yes (patchy mid-myocardial and epicardial LGE with edema)	Yes (mid myocardial and subepicardial linear and nodular LGE and mild hypokinesis)	100%
% Patients with abnormal echocardiogram (among tested)	Abnormal in 29%, normal in % 71 (5/7)	Abnormal in 57% (mild hypokinesis in 3, 1 low LVEF, 1 mild LV enlargement), Normal in 43%	Wall motion abnormality with regional or generalized hypokinesis in all (100%)	33% (2/6 with hypokinetic segments but preserved EF), 67% normal (4 /6)	n/r	LVEF <50% in 17% (4/23), no structural abnormality in any	**Did the patient have an abnormal echocardiogram ?**	n/r	No abnormality noted	normal	Abnormal, wall motion abnormality and mild pericardial effusion, NL LVEF	normal	No wall motion abnormalities, EF preserved	39 %
% Patients with LVEF < 50 % (among tested)	14% (1/7 with LVEF 47%)	14% (1 patient with LVEF 35-40%)	25% (1 patient with LVEF 35%, another 47%)	0%	25 % (1 patient with LVEF 40%)	17 (4/23)	**Did the patient have LVEF<50 %?**	No, (NL LVEF)	No, (NL LVEF)	No, (NL LVEF)	No, (NL LVEF)	No, (NL LVEF)	No, (NL LVEF)	15%
Outcome														

% Patients with symptoms resolved	100%	100%	100%	100%	100%	70% (16/23 patients)	**Did the patient's symptoms resolve?**	yes	yes	yes	yes	yes	yes	89 %
Median hospitalization LOS, days (range)	4 (2-6)	3 (2-4)	n/r (all reported as stable)	6 (4-8)	3 (2-4)	n/r	**Hospitalization LOS (days)**	7	6	7	7	n/r	4	mean 4.6 days
% Patients treated with medications for myocarditis	86% with NSAIDs, % 57 with steroids , 57% with IVIG, %43 with famotidine, % 14 with colchicine	43% with NSAIDS, 43% with colchicine, 43% with famotidine, 14% with steroids	38% with NSAID , 25 % with colchicine, 13% with steroids	100 % with NSAID and colchicine	50% with NSAIDS, 75% with colchicine, 25% with steroids	n/r	**Treatment of myocarditis**	none	"anti-inflammatory " medications	Treated with IVIG, NSAID	bisoprolol acetylsalicylic acid, steroid	beta- blocker	lisinopril, carvedilol	Varying treatment strategies

BNP elevation: BNP ≥ 35 pg/ml, NT-proBNP elevation: NT-proBNP≥125 pg/ml; CRP elevation: CRP≥ 3mgl/L, LGE: Late gadolinium enhancement, n/r: not reported, LOS: length of stay, LVEF: left ventricular ejection fraction, NSAID: nonsteroidal anti-inflammatory drugs, MRI: magnetic resonance imaging, IVIG: Intravenous immune globulin; ECG: electrocardiogram; BNP: B-type natriuretic peptide; NT-proBNP: N-terminal-pro-BNP; CRP: C-Reactive protein

Figure Legends

Figure 1. CDC working case definitions for acute myocarditis and acute pericarditis. Adapted from [5]

Figure 2. Predicted benefits of reduction in COVID-19 related hospitalizations and death and risks of myocarditis after second of dose mRNA COVID-19 vaccination by age group. Adapted from [5] (COVID-19 mRNA vaccines in adolescents and young adults: Benefit-risk presentation). Predictions for hospitalization and myocarditis rates were calculated for every million doses of mRNA vaccine based on hospitalization rates from Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET) as of May 22nd.[72] Benefit/Risk were calculated over 120 days. To meet the ECG or rhythm monitoring criterion, must include at least one of the following: ST segment or T wave abnormalities, paroxysmal or sustained atrial, supraventricular or ventricular arrhythmias, AV nodal conduction delays or intraventricular conduction defects

† Using either the original or revised Lake Louise criteria [73], ‡Using the Dallas criteria [74]

§ Autopsy cases may be classified as pericarditis on basis of meeting histopathologic criteria of the pericardium

Figure 3. Potential risk of myocarditis with COVID-19 mRNA vaccination in the 120 days following vaccination and predicted prevention of COVID-19 cases, COVID-19 related hospitalizations, ICU admissions and deaths according to age groups and sex. Adapted from [5] (COVID-19 mRNA vaccines in adolescents and young adults: Benefit-risk presentation).

Predictions for hospitalization and myocarditis rates were calculated for every million doses of mRNA vaccine based on hospitalization rates from Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET) as of May 22nd. Benefit/Risk were calculated over 120 days.

CDC Working Case Definitions

Acute Myocarditis

Probable Case

- Presence of ≥ 1 new or worsening of the following clinical symptoms
  - chest pain/ pressure/ discomfort
  - dyspnea/shortness of breath
  - palpitations
  - syncope
- AND ≥ 1 new finding of
  - elevated troponin above upper limit of normal
  - abnormal ECG or rhythm monitoring findings consistent with myocarditis*
  - abnormal cardiac function or wall motion abnormalities on echocardiogram
  - cardiac MRI findings consistent with myocarditis †
- AND no other identifiable cause of the symptoms and findings

Confirmed Case

- Presence of ≥ 1 new or worsening of the following clinical symptoms
  - chest pain/ pressure/ discomfort
  - dyspnea/shortness of breath
  - palpitations
  - syncope
- AND
  - histopathologic confirmation of myocarditis ‡
  - OR
  - elevated troponin above upper limit of normal AND cardiac MRI findings consistent with myocarditis†
- AND no other identifiable cause of the symptoms and findings

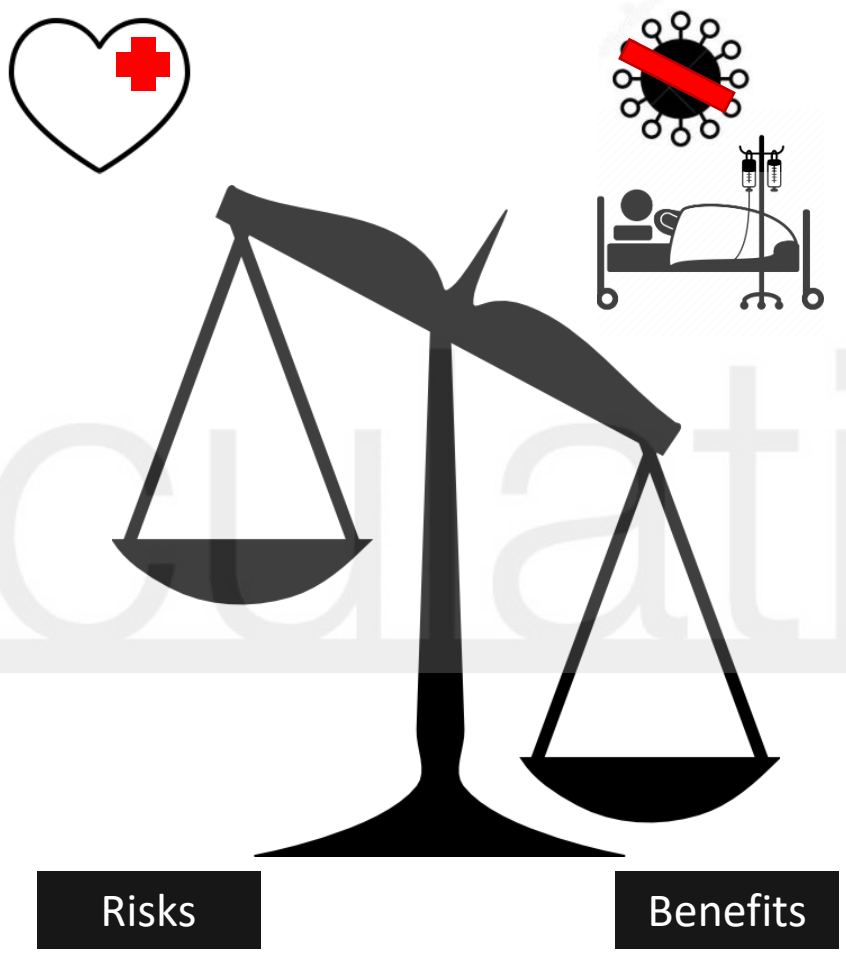
Acute Pericarditis

Probable Case

- Presence of ≥ 2 new or worsening of the following clinical symptoms
  - acute chest pain (typically described as pain made worse by lying down, deep inspiration, cough, and relieved by sitting up or leaning forward, although other types of chest pain may occur) §
  - pericarditis rub on exam
  - new ST-elevation or PR-depression on ECG
  - new or worsening pericardial effusion on echocardiogram or MRI
- Autopsy cases may be classified as pericarditis on basis of meeting histopathologic criteria of the pericardium

Potential Risk of Myocarditis with COVID-19 Vaccination

	Females	Males
12-17 Years	8-10 myocarditis cases	56-69 myocarditis cases
18-24 Years	4-5 myocarditis cases	45-56 myocarditis cases
24-29 Years	2 myocarditis cases	15-18 myocarditis cases



Potential Prevention of COVID-19, Hospitalizations, ICU admissions and Death with COVID-19 Vaccination

	Females	Males
12-17 Years	8500 Covid-19 cases 183 Hospitalizations 38 ICU admissions 1 Death	8500 Covid-19 cases 183 Hospitalizations 38 ICU admissions 1 Death
18-24 Years	14,000 Covid-19 cases 1127 Hospitalizations 93 ICU admissions 13 Deaths	12,000 Covid-19 cases 530 Hospitalizations 127 ICU admissions 3 Deaths
24-29 Years	15,000 Covid-19 cases 1459 Hospitalizations 87 ICU admissions 4 Deaths	15,000 Covid-19 cases 936 Hospitalizations 215 ICU admissions 13 Deaths

Potential prevention of COVID-19 related myocardial injury, MIS-C, post-acute sequelae SARS-CoV-2 infection

for every million second dose COVID-19 mRNA vaccinations