CJIM | Clinical Encounters

Cardiovascular Manifestations in Adolescents After the Pfizer-BioNTech COVID-19 Vaccine

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Statement of Significance: The BNT162b2 mRNA COVID-19 vaccine against the COVID-19 virus is clinically proven to be effective and safe with a high-efficiency rate. Minor adverse events (AE) such as fatigue and nausea have been reported. However, as more individuals get the vaccine, rarer adverse events have emerged. This is a case series on three adolescent males diagnosed with myocarditis or myopericarditis shortly after receiving the second dose of the BNT162b2 mRNA vaccine. Acute COVID-19 was ruled out in all three cases based on (-) severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and real-time reverse transcription polymerase chain reaction (RT-PCR) tests of specimens obtained using nasopharyngeal swabs. The otherwise healthy patients presented with acute chest discomfort two to three days after receiving their second vaccine dose. All three patients were afebrile with electrocardiogram (ECG) abnormalities, elevated C reactive protein levels ranging from 4.06-6.10 mg/dL, and elevated troponin I levels ranging from 0.26–7.61 ng/dL. Suspected cases of myocarditis and pericarditis should be reported to the Vaccine Adverse Event Reporting System (VAERS).

DOI: 10.47265/cjim.v3i1.5055

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Introduction

The COVID-19 pandemic brought about unprecedented challenges to global health and the world economy. As of December 2021, the virus had infected over 280 million people and claimed over 5.4 million lives worldwide.[1] In response to this global health crisis, the World Health Organization (WHO) declared a Public Health Emergency of International Concern on January 31st 2020.[2] The Food and Drug Administration (FDA) granted Emergency Use Authorization (EUA) for the Pfizer BioNTech mRNA (BNT162b2) and Moderna (mRNA-1273) COVID-19 vaccines in December 2020 to address rising COVID-19 infections across the United States.[3] The authorization was based on clinical trials that showed the vaccines to be effective and as safe as other vaccines currently on the market.[4] COVID-19 transmission was confirmed to have originated from bats but may have been transmitted to humans via other intermediary species likely supplied by the local seafood market in Wuhan, China.[4]

The development of the Pfizer COVID-19 vaccine was made possible by the advances in vaccine technology. Unlike traditional vaccines, which use weakened or inactivated forms of the virus to trigger an immune response, this approach involved delivering viral mRNA into the host cell resulting in the production of a viral spike protein. The mRNA is encapsulated in a lipid nanoparticle that protects it from degradation and facilitates its delivery into cells.[5] The immune system then recognizes this protein as foreign and mounts an immune response.

The vaccine was shown to be highly effective in

preventing infection and severe disease caused by the virus. Clinical trials showed that the vaccine was over 94% effective in preventing symptomatic infection and 90% effective in preventing severe disease and hospitalization.[6]

While the COVID-19 mRNA vaccines such as Pfizer and Moderna had proven to be highly effective in preventing COVID-19 infection, some adverse events were reported on the (VAERS); they included fever, fatigue, soreness, joint pain, chills, nausea, and vomiting. In addition to these events, cases of myocarditis and pericarditis were reported on VAERS.[7] Additionally, myopericarditis has been reported as a rare side effect. Myopericarditis is a condition that involved inflammation of the heart muscle (myocarditis) and the outer lining of the heart (pericarditis). It can be caused by various factors, including viral infections including COVID-19, autoimmune disorders, and certain medications.

The Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) had been monitoring Pfizer and Moderna vaccine-related myopericarditis closely and had found that the risk of myopericarditis following vaccination was highest in males under the age of 30, with most cases occurring after the second dose of the vaccine.[8] While the exact cause of the association between the Pfizer-BioNTech vaccine and myopericarditis was not yet fully understood, it was believed to be related to an immune response triggered by the vaccine.

It's important to note that while myopericarditis is a serious condition, the overall risk of developing it after receiving the Pfizer-BioNTech or Moderna vaccine is low.[7] According to data from the CDC, the rate of myocarditis following vaccination was estimated to be around 12.6 cases per second-dose mRNA vaccine in individuals 12–39 years of age.[4] The risk of myocarditis among females was even lower, at 9.1 cases per million doses for ages 12–17 and 5.5 cases per million doses for ages 18–24.[4] The reason for male predominance in myopericarditis was not well known. Proposed explanations suggest sex hormone differences in immune response and the underdiagnosis of cardiac illness in women.[4] The CDC and FDA recommend vaccination against COVID-19 for all individuals aged 6 months and older, as the benefits of vaccination in preventing COVID-19 infection and severe disease far outweigh the risk of rare side effects such as myopericarditis.[4]

This case series is a summary of the clinical course and evaluation of three adolescent males presenting with myocarditis or myopericarditis within two to four days after the administration of the second dose of the Pfizer vaccine. These patients were among the first to be admitted to our hospital with COVID-19 vaccine-related myopericarditis. The COVID-19 status of the patients was assessed by reverse transcription-polymerase chain reaction (RT-PCR) of nasopharyngeal swabs. Laboratory tests for all patients included a routine complete blood count, basic metabolic panel, troponin, PCR testing, and serological determination of antibodies against causative agents of myocarditis and pericarditis.

Case Presentation

Three patients with no significant medical history were admitted to a tertiary hospital in North Carolina in 2021 due to chest pain/discomfort (Table 1). They all presented within two to four days after receiving the Pfizer-BioNTech vaccine and had an abnormal electrocardiogram (ECG) (Figures 1-3), elevated C-reactive protein (CRP) levels (range of 4.06–6.10 mg/dL; normal: <5.0 mg/dL), and elevated troponin I levels (0.26–7.61 ng/dL; normal <0.03 ng/dL) (Table 1). Brain natriuretic peptide levels were tested in two patients and were within normal limits (normal <100 pg/mL). All patients had a normal echocardiogram, except for a residual patent foramen ovale in one patient. All three patients were closely monitored by the cardiology team and have remained asymptomatic since discharge from the hospital. They had normal ECGs,

Table 1. Clinical and diagnostic summary of the cases.

Patient No.	Age	Peak CRP	Peak Troponin-I	Peak BNP	Serology	RT-PCR	RT-PCR2	ECG
1	16	N	H	N	(-)	N/A	N/A	Nonspecific ST and T wave abnormality and minimal ST elevation in the inferior leads V5 and V6
2	17	H	H	N/A	(-)	(-)	N/A	Nonspecific ST and T wave abnormality
3	14	H	H	N	(-)	(-)	(-)	T wave inversion in lateral leads and ST-segment elevation in V2-V6

*H, high, N, normal, (-), negative

Serum C-reactive protein (CRP) level (normal range (0.0–5.0 mg/L); serum troponin I level (normal range 0.0–0.03 ng/dL. Brain natriuretic peptide (BNP) level (normal <100 pg/mL)

Serology: Epstein-Barr virus (EBV), cytomegalovirus (CMV), hepatitis B virus (HBV), parvovirus B19 RT-PCR: SARS CoV-2, respiratory syncytial virus (RSV), influenza A virus, influenza B virus, Roseola (HHV-6) RT-PCR2: Adenovirus, parainfluenza, rhinovirus, enterovirus, human metapneumovirus, Bordetella pertussis, Mycoplasma pneumoniae, Chlamydia pneumoniae.

echocardiograms, ambulatory Holter monitoring, and cardiac exercise stress tests during subsequent follow-up appointments. Additionally, patients 2 and 3 underwent normal cardiac magnetic resonance imaging (MRI).

Patient 1 - Myopericarditis

A 16-year-old male with no significant medical history was transferred to a tertiary hospital for the management of acute substernal chest pain that radiated down both arms. It was alleviated by leaning forward and worsened when supine. He had received his second dose of the Pfizer-BioNTech vaccine one to three days before presentation. At the outside hospital, he had an elevated troponin of 0.5 ng/dL. On presentation, he was afebrile, with normal vital signs. He denied any preceding illnesses, recent fevers, abdominal pain, and cough. His physical examination was normal without signs of a pericardial friction rub. His ECG was significant for nonspecific ST elevations and T-wave abnormalities (Figure 1). Laboratory studies demonstrated evidence of myocardial injury and elevated inflammatory markers. The echocardiogram showed normal cardiac function and no evidence of coronary artery abnormality or pericardial effusion. Based on clinical presentation and lab findings, the patient was diagnosed with myopericarditis. The patient's chest discomfort resolved after three days, and he was discharged on 0.6 mg of colchicine twice a day.

Patient 2 - Myopericarditis

A 17-year-old male with a medical history of patent foramen ovale and mild pectus excavatum presented with retrosternal chest pain 36 hours after his second dose of the Pfizer-BioNTech vaccine. The pain was worsened with deep inspiration; the remainder of the physical exam was normal. He was febrile with a temperature of 100.6 F; other vital signs were normal. His ECG showed a right bundle branch block during his hospital course. This finding may have been present at baseline. His laboratory studies demonstrated evidence of myocardial injury and elevated inflammatory markers. His echocardiogram was normal except for a residual patent foramen ovale with a left-to-right flow. Based on clinical presentation and lab findings, the patient was diagnosed with myopericarditis. He was monitored in the hospital for a total of four days and then discharged on a course of ibuprofen and colchicine.

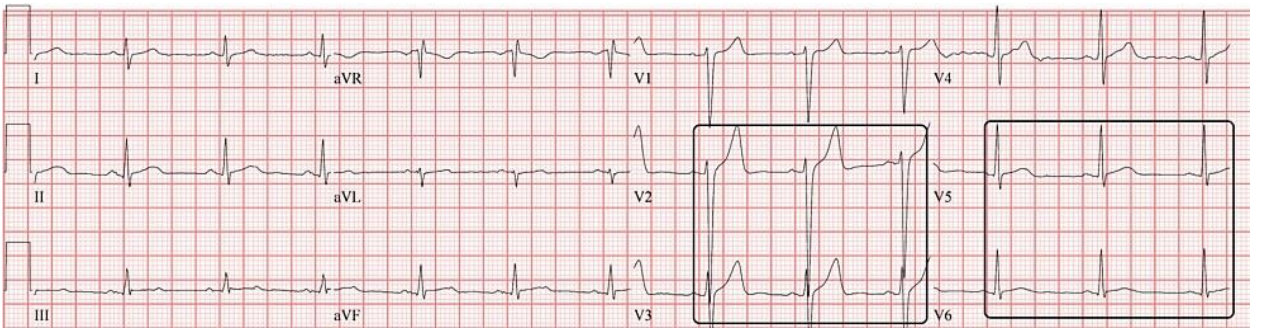

Figure 1. ECG showed nonspecific ST and T wave abnormality and minimal ST elevation in the anterior leads V2, V3, and inferior leads V5 and V6. Black boxes outline ST elevations.

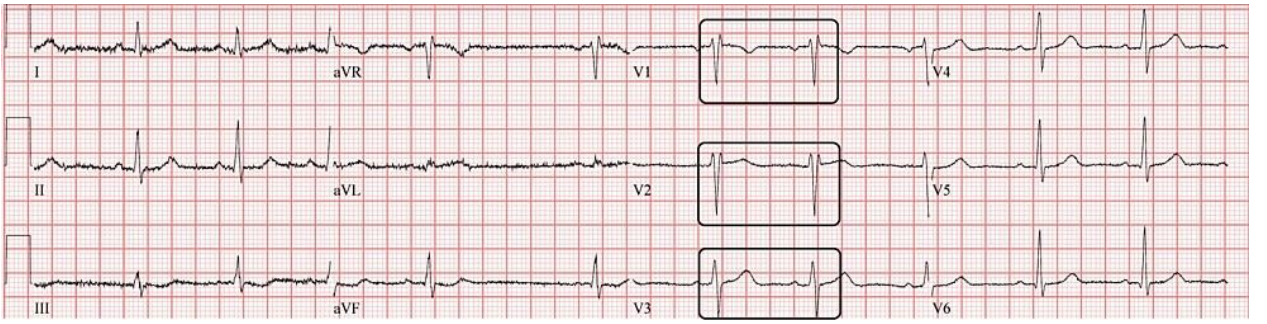

Figure 2. ECG showed nonspecific ST and T wave abnormality and minimal ST elevation in the anterior leads V2, V3, and inferior leads V5 and V6. Black boxes outline ST elevations.

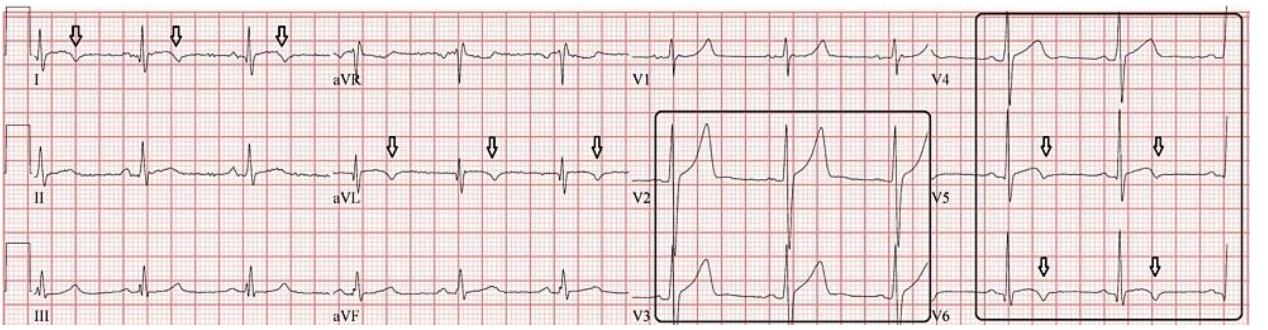

Figure 3. ECG showed ST-segment elevation in the anterolateral leads (v2-v6) and T wave inversion in lateral leads. Black boxes outline ST elevations. Arrows point to T-wave inversions.

Patient 3 - Myopericarditis

A 14-year-old male with no significant medical history presents to the hospital with a fever, a mild cough, and left precordial and midsternal chest pain. He had received his second dose of the Pfizer-BioNTech vaccine two days before presentation. Of note, the patient did have upper respiratory infection symptoms consisting of nasal congestion and a mild cough 2 weeks prior. Multiple members of his sports team experienced similar symptoms. On presentation, he was afebrile; other vital signs were normal. Physical exam and Chest-X-ray were normal. His ECG showed T wave inversion in lateral leads and ST-segment elevation (Figure 3). His chest discomfort resolved without any pharmacological interventions. Based on clinical presentation, the patient was diagnosed with myopericarditis. His symptoms resolved three days after admission, and he was discharged without any medications.

Discussion

Three cases of clinically suspected myopericarditis in otherwise healthy male patients after receiving the BNT162b2 mRNA COVID-19 vaccine were identified. A wide range of differential diagnoses for these cases was considered. The findings discussed in this report are adverse cardiovascular events that were not previously reported in clinical trials. Acute myocarditis and pericarditis have been reported to be one of the symptoms of the COVID-19 infection, but myocarditis is increasingly identified as a late manifestation seen in up to 46% to 78% of recovering COVID-19 patients.[9]

The diagnosis of myopericarditis is usually based on symptoms (chest pain, shortness of breath), ECG findings, physical examinations, and elevated cardiac biomarkers (troponin, BNP, CRP). Acute pericarditis may be associated with myocarditis due to their overlapping etiologies.[10] Additionally, clinical signs of pericarditis include a pericardial friction rub (due to friction between the 2 inflamed pericardial layers) which none of these patients had. Two patients had chest pain more specific to pericarditis (chest pain that worsened with inspiration and improved when leaning forward.[10] The most prevalent electrocardiogram (ECG) anomaly in myocarditis is sinus tachycardia with nonspecific ST/T-wave alterations. Diffuse T-wave inversions and PR-segment depression with pericarditis tend to favor a diagnosis of myopericarditis.[10] Myopericarditis can be associated with an underlying inflammatory disorder or infection. Two patients had elevated CRP and all three had elevated troponin which is suggestive of an underlying inflammatory response. Recent or current infection was ruled out clinically in two patients by past medical history and/or RT-PCT and serology suggesting the vaccine as the cause. One patient had symptoms of an upper respiratory illness, but serology and RT-PCR was (-) for common culprits. ECG findings (Figures 1-3) and clinical evaluation led to the diagnosis of myopericarditis in the three cases.

The pathophysiology of myocarditis and pericarditis due to the COVID-19 virus is believed to be due to direct myocyte injury from the virus upon binding to the ACE-2 protein receptor on cardiomyocytes, immune activation, and cytokine storm.[11] Since it takes a few days to develop protection from the COVID-19 virus after vaccine administration, an infection can still occur. However, the COVID-19 virus was ruled out with RT-PCRs as a causative agent in our three patients.

Myopericarditis is typically an uncommon manifestation of immunization.[12,13] Exceptions include myocarditis which was reported following the smallpox vaccine in adults. Among the 540,834 U.S. military personnel vaccinated against smallpox, 67 cases of myocarditis or pericarditis were reported.[12,13]

The cause of myocarditis and/or pericarditis following COVID-19 vaccination is still unclear, but various mechanisms have been suggested. Molecular mimicry between the SARS-CoV-2 spike protein and self-antigens and activation of

dysregulated immune pathways in some individuals has been suggested immune response to mRNA has been suggested.[4]

A case report found that levels of neutralizing antibodies were not significantly different in the patient with myocarditis than in vaccinated individuals without myocarditis, suggesting against a hyperimmune response. The patient did have elevated levels of certain cytokines and autoantibodies against self-antigens, and a 2-fold increase in natural killer (NK) cells, but it is not clear if these reflect a pathological immune response or reactive adaptive responses to myocardial inflammation.[4] Molecular mimicry between the spike protein of SARS-CoV-2 and self-antigens is another potential mechanism for myocarditis, but severe adverse events or autoimmune reactions have been rare.[4]

Another proposed mechanism for myocarditis is antibody-dependent enhancement (ADE). ADE was first seen with respiratory syncytial virus and measles vaccines in the 1960s.[14] It is due to the failure of non-neutralizing antibodies generated from a past infection of vaccination to appropriately fight the virus upon preexposure. This allows the virus to replicate resulting in an overactive immune response. However, studies have not shown evidence of either cellular immune enhancement or antibody-dependent enhancement of immunity in non-human primates after the SARS-CoV-2 virus challenge, either after vaccination or previous infection, and vaccine breakthrough COVID-19 cases are rare and mild.[15]Currently, there is little evidence of acute COVID-19 infection with myocarditis cases after COVID-19 vaccination, arguing against a breakthrough infection as a cause.[4] Reports to date also do not suggest a delayed hypersensitivity reaction, such as serum sickness–like reaction or eosinophilic myocarditis as a cause for myocarditis after mRNA COVID-19 vaccination.

Adverse events after the second dose of the Covid-19 vaccine were reported more often in adolescents aged 12-17 and young adults aged 18-24.[4] The median onset was 1-2 days. The population and onset of the adverse effects fit with this study's demographics. Though the clinical course was mild, with one patient requiring no treatment, pericarditis, and myocarditis may have a more severe clinical course in unhealthy patients and can result in long-term management. As a result, ongoing monitoring and research are needed to determine the cause of myocarditis and pericarditis and the potential long-term effects of COVID-19 vaccination.

Conclusions

We report one of the first case series of patients with myocarditis and pericarditis after receiving the Pfizer mRNA-based COVID-19 vaccines. While the COVID-19 vaccines have proven to be highly effective in preventing severe illness and death from the virus, there have been rare cases of myocarditis and pericarditis reported as adverse events, particularly in young males after the second dose of mRNA vaccines. The temporal association of vaccination and lack of other identified causes in our three cases suggested that the vaccine is a possible causative agent of these rare adverse events. The exact mechanism for these AEs is still being investigated, but there is evidence to suggest that they may be related to an immune response triggered by the vaccines. A registry myopericarditis registry related to COVID-19 vaccination composed of patient characteristics, symptoms, and tests such as troponin levels, ECG, echocardiography, and cardiac MRI would greatly help with understanding.

All three cases fully recovered and have had no concerns with cardiology follow-up. It is important to note, however, that the risks of COVID-19 infection far outweigh the risks of vaccination, and the benefits of vaccination in reducing the spread of the virus and protecting individuals from severe illness and death are evident.

ARTICLE INFORMATION

Accepted for Publication: July 09 2023.
Published Online: September 22 2023.
DOI: 10.47265/cjim.v3i1.5055

Cite this article: Arhin Martin, Hamad Hamad, Iheagwara Chisom, Pulver Aaron, Hales Joanna. **Cardiovascular Manifestations in Adolescents After the Pfizer-BioNTech COVID-19 Vaccine**. Carolina Journal of Interdisciplinary Medicine (CJIM) 3(1):48-55.

Conflict of Interest Disclosures: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Ethics Approval and Consent to Participate: Human subjects: Consent was obtained or waived by all participants in this study. HCA Healthcare issued approval 2021-531. What this determination is: Based on the information provided and attested as true, the research plan described does not require IRB oversight. This is because you are either a) not engaging in research with human subjects as defined by federal regulations; b) engaging in research with human subjects deemed excluded from IRB oversight per 45CFR46.102(l) OR c) engaging in research with sufficient human subject protections in the design to meet one or more IRB exemption criteria set forth in 45CFR46.104. While your research activity has been classified as not requiring IRB oversight, you must still adhere to the submitted research plan, all institutional policies and the principles of research ethics as set forth in The Belmont Report to maintain this status. All other required permissions and reporting obligations of your Institution apply, and the Institution reserves the right to contact you in the future to monitor its progress and/or to verify that there have been no changes to this research plan.

REFERENCES

1. Msemburi W, Karlinsky A, Knutson V, et al. The WHO estimates of excess mortality associated with the COVID-19 pandemic. *Nature*. 2022;613(7942):130–137. doi:doi.org/10.1038/s41586-022-05522-2.

2. Gostin LO, Hodge JG. US Emergency Legal Responses to Novel Coronavirus: Balancing Public Health and Civil Liberties. *JAMA*. 2020;323(12):1131–1132. doi:10.1001/jama.2020.2025.

3. Teo SP. Review of COVID-19 mRNA Vaccines: BNT162b2 and mRNA-1273. *Journal of Pharmacy Practice*. 2021;35:947–51. doi:10.1177/08971900211009650.

4. Bozkurt B, Kamat I, Hotez PJ. Myocarditis With COVID-19 mRNA Vaccines. . *Circulation*. 2021;144(6):471–484.

5. Elia U, Ramishetti S, Rosenfeld R, et al. Design of SARS-CoV-2 hFc-Conjugated Receptor-Binding Domain mRNA Vaccine Delivered via Lipid Nanoparticles. *ACS Nano*. 2021;15(6):9627–9637. doi:10.1021/acsnano.0c10180.

6. Ssentongo P, Ssentongo AE, Voleti N, et al. SARS-CoV-2 vaccine effectiveness against infection, symptomatic and severe COVID-19: a systematic review and meta-analysis. *BMC Infect Dis*. 2022;22(1):1–12. doi:10.1186/s12879-022-07418-y.

7. Alami A, Krewski D, Mattison D, et al. Risk of Myocarditis and Pericarditis among Young Adults following mRNA COVID-19 Vaccinations. *Vaccines*. 2022;10(5):722–722. doi:10.3390/vaccines10050722.

8. Vu SL, Bertrand M, Jabagi MJ, et al. Age and sex-specific risks of myocarditis and pericarditis following Covid-19 messenger RNA vaccines. *Nature Communications*. 2022;13(1):3633–3633. doi:10.1038/s41467-022-31401-5.

9. Bajaj R, Sinclair HC, Patel K, et al. Delayed-onset myocarditis following COVID-19. *Lancet Respir Med*. 2021;9(4):e32–e34. doi:10.1016/S2213-2600(21)00085-0.

10. Buttà C, Zappia L, Laterra G, et al. Diagnostic and prognostic role of electrocardiogram in acute myocarditis: A comprehensive review. *Annals of Noninvasive Electrocardiology*. 2020;25(3):e12726. doi:10.1111/anec.12726.

11. Oudit GY, Kassiri Z, Jiang C, et al. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. *Eur J Clin Invest*. 2009;39(7):618–625. doi:10.1111/j.1365-2362.2009.02153.x.

12. Eckart RE, Love SS, Atwood JE, et al. Incidence and follow-up of inflammatory cardiac complications after smallpox vaccination. *J Am Coll Cardiol*. 2004;44(1):201–206. doi:10.1016/j.jacc.2004.05.004.

13. Kuntz J, Crane B, Weinmann S, et al. 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.

14. De SR, Kuiken T, Timmerman HH, et al. Immunization of Macaques with Formalin-Inactivated Respiratory Syncytial Virus (RSV) Induces Interleukin-13-Associated Hypersensitivity to Subsequent RSV Infection. *J Virol*. 2002;76(22):11561–11561. doi:10.1128/jvi.76.22.11561-11569.2002.

15. Haynes BF, Corey L, Fernandes P, et al. Prospects for a safe COVID-19 vaccine. *Sci Transl Med*. 2020;12(568).