United States Senate

COMMITTEE ON
HOMELAND SECURITY AND GOVERNMENTAL AFFAIRS
WASHINGTON, DC 20510–6250

December 1, 2023

The Honorable Lloyd J. Austin III
Secretary
Department of Defense

Dear Secretary Austin:

For over two years, the Department of Defense (DoD) has failed to be transparent to my office and the public about the adverse events associated with the COVID-19 vaccines. As DoD stonewalled my requests for data that could provide service members and their families much-needed information about the health consequences of the vaccines, DoD pushed these potentially harmful products onto service members through a vaccine mandate.[1] Many service members were wrongfully discharged due to their refusal to get the COVID-19 vaccine.[2]

It now appears that the U.S. Army is allowing discharged service members to "request a correction to military personnel records, including records regarding the characterization of discharge."[3] The Army reportedly included this language in a letter sent "to approximately 1,900 individuals who had previously been separated for refusal to obey the mandatory COVID vaccination order."[4] Allowing service members to *request* to correct their records or potentially apply to return to service falls well short of providing those brave men and women any kind of compensation resulting from their involuntary separation and a profound apology for upending their lives.

---

[1] Memorandum from Secretary of Defense Lloyd Austin to Senior Pentagon Leadership, et al. (Aug. 24, 2021) (available at https://media.defense.gov/2021/Aug/25/2002838826/-1/-1/0/MEMORANDUM-FOR-MANDATORYCORONAVIRUS-DISEASE-2019-VACCINATION-OF-DEPARTMENT-OF-DEFENSE-SERVICEMEMBERS.PDF).

[2] Rebecca Kheel, Protections for troops booted over COVID vaccine mandate added to House defense bill, Military.com, June 21, 2023, https://www military.com/daily-news/2023/06/21/protections-troops-booted-over-covid-vaccine-mandate-added-house-defense-bill html (stating more than 8000 service members were discharged under the vaccine mandate).

[3] Danielle Wallace, Army sends letter to troops dismissed for refusing COVID vaccine amid military's recruitment woes, Fox News, Nov. 21, 2023, https://www.foxnews.com/us/army-sends-letter-troops-dismissed-refusing-covid-vaccine-amid-militarys-recruitment-woes; Kelly Laco, Army slammed for desperate attempt to win back favor with soldiers fired for refusing the COVID vaccine as the military enters 'panic mode' due to severe recruitment challenges, Daily Mail, Nov. 21, 2023, https://www.dailymail.co.uk/news/article-12776347/Army-slammed-desperate-attempt-win-favor-soldiers-fired-refusing-COVID-vaccine-military-enters-panic-mode-severe-recruitment-challenges html.

[4] Danielle Wallace, Army sends letter to troops dismissed for refusing COVID vaccine amid military's recruitment woes, Fox News, Nov. 21, 2023, https://www.foxnews.com/us/army-sends-letter-troops-dismissed-refusing-covid-vaccine-amid-militarys-recruitment-woes.

If DoD wants to restore its credibility and trust among current and prospective service members, it needs to show that it is willing to be transparent and forthcoming regarding the safety of the COVID-19 vaccines.[5]

The health and well-being of all service members is crucial to military readiness, which is why I have pressed DoD for information on its inappropriate and dangerous COVID-19 vaccine mandates and its tracking of increases in adverse medical conditions in the Defense Medical Epidemiology Database (DMED).

Based on reports I continue to receive from DoD whistleblowers, I am concerned that adverse medical events are persistent in DoD. DoD previously confirmed to my office that DMED data from a DoD whistleblower accurately showed increases in at least 11 serious registered medical diagnoses in DMED in 2021 compared to a five-year average from 2016-2020.[6] These conditions included:[7]

- Myocarditis, unspecified: 130.5% increase
- Malignant neoplasms of esophagus: 56.6% increase
- Pulmonary embolism: 41.2% increase
- Ovarian dysfunction: 38.2% increase
- Complications and ill-defined descriptions of heart disease: 37.7% increase

Last month, DoD admitted to my office that it has "identified an increased incidence of very rare conditions – myo/pericarditis – during COVID-19 vaccine introduction in 2021."[8] In its response, DoD attempted to downplay the significance of this by stating:

> It is difficult to report precise numbers of adverse events following immunization since establishing a causal relationship between vaccination and a clinical diagnosis can be challenging. **Nonetheless, the military has identified 80-90 cases of myo/pericarditis in Service members following administration of more than 4 million COVID-19 vaccine doses in this population.**[9]

It is clear, based on this response, that DoD still does not fully appreciate or comprehend the variety of health risks that are associated with the COVID-19 vaccines that it required all service members to receive.

---

[5] Ellen Mitchell, Army revamps recruiting in face of enlistment shortfalls, The Hill, Oct. 3, 2023, https://thehill.com/policy/defense/4236203-army-revamps-recruiting-in-face-of-enlistment-shortfalls/.
[6] Letter from Gilbert Cisneros, Jr., Dep't of Defense, to Sen. Ron Johnson, Ranking Member, Permanent Subcomm. on Investigations, July 5, 2023, https://www.ronjohnson.senate.gov/services/files/425B7B09-7BF3-4588-9231-5C7D561B05D3 at 8.
[7] Letter from Sen. Ron Johnson, Ranking Member, Permanent Subcomm. on Investigations, to Lloyd Austin, Sec., Dep't of Defense, Mar. 21, 2023, https://www ronjohnson.senate.gov/services/files/C7B70308-BB0B-451F-83B5-8B354BF83862.
[8] Letter from Ashish Vazirani, Dep't of Defense, to Sen. Ron Johnson, Ranking Member, Permanent Subcomm. on Investigations, Oct. 11, 2023 (enclosed).
[9] *Id.* (emphasis added).

Over the last two years I have sent over 60 public letters to federal agencies, including DoD, on various aspects of the pandemic. The overall lack of transparency from you and your colleagues on COVID-19 vaccine safety and efficacy is appalling.

I am particularly disappointed with DoD's failure to respond to my December 19, 2022 letter requesting Tricare data on claims filed after COVID-19 vaccination.[10] DoD officials have ignored multiple requests from my staff over the last three months for an update on the status of DoD's response to the December 2022 letter. It is unacceptable that DoD has not responded at all to that request and completely unprofessional that your representatives have ignored inquiries from my staff on this matter.

In addition, I am still waiting to receive complete answers to questions my staff sent DoD following the publication of a news article that reported on more DMED data from a DoD whistleblower. According to the article, the whistleblower presented increases in DMED medical diagnoses in 2021 compared to the five-year average from 2016-2020 including, "exposure to forces of nature (773 percent); water transport accidents (7,400 percent); land transport vehicle accidents (526 percent); suicide attempts (33 percent); assault (828 percent); slipping, tripping, stumbles, and falls (471 percent); and intentional self-harm (147 percent)."[11]

Based on information from the whistleblower, the article noted, "[h]istorically, if the Pentagon noticed a trend in certain areas such as abuse and suicide, he said, the department would hold a safety stand-down—a military-wide mandatory training and review in which all commands require 100 percent participation."[12] Below are my office's questions based on this article that remain unanswered:

1. Is DoD aware of the increases of the registered diagnoses in DMED highlighted above in 2021 compared to the five-year average (2016-2020)?

2. Does DoD agree with the reported increases of the registered diagnoses in DMED highlighted above in 2021 compared to the five-year average (2016-2020)?

3. Is DoD aware whether the registered diagnoses in DMED highlighted above increased in 2022 compared to 2021?

4. Is the following accurate: "If the Pentagon noticed a trend in certain areas such as abuse and suicide, he said, the department would hold a safety stand-down—a military-wide mandatory training and review in which all commands require 100 percent

[10] Letter from Sen. Ron Johnson, Ranking Member, Permanent Subcomm. on Investigations, to Lt. Gen. Ronald J. Place, Dir., Defense Health Agency, Dec. 19, 2023, https://www ronjohnson.senate.gov/services/files/64448E0A-264E-48C0-83C4-26F22424546A.
[11] J.M. Phelps, EXCLUSIVE: Whistleblower Who Disclosed Myocarditis Spike in Military After COVID Vaccine Rollout Goes Public, Epoch Times, Aug. 30, 2023, https://www.theepochtimes.com/us/exclusive-whistleblower-who-disclosed-myocarditis-spike-in-military-after-covid-vaccine-goes-public-5477416?utm_source=partner&utm_campaign=TheChiefNerd&src_src=partner&src_cmp=TheChiefNerd.
[12] *Id.*

participation"?[13]

5. What steps, if any, has DoD taken to investigate the increases of the registered diagnoses in DMED highlighted above?

6. Has DoD issued any mandatory training or review as a result of the increases of the registered diagnoses in DMED highlighted above?

7. When were the following medical diagnoses made available to enter into DMED: exposure to forces of nature; water transport accidents; land transport vehicle accidents; suicide attempts; assault; slipping, tripping, stumbles, and falls; and intentional self-harm. Is it common for non-medical diagnoses to be included in DMED (like water transport accidents)?

In addition to the questions above, I request the following information based on the Army's letter to discharged service members:

1. Does DoD intend to provide compensation to individuals who were "involuntarily separated for refusal to receive the COVID-19 vaccination"?[14] If so, how should those individuals obtain their compensation and when will those individuals receive compensation? If not, why not?

2. How will DoD review requests from service members who were "involuntarily separated for refusal to receive the COVID-19 vaccination" to correct "military personnel records, including records regarding the characterization of discharge"?[15] What, if any, specific criteria will DoD use in order to determine whether a former service member is eligible for such a correction? How long does this review process take? How will DoD change the "characterization of discharge" on individuals' records?[16]

3. From August 24, 2021 to September 1, 2023, how many individuals who were "involuntarily separated for refusal to receive the COVID-19 vaccination" have requested, received, or have been denied "correction[s] to military personnel records, including records regarding the characterization of discharge"?[17] In a separate chart, please list the types of characterizations of discharge and specify how many requests for corrections for each characterization were received, granted, or denied.

---

[13] *Id.*
[14] Danielle Wallace, Army sends letter to troops dismissed for refusing COVID vaccine amid military's recruitment woes, Fox News, Nov. 21, 2023, https://www.foxnews.com/us/army-sends-letter-troops-dismissed-refusing-covid-vaccine-amid-militarys-recruitment-woes; Kelly Laco, Army slammed for desperate attempt to win back favor with soldiers fired for refusing the COVID vaccine as the military enters 'panic mode' due to severe recruitment challenges, Daily Mail, Nov. 21, 2023, https://www.dailymail.co.uk/news/article-12776347/Army-slammed-desperate-attempt-win-favor-soldiers-fired-refusing-COVID-vaccine-military-enters-panic-mode-severe-recruitment-challenges html.
[15] *Id.*
[16] *Id.*
[17] *Id.*

4. After September 1, 2023, how many individuals who were "involuntarily separated for refusal to receive the COVID-19 vaccination" have requested, received, or have been denied "correction[s] to military personnel records, including records regarding the characterization of discharge"?[18] In a separate chart, please list the types of characterizations of discharge and specify how many requests for corrections for each characterization were received, granted, or denied.

5. For service members who were "involuntarily separated for refusal to receive the COVID-19 vaccination" and apply to return to service, how long will it take those individuals to be reinstated?[19] What, if any, specific criteria will DoD use in order to determine whether a former service member is eligible to be reinstated? What consequences, if any, will those individuals face if they are reinstated (e.g., demotion or relocation)?

6. Will other branches of the military issue similar letters to service members who were discharged after refusing to receive the COVID-19 vaccine? If so, what other branches, when will those letters be sent, and how many individuals from each branch will receive a letter?

Inquiries and requests for information concerning the health and well-being of service members should never be ignored, particularly when those questions are from members of Congress and their staff. During your January 19, 2021 nomination hearing in front of the Senate Armed Services Committee, you committed to providing records to Congressional committees upon request.[20] Under your leadership, DoD's overall lack of responsiveness and transparency regarding the COVID-19 vaccines calls into question your previous commitment before the Senate. I look forward to your complete responses to all of my requests by no later than December 15, 2023. Thank you for your attention to this matter.

Sincerely,

Ron Johnson
Ranking Member
Permanent Subcommittee on Investigations

Enclosure

[18] *Id.*
[19] *Id.*
[20] *Hearing to examine the expected nomination of Lloyd J. Austin III, to be Secretary of Defense*, 117th Cong. (2021) *video available at* https://www.armed-services.senate.gov/hearings/21-01-19-nomination.

cc: The Honorable Richard Blumenthal
Chairman
Permanent Subcommittee on Investigations

The Honorable Christine Wormuth
Secretary of the Army

The Honorable Carlos Del Toro
Secretary of the Navy

The Honorable Frank Kendall
Secretary of the Air Force

General Eric Smith
Commandant of the Marine Corp

General B. Chance Saltzman
Chief of Space Operations

Admiral Linda Fagan
Commandant of the U.S. Coast Guard

The Honorable Robert Storch
Inspector General
Department of Defense

The Honorable Joseph Cuffari
Inspector General
Department of Homeland Security

Enclosure

UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, D.C. 20301-4000

PERSONNEL AND
READINESS

OCT 1 1 2023

The Honorable Ron Johnson
Ranking Member
Permanent Subcommittee on Investigations
Committee on Homeland Security and
Governmental Affairs
United States Senate
Washington, DC 20510

Dear Senator Johnson:

Thank you for your July 19, 2023 letter to the Secretary of Defense regarding the Defense Medical Epidemiology Database. This letter supplements the Department's previous responses, dated July 5, 2023 and February 15, 2022, on this topic.

Enclosed are responses to each of the comments and questions posed in your letter. Thank you for your continued strong support for the health and well-being of our Service members.

Sincerely,

Ashish S. Vazirani
Acting

Enclosure:
As stated

cc:
The Honorable Richard Blumenthal
Chairman
Permanent Subcommittee on Investigations
Committee on Homeland Security and
Governmental Affairs

Enclosure

1. *Please explain DoD accounted for individuals who had prior COVID-19 infection and received COVID-19 vaccination when determining that for certain conditions, "new case rate[s] [were] higher among Service members with a prior SARS-CoV-2 infection compared to those with a prior COVID-19 vaccination. This suggests that it was more likely to be SARS-COV-2 infection and not COVID-19 vaccination that was cause of these increased cases in 2021."*

   Response: Yes, the Department of Defense (DoD) accounted for individuals who had prior coronavirus disease 2019 (COVID-19) infection and received COVID-19 vaccination. Those in the prior COVID-19 vaccination group included those with a COVID-19 vaccination with or without documented COVID-19 infection. Those in the prior COVID-19 infection group included those with a COVID-19 infection with or without documented COVID-19 vaccination.

2. *Have any Service members experienced adverse medical conditions associated with the COVID-19 vaccines? If so, how many and what are those conditions? How did DoD make this determination? Has DoD conducted any independent investigation into whether adverse medical conditions are associated with the COVID-19 vaccines? If so, what has DoD found? If not, why not?*

   Response: As expected after administration of any medication or immunization to large numbers of people, adverse events have been reported after COVID-19 vaccination. DoD routinely partners with the Centers for Disease Control and Prevention (CDC) to review all reported adverse events following immunizations.

   DoD identified an increased incidence of very rare conditions – myo/pericarditis – during COVID-19 vaccine introduction in 2021. DoD professionals promptly shared this observation with CDC and other Federal partners, who later validated that these rare adverse events were also observed in the general U.S. population and the global population. DoD's initial investigation of myo/pericarditis is detailed in reference (a). DoD's subsequent experience with rare myo/pericarditis following COVID-19 vaccination remained consistent with the global experience, as detailed in references (b) and (c).

   It is difficult to report precise numbers of adverse events following immunization since establishing a causal relationship between vaccination and a clinical diagnosis can be challenging. Nonetheless, the military has identified 80-90 cases of myo/pericarditis in Service members following administration of more than 4 million COVID-19 vaccine doses in this population.

   Similar to the U.S. and global experience, DoD also noted mild transient adverse events, such as soreness at the injection site, following COVID-19 vaccination. DoD did not receive higher-than-expected numbers of reports of other serious adverse events, beyond myo/pericarditis, following COVID-19 vaccination.

   The attachment, "Department of Defense Report on Cardiac and Kidney Issues in Service Members Prior to and Following the COVID Vaccine Requirement," demonstrates the

detailed analyses of a number of serious medical conditions that were reviewed in relationship to COVID-19 vaccination. This report validates the higher-than-expected rate of myo/pericarditis following COVID-19 vaccination. These analyses did not find higher-than-expected rates of other cardiac or kidney-related diagnoses after vaccination. Importantly, these analyses found rates of all examined diagnoses after SARS-CoV-2 infection to be significantly higher than rates after vaccination, consistent with the U.S. and global experience.

References:

(a) Montgomery J, Ryan M, Engler R, et al. Myocarditis Following Immunization With mRNA COVID-19 Vaccines in Members of the US Military. *JAMA Cardiol*. 2021;6(10):1202-1206. doi:10.1001/jamacardio.2021.2833.

(b) Ryan M, Montgomery J. Myopericarditis after COVID-19 vaccination: unexpected but not unprecedented. *Lancet Respir Med*. 2022;10(7):624-625. doi:10.1016/S2213-2600(22)00091-1.

(c) Fairweather D, Beetler DJ, Di Florio DN, Musigk N, Heidecker B, Cooper LT Jr. COVID-19, Myocarditis and Pericarditis. *Circ Res*. 2023;132(10):1302-1319. doi:10.1161/CIRCRESAHA.123.321878.

Attachment

Report to the Committee on Armed Services of the House of Representatives

Department of Defense Report on Cardiac and Kidney Issues in Service Members Prior to and Following the COVID Vaccine Requirement

September 2023

The estimated cost of this report or study for the Department of Defense is approximately $29,000 in Fiscal Years 2021 – 2022. This includes $6,470 in expenses and $23,000 in DoD labor.

Generated on 2022Dec15 RefID: C-5441633

TABLE OF CONTENTS

PURPOSE

This report is in response to House Report 117–397, page 186, accompanying H.R. 7900, the National Defense Authorization Act for Fiscal Year 2023, "Department of Defense Report on Cardiac and Kidney Issues in Service Members Prior to and Following the COVID Vaccine Requirement," which requests an analysis of prevalence and incidence of kidney and cardiac complications in Service members in 2019 compared to the same measures in 2021 and 2022. The report analyzes annual incidence of select kidney and cardiac conditions identified as rare adverse outcomes following identified coronavirus disease 2019 (COVID-19) vaccination among Service members in the Active Component between Calendar Years (CY) 2019 and 2022. Incidence rates for each adverse outcome (myocarditis, pericarditis, acute myocardial infarction (AMI), chronic kidney disease (CKD), and acute kidney injury (AKI)) were stratified by receipt of COVID-19 vaccine and history of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection with confounding factors identified and adjusted when possible. As a secondary analysis, the overall annual prevalence of each outcome was described and discussed.

INTRODUCTION

On December 11, 2020, the Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for the Pfizer-BioNTech BNT162b2 vaccine. Immediately thereafter, on December 14, 2020, the Department of Defense (DoD) mobilized to begin voluntarily administering the first doses of Pfizer-BioNTech BNT162b2 vaccine to military communities with priority given to frontline health care workers at highest risk of exposure to SARS-CoV-2 infection. Two dose Moderna mRNA-1273 and single dose Johnson & Johnson JNJ-78436735 vaccines were added to the approved distribution list as they received subsequent EUAs from FDA. A year later in December 2021, over 6.4 million doses of vaccine had been distributed. The Pfizer-BioNTech and Moderna vaccines would both go on to receive full FDA approval in August 2021 and January 2022, respectively.

Eight months after DoD vaccination distribution began, on August 24, 2021, the Secretary of Defense released a memorandum requiring that all members of the Armed Forces under DoD authority on active duty or in the Ready Reserve (including National Guard) receive a COVID-19 vaccination as part of their readiness requirements. Mandatory vaccinations are familiar to all Service members, with as many as 17 different vaccines required for military personnel in the "Joint Instruction on Immunizations and Chemoprophylaxis" as necessary to mitigate risk for various infections. Some vaccines are only required to be administered in certain special, risk-based geographical and occupational circumstances of the individual Service member. Other vaccinations, like the annual influenza vaccine, are required for all Service members regardless of the circumstances, unless the Service member is covered by an administrative (including religious) or medical exemption. All vaccination requirements, including COVID-19 when it was in effect, are in place to keep the Armed Force as a whole healthy and medically ready.

BACKGROUND

COVID-19 Vaccination Associated Cardiac Adverse Events

Severe adverse events following COVID-19 vaccinations remain rare and studies continue to support that the benefit of vaccination outweigh the risk.[1] Although extremely rare, myocarditis and pericarditis are reported following COVID-19 vaccination particularly in adolescents and young males.[2] Myocarditis is the inflammation of cardiac muscle predominantly caused by viruses including SARS-CoV-2 and other infections (e.g., influenza, hepatitis B, staphylococcus), toxins (e.g., alcohol, heavy metals, chemotherapy), and systemic immune-related diseases (e.g., sarcoidosis, celiac disease). Vaccinations such as smallpox vaccine has been causally linked to hypersensitivity myocarditis with numerous studies reporting that more than expected incidence of myocarditis and pericarditis have been found associated with COVID-19 mRNA vaccines (Pfizer-BioNTech BNT162b2 and Moderna mRNA-1273).[3,4]

The classic clinical presentation of COVID-19 vaccine-related myocarditis is acute chest pain with an average time of onset of 3 days (range 1-28 days) after vaccination. Pericarditis, an inflammation of the pericardial sac that lines the outside of the heart, occurs most often in conjunction with myocarditis, but when observed in isolation, the onset of chest pain may be somewhat later, with an average of 5 days (range 1-28 days) after vaccination.[4,5] The incidence of myocarditis as an adverse event following COVID-19 vaccination is highly dependent on the sex and age of the patient, as well as the vaccine dose and type. As a vaccine-related safety signal, myocarditis has been most firmly established in younger (ages 18-29 years) male patients after receiving their second dose of mRNA (Pfizer-BioNTech BNT162b2 and Moderna mRNA-1273) vaccine. A safety signal for myocarditis has not been clearly established after non-mRNA vaccines (e.g., Johnson & Johnson JNJ-78436735), after first dose of vaccine, or in patients over age 40 years.[6] Most of the clinical presentations have been mild for this very rare complication which continues to support the broader Centers for Disease Control (CDC) finding that the benefit of vaccination outweighs the risk.[7]

Myocarditis Incidence in the Vaccine Adverse Event Reporting System (VAERS) and the Military Health System (MHS)

Both the CDC and the FDA monitor for COVID-19 vaccination adverse events using a voluntary reporting system called VAERS. Anyone, including patients, can report any safety concerns related to vaccines in VAERS. A review of the VAERS safety data between December 2020 and August 2021 found a small but increased risk for myocarditis after receipt of mRNA COVID-19 vaccines. In the VAERS data review of myocarditis cases, 87 percent of those hospitalized had initial symptoms resolved by the discharge date and no cases of severe manifestation required transplant or ventricular assist device.[3]

Myocarditis occurring after administration of COVID-19 mRNA vaccines (Pfizer-BioNTech BNT162b2 and Moderna mRNA-1273) was first noted by the U.S. military in early 2021 reporting on a case series of 23 male military members who were diagnosed with myocarditis within 4 days of receipt of COVID-19 vaccine.[8] The MHS-specific case series observed a median age of 25 with all military members who were previously healthy with no prior history of

cardiac disease. Most cases were related to second dose of mRNA vaccine, presenting within 50 hours of receiving the vaccine with no concurrent SARS-CoV-2 infection. All patients have either recovered and or were recovering at the time results were published.

Incidence of Cardiovascular Complications – Comparison between SARS-CoV-2 Infection and COVID-19 Vaccination

COVID-19 vaccination is associated with reduced risk for cardiovascular complications such as AMI after SARS-CoV-2 infection compared to those who have never been vaccinated.[9] CDC continues to recommend COVID-19 vaccination given that many more adverse outcomes related to SARS-CoV-2 infection, including death, can be avoided even among the groups at highest risk for myocarditis as an adverse event from immunization. In the highest risk group of males ages 18-29, 300 hospitalizations, 60 ICU admissions and 3 deaths due to SARS-CoV-2 infection related complications would be prevented if vaccination had been provided compared to instead preventing 22-27 COVID-19 vaccination associated myocarditis incidents should vaccination had not occured.[6]

Furthermore, data from 40 health care systems reviewing over 14 million cases from January 1, 2021 to January 31, 2022, continue to support the benefit of COVID-19 vaccination with a significantly higher cardiac complication incidence associated with SARS-CoV-2 infection than after mRNA COVID-19 vaccination for both males and females in all age groups. Analysis also confirmed the higher incidence of myocarditis or pericarditis after mRNA COVID-19 vaccination in males, with incidence of 0-35.9 per 100,000 in males compared to 0-10.9 for females across age groups. The 12-17 age group had the highest incidence of mRNA COVID-19 vaccine associated cardiac complication, with a 1.8-5.6 times higher risk for cardiac complications after SARS-CoV-2 infection than after vaccination.[10]

Kidney Complications with COVID-19 Vaccination

Serious adverse kidney events following COVID-19 vaccine are extremely rare and vaccinations continue to provide protective benefits that far outweigh the known associated kidney complications related to SARS-CoV-2 infection. Rare cases of new onset kidney disease have been reported in literature since 2020 with early complication rates reported at 0.46 percent of all adverse events in VAERS in January 2021 and most recent analysis showing kidney complication reported at incidence of 0.006 percent based on review of VAERS data.[11,12]

The majority of reported kidney disease developed de novo which would be captured under the major category of AKI, also known as acute kidney failure. There is no specific clinical presentation although edema was reported as the most common symptom in addition to hematuria and proteinuria. Various kidney pathologies have been reported with minimal change disease observed as the most common pathology.[13,14] Pathogenesis of COVID-19 vaccine associated kidney complications is unknown although T-cell mediated immune dysregulation causing podocyte damage is one of the proposed theories.[13,14]

A causal relationship between vaccine and AKI cannot be made given many confounding factors such as advanced age, underlying kidney disease, and concurrent infections that independently

predispose increased risk for AKI regardless of vaccination administration. Review of AKI cases in the self-reported VAERS from December 2020 to June 2021 showed that the majority of AKI cases potentially associated with COVID-19 vaccination was reported among individuals of advanced age (ages ranging from 59.75 to 68.41 years). Additionally, more than half of this group also had existing comorbidities such as diabetes, hypertension and heart disease. The most common cause of VAERS reported AKI was volume depletion and sepsis, which again can independently cause AKI. Most cases of AKI developed within 2 weeks of vaccination primarily related to mRNA vaccine type.[12] Fortunately, in two separate systematic reviews of kidney complications post- COVID-19 vaccination, the majority of kidney dysfunction returned to baseline within 90 days of vaccination.[13,14]

AKI is a well-recognized complication that is commonly associated with SARS-CoV-2 infection, with a wide range of incidence rate among hospitalized patients with some reports as high as 46 percent.[15,16,17] The most common cause of AKI was acute tubular necrosis associated with multi-organ failure and shock. In critically ill adults with SARS-CoV-2 infection, AKI often required renal replacement therapy (e.g., dialysis) with mortality up to 58 percent, with more than one-third having persistent need for renal replacement therapy upon discharge from the hospital.[18] Underlying CKD is also a clearly associated risk factor for severe disease with increased risk for mortality associated with SARS-CoV-2 infection. Mortality is significantly higher in those on renal replacement therapy and in kidney transplant recipients.[19]

METHODS

The primary data source for this analysis is the Defense Medical Surveillance System (DMSS), a continuously expanding relational database of personnel demographic and medical data.[20] The DMSS contains records of ambulatory encounters and hospitalizations of Active Component members of the U.S. Armed Forces when reimbursed through TRICARE. Also included are medical encounter data from the Theater Medical Data Store (TMDS), which includes diagnoses of deployed Service members. In addition, the DMSS contains immunization records for Service members from the MHS Information Platform. Due to a gap in immunization records for Air Force members identified at the time of the analysis, immunization data for Air Force members who were missing immunization records in the DMSS were extracted from the Aeromedical Services Information Management System.

The Armed Forces Health Surveillance Division maintains a list of COVID-19 infections among Service members which is updated daily. The list is comprised of reverse transcription-polymerase chain reaction and antigen test laboratory confirmed SARS-CoV-2 infections, as well as medical event reports of SARS-CoV-2 infection from Disease Reporting System Internet. For the purpose of this analysis, SARS-CoV-2 infections were also identified from the DMSS medical encounter data using the ICD-10 code U07.1. A 90-day incidence rule was applied, such that an individual could qualify as having a repeat SARS-CoV-2 infection if at least 90 days had passed since the last diagnosis or positive laboratory test.[21]

To measure obesity status, height and weight data collected from routine medical appointments were extracted from the MHS Data Repository and MHS GENESIS Vitals table in the Medical Data Repository, as well as height and weight information recorded in the electronic annual

Periodic Health Assessment data in DMSS. Individuals were categorized as obese during a given CY if they had a record Body Mass Index (BMI) greater than or equal to 30 where the height and weight measurement were taken that year.[22] If they only had records indicating a BMI less than 30 then they were classified as not obese for that year. If they had no height and weight records, then they were classified as having an unknown weight status for that year. Height and weight measurements were excluded if they occurred within 280 days of a female Service member's medical encounter that included a diagnosis for pregnancy, childbirth, and the puerperium (ICD-10 codes beginning with "O").

This study assessed three cardiac conditions that were most frequently associated with COVID-19 vaccine complications (myocarditis, pericarditis, and AMI) and two categories of kidney conditions that would broadly capture majority of COVID-19 vaccine complications (AKI and CKD). Some case definitions for each condition were referenced from a Department of Veterans Affairs study[23] comparing safety of two versions of COVID-19 vaccines: cases of myocarditis, pericarditis, AMI, and AKI were defined by having at least two medical encounters (inpatient, outpatient, or TMDS) within 60 days of each other with a qualifying diagnosis in any diagnostic position. The incident date was defined as the first qualifying encounter of which there were two within 60 days. Cases of CKD were defined by having at least two medical encounters within 730 days (2 years) of each other with a qualifying diagnosis in any diagnostic position. The incident date was defined as the date of the first-ever encounter with a diagnosis of CKD. The ICD-9 and ICD-10 codes used to define the cases are included in Appendix A, Tables A1-A5.

For each Service member, the number of days in active military service was ascertained and aggregated for each CY between 2019 and 2021. The resultant annual totals were expressed as person-years of service and used as the denominators for the calculation of annual incidence rates for each of the five outcomes. For each outcome, person time was censored at the date of the incident diagnosis and prevalent cases (i.e., cases identified prior to the start of the surveillance period in 2019) were excluded. "At risk" periods for each of the outcomes was categorized as the 45-day period following SARS-CoV-2 infection, and the 21-day period following receipt of any dose of a COVID-19 vaccine (Appendix A, Table A6). The 45-day period following SARS-CoV-2 infection was chosen to represent a general average of variable time to symptom resolution that are reported in literature. For mild acute illness, symptoms may resolve in a few days to 2 weeks whereas prolonged recovery time for months has been observed in those with severe disease. To ensure optimal inclusion of the most appropriate clinical cases and to avoid potential confounding factors, a 45-day at risk period was chosen. The 21-day at risk period following COVID-19 vaccination was chosen to be aligned with at-risk timelines that are most commonly reported in literature, federal vaccine injury compensation programs (using 0-21 day time window for smallpox vaccine associated myocarditis), and review of data from VAERS. Person time periods considered to be not at risk for the outcome due to either SARS-CoV-2 infection or vaccination with a COVID-19 vaccine were divided into two categories: infection or vaccination occurred greater than 45 days or 21 days ago, respectively, or no previous infection or vaccination. However, for CKD, the "at risk" period following SARS-CoV-2 infection and COVID-19 vaccination was categorized as 180 days instead of 45 days to ensure inclusion of all potential CKD cases. Although CKD is defined as having a decrement in kidney function that lasts for at minimum 3 months (based on references from the Kidney Disease Improving Global Outcomes and Kidney Disease Outcomes Quality Initiative), the at-

risk period for CKD was extended to 180 days to allow adequate time for follow up with a provider and to mitigate risk for exclusion of potential cases. Incidence rates were calculated per 100,000 person-years of Active Component service.

A multivariable Poisson regression model was used to calculate the adjusted incidence rate ratios for each of the five outcomes for CY 2021 by "at risk" status. Similar to the crude (i.e., unadjusted) analysis, the "at risk" periods were defined as the 45-day period following SARS-CoV-2 infection and the 21-day period following receipt of a COVID-19 vaccine dose which aligns with most published literature (except for CKD which used a 180-day period following SARS-CoV-2 infection and vaccination). These models adjusted for age, sex, race and ethnicity, obesity status, and either SARS-CoV-2 infection within the past 45 days (180 days for CKD) or COVID-19 vaccine dose received within the past 21 days (180 days for CKD). Adjusted incidence rates were calculated per 100,000 person-years of Active Component service. Due to the small number of Service members vaccinated against COVID-19 prior to 2021, these adjusted incidence rates could only be calculated in 2021.

Finally, overall crude annual prevalence was calculated for each of the five conditions. An individual was counted as a prevalent case if they had been previously identified as an incident case for that condition and had a medical encounter for that condition during the year of interest. The denominator was calculated using the number of Active Component Service members who were in service during June of that CY. Prevalence rates were calculated as the number of prevalent cases per 100,000 Service members.

RESULTS

General Explanation of Prevalence, Incidence, and Rate Ratio

Crude annual prevalence (the unadjusted rate of new and existing cases) rates were calculated for each condition of interest at the overall population level among Active Component members. It is typically best practice to use a mid-year (June) population count as denominator for this type of rate, given this population's constant fluctuation. However, numerators for this type of measure need to be able to count cases across the same amount of time for all years in order to be comparable. For this reason, a crude annual prevalence rate for CY 2022 is not able to be calculated – its numerator would be inappropriately small leading to an equally inappropriately small prevalence rate that is incomparable and otherwise easy to misinterpret.

Incidence rates (the rate of new cases in each CY) calculated for this report, both crude and adjusted, utilize a person-time (specifically person-years of military service) type of denominator that aims to better handle fluctuations in the amount of time an individual is cared for in the MHS and, thus, is not as subject to the drawbacks of the crude annual prevalence rate. While CY 2022 incidence rates are able to be calculated and compared between previous years, it is still important to practice caution when interpreting incomplete CY 2022 incidence data. Lastly, incidence rates are also likely the most appropriate measure to examine for this report given its focus on examining the likelihood of developing cardiac and kidney adverse events associated with SAR-CoV-2 infection or COVID-19 vaccination and not the general burden of these conditions on the MHS population.

Finally, adjusted incidence rate ratios were calculated for this report. A rate ratio allows for person-time incidence rates of two groups to be compared to each other, differentiated by usually a demographic feature or by exposure to a suspected causative agent and statistical significance to be tested. In this case, the rate ratios reported are differentiated by exposure to SARS-CoV-2 infection and COVID-19 vaccination separately and compared to the "Never" exposure group consistently. Interpretation of a rate ratio is straight-forward: a rate ratio of 1.0 indicates equal rates within the groups compared, a rate ratio greater than 1.0 indicates increased risk, and a rate ratio less than 1.0 indicates decreased risk or a protective effect.

Cardiac Outcomes – Overall Prevalence Data

The overall prevalence data captures the general burden of disease and causality to specific changes related to SARS-CoV-2 infection or COVID-19 vaccine cannot be made. As explained above, incidence rates are likely the most appropriate measure to examine for this report given its focus on examining the likelihood of developing cardiac and kidney adverse events associated with SAR-CoV-2 infection or COVID-19 vaccination.

Table 1. Crude Annual Prevalence Rates of Select Cardiac Conditions within Active Component Service Members

	Calendar Year								
	2019			2020			2021		
	N	Persons	Prevalence*	N	Persons	Prevalence*	N	Persons	Prevalence*
Myocarditis	205	1,313,942	15.6	189	1,320,699	14.3	326	1,339,485	24.3
Pericarditis	363	1,313,942	27.6	334	1,320,699	25.3	351	1,339,485	26.2
AMI	283	1,313,942	21.5	314	1,320,699	23.8	353	1,339,485	26.4

Abbreviations: AMI = acute myocardial infraction;
*****Cases per 100,000 persons

In CY 2019, the crude prevalence (the unadjusted rate of new and existing cases) of myocarditis, pericarditis, and AMI was 15.6 cases per 100,000 persons, 27.6 per 100,000 persons, and 21.5 per 100,000 persons respectively (Table 1). By CY 2021, crude prevalence rates for myocarditis increased more than 50 percent to 24.3 cases per 100,000 persons. However, rates for pericarditis remained mostly unchanged and rates for AMI increased only modestly from 23.8 per 100,000 persons to 26.4 per 100,000 persons. Crude prevalence rates for CY 2022 could not be reported at this time, as explained above.

Cardiac Outcomes – Overall and Infection/Vaccination Exposure Incidence Data

Overall crude incidence rates (the unadjusted rate of new cases in each CY) for pericarditis and AMI remained mostly stable across the observed timespan from CY 2019 to available data in CY 2022 (Table 2). Unlike with AMI, rates for pericarditis did slightly decrease between CY 2021 and the first half of CY 2022. However, crude incidence rates for myocarditis decreased from 10.8 per 100,000 person-years (p-yrs) in CY 2019 to 8.7 in CY 2020 and then increased to 17.9 in CY 2021. While data for CY 2022 is currently only available between January and June 2022, the crude incidence rate for myocarditis during this 6-month period (13.0 cases per 100,000 p-yrs) is still above what was observed in CY 2019 (Table 2). These overall crude incidence rates include all Active Component members who experienced a new case of myocarditis, pericarditis,

or AMI during each year of interest, regardless of if they had a previous SARS-CoV-2 infection or received COVID-19 vaccine.

Table 2. Crude Annual Incidence Rates of Select Cardiac Conditions within Active Component Service Members, Overall and Stratified by SARS-CoV-2 Infection and COVID-19 Vaccine

	Calendar Year							
	2019		2020		2021		2022 (through June)	
	N	Incidence*	N	Incidence*	N	Incidence*	N	Incidence*
Myocarditis	142	10.8	116	8.7	239	17.9	84	13.0
SARS-CoV-2 Infection								
Yes, ≤ 45 days	0	0.0	13	142.8	27	152.1	16	59.1
No, > 45 days	0	0.0	7	56.5	55	41.9	16	11.6
Never	142	10.8	96	7.4	157	13.3	52	10.8
COVID-19 Vaccine								
Yes, ≤ 21 days	0	0.0	0	0.0	63	40.6	3	17.8
No, > 21 days	0	0.0	0	0.0	92	13.4	76	12.4
Never	142	10.8	116	8.8	84	17.1	5	33.9
Pericarditis	266	20.3	242	18.3	244	18.3	91	14.1
SARS-CoV-2 Infection								
Yes, ≤ 45 days	0	0.0	6	66.0	18	101.5	13	48.0
No, > 45 days	0	0.0	5	40.4	41	31.2	27	19.5
Never	266	20.3	231	17.7	185	15.6	51	10.6
COVID-19 Vaccine								
Yes, ≤ 21 days	0	0.0	1	133.9	48	30.9	5	29.7
No, > 21 days	0	0.0	0	0.0	115	16.8	82	13.3
Never	266	20.3	241	18.2	81	16.5	4	27.1
AMI	198	15.1	229	17.3	244	18.3	117	18.1
SARS-CoV-2 Infection								
Yes, ≤ 45 days	0	0.0	9	98.9	8	45.1	16	59.1
No, > 45 days	0	0.0	2	16.1	20	15.2	23	16.6
Never	198	15.1	218	16.7	216	18.2	78	16.2
COVID-19 Vaccine								
Yes, ≤ 21 days	0	0.0	0	0.0	35	22.6	0	0.0
No, > 21 days	0	0.0	0	0.0	120	17.5	115	18.7
Never	198	15.1	229	17.3	89	18.1	2	13.6

Abbreviations: AMI = acute myocardial infarction;
*****Cases per 100,000 person-years of Active Component service

The overall crude incidence rates reported above were then stratified by cases that occurred within 45 days after SARS-CoV-2 (180 days for CKD) infection and cases that occurred within 21 days after COVID-19 vaccination (180 days for CKD). Given that the first laboratory confirmed case of SARS-CoV-2 in the United States occurred in January 2020 and DoD did not begin administering vaccine until December 2020, there are no cases of myocarditis, pericarditis, or AMI with previous infection or vaccine in CY 2019. In CY 2020, there were overall low number of cases related to either SARS-CoV-2 infection or COVID-19 vaccine. Specifically, in

CY 2020, there were 13, 6, and 9 cases of myocarditis, pericarditis, and AMI, respectively, which occurred within 45 days after SARS-CoV-2 infection, and only a single case of pericarditis within 21 days of receiving COVID-19 vaccine (Table 2).

In CY 2021, the crude incidence of myocarditis was 11 times higher in those with a past 45-day SARS-CoV-2 infection (152.1 per 100,000 p-yrs) compared to those with no prior SARS-CoV-2 infection (13.3 per 100,000 p-yrs) (Table 2). In contrast, the crude incidence of myocarditis was 2.4 times higher among those who received a vaccine dose within 21 days prior (40.6 per 100,000 p-yrs) compared to those who did not receive any prior dose of vaccine (17.1 per 100,000 p-yrs). The crude incidence of pericarditis was 6 times higher in those with a previous infection (101.5 per 100,00 p-yrs) compared to those without, and 1.9 times higher in those with a previous vaccination (30.9 per 100,000 p-yrs) compared to those without. Finally, incidence of AMI was 2.5 times higher in those with a recent infection and 1.2 times higher in those with a recent vaccination. For the most part, these trends continue in the 6 months available for CY 2022 at lesser magnitudes.

Cardiac outcome results showed similar patterns after adjusting for age, sex, race/ethnicity, obesity status, and either prior infection or prior vaccination (Table 3). In CY21, those with a recent SARS-CoV-2 infection had a rate ratio that showed incidence of myocarditis and pericarditis was 10.4 and 6.1 (respectively) times higher in this group compared to the incidence rates of those who were never infected. Those who were recently vaccinated had a rate ratio that showed their incidences of myocarditis and pericarditis were 2.6 and 2.0 times higher compared to those who were never vaccinated. These findings were statistically significant ($p<0.001$). In addition, those with a recent infection had a rate ratio that showed incidence for AMI was 2.4 times higher in this group compared to those who were never infected. Unlike with myocarditis and pericarditis rate ratios showing increased risk associated with vaccination, those who were recently vaccinated did not have increased incidence of AMI compared to those who were not vaccinated. The rate ratio for AMI comparing those who were vaccinated to those who were never vaccinated was at 1.1, effectively implying there was no difference between vaccination groups, although the association is not statistically significant.

Table 3: Adjusted Incidence Rates and Rate Ratios of Selected Cardiac Conditions Stratified by SARS-CoV-2 Infection and COVID-19 Vaccine, 2021

	Incidence*		Rate Ratio	
	SARS-CoV-2 Infection	COVID-19 Vaccine	SARS-CoV-2 Infection	COVID-19 Vaccine
Myocarditis				
Yes	98.2	57.2	10.4**	2.6**
No	27.8	20.3	2.9**	0.9
Never	9.5	22.2	Ref	Ref
Pericarditis				
Yes	55.5	30.8	6.1**	2.0**
No	16.3	17.5	1.8**	1.1
Never	9.1	15.3	Ref	Ref
AMI				
Yes	27.1	16.3	2.4**	1.1
No	9.9	12.1	0.9	0.8
Never	11.2	15.2	Ref	Ref

Abbreviations: AMI = acute myocardial infarction;
*****Cases per 100,000 person-years in Active Component service, adjusted for age, sex, race and ethnicity, obesity status, and either COVID-19 infection within the past 45 days (180 days for CKD) or COVID-19 vaccine dose received within the past 21 days
**Statistically significant, p-value at least <0.05

Kidney Outcomes – Overall Prevalence Data

In CY 2019, the crude prevalence rates for AKI and CKD were 110.3 cases per 100,000 persons and 121.3 per 100,000 persons, respectively (Table 4). Both conditions had similar prevalence rates in both CY 2020 and CY 2021. Prevalence data for CY 2022 could not be reported as explained above.

Table 4. Crude Annual Prevalence Rates of Select Kidney Conditions within Active Component Service Members

	Calendar Year								
	2019			2020			2021		
	N	Persons	Prevalence*	N	Persons	Prevalence*	N	Persons	Prevalence*
AKI	1,449	1,313,942	110.3	1,433	1,320,699	108.5	1,533	1,339,485	114.5
CKD	1,594	1,313,942	121.3	1,547	1,320,699	117.1	1,607	1,339,485	120.0

Abbreviations: AKI = acute kidney injury; CKD = chronic kidney disease
*****Cases per 100,000 persons

Kidney Outcomes – Overall and Infection/Vaccination Exposure Incidence Data

Crude annual incidence rates for AKI and CKD showed the same pattern – a slight decrease during CY 2020 followed by a return to roughly the same rate in CY 2021 as in CY 2019 (Table 5). While data for CY 2022 is only partially available at this time, the crude incidence rates for both conditions appear to be on track to end up similar to CY 2019 and CY 2021.

Table 5. Crude Annual Incidence Rates of Select Kidney Conditions within Active Component Service Members, Overall and Stratified by SARS-CoV-2 Infection and COVID-19 Vaccine

	Calendar Year							
	2019		2020		2021		2022 (through June)	
	N	Incidence*	N	Incidence*	N	Incidence*	N	Incidence*
AKI	1340	102.3	1307	98.9	1406	105.8	625	97.0
SARS-CoV-2 Infection								
Yes, ≤ 45 days	0	0.0	74	816.2	136	769.8	55	203.8
No, > 45 days	0	0.0	17	137.8	164	125.4	143	103.8
Never	1340	102.3	1216	93.5	1106	93.7	427	89.0
COVID-19 Vaccine								
Yes, ≤ 21 days	0	0.0	1	134.3	138	89.2	13	77.5
No, > 21 days	0	0.0	0	0.0	663	96.9	588	95.9
Never	1340	102.3	1306	98.8	605	123.5	24	163.2
CKD	724	55.2	648	48.9	680	51.1	230	35.6
SARS-CoV-2 Infection	0	0.0	18.0	88.2	64	88.6	42	44.4
Yes, ≤ 180 days	0	0.0	1.0	95.1	36	47.0	26	36.8
No, > 180 days	724	55.2	629.0	48.3	580	49.1	162	33.7
Never	0	0.0	18.0	88.2	64	88.6	42	44.4
COVID-19 Vaccine								
Yes, ≤ 180 days	0	0.0	1	134.1	339	51.4	85	36.2
No, > 180 days	0	0.0	0	0.0	85	46.4	137	34.2
Never	724	55.2	647	48.9	256	52.4	8	56.8

Abbreviations: AKI = acute kidney injury; CKD = chronic kidney disease
*****Cases per 100,000 person-years of active component service

Once crude incidence rates were stratified by SARS-CoV-2 infection and COVID-19 vaccination, similar low case counts occur in these categories during CY 2020 for kidney conditions as they do for cardiac conditions with the exception of AKI. There was a total of 74 cases of AKI with prior SARS-CoV-2 infection within 45 days, which correlates with initial published reports of AKI complicating SARS-CoV-2 infection in as much as about 46 percent of all cases.[15] In CY 2021, the crude incidence of AKI was 8.2 times higher in those with a past 45-day SARS-CoV-2 infection (769.8 per 100,000 p-yrs) compared to those with no prior SARS-CoV-2 infection (93.7 per 100,000 p-yrs) (Table 5). In contrast, the crude incidence of AKI was reduced 28 percent among those who received a vaccine dose within 21 days prior (89.2 per 100,000 p-yrs) compared to those who did not receive any prior dose of vaccine (123.5 per 100,000 p-yrs). The crude incidence of CKD in CY 2021 was 1.8 times higher in those with an infection in the past 180 days compared to those never infected. Crude incidence rates of CKD between those with previous COVID-19 vaccination in the past 180 days (51.4 per 100,000 p-yrs) was similar to those who never had the vaccine (52.4 per 100,000 p-yrs).

Kidney outcomes again showed similar patterns after adjusting for age, sex, race/ethnicity, obesity status, and either prior infection or vaccination (Table 6). Those with a recent SARS-CoV-2 infection had a rate ratio that showed AKI incidence was 7.6 times higher among this group compared to those who were never infected. Similar for CKD, those with a recent SARS-

CoV-2 infection had a rate ratio that showed their CKD incidence was 1.8 times higher compared to those who were never infected. Those who were recently vaccinated had a rate ratio that showed they had a 20 percent reduced incidence of AKI and 20 percent reduced incidence of CKD compared to those who were never vaccinated.

Table 6: Adjusted Incidence Rates and Rate Ratios of Selected Kidney Conditions Stratified by SARS-CoV-2 Infection and COVID-19 Vaccine, 2021

	Incidence*		Rate Ratio	
	SARS-CoV-2 Infection	COVID-19 Vaccine	SARS-CoV-2 Infection	COVID-19 Vaccine
AKI				
Yes	537.8	132.8	7.6**	0.8**
No	92.5	150.4	1.3**	0.9**
Never	71.0	176.8	Ref	Ref
CKD				
Yes	64.4	44.2	1.8**	0.8**
No	36.8	34.8	1.1	0.6**
Never	35.0	54.0	Ref	Ref

Abbreviations: AKI = acute kidney injury; CKD = chronic kidney disease
*****Cases per 100,000 person-years in Active Component service, adjusted for age, sex, race and ethnicity, obesity status, and either COVID-19 infection within the past 45 days (180 days for CKD) or COVID-19 vaccine dose received within the past 21 days
**Statistically significant, p-value at least <0.05

DISCUSSION

In response to the public health emergency of pandemic level spread of SARS-CoV-2 virus, DoD began administering COVID-19 vaccines in December 2020 with the full 2-dose vaccination against COVID-19 being required for all Active Component (and Ready Reserve) Service members starting in August 2021. Almost 1.5 million Active Component members have received at least one dose of the COVID-19 vaccine and the report findings suggest overall stable incidence and prevalence rates of most cardiac and kidney conditions from 2019 to 2022. Similar to numerous studies reporting an increase in myocarditis incidence as a rare complication of mRNA COVID-19 vaccination, MHS data review from January 2019 to June 2022 showed an overall small increase in myocarditis incidence and prevalence among Active Component Service members.[3-10]

The overall small increase in myocarditis incidence, which was most profound in 2021, is potentially related to the general increased incidence of SARS-CoV-2 infection that was observed nationwide and also within DoD during the surge from the Delta variant spread in summer 2021. After adjusting for confounding factors, there was a 10.4 times increased risk for myocarditis associated with recent SARS-CoV-2 infection compared to 2.6 times increased risk for myocarditis associated with COVID-19 vaccine. MHS data align with published studies acknowledging a small increase in myocarditis incidence potentially related to COVID-19 vaccine but with far worse outcomes that was potentially avoided with SARS-CoV-2 infection.[9,10]

The only other clinical outcome with a trend toward increased overall prevalence, although slight, was in AMI. To reiterate, prevalence data captures the general burden of disease and incidence rates are most appropriate to examine for this report for potential causality to changes related to SARS-CoV-2 infection or COVID-19 vaccination. Specifically, the crude prevalence rates for AMI modestly increased across the 2019-2021 time period. Conversely, the crude incidence rate for AMI started low at 15.1 cases per 100,000 p-yrs in 2019 before increasing to 17.3 in 2020 and remaining relatively stable at this increased level for 2021 and through June 2022. Both prior SARS-CoV-2 infection and receipt of COVID-19 vaccine resulted in higher crude incidence rates of AMI compared to never being infected or never receiving the vaccine. However, SARS-CoV-2 infection associated AMI crude incidence rates were markedly higher than vaccine-associated AMI crude incidence rates. Similarly, after adjusting for confounding factors, there was 2.4 times increased risk for AMI associated with recent SARS-CoV-2 infection compared to 1.1 times increased risk for AMI associated with COVID-19 vaccination. The higher and statistically significant rate ratio of 2.4 suggests that having previous SARS-CoV-2 infection had a more significant impact on AMI incidence rate than COVID-19 vaccine, the rate ratio of which was not statistically significant and nearly 1.0 (implying almost no difference in incidence rates between those who received COVID-19 vaccine and those who never received COVID-19 vaccine). At the very least, this could be a weak signal inferring that SARS-CoV-2 infection did indeed drive the moderate increase in observed AMI prevalence, but a more detailed analysis is likely needed to confirm.

The incidence and prevalence of pericarditis and both kidney outcomes (AKI and CKD) evaluated in this report remained similar or at least mostly similar in 2021 compared to previous years. The association between CKD and COVID-19 vaccine is difficult to make given multiple confounding factors and the prolonged timeline associated with CKD development. However, crude incidence rates between those with previous COVID-19 vaccination (51.4 per 100,000 p-yrs) were similar to those who never had the vaccine (52.4 per 100,000 p-yrs). Overall, our data suggests that there was a trend showing no differences in CKD incidence.

Although the incidence and prevalence of pericarditis remained stable from 2019 to 2021 with a trend toward decrease in 2022, the adjusted rate ratio of 2.0 showed a potential increase in the risk for pericarditis associated with COVID-19 vaccine. However, similar to the myocarditis findings, there was a significantly 6.1 times higher increased risk for pericarditis associated with SARS-CoV-2 infection compared to 2.0 times increased risk for pericarditis associated with the vaccine. To date and based on published clinical case reports and case series, it remains difficult to separate pericarditis from myocarditis (possible myocarditis cases) because features of myocarditis and pericarditis may overlap and commonly present as myopericarditis.[4,7] While diagnostic criteria exist for the diagnosis of pericarditis, without further review of the individual cases to confirm the clinical evaluation and diagnosis of pericarditis, it is difficult to accurately estimate the prevalence and incidence of infection or vaccine associated pericarditis as this condition may present across a spectrum of severity and symptoms that can overlap with myocarditis.

Similar to data reported in literature, the incidence of all cardiac and kidney conditions evaluated in this report were higher in those with a recent SARS-CoV-2 infection compared to without infection (rate ratios ranging from 1.8-10.4, all statistically significant).[9-10] While there was also

increased incidence for myocarditis and pericarditis in the 21 days following COVID-19 vaccination compared to those without vaccination (rate ratios of 2.6 and 2.0 respectively, both statistically significant), this increase was much lesser in magnitude compared to those observed following infection with SARS-CoV-2. Furthermore, there was no observed increase in risk for AMI, AKI, or CKD incidence following COVID-19 vaccination. In fact, rate ratios for these conditions implied either no difference in incidence rates following vaccine (AMI, though not statistically significant) or a reduced effect in incidence rates following vaccine (AKI and CKD, both statistically significant). These observations are consistent with what is reported in literature for the selected cardiac and kidney conditions.

Global studies have shown that COVID-19 vaccines are effective in protecting against SARS-CoV-2 infections and complications of infection. While vaccine effectiveness against mild infection is dependent on viral variants,[24,25] effectiveness calculations against severe disease, hospitalization, and death have been consistently estimated as high as 80-90 percent.[26,27] Vaccine effectiveness has been established in vulnerable populations as well as the relatively healthy military population.[28] The COVID-19 vaccination program in the United States has been estimated as preventing nearly 120 million infections, 18.5 million hospitalizations, and 3.2 million deaths.[29] Prevention of SARS-CoV-2 infections and complications has also been translated into substantial economic value.[29,30] Expanded understanding of post-acute sequelae of SARS-CoV-2 infection, or long-COVID, and recent research demonstrating effectiveness of vaccination in preventing long-COVID,[31] will make future calculations of vaccine value even higher than previous robust estimates. Although all vaccinations carry some risk of rare adverse events, the benefit of COVID-19 vaccination during the current pandemic has been strongly established by all international public health authorities.[32]

The findings in this report are subject to at least three limitations. First, this is a population-level evaluation of administrative data records within the MHS. Time period risk windows were used to associate outcomes with COVID-19 infection or vaccination. However, this does not necessarily mean that a case occurring during the risk window was caused by COVID-19 infection or vaccination. Detailed chart review confirmation would be needed to determine causality of the cardiac and kidney conditions included in this study. The use of administrative data for outcome definition may also result in misclassification of diagnoses due to miscoding in patient records. Furthermore, only individuals who show up for healthcare services billable to military insurance are able to be included for evaluation. While this report did focus on Active Component members, a subgroup of the MHS population that receives the majority of its health care covered by military insurance, it is still possible that cases of SARS-CoV-2 infection, myocarditis, pericarditis, AMI, AKI, and CKD were missed due to the nature of the data source. Second, this report only evaluates vaccinations administered while an Active Component member is in Military Service and may have missed vaccinations completed prior to the first date in military. Third, while the report did observe an increased risk for certain cardiac conditions after SARS-CoV-2 infection and COVID-19 vaccination, these associations are far from causal and too many factors are unable to be controlled for. Rather, the report serves as soft confirmation of trends also observed in the general population: while the COVID-19 vaccine does carry increased risk for certain cardiac conditions, the risk for those same conditions is higher still following SAR-CoV-2 infection, albeit overall a rare event in both cases.

There are no long-term outcome data available for the increased myocarditis incidence associated with both COVID-19 vaccine and SARS-CoV-2 infection globally and also within MHS. Active and continued long-term surveillance of potential incident cases with diagnosis confirmation through detailed case reviews may be pursued to assist in mitigating potential risk factors associated with increased myocarditis risk for Service members.

CONCLUSION

Review of MHS data spanning January 2019 to June 2022 demonstrates that both the prevalence and incidence of myocarditis has increased among Active Component members of the Armed Forces. All other cardiac and kidney outcomes remained mostly stable through the time period. Recent receipt of COVID-19 vaccine was shown to carry increased risk for development of both myocarditis and pericarditis, but without increased risk for AMI and with a slightly reduced risk for AKI and CKD. However, recent SARS-CoV-2 infection was associated with a significantly higher magnitude of increased risk for all observed cardiac and kidney conditions when compared to vaccine administration. While all vaccinations including COVID-19 carry some amount of risk for rare adverse events, the MHS data shows that risks for cardiac and kidney complications are higher after SARS-CoV-2 infection than they are after COVID-19 vaccine, supporting similar conclusions drawn by previous published studies.

REFERENCES

1. Centers for Disease Control and Prevention. Selected Adverse Events Reported after COVID-19Vaccination. Updated August 30, 2022. Available at: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html.
2. Centers for Disease Control and Prevention. Myocarditis and Pericarditis After mRNA COVID-19Vaccination. Updated July 14, 2022. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myocarditis.html.
3. Oster ME, Shay DK, Su JR, et al. Myocarditis Cases Reported After mRNA-Based COVID-19 Vaccination in the US From December 2020 to August 2021. JAMA. 2022;327(4):331–340.
4. Pepe S, Gregory AT, Denniss AR. Myocarditis, Pericarditis, and Cardiomyopathy after COVID-19 Vaccination. Heart Lung Cir. 2021; 30(10):1425-9.
5. Witberg G, Barda N, Hoss S, Richter I, Wiessman M, Aviv Y, et al. Myocarditis after Covid-19 Vaccination in a Large Health Care Organization. New England Journal of Medicine. 2021; 385(23): 2132-213.
6. Rosenblum HG. Use of COVID-19 Vaccines After Reports of Adverse Events Among Adult Recipients of Janssen (Johnson & Johnson) and mRNA COVID-19 Vaccines (Pfizer-BioNTech and Moderna): Update from the Advisory Committee on Immunization Practices – United States, July 2021. MMWR Morbidity and Mortality Weekly Report. 2021; 70(32): 1094-1099.
7. Gargano JW, Wallace M, et al. Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices – United States, June 2021. MMWR Morbidity and Mortality Weekly Report. 2021; 70(27): 977-982.
8. Montgomery J, Ryan M, Engler R, Hoffman D, McClenathan B, Collins L, et al. Myocarditis Following Immunization with mRNA COVID-19 Vaccines in Members of the US Military. JAMA Cardiology. 2021; 6(10): 1202-1206.
9. Kim Y, Huh K, Park Y, Peck KR, Jung J. Association Between Vaccination and Acute Myocardial Infarction and Ischemic Stroke After COVID-19 Infection. JAMA. Published online July 22, 2022; 328(9): 887-889.
10. Block J, Boehmer T, Forrest C, Carton T, Lee G, et al. Cardiac Complications After SARS-CoV-2 Infection and mRNA COVID-19 Vaccination – PCORnet, United States, January 2021-January 2022. MMWR Morbidity and Mortality Weekly Report. 2022; 71 (14): 517-523.
11. Chen G, Li X, Sun M, et al. COVID-19 mRNA Vaccines Are Generally Safe in the Short Term: A Vaccine Viligance Real-World Study Says. Front Immunol. 2021; 21:669010.
12. Luo H, Li X, Ren Q, et al. Acute kidney injury after COVID-19 vaccines: a real-world study. RenFail. 2022;44(1):958-965.
13. Li Y, Rao M, Xu Gaosi. New-Onset Acute Kidney Disease Post COVID-19 Vaccination. Vaccines. 2022; 10(5): 742.
14. Wu H, Kalra P, Chinnadurai R. New-Onset and Relapsed Kidney Histopathology Following COVID-19 Vaccination: A Systematic Review. Vaccines. 2021; 9(11): 1252.
15. Chan L, Chaudhary K, Saha A, Chauhan K, Vaid A, Baweja M, et al. Acute Kidney Injury in Hospitalized Patients with COVID-19. J Am Soc Nephrol. 2021; 32(1): 151-160.

16. Mohamed MMB, Lukitsch I, Torres-Ortiz AE, Walker JB, Varghese V, Hernandez-Arroyo CF, et al. Acute Kidney Injury Associated with Coronavirus Disease 2019 in Urban New Orleans. Kidney360. 2020: 1(7): 614-622.
17. Hirch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int. 2020; 98(1): 209-218.
18. Gupta S, Coca SG, Chan L, Melamed ML, Brenner SK, et al. AKI Treated with Renal Replacement Therapy in Critically Ill Patients with COVID-19. J Am Soc Nephrol. 2021; 32(1): 161-176.
19. Chung EY, Palmer SC, Natale P, Krishnan A, Cooper T. Incidence and Outcomes of COVID-19 in People with CKD: A Systematic Review and Meta-analysis. Am J Kidney Dis. 2021; 78(6): 804-815.
20. Rubertone MV, Brundage JF. The Defense Medical Surveillance System and the Department of Defense serum repository: glimpses of the future of public health surveillance. Am J Public Health. 2002;92(12):1900-1904.
21. Centers for Disease Control and Prevention (CDC). Coronavirus Disease 2019 (COVID-19) 2021 Case Definition. Accessed October 20, 2022. Available at: https://ndc.services.cdc.gov/case-definitions/coronavirus-disease-2019-2021/.
22. Centers for Disease Control and Prevention (CDC). Overweight and obesity. Defining adult overweight and obesity. Accessed October 20, 2022. Available at: https://www.cdc.gov/obesity/basics/adult-defining.html.
23. Dickerman BA, Madenci AL, Gerlovin H, et al. Comparative safety of BNT162b2 and mRNA-1273 vaccines in a nationwide cohort of US veterans. JAMA Intern Med. Published online June 13, 2022. doi:10.1001/jamainternmed.2022.2109
24. Lauring AS, Tenforde MW, Chappell JD, et al. Clinical severity of, and effectiveness of mRNA vaccines against, covid-19 from omicron, delta, and alpha SARS-CoV-2 variants in the United States: prospective observational study. *BMJ*. 2022;376:e069761. Published 2022 Mar 9. doi:10.1136/bmj-2021-069761
25. Link-Gelles R, Levy ME, Gaglani M, et al. Effectiveness of 2, 3, and 4 COVID-19 mRNA Vaccine Doses Among Immunocompetent Adults During Periods when SARS-CoV-2 Omicron BA.1 and BA.2/BA.2.12.1 Sublineages Predominated - VISION Network, 10 States, December 2021-June 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(29):931-939. Published 2022 Jul 22. doi:10.15585/mmwr.mm7129e1
26. Tenforde MW, Self WH, Naioti EA, et al. Sustained Effectiveness of Pfizer-BioNTech and Moderna Vaccines Against COVID-19 Associated Hospitalizations Among Adults - United States, March-July 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(34):1156-1162. Published 2021 Aug 27. doi:10.15585/mmwr.mm7034e2
27. Adams K, Rhoads JP, Surie D, et al. Vaccine effectiveness of primary series and booster doses against covid-19 associated hospital admissions in the United States: living test negative design study. *BMJ*. 2022;379:e072065. Published 2022 Oct 11. doi:10.1136/bmj-2022-072065
28. Eick-Cost AA, Ying S, Wells N. Effectiveness of mRNA-1273, BNT162b2, and JNJ-78436735 COVID-19 Vaccines Among US Military Personnel Before and During the Predominance of the Delta Variant. *JAMA Netw Open.* 2022;5(4):e228071. doi:10.1001/jamanetworkopen.2022.8071

29. Fitzpatrick MC, et al., "Two Years of U.S. COVID-19 Vaccines Have Prevented Millions of Hospitalizations and Deaths," To the Point (blog), Commonwealth Fund, 13 Dec 2022. https://doi.org/10.26099/whsf-fp90.
30. Sah P, Vilches TN, Moghadas SM, et al. Return on Investment of the COVID-19 Vaccination Campaign in New York City. *JAMA Netw Open.* 2022;5(11):e2243127. doi:10.1001/jamanetworkopen.2022.43127
31. Perlis RH, Santillana M, Ognyanova K, et al. Prevalence and Correlates of Long COVID Symptoms Among US Adults. *JAMA Netw Open*. 2022;5(10):e2238804. Published 2022 Oct 3. doi:10.1001/jamanetworkopen.2022.38804
32. World Health Organization. Strategic Advisory Group of Experts on Immunization (SAGE) Roadmap for prioritizing uses of COVID-19 vaccines. 21 Jan 2022. WHO/2019-nCoV/Vaccines/SAGE/Prioritization/2022.

APPENDIX A: ICD-9, ICD-10, and CVX Codes for Case Definitions of Cardiac, Kidney, and COVID-19 Vaccination

Table A1. ICD codes for Myocarditis

ICD-10	ICD-10 Description	ICD-9	ICD-9 Description
I51.4	Myocarditis, unspecified	429.0	Myocarditis, unspecified
I40.9	Acute myocarditis, unspecified	422.90	Acute myocarditis, unspecified
I40.8	Other acute myocarditis	422.93, 422.99	Toxic myocarditis, Other acute myocarditis
I40.1	Isolated myocarditis	422.91	Idiopathic myocarditis
I40.0	Infective myocarditis	422.92	Septic myocarditis
I41	Myocarditis in diseases classified elsewhere	422.0	Acute myocarditis in diseases classified elsewhere
I01.2	Acute rheumatic myocarditis	391.2	Acute rheumatic myocarditis
I09.0	Rheumatic myocarditis	398.0	Rheumatic myocarditis

Table A2. ICD codes for Pericarditis

ICD-10	ICD-10 Description	ICD-9	ICD-9 Description
I32	Pericarditis in diseases classified elsewhere	420.0	Acute pericarditis in diseases classified elsewhere
I30.9	Acute pericarditis, unspecified	420.90	Acute pericarditis, unspecified
I30.8	Other forms of acute pericarditis	420.99	Other acute pericarditis
I30.1	Infective pericarditis	420.90	Acute pericarditis, unspecified
I30.0	Acute nonspecific idiopathic pericarditis	420.91	Acute idiopathic pericarditis
M32.12	Pericarditis in systemic lupus erythematosus	423.9	Unspecified disease of pericardium

Table A3. ICD codes for Acute Myocardial Infarction

ICD-10	ICD-10 Desc	ICD-9	ICD-9 Desc
I21.0*	ST elevation (STEMI) myocardial infarction of anterior wall	410*	Acute myocardial infarction
I21.1*	ST elevation (STEMI) myocardial infarction of inferior wall	As above	
I21.2*	ST elevation (STEMI) myocardial infarction of other sites	As above	
I21.3	ST elevation (STEMI) myocardial infarction of unspecified site	As above	
I21.4	Non-ST elevation (NSTEMI) myocardial infarction	As above	
I21.9	Acute myocardial infarction, unspecified	As above	
I22*	Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction	As above	

*Indicates that all subsequent digits/characters are included

Table A4. ICD codes for Acute Kidney Failure

ICD-10	ICD-10 Desc	ICD-9	ICD-9 Desc
N17.0	Acute kidney failure with tubular necrosis	584.5	Acute kidney failure with lesion of tubular necrosis
N17.1	Acute kidney failure with acute cortical necrosis	584.6	Acute kidney failure with lesion of renal cortical necrosis
N17.2	Acute kidney failure with medullary necrosis	584.7	Acute kidney failure with lesion of renal medullary [papillary] necrosis

N17.8	Other acute kidney failure	584.8	Acute kidney failure with other specified pathological lesion in kidney
N17.9	Acute kidney failure, unspecified	584.9	Acute kidney failure, unspecified

Table A5. ICD codes for Chronic Kidney Disease

ICD-10	ICD-10 Desc	ICD-9	ICD-9 Desc
I12.0	Hypertensive chronic kidney disease with stage 5 chronic kidney disease or end stage renal disease	403.01, 403.11, 403.91	Hypertensive chronic kidney disease, malignant, with chronic kidney disease stage V or end stage renal disease; Hypertensive chronic kidney disease, benign, with chronic kidney disease stage V or end stage renal disease; Hypertensive chronic kidney disease, unspecified, with chronic kidney disease stage V or end stage renal disease
I13.1	Hypertensive heart and chronic kidney disease without heart failure		
I13.10	Hypertensive heart and chronic kidney disease without heart failure, with stage 1 through stage 4 chronic kidney disease, or unspecified chronic kidney disease	404.00, 404.10, 404.90	Hypertensive heart and chronic kidney disease, malignant, without heart failure and with chronic kidney disease stage I through stage IV, or unspecified; Hypertensive heart and chronic kidney disease, benign, without heart failure and with chronic kidney disease stage I through stage IV, or unspecified; Hypertensive heart and chronic kidney disease, unspecified, without heart failure and with chronic kidney disease stage I through stage IV, or unspecified
I13.11	Hypertensive heart and chronic kidney disease without heart failure, with stage 5 chronic kidney disease, or end stage renal disease	404.02, 404.12, 404.92	Hypertensive heart and chronic kidney disease, malignant, without heart failure and with chronic kidney disease stage V or end stage renal disease; Hypertensive heart and chronic kidney disease, benign, without heart failure and with chronic kidney disease stage V or end stage renal disease; Hypertensive heart and chronic kidney disease, unspecified, without heart failure and with chronic kidney disease stage V or end stage renal disease
N03.2	Chronic nephritic syndrome with diffuse membranous glomerulonephritis	582.0	Chronic glomerulonephritis with lesion of proliferative glomerulonephritis
N03.3	Chronic nephritic syndrome with diffuse mesangial proliferative glomerulonephritis	582.1	Chronic glomerulonephritis with lesion of membranous glomerulonephritis
N03.4	Chronic nephritic syndrome with diffuse endocapillary proliferative glomerulonephritis	582.2	Chronic glomerulonephritis with lesion of membranoproliferative glomerulonephritis
N03.5	Chronic nephritic syndrome with diffuse mesangiocapillary glomerulonephritis	As above	
N03.6	Chronic nephritic syndrome with dense deposit disease	As above	
N03.7	Chronic nephritic syndrome with diffuse crescentic glomerulonephritis	As above	
N18*	Chronic kidney disease (CKD)	585*	Chronic kidney disease (CKD)
N19	Unspecified kidney failure	586	Renal failure, unspecified

N05.2	Unspecified nephritic syndrome with diffuse membranous glomerulonephritis	583.1	Nephritis and nephropathy, not specified as acute or chronic, with lesion of membranous glomerulonephritis
N05.3	Unspecified nephritic syndrome with diffuse mesangial proliferative glomerulonephritis	583.2	Nephritis and nephropathy, not specified as acute or chronic, with lesion of membranoproliferative glomerulonephritis
N05.4	Unspecified nephritic syndrome with diffuse endocapillary proliferative glomerulonephritis	As above	
N05.5	Unspecified nephritic syndrome with diffuse mesangiocapillary glomerulonephritis	As above	
N05.6	Unspecified nephritic syndrome with dense deposit disease	583.89	Nephritis and nephropathy, not specified as acute or chronic, with other specified pathological lesion in kidney
N05.7	Unspecified nephritic syndrome with diffuse crescentic glomerulonephritis	As above	
N25.0	Renal osteodystrophy	588.0	Renal osteodystrophy
Z49.01, Z49.02	Encounter for fitting and adjustment of extracorporeal dialysis catheter; Encounter for fitting and adjustment of peritoneal dialysis catheter	V56.1, V56.2	Fitting and adjustment of extracorporeal dialysis catheter; Fitting and adjustment of peritoneal dialysis catheter
Z94.0	Kidney transplant status	V42.0	Kidney replaced by transplant
Z99.2	Dependence on renal dialysis	V45.11	Renal dialysis status

*Indicates that all subsequent digits/characters are included

Table A6. CVX codes for COVID-19 vaccination

Imm_type	Description	Comments
510	SARS-COV-2 COVID-19 Inactivated Virus Non-U.S. Vaccine Product (BIBP, Sinopharm)	WHO authorized pandemic vaccine. Recognized towards immunity in U.S.
511	SARS-COV-2 COVID-19 Inactivated Virus Non-U.S. Vaccine Product (CoronaVac, Sinovac)	WHO authorized pandemic vaccine. Recognized towards immunity in U.S.
502	SARS-COV-2 COVID-19 Inactivated Virus Non-U.S. Vaccine Product (COVAXIN)	Pandemic Non-U.S. Vaccine Authorized by WHO 11-3-2021, recognized toward immunity in U.S., https://extranet.who.int/pqweb/vaccines/who-recommendation-bharat-biotech-international-ltd-covid-19-vaccine-whole-virion.
212	SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-Ad26, preservative free, 0.5 mL	FDA EUA 02/27/2021, 1-dose vaccine. Used to record Janssen/J&J vaccines administered in the U.S. and in non-U.S. locations
210	SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-ChAdOx1, preservative free, 0.5 mL	Potential FDA EUA, 2-dose vaccine. AstraZeneca vaccine is authorized by the WHO and recognized towards immunity in the U.S. Non-U.S. WHO authorized tradenames/identifiers include VAXZEVRIA, AZD1222, ChAdOx1 nCoV-19, COVISHIELD
207	SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 100 mcg/0.5mL dose or 50 mcg/0.25mL dose	FDA EUA 12/18/2020, 2-dose vaccine. Used to record Moderna vaccines administered in the U.S. and in non-U.S. locations (includes tradename Spikevax)
208	SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 30 mcg/0.3mL dose	FDA BLA 08/23/2021 for adult dose (16+ years). Still under EUA for adolescent doses and presentations. EUA 12/11/2020, 2-dose vaccine. Used to record Pfizer vaccines administered in the U.S. and in non-U.S. locations (includes tradename Comirnaty)

217	SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 30 mcg/0.3mL dose, tris-sucrose formulation	EUA 12+ yrs, BLA 16+ yrs Pfizer tris-sucrose formulation vaccine for ages 12 and older
221	SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 50 mcg/0.5 mL dose	FDA EUA 03/29/2022, Moderna booster dose 2.5mL vial presentation only
211	SARS-COV-2 (COVID-19) vaccine, subunit, recombinant spike protein-nanoparticle+Matrix-M1 Adjuvant, preservative free, 0.5mL dose	Pre-EUA Authorization - Novavax Primary Series dose
229	SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, bivalent booster, preservative free, 50 mcg/0.5 mL or 25 mcg/0.25 mL dose	Pre-EUA Moderna bivalent booster, ages 6yr+ as authorized, original strain + omicron BA.4/BA.5
300	SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, bivalent booster, preservative free, 30 mcg/0.3 mL dose, tris-sucrose formulation	Pre-EUA Pfizer bivalent booster, ages adult 12+, original strain + omicron BA.4/BA.5

Note: CVX codes 207, 208, 217, 221, 229, 300 are categorized as “mRNA”, 212 is “JNJ”, and all others are categorized as “other”

Reference (a)

JAMA Cardiology | Brief Report

Myocarditis Following Immunization With mRNA COVID-19 Vaccines in Members of the US Military

Jay Montgomery, MD; Margaret Ryan, MD, MPH; Renata Engler, MD; Donna Hoffman, MSN; Bruce McClenathan, MD; Limone Collins, MD; David Loran, DNP; David Hrncir, MD; Kelsie Herring, MD; Michael Platzer, MD; Nehkonti Adams, MD; Aliye Sanou, MD; Leslie T. Cooper Jr, MD

IMPORTANCE Myocarditis has been reported with COVID-19 but is not clearly recognized as a possible adverse event following COVID-19 vaccination.

OBJECTIVE To describe myocarditis presenting after COVID-19 vaccination within the Military Health System.

DESIGN, SETTING, AND PARTICIPANTS This retrospective case series studied patients within the US Military Health System who experienced myocarditis after COVID-19 vaccination between January and April 2021. Patients who sought care for chest pain following COVID-19 vaccination and were subsequently diagnosed with clinical myocarditis were included.

EXPOSURE Receipt of a messenger RNA (mRNA) COVID-19 vaccine between January 1 and April 30, 2021.

MAIN OUTCOMES AND MEASURES Clinical diagnosis of myocarditis after COVID-19 vaccination in the absence of other identified causes.

RESULTS A total of 23 male patients (22 currently serving in the military and 1 retiree; median [range] age, 25 [20-51] years) presented with acute onset of marked chest pain within 4 days after receipt of an mRNA COVID-19 vaccine. All military members were previously healthy with a high level of fitness. Seven received the BNT162b2-mRNA vaccine and 16 received the mRNA-1273 vaccine. A total of 20 patients had symptom onset following the second dose of an appropriately spaced 2-dose series. All patients had significantly elevated cardiac troponin levels. Among 8 patients who underwent cardiac magnetic resonance imaging within the acute phase of illness, all had findings consistent with the clinical diagnosis of myocarditis. Additional testing did not identify other etiologies for myocarditis, including acute COVID-19 and other infections, ischemic injury, or underlying autoimmune conditions. All patients received brief supportive care and were recovered or recovering at the time of this report. The military administered more than 2.8 million doses of mRNA COVID-19 vaccine in this period. While the observed number of myocarditis cases was small, the number was higher than expected among male military members after a second vaccine dose.

CONCLUSIONS AND RELEVANCE In this case series, myocarditis occurred in previously healthy military patients with similar clinical presentations following receipt of an mRNA COVID-19 vaccine. Further surveillance and evaluation of this adverse event following immunization is warranted. Potential for rare vaccine-related adverse events must be considered in the context of the well-established risk of morbidity, including cardiac injury, following COVID-19 infection.

Editorial pages 1115 and 1117

Related article page 1196

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Jay Montgomery, MD, Walter Reed National Military Medical Center, 4954 N Palmer Rd, Bldg 19, Room 4026, Bethesda, MD 20889 (jay.r.montgomery.civ@mail.mil); Margaret Ryan, MD, MPH, Naval Medical Center San Diego, 34800 Bob Wilson Dr, Bldg 6, Room 4V7C1, San Diego, CA 92134 (margaret.a.ryan6.civ@mail.mil).

JAMA Cardiol. 2021;6(10):1202-1206. doi:10.1001/jamacardio.2021.2833
Published online June 29, 2021.

Myocarditis is a heterogeneous disease with diverse clinical patterns, etiologies, and therapeutic responses, reflecting inflammatory injury to myocardial tissue in the absence of ischemia.[1] While viral infections, now including SARS-CoV-2, are the most common triggers of the disease, some myocarditis cases are associated with certain drugs and vaccine exposures.[1] With the exception of cases following live-attenuated smallpox vaccine in the military population,[2] myocarditis as an adverse event following immunization is described in rare published case reports and infrequent submissions to the Vaccine Adverse Events Reporting System (VAERS).[3,4]

Serious adverse events associated with receipt of new vaccines targeting COVID-19 are of high interest to the public and to public health vaccine safety surveillance. We describe a series of 23 individuals who developed probable hypersensitivity myocarditis in temporal association with COVID-19 messenger RNA (mRNA) vaccination.

Key Points

Question Should myocarditis be considered a potential adverse event following immunization with messenger RNA (mRNA) COVID-19 vaccines?

Findings In this case series of 23 male patients, including 22 previously healthy military members, myocarditis was identified within 4 days of receipt of a COVID-19 vaccine. For most patients (n = 20), the diagnosis was made after the second dose of mRNA COVID-19 vaccine; these episodes occurred against the backdrop of 2.8 million doses of mRNA COVID-19 vaccines administered.

Meaning Vigilance for rare adverse events, including myocarditis, after COVID-19 vaccination is warranted but should not diminish overall confidence in vaccination during the current pandemic.

Methods

The US military initiated COVID-19 vaccination following US Centers for Disease Control and Prevention (CDC)–defined phased distribution in December 2020. Adverse events following immunizations were identified from referrals to Defense Health Agency clinical specialists and through review of VAERS reports. Retrospective review of cases was conducted in accordance with the Walter Reed National Military Medical Center Institutional Review Board–approved protocol, "Adverse Events Following Immunization: Case Definitions and Outcomes Retrospective Review," and exempt from formal consent procedures.

Results

A total of 23 male patients (22 currently serving in the military and 1 retiree; median [range] age, 25 [20-51] years) were evaluated between January and April 2021 for acute-onset chest pain following mRNA COVID-19 vaccination. Care was provided in 15 distinct geographic locations globally with varying diagnostic evaluations. Each patient had a final diagnosis of myocarditis without infectious, ischemic, or autoimmune etiologies identified. Diagnoses were reviewed by an adjudication process and met the CDC case definition criteria for probable myocarditis (**Table 1**). A total of 8 patients had cardiac magnetic resonance imaging (cMRI) with T2 weighting showing subepicardial late gadolinium enhancement and/or focal myocardial edema, consistent with Lake Louise criteria for myocarditis.[1] The eFigure in the Supplement exemplifies cMRI findings for one of these patients.

The demographic and clinical characteristics of patients are summarized in **Table 2**. All military service members were physically fit by military standards and lacking any known history of cardiac disease, significant cardiac risk factors, or exposure to cardiotoxic agents. All patients presented with acute chest pain and significantly elevated cardiac troponin levels (10-fold to 400-fold the upper limits of their respective reference ranges). Their symptoms began within 12 to 96 hours following immunization with an mRNA COVID-19 vaccine. Sixteen had received the mRNA-1273 vaccine (Moderna), and 7 had received the BNT162b2-mRNA vaccine (Pfizer-BioNTech). For all but 3 patients, the second dose of vaccine preceded their myocarditis presentations. Among the 3 patients presenting after an initial vaccine dose, all had confirmed COVID-19 infection more than 2 months prior to vaccination.

All patients underwent electrocardiography and echocardiography (Table 2). Abnormal electrocardiography findings were recorded in 19 patients (83%); findings included ST-segment elevations, T-wave inversions, and nonspecific ST changes. Echocardiography in 4 patients (17%) demonstrated reduced left ventricular ejection fractions (40% to 50%).

Table 1. Case Definition Criteria for Myocarditis Following Immunization[a]

Suspected case	Probable case	Confirmed case
Dyspnea, palpitations, or chest pain of probable cardiac origin, with either one of the following: A. ECG abnormalities beyond normal variants, not documented previously, including: • ST-segment/T-wave abnormalities • Paroxysmal or sustained atrial or ventricular arrhythmias • AV nodal conduction delays or intraventricular conduction defects • Continuous ambulatory ECG monitoring that detects frequent atrial or ventricular ectopy B. Focal or diffuse depressed LV function of indeterminate age identified by an imaging study	Meets criteria for suspected myocarditis, in the absence of other likely cause of symptoms, in addition to one of the following: A. Elevated cardiac enzymes (troponin-I, troponin-T, or creatine kinase-MB) B. New-onset or increased degree of severity of focal or diffuse depressed LV function by imaging C. Abnormal imaging findings indicating myocardial inflammation (cardiac MRI with gadolinium, gallium-67 scanning, antimyosin antibody scanning)	Histopathologic evidence of myocarditis by endomyocardial biopsy or autopsy

Abbreviations: ECG, electrocardiography; LV, left ventricular; MRI, magnetic resonance imaging.

[a] This definition was originally developed to evaluate cardiac events after smallpox vaccine. The definition is currently being reviewed by the international Brighton Collaboration for application to COVID-19 vaccine.

Table 2. Demographic and Clinical Characteristics of 23 Military Health System Patients With Myocarditis Following COVID-19 Vaccination, January-April 2021

Characteristic	No. (%)
Age, median (range), y	25 (20-51)
Sex	
Male	23 (100)
Female	0
Military status	
Currently serving	22 (96)
Retired	1 (4)
Proximate vaccine dose	
Second mRNA-1273 dose	14 (61)
Second BNT162b2-mRNA dose	6 (26)
First mRNA-1273 dose	2 (9)
First BNT162b2-mRNA dose	1 (4)
Time to symptom onset, mean (range), h	50 (12-96)
Troponin level[a]	
Elevated	23 (100)
Not elevated	0
Electrocardiogram findings[b]	
Abnormal	19 (83)
Normal	4 (17)
Echocardiogram findings[c]	
LVEF <50%	4 (17)
LVEF ≥50%	19 (83)
Coronary artery imaging	
Abnormal	0
Normal	16 (70)
Not performed	7 (30)
Cardiac MRI[d]	
Abnormal	8 (35)
Normal	0
Not performed	15 (65)
SARS-CoV-2 PCR findings at presentation	
Positive	0
Negative	19 (83)
Not performed	4 (17)
Other viral testing at presentation[e]	
Positive	0
Negative	13 (57)
Not performed	10 (43)
History of prior SARS-CoV-2 infection	
Positive	3 (13)
Negative	20 (87)

Abbreviations: LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; mRNA, messenger RNA; PCR, polymerase chain reaction.

[a] Inconsistencies in troponin types and laboratory sensitivity of testing preclude reporting combined quantified results.

[b] Electrocardiogram findings included ST elevations, T-wave inversions, and nonspecific ST changes.

[c] Echocardiogram findings are reported as LVEF; no structural abnormalities were noted in any patients.

[d] All abnormal cardiac MRIs reportedly met current Lake Louise criteria for myocarditis, with subepicardial late gadolinium enhancement and/or focal myocardial edema.

[e] Testing for other acute viral infections varied in each case; panels included some or all of these pathogens: coxsackie viruses, cytomegalovirus, Epstein-Barr virus, hepatitis A virus, hepatitis B virus, hepatitis C virus, herpes simplex virus, human herpesvirus 6, HIV, influenza viruses, and parvoviruses.

Table 3. Expected vs Observed Cases of Myocarditis in Military Health System Patients Based on Number of Messenger RNA (mRNA) COVID-19 Vaccine Doses Administered

Doses of mRNA COVID-19 vaccine (through April 30, 2021)	No. of myocarditis cases	
	Expected[a]	Observed
2 810 000 Total doses	2 to 52	23
1 065 000 Second doses	1 to 20	20
544 000 Second doses to military members	0 to 10	19
436 000 Second doses to male military members	0 to 8	19

[a] Expected number is based on an expected annual incidence ranging from 1 per 100 000 person-years to 22 per 100 000 person-years[5,6] presenting within a 30-day period after vaccination.

No structural abnormalities were noted on any echocardiograms. A total of 16 patients underwent coronary artery imaging (11 had cardiac catheterization and 5 had coronary computed tomography angiography); none showed evidence of coronary artery disease.

Nineteen patients had respiratory specimens tested for SARS-CoV-2 by polymerase chain reaction at the time of presentation; none had evidence of acute SARS-CoV-2 infection. There were no positive findings among 13 patients who were tested for other infections, nor among 9 patients who were tested for autoimmune diseases.

Cardiac symptoms resolved within 1 week of onset for 16 patients. Seven patients continued to have chest discomfort at the time of this report; follow-up is ongoing.

The number of doses of mRNA COVID-19 vaccine administered by the Military Health System through April 30, 2021, is shown in **Table 3**. Overall, 2 810 000 doses were administered; 1 065 000 second doses were administered; 544 000 second doses were administered to military service members; and 436 000 second doses were administered to male military service members. The expected number of myocarditis cases occurring in a 30-day period after vaccination may be estimated using an international incidence of 22 cases per 100 000 person-years[5] or a US incidence of 1 to 10 cases per 100 000 person-years.[6] Observed numbers of myocarditis in the Military Health System were higher than some estimates of expected numbers, especially when considering the subset of the population who were military service members who received second doses of an mRNA COVID-19 vaccine (Table 3).

Discussion

In this case series, we describe 23 patients with clinical evidence of myocarditis following mRNA COVID-19 vaccination and meeting the CDC case definition for probable myocarditis. Eight patients had cMRI findings consistent with myocarditis. All patients in this series reflect substantial similarities in demographic characteristics, proximate vaccine dose, onset interval, and character of vaccine-associated myocarditis. The consistent pattern of clinical presentation, rapid recovery, and absence of evidence of other causes support the diagnosis of hypersensitivity myocarditis. Without myocardial

biopsy, histology cannot be defined, but the clinical course suggests eosinophilic hypersensitivity myocarditis as described in the context of other drug-associated and vaccine-associated myocarditis.[1-3] Presentation after second vaccine dose or, in 3 patients, when vaccination followed SARS-CoV-2 infection, suggests that prior exposure was relevant in the hypersensitivity response.

With the exception of the smallpox vaccine, immunizations are rarely associated with hypersensitivity myocarditis. The spectrum of clinical presentation and reliance on patients seeking health care and on health care professionals recognizing a rare vaccine-associated adverse event limits determination of the true incidence of this condition.[7] In contrast to passive case finding, Engler et al[2] reported a significantly higher incidence of myocarditis and pericarditis after smallpox vaccination through active prospective follow-up of vaccinated participants. They noted that 60% of these patients would not have sought medical care for symptoms outside of the study protocol.[2] Recognition of vaccine-associated myocarditis is clinically important since diagnosis impacts management, recommendations for exercise, and monitoring for cardiomyopathy.[8]

Notably, myocarditis cases were not reported following vaccination in clinical trials of current COVID-19 vaccines.[9,10] Adverse cardiac events of any kind were reported in less than 0.1% of trial participants, and rates were not higher in recipients of vaccine compared with placebo. The inability to identify rare adverse events is understandable in preauthorization testing since fewer than 20 000 participants received a vaccine in each trial.

Background rates of myocarditis in the general population are variable and may be challenging to determine. As noted, a global estimate of incidence is 22 cases per 100 000 person-years.[5] More recent estimates of US incidence are lower (1 to 10 cases per 100 000 person-years) and may be more appropriate for estimating expected rates of diagnoses in evaluations of immunization safety.[6] Applying both the US and global background incidence to the population vaccinated by the US military yields a range of expected numbers of cases of myocarditis in this period (Table 3). The observed number of male military members who experienced myocarditis after their second dose of mRNA vaccine, while relatively small, is substantially higher than the expected number.

Finally, it is important to frame concerns about potential vaccine-associated myocarditis within the context of the current pandemic. Infection with SARS-CoV-2 is a clear cause of serious cardiac injury in many patients.[11] The mechanism of injury may be direct infection, an immune-mediated response, or a combination of direct or indirect effects. Prevalence of cardiac injury may be as high as 60% in seriously ill patients. Notably, nearly 1% of highly fit athletes with mild COVID-19 infection have evidence of myocarditis on cMRI.[12,13] Given that COVID-19 vaccines are remarkably effective at preventing infection, any risk of rare adverse events following immunization must be carefully weighed against the very substantial benefit of vaccination.

Limitations

Important limitations to this case series should be considered. Passive surveillance, even when stimulated by global attention on vaccine safety, may not identify all cases. The patients described in this report were identified in a brief period of observation after vaccine implementation from a cohort of essential workers who are not necessarily representative of the general population. Clinical evaluations varied and did not include complete testing in some patients who received care in different hospitals and in different countries. In particular, consistent application of cMRI and thorough viral testing would have strengthened clinical conclusions. This early report is also unable to describe longer-term outcomes among these patients. Despite limitations of this review, it is notable that the clinical presentations of these 23 patients appear consistent with other recent case reports of myocarditis after second doses of mRNA COVID-19 vaccines.[14,15]

Conclusions

We report a case series of probable hypersensitivity myocarditis with consistent temporal association to receipt of an mRNA COVID-19 vaccine. While the true incidence of this adverse event is unknown at this time, the presentation pattern and clinical course suggest an association with an inflammatory response to vaccination. Increased attention to myocarditis as a potential adverse event following immunization is warranted. Recognition of the substantial morbidity associated with COVID-19 infection, including risk of cardiac injury, and the strong effectiveness of immunization in preventing infection provide important context for this topic. Concerns about rare adverse events following immunization should not diminish overall confidence in the value of vaccination.

ARTICLE INFORMATION

Accepted for Publication: June 1, 2021.

Published Online: June 29, 2021. doi:10.1001/jamacardio.2021.2833

Author Affiliations: Immunization Healthcare Division, Defense Health Agency, Falls Church, Virginia (Montgomery, Ryan, Hoffman, McClenathan, Collins, Loran, Hrncir); Walter Reed National Military Medical Center, Bethesda, Maryland (Montgomery, Hoffman); Naval Medical Center, San Diego, California (Ryan, Loran); Uniformed Services University of the Health Sciences, Bethesda, Maryland (Engler, Adams); Womack Army Medical Center, Fort Bragg, North Carolina (McClenathan); Wilford Hall Ambulatory Surgical Center, Lackland Air Force Base, San Antonio, Texas (Hrncir); Naval Hospital Bremerton, Bremerton, Washington (Herring); Marine Expeditionary Forces, Okinawa, Japan (Platzer, Adams, Sanou); Mayo Clinic, Jacksonville, Florida (Cooper).

Author Contributions: Drs Montgomery and Ryan had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Montgomery, Ryan, McClenathan, Collins, Hrncir, Herring.
Acquisition, analysis, or interpretation of data: Montgomery, Ryan, Engler, Hoffman, McClenathan, Loran, Hrncir, Herring, Platzer, Adams, Sanou, Cooper.
Drafting of the manuscript: Montgomery, Ryan, Engler, Cooper.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Ryan, McClenathan.

Administrative, technical, or material support: Montgomery, Ryan, Engler, Hoffman, McClenathan, Collins, Loran, Hrncir, Herring, Platzer, Adams, Sanou.
Study supervision: Montgomery, Ryan, Cooper.

Conflict of Interest Disclosures: Dr Cooper has received personal fees from Bristol Myers Squibb, Cantargia, CardioPath, Kiniksa Pharmaceuticals, and Cardiol Therapeutics. No other disclosures were reported.

Disclaimer: The views expressed are those of the authors and do not necessarily reflect official policy of the Department of Defense or the US government.

Additional Contributions: We thank the eldest patient for granting permission to publish identifiable information. We appreciate the contributions of the many clinicians who provided care or consultation for these patients worldwide, including, but not limited to, Todd Looney, MD; Matthew Needleman, MD; J. Edwin Atwood, MD; Carlie Cerne, MD; P. Gabriel Peterson, MD; Benjamin St. Clair, MD; and Nathan Boggs, MD (Walter Reed National Military Medical Center, Bethesda, Maryland); and Michael Romero, HM1, USN. We appreciate the support of Col Tonya Rans, USAF, MC; Laurie Duran, MSN; Laurie Housel, MSN; Ann Morse, MSN; Catherine Skerrett, MSN (Immunization Healthcare Division, Defense Health Agency, Falls Church, Virginia); and the Clinical Immunization Safety Assessment professionals at the US Centers for Disease Control and Prevention.

REFERENCES

1. Tschöpe C, Ammirati E, Bozkurt B, et al. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. *Nat Rev Cardiol*. 2021;18(3):169-193. doi:10.1038/s41569-020-00435-x

2. Engler RJ, Nelson MR, Collins LC Jr, et al. A prospective study of the incidence of myocarditis/pericarditis and new onset cardiac symptoms following smallpox and influenza vaccination. *PLoS One*. 2015;10(3):e0118283. doi:10.1371/journal.pone.0118283

3. Aslan I, Fischer M, Laser KT, Haas NA. Eosinophilic myocarditis in an adolescent: a case report and review of the literature. *Cardiol Young*. 2013;23(2):277-283. doi:10.1017/S1047951112001199

4. Mei R, Raschi E, Forcesi E, Diemberger I, De Ponti F, Poluzzi E. Myocarditis and pericarditis after immunization: gaining insights through the Vaccine Adverse Event Reporting System. *Int J Cardiol*. 2018;273:183-186. doi:10.1016/j.ijcard.2018.09.054

5. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;386(9995):743-800. doi:10.1016/S0140-6736(15)60692-4

6. Gubernot D, Jazwa A, Niu M, et al. U.S. population-based background incidence rates of medical conditions for use in safety assessment of COVID-19 vaccines. *Vaccine*. Published online May 14, 2021. doi:10.1016/j.vaccine.2021.05.016

7. Kuntz J, Crane B, Weinmann S, Naleway AL; Vaccine Safety Datalink Investigator Team. Myocarditis and pericarditis are rare following live viral vaccinations in adults. *Vaccine*. 2018;36(12):1524-1527. doi:10.1016/j.vaccine.2018.02.030

8. Hurwitz B, Issa O. Management and treatment of myocarditis in athletes. *Curr Treat Options Cardiovasc Med*. 2020;22(12):65. doi:10.1007/s11936-020-00875-1

9. US Food and Drug Administration. Pfizer-BioNTech COVID-19 vaccine (BNT162, PF-07302048): Vaccines and Related Biological Products Advisory Committee briefing document. Accessed May 26, 2021. https://www.fda.gov/media/144246/download

10. US Food and Drug Administration. Moderna MRNA-1273 sponsor briefing document for Vaccines and Related Biological Products Advisory Committee. Accessed May 26, 2021. https://www.fda.gov/media/144452/download

11. Castiello T, Georgiopoulos G, Finocchiaro G, et al. COVID-19 and myocarditis: a systematic review and overview of current challenges. *Heart Fail Rev*. 2021;1-11. doi:10.1007/s10741-021-10087-9

12. Starekova J, Bluemke DA, Bradham WS, et al. Evaluation for myocarditis in competitive student athletes recovering from coronavirus disease 2019 with cardiac magnetic resonance imaging. *JAMA Cardiol*. Published online January 14, 2021. doi:10.1001/jamacardio.2020.7444

13. Martinez MW, Tucker AM, Bloom OJ, et al. Prevalence of inflammatory heart disease among professional athletes with prior COVID-19 infection who received systematic return-to-play cardiac screening. *JAMA Cardiol*. Published online March 4, 2021. doi:10.1001/jamacardio.2021.0565

14. Bautista García J, Peña Ortega P, Bonilla Fernández JA, Cárdenes León A, Ramírez Burgos L, Caballero Dorta E. Acute myocarditis after administration of the BNT162b2 vaccine against COVID-19. *Rev Esp Cardiol (Engl Ed)*. Published online March 20, 2021. doi:10.1016/j.rec.2021.04.005

15. Albert E, Aurigemma G, Saucedo J, Gerson DS. Myocarditis following COVID-19 vaccination. *Radiol Case Rep*. 2021;16(8):2142-2145. doi:10.1016/j.radcr.2021.05.033

Reference (b)

Myopericarditis after COVID-19 vaccination: unexpected but not unprecedented

Published Online
April 11, 2022
https://doi.org/10.1016/S2213-2600(22)00091-1

See Articles page 679

In the midst of the devastating COVID-19 pandemic, rapid development of highly effective vaccines was enthusiastically welcomed. Unfortunately, myopericarditis after COVID-19 vaccination was an unanticipated adverse event. In *The Lancet Respiratory Medicine*, Ryan Ruiyang Ling and colleagues commendably review the risk of this adverse event in the context of risk after other vaccines.[1] Their study provides an important perspective on the historical global experience with cardiac adverse events after vaccination.

Ling and colleagues applied rigorous statistical analyses to the available literature and confirmed the conclusions of other reviewers. Specifically, the overall incidence of myopericarditis after COVID-19 vaccination (18·2 cases [95% CI 10·9–30·3] per million doses) is not higher than expected outside of the context of vaccination, and not significantly higher than the incidence of myopericarditis reported after the standard immunisations included in the study, such as influenza vaccines (1·3 [0·0–884·1], p=0·43 *vs* COVID-19 vaccines). There is, however, an important demographic and vaccine-related component to this adverse event that is obscured in reporting the overall incidence. The risk of myopericarditis in young males after their second dose of mRNA COVID-19 vaccine is remarkably higher than expected.

This pattern has been seen before. As Ling and colleagues found when they reviewed the extant literature, myopericarditis risk is well established after receipt of live-replicating smallpox vaccine. Notably, in a study by Oster and colleagues[2] of myocarditis after mRNA COVID-19 vaccination, the rate of myocarditis reported in the highest-risk group of recipients (105·86 cases [95% CI 91·65–122·27] per million doses in males aged 16–17 years receiving a second dose) approached the historical rate of myopericarditis after smallpox vaccination (132·1 cases [81·3–214·6] per million doses) according to Ling and colleagues' study.[1] US military professionals, who are very familiar with adverse events following smallpox vaccination, were among the first to observe myocarditis cases after mRNA COVID-19 vaccines,[3] most likely because the US military includes a large number of young men who received two doses of COVID-19 vaccine very early in the 2021 pandemic vaccine rollout.

Although there are common demographic and clinical features between the myopericarditis cases that followed smallpox vaccine and those that followed mRNA COVID-19 vaccines, better understanding of the pathophysiology of these adverse events following vaccination is an important area for future research. Because smallpox vaccination has very limited global application in the modern era, the experience of mRNA COVID-19 vaccination must now propel the field forward. Analyses of the pathology and immunological mechanisms behind these demographic-dependent adverse events following vaccination are likely to advance our understanding of cardiology and immunology.[4–6] These advances could spur the development of safer vaccines or precision vaccination practices.[7]

Ling and colleagues' analysis[1] also raises important questions about whether cardiac adverse events following vaccination have historically been well evaluated outside of the realm of smallpox vaccine. In a literature review spanning 75 years, it is remarkable that the study team identified only five publications addressing myocarditis following immunisations other than smallpox or COVID-19 vaccination. The 7 million vaccine doses described in these publications represent a small fraction of the billions of vaccinations administered globally every year.[8] This challenge might impact the interpretation of the results. Among the populations who received billions of vaccine doses after which myopericarditis was not observed or very rarely observed, published literature might not exist; reassuring data from background populations would not be captured in analyses of the literature, such as those conducted by Ling and colleagues. The safety signal observed after COVID-19 vaccination is, therefore, even more important to fully investigate.[9]

Reports of unexpected adverse events—albeit rare and limited to a specific subset of vaccine recipients—have the potential to damage vaccine confidence at a crucial point in the pandemic response. Like Ling and colleagues, all professionals who have described myopericarditis following COVID-19 vaccination have emphasised that the benefits of vaccination far outweigh the risks

during the current pandemic. Nonetheless, scientific knowledge and public health strategies must continue to evolve. Alternative vaccine platforms, vaccine doses, or vaccine schedules could reduce the risk of rare adverse events and must be explored in the context of changing infection risk.[10] Vaccine confidence is one our most valuable resources, and it is dependent upon trust in public health. Trust is a fragile commodity that is strengthened by reporting challenges transparently and addressing these challenges with scientific rigour and appropriate concern.

We declare no competing interests.

*Margaret Ryan, Jay Montgomery
m1ryan@ucsd.edu

Immunization Healthcare Division, Defense Health Agency, Falls Church, VA, USA (MR, JM); University of California San Diego, San Diego, CA 92134, USA (MR); Walter Reed National Military Medical Center, Bethesda, MD, USA (JM)

1 Ling RR, Ramanathan K, Tan FL, et al. Myopericarditis following COVID-19 vaccination and non-COVID-19 vaccination: a systematic review and meta-analysis. *Lancet Respir Med* 2022; published online April 11. https://doi.org/10.1016/S2213-2600(22)00059-5.

2 Oster ME, Shay DK, Su JR, et al. Myocarditis cases reported after mRNA-based COVID-19 vaccination in the US from December 2020 to August 2021. *JAMA* 2022; **327:** 331–40.

3 Montgomery J, Ryan M, Engler R, et al. Myocarditis following immunization with mRNA COVID-19 vaccines in members of the US military. *JAMA Cardiol* 2021; **6:** 1202–06.

4 Kiblboeck D, Klingel K, Genger M, et al. Myocarditis following mRNA COVID-19 vaccination: call for endomyocardial biopsy. *ESC Heart Fail* 2022; published online Feb 23. https://doi.org/10.1002/ehf2.13791.

5 Mormile R. Myocarditis and pericarditis following mRNA COVID-19 vaccination in younger patients: is there a shared thread? *Expert Rev Cardiovasc Ther* 2022; **20:** 87–90.

6 Hajjo R, Sabbah DA, Bardaweel SK, Tropsha A. Shedding the light on post-vaccine myocarditis and pericarditis in COVID-19 and non-COVID-19 vaccine recipients. *Vaccines (Basel)* 2021; **9:** 1186.

7 Kennedy RB, Ovsyannikova IG, Palese P, Poland GA. Current challenges in vaccinology. *Front Immunol* 2020; **11:** 1181.

8 Strategic Advisory Group of Experts on Immunization. The Global Vaccine Action Plan 2011–2020. Review and lessons learned (WHO/IVB/19.07). Geneva: World Health Organization, 2019.

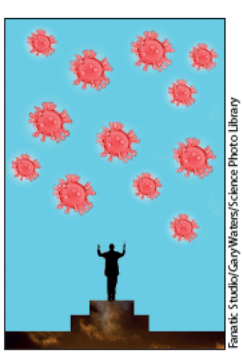
9 Arnaud M, Bégaud B, Thurin N, Moore N, Pariente A, Salvo F. Methods for safety signal detection in healthcare databases: a literature review. *Expert Opin Drug Saf* 2017; **16:** 721–32.

10 Shiri T, Evans M, Talarico CA, et al. The population-wide risk-benefit profile of extending the primary COVID-19 vaccine course compared with an mRNA booster dose program. *Vaccines (Basel)* 2022; **10:** 140.

Early-phase clinical trials in a pandemic: learning from the response to COVID-19

The first cases of the novel SARS-CoV-2 virus emerged at the end of 2019 in Wuhan, China. Within 2 months, WHO had declared a public health emergency and the first cases were detected in the UK. The rapid spread of SARS-CoV-2 caused widespread disruption across society and health care, and left little time to plan and design research needed in the context of a new pandemic. Some studies (eg, ISARIC and REMAP-CAP) had pre-existing protocols that were rapidly adjusted, but in most instances, new research studies and clinical trials had to be set up rapidly to respond to the unique environment and challenges created by COVID-19. The success or otherwise of the adaptations made as part of this research response has been highly informative and provides an opportunity to plan effectively for future threats.

The UK adopted a streamlined approach to the delivery of vaccines and therapeutics, capitalising on a single National Health Service (NHS) and the UK National Institute for Health and Care Research (NIHR), a government-funded health research system linked to the NHS. The NIHR Respiratory Translational Research Collaboration (R-TRC) network was in a unique position to coordinate, set up, and conduct early-phase (typically phase 1 and phase 2) clinical trials required to test repurposed or unlicensed drugs for a new disease. Before the pandemic, the R-TRC's main objective was to accelerate delivery of new respiratory drugs via collaborative UK-wide efforts in partnership with industry. In the first few weeks of the pandemic, the R-TRC pivoted to work on mechanistic human immunology studies and phase 2 clinical trials of therapeutics across our ten major teaching hospitals and universities members. We supported one of the first immunology studies on COVID-19 in the UK[1] and used nascent scientific findings to help to select repurposed drugs for early-phase therapeutic trials. Ultimately, the R-TRC helped to deliver 15 phase 2 trials and two large, national phase 2 platform trials,[2,3] and contributed to drug selection via the national centralised UK COVID-19 Therapeutic Advisory Panel process.[4] Here, we discuss our experiences and lessons learned from the first year of the pandemic in the UK[5] and present recommendations for future planning of early-phase clinical trials during a pandemic.



Fanatic Studio/Gary Waters/Science Photo Library

Published Online
June 13, 2022
https://doi.org/10.1016/S2213-2600(22)00062-5

See Personal View page 700

For more on **ISARIC** see https://isaric.org/

For more on **REMAP-CAP** https://www.remapcap.org/

For more on **RECOVERY** see https://www.recoverytrial.net/

For more on the **R-TRC** see https://www.nihr.ac.uk/partners-and-industry/industry/collaborate-with-us/respiratory-trc.htm

Reference (c)

Circulation Research

COMPENDIUM ON COVID-19 AND CARDIOVASCULAR DISEASE

COVID-19, Myocarditis and Pericarditis

DeLisa Fairweather,* Danielle J. Beetler,* Damian N. Di Florio, Nicolas Musigk, Bettina Heidecker, Leslie T. Cooper Jr

ABSTRACT: Viral infections are a leading cause of myocarditis and pericarditis worldwide, conditions that frequently coexist. Myocarditis and pericarditis were some of the early comorbidities associated with SARS-CoV-2 infection and COVID-19. Many epidemiologic studies have been conducted since that time concluding that SARS-CoV-2 increased the incidence of myocarditis/pericarditis at least 15× over pre-COVID levels although the condition remains rare. The incidence of myocarditis pre-COVID was reported at 1 to 10 cases/100 000 individuals and with COVID ranging from 150 to 4000 cases/100 000 individuals. Before COVID-19, some vaccines were reported to cause myocarditis and pericarditis in rare cases, but the use of novel mRNA platforms led to a higher number of reported cases than with previous platforms providing new insight into potential pathogenic mechanisms. The incidence of COVID-19 vaccine-associated myocarditis/pericarditis covers a large range depending on the vaccine platform, age, and sex examined. Importantly, the findings highlight that myocarditis occurs predominantly in male patients aged 12 to 40 years regardless of whether the cause was due to a virus-like SARS-CoV-2 or associated with a vaccine—a demographic that has been reported before COVID-19. This review discusses findings from COVID-19 and COVID-19 vaccine-associated myocarditis and pericarditis considering the known symptoms, diagnosis, management, treatment, and pathogenesis of disease that has been gleaned from clinical research and animal models. Sex differences in the immune response to COVID-19 are discussed, and theories for how mRNA vaccines could lead to myocarditis/pericarditis are proposed. Additionally, gaps in our understanding that need further research are raised.

Key Words: COVID-19 vaccines ■ models, animal ■ mRNA vaccines ■ sex characteristics ■ vaccines

Nearly 3 years have passed since the World Health Organization declared SARS-CoV-2–induced COVID-19 as a pandemic. Some of the early comorbidities reported for COVID-19 were cardiovascular complications including arrhythmias, myocardial infarct, myocarditis, pericarditis, and thromboembolic events. Since that time, many population-based studies have been conducted to examine the incidence or prevalence of myocarditis or pericarditis associated with SARS-CoV-2 infection or COVID-19. Vaccines against SARS-CoV-2 were rapidly developed, including a new mRNA vaccine platform that utilizes mRNA against the dominant antigen of the virus encapsulated in lipid nanoparticles also known as extracellular vesicles (EVs). Soon after the vaccination programs started, case reports describing myocarditis and pericarditis appeared[1,2] with data obtained from passive vaccine surveillance programs, hospital data, and from countries with mandatory vaccination programs or integrated health care systems. Over time, many large population-based studies examined the incidence or prevalence of vaccine-associated myocarditis. This review provides a summary of data on the ability of SARS-CoV-2 to infect the heart, the immune response that it generates, animal models of COVID-19 and their relevance to the heart, as well as the epidemiology, symptoms, diagnosis, and management of COVID-19–associated myocarditis and pericarditis including COVID-19 vaccine–associated cases and proposed mechanisms.

SARS-COV-2 CARDIAC VIRAL ENTRY

SARS-CoV-2 is a large enveloped RNA virus that shares around 80% sequence homology with SARS-CoV and

Correspondence to: DeLisa Fairweather, PhD, FAHA, FHFSA, Department of Cardiovascular Medicine, Birdsall Room 313, 4500 San Pablo Road, Mayo Clinic, Jacksonville, FL, 32224. Email Fairweather.DeLisa@mayo.edu
*D. Fairweather and D.J. Beetler contributed equally.
Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCRESAHA.123.321878.
For Sources of Funding and Disclosures, see page 1314.

Nonstandard Abbreviations and Acronyms

ACE2	angiotensin-converting enzyme 2
Ang II	angiotensin II
Ang 1–7	angiotensin 1–7
APC	antigen-presenting cell
ATR1	angiotensin II receptor 1
cMRI	cardiac magnetic resonance imaging
CR	complement receptor
CRP	C-reactive protein
CVB3	coxsackievirus B3
DCM	dilated cardiomyopathy
EAM	experimental autoimmune myocarditis
EMB	endomyocardial biopsy
EV	extracellular vesicle
IFN	interferon
IL	interleukin
NLRP3	nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3
NRP1	neuropilin-1 receptor
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PCR	polymerase chain reaction
TGF	transforming growth factor
Th	T helper
Tim-3	T-cell immunoglobulin mucin domain 3
TLR	toll-like receptor
TMPRSS2	transmembrane serine protease-2
TNFα	tumor necrosis factor-alpha

50% homology with the Middle Eastern respiratory syndrome coronavirus.[3] Importantly, ACE2 (angiotensin-converting enzyme 2) had been identified as the receptor for SARS-CoV[4,5] and SARS-CoV-2.[6–8] The spike protein of SARS-CoV-2 binds ACE2 and is cleaved by human type II TMPRSS2 (transmembrane serine protease-2) facilitating viral entry into the cytosol.[6] TMPRSS2 is also required for SARS-CoV and Middle Eastern respiratory syndrome coronavirus viral entry.[9,10] COVID-19 occurs predominantly in men,[11–13] which may be explained, at least in part, by a higher expression of ACE2 on male versus female cells.[14] Thus, these 3 coronaviruses that cause myocarditis share many similarities in the receptors they use for viral entry.

ACE2 expression has been reported for many tissues/organs including the lung (ie, lung type II alveolar cells/AT2, bronchial epithelial cells), brain, kidney, small intestine, colon, and heart.[9,14–17] Zou et al[16] examined published single-cell RNA sequencing data and found that 7.5% of cells in the heart expressed ACE2. In the heart, ACE2 has been reported to be expressed on cardiomyocytes, pericytes (cells present along the walls of capillaries), and macrophages with lower expression on fibroblasts and endothelial cells.[18,19] TMPRSS2 is also expressed on endothelial cells and pericytes.[10] The SARS-CoV-2 genome has been detected by polymerase chain reaction (PCR) in cardiac tissues from autopsies of patients with COVID-19,[20,21] suggesting the virus can infect the heart. Thus, cardiomyocytes and pericytes express ACE2 and TMPRSS2, as well as other accessory proteins (ie, NRP1 [neuropilin-1 receptor], CD147, integrin $\alpha5\beta1$, and cathepsin B/L) needed for viral infection by SARS-CoV-2 (Figure 1; reviewed in the study by Abdi et al[22]).[23–27] In a study examining the prevalence of ACE2 on immune cells, it was found to be expressed primarily on activated tissue macrophages but not on peripheral blood mononuclear cells in healthy people.[28] ACE2, TMPRSS2, NRP1, integrins, and cathepsins are also expressed on mast cells (Figure 1),[28,29] which can act as antigen-presenting cells (APCs) in addition to their typical activity in promoting T helper (Th) 2 immune responses, remodeling, and fibrosis. Because the level of virus in the heart is thought to be low based on autopsy studies,[20,21] it has been questioned whether low SARS-CoV-2 levels in the heart can cause myocarditis.

SARS-COV-2–MEDIATED CARDIAC DAMAGE: POTENTIAL MECHANISMS

Clinicians typically assess myocardial damage (ie, necrosis) by examining serum cardiac troponins.[30,31] However, myocarditis often occurs without necrosis so that the absence of elevated troponin does not rule out the presence of myocarditis, even severe myocarditis.[32,33] Potentially low SARS-CoV-2 infection may damage cardiomyocytes leading to cardiac myosin release and activation of resident APCs like mast cells and macrophages to recruit inflammation to the heart. Autopsy studies conducted retrospectively to determine the number of myocarditis cases from COVID-19 often have several issues, including requiring the histology to display inflammation and necrosis and not providing or analyzing data according to sex and age. For example, 1 study of 277 autopsy cases from patients with COVID-19 reported myocarditis in 7.2% of cases,[34] but the median age of subjects in the study was 75 year-old-men and women while myocarditis predominantly occurs in men under the age of 50 years.

One important question is whether direct infection of cardiac tissues by SARS-CoV-2 can lead to myocarditis or whether other mechanisms such as cytokine storm, indirect infection from EVs, or molecular mimicry are needed. Direct infection with high viral levels is presumed to be the cause of viral myocarditis. However, several animal models of viral myocarditis have

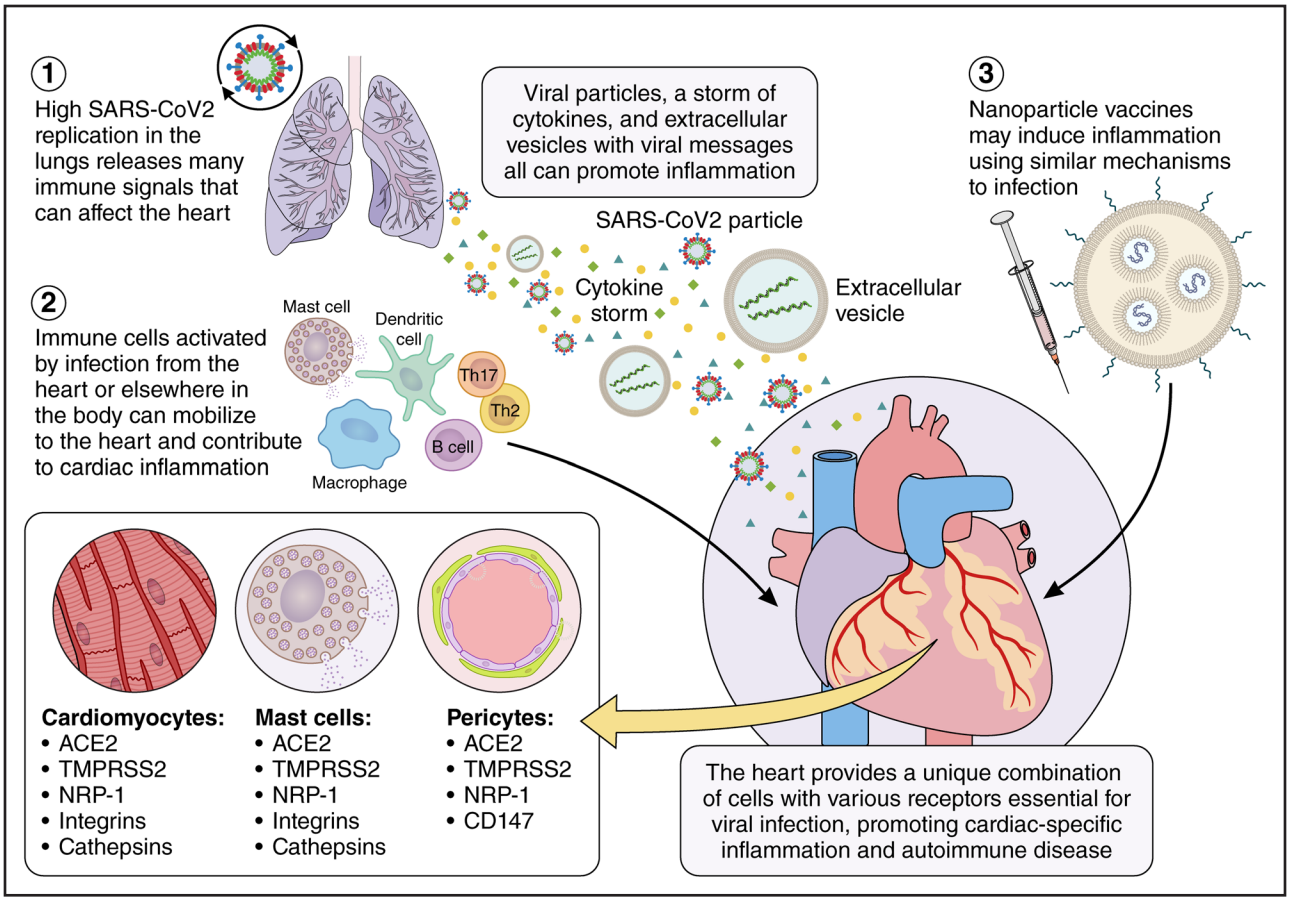


Figure 1. Potential mechanisms leading to myocarditis/pericarditis following SARS-CoV-2 infection or vaccination. SARS-CoV-2 initially infects the lungs generating a cytokine storm including TNFα (tumor necrosis factor-alpha), IL (interleukin)-1β, and IL-6 and releasing extracellular vesicles (EVs) that contain virus or virus particles. 2. EVs may traffic through the blood or lymph to the heart where they infect cardiac cells that express the necessary receptors (ACE2 [angiotensin-converting enzyme 2], TMPRSS2 [transmembrane serine protease-2], and NRP1 [neuropilin-1 receptor]) such as cardiomyocytes, pericytes, mast cells, and macrophages. Additionally, resident antigen-presenting cells like mast cells, dendritic cells, and macrophages respond to virus and damaged cardiac tissue by activating an adaptive autoimmune response leading to myocarditis. 3. COVID-19 vaccines may activate resident mast cells or macrophages at the injection site that in susceptible individuals who have cardiac injury may promote an autoimmune response leading to myocarditis. Illustration credit: Sceyence Studios.

low or barely detectable levels of virus in the heart (or use complete Freund's adjuvant with inactivated *Mycobacterium tuberculosis*), and these autoimmune models closely resemble the time course and pathogenesis of clinical lymphocytic myocarditis (data shown in review[35]; Table S1).[35–37] A comparison of viral autoimmune myocarditis models to virus- or autoimmune-only models is summarized in Table S1 and reviewed in previous studies.[35,37–39] It is important to realize that the dominant immune infiltrate during COVID-19 myocarditis, acute lymphocytic myocarditis, and in autoimmune models of myocarditis are macrophages (50%–80%) with fewer T and B cells (15%; Figure 2), and so the name for this most common form of myocarditis (ie, lymphocytic) is somewhat misleading. Thus, based on findings in autoimmune models of myocarditis, it is not necessary for SARS-CoV-2 to replicate in the heart at a high level to cause myocarditis.

Because COVID-19 is associated with cytokine storm,[40] it has been proposed that this may lead to myocarditis. However, no animal models of myocarditis exist where administration of proinflammatory cytokines alone induce cardiac inflammation without the use of an adjuvant (ie, active or inactive virus, bacteria, or parasite) and damaged self-tissue. The fundamental question is how inflammation would be directed to the heart unless cardiac damage has occurred or a microbe infects the heart (even at a low level). In this context, elevated circulating cytokines could increase myocarditis as has been shown previously when recombinant TNFα (tumor necrosis factor-alpha), IL (interleukin)-1β, or IL-33 was administered in coxsackievirus B3 (CVB3) virus-only or autoimmune CVB3 animal models.[41,42] Similarly, molecular mimicry has been examined for its potential role in virus-induced myocarditis for many years.[43,44] Gil-Cruz et al[44] found that cross-reactivity

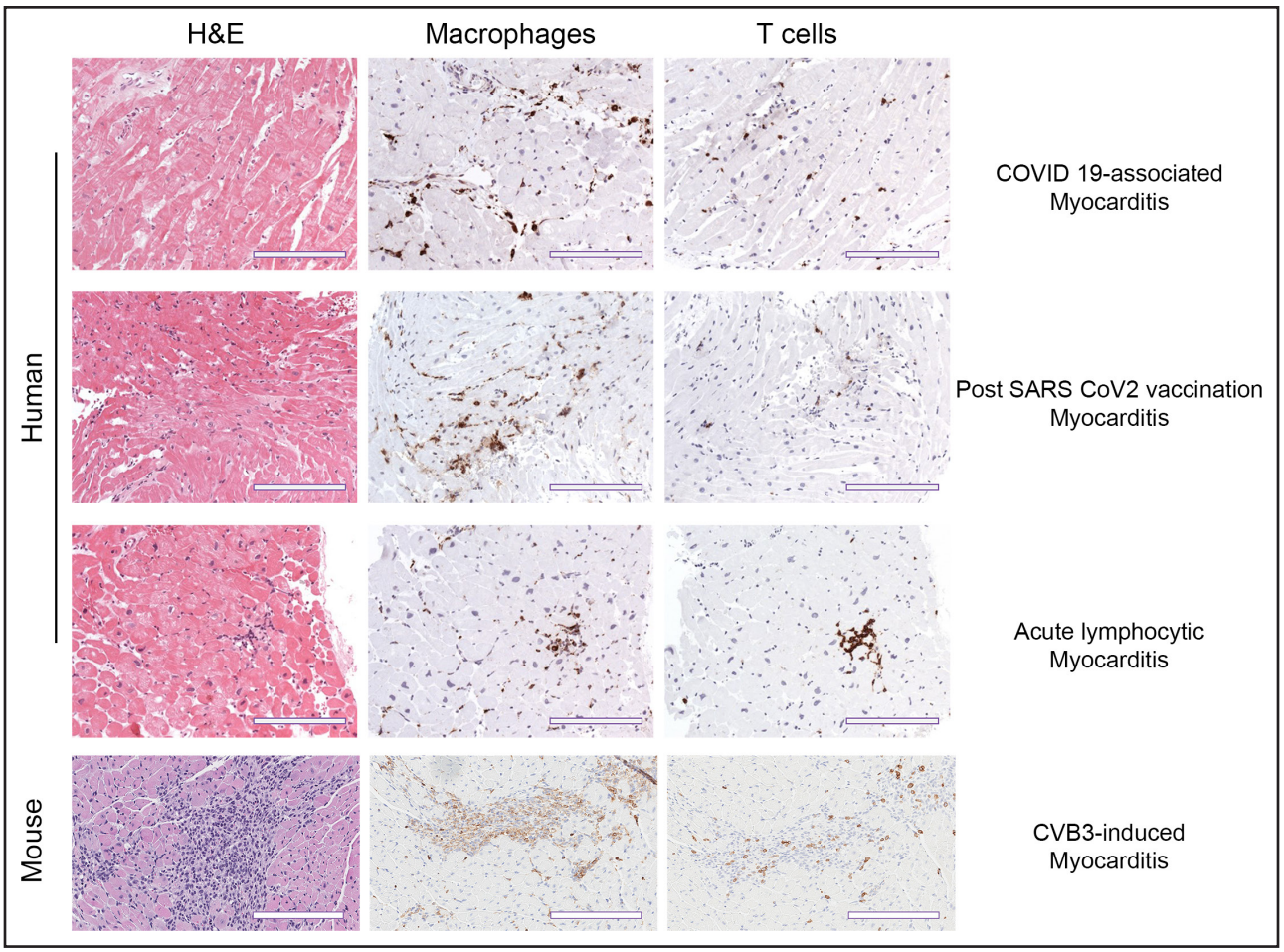


Figure 2. Similarity in histological staining ratio for macrophages and T cells during COVID-19 myocarditis and vaccination versus pre-COVID myocarditis in humans and mice.
Representative immunohistochemistry staining of myocardium in both human and mouse samples. Hematoxylin and eosin (H&E) staining shows inflammatory foci. Species-specific markers for macrophages (CD63+ human, CD11b+ mouse) and T cells (CD3+) show immune cell composition of the inflammatory infiltrate. Human scale bars, 100 μm; mouse scale bars, 200 μm.

between gut bacteria and cardiac myosin-specific T cells promotes myocarditis in the context of a cardiac viral infection. Thus, the simplest explanation for how SARS-CoV-2 infection leads to myocarditis is that damage to the heart from viral infection draws inflammation to the heart and that an autoimmune response to virus and cardiac damage is amplified by the strong circulating proinflammatory milieu in susceptible individuals (ie, young men with more mast cells; Figure 1).

An emerging mechanism that may also be involved in promoting myocarditis following SARS-CoV-2 infection includes EVs that harbor viral mRNA. Many viruses such as HIV, coxsackievirus, hepatitis B and C, influenza, Epstein-Barr virus, and SARS-CoV-2 highjack cellular and mitochondrial programs to enhance viral replication, package virus into EVs, and use EVs containing virus or viral components to subvert the immune response to obtain a replicative advantage in the host (Figure 1).[45–47] This is also true for SARS-CoV-2 RNA, which has been detected in EVs.[48–50] Virus-containing EVs could enter the circulation from the lungs or other organs and enter the heart to be taken up by resident APCs like mast cells and macrophages to promote myocarditis (Figure 1). Additionally, it is possible that virus-containing EVs may be taken up by cells that do not express ACE2 using surface ligands on EVs.[51]

ACE2 AS A MODULATOR OF VASCULAR FUNCTION

ACE2 not only functions as a viral receptor for SARS-CoV-2 but also regulates blood pressure.[52] When SARS-CoV-2 binds ACE2, it reduces its expression. ACE2 on endothelial cells of the arteries, arterioles, and venules of the heart and kidney determines its ability to regulate vascular function and blood pressure, as reviewed previously.[19,53,54] ACE2 is a cell surface metalloenzyme and carboxypeptidase that regulates Ang II (angiotensin II) and Ang 1–7 (angiotensin 1–7). Ang II binds the ATR1 (Ang II receptor 1) receptor leading to release of

TNFα and IL-6,[55] which is associated with hypertension, diabetes, and heart disease[52,56,57]—major comorbidities in severe COVID-19.[58] ATR1 also increases reactive oxygen species from mitochondria in monocytes/macrophages leading to DNA damage and apoptosis of T cells resulting in endothelial injury and lymphopenia.[59,60] This leads to upregulation of complement pathways and TLR (Toll-like receptor) 2, TLR3, and TLR4 leading to elevated IFNs (interferons) and activation of the inflammasome resulting in amplified TNFα, IL-1β, and IL-6 to produce a cytokine storm. [61,62] We have published previously that upregulation of complement and TLRs including TLR4 are key immune pathways that promote myocarditis in the autoimmune-CVB3 animal model (reviewed in the studies by Di Florio et al[63] and Fairweather et al[64]), although we have not examined the role of ACE2/Ang II/ATR1 in this model. However, Tanaka et al[65] found that inhibiting Ang II reduced death in a viral-only model of ECMV-induced myocarditis, suggesting that this pathway could be important in viral myocarditis.

COVID-19 MYOCARDITIS AND PERICARDITIS

Myocardial damage similar to myocarditis was one of the first complications reported from patients with COVID-19 in Wuhan, China, at the beginning of the pandemic.[66,67] Although respiratory complications from the virus were the most commonly reported, it became clear early on that SARS-CoV-2 infection was also leading to adverse cardiac events including ventricular arrhythmias, acute coronary syndromes with obstructive coronary artery disease such as myocardial infarct, thromboembolic syndromes including stroke, acute myocardial damage with elevated troponin levels without evidence of coronary artery disease (ie, myocarditis), and heart failure.[66,68,69] In patients with severe COVID-19, elevated biomarkers of cardiac damage that predict heart failure including troponins and NT-proBNP (N-terminal pro-B-type natriuretic peptide) were strongly and independently associated with in-hospital mortality.[70–72] Myocarditis is defined as inflammation of the myocardium with or without necrosis and is a leading cause of sudden cardiac death in children and adults worldwide.[73,74] Pericarditis is defined as inflammation of the pericardium and in developed countries is primarily caused by viral infections, whereas in developing countries, tuberculosis is a common cause and associated with poor outcomes. Acute myocarditis and pericarditis, termed myopericarditis or perimyocarditis, are often detected together in clinical practice and animal models of myocarditis (Figure 3), and the terms were often used interchangeably in the COVID-19 literature.

Myocarditis and pericarditis/myopericarditis from COVID-19 present similarly to other forms of viral myocarditis and pericarditis, with symptoms including fever, cough, chest pain/pressure, dyspnea, palpitations, and syncope.[2,31] As for other causes of myocarditis, probable cases of COVID-19 myocarditis are diagnosed as ≥1 new or worsening clinical symptoms, as well as ≥1 of the following: arrhythmias on electrocardiogram, cardiac dysfunction using echocardiography, or cardiac magnetic resonance imaging (cMRI) indicative of myocarditis.[31,75] Confirmed diagnosis of myocarditis requires an endomyocardial biopsy (EMB), which was typically not conducted during the pandemic due to heightened concerns for viral transmission to staff.[68,76] The diagnosis of myocarditis in patients with COVID-19, in general, relied more heavily on clinical symptoms and the presence of elevated troponins without evidence of coronary artery disease, especially in the United States where EMB is not typically acquired for lymphocytic myocarditis cases.

Management of COVID-19 myocarditis is essentially the same as pre-COVID myocarditis and is based on the expert opinion recommendations by the American College of Cardiology and the European Society of

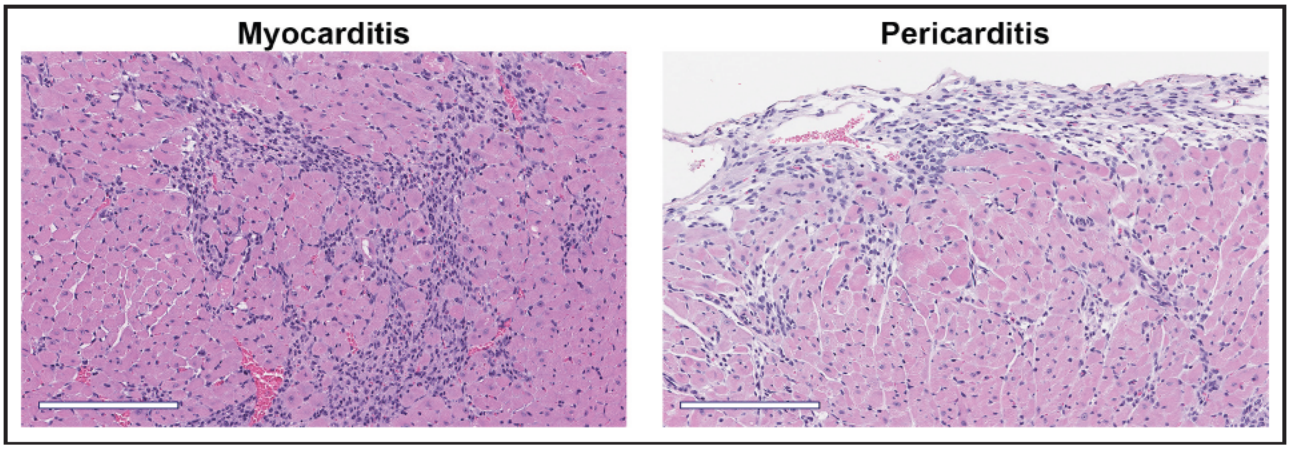


Figure 3. Myocarditis and pericarditis/perimyocarditis in the autoimmune CVB3 model.
Male BALB/c mice received 10^3 plaque-forming units of CVB3 with damaged heart protein on day 0 and myocarditis and pericarditis assessed histologically at day 10 after infection. Hematoxylin and eosin staining. Scale bars, 200 μm.

Cardiology guidelines.[31,77] There has been some controversy regarding the effect of immunosuppressive therapies such as glucocorticoids for myocarditis, while recent long-term data support its benefits.[78,79] Successful application of anti-inflammatory approaches in patients with COVID-19 has been reported in the literature, likely because of the overwhelming proinflammatory and cytokine response observed early after SARS-CoV-2 infection.[31,80,81]

EPIDEMIOLOGY OF COVID-19 MYOCARDITIS/PERICARDITIS

The latest Global Burden of Disease statistics before the COVID-19 pandemic place the worldwide prevalence of myocarditis and cardiomyopathy at 10.2 to 105.6 cases/100 000 individuals.[74,82] A recent study estimated pre-COVID myocarditis in the United States at 1 to 10 cases/100 000 individuals (Table 1).[84] The incidence of acute pericarditis pre-COVID in a large Finnish registry of all cardiovascular patients (n=670 409) was 3.3 cases/100 000 individuals.[95,96] Many epidemiology studies of myocarditis in patients with COVID-19 have been conducted since the pandemic started, with some of the larger studies listed in Table S2. The overall incidence of myocarditis in the United States from SARS-CoV-2 infection has been estimated in a study by the Centers for Disease Control and Prevention at around 150 cases/100 000 versus 9 cases/100 000 individuals in non-COVID cases during the same time period (Table 1).[2,85,97] A separate study in the United States and Europe estimated 240 cases/100 000 individuals of definite or probable myocarditis and 410 cases/100 000 individuals for possible myocarditis (Table 1).[92] These data indicate around a ≥15-fold increased risk of developing myocarditis from SARS-CoV-2 infection compared with other causes (Table 1).[74,84]

SARS-COV-2 STRAINS AND MYOCARDITIS

As is characteristic for rapidly replicating small RNA viruses like coxsackievirus and coronaviruses, mutations in key epitopes of the virus allow it to evade the adaptive immune response and promote infectivity depending on the location of the mutation. Table 2 lists the primary SARS-CoV-2 strains that were termed by the World Health Organization as a variant of interest or a variant of concern with the number of their mutations and the approximate date they were identified. According to the Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report, the Alpha variant led to more hospitalization and death than the original SARS-CoV-2 strain.[98] Mutations in SARS-CoV-2 that occurred with Delta were found to cause more severe disease in individuals who were not vaccinated than other strains like Alpha.[99] Delta remained the dominant strain until Omicron arrived around November 2021. Omicron cases had greater infectivity and the highest hospital admission

Table 1. Summary of Cases of Myocarditis Reported Before and During COVID-19 and Related to Vaccines

Time period assessed	No. of cases reported	References
Non-COVID		
Hong Kong non-COVID but during pandemic	0.55 cases/100 000 individuals	83
US VAERS pre-COVID	1–10 cases/100 000 individuals	84
US CDC non-COVID but during pandemic	9 cases/100 000 individuals	85
COVID-19		
US CDC COVID associated	150 cases/100 000 individuals	85
US VAERS COVID associated	1000–4000 cases/100 000 individuals	84
COVID-19 vaccines		
Singapore Pfizer and Moderna overall	0.1–1 case/100 000 individuals	86
US VAERS vaccine–associated 1990–2022 overall	0.38 cases/100 000 individuals	84
UK AstraZeneca overall	0.5 cases/100 000 individuals	87
Hong Kong vaccine associated	0.55 cases/100 000 individuals	83
US vaccine-associated overall	1 case/100 000 individuals	88
UK Pfizer overall	1 case/100 000 individuals	87
UK Moderna overall	1.4 cases/100 000 individuals	87
Israel Pfizer overall	2.1 cases/100 000 individuals	89
Israel Pfizer overall	2.7 cases/100 000 individuals	90
Moderna worldwide overall	9.2 cases/100 000 individuals	91
Israel vaccine-associated overall	11 cases/100 000 individuals	90
US/Europe vaccine-associated overall	410 cases/100 000 hospitalized patients	92
COVID-19 vaccines by sex and age		
US Pfizer 18- to 39-y olds	2.2 cases/100 000 individuals	93
US Moderna 18- to 39-y olds	3.1 cases/100 000 individuals	93
US VAERS Pfizer second dose 18- to 24-y-old male patients	5.2 cases/100 000 individuals	94
Israel Pfizer 16- to 29-y-old male patients	10.7 cases/100 000 individuals	89
Moderna worldwide 18- to 24-y-old male patients	53.8 cases/100 000 individuals	91

CDC indicates Centers for Disease Control and Prevention; UK, United Kingdom; US, United States; and VAERS, Vaccine Adverse Event Reporting System.

Table 2. SARS-CoV-2 Variant Strains

Strain	No. of mutations	Month and year emerged
Alpha (B.1.1.7)	20	September 2020
Beta (B.1.351)	17	May 2020
Gamma (P.1)	22	November 2020
Epsilon (B.1.429)	10	July 2020
Lota (B.1.526.1)	17	November 2020
Delta (B.1.617.2)	18	October 2020
Omicron (B.1.1.529)	42	November 2021
Omicron (XBB.1.5)	…	November 2022

frequency, but severe illness was lower than Delta and Alpha variants.[100,101]

Zhang et al[102] examined cardiovascular complications from 44 patients recovering from the Delta variant versus 25 controls and found that 32% had abnormal findings on cMRI and 20% with evidence of myocarditis. The study had 64% women with a median age of 51 (range, 39–62) years. Myocarditis typically occurs more often in young men aged 16 to 30 years, and the sex ratio for COVID-19 studies is typically observed to be 60% men to 40% women.[64,103–105] Thus, if a younger cohort with a more typical sex ratio had been examined, they may have found a higher percentage of possible myocarditis cases. However, multiple studies reported cardiovascular complications from COVID-19 including myocarditis that ranged from 18% to 60% of cases.[106–108] Soon after the Omicron variant emerged, case reports of myocarditis appeared.[109] A prospective study of 998 patients with COVID-19 that examined cardiovascular outcomes found that traditional biomarkers such as troponins and NT-proBNP predicted mortality regardless of the SARS-CoV-2 strain (ie, Alpha, Beta, Gamma, and Delta),[110] but they did not specifically examine myocarditis. Another study examined several strains of SARS-CoV-2 for their ability to infect and kill cultured cardiomyocytes and found that virus replicated to high levels for all strains, but Delta replicated at a higher level, caused more death, worsened function (ie, beating ability), and increased proinflammatory cytokines including IL-1β and IFNs compared with Omicron.[111] These findings suggest that Delta may have been more affective at inducing myocarditis than Omicron. In a separate study, investigators found that only coronary artery endothelial cells expressed ACE2, with infection occurring regardless of which variant was examined.[112] A recent pediatric study reported that Omicron had the highest admission frequency for poor outcome including death, but severe illness was lower than with Delta and Alpha variants.[101] The study included myocarditis as part of the score for worse outcomes but did not examine myocarditis specifically. Thus, myocarditis/pericarditis has been reported as a complication of COVID-19 for all strains of SARS-CoV-2 thus far.

SEX/GENDER DIFFERENCES IN COVID-19 MYOCARDITIS AND PERICARDITIS

Myocarditis pre-COVID is known to occur more often in young men under the age of 50 years, with a sex ratio of 2 to 4:1 men to women, while women are more likely to develop myocarditis after menopause, which is reviewed in previous studies.[64,113–117] Similar to myocarditis, pre-COVID pericarditis occurs more often in young men under the age of 50 years with a sex ratio of around 2:1.[64,95,118] Most studies of COVID-19 report a male dominance of around 60% men to 40% women.[12,13] Similarly, myocarditis associated with COVID-19 occurs more often in men than in women (60%–70% men to 30%–40% women).[103–105] Two large studies of 3 000 000 and 200 000 patients, respectively, detected no sex difference in whether patients tested PCR positive for SARS-CoV-2, although men had higher rates of hospitalization, intensive care unit admission, and mortality.[13,119] This was not the case for all studies. A study of ≈100 000 patients found that men were more often PCR positive for SARS-CoV-2 and had greater mortality than women.[120] Proinflammatory cytokines and cardiac biomarkers have been reported to be elevated in men with COVID-19 compared with women including ferritin, CRP (C-reactive protein), IL-6, IL-8, and IL-18.[13,121–123] And men have more neutrophils and monocytes, whereas women have more T cells,[13,121–123] similar to autoimmune myocarditis.[124,125] Thus, cytokines and biomarkers display the same sex differences as clinical myocarditis and animal models before SARS-CoV-2.

INFLAMMATORY RESPONSE ASSOCIATED WITH COVID-19

Inflammation is a key factor driving cardiac dysfunction in myocarditis. In 1 study, cardiac dysfunction based on echocardiography-derived global longitudinal strain was found in ≈80% of COVID-19 cases that had elevated serum IL-6.[126] CD68+ macrophages with fewer T cells are a characteristic finding of immunohistochemistry performed on EMB from patients with COVID-19 myocarditis/pericarditis, and macrophages are the primary infiltrate with fewer T cells in autoimmune models of myocarditis (Figure 2).[2,31,127] Thus, the characteristics of myocardial inflammation are similar between COVID-19 myocarditis and CVB3 and autoimmune myocarditis animal models.

cMRI is most often used to diagnose myocarditis using specific sequences that identify myocardial water content and fibrosis. cMRI cannot identify specific cellular components of inflammation and may be less accurate in the early stages of myocarditis because fibrosis typically develops weeks after acute myocarditis.[128–130]

The accuracy of cMRI depends on the amount of scar tissue present, with men developing more scar tissue and dilated cardiomyopathy (DCM) than women.[64,124,131] In support of this hypothesis, myocarditis is often detected using cMRI in patients with COVID-19 1 to 6 months after acute viral infection based on distinct SARS-CoV-2 or COVID-19 symptoms and a positive PCR or antigen test.[132] These observations further suggest that many cases of acute myocarditis may be asymptomatic.

The prognosis for viral or idiopathic pericarditis is good, based primarily on the effectiveness of colchicine combined with anti-inflammatories as therapies.[118,133] The effectiveness of colchicine as a therapy provides insight into the pathogenesis of pericarditis, which mirrors myocarditis. Colchicine impairs neutrophil adhesion to vascular endothelium and degranulation and blocks activation of the NLRP3 (NOD-, LRR-, and pyrin domain-containing protein 3) inflammasome, which is required for cleaving caspase-1 leading to the production of IL-1β and IL-18.[134–136] In myocarditis and pericarditis, neutrophil cardiac inflammation occurs before acute myocarditis (around 5–7 days after infection) and is mainly replaced by macrophage/T-cell inflammation during peak disease (7–14 days after infection). Colchicine also increases leukocytic cAMP levels and inhibits IL-1β and TNFα release from macrophages. The TLR4/NLRP3/caspase-1/IL-1β pathway is upregulated in men with myocarditis and is central to both the development of acute myocarditis and the remodeling that leads to DCM, which could explain the increased pericarditis incidence in younger men.

SARS-CoV-2 infection has been documented to strongly activate complement and to activate other innate immune pathways such as TLR4 and the inflammasome, which leads to increased IL-1β and IL-18 levels.[137–142] TLR4 signaling is key in driving proinflammatory responses associated with COVID-19 and contributes to an increased Th1-type immune response because IL-18 (and IL-1β) strongly induces IFNs.[143–145] Other key innate cytokines that are elevated during COVID-19 include TNFα and IL-6, which is increased by IL-1β.[137–142] Tim-3 (T-cell immunoglobulin mucin domain 3) is a receptor that is upregulated on mast cells and macrophages after viral infection that inhibits T-cell responses and is associated with increased IL-10 release from alternatively activated macrophages.[124,125,146] This response has been found to be important in CVB3-induced myocarditis in mice. Tim-3 and IL-10 upregulation is also observed in patients with COVID-19.[139] This pathway may be responsible for the inhibited T-cell responses that have been reported during COVID-19 in some patients.[138,139] COVID-19 is also associated with thromboembolism and clotting, which is driven by a number of factors including complement and mast cell activation.[147,148] As is typical for many viruses, IFNs inhibit viral replication and are elevated during COVID-19, which helps drive Th1 and Th17 responses.[149,150] Also similar to other viruses, SARS-CoV-2 has developed a number of methods to inhibit the protective IFN response resulting in poorly protective immune responses in some patients with COVID-19.[69,150] Mathew et al[151] conducted deep immune profiling of T and B cells obtained by flow cytometry from 125 patients with COVID-19 versus healthy controls and identified 3 immune phenotypes associated with worse disease outcome. They observed that COVID-19 results in hyperactivation of innate immune pathways, especially complement and TLR4-related pathways. The prototypical immune response associated with COVID-19 is more severe, but otherwise the immune response to SARS-CoV-2 closely resembles what has already been described for patients with myocarditis and animal models of viral and autoimmune myocarditis.

IMMUNE RESPONSE DURING MURINE AUTOIMMUNE CVB3 MYOCARDITIS AND EXPERIMENTAL AUTOIMMUNE MODEL

Animal models of myocarditis have yielded a wealth of information about the pathogenesis of disease including a number of landmark articles that demonstrate that myocarditis is an autoimmune disease that requires TLR activation by microbes.[44,152,153] Immune pathways that are similar between COVID-19 and the pathogenesis of myocarditis in autoimmune animal models (and verified to some extent in patients) are summarized below. All 3 pathways of complement are upregulated in the serum of patients with myocarditis and predict progression to DCM.[154] Mice with experimental autoimmune myocarditis (EAM) or autoimmune CVB3 myocarditis also upregulate complement components during the innate immune response and acute myocarditis including C3, CD11b (also known as CR [complement receptor] 3), C3aR, and C5aR.[155–157] Elevated expression of C3aR (and CD68+ macrophages) was found in patients with myocarditis compared with those with cardiomyopathy without inflammation.[158] The majority of immune cells in the heart during acute myocarditis in EAM, the autoimmune CVB3 myocarditis model, and humans are CD11b+ cells that include neutrophils, macrophages, mast cells, and some dendritic cells.[124,146,152,159] Mouse strains that have many mast cells like BALB/c and A/J develop myocarditis that most closely resembles lymphocytic myocarditis that progresses to DCM. Mast cells work in cooperation with macrophages to increase profibrotic inflammation and remodeling that leads to scar and DCM (Figure 4).[129,157,158,160]

Another key pathway upregulated in patients, EAM, autoimmune CVB3 myocarditis, and CVB3-only models is the TLR4, caspase-1, and NLRP3 pathways that increase IL-1β and IL-18 levels in

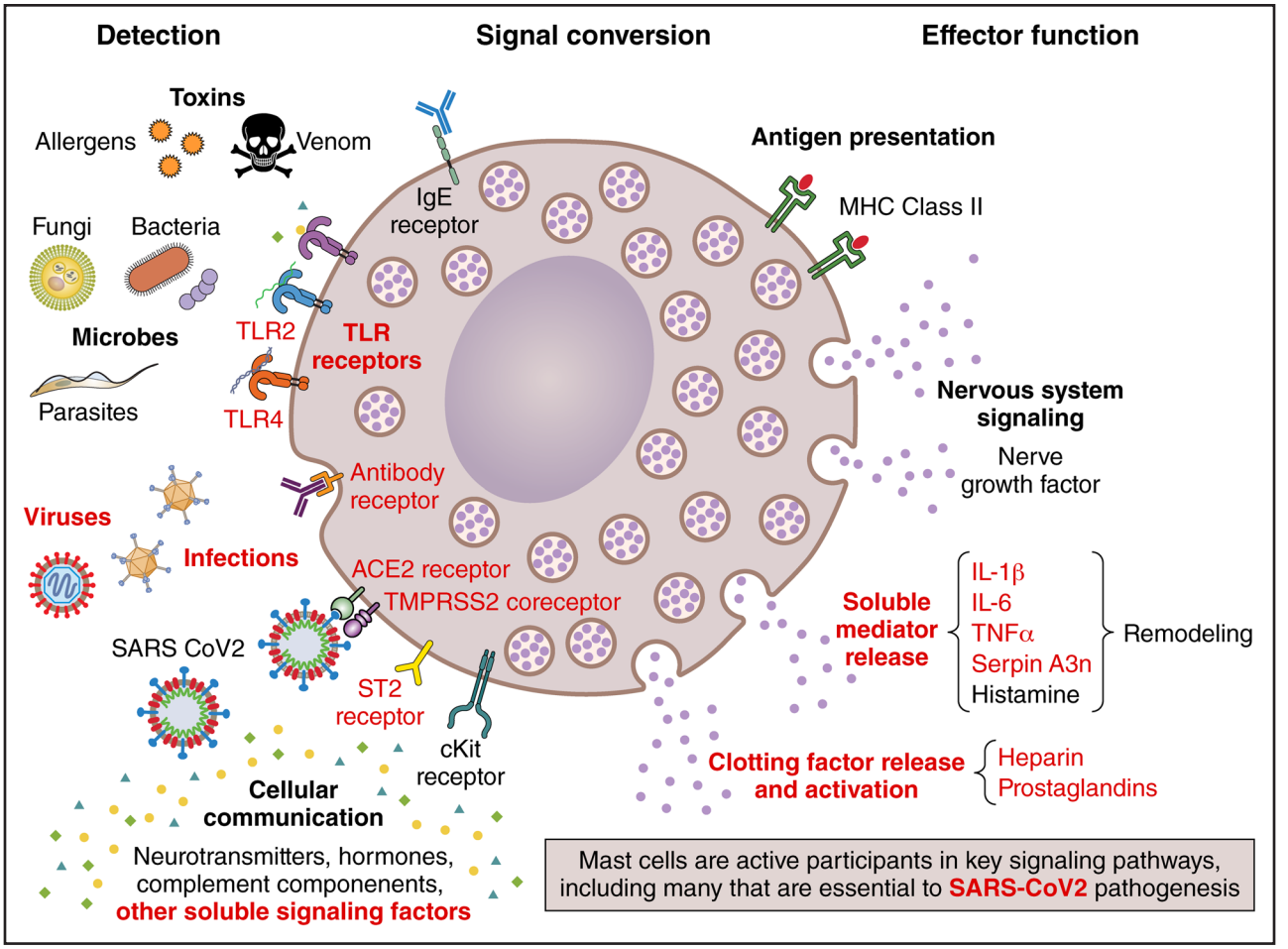


Figure 4. Mast cell signaling contributes to myocarditis and may contribute to SARS-CoV-2 or vaccine-associated myocarditis. ACE2 indicates angiotensin-converting enzyme 2; cKit, receptor tyrosine kinase; IL, interleukin; MHC, major histocompatibility complex; serpin A3n, serpin family A member 3n (α1-antichymotrypsin); ST2, interleukin-1 receptor-like 1/IL-1RL1; TLR, Toll-like receptor; TMPRSS2, transmembrane protease serine-2; and TNFα, tumor necrosis factor-alpha. Illustration credit: Sceyence Studios.

the heart.[124,146,152,156,161–164] IL-18, originally named IFN-γ–inducing factor, strongly drives Th1 immune responses,[143–145] but in BALB/c mice, this produces a mixed Th1/Th2 response that promotes fibrosis and DCM rather than a classical STAT-driven Th1 respo nse.[115,146,160,165] Importantly, elevated TLR4 and IL-1β are found on CD11b/CR3-expressing macrophages and mast cells during the innate immune response in the spleen and heart and in the heart during acute myocarditis.[124,146] TLR4 was also found to be expressed in the heart of patients with myocarditis and DCM.[166,167] IL-1β levels in the heart correlate to the severity of inflammation in male BALB/c mice with autoimmune CVB3 myocarditis.[115,129] Additionally, testosterone increases TLR4, caspase-1, and IL-1β levels during CVB3 myocarditis in male mice, which have higher levels of cardiac inflammation.[129] Importantly, inhibition of TLR4 and NLRP3 pathways reduces myocarditis in mouse models.[161,168] An important regulator of T cells following TLR4 activation is Tim-3, which displays sex differences during CVB3 myocarditis.[124,125,146]

Type I and II IFNs are a dominant immune response in CVB3 myocarditis models (and EAM) where inhibition of these pathways leads to increased viral replication, pericardial and myocardial inflammation, and DCM.[124,128,152,169,170] However, IFNs reduce viral replication and prevent remodeling and fibrosis and thereby progression to DCM.[128,169,170] Mast cells are critical for the remodeling and fibrosis that lead to DCM, due to their release of profibrotic cytokines (eg, IL-1β, TGFβ1 [transforming growth factor beta 1], and TNFα), and many enzymes, including Serpin A3n (α1-antichymotrypsin), that are required to activate IL-1β and matrix metalloproteinases that are required for fibrosis (Figure 4).[129,171] Mast cells and macrophages work together to drive inflammation and fibrosis.[129,158] IL-1β also increases serum and cardiac IL-6 levels that are needed to drive Th17 responses, which also promote fibrosis and progression to DCM and heart failure in patients with myocarditis and in animal models.[36,165,172–174] Overall, all of the key immunological features that characterize the immune response to

SARS-CoV-2 have previously been reported to play a role in the pathogenesis of EAM and autoimmune CVB3 models of myocarditis.

INSIGHTS ON THE PATHOGENESIS OF MYOCARDITIS FROM SARS-COV-2 MODELS

An engineered heart tissue model of COVID-19 found that SARS-CoV-2 infection of the heart tissue led to contractile issues, sarcomere disassembly, TNFα cytokine production, macrophage infiltration, and cell death, mimicking viral myocarditis.[27] A number of animal models have been developed to examine the pathogenesis of SARS-CoV-2 with an emphasis on understanding the effect on the lungs, but several studies also examined the heart. The primary animal models of COVID-19 from SARS-CoV-2 infection include the golden hamster, ferret, nonhuman primates, and mouse models (reviewed in the studies by Munoz-Fontela et al[175] and Chu et al[176]). Although mouse models have the most information available about their biology and many research tools, the ACE2 receptor is significantly different between mice and humans; so mouse models most often use a humanized ACE2 or lung passage to overcome this obstacle.[177–179] Investigators found viral replication in a number of organs with the highest expression in the lung and brain and increased serum cytokines including IFNγ; however, the mouse background used in these models was C57BL/6, which responds to antigens with elevated Th1-type immune responses because they have few mast cells.[160,177,178] In a BALB/c mouse model (high mast cells) where the virus was passaged through the lung 6× to increase viral tropism for the lung, SARS-CoV-2 was detected in the heart at days 3 and 5 after infection, and disease was worse in old (9 months old) versus young (6 weeks old) mice with elevated IL-1β and IL-6.[179] But they did not describe whether inflammation was found in the heart using this model. In another model of COVID-19 using BALB/c mice, TNFα, IL-1β, and IL-6 were increased in the lung during peak disease, but investigators did not describe the response in the heart.[180] In a humanized transgenic mouse model, ACE2 was expressed in the heart and virus replication detected, but they did not observe cardiac inflammation.[181] Most of these articles did not describe whether they examined male or female mice/cells while significant differences in myocarditis occur by sex in patients and animal models as already described.

SARS-CoV-2 infection of male Syrian hamsters caused viral infection and induced inflammation in the heart according to quantitative real-time PCR and immunohistochemistry (individually positive cells), but myocardial foci were not described.[182] They also found increased TNFα and IL-1β in the heart and perivascular fibrosis, which in our experience typically indicates perivascular mast cell degranulation.[157,160,182,183] They found increased CD15+ cells (a marker of myeloid cells such as granulocytes, neutrophils, eosinophils, mast cells, and macrophages), CD68+ macrophages, and CD4 and CD8 T cells in the heart in SARS-CoV-2–infected hamsters, but they did not specifically examine mast cells.[182] This immune response (ie, dominant macrophages with fewer T cells) is typical of EAM, autoimmune CVB3 myocarditis, and human myocarditis in males (Figure 2).[182,184,185] Male Syrian hamsters also develop worse myocarditis compared with females.[186] In a separate study using female Syrian hamsters, cardiomyocyte hypertrophy (at days 4 and 35 after infection) and cardiac fibrosis and diastolic dysfunction were observed at day 35 after SARS-CoV-2 infection using echocardiography.[187] This time course is the same as is observed with the autoimmune CVB3 and murine cytomegalovirus models of myocarditis and EAM (Table S1).[35,124,170,188] However, they did not show a change in LV end diastolic dimension or end LV systolic dimension indicative of DCM; however, this may be because they examined females rather than males. Few females progress to DCM in humans or autoimmune/viral myocarditis animal models.[64,124]

Although mast cells are typically associated with IgE-mediated allergic responses, they have a wide array of roles including as APCs that respond to infections (Figure 4).[171] Although resident mast cells are found in tissues such as the heart in small numbers, they are highly potent with local and far-ranging effects that influence the immune, hormone (including sex hormones), and central/peripheral nervous systems (Figure 4).[171] We showed that mast cells are the first APCs to respond to CVB3 within 15 minutes of intraperitoneal infection during autoimmune CVB3 myocarditis, leading to upregulation of TLR4, and that this response leads to rapid increases in TNF, IL-1β, IL-6, and IFNγ in many organs including the heart.[124,146,160] The critical role of mast cells as APCs during viral infections and in promoting myocarditis and pericarditis highlights their importance in the pathogenesis of disease. The activation of mast cells via ACE2, TMPRSS2, and NRP1 associated with COVID-19 is likely to be a crucial factor in promoting myocarditis/pericarditis following SARS-COV-2 infection (Figures 1 and 4).

COVID-19 VACCINE–ASSOCIATED MYOCARDITIS AND PERICARDITIS

Not long after COVID-19 vaccination began in the general population, case reports appeared identifying myocarditis and pericarditis as a side effect of vaccination, especially after the second dose. Since that time, many

large, population-based epidemiology studies have been conducted around the world that report myocarditis/pericarditis after vaccination (Table S3; reviewed in the study by Heidecker et al[2]). Many COVID-19 vaccines have been developed using various platforms and with several names for the same vaccine (summarized in Table S4). The reported incidence of myocarditis or pericarditis varies widely depending on the vaccine type and how many doses were administered, with the highest levels reported for the Moderna mRNA vaccine, with an overall incidence of ≈10/100 000 and around 50/100 000 in men under 40 years of age (Table 1).[91] All reports agree that the greatest risk of developing myocarditis occurs after the second vaccine dose in young men aged 12 to 39 years. Ages past 50 years had few reports of vaccine-associated myocarditis, similar to pre- and COVID-19–associated myocarditis. It is difficult to compare these incidence figures to prepandemic cases as previous reports did not typically report myocarditis by sex and age (or race).

A comprehensive study of all cases of myocarditis, pericarditis, or myopericarditis from vaccines passively reported in the United States to the Vaccine Adverse Events System from January 1, 1990, to July 20, 2021, identified 1841 definitive, probable, or possible cases out of 1 048 575 individuals.[84] They found that 67.9% of myocarditis or pericarditis cases were related to mRNA vaccines. Smallpox vaccines were next most common followed by other vaccine platforms. Over this time, 80.5% of cases of myocarditis were male and 83.5% aged 12 to 40 years, while 71.2% of pericarditis cases were male and 58.7% aged 12 to 40 years. Of the cases, 38.1% were reported for ages 12 to 20 and <5% for those over 60 years; 60.1% were reported after the second dose regardless of the vaccine platform. The study found 0.38 cases/100 000 individuals for COVID-19 vaccines in the United States compared with 1000 to 4000 cases/100 000 individuals for COVID-19 (Table 1).[84] The highest number of cases were reported for men under 30 years of age, but it is important to realize that only around 50% of individuals in the United States in this age group were vaccinated during this time. Additionally, studies in the United States using the passive reporting system Vaccine Adverse Events System report a lower incidence of myocarditis/pericarditis than population-based studies from countries with integrated health care systems or a requirement for vaccination (Table 1; Table S3).

Myocarditis has been reported as a rare adverse event for other vaccines before the COVID-19 pandemic, mainly smallpox vaccines.[189,190] Studies indicate that the highest risk for myocarditis from vaccination are the new mRNA vaccines (eg, Moderna and Pfizer), especially for Moderna (Table 1; Table S3). The mRNA vaccines against COVID-19 contain modified mRNA that encodes the viral spike glycoprotein of SARS-CoV-2 encapsulated by lipid nanoparticles or EVs (Figure 1). Importantly, the mRNA vaccines do not contain live or heat-inactivated virus. Other COVID-19 vaccine platforms associated with myocarditis/pericarditis include adenovirus-vector and attenuated live virus vaccines (Tables S3 and S4).[88]

Signs and symptoms of COVID-19 vaccine–associated myocarditis include shortness of breath, chest pain or pressure, palpitations, malaise, or fatigue, similar to other forms of myocarditis.[2] Signs may include elevated serum biomarkers including troponins and potentially elevated CRP (especially if pericarditis is present), arrhythmias, and symptoms of heart failure. Electrocardiogram changes are typically subtle and nonspecific and may include mild diffuse ST-segment changes, PQ-segment depressions, nonspecific ST-segment changes, sinus tachycardia, and supraventricular or rarely ventricular arrhythmias.[2] In 1 study from Israel, 81% of patients presented with chest pain, 2% with palpitations, 6% with dyspnea, 9% with fever, and 20% with pericardial effusion.[89] In this study, troponin T was required to be elevated in all patients as part of the diagnostic criteria for myocarditis. Seventy-nine percent presented with abnormal electrocardiogram, while the left ventricular ejection fraction was normal in 71% of patients; the majority of patients presented with mild to moderate cardiac dysfunction.[89] A study of 40 hospitals located in Washington, Oregon, Montana, and California of over 2 million people distinguished between patients with myocarditis or pericarditis without myocarditis (ie, not perimyocarditis) following the COVID-19 vaccination.[88] They found that 80% of myocarditis cases occurred after the second dose of one of the RNA vaccines (Pfizer and Moderna) versus 60% of pericarditis cases occurred after a single dose or with Ad26.COV2.S (Johnson and Johnson) vaccine, and 75% were men. Symptom onset after vaccination was early for myocarditis (median, 3–11 days), whereas for pericarditis symptoms, the median was 20 days after vaccination. Myocarditis occurred primarily in young men under 40 years of age, while pericarditis occurred primarily in men over 50 years of age. Ninety-five percent of patients who developed myocarditis were White compared with 84% of pericarditis patients. Ninety-five percent of patients with myocarditis were admitted to the hospital for 3 days with 10% in the intensive care unit compared with only 35% of pericarditis patients admitted to the hospital and 3% in intensive care. Seventy-five percent of patients with myocarditis received NSAIDs versus 49% with pericarditis. Similar percentages of patients received colchicine as a therapy. Forty percent of patients with myocarditis were treated for heart failure versus 14% with pericarditis.[88] Treatment for vaccine-associated myocarditis is summarized in a recent European Society of Cardiology Consensus Statement.[2]

Overall, most cases of myocarditis associated with vaccines have been reported to be mild and of short duration. Most patients are hospitalized only to monitor for arrhythmias and heart failure, rather than for severe signs and symptoms. Cases of vaccine-related myocarditis are

similar to cases of lymphocytic myocarditis attributed to viral and autoimmune myocarditis, which are also mild, with normal left ventricular ejection fraction and a moderately quick recovery. Because most of the vaccine cases appear mild, evaluation of the heart using cMRI or EMB is typically not conducted. This is likely also true for many mild cases of non–vaccine-related myocarditis. Most cases of vaccine-induced myocarditis fall into the clinically suspected or probable cases diagnostic categories.[75] Several studies included only cases with elevated troponins, but as discussed earlier, elevated troponins should not be required for a diagnosis of myocarditis as they are unreliable biomarkers for myocarditis and may select only more severe cases.

MECHANISMS FOR COVID-19 VACCINE–INDUCED MYOCARDITIS/PERICARDITIS

A number of mechanisms have been hypothesized for how vaccines, and mRNA vaccines in particular, could cause myocarditis including molecular mimicry between the spike protein of SARS-CoV-2 and cardiac myosin, cytokine storm from the immune response to the vaccine, and bystander activation—all long-standing hypotheses for how viruses could cause myocarditis.[2,31,191–193] mRNA vaccines mount an immune response directed against the spike protein of SARS-CoV-2 leading to the development of spike protein–specific IgG antibodies that bind ACE2 and prevent binding by the virus to ACE2. Modifications to the spike protein are intended to reduce the innate immune response by inhibiting proinflammatory cytokines, while at the same time, the lipid nanoparticle vehicle/EV for the mRNA acts as an adjuvant to enhance the immune response.[194–196] mRNA vaccines have been found to produce symptoms associated with myocarditis within 3 to 11 days after the second vaccine dose and to produce a mixed infiltrate (macrophages and lymphocytes) in EMB (Figure 2), which is the typical time course of inflammation based on histology from viral and autoimmune myocarditis in patients and animal models (eg, lymphocytic, giant cell myocarditis, and CVB3 myocarditis).[2,126,197] The fact that rare cases of myocarditis and pericarditis that are reported following vaccination with mRNA vaccines predominantly occur in the same demographic (men aged 12–30 years) with a similar cardiac immune infiltrate as pre-COVID and COVID myocarditis suggests a similar pathogenic mechanism (Figure 1). Especially because myocarditis is always rare, no matter the cause. Most evidence from translational animal models indicates that a microbial infection or antigen stimulation of TLRs is needed in the context of damaged heart protein to cause myocarditis, and so common and ubiquitous infections such as coxsackievirus, influenza, and SARS-CoV-2 are not likely to cause myocarditis on their own, otherwise the incidence of myocarditis would be far, far higher. Animal models suggest that autoimmunity is important.

A recent study provides a glimpse at a possible mechanism for vaccine-associated myocarditis. Thurner et al[12] found that patients with biopsy-confirmed myocarditis following COVID-19 vaccination had elevated levels of antibodies directed against IL-1RA, which is part of the TLR4/IL-1R signaling family. They found that patients with elevated IL-1RA antibodies had higher levels of cardiac inflammation, CRP, and troponin.[12] As described earlier, the TLR4/IL-1R signaling pathway that produces IL-1β is upregulated on mast cells and macrophages in males and is key in initiating myocarditis/pericarditis in animal models. Since ACE2/TMPRSS2/NRP1 receptors are found on mast cells, they may be directly activated at the site of vaccination and possibly at distant sites, such as the heart, at the time of vaccination. We see this occur in the autoimmune CVB3 model.[160] Additionally, mast cells drive Th2-type immune responses that increase Th2 responses, antibody levels, and autoantibody levels, which are important in the development of autoimmune myocarditis. All autoimmune animal models require 2 signals: one from self and another from an adjuvant. Possibly both the mRNA against the SARS-CoV-2 spike protein and the lipid nanoparticle vehicle could provide the adjuvant effect needed to promote myocarditis following vaccination with an mRNA vaccine.[35,51,198]

CONCLUSIONS, GAPS, AND FUTURE DIRECTIONS

Myocarditis and pericarditis associated with COVID-19 in the United States increased around 15× compared with pre-COVID levels. In adults, myocarditis/pericarditis occurs predominantly in men under the age of 50 years regardless of the cause, with sudden cardiac death from myocarditis occurring predominantly in young men under 30 years of age. This demographic is also reported for myocarditis and pericarditis associated with COVID-19 and COVID-19 vaccination, providing insight into how live viruses or virus antigens may cause myocarditis. Animal models of viral and autoimmune myocarditis have provided valuable translational information about the pathogenesis of myocarditis and suggest that pathogens/adjuvants (ie, virus, bacteria, parasite, and vaccine) can serve as an adjuvant trigger in the context of an autoimmune response. Thus, a reason why myocarditis could be so rare, regardless of cause, is because it is an autoimmune disease with susceptibility determined by sex, race/ethnicity, presence of mast cells (their presence determines genetic predisposition to lymphocytic myocarditis that progresses to DCM in animal models), pathogen antigen (activating TLRs), and damaged heart tissue, which must be presented to APC at the same time in order to develop autoimmune disease (Figure 1). Data from autoimmune animal models

also indicate that low levels of viral replication in the heart may be sufficient to induce autoimmune disease if other susceptibility factors are present.

Several gaps exist that need further investigation. Because myocarditis occurs primarily in young men under the age of 50 years regardless of cause, data on myocarditis including autopsy studies should be reported according to sex, age, and race (myocarditis in the United States primarily occurs in White people). Currently, there is no standard method of reporting cases and incidence. Additionally, researchers should indicate whether necrosis was present histologically for autopsy studies and EMBs and not exclude samples if it is absent. The selection of potential myocarditis patients for research studies should not be restricted to those with elevated troponins as this biomarker is an unreliable indicator of myocarditis, especially for milder cases. The presence of SARS-CoV-2 in EVs of patients with COVID-19 suggests that mRNA vaccine platforms that resemble EVs could activate the immune response similar to natural EVs containing virus leading to myocarditis/pericarditis. Future investigation should explore the mechanism for how an immune response that is activated by EVs containing mRNA could be directed to the heart.

ARTICLE INFORMATION

Affiliations

Department of Cardiovascular Medicine (D.F., D.J.B., D.N.D., L.T.C.) and Mayo Clinic Graduate School of Biomedical Sciences (D.J.B., D.N.D.), Mayo Clinic, Jacksonville, FL. Department of Environmental Health Sciences and Engineering, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (D.F.,). Center for Clinical and Translational Science, Mayo Clinic, Rochester, MN (D.F., D.J.B., D.N.D.). Deutsches Herzzentrum der Charité, Berlin, Germany (N.M., B.H.).

Acknowledgments

We thank Presley Giresi and Brandy Edenfield for help with mouse immunohistochemistry staining.

Sources of Funding

This work was supported by the National Institutes of Health (NIH) R01 HL164520, R21 AI145356, R21 AI152318, and R21 AI154927 to D. Fairweather; American Heart Association 20TPA35490415 to D. Fairweather; NIH grant TL1 TR002380 to D.J. Beetler, D.N. Di Florio, and D. Fairweather; R01 HL135165 to L.T. Cooper; the For Elyse Foundation to D. Fairweather; and Mayo Clinic Center for Regenerative Medicine to D. Fairweather.

Disclosures

D. Fairweather is on the advisory board of Cytokinetics. B. Heidecker is an inventor on patents that use RNA for diagnosis of myocarditis. L.T. Cooper has served as a consultant for myocarditis to Bristol Meyers Squibb, CardiolRx, Kiniksa, and Moderna. He has equity ownership in Stromal Therapeutics, Inc. The other authors report no conflicts.

REFERENCES

1. Shay DK, Shimabukuro TT, DeStefano F. Myocarditis occurring after immunization with mRNA-based COVID-19 vaccines. *JAMA Cardiol.* 2021;6:1115–1117. doi: 10.1001/jamacardio.2021.2821
2. Heidecker B, Dagan N, Balicer R, Eriksson U, Rosano G, Coats A, Tschöpe C, Kelle S, Poland GA, Frustaci A, et al. Myocarditis following COVID-19 vaccine: incidence, presentation, diagnosis, pathophysiology, therapy, and outcomes put into perspective. A clinical consensus document supported by the Heart Failure Association of the European Society of Cardiology (ESC) and the ESC working group on myocardial and pericardial diseases. *Eur J Heart Fail.* 2022;24:2000–2018. doi: 10.1002/ejhf.2669
3. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature.* 2020;579:270–273. doi: 10.1038/s41586-020-2012-7
4. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med.* 2005;11:875–879. doi: 10.1038/nm1267
5. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature.* 2003;426:450–454. doi: 10.1038/nature02145
6. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu N-H, Nitsche A, et al. SARS-VoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell.* 2020;181:271–280.e8. doi: 10.1016/j.cell.2020.02.052
7. Lan J, Ge J, Yu J, Shan S, Zhou H, Fan S, Zhang Q, Shi X, Wang Q, Zhang L, et al. Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature.* 2020;581:215–220. doi: 10.1038/s41586-020-2180-5
8. Shang J, Ye G, Shi K, Wan Y, Luo C, Aihara H, Geng Q, Auerbach A, Li F. Structural basis of receptor recognition by SARS-CoV-2. *Nature.* 2020;581:221–224. doi: 10.1038/s41586-020-2179-y
9. Qi F, Qian S, Zhang S, Zhang Z. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. *Biochem Biophys Res Commun.* 2020;526:135–140. doi: 10.1016/j.bbrc.2020.03.044
10. Theoharides TC. Potential association of mast cells with coronavirus disease 2019. *Ann Allergy Asthma Immunol.* 2021;126:217–218. doi: 10.1016/j.anai.2020.11.003
11. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, Holden KA, Read JM, Dondelinger F, Carson G, et al; ISARIC4C investigators. Features of 20133 UK patients in hospital with COVID-19 using the ISARIC WHO clinical characterisation protocol: prospective observational cohort study. *BMJ.* 2020;369:m1985. doi: 10.1136/bmj.m1985
12. Thurner L, Kessel C, Fadle N, Regitz E, Seidel F, Kindermann I, Lohse S, Kos I, Tschöpe C, Kheiroddin P, et al. IL-1RA antibodies in myocarditis after SARS-CoV-2 vaccination. *N Engl J Med.* 2022;387:1524–1527. doi: 10.1056/NEJMc2205667
13. Scully EP, Schumock G, Fu M, Massaccesi G, Muschelli J, Betz J, Klein EY, West NE, Robinson M, Garibaldi BT, et al. Sex and gender differences in testing, hospital admission, clinical presentation, and drivers of severe outcomes from COVID-19. *Open Forum Infect Dis.* 2021;8:ofab448. doi: 10.1093/ofid/ofab448
14. Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-cell RNA expression profiling of ACE2, the receptor of SARS-CoV-2. *Am J Respir Crit Care Med.* 2020;202:756–759. doi: 10.1164/rccm.202001-0179LE
15. Fodoulian L, Tuberosa J, Rossier D, Boillat M, Kan C, Pauli V, Egervari K, Lobrinus JA, Landis BN, Carleton A, et al. SARS-CoV-2 receptors and entry genes are expressed in the human olfactory neuroepithelium and brain. *iScience.* 2020;23:101839. doi: 10.1016/j.isci.2020.101839
16. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-NCOV infection. *Front Med.* 2020;14:185–192. doi: 10.1007/s11684-020-0754-0
17. Zhang H, Kang Z, Gong H, Xu D, Wang J, Li Z, Li Z, Cui X, Xiao J, Zhan J, et al. Digestive system is a potential route of COVID-19: an analysis of single-cell coexpression pattern of key proteins in viral entry process. *Gut.* 2020;69:1010–1018. doi: 10.1136/gutjnl-2020-320953
18. Hikmet F, Mear L, Edvinsson A, Micke P, Uhlen M, Lindskog C. The protein expression profile of ACE2 in human tissues. *Mol Syst Biol.* 2020;16:e9610. doi: 10.15252/msb.20209610
19. Devaux CA, Camoin-Jau L. An update on angiotensin-converting enzyme 2 structure/functions, polymorphism, and duplicitous nature in the pathophysiology of coronavirus disease 2019: implications for vascular and coagulation disease associated with severe acute respiratory syndrome coronavirus infection. *Front Microbiol.* 2022;13:1042200. doi: 10.3389/fmicb.2022.1042200
20. Lindner D, Fitzek A, Brauninger H, Aleshcheva G, Edler C, Meissner K, Scherschel K, Kirchhof P, Escher F, Schultheiss H-P, et al. Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases. *JAMA Cardiol.* 2020;5:1281–1285. doi: 10.1001/jamacardio.2020.3551

21. Poloni TE, Moretti M, Medici V, Turturici E, Belli G, Cavriani E, Visonà SD, Rossi M, Fantini V, Ferrari RR, et al. COVID-19 pathology in the lung, kidney, heart and brain: the different roles of T-cells, macrophages, and microthrombosis. *Cells*. 2022;11:3124. doi: 10.3390/cells11193124
22. Abdi A, AlOtaiby S, Badarin FA, Khraibi A, Hamdan H, Nader M. Interaction of SARS-CoV-2 with cardiomyocytes: insight into the underlying molecular mechanisms of cardiac injury and pharmacotherapy. *Biomed Pharmacother*. 2022;146:112518. doi: 10.1016/j.biopha.2021.112518
23. Bojkova D, Wagner JUG, Shumliakivska M, Aslan GS, Saleem U, Hansen A, Luxán G, Günther S, Pham MD, Krishnan J, et al. SARS-CoV-2 infects and induces cytotoxic effects in human cardiomyocytes. *Cardiovasc Res*. 2020;116:2207–2215. doi: 10.1093/cvr/cvaa267
24. Robinson EL, Alkass K, Bergmann O, Maguire JJ, Roderick HL, Davenport AP. Genes encoding ACE2, TMPRSS2 and related proteins mediating SARS-CoV-2 viral entry are upregulated with age in human cardiomyocytes. *J Mol Cell Cardiol*. 2020;147:88–91. doi: 10.1016/j.yjmcc.2020.08.009
25. Yang J, Chen T, Zhou Y. Mediators of SARS-CoV-2 entry are preferentially enriched in cardiomyocytes. *Hereditas*. 2021;158:4. doi: 10.1186/s41065-020-00168-4
26. Yang J, Petitjean SJL, Koehler M, Zhang Q, Dumitru AC, Chen W, Derclaye S, Vincent SP, Soumillion P, Alsteens D. Molecular interaction and inhibition of SARS-CoV-2 binding to the ACE2 receptor. *Nat Commun*. 2020;11:4541. doi: 10.1038/s41467-020-18319-6
27. Bailey AL, Dmytrenko O, Greenberg L, Bredemeyer AL, Ma P, Liu J, Penna V, Winkler ES, Sviben S, Brooks E, et al. SARS-CoV-2 infects human engineered heart tissues and models COVID-19 myocarditis. *JACC Basic Transl Sci*. 2021;6:331–345. doi: 10.1016/j.jacbts.2021.01.002
28. Song X, Hu W, Yu H, Zhao L, Zhao Y, Zhao X, Xue HH, Zhao Y. Little to no expression of angiotensin-converting enzyme-2 on most human peripheral blood immune cells but highly expressed on tissue macrophages. *Cytometry A*. 2020;103:136–145. doi: 10.1002/cyto.a.24285
29. Chen L, Li X, Chen M, Feng Y, Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. *Cardiovasc Res*. 2020;116:1097–1100. doi: 10.1093/cvr/cvaa078
30. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054–1062. doi: 10.1016/S0140-6736(20)30566-3
31. Lovell JP, Cihakova D, Gilotra NA. COVID-19 and myocarditis: review of clinical presentations, pathogenesis and management. *Heart Int*. 2022;16:20–27. doi: 10.17925/HI.2022.16.1.20
32. Gilotra NA, Minkove N, Bennett MK, Tedford RJ, Steenbergen C, Judge DP, Halushka MK, Russell SD. Lack of relationship between serum cardiac troponin I level and giant cell myocarditis diagnosis and outcomes. *J Card Fail*. 2016;22:583–585. doi: 10.1016/j.cardfail.2015.12.022
33. Berg J, Kottwitz J, Baltensperger N, Kissel CK, Lovrinovic M, Mehra T, Scherff F, Schmied C, Templin C, Lüscher TF, et al. Cardiac magnetic resonance imaging in myocarditis reveals persistent disease activity despite normalization of cardiac enzymes and inflammatory parameters at 3-month follow-up. *Circ Heart Fail*. 2017;10:e004262. doi: 10.1161/CIRCHEARTFAILURE.117.004262
34. Halushka MK, Vander Heide RS. Myocarditis is rare in COVID-19 autopsies: cardiovascular findings across 277 postmortem examinations. *Cardiovasc Pathol*. 2021;50:107300. doi: 10.1016/j.carpath.2020.107300
35. Fairweather D, Kaya Z, Shellam GR, Lawson CM, Rose NR. From infection to autoimmunity. *J Autoimmun*. 2001;16:175–186. doi: 10.1006/jaut.2000.0492
36. Myers JM, Cooper LT, Kem DC, Stavrakis S, Kosanke SD, Shevach EM, Fairweather DL, Stoner JA, Cox CJ, Cunningham MW. Cardiac myosin-Th17 responses promote heart failure in human myocarditis. *JCI Insight*. 2016;1:e85851.
37. Poli V BK, Fairweather D. Autoimmune myocarditis: animal models. In: Caforio A, ed. *Myocarditis: Pathogenesis, Diagnosis and Treatment*. Springer Nature; 2020:111–128.
38. Fairweather D, Stafford KA, Sung YK. Update on coxsackievirus B3 myocarditis. *Curr Opin Rheumatol*. 2012;24:401–407. doi: 10.1097/BOR.0b013e328353372d
39. Pankuweit S KK. Viral myocarditis: From experimental models to diagnosis in patients. In: Caforio A, ed. *Myocarditis: Pathogenesis, diagnosis and treatment*. Springer Nature; 2020:91–110.
40. Ryabkova VA, Churilov LP, Shoenfeld Y. Influenza infection, SARS, MERS and COVID-19: cytokine storm - the common denominator and the lessons to be learned. *Clin Immunol*. 2021;223:108652. doi: 10.1016/j.clim.2020.108652
41. Lane JR, Neumann DA, Lafond-Walker A, Herskowitz A, Rose NR. Role of IL-1 and tumor necrosis factor in coxsackie virus-induced autoimmune myocarditis. *J Immunol*. 1993;151:1682–1690.
42. Abston ED, Coronado MJ, Bucek A, Bedja D, Shin J, Kim JB, Kim E, Gabrielson KL, Georgakopoulos D, Mitzner W, et al. Th2 regulation of viral myocarditis in mice: different roles for TLR3 versus TRIF in progression to chronic disease. *Clin Dev Immunol*. 2012;2012:129486. doi: 10.1155/2012/129486
43. Massilamany C, Huber SA, Cunningham MW, Reddy J. Relevance of molecular mimicry in the mediation of infectious myocarditis. *J Cardiovasc Transl Res*. 2014;7:165–171. doi: 10.1007/s12265-013-9519-3
44. Gil-Cruz C, Perez-Shibayama C, De Martin A, Ronchi F, van der Borght K, Niederer R, Onder L, Lütge M, Novkovic M, Nindl V, et al. Microbiota-derived peptide mimics drive lethal inflammatory cardiomyopathy. *Science*. 2019;366:881–886. doi: 10.1126/science.aav3487
45. Robinson SM, Tsueng G, Sin J, Mangale V, Rahawi S, McIntyre LL, Williams W, Kha N, Cruz C, Hancock BM, et al. Coxsackievirus B exits the host cell in shed microvesicles displaying autophagosomal markers. *PLoS Pathog*. 2014;10:e1004045. doi: 10.1371/journal.ppat.1004045
46. Sin J, McIntyre L, Stotland A, Feuer R, Gottlieb RA. Coxsackievirus B escapes the infected cell in ejected mitophagosomes. *J Virol*. 2017;91:e01347–1417.
47. Rodrigues M, Fan J, Lyon C, Wan M, Hu Y. Role of extracellular vesicles in viral and bacterial infections: pathogenesis, diagnostics, and therapeutics. *Theranostics*. 2018;8:2709–2721. doi: 10.7150/thno.20576
48. Clough E, Inigo J, Chandra D, Chaves L, Reynolds JL, Aalinkeel R, Schwartz SA, Khmaladze A, Mahajan SD. Mitochondrial dynamics in SARS-CoV-2 spike protein treated human microglia: implications for neuro-COVID. *J Neuroimmune Pharmacol*. 2021;16:770–784. doi: 10.1007/s11481-021-10015-6
49. Yang Y, Wu Y, Meng X, Wang Z, Younis M, Liu Y, Wang P, Huang X. SARS-CoV-2 membrane protein causes the mitochondrial apoptosis and pulmonary edema via targeting bok. *Cell Death Differ*. 2022;29:1395–1408. doi: 10.1038/s41418-022-00928-x
50. Faizan MI, Chaudhuri R, Sagar S, Albogami S, Chaudhary N, Azmi I, Akhtar A, Ali SM, Kumar R, Iqbal J, et al. NSP4 and ORF9B of SARS-CoV-2 induce pro-inflammatory mitochondrial DNA release in inner membrane-derived vesicles. *Cells*. 2022;11:2969. doi: 10.3390/cells11192969
51. Beetler DJ, Di Florio DN, Bruno KA, Ikezu T, March KL, Cooper LT Jr, Wolfram J, Fairweather D. Extracellular vesicles as personalized medicine. *Mol Aspects Med*. 2022;91:101155. doi: 10.1016/j.mam.2022.101155
52. Crackower MA, Sarao R, Oudit GY, Yagil C, Kozieradzki I, Scanga SE, Oliveira-dos-Santos AJ, da Costa J, Zhang L, Pei Y, et al. Angiotensin-converting enzyme 2 is an essential regulator of heart function. *Nature*. 2002;417:822–828. doi: 10.1038/nature00786
53. Iwai M, Horiuchi M. Devil and angel in the renin-angiotensin system: ACE-angiotensin II-AT1 receptor axis vs. ACE2-angiotensin-(1-7)-mas receptor axis. *Hypertens Res*. 2009;32:533–536. doi: 10.1038/hr.2009.74
54. Beyerstedt S, Casaro EB, Rangel EB. Covid-19: angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. *Eur J Clin Microbiol Infect Dis*. 2021;40:905–919. doi: 10.1007/s10096-020-04138-6
55. Eguchi S, Kawai T, Scalia R, Rizzo V. Understanding angiotensin II type 1 receptor signaling in vascular pathophysiology. *Hypertension*. 2018;71:804–810. doi: 10.1161/HYPERTENSIONAHA.118.10266
56. Tikellis C, Pickering R, Tsorotes D, Du XJ, Kiriazis H, Nguyen-Huu TP, Head GA, Cooper ME, Thomas MC. Interaction of diabetes and ACE2 in the pathogenesis of cardiovascular disease in experimental diabetes. *Clin Sci (Lond)*. 2012;123:519–529. doi: 10.1042/CS20110668
57. Sahara M, Ikutomi M, Morita T, Minami Y, Nakajima T, Hirata Y, Nagai R, Sata M. Deletion of angiotensin-converting enzyme 2 promotes the development of atherosclerosis and arterial neointima formation. *Cardiovasc Res*. 2014;101:236–246. doi: 10.1093/cvr/cvt245
58. Kim L, Garg S, O'Halloran A, Whitaker M, Pham H, Anderson EJ, Armistead I, Bennett NM, Billing L, Como-Sabetti K, et al. Risk factors for intensive care unit admission and in-hospital mortality among hospitalized adults identified through the us coronavirus disease 2019 (COVID-19)-associated hospitalization surveillance network (COVID-NET). *Clin Infect Dis*. 2021;72:e206–e214. doi: 10.1093/cid/ciaa1012
59. Nabah YN, Mateo T, Estelles R, Mata M, Zagorski J, Sarau H, Cortijo J, Morcillo EJ, Jose PJ, Sanz M-J. Angiotensin II induces neutrophil accumulation in vivo through generation and release of cxc chemokines. *Circulation*. 2004;110:3581–3586. doi: 10.1161/01.CIR.0000148824.93600.F3
60. Dikalov SI, Nazarewicz RR. Angiotensin II-induced production of mitochondrial reactive oxygen species: potential mechanisms and relevance for

cardiovascular disease. *Antioxid Redox Signal*. 2013;19:1085–1094. doi: 10.1089/ars.2012.4604
61. Han Y, Runge MS, Brasier AR. Angiotensin II induces interleukin-6 transcription in vascular smooth muscle cells through pleiotropic activation of nuclear factor-kappa B transcription factors. *Circ Res*. 1999;84:695–703. doi: 10.1161/01.res.84.6.695
62. Ruiz-Ortega M, Lorenzo O, Suzuki Y, Ruperez M, Egido J. Proinflammatory actions of angiotensins. *Curr Opin Nephrol Hypertens*. 2001;10:321–329. doi: 10.1097/00041552-200105000-00005
63. Di Florio DN, Sin J, Coronado MJ, Atwal PS, Fairweather D. Sex differences in inflammation, redox biology, mitochondria and autoimmunity. *Redox Biol*. 2020;31:101482. doi: 10.1016/j.redox.2020.101482
64. Fairweather D, Beetler DJ, Musigk N, Heidecker B, Lyle MA, Cooper LT Jr, Bruno KA. Sex and gender differences in myocarditis and dilated cardiomyopathy: an update. *Front Cardiovasc Med*. 2023;10:1129348. doi: 10.3389/fcvm.2023.1129348
65. Tanaka A, Matsumori A, Wang W, Sasayama S. An angiotensin II receptor antagonist reduces myocardial damage in an animal model of myocarditis. *Circulation*. 1994;90:2051–2055. doi: 10.1161/01.cir.90.4.2051
66. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497–506. doi: 10.1016/S0140-6736(20)30183-5
67. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323:1061–1069. doi: 10.1001/jama.2020.1585
68. Hendren NS, Drazner MH, Bozkurt B, Cooper LT Jr. Description and proposed management of the acute COVID-19 cardiovascular syndrome. *Circulation*. 2020;141:1903–1914. doi: 10.1161/CIRCULATIONAHA.120.047349
69. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol*. 2020;17:259–260. doi: 10.1038/s41569-020-0360-5
70. Deng P, Ke Z, Ying B, Qiao B, Yuan L. The diagnostic and prognostic role of myocardial injury biomarkers in hospitalized patients with COVID-19. *Clin Chim Acta*. 2020;510:186–190. doi: 10.1016/j.cca.2020.07.018
71. O'Donnell C, Ashland MD, Vasti EC, Lu Y, Chang AY, Wang P, Daniels LB, de Lemos JA, Morrow DA, Rodriguez F, et al. N-terminal pro-B-type natriuretic peptide as a biomarker for the severity and outcomes with COVID-19 in a nationwide hospitalized cohort. *J Am Heart Assoc*. 2021;10:e022913. doi: 10.1161/JAHA.121.022913
72. de Falco R, Vargas M, Palma D, Savoia M, Miscioscia A, Pinchera B, Vano M, Servillo G, Gentile I, Fortunato G, et al. B-type natriuretic peptides and high-sensitive troponin I as COVID-19 survival factors: which one is the best performer? *J Clin Med*. 2021;10:2726. doi: 10.3390/jcm10122726
73. Aretz HT, Billingham ME, Edwards WD, Factor SM, Fallon JT, Fenoglio JJ Jr, Olsen EG, Schoen FJ. Myocarditis. A histopathologic definition and classification. *Am J Cardiovasc Pathol*. 1987;1:3–14.
74. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, et al; GBD-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. *J Am Coll Cardiol*. 2020;76:2982–3021. doi: 10.1016/j.jacc.2020.11.010
75. Montgomery J, Ryan M, Engler R, Hoffman D, McClenathan B, Collins L, Loran D, Hrncir D, Herring K, Platzer M, et al. Myocarditis following immunization with mRNA COVID-19 vaccines in members of the US military. *JAMA Cardiol*. 2021;6:1202–1206. doi: 10.1001/jamacardio.2021.2833
76. Welt FGP, Shah PB, Aronow HD, Bortnick AE, Henry TD, Sherwood MW, Young MN, Davidson LJ, Kadavath S, Mahmud E, et al; American College of Cardiology's Interventional Council and the Society for Cardiovascular Angiography and Interventions. Catheterization laboratory considerations during the coronavirus (COVID-19) pandemic: from the ACC's Interventional Council and SCAI. *J Am Coll Cardiol*. 2020;75:2372–2375. doi: 10.1016/j.jacc.2020.03.021
77. Anwar HK, Qudsia U. Pathology and therapeutics of COVID-19: a review. *Int J Medical Students*. 2020;8:4–11.
78. Chimenti C, Russo MA, Frustaci A. Immunosuppressive therapy in virus-negative inflammatory cardiomyopathy: 20-year follow-up of the TIMIC trial. *Eur Heart J*. 2022;43:3463–3473. doi: 10.1093/eurheartj/ehac348
79. Brala D, Thevathasan T, Grahl S, Barrow S, Violano M, Bergs H, Golpour A, Suwalski P, Poller W, Skurk C, et al. Application of magnetocardiography to screen for inflammatory cardiomyopathy and monitor treatment response. *J Am Heart Assoc*. 2023;12:e027619. doi: 10.1161/JAHA.122.027619
80. Sawalha K, Abozenah M, Kadado AJ, Battisha A, Al-Akchar M, Salerno C, Hernandez-Montfort J, Islam AM. Systematic review of COVID-19 related myocarditis: insights on management and outcome. *Cardiovasc Revasc Med*. 2021;23:107–113. doi: 10.1016/j.carrev.2020.08.028
81. Kamarullah W, Nurcahyani, Mary Josephine C, Bill Multazam R, Ghaezany Nawing A, Dharma S. Corticosteroid therapy in management of myocarditis associated with COVID-19; a systematic review of current evidence. *Arch Acad Emerg Med*. 2021;9:e32. doi: 10.22037/aaem.v9i1.1153
82. Zhang K, Cheng X, Qu N, Song H, Luo Y, Ye T, Xu Q, Tian H, Kan C, Hou N. Global burden of cardiomyopathy and myocarditis in the older adults from 1990 to 2019. *Front Public Health*. 2022;10:1018385. doi: 10.3389/fpubh.2022.1018385
83. Chou OHI, Zhou J, Lee TTL, Kot T, Lee S, Wai AKC, Wong WT, Zhang Q, Cheng SH, Liu T, et al. Comparisons of the risk of myopericarditis between COVID-19 patients and individuals receiving COVID-19 vaccines: a population-based study. *Clin Res Cardiol*. 2022;111:1098–1103. doi: 10.1007/s00392-022-02007-0
84. Rafaniello C, Gaio M, Zinzi A, Sullo MG, Liguori V, Ferraro M, Petronzelli F, Felicetti P, Marchione P, Marra AR, et al. Disentangling a thorny issue: myocarditis and pericarditis post COVID-19 and following mRNA COVID-19 vaccines. *Pharmaceuticals (Basel)*. 2022;15:525. doi: 10.3390/ph15050525
85. Boehmer TK, Kompaniyets L, Lavery AM, Hsu J, Ko JY, Yusuf H, Romano SD, Gundlapalli AV, Oster ME, Harris AM. Association between COVID-19 and myocarditis using hospital-based administrative data - United States, March 2020-January 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:1228–1232. doi: 10.15585/mmwr.mm7035e5
86. Singapore Health Sciences Authority. HSA's safety update #9 COVID-19 vaccine. 2021; https://www.hsa.gov.sg/docs/default-source/hprg-vcb/safety-update-on-covid19-vaccines/hsa-safety-update-no-13-on-covid-19-vaccines-(31-august-2022).pdf.
87. GOV.UK. Archived - coronavirus vaccine - summary of yellow card reporting. 2023.
88. Diaz GA, Parsons GT, Gering SK, Meier AR, Hutchinson IV, Robicsek A. Myocarditis and pericarditis after vaccination for COVID-19. *JAMA*. 2021;326:1210–1212. doi: 10.1001/jama.2021.13443
89. Witberg G, Barda N, Hoss S, Richter I, Wiessman M, Aviv Y, Grinberg T, Auster O, Dagan N, Balicer RD, et al. Myocarditis after COVID-19 vaccination in a large health care organization. *N Engl J Med*. 2021;385:2132–2139. doi: 10.1056/NEJMoa2110737
90. Barda N, Dagan N, Ben-Shlomo Y, Kepten E, Waxman J, Ohana R, Hernán MA, Lipsitch M, Kohane I, Netzer D, et al. Safety of the BNT162B2 mRNA COVID-19 vaccine in a nationwide setting. *N Engl J Med*. 2021;385:1078–1090. doi: 10.1056/NEJMoa2110475
91. Straus W, Urdaneta V, Esposito DB, Mansi JA, Rodriguez CS, Burton P, Vega JM. Analysis of myocarditis among 252 million mRNA-1273 recipients worldwide. *Clin Infect Dis*. 2022;76:e544-e552. doi: 10.1093/cid/ciac446
92. Ammirati E, Lupi L, Palazzini M, Hendren NS, Grodin JL, Cannistraci CV, Schmidt M, Hekimian G, Peretto G, Bochaton T, et al. Prevalence, characteristics, and outcomes of COVID-19-associated acute myocarditis. *Circulation*. 2022;145:1123–1139. doi: 10.1161/CIRCULATIONAHA.121.056817
93. Goddard K, Lewis N, Fireman B, Weintraub E, Shimabukuro T, Zerbo O, Boyce TG, Oster ME, Hanson KE, Donahue JG, et al. Risk of myocarditis and pericarditis following BNT162B2 and mRNA-1273 COVID-19 vaccination. *Vaccine*. 2022;40:5153–5159. doi: 10.1016/j.vaccine.2022.07.007
94. Oster ME, Shay DK, Su JR, Gee J, Creech CB, Broder KR, Edwards K, Soslow JH, Dendy JM, Schlaudecker E, et al. Myocarditis cases reported after mRNA-based COVID-19 vaccination in the US from December 2020 to August 2021. *JAMA*. 2022;327:331–340. doi: 10.1001/jama.2021.24110
95. Kyto V, Sipila J, Rautava P. Clinical profile and influences on outcomes in patients hospitalized for acute pericarditis. *Circulation*. 2014;130:1601–1606. doi: 10.1161/CIRCULATIONAHA.114.010376
96. Jain A. BK, Matsumori A, Cooper LT Jr, Yamani MH, Fairweather D. Myocardits and pericarditis. In: Kenakin T, ed. *Comprehensive Pharmacology*. Elsevier; 2022:413–431.
97. Heymans S, Cooper LT. Myocarditis after COVID-19 mRNA vaccination: clinical observations and potential mechanisms. *Nat Rev Cardiol*. 2022;19:75–77. doi: 10.1038/s41569-021-00662-w
98. Paul P, France AM, Aoki Y, Batra D, Biggerstaff M, Dugan V, Galloway S, Hall AJ, Johansson MA, Kondor RJ, et al. Genomic surveillance for SARS-CoV-2 variants circulating in the United States, December 2020-May 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:846–850. doi: 10.15585/mmwr.mm7023a3
99. Twohig KA, Nyberg T, Zaidi A, Thelwall S, Sinnathamby MA, Aliabadi S, Seaman SR, Harris RJ, Hope R, Lopez-Bernal J, et al; COVID-19 Genomics UK (COG-UK) consortium. Hospital admission and emergency care attendance risk for SARS-CoV-2 delta (B.1.617.2) compared with alpha (B.1.1.7)

variants of concern: a cohort study. *Lancet Infect Dis*. 2022;22:35–42. doi: 10.1016/S1473-3099(21)00475-8
100. Nyberg T, Ferguson NM, Nash SG, Webster HH, Flaxman S, Andrews N, Hinsley W, Bernal JL, Kall M, Bhatt S, et al; COVID-19 Genomics UK (COG-UK) consortium. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. *Lancet*. 2022;399:1303–1312. doi: 10.1016/S0140-6736(22)00462-7
101. Bahl A, Mielke N, Johnson S, Desai A, Qu L. Severe COVID-19 outcomes in pediatrics: an observational cohort analysis comparing alpha, delta, and omicron variants. *Lancet Reg Health Am*. 2023;18:100405. doi: 10.1016/j.lana.2022.100405
102. Zhang L, Wei X, Wang H, Jiang R, Tan Z, Ouyang J, Li X, Lei C, Liu H, Liu J. Cardiac involvement in patients recovering from Delta variant of COVID-19: a prospective multi-parametric MRI study. *ESC Heart Fail*. 2022;9:2576–2584. doi: 10.1002/ehf2.13971
103. Bemtgen X, Kaier K, Rilinger J, Rottmann F, Supady A, von Zur Muhlen C, Westermann D, Wengenmayer T, Staudacher DL. Myocarditis mortality with and without COVID-19: insights from a national registry. *Clin Res Cardiol*. 2022;Dec 24: 1–7. doi: 10.1007/s00392-022-02141-9
104. Davis MG, Bobba A, Chourasia P, Gangu K, Shuja H, Dandachi D, Farooq A, Avula SR, Shekhar R, Sheikh AB. COVID-19 associated myocarditis clinical outcomes among hospitalized patients in the United States: a propensity matched analysis of national inpatient sample. *Viruses*. 2022;14:2791. doi: 10.3390/v14122791
105. Pommier T, Benzenine E, Bernard C, Mariet AS, Bejot Y, Giroud M, Morgant M-C, Steinmetz E, Guenancia C, Bouchot O, et al. Trends of myocarditis and endocarditis cases before, during, and after the first complete COVID-19-related lockdown in 2020 in France. *Biomedicines*. 2022;10:1231. doi: 10.3390/biomedicines10061231
106. Ng MY, Ferreira VM, Leung ST, Yin Lee JC, Ho-Tung Fong A, To Liu RW, Man Chan JW, Wu AKL, Lung KC, Crean AM, et al. Patients recovered from COVID-19 show ongoing subclinical myocarditis as revealed by cardiac magnetic resonance imaging. *JACC Cardiovasc Imaging*. 2020;13:2476–2478. doi: 10.1016/j.jcmg.2020.08.012
107. Kotecha T, Knight DS, Razvi Y, Kumar K, Vimalesvaran K, Thornton G, Patel R, Chacko L, Brown JT, Coyle C, et al. Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assessed by cardiovascular magnetic resonance. *Eur Heart J*. 2021;42:1866–1878. doi: 10.1093/eurheartj/ehab075
108. Weckbach LT, Curta A, Bieber S, Kraechan A, Brado J, Hellmuth JC, Muenchhoff M, Scherer C, Schroeder I, Irlbeck M, et al. Myocardial inflammation and dysfunction in COVID-19-associated myocardial injury. *Circ Cardiovasc Imaging*. 2021;14:e012220. doi: 10.1161/CIRCIMAGING.120.011713
109. Fishman B, Goitein O, Berkovitch A, Rahav G, Matetzky S. First report of myocarditis in two patients with COVID-19 omicron variant: case report. *Eur Heart J Case Rep*. 2022;6:ytac407. doi: 10.1093/ehjcr/ytac407
110. Lionte C, Sorodoc V, Haliga RE, Bologa C, Ceasovschih A, Petris OR, Elena Coman A, Stoica A, Sirbu O, Puha G, et al. Inflammatory and cardiac biomarkers in relation with post-acute COVID-19 and mortality: what we know after successive pandemic waves. *Diagnostics (Basel)*. 2022;12:1373. doi: 10.3390/diagnostics12061373
111. Nchioua R, Diofano F, Noettger S, von Maltitz P, Stenger S, Zech F, Münch J, Sparrer KMJ, Just S, Kirchhoff F. Strong attenuation of SARS-CoV-2 omicron BA.1 and increased replication of the BA.5 subvariant in human cardiomyocytes. *Signal Transduct Target Ther*. 2022;7:395. doi: 10.1038/s41392-022-01256-9
112. Wagner JUG, Bojkova D, Shumliakivska M, Luxan G, Nicin L, Aslan GS, Milting H, Kandler JD, Dendorfer A, Heumueller AW, et al. Increased susceptibility of human endothelial cells to infections by SARS-CoV-2 variants. *Basic Res Cardiol*. 2021;116:42. doi: 10.1007/s00395-021-00882-8
113. Fairweather D, Cooper LT Jr, Blauwet LA. Sex and gender differences in myocarditis and dilated cardiomyopathy. *Curr Probl Cardiol*. 2013;38:7–46. doi: 10.1016/j.cpcardiol.2012.07.003
114. Kyto V, Sipila J, Rautava P. The effects of gender and age on occurrence of clinically suspected myocarditis in adulthood. *Heart*. 2013;99:1681–1684. doi: 10.1136/heartjnl-2013-304449
115. Coronado MJ, Bruno KA, Blauwet LA, Tschope C, Cunningham MW, Pankuweit S, van Linthout S, Jeon E-S, McNamara DM, Krejčí J, et al. Elevated sera sST2 is associated with heart failure in men ≤50 years old with myocarditis. *J Am Heart Assoc*. 2019;8:e008968. doi: 10.1161/JAHA.118.008968
116. Ozieranski K, Tyminska A, Kruk M, Kon B, Skwarek A, Opolski G, Grabowski M. Occurrence, trends, management and outcomes of patients hospitalized with clinically suspected myocarditis-ten-year perspectives from the MYO-PL nationwide database. *J Clin Med*. 2021;10:4672. doi: 10.3390/jcm10204672
117. Ferreira VM, Schulz-Menger J, Holmvang G, Kramer CM, Carbone I, Sechtem U, Kindermann I, Gutberlet M, Cooper LT, Liu P, et al. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. *J Am Coll Cardiol*. 2018;72:3158–3176. doi: 10.1016/j.jacc.2018.09.072
118. Imazio M, Brucato A, Cemin R, Ferrua S, Maggiolini S, Beqaraj F, Demarie D, Forno D, Ferro S, Maestroni S, et al; ICAP Investigators. A randomized trial of colchicine for acute pericarditis. *N Engl J Med*. 2013;369:1522–1528. doi: 10.1056/NEJMoa1208536
119. Peckham H, de Gruijter NM, Raine C, Radziszewska A, Ciurtin C, Wedderburn LR, Rosser EC, Webb K, Deakin CT. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ICU admission. *Nat Commun*. 2020;11:6317. doi: 10.1038/s41467-020-19741-6
120. Vahidy FS, Pan AP, Ahnstedt H, Munshi Y, Choi HA, Tiruneh Y, Nasir K, Kash BA, Andrieni JD, McCullough LD. Sex differences in susceptibility, severity, and outcomes of coronavirus disease 2019: cross-sectional analysis from a diverse US metropolitan area. *PLoS One*. 2021;16:e0245556. doi: 10.1371/journal.pone.0245556
121. Del Valle DM, Kim-Schulze S, Huang HH, Beckmann ND, Nirenberg S, Wang B, Lavin Y, Swartz TH, Madduri D, Stock A, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med*. 2020;26:1636–1643. doi: 10.1038/s41591-020-1051-9
122. Takahashi T, Ellingson MK, Wong P, Israelow B, Lucas C, Klein J, Silva J, Mao T, Oh JE, Tokuyama M, et al; Yale IMPACT Research Team. Sex differences in immune responses that underlie COVID-19 disease outcomes. *Nature*. 2020;588:315–320. doi: 10.1038/s41586-020-2700-3
123. Lau ES, McNeill JN, Paniagua SM, Liu EE, Wang JK, Bassett IV, Selvaggi CA, Lubitz SA, Foulkes AS, Ho JE. Sex differences in inflammatory markers in patients hospitalized with COVID-19 infection: insights from the MGH COVID-19 patient registry. *PLoS One*. 2021;16:e0250774. doi: 10.1371/journal.pone.0250774
124. Frisancho-Kiss S, Davis SE, Nyland JF, Frisancho JA, Cihakova D, Barrett MA, Rose NR, Fairweather D. Cutting edge: cross-regulation by TLR4 and T cell Ig mucin-3 determines sex differences in inflammatory heart disease. *J Immunol*. 2007;178:6710–6714. doi: 10.4049/jimmunol.178.11.6710
125. Frisancho-Kiss S, Coronado MJ, Frisancho JA, Lau VM, Rose NR, Klein SL, Fairweather DL. Gonadectomy of male BALB/c mice increases Tim-3(+) alternatively activated M2 macrophages, Tim-3(+) T cells, Th2 cells and Treg in the heart during acute coxsackievirus-induced myocarditis. *Brain Behav Immun*. 2009;23:649–657. doi: 10.1016/j.bbi.2008.12.002
126. Minhas AS, Gilotra NA, Goerlich E, Metkus T, Garibaldi BT, Sharma G, Bavaro N, Phillip S, Michos ED, Hays AG. Myocardial work efficiency, a novel measure of myocardial dysfunction, is reduced in COVID-19 patients and associated with in-hospital mortality. *Front Cardiovasc Med*. 2021;8:667721. doi: 10.3389/fcvm.2021.667721
127. Basso C, Leone O, Rizzo S, De Gaspari M, van der Wal AC, Aubry MC, Bois MC, Lin PT, Maleszewski JJ, Stone JR. Pathological features of COVID-19-associated myocardial injury: a multicentre cardiovascular pathology study. *Eur Heart J*. 2020;41:3827–3835. doi: 10.1093/eurheartj/ehaa664
128. Fairweather D, Frisancho-Kiss S, Yusung SA, Barrett MA, Davis SE, Gatewood SJ, Njoku DB, Rose NR. Interferon-gamma protects against chronic viral myocarditis by reducing mast cell degranulation, fibrosis, and the profibrotic cytokines transforming growth factor-beta 1, interleukin-1 beta, and interleukin-4 in the heart. *Am J Pathol*. 2004;165:1883–1894. doi: 10.1016/s0002-9440(10)63241-5
129. Coronado MJ, Brandt JE, Kim E, Bucek A, Bedja D, Abston ED, Shin J, Gabrielson KL, Mitzner W, Fairweather DL. Testosterone and interleukin-1beta increase cardiac remodeling during coxsackievirus B3 myocarditis via serpin A 3n. *Am J Physiol Heart Circ Physiol*. 2012;302:H1726–H1736. doi: 10.1152/ajpheart.00783.2011
130. Schultheiss HP, Fairweather D, Caforio ALP, Escher F, Hershberger RE, Lipshultz SE, Liu PP, Matsumori A, Mazzanti A, McMurray J, et al. Dilated cardiomyopathy. *Nat Rev Dis Primers*. 2019;5:32. doi: 10.1038/s41572-019-0084-1
131. Cocker MS, Abdel-Aty H, Strohm O, Friedrich MG. Age and gender effects on the extent of myocardial involvement in acute myocarditis: a cardiovascular magnetic resonance study. *Heart*. 2009;95:1925–1930. doi: 10.1136/hrt.2008.164061

132. Blagova OV, Kogan EA, Lutokhina YA, Kukleva AD, Ainetdinova DH, Novosadov VM, Rud RS, Zaitsev AY, Zaidenov VA, Kupriyanova AG, et al. Subacute and chronic post-COVID myoendocarditis: clinical presentation, role of coronavirus persistence and autoimmune mechanisms. *Kardiologiia*. 2021;61:11–27. doi: 10.18087/cardio.2021.6.n1659
133. Imazio M, Bobbio M, Cecchi E, Demarie D, Demichelis B, Pomari F, Moratti M, Gaschino G, Giammaria M, Ghisio A, et al. Colchicine in addition to conventional therapy for acute pericarditis: results of the colchicine for acute pericarditis (COPE) trial. *Circulation*. 2005;112:2012–2016. doi: 10.1161/CIRCULATIONAHA.105.542738
134. Bhattacharyya B, Panda D, Gupta S, Banerjee M. Anti-mitotic activity of colchicine and the structural basis for its interaction with tubulin. *Med Res Rev*. 2008;28:155–183. doi: 10.1002/med.20097
135. Martinon F, Petrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature*. 2006;440:237–241. doi: 10.1038/nature04516
136. Deftereos S, Giannopoulos G, Papoutsidakis N, Panagopoulou V, Kossyvakis C, Raisakis K, Cleman MW, Stefanadis C. Colchicine and the heart: pushing the envelope. *J Am Coll Cardiol*. 2013;62:1817–1825. doi: 10.1016/j.jacc.2013.08.726
137. Carvelli J, Demaria O, Vely F, Batista L, Chouaki Benmansour N, Fares J, Carpentier S, Thibult M-L, Morel A, Remark R, et al; Explore COVID-19 IPH group. Association of COVID-19 inflammation with activation of the C5a-C5aR1 axis. *Nature*. 2020;588:146–150. doi: 10.1038/s41586-020-2600-6
138. Huber S, Massri M, Grasse M, Fleischer V, Kellnerova S, Harpf V, Knabl L, Knabl L, Heiner T, Kummann M, et al. Systemic inflammation and complement activation parameters predict clinical outcome of severe SARS-CoV-2 infections. *Viruses*. 2021;13:2376. doi: 10.3390/v13122376
139. Shahbazi F, Karami M, Mirzaei M, Mohammadi Y. Survival rates and prognostic factors in patients with coronavirus disease 2019: a registry-based retrospective cohort study. *J Res Health Sci*. 2021;21:e00515. doi: 10.34172/jrhs.2021.47
140. Toldo S, Bussani R, Nuzzi V, Bonaventura A, Mauro AG, Cannata A, Pillappa R, Sinagra G, Nana-Sinkam P, Sime P, et al. Inflammasome formation in the lungs of patients with fatal COVID-19. *Inflamm Res*. 2021;70:7–10. doi: 10.1007/s00011-020-01413-2
141. Amin S, Aktar S, Rahman MM, Chowdhury MMH. NLRP3 inflammasome activation in COVID-19: an interlink between risk factors and disease severity. *Microbes Infect*. 2022;24:104913. doi: 10.1016/j.micinf.2021.104913
142. Ren X, Wen W, Fan X, Hou W, Su B, Cai P, Li J, Liu Y, Tang F, Zhang F, et al. COVID-19 immune features revealed by a large-scale single-cell transcriptome atlas. *Cell*. 2021;184:1895–1913.e19. doi: 10.1016/j.cell.2021.01.053
143. Hunter CA, Chizzonite R, Remington JS. IL-1 beta is required for IL-12 to induce production of IFN-gamma by NK cells. A role for IL-1 beta in the T cell-independent mechanism of resistance against intracellular pathogens. *J Immunol*. 1995;155:4347–4354.
144. Cai G, Kastelein R, Hunter CA. Interleukin-18 (IL-18) enhances innate IL-12-mediated resistance to Toxoplasma gondii. *Infect Immun*. 2000;68:6932–6938. doi: 10.1128/IAI.68.12.6932-6938.2000
145. Clark JT, Weizman OE, Aldridge DL, Shallberg LA, Eberhard J, Lanzar Z, Wasche D, Huck JD, Zhou T, Ring AM, et al. IL-18bp mediates the balance between protective and pathological immune responses to *Toxoplasma gondii*. *Cell Rep*. 2023;42:112147. doi: 10.1016/j.celrep.2023.112147
146. Frisancho-Kiss S, Nyland JF, Davis SE, Frisancho JA, Barrett MA, Rose NR, Fairweather DL. Sex differences in coxsackievirus B3-induced myocarditis: IL-12Rbeta1 signaling and IFN-gamma increase inflammation in males independent from STAT4. *Brain Res*. 2006;1126:139–147. doi: 10.1016/j.brainres.2006.08.003
147. Cuker A, Tseng EK, Nieuwlaat R, Angchaisuksiri P, Blair C, Dane K, Davila J, DeSancho MT, Diuguid D, Griffin DO, et al. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19. *Blood Adv*. 2021;5:872–888. doi: 10.1182/bloodadvances.2020003763
148. Gao LN, Li Q, Xie JQ, Yang WX, You CG. Immunological analysis and differential genes screening of venous thromboembolism. *Hereditas*. 2021;158:2. doi: 10.1186/s41065-020-00166-6
149. Zheng Y, Zhuang MW, Han L, Zhang J, Nan ML, Zhan P, Kang D, Liu X, Gao C, Wang P-H. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) membrane (M) protein inhibits type I and III interferon production by targeting RIG-I/MDA-5 signaling. *Signal Transduct Target Ther*. 2020;5:299. doi: 10.1038/s41392-020-00438-7
150. Zhu Y, Zhang Z, Song J, Qian W, Gu X, Yang C, Shen N, Xue F, Tang Y. SARS-CoV-2-encoded miRNAs inhibit host type I interferon pathway and mediate allelic differential expression of susceptible gene. *Front Immunol*. 2021;12:767726. doi: 10.3389/fimmu.2021.767726
151. Mathew D, Giles JR, Baxter AE, Oldridge DA, Greenplate AR, Wu JE, Alanio C, Kuri-Cervantes L, Pampena MB, D'Andrea K, et al. Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications. *Science*. 2020;369:eabc8511.
152. Eriksson U, Ricci R, Hunziker L, Kurrer MO, Oudit GY, Watts TH, Sonderegger I, Bachmaier K, Kopf M, Penninger JM. Dendritic cell-induced autoimmune heart failure requires cooperation between adaptive and innate immunity. *Nat Med*. 2003;9:1484–1490. doi: 10.1038/nm960
153. Lv H, Havari E, Pinto S, Gottumukkala RV, Cornivelli L, Raddassi K, Matsui T, Rosenzweig A, Bronson RT, Smith R, et al. Impaired thymic tolerance to alpha-myosin directs autoimmunity to the heart in mice and humans. *J Clin Invest*. 2011;121:1561–1573. doi: 10.1172/JCI44583
154. Cooper LT Jr, Onuma OK, Sagar S, Oberg AL, Mahoney DW, Asmann YW, Liu P. Genomic and proteomic analysis of myocarditis and dilated cardiomyopathy. *Heart Fail Clin*. 2010;6:75–85. doi: 10.1016/j.hfc.2009.08.012
155. Kaya Z, Afanasyeva M, Wang Y, Dohmen KM, Schlichting J, Tretter T, Fairweather D, Holers VM, Rose NR. Contribution of the innate immune system to autoimmune myocarditis: a role for complement. *Nat Immunol*. 2001;2:739–745. doi: 10.1038/90686
156. Eriksson U, Kurrer MO, Schmitz N, Marsch SC, Fontana A, Eugster HP, Kopf M. Interleukin-6-deficient mice resist development of autoimmune myocarditis associated with impaired upregulation of complement C3. *Circulation*. 2003;107:320–325. doi: 10.1161/01.cir.0000043802.38699.66
157. Fairweather D, Frisancho-Kiss S, Njoku DB, Nyland JF, Kaya Z, Yusung SA, Davis SE, Frisancho JA, Barrett MA, Rose NR. Complement receptor 1 and 2 deficiency increases coxsackievirus B3-induced myocarditis, dilated cardiomyopathy, and heart failure by increasing macrophages, IL-1beta, and immune complex deposition in the heart. *J Immunol*. 2006;176:3516–3524. doi: 10.4049/jimmunol.176.6.3516
158. Mueller KAL, Patzelt J, Sauter M, Maier P, Gekeler S, Klingel K, Kandolf R, Seizer P, Gawaz M, Geisler T, et al. Myocardial expression of the anaphylatoxin receptor C3AR is associated with cardiac inflammation and prognosis in patients with non-ischaemic heart failure. *ESC Heart Fail*. 2018;5:846–857. doi: 10.1002/ehf2.12298
159. Fairweather D, Coronado MJ, Garton AE, Dziedzic JL, Bucek A, Cooper LT Jr, Brandt JE, Alikhan FS, Wang H, Endres CJ, et al. Sex differences in translocator protein 18 kDa (TSPO) in the heart: implications for imaging myocardial inflammation. *J Cardiovasc Transl Res*. 2014;7:192–202. doi: 10.1007/s12265-013-9538-0
160. Fairweather D, Frisancho-Kiss S, Gatewood S, Njoku D, Steele R, Barrett M, Rose NR. Mast cells and innate cytokines are associated with susceptibility to autoimmune heart disease following coxsackievirus B3 infection. *Autoimmunity*. 2004;37:131–145. doi: 10.1080/0891693042000196200
161. Fairweather D, Yusung S, Frisancho S, Barrett M, Gatewood S, Steele R, Rose NR. IL-12 receptor beta 1 and Toll-like receptor 4 increase IL-1 beta- and IL-18-associated myocarditis and coxsackievirus replication. *J Immunol*. 2003;170:4731–4737. doi: 10.4049/jimmunol.170.9.4731
162. Roberts BJ, Dragon JA, Moussawi M, Huber SA. Sex-specific signaling through Toll-like receptors 2 and 4 contributes to survival outcome of coxsackievirus B3 infection in C57BL/6 mice. *Biol Sex Differ*. 2012;3:25. doi: 10.1186/2042-6410-3-25
163. Tschope C, Muller I, Xia Y, Savvatis K, Pappritz K, Pinkert S, Lassner D, Heimesaat MM, Spillmann F, Miteva K, et al. Nod2 (nucleotide-binding oligomerization domain 2) is a major pathogenic mediator of coxsackievirus B3-induced myocarditis. *Circ Heart Fail*. 2017;10:e003870. doi: 10.1161/CIRCHEARTFAILURE.117.003870
164. Fallach R, Shainberg A, Avlas O, Fainblut M, Chepurko Y, Porat E, Hochhauser E. Cardiomyocyte Toll-like receptor 4 is involved in heart dysfunction following septic shock or myocardial ischemia. *J Mol Cell Cardiol*. 2010;48:1236–1244. doi: 10.1016/j.yjmcc.2010.02.020
165. Eriksson U, Kurrer MO, Sonderegger I, Iezzi G, Tafuri A, Hunziker L, Suzuki S, Bachmaier K, Bingisser RM, Penninger JM, et al. Activation of dendritic cells through the interleukin 1 receptor 1 is critical for the induction of autoimmune myocarditis. *J Exp Med*. 2003;197:323–331. doi: 10.1084/jem.20021788
166. Satoh M, Nakamura M, Akatsu T, Iwasaka J, Shimoda Y, Segawa I, Hiramori K. Expression of Toll-like receptor 4 is associated with enteroviral replication in human myocarditis. *Clin Sci (Lond)*. 2003;104:577–584. doi: 10.1042/CS20020263
167. Satoh M, Nakamura M, Akatsu T, Shimoda Y, Segawa I, Hiramori K. Toll-like receptor 4 is expressed with enteroviral replication in myocardium from

patients with dilated cardiomyopathy. *Lab Invest*. 2004;84:173–181. doi: 10.1038/labinvest.3700031
168. Pappritz K, Lin J, El-Shafeey M, Fechner H, Kuhl U, Alogna A, Spillmann F, Elsanhoury A, Schulz R, Tschöpe C, et al. Colchicine prevents disease progression in viral myocarditis via modulating the NLRP3 inflammasome in the cardiosplenic axis. *ESC Heart Fail*. 2022;9:925–941. doi: 10.1002/ehf2.13845
169. Fairweather D, Frisancho-Kiss S, Yusung SA, Barrett MA, Davis SE, Steele RA, Gatewood SJL, Rose NR. IL-12 protects against coxsackievirus B3-induced myocarditis by increasing IFN-gamma and macrophage and neutrophil populations in the heart. *J Immunol*. 2005;174:261–269. doi: 10.4049/jimmunol.174.1.261
170. Afanasyeva M, Georgakopoulos D, Fairweather D, Caturegli P, Kass DA, Rose NR. Novel model of constrictive pericarditis associated with autoimmune heart disease in interferon-gamma-knockout mice. *Circulation*. 2004;110:2910–2917. doi: 10.1161/01.CIR.0000147538.92263.3A
171. Legere SA, Haidl ID, Legare JF, Marshall JS. Mast cells in cardiac fibrosis: new insights suggest opportunities for intervention. *Front Immunol*. 2019;10:580. doi: 10.3389/fimmu.2019.00580
172. Baldeviano GC, Barin JG, Talor MV, Srinivasan S, Bedja D, Zheng D, Gabrielson K, Iwakura Y, Rose NR, Cihakova D. Interleukin-17A is dispensable for myocarditis but essential for the progression to dilated cardiomyopathy. *Circ Res*. 2010;106:1646–1655. doi: 10.1161/CIRCRESAHA.109.213157
173. Blanco-Dominguez R, Sanchez-Diaz R, de la Fuente H, Jimenez-Borreguero LJ, Matesanz-Marin A, Relano M, Jiménez-Alejandre R, Linillos-Pradillo B, Tsilingiri K, Martín-Mariscal ML, et al. A novel circulating microRNA for the detection of acute myocarditis. *N Engl J Med*. 2021;384:2014–2027. doi: 10.1056/NEJMoa2003608
174. Heidecker B, Kittleson MM, Kasper EK, Wittstein IS, Champion HC, Russell SD, Hruban RH, Rodriguez ER, Baughman KL, Hare JM. Transcriptomic biomarkers for the accurate diagnosis of myocarditis. *Circulation*. 2011;123:1174–1184. doi: 10.1161/CIRCULATIONAHA.110.002857
175. Munoz-Fontela C, Dowling WE, Funnell SGP, Gsell PS, Riveros-Balta AX, Albrecht RA, Andersen H, Baric RS, Carroll MW, Cavaleri M, et al. Animal models for COVID-19. *Nature*. 2020;586:509–515. doi: 10.1038/s41586-020-2787-6
176. Chu H, Chan JF, Yuen KY. Animal models in SARS-CoV-2 research. *Nat Methods*. 2022;19:392–394. doi: 10.1038/s41592-022-01447-w
177. Bao L, Deng W, Huang B, Gao H, Liu J, Ren L, Wei Q, Yu P, Xu Y, Qi F, et al. The pathogenicity of SARS-CoV-2 in hACE2 transgenic mice. *Nature*. 2020;583:830–833. doi: 10.1038/s41586-020-2312-y
178. Sun SH, Chen Q, Gu HJ, Yang G, Wang YX, Huang XY, Liu S-S, Zhang NN, Li XF, Xiong R, et al. A mouse model of SARS-CoV-2 infection and pathogenesis. *Cell Host Microbe*. 2020;28:124–133.e4. doi: 10.1016/j.chom.2020.05.020
179. Gu H, Chen Q, Yang G, He L, Fan H, Deng YQ, Wang Y, Teng Y, Zhao Z, Cui Y, et al. Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy. *Science*. 2020;369:1603–1607. doi: 10.1126/science.abc4730
180. Dinnon KH 3rd, Leist SR, Schafer A, Edwards CE, Martinez DR, Montgomery SA, West A, Yount BL, Hou YJ, Adams LE, et al. A mouse-adapted model of SARS-CoV-2 to test COVID-19 countermeasures. *Nature*. 2020;586:560–566. doi: 10.1038/s41586-020-2708-8
181. Winkler ES, Bailey AL, Kafai NM, Nair S, McCune BT, Yu J, Fox JM, Chen RE, Earnest JT, Keeler SP, et al. SARS-CoV-2 infection of human ACE2-transgenic mice causes severe lung inflammation and impaired function. *Nat Immunol*. 2020;21:1327–1335. doi: 10.1038/s41590-020-0778-2
182. Viveiros A, Noyce RS, Gheblawi M, Colombo D, Bilawchuk LM, Clemente-Casares X, Marchant DJ, Kassiri Z, Del Nonno F, Evans DH, et al. SARS-CoV-2 infection downregulates myocardial ACE2 and potentiates cardiac inflammation in humans and hamsters. *Am J Physiol Heart Circ Physiol*. 2022;323:H1262–H1269. doi: 10.1152/ajpheart.00578.2022
183. Bruno KA, Mathews JE, Yang AL, Frisancho JA, Scott AJ, Greyner HD, Molina FA, Greenaway MS, Cooper GM, Bucek A, et al. BPA alters estrogen receptor expression in the heart after viral infection activating cardiac mast cells and T cells leading to perimyocarditis and fibrosis. *Front Endocrinol (Lausanne)*. 2019;10:598. doi: 10.3389/fendo.2019.00598
184. Hou X, Chen G, Bracamonte-Baran W, Choi HS, Diny NL, Sung J, Hughes D, Won T, Wood MK, Talor MV, et al. The cardiac microenvironment instructs divergent monocyte fates and functions in myocarditis. *Cell Rep*. 2019;28:172–189.e7. doi: 10.1016/j.celrep.2019.06.007
185. Barin JG, Baldeviano GC, Talor MV, Wu L, Ong S, Quader F, Chen P, Zheng D, Caturegli P, Rose NR, et al. Macrophages participate in IL-17-mediated inflammation. *Eur J Immunol*. 2012;42:726–736. doi: 10.1002/eji.201141737
186. Yuan S, Ye ZW, Liang R, Tang K, Zhang AJ, Lu G, Ong CP, Man Poon VK, Chan CC, Mok BW, et al. Pathogenicity, transmissibility, and fitness of SARS-CoV-2 Omicron in Syrian hamsters. *Science*. 2022;377:428–433. doi: 10.1126/science.abn8939
187. Daems M, Liesenborghs L, Boudewijns R, Simmonds SJ, Kraisin S, Van Wauwe J, Cuijpers I, Raman J, Geuens N, Buyten TV, et al. SARS-CoV-2 infection causes prolonged cardiomyocyte swelling and inhibition of HIF1alpha translocation in an animal model COVID-19. *Front Cardiovasc Med*. 2022;9:964512. doi: 10.3389/fcvm.2022.964512
188. Lenzo JC, Fairweather D, Cull V, Shellam GR, James Lawson CM. Characterisation of murine cytomegalovirus myocarditis: cellular infiltration of the heart and virus persistence. *J Mol Cell Cardiol*. 2002;34:629–640. doi: 10.1006/jmcc.2002.2003
189. Eckart RE, Love SS, Atwood JE, Arness MK, Cassimatis DC, Campbell CL, Boyd SY, Murphy JG, Swerdlow DL, Collins LC, et al; Department of Defense Smallpox Vaccination Clinical Evaluation Team. Incidence and follow-up of inflammatory cardiac complications after smallpox vaccination. *J Am Coll Cardiol*. 2004;44:201–205. doi: 10.1016/j.jacc.2004.05.004
190. Engler RJ, Nelson MR, Collins LC Jr, Spooner C, Hemann BA, Gibbs BT, Atwood JE, Howard RS, Chang AS, Cruser DL, et al. A prospective study of the incidence of myocarditis/pericarditis and new onset cardiac symptoms following smallpox and influenza vaccination. *PLoS One*. 2015;10:e0118283. doi: 10.1371/journal.pone.0118283
191. Bozkurt B, Kamat I, Hotez PJ. Myocarditis with COVID-19 mRNA vaccines. *Circulation*. 2021;144:471–484. doi: 10.1161/CIRCULATIONAHA.121.056135
192. Root-Bernstein R, Fairweather D. Complexities in the relationship between infection and autoimmunity. *Curr Allergy Asthma Rep*. 2014;14:407. doi: 10.1007/s11882-013-0407-3
193. Root-Bernstein R, Fairweather D. Unresolved issues in theories of autoimmune disease using myocarditis as a framework. *J Theor Biol*. 2015;375:101–123. doi: 10.1016/j.jtbi.2014.11.022
194. Kariko K, Buckstein M, Ni H, Weissman D. Suppression of RNA recognition by Toll-like receptors: the impact of nucleoside modification and the evolutionary origin of RNA. *Immunity*. 2005;23:165–175. doi: 10.1016/j.immuni.2005.06.008
195. Alameh MG, Tombacz I, Bettini E, Lederer K, Sittplangkoon C, Wilmore JR, Gaudette BT, Soliman OY, Pine M, Hicks P, et al. Lipid nanoparticles enhance the efficacy of mRNA and protein subunit vaccines by inducing robust T follicular helper cell and humoral responses. *Immunity*. 2021;54:2877–2892.e7. doi: 10.1016/j.immuni.2021.11.001
196. Reichmuth AM, Oberli MA, Jaklenec A, Langer R, Blankschtein D. mRNA vaccine delivery using lipid nanoparticles. *Ther Deliv*. 2016;7:319–334. doi: 10.4155/tde-2016-0006
197. Nagasaka T, Koitabashi N, Ishibashi Y, Aihara K, Takama N, Ohyama Y, Yokoyama T, Kaneko Y. Acute myocarditis associated with COVID-19 vaccination: a case report. *J Cardiol Cases*. 2022;25:285–288. doi: 10.1016/j.jccase.2021.11.006
198. Afanasyeva M, Georgakopoulos D, Belardi DF, Bedja D, Fairweather D, Wang Y, Kaya Z, Gabrielson KL, Rodriguez ER, Caturegli P, et al. Impaired up-regulation of CD25 on CD4+ T cells in IFN-gamma knockout mice is associated with progression of myocarditis to heart failure. *Proc Natl Acad Sci USA*. 2005;102:180–185. doi: 10.1073/pnas.0408241102