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# Risk and Pathogenesis of Myocarditis: COVID-19 Infection vs. Vaccination

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***Abstract***

*Myocarditis, a potentially serious inflammation of the heart muscle, has emerged as a notable complication of both SARS-CoV-2 infection and COVID-19 vaccination, albeit with distinct frequencies and severities. This review explores myocarditis risk, pathogenesis, and mechanisms in these two contexts. COVID-19-related myocarditis is linked to direct viral invasion, immune dysregulation, and systemic inflammation, often presenting with severe outcomes. Vaccine-associated myocarditis, while rare and typically milder, involves immune overactivation and molecular mimicry. Comparative analysis highlights the significantly higher myocarditis risk and severity following SARS-CoV-2 infection, underscoring the importance of vaccination to mitigate severe disease.*

**Keywords: Myocarditis, COVID-19, Vaccine, Vaccination, Immunology, Risk, Pathogenesis**

## Introduction

Myocarditis, an inflammatory condition of the heart muscle, has become a significant concern linked to both COVID-19 infection and mRNA-based COVID-19 vaccines [1]. While both infection and vaccination share some overlapping mechanisms in the pathogenesis of myocarditis, the associated risks differ markedly. COVID-19 infection poses a considerably higher risk and is often accompanied by severe complications and long-term cardiac sequelae. In contrast, vaccine-associated myocarditis is rare and typically mild and self-limiting, with most cases resolving swiftly and without lasting effects [1-4]. Despite differences in the underlying mechanisms, public health data overwhelmingly support vaccination as a safer choice, significantly reducing the risk of severe COVID-19 outcomes, including myocarditis. This review delves into the immunological mechanisms underlying myocarditis associated with both COVID-19 infection and vaccination, emphasizing that the protective benefits of vaccination far outweigh its rare risks, underscoring the importance of continued immunization efforts.

## Myocarditis Risk from COVID-19 Infection

SARS-CoV-2, the virus responsible for COVID-19, has been linked to various cardiovascular complications, including myocarditis [1-3]. Myocarditis following COVID-19 infection is believed to be caused by direct viral invasion of the myocardium or as a result of the intense inflammatory response triggered by the virus, which may involve cytokine storm or immune dysregulation.

**Incidence and Severity** Several studies have reported varying rates of myocarditis among COVID-19 patients. For instance, a study published in JAMA Cardiology found that myocarditis occurred from approximately 0.13% to 12-20% of hospitalized COVID-19 patients, with rates varying depending on the severity of the infection [5-7]. Severe COVID-19 cases, particularly those requiring intensive care, have been shown to have a higher incidence of myocarditis [7]. However, even mild cases have been associated with subclinical myocardial inflammation, detectable through cardiac MRI [8-10]. Overall, myocarditis incidence during the pandemic increased by approximately fourfold compared to pre-pandemic levels, affecting 1.5–4.0% of patients [11].

**Risk Factors** The risk of myocarditis from COVID-19 infection is elevated in individuals with certain underlying conditions, including cardiovascular disease, obesity, and diabetes. Age and sex also play a role, with older adults and those with pre-existing heart conditions being more susceptible. Additionally, men appear to be at higher risk than women, similar to the patterns observed with vaccine-related myocarditis [12-15].

In terms of severity, myocarditis associated with COVID-19 infection has been found to cause more severe outcomes compared to vaccine-induced myocarditis [12, 16]. Some patients may develop long-term complications, including heart failure and arrhythmias, necessitating long-term management [12].

## Myocarditis Risk from COVID-19 Vaccination

As mass vaccination campaigns against COVID-19 rolled out globally, reports of myocarditis, particularly following mRNA vaccines (Pfizer-BioNTech and Moderna), began to surface. Vaccine-associated myocarditis has primarily affected younger males, particularly those aged 16-29, typically after the second dose of the vaccine [14, 15]. However, the risk remains rare when considering the overall vaccinated population.

**Incidence and Severity** It was reported that the incidence of myocarditis following mRNA vaccination ranges from 10 to 30 cases per million doses, with the highest rates observed in males under 30 years of age. Importantly, most cases of vaccine-related myocarditis have been mild and self-limiting, with patients recovering after a short period of monitoring and treatment. Few cases require intensive care or lead to long-term complications [15-20].

**Risk Factors** The precise mechanisms behind vaccine-induced myocarditis are still under investigation, though it is hypothesized that the mRNA vaccines may trigger an exaggerated immune response in some individuals, particularly in younger males [14, 20]. Although this response is uncommon, it is thought to be related to the activation of the innate and adaptive immune systems by the mRNA, which mimics viral infection without the presence of the actual virus [14, 15].

Non-mRNA COVID-19 vaccines, such as viral vector vaccines (e.g., AstraZeneca and Johnson & Johnson), have been associated with only a few reported cases of myocarditis, suggesting that these vaccines are not linked to significant rates of this condition [21, 22]. Ongoing research continues to enhance our understanding of their safety profiles. The overall rarity of myocarditis across all vaccine platforms highlights the robust safety of COVID-19 vaccines, especially when weighed against the considerable risks posed by SARS-CoV-2 infection. Notably, in our studies using mice immunized intramuscularly with an influenza DNA vaccine, vaccine DNA was detectable via PCR in all analyzed tissues, including the heart and brain, for up to four weeks post-vaccination [23]. The clinical relevance of this finding remains uncertain and warrants further investigation.

## Comparative Analysis: Myocarditis Risk from Infection vs. Vaccination

When comparing the risk of myocarditis from COVID-19 infection versus vaccination, the data consistently show that the risk of myocarditis is significantly higher following infection. Multiple studies have demonstrated that the incidence of myocarditis in individuals who contract COVID-19 far exceeds the rare cases seen after vaccination. For example, a study published in Nature Medicine analyzed data from the U.S. and the UK and found that the risk of myocarditis following SARS-CoV-2 infection was up to 16 times higher than that after mRNA vaccination [24].

**Incidence Rates** As previously mentioned, myocarditis following COVID-19 infection can affect 2-4% of hospitalized patients, especially those with severe disease, whereas the incidence of myocarditis after mRNA vaccines is estimated to be around 10 to 30 cases per million doses. These numbers make it clear that, on a population level, the risk posed by infection is significantly greater. Furthermore, myocarditis post-infection tends to be more severe, often requiring intensive medical care, compared to the typically mild and self-limiting nature of vaccine-induced myocarditis [14-20]. A meta analysis further showed that SARS-CoV-2 infection in unvaccinated patients significantly increased risk of myocarditis in comparison with those vaccinated [25].

**Severity and Outcomes** Myocarditis resulting from COVID-19 infection is associated with more severe and long-term complications, including heart failure and arrhythmias. Recovery in these cases can take months, with some patients requiring prolonged treatment or ongoing medical care [4-6]. In contrast, myocarditis following vaccination is typically mild and resolves with minimal intervention, such as anti-inflammatory medications and rest [26, 27]. Follow-up studies

on vaccine-associated myocarditis have shown that most cases resolve completely within a few months without lasting damage. However, a subset of patients may experience persistent symptoms or laboratory abnormalities lasting beyond six months [27-32].

Similar to the myocarditis caused by COVID infection, male young patients with vaccine-associated myocarditis had a higher chance for earlier and more complete symptom recovery, despite clinical data showed their myocarditis are more severe. [30, 31].

**Balancing Risks** From a public health standpoint, the benefits of COVID-19 vaccination significantly outweigh the risks of potential side effects, including myocarditis. Data consistently demonstrate that the risk of severe outcomes from myocarditis due to COVID-19 infection is substantially higher than that associated with vaccination. In this context, vaccination remains the most effective strategy to minimize the risk of severe disease and myocarditis at both individual and community levels. The development of novel approaches, such as polarized vaccines, holds promise for further enhancing vaccine safety and efficiency, particularly for younger populations, by potentially reducing the risk of myocarditis [33].

## Mechanisms behind Myocarditis Development

The underlying mechanisms that lead to myocarditis from both COVID-19 infection and vaccination share some common elements but also involve distinct processes.

**Mechanisms in COVID-19 Infection** In COVID-19 infection, myocarditis is believed to result from two primary mechanisms: direct viral invasion of the heart tissue and an excessive immune response. During viremia, SARS-CoV-2 can reach the heart via the bloodstream or be carried there by macrophages [34, 35]. The virus then infects cardiomyocytes through the ACE2 receptor expressed on these cells, leading to inflammation and damage to the myocardium [35]. Histological studies of myocarditis in COVID-19 patients have shown that infiltration of T lymphocytes, particularly CD4+ helper T cells, along with scattered CD8+ cytotoxic T cells, may contribute to myocardial damage [36].

In severe cases of COVID-19, immune dysregulation can lead to a "cytokine storm," characterized by the excessive release of pro-inflammatory cytokines such as IL-6 and TNF-α. This results in widespread inflammation, including in the heart, contributing to the development of myocarditis. During a cytokine storm, a variety of immune cells, including T and B lymphocytes, macrophages, neutrophils, and natural killer (NK) cells, are involved in the inflammatory damage to the myocardium [35, 37-39].

Stein SR et al. reported in their autopsy studies [40] that SARS-CoV-2 can be detected in tissues up to six months post-infection, suggesting that viral-induced myocardial inflammation and injury may manifest long after the initial infection and can persist for several months. Given the immune response to infected cells, myocarditis associated with COVID-19 infection could last even longer.

The ACE2 receptors on cardiomyocytes not only mediate the entry of intact SARS-CoV-2 particles into cells but also bind to free spike proteins in the bloodstream, potentially triggering immune attacks on heart tissue. This represents one of the molecular immunological mechanisms underlying myocarditis. In severe SARS-CoV-2 infections, the levels of both free virus and spike protein are significantly elevated, which increases the likelihood and severity of myocarditis. This may explain why the incidence of myocarditis in hospitalized COVID-19 patients can reach as high as 20% [7].

Another contributing factor is the systemic stress caused by severe COVID-19, which can exacerbate underlying cardiovascular conditions, leading to secondary myocardial injury.

**Mechanisms in Vaccine-Associated Myocarditis** The exact mechanisms underlying myocarditis following mRNA vaccination are still being investigated. However, it is hypothesized that, in rare cases, mRNA vaccines may trigger an exaggerated immune response, particularly in younger individuals [41, 42]. mRNA or DNA vaccines use a small piece of the virus's genetic material to produce the spike protein, which activates the immune system. In some cases, this immune activation may result in inflammation of the heart tissue.

1. **Molecular Mimicry:** The SARS-CoV-2 spike protein shares structural similarities with cardiac antigens, such as α-myosin [43-45], which could potentially trigger autoimmunity in genetically predisposed individuals. Some researchers have proposed that molecular mimicry [27] - where the immune system mistakes proteins in the heart for viral proteins - could play a role in this process, leading to

an autoimmune-like response.

2. **Immune Priming:** Prior COVID-19 infection may prime T cells to react against both the vaccine's spike protein and cardiac antigens, exacerbating inflammation. Typically, the primary induction of autoimmunity by antigens takes several days, with most cases of autoimmune myocarditis developing 5 to 14 days after exposure to the antigen. According to current reports, some cases of vaccine-associated myocarditis occurred within 0-4 days post-vaccination, suggesting these patients were primed by a prior infection. Unfortunately, most reports on post-vaccination myocarditis do not include information about the patients' COVID-19 infection history, particularly lacking serological examination results [31, 36, 41]. In our examination of serum samples from patients clinically diagnosed with myocarditis, eight patients who received the COVID vaccine within 5 days of developing heart symptoms were all positive for SARS-CoV-2 nucleocapsid IgM and IgG antibodies, indicating prior infection. Seven out of these eight patients were asymptomatic for COVID-19. This suggests that their myocarditis may be coincident with vaccination, or the vaccination could have triggered or exacerbated pre-existing myocarditis due to the prior COVID-19 infection.
3. **Cytokine Dysregulation:** Vaccine-induced immune activation can lead to dysregulated cytokine release, promoting inflammation and myocardial damage [20, 27]. This may clinically trigger myocarditis or worsen pre-existing myocarditis. It is also possible that the COVID vaccine could induce a cytokine storm, further contributing to myocarditis.
4. **mRNA Immunogenicity:** The inherent immunogenicity of mRNA and lipid nanoparticles (LNPs) used in vaccines may activate inflammatory cascades, particularly in genetically predisposed individuals [46]. This should be of particular concern in patients who experience high fever and chills following vaccination.
5. **IgG4 Antibody Response:** Repeated mRNA vaccination has been linked to an abnormal increase in IgG4 antibodies, potentially dampening immune responses and contributing to persistent inflammation [47, 48]. These antibodies may not neutralize the SARS-CoV-2 virus but could promote the development of autoimmune myocarditis [47, 48].

Unlike COVID-19-associated myocarditis reported during the early stages of the pandemic, before vaccines were available [3, 4, 10, 49], myocarditis post-vaccination has been reported after the virus became widespread. Therefore, it is crucial to carefully exclude the influence of COVID-19 infection when studying myocarditis caused by vaccination. This remains a significant limitation in many studies on vaccine-associated myocarditis [48, 50, 51], greatly compromising the reliability of their conclusions.

Another theory is that certain individuals may have a predisposition to heightened immune reactions, which may be triggered by the vaccine's immune-stimulating components.

**Differences in Severity and Resolution** While both scenarios involve immune system activation, the severity of myocarditis appears to be more pronounced following COVID-19 infection due to the more widespread and intense inflammation caused by the virus. In contrast, vaccine-induced myocarditis is generally milder, likely due to the localized and controlled immune response prompted by the vaccine [52, 53].

## Conclusion

The comparison of myocarditis risk from COVID-19 infection and vaccination highlights a clear difference in both incidence and severity. While myocarditis can occur after COVID-19 vaccination, particularly with mRNA vaccines, these cases are rare, generally mild, and resolve with minimal intervention. In contrast, myocarditis following COVID-19 infection occurs more frequently and often leads to more severe outcomes, including prolonged hospitalization and long-term cardiac complications.

Given the overwhelming data supporting the higher risk of myocarditis from SARS-CoV-2 infection, vaccination remains the most effective strategy to mitigate severe illness, including myocarditis, at both the individual and population levels. Public health messaging should continue to emphasize the importance of vaccination while addressing concerns regarding rare adverse events. By doing so, the benefits of vaccination-prevention of severe COVID-19 complications and broader community protection-are reinforced.

Ultimately, balancing these risks, the protective benefits of vaccination far outweigh the small risk of myocarditis, ensuring that vaccination is a key tool in the ongoing fight against COVID-19.

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