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REVIEW

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Myocarditis after SARS-CoV-2 infection and COVID-19 vaccination: Epidemiology, outcomes, and new perspectives

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ABSTRACT

Myocarditis, typically manifesting as *myopericarditis*, is among the serious cardiac consequences observed over the course of the COVID-19 pandemic. We performed a comprehensive, evidence-based literature synthesis of findings from clinical trial data reanalyses, post-marketing surveillance, large observational studies, and other diverse research sources that help shed light on the phenomenon of myocarditis post SARS-CoV-2 infection versus COVID-19 vaccine-induced myocarditis. Our conclusions refute several claims previously made by public health agencies and professional associations, namely the following: (1) the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and Omicron infections have caused more cases of myocarditis than the COVID-19 mRNA immunizations; (2) mRNA vaccine-induced myocarditis is typically mild, transient, and rare, with no long-term sequelae; and (3) the risk-benefit calculus favors continued use of these products despite evidence of more iatrogenic cases. We address each of these misconceptions by applying a combination of epidemiological, clinical, and immunological perspectives. We urge governments to remove the COVID-19 mRNA products from the market due to the well-documented risk of myocardial damage, a risk that is strongest for younger males (<40 years old).

KEYWORDS

Myocarditis; Pericarditis; Myopericarditis; Modified mRNA products; Vaccination; SARS-CoV-2 infections; Cardiovascular disease; Adverse events; Risk-benefit analysis

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Introduction

Myocarditis, or inflammation of the myocardium, was largely unknown to the general public but became a household word during the COVID-19 pandemic as the condition rapidly increased in incidence worldwide [1-2]. Common symptoms of myocarditis following COVID-19 modified mRNA vaccinations include chest tightness, palpitations, and physical effort intolerance [3]. Other symptoms may include fever, myalgia, dyspnea, and fatigue. The chest pain of pericarditis, inflammation of the pericardial sac, is characterized by a sharp pain behind the sternum. This pain may improve when the patient sits or leans forward but often worsens when lying down, coughing, or breathing deeply. Coronary artery spasm is less commonly involved. In its acute form, myocarditis is frequently identified as nonischemic dilated cardiomyopathy in patients presenting with symptoms [4].

Most individuals diagnosed with myocarditis also show some degree of pericardial involvement on cardiac magnetic resonance (CMR) imaging and thus may also be referred to as *myopericarditis* [5]. Berg et al. defined pericardial involvement as pericardial thickening or effusion on CMR and found that such involvement is commonly seen in myocarditis cases [6]. Additionally, the presence of pericardial effusion is considered suggestive of inflammation in suspected myocarditis, indicating concurrent pericardial involvement [7]. For these reasons, *myopericarditis* is a more accurate term for most cases of myocarditis, and the two terms may be used interchangeably, depending on the context. (Note: In the context of epidemiological studies, the term myopericarditis may be used when both myocarditis and pericarditis are analyzed together, even if individuals within the sample have only one of the two diagnoses.)

Prior to 2021, myocarditis was most often linked to viral infections, though bacterial infections, autoimmune etiologies, vaccines, and drug exposures (e.g., antipsychotics, salicylates, immune checkpoint inhibitors, and gene therapy drugs) were also known to trigger the condition [5,8,9]. In the decades leading up to the COVID-19 pandemic, vaccination has been recognized as a potential cause of this condition, most often associated with vaccines used to prevent smallpox and anthrax [10]. In the case of the COVID-19 mRNA products, both Pfizer-BioNTech's BNT162b2 and Moderna's mRNA-1273 encode the SARS-CoV-2 spike protein, eliciting endogenous production of that target protein [11]. COVID-19 mRNA vaccine-induced myopericarditis is characterized by the onset

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of cardiac symptoms temporally associated with the administration of the mRNA product, without an identifiable alternative or primary cause. The lion's share of research concerning cardiovascular effects of the the COVID-19 mRNA vaccinations has focused on myocarditis, the most commonly reported cardiac adverse event (AE) associated with these products [12-14].

Temporal evidence from multiple large observational studies and vaccine safety monitoring systems worldwide suggests a causal relationship between the COVID-19 mRNA vaccinations and new-onset myocarditis [15-18]. For example, a population-based cohort study in South Korea (n=4.5 million), with 15 months of observation following the day of COVID-19 mRNA inoculation, showed a 620% increased risk of myocarditis (adjusted hazard ratio, 7.20; 99% CI, 4.37–11.86) and a 175% increased risk of pericarditis (adjusted HR, 2.75; 99% CI, 1.95–3.88), compared to historical controls [19]. The study also found significantly increased risks for various autoimmune disorders. A subsequent analysis of South Korea's COVID-19 database from 2018–2022 (n=10.6 million) examined the associations between COVID-19 immunizations and acute cardiac conditions (e.g., myocarditis, arrhythmias) within 21 days post-vaccination [20]. Short-term cardiac risks, particularly myocarditis, were 48% higher among the mRNA recipients (adjusted HR, 1.48; 95% CI, 1.35–1.62). Due to South Korea's extremely high vaccination coverage and reliable reporting systems, such large population studies offer robust data for assessing the COVID-19 mRNA products' risks and benefits in the context of myocarditis and other cardiac diseases.

In addition to chest pain and the other symptoms mentioned above, the diagnosis of myocarditis is typically determined by a combination of the following: (a) blood troponin levels to indicate possible myocardial injury (high-sensitivity cardiac troponin being preferable for earlier identification of myocardial injury) along with echocardiogram (ECG); (b) echocardiography for structural and functional abnormalities, coupled with diffuse ST elevation (reflecting myocardial injury or pericardial involvement); and (c) CMR to reveal tissue changes, such as scarring (fibrosis) and late gadolinium enhancement (LGE), consistent with myocardial inflammation in the outer myocardium, visceral pericardium, and commonly the parietal pericardium. [21-25] Endomyocardial biopsy with tissue histopathological analysis is the gold standard for confirming the diagnosis in severe or ambiguous cases [5]. Electrocardiograms often detect electrical abnormalities secondary to myopericarditis manifesting as arrhythmias, notably atrial fibrillation and ventricular tachycardia. A history of recent SARS-CoV-2 infection and/or immune-related conditions may help guide further investigations. Differential diagnoses, including coronavirus infections or other viral infections, must be considered and ruled out [26].

Since the initial vaccine rollouts in December 2020, numerous cardiovascular AEs have been linked to the COVID-19 mRNA injectable products manufactured by Pfizer-BioNTech and Moderna. Postmarketing surveillance and pharmacovigilance data in 2021 revealed a significantly increased risk of adverse cardiac events along with a wide variety of hematologic, neurological, autoimmune, and reproductive AEs [27-35]. Among the cardiovascular AEs most commonly associated with the COVID-19 mRNA vaccines are myocarditis, arrhythmias, thromboembolism, myocardial infarction, acute heart failure, acute coronary syndrome, coronary artery disease (CAD), postural orthostatic tachycardia syndrome (POTS), and Takotsubo cardiomyopathy [13,36]. A 2023 systematic review of studies focusing on cardiovascular complications concluded that "events such as thrombosis, thrombocytopenia, stroke, and myocarditis frequently occur with the mRNA vaccines studied [16]." In the largest multinational cohort study to date (n=99,068,901), using electronic health records to investigate the association between the COVID-19 vaccinations and 13 AEs of special interest, the Global Vaccine Data Network identified "prioritized" warning signals for myocarditis, pericarditis, and acute disseminated encephalomyelitis [37].

The CDC initially reported a safety signal for myocarditis in May 2021 [38]. By June 2021, approximately 296 million doses of the COVID-19 mRNA vaccines had been administered across the United States [39]. Of the total doses, 52 million were administered to individuals aged 12–29 years, including 30 million first doses and 22 million second doses. From December 29, 2020, to June 11, 2021, a total of 1,226 probable myocarditis cases were received by the Vaccine Adverse Event Reporting System (VAERS). About 58% of the patients for whom age data were available were under 30 years of age, and three out of every four cases were males. Physicians at the CDC evaluated 484 of the patient records and produced 323 confirmed cases that met the agency's case definition. Of these reports, 309 (96%) required hospitalization and were later discharged. In 2021-2022, observations of increased cardiac emergencies among COVID-19 mRNA-inoculated Israeli men and women under age 40 raised concerns of these vaccines as "a frequent cause of unexpected cardiac arrest in young individuals." Nevertheless, early official reports on AEs associated with COVID-19 mRNA products did not highlight a signal for either myocarditis or pericarditis [40]. The CDC's V-Safe active surveillance system, utilizing a smartphone app for voluntary reporting of adverse reactions, did not include "chest pain" as an option for symptom reporting [41].

A large study of health outcomes in children (ages 5-17, n=>3 million) who had received the Pfizer mRNA product between December 2021 and June 2022 found the number of cases of both myocarditis and pericarditis was high enough to meet CDC's criteria for a safety signal [42]. Official government estimates in 2021 placed the incidence of COVID-19 mRNA vaccine-related myocarditis at approximately 1-3 per 100,000 mRNA recipients, leading the FDA to issue a warning about the risk of myocarditis associated with the BNT162b2 and mRNA-1273 products. These rates were consistent with what Pfizer reported in its initial post-authorization safety document sent to the FDA. However, the estimates of COVID-19 mRNA vaccine-related myocarditis incidence obtained from prospective studies are orders of magnitude higher than the government's estimates based on passive surveillance methods [43].

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COVID-19 mRNA products are, by definition, *gene therapy products* that rely on synthetic, modified mRNA (or adenoviral vector DNA), encapsulated within a protective lipid nanoparticle vehicle [44]. These nucleic acids are designed to instruct the ribosomes in the body's cells to produce the SARS-CoV-2 spike protein, the intended target antigen. Although the Pfizer and Moderna products are different, they both utilize the synthetic, modified mRNA, which encodes for the same recombinant spike protein corresponding with the protein identified on the surface of SARS-CoV-2. For this reason, both mRNA products could also be labeled "gene therapy vaccines" The products also meet the definition of "prodrugs", as they prompt the recipient's cells to synthesize the spike protein, the final product and main constituent of this immunization strategy [11,45]. The FDA's regulatory guidance for gene therapy products calls for 5-15 years of safety follow-up due to the anticipated long-term persistence of the genetic material, along with the possibility that it may incorporate into DNA and cause semi-permanent change to a mosaic of cells. Throughout this review, we adhered to writing guidelines and reporting standards in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Individual Susceptibility Factors

Factors such as age, sex, genetics, chronic inflammation, and preexisting comorbidities may influence susceptibility to COVID-19 mRNA vaccination-related myocarditis.

Age and gender

There are strong associations between COVID-19 mRNA-related acute myocarditis and both younger age and male predominance. Men under age 40 are at a heightened risk of acute myocarditis following mRNA vaccination [46, 47]. The risk appears to be greatest for adolescent men (ages 12-24). For this population subgroup, the risk of mRNA vaccine-related myocarditis or pericarditis is nearly seven times higher than that of adolescent women [48]. Mechanistically, the age-related aspect may be attributed to the younger individual's robust immune response, triggered by the lipid-nanoparticle- encapsulated synthetic mRNA and resultant spike protein, with both potentially interacting directly with cardiac tissues [49,50]. Adolescents possess a developing immune system, which might exhibit heightened sensitivity to the spike protein's presence, leading to more robust inflammatory cardiac responses [51]. The predilection for young men points to the possible involvement of androgen receptors in host cardiac and immune cells, setting the stage for a hormonal interaction in the genesis of some cardiac disorders [52,53]. In addition, compared to their female counterparts, men with myocarditis show increased levels of heart failure biomarkers, such as soluble ST2, creatine kinase, myoglobin, and T helper 17-associated cytokines, indicating a heightened inflammatory response and myocardial injury that may elevate heart failure risk and worsen outcomes [54]. Although young women are also at risk, myocarditis risk in general is greater in older women (<50 years old). The latter sex-specific age-related phenomenon may be attributed to the multiple cardioprotective properties of estrogen, which is highest in younger women [55].

Chronic inflammation and comorbidities

COVID-19 mRNA may interact with chronic inflammatory conditions. A study by Jeon et al. investigated the effects of COVID-19 mRNA vaccines in a mouse model with chronic inflammation, focusing on cardiac toxicity and immune responses [49]. Intravenous (IV) administration of mRNA, with or without pre-existing inflammation, was linked to increased cardiac inflammation, including myocarditis. Inflammatory cytokines IL-1β and IL-6 were elevated, and mice with pre-existing chronic inflammation showed significant cardiac damage, evidenced by increased serum troponin I levels. These findings suggest that mRNA vaccines may amplify cardiac AEs in individuals with chronic inflammatory conditions, such as obesity, diabetes, or arthritis [56-59]. Individuals with various chronic conditions appear to be at increased risk of developing myocarditis [60]. Chronic low-grade inflammation and hypercoagulation (increasing thrombosis risk) may interact synergistically with the adverse cardiovascular effects of the mRNA vaccinations [61]. Heil hypothesizes that mRNA vaccine products may generate pro-inflammatory self-DNA (e.g., cell-free, double-stranded DNA), which can drive systemic inflammation and autoimmune reactions targeting cardiac tissues and potentially causing myocarditis [62,63].These findings underscore the need for further research on the potential amplification of myocarditis risks following mRNA vaccines in individuals with preexisting chronic inflammation and related comorbidities.

Genetic factors

Various genetic factors may determine the relative susceptibility of the recipient. Ittiwut and colleagues have identified genetic predisposition as a potential factor influencing the variability in sudden death cases [64]. Their research highlighted a strong association between polymorphisms in the SCN5A channel and an increased incidence of sudden death. In a cohort study of Hong Kong adolescents (n=43) diagnosed with myocarditis shortly after the BNT162b2 vaccination, She et al. performed a pathway analysis and identified 2,182 genomic clusters potentially associated with myocarditis and other cardiac AEs, due in part to their associations with cardiac conduction, ion channel regulation, plasma membrane adhesion, and axonogenesis [65]. The findings indicate a possible genetic predisposition in these cardiac-functional domains. Finally, Chen and colleagues identified several single nucleotide polymorphisms (SNPs) that were associated with AEs after the first or second dose of the mRNA vaccines [66]. These same SNPs play key roles in immune regulation and have been associated with several autoimmune diseases and cancer types. In the future, it may be possible to construct a comprehensive genomic panel that could help predict increased susceptibility to myocarditis and other AEs linked with COVID-19 mRNA inoculations. More research is needed in this area. In the meantime, clinicians should perform a comprehensive arrhythmia and cardiomyopathy panel in serious cases of vaccine-induced myocarditis [67].

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Table 1. Observational studies of myocarditis following COVID-19 mRNA vaccines.

Study	Study Type	Sample Size	Key Findings (Risk, Incidence Rate)	Other Specific Details
Patone et al., 2022 [68]	Self-controlled case series	42.8M vaccinated	~10 excess myocarditis events per 100K [9.7, 95% CI, 9.1-9.9] persons/doses after mRNA-1273 dose 2 in males <40 yrs; compared to 1.6 per 100K after infection [95% CI, 1.2-1.8] for the same age group.	Risk higher in younger males, especially after second dose of mRNA-1273. Non-stratified risk higher after infection.
Buchan et al., 2022 [69]	Population cohort, 14.7 M	19.7M doses	~30 myocarditis cases per 100K in males 18-24 after mRNA-1273 dose 2 [29.95, 95% CI, 17.12-48.64]; lower for BNT162b2, ~6 per 100K [5.92, 95% CI, 1.92-13.81]	Higher rates with shorter interdose intervals (<30 days).
Sharff et al., 2022 [70]	Cohort (Kaiser Permanente)	~147K vaccinated with mRNA (Pfizer and Moderna)	~10 cases of myopericarditis per 100K [9.54, 95% CI, 5.21-16.0] doses in males 12-39 after dose 2; 37.7 per 100K doses in males 12-17 after dose 2 of BNT162b2; 53.7 cases per 100K doses in males 18–24 after dose 2 (see Fig. 1)	Study highlights underreporting in prior methods and improves incidence estimation using text analysis.
Stowe et al. 2023 [71]	Self-controlled case series	50 M eligible to receive mRNA for priming or boosting	For mRNA-1273, 2nd dose, in 16-39 year-olds: 4.24 (4.19 - 4.27) excess myocarditis cases per 100K, within the risk window (0–6 days post-injection). For males over age 16, this number was 5.50 (5.43-5.53) excess cases (see Table 4).	Increased risk within 1st week after priming & booster doses of mRNA, predominantly in males <40
Karlstad et al. 2022 [14]	Cohort studies (4): Denmark, Finland, Norway, Sweden	23,122,522 residents, >12 years	5.55 (95% CI, 3.70-7.39) excess events per 100K persons after 2nd dose of BNT162b2 and 18.39 (9.05-27.72) excess events per 100K mRNA-1273 recipients after 2nd dose, males 16-24	Data obtained from linked nationwide health registers
Li X, et al., 2022 [72]	Cohort (Hong Kong - electronic health record database)	Adolescents, 224,560 1st doses and 162,518 2nd doses of BNT162b2 administered;	~22 total cases myocarditis per 100K after 2nd BNT162b2 dose [22.15, 95% CI, 15.51-30.67]. 39 cases among males (ages 12-19) per 100K after the 2nd dose [95% CI, 26.69-55.08].	Report suggests significant risks in adolescent males compared to females.
Chua et al., 2022 [73]	Cohort (Hong Kong - Pharmacovigilance System)	Adolescents	~37 cases per 100K in males ages 12-17, following the 2nd dose of BNT162b2. [37.32, 95% CI, 26.98-51.25]	Myocarditis incidence higher among males; mild cases requiring conservative management.
Krug et al., 2022 [74]	Risk-benefit analysis (VAERS)	Adolescents	~16 cases per 100K [16.2, 95% CI, 13.2-19.7] in males, ages 12-15, and ~9 cases per 100K [9.3, 95% CI, 7.54-11.4] in males ages 16-17after 2nd dose of BNT162b2.	Risk-benefit ratio suggests reconsideration of dosing strategies in low-risk cohorts.
Witberg et al., 2021 [75]	Observational (Israel)	~2.5M vaccinated	~11 cases per 100K [10.69, 95% CI, 6.93-14.46] in males ages 16-29 after BNT162b2 (SIR: 5.3, 95% CI: 4.48–6.40).	Estimated incidence among entire cohort was 2.13 cases per 100K persons
Nygaard et al., 2022 [76]	Population-based cohort	~260K adolescents	~10 cases per 100K in males [9.7, 95% CI, 6.93-14.46] ages 12-17 after BNT162b2, 2nd injection	Incidence slightly higher in males than previously reported in U.S.
Mevorach et al., 2021 [77]	Retrospective cohort analysis	5.1M vaccinated	~14 cases per 100K [13.73, 95% CI, 8.11-19.46] in males ages 16-19 after 2nd dose of BNT162b2	Risk highest in younger males, most cases were mild.

Note: In this table, we are highlighting the higher rates found in these observational studies, focusing on dose 2 of the primary series (which represents the combined impact of doses 1 and 2; see text). Myocarditis cases are defined differently in different studies. For example, Patone et al. and Stowe et al. required hospitalization, while for Buchan et al, only 70.7% of cases were hospitalized.

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Dose Number, Manufacturer, and Batch Variability

One of the most consistent findings from large observational studies to date (see Table 1) is the myocarditis-related impact of the second dose of the COVID-19 mRNA products. Foltran and colleagues evaluated more than 4,900 AEs of COVID-19 mRNA vaccines in adolescents (ages 12-17) based on pharmacovigilance data from 148 countries [78]. Compared to the first dose, the second dose of synthetic mRNA was associated with a five-fold increase in the reporting odds of myocarditis and/or pericarditis, with 85% of reports being among boys. A systematic review and meta-analysis of the observational study evidence by Gao et al. (n=59 million) showed a significant correlation between COVID-19 mRNA vaccines and risk of myocarditis, with a four-fold increased risk in those who received the second dose compared with those who had received the first dose (RR, 4.06; 95% CI: 2.08-7.92) [15]. Moreover, the review found that Moderna's mRNA-1273 resulted in twice the risk of myocarditis or pericarditis when compared to Pfizer's BNT162b2 (RR, 4.15; 95% CI=1.87-9.22, versus RR, 2.19; 95% CI=1.46-3.29, respectively). In large cohort studies in Canada and Scandinavia, the incidence of excess myocarditis events was three to five times higher for younger males (age range: 16-24) after the second dose of mRNA-1273 when compared to the second dose of BNT162b2 [14,69]. Myocarditis rates associated with the second dose of either mRNA product have been consistently higher than the rates associated with the first and third doses.

The following points provide further insight into the variability in mRNA vaccination effects among individuals:

Increased mRNA dose of mRNA-1273

The mRNA dose is different for the Pfizer and Moderna products, with Moderna's mRNA-1273 having the highest concentration and consistently showing a stronger effect. The primary series for mRNA-1273 contains about three times the concentration of mRNA (100 micrograms) when compared to BNT162b2 (30 micrograms) [79]. Given the consistency of findings with regard to myocarditis and many other serious AEs, this suggests a dose-response relationship.

Lower mRNA concentration in third dose ("booster") of mRNA-1273

The booster dose for mRNA-1273 contains only half the amount of mRNA (50 micrograms) as compared to the primary series. Stowe et al. found that the myocarditis risk difference between the second and the third doses was most pronounced for mRNA-1273 when used for boosting instead of priming [71]. This further suggests that the degree of risk of myocarditis following vaccination could be associated with the relative dosage of the mRNA products.

Impact of repeated or successive doses

There is ample evidence that repeated injections of the mRNA products may increase the likelihood of autoimmune and autoinflammatory phenomena associated with myocarditis and other serious cardiac events [80,81]. The recommendation for ongoing boosters may result in chronic immune dysfunction (in particular, T-cell exhaustion and antibody class-switching to IgG4), thus reducing protection against infections while also inducing new-onset autoimmune disease and accelerating latent autoimmune diseases [81-83]. Also relevant is the repeated exposure to plasmid DNA process-related impurities such as the double-stranded RNA found within COVID-19 mRNA products [84]. This aberrant RNA may trigger dose-dependent activation of the innate immune system and subsequent inflammatory AEs that may be pivotal to the pathogenesis of myocarditis [85].

Exposure risk for dose 2 represents the sum of two doses

The choice to receive the mRNA vaccination originally meant the choice to take two doses approximately 21-28 days apart. Thus, with regard to data from 2021-2022, an individual's choice to "fully vaccinate" meant deciding to take dose 1 and subsequently, dose 2, assuming no severe reactions occurred after dose 1. Because the biological impact of these mRNA vaccines persists for at least six months, the myocarditis risk associated with the choice to fully vaccinate represents the sum of risks for both doses. (For additional insight, see Section 4.1 of the preprint by Bourdon et al.) [86].

Most studies suggest that the median time to onset of myocarditis symptoms after administration of the COVID-19 mRNA products is 2-4 days following the second dose [87,88]. The rapid appearance of symptoms, which can arise after either dose in the primary series, further supports the likelihood of a direct causal relationship. It is for these reasons that observational studies of mRNA vaccine-related myocarditis risk should not only stratify by age and sex, but also by dose number and manufacturer.

Product type and batch variability

An additional explanation for the wide range of individual responses and AEs following COVID-19 mRNA vaccinations is product type and batch variability. Because mRNA technology is inherently unstable, some mRNA batches may contain low levels of intact mRNA [89]. Additionally, the European Medicines Agency identified double-stranded RNA (dsRNA) contamination in the Pfizer and Moderna mRNA products [90,91]. This dsRNA can activate innate immune responses through the MDA5 protein, leading to pro-inflammatory cytokine release, chronic inflammation, and increased risk of conditions such as myopericarditis [92-94]. The Pfizer product has been shown to contain physiologically significant levels of dsRNA, with evidence suggesting partial dependence of adaptive immune responses on MDA5 in preclinical models [95]. Current manufacturing processes aim to eliminate bacterial DNA templates, yet contamination persists, raising grave concerns about long-term safety. Quality control challenges are further complicated by the need for stringent cold-chain maintenance, with improper handling potentially exacerbating variability in AEs. A novel assay for detecting dsRNA impurities in mRNA products, including those with N1-methyl-pseudouridine, has improved sensitivity and efficiency, offering the potential to enhance quality control practices [93]. However, variability in AE rates may also stem from batch-specific impurities and differences in handling practices [96].

Schmeling et al. analyzed serious AE data from Pfizer

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mRNA batches in Denmark and identified significant heterogeneity in AE rates, with a median of 2.32 AEs per 1000 doses (IQR: 0.09–3.59; $p < 0.0001$) [97]. This batch-dependent safety signal highlights the need for further investigation, though temporal trends were not explored. Sequencing studies have revealed high levels of DNA contamination in Pfizer and Moderna booster products, exceeding EMA and FDA safety thresholds [98,99]. Such contamination underscores the importance of robust mRNA purification processes to minimize risks. In summary, batch variability and process-related impurities, including dsRNA and DNA contaminants, may contribute to differences in COVID-19 mRNA vaccine-related AE rates, including myocarditis.

Warning Signs from Diverse Epidemiological Sources

Various sources of epidemiological data collectively highlight an emerging pattern suggesting that the risks of myocarditis associated with COVID-19 mRNA vaccines, particularly when administered to younger populations, may have been underestimated by regulatory agencies. Spanning a wide range of methodologies and contexts, these sources include the following: (1) registrational trial data from Pfizer and Moderna; (2) confidential post-EUA safety data; (3) prospective cardiac function studies; (4) autopsy findings; (5) analyses from the U.S. military health system, (6) actuarial data from life insurance companies, (7) large-scale passive surveillance data, (8) individual case reports, and (9) observations from professional athletic organizations. The convergence of evidence across these varied sources creates a compelling narrative and indicates a coherent framework of causation that merits serious attention from public health and medical authorities.

Re-analyses of Pfizer and Moderna trial data

The most striking revelations concerning these serious cardiac events come from meticulous reanalyses of the registrational trial data that led to global distribution of the COVID-19 mRNA products [100,101]. A combined reanalysis of the Pfizer and Moderna pivotal found a 45% trend increase for cardiovascular death (RR, 1.45; 95% CI 0.67-3.13) in the mRNA arms compared to the placebo arms [102]. In the Pfizer trial, there were twice as many cardiovascular AEs in the mRNA arm versus placebo [103]. The rigorous reanalysis of this trial by Fraiman and colleagues demonstrated a statistically significant 36% higher risk (RR, 1.36; 95% CI: 1.02-1.83) of serious AEs in the mRNA group versus placebo. Performed by an international team of established vaccine safety experts utilizing the Brighton Collaboration's Safety Platform for Emergency vACcines (SPEAC), the analysis also found significantly more cardiovascular AEs of special interest (categorized as "myocarditis/pericarditis" and "other forms of acute cardiac injury", see Table 3 of Fraiman et al.) in the COVID-19 mRNA group than in the placebo group.

Similarly, Michels and colleagues conducted an in-depth reanalysis of data pertaining to Pfizer's six-month interim report along with additional narrative reports not originally shared with the FDA's vaccine advisory committee prior to authorization. Their study showed a significant 3.7-fold increase (OR 3.7; 95% CI 1.02–13.2, p=0.03) in serious cardiac events among the BNT162b2 recipients [104]. Two of the sudden deaths (by cardiac arrest) among women in the trial were concealed by Pfizer until after the emergency use authorizations (EUAs) were issued [105]. Remarkably, neither the original trial publication nor Pfizer's Summary Clinical Safety report had addressed the trial's own safety signal regarding serious cardiac events [106,107]. Had these findings concerning cardiac risks been openly shared with FDA's advisory committee, the agency likely would have denied or delayed the EUA.

Confidential post-EUA safety data

According to confidential Pfizer documents initially requested by the European Medicines Agency and later by the Public Health and Medical Professionals for Transparency (via lawsuit, after the FDA refused to comply with a Freedom of Information Act request), as of August 2022, the manufacturer had accrued data for approximately 1.6 million AEs linked with the mRNA vaccines [28,108,109]. Collectively, these documents included detailed records of the following:

- Nearly 127,000 reported cardiac disorders;
- Approximately 270 categories of heart damage, including myocarditis and pericarditis;
- Approximately 260 categories of vascular disorders, encompassing 73,542 cases;
- Nearly four (3.66) times more cardiovascular adverse events in women as in men [110];
- Twice as many serious cardiovascular events as non-serious cardiovascular events [28].
- Most of the serious cardiovascular events occurred in younger adults (<40), 92% of whom had no comorbidities [109].

The confidential Pfizer documents cited above revealed that myocarditis occurred most often in young men age 16 and over, with a mean age of 37.2 years and a median age of 32.0 years [111]. It should be noted that Pfizer classified myocarditis under the "Immune-Mediated/Autoimmune" category rather than in the "Cardiovascular" category [112]. Although myocarditis can have an immune-mediated pathogenesis, omitting it from the "Cardiovascular" category raises concerns about data transparency. Regardless, the serious cardiac event findings revealed by the previously concealed Pfizer documents have led many medical scientists to question the products' safety, along with triggering speculations that the rise in excess mortality in extensively "vaccinated" countries observed in 2021-2022 was more strongly linked with the worldwide COVID-19 vaccination campaign than with SARS-CoV-2 infection [113-117].

Prospective measurements of cardiac function and cardiomyocyte injury

Whenever sufficient randomized trial safety data are lacking, prospective studies offer the most reliable way to assess potential safety issues and should take precedence over most other study designs. Most essential are prospective studies that monitor cardiac function via pre- and post- vaccination troponin levels, along with ECG and possibly echocardiography. In an elegant cohort study, Mansanguan et al. enrolled students from two schools in Thailand aged 13-18 years who received the second dose of BNT162b2 [118]. The

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researchers prospectively collected pre- and post-vaccination data on demographics, symptoms, vital signs, ECG, echocardiography, and cardiac enzymes, at four different times within a 14-day period. Cardiovascular symptoms occurred in nearly one-third (29.24%) of all participants, with the most common symptoms being tachycardia (7.64%), shortness of breath (6.64%), chest pain (4.32%), palpitation (4.32%), and hypertension (3.99%). Out of 301 students, four had subclinical myocarditis, two individuals had suspected pericarditis, and one was diagnosed with acute myopericarditis. One in every 43 participants (2.3%) showed some form of cardiac inflammation following COVID-19 mRNA vaccination. The clinical presentation of myopericarditis following vaccination was typically mild and transient, with all cases fully recovering within 14 days. This study's incidence rate is much higher than the rates for males who are roughly in that age range, based on large observational studies: 13-37 cases per 100,000 (0.013%-0.037%) after the second BNT162b2 dose (see Table 1) [73,119]. According to the CDC, the risk of myocarditis in boys (12–17 years) after the second mRNA dose is only 6.67 cases per 100,000, versus 0.14 cases per 100,000 in those aged ≥65 years [120].

In a Taipei City (Taiwan) study of 4928 students (12-18 years) and a male/female ratio of 4576/352, 763 students (17.1%) had at least one cardiac symptom after the second BNT162b2 dose, mainly chest pain and palpitations [121]. The researchers obtained pre- and post-vaccination ECGs on all students. Heart rate increased significantly after the vaccine, with a mean increase of heart rate of 2.6 beats per minute. The depolarization and repolarization parameters (QRS duration and QT interval) decreased significantly after the vaccination with increasing heart rate. Abnormal ECGs were observed in 51 (1.0%) of the students, one of whom was diagnosed with "mild" myocarditis and another four with significant new-onset arrhythmias. Thirty-three students sought medical help after positive ECG findings; troponins and other biomarkers were subsequently measured. Ten subjects (23.2%) were suspected of having pericarditis due to ST-T change and increased C-reactive protein, but echocardiography findings were negative as is often the case in early pericarditis. Thus, cardiac symptoms in young people appear to be quite common after the second dose of BNT162b2, as high as 1.5 per 10,000 persons, though the incidence of myocarditis was relatively low at 0.02%. However, a major limitation of this study was the selective use of troponin measurements, rather than applying these measures to the entire study sample.

In a Swiss study, Buergin et al. analyzed high-sensitivity cardiac troponins and other biomarkers of myocardial injury in hospital employees (n=777) before and after receiving the mRNA-1273 booster (third dose) [122]. One out of every 35 persons injected, or 2.8% [95% CI: 1.7-4.3%], showed evidence of mRNA-associated subclinical myocarditis. None of the individuals with elevated markers of myocardial injury had a prior history of cardiac disease. Half of the participants with myocardial injury (11 out of 22) reported nonspecific symptoms such as fever and chills, while two experienced chest pain, which met the Brighton Collaboration criteria for probable myocarditis. Notably, none of these adjudicated cases exhibited ST-segment depression or T-wave inversion. The median age of individuals with myocardial injury after the mRNA-1273 booster was 46 years, which differs considerably from the age profile commonly reported for clinical myocarditis cases associated with the mRNA inoculations. However, the Swiss cohort had a median age of 37 years and was mostly comprised of women (69.5%), thereby skewing the sex-specific findings: the mRNA-1273 booster was linked with significantly higher rates of myocardial injury in women compared to men (3.7% vs. 0.8%). Again, this finding contrasts sharply with the observed sex distribution of COVID-19 mRNA vaccine-related myocardial injury during passive surveillance of clinically significant myocarditis following the second dose, where cases are predominantly seen in young males [123].

COVID-19 mRNA-associated myocardial injury may be far more common than is generally understood, as symptoms are often mild, nonspecific, or even absent, thus escaping passive surveillance and observational studies of hospitalized cases. Thus non-hospitalized cases with mild cardiovascular symptoms are appropriately diagnosed as subclinical vaccine-induced myocarditis. The prospective studies of Mansanguan et al. and Buergin et al., despite their relatively small size, provide more meaningful estimates due to the cardiac assessments being made before and after the second and third doses. Taking into consideration results from both of these studies, the rate of myocarditis in young adults may be estimated to be 2.5% (2,500 cases per 100,000) after the second or third COVID-19 mRNA dose. This estimate is markedly higher than rates reported in large observational studies, typically in the range of 5-40 myocarditis cases per 100,000 younger male adolescents after the second mRNA dose (see Table 1).

Autopsy data

Whereas most reported cases of myocarditis have shown a clinically mild course with rapid symptom resolution, in some instances the individual with myocarditis has required hospitalization with intensive care support or even died from acute heart failure. Direct evidence of such fatal harms comes from autopsy studies. Schwab et al., conducted a case-series study analyzing autopsy findings from 25 individuals in Germany who died unexpectedly at home within 20 days of receiving a COVID-19 vaccination [124]. In five cases (20%), unique histological evidence of lymphocytic myocarditis was identified in the form of focal and interstitial inflammatory infiltration of the myocardium. These findings establish the histological phenotype of lethal mRNA-associated myocarditis. Extensive testing ruled out infectious agents as potential causes, leading the researchers to conclude that the COVID-19 mRNA products were the most plausible cause of these deaths. Other details about the myocarditis fatalities were as follows: "Three of the deceased persons were women, two men. Median age at death was 58 years (range 46–75 years). Four persons died after the first vaccine jab, the remaining case after the second dose. All persons died within the first week following vaccination (mean 2.5 days, median 2 days)."

In the largest study of its kind, Hulscher and colleagues performed a systematic review of autopsy findings following COVID-19 vaccination based on the findings from 44 studies, comprising 325 autopsy cases and one necropsy case (mean age of death, 70.4 years) [125]. Three independent physicians

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reviewed and adjudicated each case to determine whether the COVID-19 vaccination was a direct or significant contributing factor to death. Their analysis revealed that 240 deaths (73.9%) were directly or significantly associated with the vaccines. For these 240 adjudicated cases, the mean age of death was 55.8 years, with a range of 14 to 94 years. The causes of death included sudden cardiac death (35%), pulmonary embolism (12.5%), myocardial infarction (12%), vaccine-induced immune thrombotic thrombocytopenia (7.9%), myocarditis (7.1%), multisystem inflammatory syndrome (4.6%), and cerebral hemorrhage (3.8%). The authors concluded that the patterns of mortality observed aligned with known mechanisms of COVID-19 vaccine-related AEs, supporting a probable causal link between mRNA vaccines and the reported deaths. They emphasized that these findings underscore existing concerns about COVID-19 mRNA-induced myocarditis, myocardial infarction, and broader effects of the spike protein. On average, deaths occurred 14.3 days after the mRNA inoculation, with most of the deaths occurring within one week, similar to the Schwab et al. study. In a follow-up adjudicated autopsy review, Hulscher et al., reported in greater detail on 28 other deaths that were attributed to the mRNA vaccines [126].

Such extensive post-mortem examinations provide critical causal insights into the more serious AEs linked with the COVID-19 mRNA vaccines. It is important to emphasize that, in both the Schwab et al. and Hulscher et al. studies, these deaths attributed to myocarditis occurred among older groups. Older adults may be more vulnerable to myocarditis-related deaths following mRNA vaccines due to age-related immune dysregulation, which can exacerbate inflammatory responses [127]. Additionally, pre-existing cardiovascular conditions or comorbidities common in older populations may heighten susceptibility to myocarditis complications. This combination of increased age-related inflammation and pre-existing cardiac vulnerability may account for the heightened risk of fatal outcomes among older adults. Despite these alarming findings, administrative obstacles, such as discouragement of autopsies and delayed autopsy reports, often impeded thorough risk assessments during the pandemic, thereby misinforming the public about vaccine safety and weakening public health policy [128].

U.S. military data

It was the U.S. military health system that initially identified a myocarditis signal in young, predominantly white males after receiving the COVID-19 mRNA vaccines [21,129,130]. This rapid identification was facilitated by prior experience with enhanced smallpox vaccine safety monitoring (to help protect against aerosolized smallpox, a Category A bioterrorism infectious agent), which emphasized the importance of detecting and reporting new-onset cardiac symptoms. In the first two years of the COVID-19 mRNA rollouts, approximately 80% of the U.S. military consisted of males, with about 75% being 35 years old or younger [131,132]. From the outset, all military personnel were required to receive two doses of the COVID-19 mRNA vaccination [133]. The Defense Medical Epidemiology Database (DMED) is the medical events database for all active and reserve U.S. military. Romero and colleagues examined the 2021 DMED data for the incidence of myocarditis and many other medical conditions in order to investigate a potential relationship with COVID-19 mRNA vaccines [134]. They compared annual incidence rates from five prepandemic years to 2021 and took into account the total number of military personnel for each study year. When the data were adjusted to reflect cases per month per 1,000 individuals, the incidence of myocarditis in 2021 was more than double that of each of the preceding five years. This finding aligned with age-stratified myocarditis data from VAERS, which revealed myocarditis reports for COVID-19 vaccines to be over four times higher than those for influenza vaccines and nearly thirteen times higher than for pertussis vaccines, based on the percentage of total reports. Overall, the DMED trends were consistent with VAERS and other surveillance systems, showing significant increases in numerous medical conditions in 2021 following the introduction of the COVID-19 mRNA vaccinations compared to the pre-pandemic reference period.

U.S. life insurance data

The adverse cardiovascular impact of the COVID-19 mRNA vaccines on younger age groups was further highlighted by the extraordinary reports from U.S. life insurance companies during the latter half of 2021. Mortality data from these sources are meticulously collected and audited for financial and actuarial accuracy, ensuring a high level of precision. Because the datasets are continuously updated and represent a substantial segment of the insured population, they provide real-time insights into mortality trends that complement public health data. Data from the Group Life insurance survey indicated that mortality in the general U.S. population increased by 32% during the third and fourth quarters of 2021, while the Group Life policyholders experienced a 40% rise, a notable 8% difference [135]. Group Life policyholders are typically younger, well-employed, and generally healthy individuals who, according to a 2016 U.S. Society of Actuaries (SOA) analysis, historically died at approximately one-third the rate of the broader U.S. population. The 2021 data revealed a stark reversal of this trend.

Excess mortality within the Group Life cohort was assessed by comparing the baseline death rates from 2017 to 2019, adjusted for seasonal variations, and incorporating CDC data. Notably, between the second and third quarters of 2021 (coinciding with the start of the second phase of the U.S. vaccination campaign), excess mortality rates surged. The same SOA analysis documented a 36% increase for individuals aged 25–34, 50% for those aged 35–44, and 52% for the 45–54 age group. This represents an unprecedented average increase of 46% in excess deaths across these age groups, though averaging obscures the more severe impacts within specific cohorts. SOA insurance analysts have described these increases as “catastrophic” and “unparalleled” in scope. These mortality trends were most likely attributable, in large part, to cardiovascular deaths. Based on both the Group Life and U.S. Population data, the deaths from major cardiovascular disease showed the steepest upward trend from March 2021 to December 2021 (Figure 1).

Overall, the US SOA data indicate a strong temporal

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Table 2. Excess mortality by detailed age band. From the SOA report (Table 5.9), p. 27 [135].

EXCESS MORTALITY BY DETAILED AGE BAND														
Age	Q3 2020	Q4 2020	Q1 2021	Q2 2021	Q3 2021	Q4 2021	Q1 2022	Q2 2022	Q3 2022	Q4 2022	Apr. 2020 -Dec. 2022	COVID (%)	Non-COVID (%)	Count (%)
0-24	124%	104%	101%	119%	128%	112%	99%	104%	119%	108%	112%	2.80%	9.30%	2%
25-34	131%	120%	118%	132%	179%	137%	126%	121%	127%	123%	131%	9.90%	21.10%	2%
35-44	133%	127%	129%	134%	201%	158%	134%	123%	126%	134%	139%	17.20%	21.30%	4%
45-54	126%	129%	132%	119%	179%	151%	128%	107%	112%	123%	130%	19.90%	10.00%	9%
55-64	122%	129%	129%	114%	152%	139%	123%	100%	105%	116%	122%	17.40%	5.10%	18%
65-74	115%	132%	130%	108%	130%	124%	116%	95%	100%	104%	116%	14.00%	1.50%	17%
75-84	113%	133%	123%	105%	119%	122%	121%	102%	107%	107%	115%	11.30%	3.80%	20%
85+	103%	124%	111%	92%	105%	107%	105%	91%	93%	92%	103%	8.60%	-5.50%	27%
All Ages	115%	128%	123%	107%	134%	126%	117%	99%	104%	107%	116%	13.00%	2.90%	100%

a. Includes only companies that provided Age splits; see second bullet at the beginning of section 5.

Table 3. Excess Mortality by Detailed Age Band – Non-COVID Only. From the SOA report (Table 5.10), p. 27 [135].

EXCESS MORTALITY BY DETAILED AGE BAND–NON-COVID ONLY													
Age	Q1 2020	Q2 2020	Q2 2020	Q4 2020	Q1 2021	Q2 2021	Q3 2021	Q4 2021	Q1 2022	Q2 2022	Q3 2022	Q4 2022	Apr. 2020-Dec. 2022
0-24	93%	113%	123%	101%	98%	117%	120%	107%	95%	103%	118%	107%	109%
25-34	100%	119%	125%	112%	108%	126%	145%	116%	114%	120%	126%	122%	121%
35-44	105%	113%	122%	112%	112%	123%	140%	118%	116%	121%	124%	133%	121%
45-54	98%	110%	114%	107%	105%	106%	121%	109%	102%	105%	110%	122%	110%
55-64	97%	104%	110%	105%	99%	103%	115%	105%	99%	99%	103%	114%	105%
65-74	98%	103%	105%	107%	101%	101%	109%	103%	95%	93%	97%	102%	102%
75-84	100%	102%	105%	108%	99%	101%	108%	109%	103%	99%	103%	105%	104%
85+	96%	99%	97%	103%	94%	89%	98%	99%	93%	88%	89%	90%	95%
Unknown	56%	55%	61%	51%	59%	45%	62%	76%	53%	68%	87%	99%	65%
All Excl Unknown	98%	104%	106%	106%	99%	100%	110%	105%	99%	97%	101%	105%	103%
All Ages [3]	98%	103%	106%	106%	99%	100%	110%	105%	99%	97%	101%	105%	103%

a. Includes only companies that provided claims splits Age; see second bullet at the beginning of section 5.

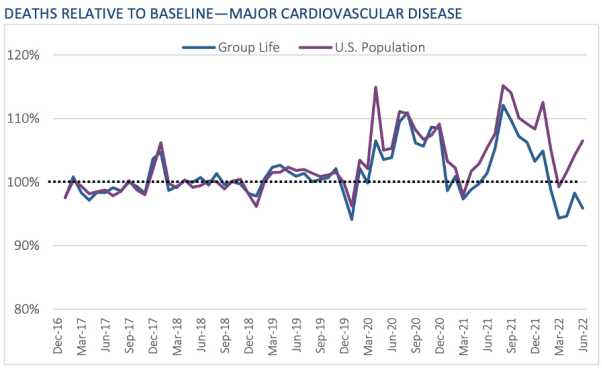

Figure 1. Cardiovascular disease mortality relative to baseline from December 2016 to June 2022. Group Life Insurance and U.S. population data. From the SOA report (Figure 9.7), p. 50164 [135].

correlation between the onset of COVID-19 vaccine mandates for employment in the third quarter of 2021 and a significant rise in excess mortality among working-age Americans (25–64 years old). Given that these individuals were predominantly young and healthy, the notion that COVID-19 significantly contributed to this rise in mortality is implausible, particularly considering the low infection fatality rate (IFR) among these age groups. Furthermore, the SOA's Group Life data indicated that the excess deaths for all younger adults (<45) were "non-COVID-19" fatalities, with no direct attribution to the virus. Specifically, the SOA report (2023) states: "The 0–44 age band exhibited the highest A/E ratio [actual-to-expected ratios, relative to baseline] across the pandemic period and has consistently shown the highest A/E by quarter since the middle of 2021. The 45–64 age band has the highest excess mortality directly attributable to

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COVID (18.2%), whereas the 0–44 age band has the highest excess mortality from non-COVID causes (18.8%). The working-age population continues to see the highest A/E ratios. The 35–44 age band continues to have the highest cumulative A/E during the pandemic and has the highest non-COVID excess mortality as well" [135].

In a public statement, the CEO of OneAmerica insurance company reported a 40% increase in mortality among working-age individuals (18–64) during the third and fourth quarters of 2021 compared to pre-pandemic baselines [136]. Notably, the majority of these excess deaths were not directly attributed to COVID-19. A mortality increase of this magnitude is statistically extraordinary, as even a 10% rise in excess deaths is typically considered a rare, 1-in-200-year event [136]. The spike in excess deaths for all U.S. adults under age 55 coincided with the enforcement of vaccine mandates, particularly among military and healthcare workers, during the summer and fall of 2021 [137]. Between March 2021 and February 2022, an estimated 61,000 excess deaths occurred among Americans under 40 years old, comparable to the total U.S. servicemen fatalities during the Vietnam War [138]. This astonishing death toll went unreported by major U.S. news organizations.

VAERS data (U.S.)

The VAERS pharmacovigilance database is a collection of voluntary reports from individuals who have experienced or observed side effects or AEs from vaccines and biological products. Individuals reporting to VAERS typically include patients, parents or guardians, and healthcare professionals comprising approximately 67% of the reporters [139]. The database is designed to inform the owners of these data (CDC, FDA, and Health & Human Services) of emergent safety signals, thus providing an early-warning system for potential vaccine safety problems [140]. Subsequent assessment of harms associated with pharmaceutical and biological products can be performed using Bayesian analyses, Proportional Reporting Ratio (PRR) analyses and the Bradford Hill criteria for causality assessments. For example, following a query of the VAERS database, disproportionality measures utilizing PRR analyses indicated a statistically significant association (i.e., signal) between the COVID-19 mRNA vaccines and various cardiovascular events [141]. In the VAERS study by Gargano et al., myocarditis reporting rates were 40.6 cases per million second doses of the COVID-19 mRNA inoculations administered to males aged 12–29 years and 2.4 per million second doses administered to males aged ≥30 years [39]. The highest myocarditis reporting rates were for male adolescents 12–17 years and those aged 18–24 years (62.8 and 50.5 cases per million second doses of the COVID-19 mRNA administered, respectively). These data are not valid because VAERS is not a prospective cohort with baseline and followup measures in all vaccine recipients.

It is important to acknowledge that underreporting and variability in report quality are major limitations of large passive surveillance systems [142]. Harvard-sponsored research estimates that, on average, less than one in every 100 AEs (<1%) experienced in the general population is submitted to VAERS [143]. For this reason, any estimates generated from VAERS must be deemed conservative and are best used to spotlight a signal in the population and to help stimulate the conduct of large observational studies. Large observational studies will generally provide more reliable data, although they too must be considered estimates due to the pervasive reality of subclinical myocarditis. For example, a study by Sharff et al. examined myocarditis rates in a group of 65,785 individuals aged 18 to 39 and reported an incidence of 9.1 cases per 100,000 booster doses within 21 days post-vaccination [70]. This figure greatly exceeded the 0.2 cases per 100,000 reported for that age group by VAERS, which cannot be utilized for incidence estimates [144]. Nonetheless, because there was no prospective monitoring of cardiac function by Sharff et al., the subclinical cases were vastly underreported.

Note: A crude estimate of the underreporting factor for myocarditis in adolescents, ages 12-18, may be derived using the estimate from Mansanguan et al., which found 1 in 60 (1.7%) male adolescents developed either myocarditis or myocarditis (excluding the 2 pericarditis cases) [118,145]. , Combining that estimate with the more conservative estimates from Chua et al. (18.5/100,000 = ~0.02%) and Sharff et al. (37.7/100,000 = ~0.04%), the underreporting factor for mRNA vaccine-related myocarditis for these younger individuals would be 1.7/0.03 = 57. Thus every incidence estimate from large observational or surveillance studies could be multiplied by 57 to arrive at a more accurate number [73].

A recent VAERS analysis revealed that myocarditis cases reported in VAERS following the 2021 COVID-19 vaccine rollouts were 223 times higher than the combined average for all vaccines over the previous 30 years [47]. This translates to a dramatic 2500% increase in reported cases compared to the period before 2021. Demographic data from the study showed that youths accounted for 50% of the cases, with males comprising 69%. Notably, 76% of those cases reported to VAERS required emergency medical care or hospitalization, and tragically, 92 individuals died (3% of cases). The study also found a significantly higher risk of myocarditis after the second mRNA dose ($p < 0.00001$), with younger individuals (under 30 years) being particularly vulnerable compared to older populations ($p < 0.00001$). The Rose et al. findings suggest a strong association between COVID-19 mRNA vaccines and myocarditis, particularly among young males, leading to hospitalization and, in some cases, death.

As of October 2024, there were over 1.6 million VAERS reports of injury in the context of the COVID-19 mRNA products alone, with 25% of these being considered serious AEs, to include death, disability and life-threatening illnesses. This finding is 10% above the upper limit for an acceptable percentage of SAEs as per any standard list of AEs.† The staggering increase in reports as of 2021 when compared to the total number of reports for all vaccines combined for the past 30 years is clearly depicted in Figure 2.

† Readers may refer to the VAERS Data Use Guide - HHS.gov [Internet]. Department Of Health And Human Services; 2020 Available from: https://vaers.hhs.gov/docs/VAERSDataUseGuide_November20 20.pdf

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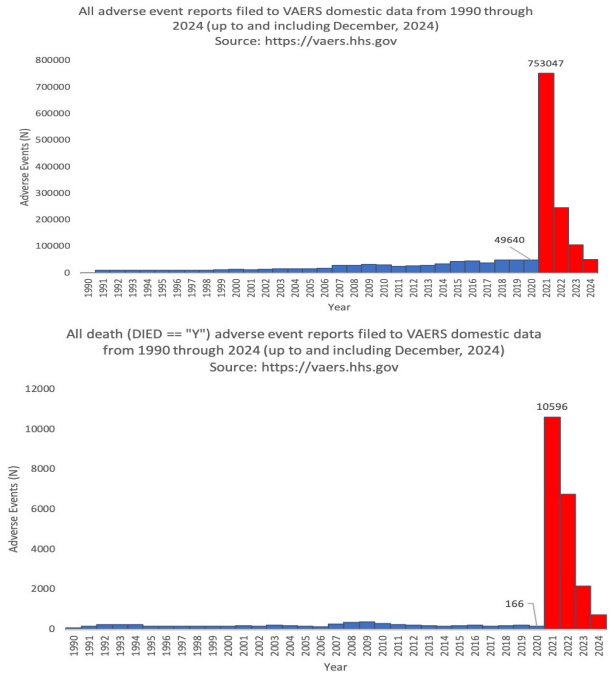

Figure 2. All AE reports in VAERS per year (top) and death reports per year (bottom). Blue bars represent all vaccines combined; red bars represent COVID-19 vaccines. The red bars represent only the reports in the context of the COVID-19 vaccines, whereas the blue bars represent all the reports for all vaccines combined. This surfeit of reporting is not simply because more shots were administered, as some have argued.

In a timeframe-matched period consisting of 462 days, 2.3 times as many COVID-19 vaccines were administered than for influenza vaccines. Figure 3 shows that in spite of this, the COVID-19 vaccinations were associated with 118 times more reports (Figure 3 - right) and perhaps even more alarming, 6.2 times as many types of AEs (Figure 3 - left). This suggests that the COVID-19 product harms are systemic as indicated by the high number of a wide range of AE reports, which alludes to an immune system dysfunction. There is no other reasonable explanation for such a disparity between the types of AEs reported when comparing COVID-19 products to influenza vaccines.

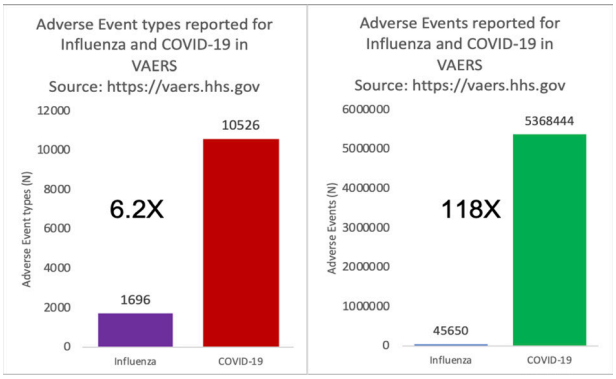

Figure 3. AE types (left) and absolute counts of AEs (right); comparing COVID-19 products to influenza vaccines during a 462-day timeframe. For this same timeframe, there were 2.3 times more COVID-19 shots than Flu shots. However, the AE types and absolute counts (or numbers) of AE reports for COVID-19 compared to the Flu are 6.2 and 118 times higher, respectively.

The total number of AE reports in VAERS in the context of the COVID-19 mRNA vaccinations normalized per million doses administered per age group is shown in Figure 4. It is notable that the rate for the 0-4 age group is high considering the administration roll-out to infants began long after the older age groups. It makes sense that the highest rates are seen for the older age groups considering that they were first in line to be administered these products as part of the roll-out.

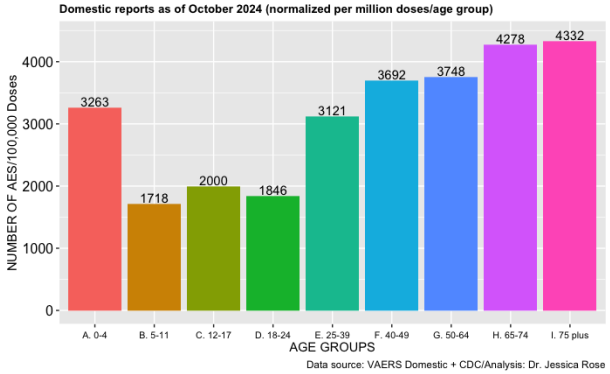

Figure 4. Total numbers of VAERS reports per age group normalized per million doses, as of October 2024.

The increase in AEs is not due to an increase in the number of COVID-19 mRNA doses administered. Figure 5 shows that when the number of AEs per million doses administered for influenza vaccines in 2019 (so as to exclude bias from 2020) are compared with the number of AEs per million doses administered for COVID-19 mRNA products in 2021, there are 25 times more total AE reports and 200 times more myocarditis reports. This normalization of the data demonstrates very clearly that not only are the COVID-19 products associated with higher total AE reports, but many other AE types as well, including myocarditis.

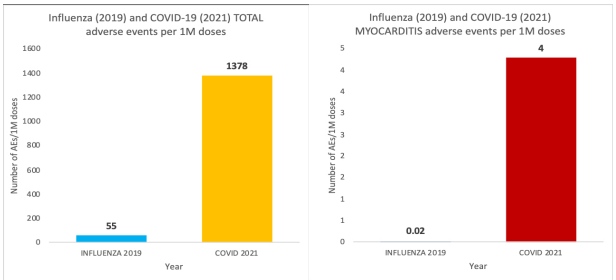

Figure 5. AEs per million doses for all AEs (left) and for myocarditis (right); comparing COVID-19 mRNA product reports in 2021 to influenza vaccine reports in 2019.

Figure 6 shows VAERS myocarditis reports as of September 29, 2023 by age and dose number. Notably, there was a five-fold increase in myocarditis reports among 15-year-old males following the second dose (green bars), with a general trend of increased cases after subsequent doses [141]. Across all ages, myocarditis reports were more prevalent following the second mRNA dose, suggesting a potential causal link between myocarditis and COVID-19 vaccinations [141]. This conclusion is further supported by a large disproportionality analysis of VAERS data, which demonstrated a statistically significant association between cardiovascular events and administration of the COVID-19 mRNA products [146].

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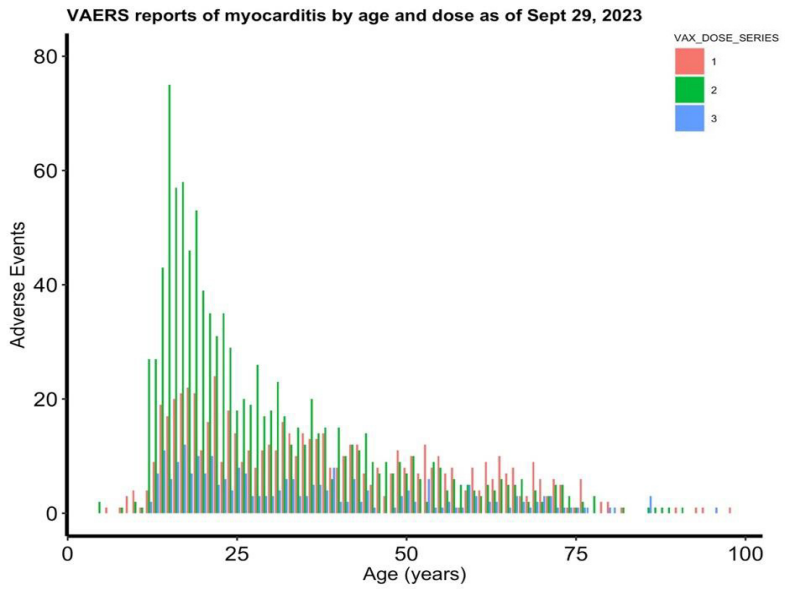

Figure 6. VAERS reports of myocarditis as of September 29, 2023 plotted by age and dose (dose 1 (pink), dose 2 (green), and dose 3 (blue)).

Case report data

Epidemiological studies have revealed a strong temporal relationship between the COVID-19 mRNA products and acute myocarditis. Since June 2021, hundreds of peer-reviewed studies have focused on cardiac events following COVID-19 vaccination against the coronavirus infection (SARS-CoV-2 and Omicron variants). One of the earliest reports, published in *Circulation*, was a case series of seven myocarditis patients, all men under age 40, only one of whom had been previously infected with SARS-CoV-2 [4]. We performed a Pubmed search (15 November 2024) using "myocarditis" and "myopericarditis" in the title, and the terms "COVID-19" and "case reports" in all fields. Systematic reviews and large case-series reports were excluded from this search strategy. Only case reports and small case series (<10) were included to allow for a more granular analysis of individual factors such as number of doses, interval between injections, and coronavirus reinfections.

Prior to May 2021, there were 13 case reports of myocarditis in the pandemic literature, all of which attributed the heart inflammation to SARS-CoV-2 infection. From May 2021 to November 2024 (42 months, or 3.5 years), the search produced a total of 267 case reports that identified either the coronavirus infections or COVID-19 vaccinations as the precipitating factor for myocarditis. Of this total, 241 cases (90%) attributed the myocarditis to the COVID-19 mRNA vaccinations, while the remaining 26 reports (10%) identified the coronavirus infection as the most likely cause of the myocarditis, bringing the total number of "Covid infection" case reports to 39. Thus there were about six times as many case reports of myocarditis linked with the COVID-19 mRNA vaccinations as there were reports linking myocarditis with SARS-CoV-2 infection.

The sharp increase in case reports following the rollout of COVID-19 modified mRNA vaccines suggests a significant link between these products and the incidence of myocarditis. From May 2021 to November 2024, there were 241 case reports of myocarditis in PubMed with mRNA vaccines cited as the contributing factor, compared to only 39 cases linked with the coronavirus infection. It is noteworthy, moreover, that many of those case reports in the infection group did not mention the vaccination status of the individual, which would have been critically important information after May 2021. To summarize, since 2021, there has been a marked increase in myocarditis case reports, mostly focused on young males, a demographic known to have a relatively low risk of severe COVID-19. Most of these cases were diagnosed within a few days or weeks following the mRNA injection.

Sudden death in athletes

The higher rates of myocarditis that were reported in U.S. military personnel may be related to their more strenuous physical activity levels [21,134]. Such physical stress could contribute to the more serious outcomes related to myocarditis, due to the fact that a surge of adrenalin (following vigorous exercise or physically stressful activity) may trigger cardiac arrest in younger adults in the setting of clinical or subclinical myocarditis [147]. Some of the histopathological features of adolescent cases (e.g., contraction band necrosis, along with neutrophil and histiocyte infiltrates) suggest catecholamine-induced inflammation of the myocardium [148,149]. It also appears that younger populations are more susceptible to suffer from fulminant myocardial injury due to their stronger immune-inflammatory response compared to elderly people [150].

The combined effects of exercise-induced inflammation and increased stress hormone output may help explain the surge in serious cardiac events and "sudden deaths" among professional athletes since 2021. This well-documented myocarditis-related phenomenon explains why, even before the pandemic, young athletes were more prone to sudden cardiac death compared to their non-athletic counterparts [151]. In a recent 38-year timeframe, 1101 athletes under the age of 35 died due to various heart-related conditions, 50% of whom had congenital anatomical heart disease and cardiomyopathies; while 10% had atherosclerotic heart disease with early onset [151]. Thus the average annual number of lethal cardiac arrests among professional athletes on the field in Europe was about 29 deaths per year prior to 2021. Beginning in 2021, however, this figure increased by nearly 10-fold to 283 per year, based on the annualized rate of cardiac arrests observed after the rollout of COVID-19 mRNA products to active players aged 35 and under; tragically, two-thirds of these players were never resuscitated [152]. Many professional athletes were barred from competition if they did not consent to receiving the mRNA vaccines, placing many individuals at heightened risk of suffering from myocardial injury.

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Misconception 1: Coronavirus Infections Cause More Myocarditis Than COVID-19 Vaccinations

Myocarditis in the COVID-19 era has been officially associated with either SARS-CoV-2 infections or COVID-19 mRNA vaccines, or both. Research from the early 1990s demonstrated the potential for coronaviruses to induce myocarditis and cardiomyopathy, prompting concern among scientists when SARS-CoV-2 emerged in 2020 regarding its potential to cause this condition [153,154]. Unadjudicated myocarditis cases related to the SARS-CoV-2 infections were suspected in 2020, prior to the vaccine rollouts [155-157]. Following the mass vaccination, many more clinically adjudicated and confirmed cases of mRNA vaccine-attributable myocarditis were reported. Nonetheless, in an attempt to reduce vaccine hesitancy, most all public health authorities continue to claim that coronavirus infections cause more myocarditis than the mRNA vaccines.

The following explanations support our overall premise: (1) hospitalized COVID-19 patients with cardiovascular conditions and elevated cardiac troponins triggered clusters of International Classification of Diseases (ICD) codes, with the troponin testing enabling codified data to then be analyzed and reported as false positive "COVID-related" myocarditis; (2) overreliance on data from hospitalized COVID-19 cases without clinical confirmation of myocardial inflammation (CMR, biopsy); (3) lack of autopsy confirmation; (4) differences in how myocarditis incidence is calculated in relation to the coronavirus infection versus the mRNA injection, resulting in an underestimation of the latter's impact; and (5) failure to consider that the SARS-CoV-2 infection is a "breakthrough" infection which is (by definition) superimposed on a baseline of failed COVID-19 vaccination. Despite these serious limitations, Erick Stecker, MD, the American College of Cardiology's chair of the Science and Quality Committee, stated: "There is no question that the benefits of COVID-19 vaccination generally outweigh the risks. While we do acknowledge that there is a very small risk of myocarditis after vaccination, particularly in adolescent boys and young men receiving mRNA vaccines, these instances are extremely rare, generally mild and treatable, and in most cases resolve quickly and without intervention. We should be clear that the risk of long COVID, heart damage, and death are higher among unvaccinated COVID-19 patients, and we therefore encourage everyone, including young men, to receive a primary (two-shot) vaccination for COVID-19" [158].

We now consider each of the key limitations concerning the ACC's official position:

ICD codes triggered by cardiac troponins in COVID-19 patients

We begin with the issue of increased cardiac troponins triggering ICD codes in hospitalized COVID-19 patients. In 2020, the COVID-19 hospitalized population began overlapping with the cardiovascular disease population, both directly and indirectly. Patients with CAD have long represented a large cross-section of the U.S. hospital population. Thus it is not surprising that, in that first year of the pandemic, so many PCR-positive hospitalized individuals also had CAD, hypertension, and other conditions that predisposed those patients to cardiac problems and increased troponins [159]. Measurement of cardiac troponins is part of routine medical care for persons hospitalized for heart disease and other cardiovascular-related conditions. High troponin levels are often linked to concomitant CAD, myocardial infarction, stress-induced cardiomyopathy, pulmonary embolism, congestive heart failure, or acute coronary syndromes [160]. These cardiovascular conditions are all associated with increased cardiac troponin levels, which also happens to be an independent risk factor for hospitalization in the COVID-19 setting (OR = 3.65, 95% CI, 2.03-6.57) [161]. Even non-cardiac situations like sepsis, chronic kidney disease, renal failure, and extreme physical exertion can produce similar findings [162,163]. In short, although elevated troponins can signify myocardial injury, they are not specific to myocarditis (or to inflammation in general) and must be considered and interpreted within the proper clinical context.

Attributing the troponin elevations to myocarditis without a comprehensive evaluation not only risks overlooking other potentially life-threatening diagnoses but, in the research setting, leads to a miscategorization of myocarditis cases as being caused by SARS-CoV-2. The problem is further complicated by the fact that, during the pandemic, cardiac injury was not uncommon during severe COVID-19 illness [164-166]. Moreover, troponin elevations were consistent with findings seen in other severe ICU-level illnesses, such as pneumococcal pneumonias, also associated with cardiorespiratory distress [167]. Reports in the hospitalization literature suggested a trend of elevated cardiac troponin levels among patients admitted to ICUs who tested positive for SARS-CoV-2 [168]. In these same PCR-positive cases, preexisting cardiovascular disease and cancers (frequently treated with cardiotoxic chemotherapy drugs) were independently associated with a greater risk of developing cardiac injury. Among patients who were hospitalized "with COVID-19", arrhythmias and other cardiovascular complications were common; moreover, age, arrhythmias, heart failure, cancer, autoimmune disease, and overall disease severity were all independent predictors of all-cause mortality during and after "hospitalization for COVID-19 cardiovascular complications." [169].

An example of this pervasive research problem is the large self-controlled case series study by Patone et al., published in *Circulation*. This study evaluated the association between COVID-19 vaccinations and myocarditis for different ages and sex groups by tracking hospital admissions and deaths from myocarditis by age and gender and in relation to how many doses of the gene-based injections each individual received. Though the study also considered the recombinant adenoviral vector products manufactured by AstraZeneca (and found similar elevations in myocarditis rates post injection), our primary interest in this paper are the COVID-19 mRNA products. After the first dose of BNT162b2, the incidence rate ratio for men under 40 years old was 1.85 (95% CI, 1.30-2.62), rose to 3.08 (95% CI, 2.24–4.24) after the second dose, and 2.28 (95% CI, 0.77–6.80) after the third dose. After the first dose of mRNA-1273, the rate ratio was 3.06 (95% CI, 1.33-7.03); this

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increased to 16.83 (95% CI, 9.11-31.1) after a second dose, with insufficient data for the third dose. The authors offer the following conclusion: "The risk of myocarditis was higher 1 to 28 days after a second dose of mRNA-1273 (11.76 [95% CI, 7.25–19.08]) and persisted after a booster dose (2.64 [95% CI, 1.25–5.58]) [68]. Associations were stronger in men younger than 40 years for all doses and, notably, *the mRNA-1273-related myocarditis risk surpassed the myocarditis risk associated with SARS-CoV-2 infections*. [Emphasis added] Specifically, in men younger than 40 years old, the number of excess myocarditis events per million people was higher after a second dose of mRNA-1273 than after a positive SARS-CoV-2 test (97 [95% CI, 91–99] versus 16 [95% CI, 12–18])." In short, men under age 40 were six times more likely to develop myocarditis after the second mRNA-1273 injection than after SARS-CoV2 infection. Although these conclusions support our counterargument, they do so only weakly, as the overall findings are based on serious underestimates. To begin with, Patone et al. relied on ICD-10 codes to identify cases of myocarditis among hospitalized patients with COVID-19. The study defined myocarditis events based on the earliest date of hospital admission attributed to myocarditis or a death certificate listing myocarditis-related ICD-10 codes during the study period (December 1, 2020, to December 15, 2022). According to the Methods section, the determination of myocarditis relied on the presence of relevant ICD-10 codes, which are typically triggered by elevated cardiac troponin levels measured during hospitalization. As we noted above, however, elevated cardiac troponin alone is not definitive for diagnosing myocarditis. In the cohort of patients with COVID-19, hospitalization was primarily due to COVID-19 infection rather than confirmed myocarditis, and there was no adjudication or additional diagnostic testing, such as CMR, to substantiate the diagnosis of myocarditis. By contrast, mRNA vaccine-related myocarditis cases in the study were identified through standard clinical diagnostic protocols, including ECGs, troponins, echocardiography, and CMR, ensuring a more robust confirmation of myocarditis in vaccine-associated cases. Consequently, while mRNA-associated myocarditis cases represent confirmed diagnoses, COVID-19-related myocarditis cases in the study lack comparable diagnostic rigor. (In subsequent sections, we describe other major weaknesses of the Patone et al. study, all of which contributed to an overestimation of the infection-related myocarditis risk in this population.)

The problem of ICD codes linked with high troponin levels incidental to many COVID-19 hospitalizations was further compounded by the U.S. government's financial incentives to hospitals in 2020-2021. Under the provisions of the US Coronavirus Aid, Relief and Economic Security (CARES) Act, U.S. hospitals were eligible for supplementary payments averaging $76,975 for each COVID-19 patient who either required mechanical ventilation or passed away during their stay [170]. This legislation allowed hospitals to receive a 20% increase in reimbursement for Medicare patients classified as "COVID cases," regardless of whether this classification was based on a prior reverse transcription polymerase chain reaction (RT-PCR) test result or a clinician's judgment (symptoms were deemed sufficient, based on the CDC's COVID-19 case definition) [170]. Healthcare workers and administrators were therefore heavily incentivized to classify patients with pre-existing cardiovascular diseases as COVID-19 cases. If the RT-PCR test finding coincided with a high troponin reading, the diagnosis became "myocarditis with COVID-19", even though the PCR result was often only incidental and the patient, asymptomatic. Moreover, many of the positive PCR findings were false, with a false-positive range of 30-95% depending on the cycle threshold used [171,172]. Higher cycle thresholds (>35) were routinely used, yet frequently led to more false positives [173]. This phenomenon, together with the CARES incentives, engendered a dramatic inflation of case counts along with a distortion of official statistics concerning hospital myocarditis cases associated with SARS-CoV-2 infection [174].

Many SARS-CoV-2 infections are not confirmed by RT-PCR testing

Data from hospitalized COVID-19 cases tend to greatly undercount the true number of infections, thus overestimating the relative contribution of infection-related myocarditis in the general population. This relates to the overuse of RT-PCR testing as the basis for determining COVID-19 cases, and the assumption that those case rates reflect infection rates in the generation population. As a rule, however, there are significantly more SARS-CoV-2 infections than positive COVID-19 tests, and this is due to the following factors:

- Asymptomatic infections: Many individuals infected with SARS-CoV-2 do not develop noticeable symptoms and may never seek testing. A substantial proportion of these infections are asymptomatic, particularly in younger populations [175,176].
- Undocumented infections: Before widespread testing infrastructure was established, many cases of SARS-CoV-2 infection were undocumented. Seroprevalence studies later revealed higher levels of past infection than indicated by testing data [177,178].
- Test sensitivity and timing: Tests for COVID-19, especially early in the pandemic, had variable sensitivity. Infections could be missed (false negatives) if the test was taken too early or late relative to the infection timeline or if sample collection was inadequate [179,180].
- Limited testing accessibility and usage: In the early stages of the pandemic, and even later in some regions, access to COVID-19 testing was limited, or many could not easily access testing facilities. Moreover, people without severe symptoms often did not seek out testing [181,182].
- Undiagnosed cases: Some symptomatic individuals might not recognize their symptoms as COVID-19 or attribute them to other illnesses, leading to missed diagnoses [183]. Others may avoid testing due to stigma, fear, or inconvenience [184].
- COVID-19 testing frequency varied by region, depending on public health policies, prevailing attitudes, individual compliance and personal preference. Many individuals who suspected they had COVID-19 (based on symptoms and known exposures) chose not to confirm their infection through testing.

Given all of these factors, when assessing the rates of myocarditis per exposure to SARS-CoV-2, the denominator should not be the number of positive tests of study-population

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members during the study period, but rather the number of actual infections occurring in the study population during the study period, which again would be substantially larger than the number of positive tests. CDC analyses estimated that *there were four coronavirus infections for every positive test in the U.S. through September 2021* [185]. Ferguson et al. posit that fewer than a third of infected individuals were tested through England's community surveillance system (also known as Pillar 2, which is routine community-based testing, in contrast with Pillar 1, in-hospital testing) [186]. Furthermore, SARS-CoV-2 infections resulting in diagnosed myocarditis cases are much more likely to be associated with a positive test than infections in the general population, most of which are mild or asymptomatic. Any study of infection-related myocarditis that relies on positive RT-PCR tests as an inclusion criterion will tend to underestimate the total number of infections, thus artificially inflating the infection-related myocarditis rate. Realistically, given the official U.S. and U.K. sources cited above, the number of infections in a study population might be 3 to 4 times the number of test-positive "cases."

In the aforementioned study by Patone et al., the authors wrongly assumed that testing for SARS-CoV-2 infections is an accurate and reliable measure of infection, directly comparable to mRNA vaccine-related myocarditis rates [68]. When considering any dose of Pfizer's mRNA product, for example, the authors conclude that "the risk of myocarditis is substantially higher after SARS-CoV-2 infection in unvaccinated individuals than the increase in risk [after BNT162b2 injections]." This statement, however, is based on the erroneous assumption that all infections in the study population are associated with positive COVID-19 test reports. Patone et al. analyzed data from 42,842,345 individuals aged 13 and older in England who received at least one dose of a COVID-19 vaccine between December 1, 2020, and December 15, 2021. They reported that 5,934,153 participants had a SARS-CoV-2 infection either before or after vaccination (see Results, p. 743). Data from the UK's Office of National Statistics (ONS) indicate that approximately 8.3% of the population had been infected by the study's start and 43.2% by its end [187]. This suggests around 35% (34.9%) of the study population, or roughly 14,951,978 people, likely experienced their first infection during the study period—far exceeding the reported 5,934,153 [188]. This discrepancy arises from the study's definition of infection, which considered only the first SARS-CoV-2-positive test recorded during the study period.

Assuming the ONS data are accurate, Bourdon and Pantazatos establish 4,685,095 as a lower bound on the number of infections among Patone et al.'s study-population members while unvaccinated. Patone et al., however, report a total of 2,958,026 positive SARS-CoV-2 tests for study-population members while they were unvaccinated [188]. Bourdon and Pantazatos examined the risk of myocarditis in men under 40 following the COVID-19 inoculations or a positive SARS-CoV-2 test using incident-rate ratios (IRRs). Applying various reasonable assumptions, they estimate that the Patone et al. IRR of 4.35 for positive-test-linked incidence would be adjusted to 2.75, which is lower than the IRRs for the second dose of Pfizer's BNT162b2 (3.08) and the first dose of Moderna's mRNA-1273 (3.06). This would have substantially altered the *Circulation* paper's conclusions.

According to Stowe et al., "[T]he attributable risk estimates for COVID-19 used laboratory confirmed cases as the denominator and will be affected by the proportion of all SARS-CoV-2 infections captured by testing, precluding a direct comparison with vaccine-associated attributable risks" [71]. This statement is of great importance, given the widespread use of RT-PCR testing as a benchmark for measuring infections. Other authors have commented on the difficulty of arguing that post-infection myocarditis is more common than post-injection myocarditis, and why the laboratory-confirmed case count, as the denominator, captures only a fraction of true infections [188]. As explained above, issues such as asymptomatic cases, variable testing access, and under-testing, can all result in undiagnosed infections. It was common practice in many hospitals to forgo testing for SARS CoV-2 infections if patients had received the mRNA vaccines in recent months. In addition, many of the observational studies' risk estimates for positive-test-associated myocarditis, as represented in Table 1, may not directly apply to the Omicron variant of SARS-CoV-2, the current public health concern.

Lack of stratification weakens the findings from large observational studies

A third component of our counter-argument concerns the lack of stratification in many observational studies. In a review paper focusing on this issue, Knudsen and Prasad note that around 70% of studies on AEs following mRNA vaccines have not stratified data by age or other confounding factors [189]. This limits the ability to assess myocarditis risk among the highest-risk demographic, which is men under 40, following the second mRNA dose. Studies that do not stratify data by age and sex dilute risk estimates for this higher-risk group while inflating them for lower-risk groups, such as older women. A classic example is the study by the Global Vaccine Data Network (GVDN) of 99 million vaccinated individuals across multiple countries [37]. The GVDN investigators found that the myocarditis risk was 510% and 186% higher than baseline rates following the second doses of the mRNA-1273 and BNT162b2 products, respectively. Nonetheless, because the GVDN study did not stratify by demographic group, the increased risk of myocarditis applied across all ages and genders and was therefore a lower-bound estimate. Indeed, all of the signals identified must be considered lower-bound estimates; the true extent of harms is unknown but likely to be many times greater.

Similarly, some of the large observational studies in Table 1 did not adequately stratify for age. For example, the study by Patone et al. had insufficient age stratification (notably for the 13-17 year-olds), thus compromising the post-injection incidence estimates for high-risk groups [68]. Furthermore, most meta-analyses of mRNA vaccine-related myocarditis have omitted age stratification. For example, the intention-to-treat meta-analysis by Cordero et al. included 7 population studies and reported a mRNA vaccine-related myocarditis incidence of 0.0035% (95% CI 0.0034–0.0035%) [190]. The Wang et al. meta-analysis included 5 studies and reported an incidence of myocarditis of approximately 0.0011% (95% CI, 0.0005 to 0.0025%) among mod-mRNA-injected individuals [191]. Both

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studies failed to stratify by age and gender, thereby masking the serious harm signal to younger age groups and perpetuating the misperception of mRNA vaccine-related myocarditis as a "rarity", regardless of age or sex.

For their analysis, Knudsen and Prasad organized the selected studies according to the number of stratifiers (sex, age, dose number and manufacturer). Only 28% (eight of 29) of studies utilized all four stratifiers (see Figure 1 of their paper); the incidence of myocarditis ranged from 8.1 to 39 cases per 100,000 persons/doses when four stratifiers were examined [189]. The analysis shows that proper stratification of the data consistently results in reports of higher myocarditis incidence among younger males, with few exceptions. Analyses that use unstratified, population-wide myocarditis incidence estimates to inform vaccination policies for young men are misleading and have likely obscured a critical safety signal for males under 40. This, in turn, has helped to reinforce the common misconception that mRNA vaccine-related myocarditis in younger men is still relatively rare compared to infection-related myocarditis.

Variable precision in calculations of myocarditis risk will depend on the type of exposure

Knudsen and Prasad also highlight differences in how myocarditis incidence is calculated in relation to coronavirus infection versus mRNA injection. Myocarditis incidence following COVID-19 vaccination is relatively straightforward to estimate, as both the number of cases and the number of mRNA doses are well-documented. However, determining myocarditis incidence post-SARS-CoV-2 infection is far more challenging and less reliable, as the total number of infections remains unknown and cannot be accurately calculated, regardless of the number of RT-PCR tests conducted [192,193]. Thus, unlike the vagaries of determining infection-related myocarditis risks, vaccine-associated risk estimates use well-defined denominators—often total vaccinated individuals—ensuring a more accurate reflection of exposure. This discrepancy skews direct comparisons, as the infection risk denominator represents a subset, not the full infected population, whereas the vaccination denominator typically captures all exposed individuals. Again, studies typically rely on documented infections, which are often underreported due to undiagnosed cases. As we have seen, the number of positive COVID-19 tests often underestimates the true number of infections, with estimates suggesting the true infection count could be on the order of 3–4 times higher than confirmed cases. Thus myocarditis incidence may be grossly exaggerated in the context of SARS-CoV-2 infection studies.

Myocarditis linked to SARS-CoV-2 infection is typically associated with active viral replication or immune-mediated damage occurring during the acute phase of infection (7 to 14 days from the onset of symptoms). This may be viewed as a very brief window of exposure when compared to that associated with the COVID-19 mRNA inoculations: 245 days of mRNA-induced spike protein exposure, potentially causing chronic inflammation and immune dysregulation throughout this period [194,195]. This extended exposure window could disproportionately amplify susceptibility to mRNA vaccine-related myocarditis, highlighting a need for further research into the long-term immune-inflammatory effects of such prolonged exposure to the lipid nanoparticles and mRNA-induced spike protein production.

"COVID-related myocarditis" falsely diagnosed in athletes in 2021-2023

Such overdiagnosis occurred in test-positive younger, physically active individuals, due in part to the fact that physiologic changes from exercise training can mimic laboratory and structural abnormalities used to diagnose myocarditis [196]. Intensive exercise leads to physiologic cardiac remodeling, with endurance training enlarging all four heart chambers and resistance training causing mild left ventricular hypertrophy (LVH) without chamber enlargement. Transient elevations in cardiac injury markers, such as troponins and BNP, are common after intense exercise [197]. Limited CMR studies in athletes have identified LGE, often at ventricular hinge points, and higher native T1 values compared to non-athletes [198]. LGE consistent with overt myocardial scarring has been observed in older athletes [199]. These exercise-induced changes can overlap with features used to diagnose myocarditis, underscoring the need for careful interpretation of imaging and laboratory findings in athletes. Moreover, CMR interpretation is inherently subjective, and there is a risk of overestimating myocardial involvement in patients diagnosed with COVID-19. Studies evaluating cardiac abnormalities in athletes have predominantly identified mild changes, such as elevated T1 and T2 values [196]. While these findings may indicate myocarditis when consistent with the clinical context, similar elevations in T1 and the presence of LGE have also been observed in asymptomatic athletes without a history of COVID-19 infection [199,200]. Because of the temporal ambiguity in COVID-19, it is logical to postulate that the misdiagnosis of myocarditis among athletes would be more likely to result in a miscategorization of "COVID-related myocarditis", thus reinforcing the false claim that these cases are more commonly linked with the coronavirus infections than with the mRNA vaccines.

The above-mentioned temporal ambiguity, combined with undercounting of true infections and overcounting of "COVID-related myocarditis" (particularly in younger athletic individuals), further undermines the accuracy and reliability of the infection-related myocarditis count and complicates direct risk comparisons. Ultimately, while mRNA vaccine-related myocarditis cases show a clear temporal association with the vaccines, infection-related cases are subject to both denominator inaccuracy and a prolonged window of potential attribution, with elevated rates of incidental COVID-19 hospitalizations. These differences underscore the methodological challenges in drawing direct comparisons between the two, reinforcing the importance of carefully contextualizing risk estimates.

The frequent occurrence of subclinical myocarditis results in an undercounting of injection-related myocarditis and an overcounting of infection-related cases

The reality of subclinical myocarditis further complicates the infection-versus-injection argument. In most cases, myocarditis has a mild or subclinical outward presentation, and several studies have highlighted the frequent occurrence of this phenomenon, particularly among younger adults [122,201]. For

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example, the cohort study by Daniels et al., focused on 1,597 competitive college athletes with CMR screening after COVID-19 infection [201]. A total of 37 athletes (2.3%) were diagnosed with putative COVID-related myocarditis, subclinical cases outnumbering clinical cases by threefold (28 to 9, respectively). The prevalence of clinical myocarditis based on the initial symptom-based screening strategy was only 0.31% (7.4 times lower than CMR). The subclinical cases involved milder inflammation with transient symptoms that resolved without intervention. Detection of subclinical myocarditis and understanding its progression requires a combination of diagnostic tools (notably cardiac MRI) and careful patient monitoring. As mentioned earlier, the detection of troponin elevations in "COVID-19 patients" (i.e., anyone testing RT-PCR-positive in the hospital setting, or showing symptoms) was often interpreted by clinicians as indicative of "suspected" or "probable" myocarditis, thus bolstering the case numbers linked with any positive RT-PCR test result. Unlike the case series of vaccine myocarditis, Daniels reported no hospitalizations and deaths in the 37 suspected cases.

Flawed study methodologies and misreporting issues have distorted the infection-vs-injection argument

A final component of our counterargument pertains to the flawed study designs, methodologies, and reporting practices, all of which may greatly compromise the integrity of the data and reliability of the findings. For example, as we noted previously, most observational studies have used the CDC definition of "vaccination status": The individual is considered "unvaccinated" until 14 days after dose 2. Conversely, individuals are counted as "vaccinated" only 14 days after the second dose of a two-dose COVID-19 vaccine series. This practice has two fundamental implications: (1) individuals testing positive for SARS-CoV-2 before this period, any time prior to the 14 days after dose 2, are considered "unvaccinated", or not sufficiently protected; and (2) any AE occurring after the first dose or within 14 days of the second dose will be classified as occurring among the "unvaccinated" and counted as such. Implication #2 represents an obvious misclassification that, in turn, results in two major distortions. First, with regard to the "vaccinated" individuals in an observational study, this results in a consistently lower number of reported myocarditis cases following the first mRNA dose and 14 days up to the second dose, as early post-mRNA injection events will not be accurately captured. Second, all myocarditis cases occurring in the first 3-4 weeks of the first injection, or in the first 2 weeks following the second injection, will be classified as "unvaccinated". This outcome has resulted in the common yet erroneous belief that the mRNA vaccines prevent more myocarditis than they cause, and therefore mRNA-attributable myocarditis is rare. This problem was intrinsic to the many studies that adhered to the CDC definition of vaccination status. (For a careful review of the various statistical "tricks" employed in these fraudulent studies, we refer readers to the book by Fenton and Neil.) [202].

In epidemiological terms, because of the CDC's "non-vaccinated" 2-week rule, any cardiac events occurring within the specified timeframe are misclassified as events among the "unvaccinated", leading to extremely biased estimates of risk associated with the mRNA products. This also overestimates myocarditis cases attributed to SARS-CoV-2 infection because, again, any test-positive individual who develops myocarditis prior to 14 days after their second mRNA dose are classified as "unvaccinated", with a diagnosis of "infection-related myocarditis". This misclassification skews the data, as early mRNA vaccine-related myocarditis cases are excluded from the "vaccinated" cohort and reassigned to the "unvaccinated" or infection-related cohort. This explains how, in many large observational studies, myocarditis cases caused by the mRNA injection are easily misattributed to SARS-CoV-2 infection. Whereas the risk of infection-related myocarditis is inflated, the risk associated with mRNA products is profoundly underestimated.

There are numerous examples in the pandemic literature of how such distortions created a false impression of the impact of vaccination status on disease outcomes, hospitalizations, and mortality. One such study, by Birtolo et al., compared a range of outcomes among vaccinated and unvaccinated hospitalized COVID-19 survivors [203]. In this study, "vaccinated" individuals had fewer ICU admissions, respiratory complications, and persistent lung abnormalities (e.g., ground-glass opacities) than unvaccinated patients. Myocarditis occurred more frequently in unvaccinated patients (4.8% vs. 0.9%, p=0.013), as did pulmonary embolism and respiratory impairment during follow-up. The authors concluded that COVID-19 vaccination reduced myocarditis and other severe complications. However, the authors failed to disclose in their methods section that they used the standard CDC definition of vaccination status, meaning that patients who experienced either myocarditis or pulmonary embolism before the 14-day point (following dose 2) were counted as "unvaccinated" [101]. As explained above, this statistical stratagem inevitably results in a diametrical inversion of the true cardiac risks associated with the COVID-19 mRNA products.

A crucial flaw in the Patone et al. study is the exclusion of day-zero post-injection myocarditis events from their analysis. The authors justified this omission by citing "small numbers." However, this rationale appears inconsistent, as the number of day-zero events associated with infection is certainly not negligible (51 events out of a total of 228 across days 0–28) [68]. Notably, this figure closely aligns with Stowe et al.'s reported day-zero myocarditis events (54 cases, with 35 linked to vaccination; see Table 3 of that report) [71]. The decision by Patone et al. to withhold the specific number of day-zero myocarditis events following vaccination raises concerns about transparency and the integrity of their reporting.

Population studies

To lend further support to our counterargument, we will consider the pediatric findings of the Open SAFELY study (n=58 million) [204]. That study examined myocarditis risk in children by analyzing linked health records to identify cases following either COVID-19 infection or the mRNA inoculations. The study assessed incidence rates, timing, and associated factors, comparing risks associated with either the infections or the vaccines. The authors reported that myocarditis occurred exclusively in children (predominantly adolescents) who received the COVID-19 mRNA vaccines, with no cases identified among those infected with SARS-CoV-2,

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based on data from approximately 1.7 million participants in the pediatric cohort.

Along similar lines, in addressing limitations of their study, Patone et al. state: "[A]lthough we were able to include 2,230,058 children age 13 to 17 years in this analysis, the number of myocarditis events was small (56 events in all periods and 16 events in the 1 to 28 days after vaccination) in this subpopulation and precluded a separate evaluation of risk." [68] To their credit, Patone et al. do report 16 myocarditis events post vaccination (within 28 days) for the 13-17 year-old adolescents, but they do not report any events after positive tests (within 28 days). Thus, it appears there were no cases of myocarditis linked to positive SARS-CoV-2 tests among these younger individuals. The low event count likely prevented a granular risk assessment. Nevertheless, the absence of infection-related myocarditis cases in this large adolescent cohort suggests a negligible baseline risk from natural infection. †

The absence of infection-related myocarditis cases in the 13-17 year-old cohort in Patone et al. aligns with findings from the OpenSAFELY study cited above. It also aligns with a large multi-country analysis that reported zero myocarditis cases associated with SARS-CoV-2 infection in males and females aged 12–15 living in Scandinavia [14]. Taken together, these three large data sources indicate that, for children aged 12–17, the risk of myocarditis following the mRNA vaccines far exceeds the risk associated with SARS-CoV-2 infection. The consistency across large, independent datasets indicates that SARS-CoV-2 infection poses minimal myocarditis risk to healthy adolescents, in contrast with patterns observed in older age groups, for whom viral myocarditis risk is more pronounced.

Karlstad et al. performed estimates of excess myocarditis events following the COVID-19 mRNA vaccinations in a large population study (n=23 million) taking place in Denmark, Finland, Norway, and Sweden [14]. The Nordic countries offer an ideal case study due primarily to their demographic comparability and high-quality data reporting systems. In this study, a myocarditis event referred to a hospitalization with a primary or secondary discharge diagnosis for myocarditis. The risks of myopericarditis were highest within the first week, particularly for young men aged 16-24 years. For that subgroup, there were 5.55 excess events per 100,000 second doses of BNT162b2, and 18.39 (excess) events per 100,000 second doses of mRNA-1273. For this same age group, the authors also calculated a rate of 1.37 excess myocarditis events per 100,000 positive SARS-CoV-2 tests over a 28-day risk period following the positive test result. Given that there are many more infections than there are positive COVID-19 test findings, these numbers are underestimates of the true infection rate, thereby increasing the denominator and making the true number of infection-related myocarditis cases substantially lower. Nonetheless, the Karlstad et al. data show that the rate of mRNA vaccine-related myocarditis was markedly higher than the rate of infection-related myocarditis based on positive test results. For males ages 16-24, there were four times more mRNA vaccine-related myocarditis events after the second BNT162b2 dose than infection-related myocarditis events (5.55/1.37= 4.05). In this same age group, there were more than 13 times more mRNA vaccine-related myocarditis events after the second mRNA-1273 dose than infection-related myocarditis events (18.39/1.37=13.42).

In a large self-controlled case series analysis of hospital admissions for myocarditis or pericarditis in England between 22 February 2021 and 6 February 2022 (n=50 million), Stowe et al. sought to further investigate the increased risk of COVID-19 mRNA vaccine-related myocarditis and to provide new insights into the risks associated with the booster. The authors state that elevated relative incidence (RI) rates of hospital admission were only observed in 16- to 39-year-olds 0 to 6 days post-injection, mainly in males for myocarditis [71]. However, the data in Table 2 of their paper contradicts this claim. For subjects over age 40, we see there are elevated RI's (those exceeding 1) with statistically significant elevations for 7-13 days after the BNT162b2 booster, and 0-6 days after Dose 1 of mRNA-1273; also, for those 16–39, there was a statistically significant elevation 7-13 days after dose 2 of BNT162b2. Moreover, the authors' claim that elevated RI's were observed only during days 0-6 post injection is inconsistent with findings by Patone et al. based on data drawn from a demographically similar study population in England [68]. Table S3 of the Patone et al report shows statistically significant elevations days 1-7 and days 22-28 after dose 1 of BNT162b2, and days 1–14 after dose 2. For the mRNA-1273 vaccines, after dose 1, data were more limited: RI's were significantly elevated for days 1-7, though not statistically significant for days 8-14.

In the Stowe et al. study, the authors also provided hospital myocarditis data for 16–39 year-olds, for days 1–27 after a positive test for SARS-CoV-2. For this age group, Table 4 of their paper indicates that there were 113 admissions, 58.9 attributable myocarditis cases, and 8,398,257 positive SARS-CoV-2 test results. Thus the attributable risk per million can be derived as the quotient 58.9/8.398257 ~= 7.013 (95% CI: 5.5-8.3) [86]. This is likely to be an overestimate because routine community SARS-CoV-2 testing disproportionately captures symptomatic individuals, who are inherently at higher risk for severe outcomes like myocarditis, pericarditis, or COVID-related pneumonia [187,205]. In other words, we might expect a sample of 8,398,257 infections, representative of all infections (symptomatic and asymptomatic) occurring among those ages 16–39 to yield fewer than about 60 hospitalized myocarditis cases attributable to infection [86].

The large self-controlled case-series study by Patone et al. focused on approximately 43 million people in England who had received at least one dose of the COVID-19 vaccinations [68]. According to the authors, nearly 6 million individuals "had SARS-CoV-2 infection before or after vaccination." For men under age 40, they obtained an estimate of 11 attributable myocarditis cases per million second doses of BNT162b2 and 97 attributable cases per million second doses of mRNA-1273. Thus the mRNA vaccine-related myocarditis rate is 1-10 times higher than the rate of infection-related myocarditis, based on the Stowe et al. data for a comparable age group. For the overall population, however, Patone et al. claim that "the risk of myocarditis is substantially higher after SARS-CoV-2 infection in unvaccinated individuals [than in BNT162b2-injected individuals]." The statement is misleading because the authors do not actually attempt to measure the number of SARS-CoV-2

† Patone et al., offer the following conclusion: "[T]he risk of hospitalization or death from myocarditis after SARS-CoV-2 infection is substantially higher than the risk associated with a first dose of ChAdOx1, and a first, second, or booster dose of BNT162b2 mRNA vaccine." One would assume that this sweeping claim applies to adolescents 13 through 17 years of age in their study. However, on the last page of their Circulation paper, the authors inform readers that their "clinical perspective" does not apply to children ages 13-17.

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infections in members of their study population that occurred during the period in which those members were unvaccinated. Instead, Patone et al assume "number of positive tests = number of infections", an entirely untenable proposition [188].

One natural comparison suggested by the Stowe et al. data can be derived from the final four rows of Table 1 in their paper [71]. This enables us to compare the hospitalized myocarditis risk associated with the choice to vaccinate during the Stowe et al. study period compared with the choice to remain unvaccinated. As we show in Table 4, the unvaccinated risk is 2.03 hospitalizations per 100,000 person-years of risk, compared to 6.29 myocarditis cases per 100,000 among the BNT162b2 recipients and 14.12 cases per 100,000 among those receiving the mRNA-1273 vaccines.

In reference to the data we display above in Table 4, Stowe et al. state that, whereas ECDS consultation rates were higher for pericarditis than myocarditis, admission rates for myocarditis were generally higher than for pericarditis. In both the SUS and ECDS datasets, admission rates per 100,000 person years in males were approximately double those in females and increased sharply with age between 12 and 19 years, remaining fairly constant thereafter. The hospitalizations contributing to these rates do not all occur within a short period following either injection or infection.

In the supplemental tables for their paper, Stowe et al. provide SUS incidence rates for myocarditis or pericarditis based on various windows of exposure for "unvaccinated" persons and those receiving the COVID-19 mRNA vaccines. Below are the unadjusted SUS myocarditis rates from Table E (see "S2 Appendix") for individuals ages 16-39 (young adults <40). These estimates offer further confirmation for the observations we present in Table 3 showing lower risk among the unvaccinated. We chose the exposure period from the day of the injection to six days out, as this is the timeframe in which most mRNA vaccine-related mycocarditis cases are typically identified. The published case reports we reviewed for this paper suggest that myocarditis after exposure to SARS-CoV-2, symptoms typically manifest within one to two weeks following infection, ostensibly aligning with the acute or early post-acute phase of the illness. The data represented in this table, although unadjusted, suggest a substantially lower risk for SUS hospital admissions for myocarditis/pericarditis among the unvaccinated. The high myocarditis rate associated with dose two of the Moderna product (242.65 cases per 100,000 person years) is consistent with other studies we have cited. Even with adjustments for age, sex, and other variables, it is unreasonable to discount the huge disparity regarding myocarditis rates between vaccinated and unvaccinated.

Table 4. Clinical features of hospitalized individuals for myocarditis: data from entire eligible population in England (excerpted from Table 1 of Stowe et al.) [71].

Vaccination Status	Person-Years	SUS Myocarditis Case Count = 2284	SUS Myocarditis Risk per 100,000	ECDS Myocarditis Case Count = 1472 total	ECDS Myocarditis Risk per 100,000
Unvaccinated	16751085	340	2.03	225	1.34
BNT162b2	15459412	972	6.29	728	4.71
mRNA1273	793417	112	14.12	79	9.96

*Eleven SUS cases had an official diagnosis of both myocarditis and pericarditis (myopericarditis).
Abbreviations: SUS, Secondary Uses Service; ECDS, Emergency Care Data Set.

Table 5. Myopericarditis incidence rates, days 0-6 post exposure, from Stowe et al.'s self-controlled case-series analysis in England (2023).

Vaccination status (ages 16-39 years)	Case count	Person years (pyrs)	SUS case rate myocarditis or pericarditis (unadjusted), per 100,000 pyrs	SUS case rate myocarditis or pericarditis (adjusted), per 100,000 pyrs	Adjusted relative risk (aRR) w/ 95% CI
Unvaccinated	580	9667615	6	baseline	
Pfizer, BNT126b2					
BNT126b2, dose 1	27	186142	14.51	14.64	2.44 (1.65,3.62)
BNT126b2, dose 2	45	182573	24.65	23.4	3.9 (2.86,5.32)
BNT126b2, booster	14	73115	19.15	16.62	2.77 (1.6,4.79)
mRNA-1273, booster	8	27433	29.16	27.36	4.56 (2.22,9.35)
Moderna, mRNA-1273					
mRNA-1273, dose 1	9	19635	45.84	44.76	7.46 (3.84,14.51)
mRNA-1273, dose 2	41	16897	242.65	212.16	35.36 (25.39,49.23
BNT126b2, booster	n<2	5132	---	---	---
mRNA-1273, booster	n<2	4088	---	---	---

Note: These data are excerpted from Table E (S2 Appendix) of Stowe et al. The authors' description: "Table E. Adjusted (for time period (4 weekly period)) relative risk (aRR) of attendances with myocarditis or pericarditis in SUS using a cohort analysis after a COVID-19 vaccine by postvaccination risk interval. Adjusted for time period, age group, gender, region, ethnic group, CEV, and other clinical risk group." Adjusted case rates were not provided by Stowe et al., but can be calculated by multiplying the aRR by the baseline rate.

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Ideally, in principle, our Table 5 comparisons would be adjusted for age and sex in order to minimize the chance of misleading interpretations. Myocarditis risk may vary significantly across narrower age bands within the group (e.g., 16–24 vs. 31–39 years), and differences in age or sex distributions could bias crude comparisons. The unvaccinated, on average, are going to be younger than the vaccinated. Unfortunately, however, such adjustments are not soon forthcoming, as Stowe et al. state: "The raw study data are protected and are not freely available due to data privacy laws." (We view this statement as disingenuous, given that the use of de-identified data offers a straightforward and standard legal option.)

The adjusted relative risks (aRRs) of Stowe et al.'s Table E (S2 Appendix), comparing admissions for myocarditis or pericarditis for mRNA recipients and non-recipients ("unvaccinated"), suggest for 16–39 year-olds elevated risk among the mRNA recipients during all periods 0-6 days, 7-13 days, and 14+ days after doses 1 and 2 of both the Pfizer and Moderna mRNA vaccines. After a Pfizer primary series, the aRRs indicate elevated risk for periods 0-6, and 14+ days after a Pfizer booster (third injection) as well as for periods 0-6 and 7-13 days following a Moderna booster [86]. Given the impressive size of this study (n=~50 million), these results suggest a substantial myocarditis/pericarditis risk for vaccine recipients compared to unvaccinated individuals.

Lastly, in a commentary on the Buergin et al., study, Klement and Walach criticize the claim that, without the mass vaccination program, the incidence and extent of myocardial damage associated with COVID-19 infection would have been much higher [206]. After obtaining data from Germany and Switzerland and calculating the expected frequency of increased cardiac troponins following COVID-19 infection in hospitalized and non-hospitalized individuals, Klement and Walach find that the extent of myocardial damage after administering the COVID-19 mRNA vaccines to a considerable proportion of the general population would likely be much higher than after the SARS-CoV-2 infections. They conclude: "The claim that the extent of myocardial injury after COVID-19 infection would be higher than after vaccination is not supported by empirical evidence and therefore wrong." They further encourage the conduct of multi-country systematic observational studies to enable a more precise estimation of the risk-benefit ratio of COVID-19 mRNA vaccines.

Misconception 2. COVID-19 Vaccine-Induced Myocarditis is Usually Mild and Transient

It is a clinical reality that many cases of myocarditis go unnoticed or undiagnosed because the sole symptoms may include mild fatigue, muscle soreness, abnormal heart rhythm, or a temporary increase in heart rate. Some cases are asymptomatic and only initially identifiable with elevated cardiac troponin levels indicating stress and damage to the myocardium. Most cases of mRNA vaccine-related myocarditis are self-limiting. Some individuals remain asymptomatic or experience only mild symptoms. The majority of vaccine-associated myocarditis cases are classified as mild based on clinical presentation, with LGE resolving in approximately 50% of cases by 90 days [207]. Positron emission tomography (PET) imaging data often indicate resolution within 180 days [208].

Because of the typically mild outward presentation, medical publications and media reports during the pandemic often referred to myocarditis as a "mild condition" that would disappear without treatment. This view implies that "mild myocarditis" is synonymous with clinically insignificant myocarditis; however, this is a fallacy. It is important to distinguish among different definitions of "mild," which may refer to clinical presentation, echocardiographic findings, or abnormalities detected on CMR. For instance, a patient may exhibit mild clinical symptoms but demonstrate significant abnormalities on MRI, or they may have elevated troponin levels despite otherwise unremarkable findings. These distinctions are critical for accurate risk assessment and patient management.

Even with mild symptoms, the underlying physiological effects and anatomical scarring may be more severe or potentially lethal in the long term. Myocarditis may eventually develop into congestive heart failure, dilated cardiomyopathy, cardiogenic shock (severe reduction in cardiac output leading to systemic hypoperfusion and organ failure), and, in some instances, sudden cardiac death [209-212]. COVID-19 mRNA vaccine-related myocarditis should be considered in the pathogenesis of these cardiac conditions, either as a primary cause/diagnosis or as a contributing factor to a pre-existing myocardial injury [213].

Clinical myocarditis (typically without mild symptoms) is recognized as a major cause of sudden and unexpected death in infants, adolescents, and young adults, with frequencies ranging up to 14% among these younger age groups [214-217]. Most of the serious cardiac AEs have been reported within the first 14 days following the mRNA inoculations. However, some sudden deaths linked with the vaccines have occurred months to years later, as painstakingly documented by one of the authors of this paper (WM recorded over 7000 sudden deaths during a 20-month period, from April 2023 to Nov.2024) [218]. Hulscher et al. assessed excess cardiopulmonary arrest mortality in King County, WA, in relation to COVID-19 vaccination rates [219]. By 2023, 98% of the population had received at least one mRNA dose. Cardiopulmonary arrests showed an increasing trend from 2015 to 2020, followed by even stronger trends in 2021 and 2022. Excess cardiopulmonary arrest deaths increased by 1,236%, from 11 in 2020 to 147 in 2023. A quadratic model revealed a strong correlation between higher mRNA injection rates and mortality, with myocarditis and thromboembolism as potential contributing factors. King County's 0.94% population decline in 2021 coincided with the mortality rise. Extrapolation estimated 49,240 U.S. excess deaths (2021–2023). These findings align with prior studies linking the mRNA immunization campaigns to increased cardiopulmonary events [220-223]. For example, Sun et al. observed a 25% rise in cardiac-related EMS calls among 16–39-year-olds in Israel during the first population-wide vaccine rollout [40].

If the myocardium becomes scarred (correlating with the degree of LGE found on CMR), fibrotic tissue can lead to arrhythmias and eventually to heart failure and cardiogenic shock, potentially fatal events that may occur in under 10% of myocarditis cases [224]. Unlike skeletal muscle, cardiac muscle

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displays a limited capacity for regeneration following injury. Instead of regenerating functional myocytes, damaged cardiac tissue is replaced by fibrotic scar tissue, which is permanent [225]. This structural remodeling disrupts the electrical and mechanical integrity of the myocardium, increasing the risk of arrhythmias and contributing to a higher likelihood of premature death over the individual's lifetime [226].

Emergent evidence suggests the possibility of myocardial fibrosis and potential long-term sequelae in symptomatically mild or even asymptomatic or subclinical myocarditis. These "mild clinical cases" can involve severe cardiac fibrosis (scarring), with permanent damage to the heart muscle and a lifelong risk of potentially fatal arrhythmias [227,228]. Over time, such damage can progress to congestive heart failure and premature death [229]. The pivotal Pfizer and Moderna trials were not designed to capture these long-term risks, most of which only became apparent after 2.5 years of follow-up and the administration of over a billion mRNA doses. Three case series (n=38) indicated that >50% of myocarditis patients exhibited persistent echocardiogram abnormalities, ongoing symptoms, or required medication or activity restrictions after three months of follow-up observation [29]. A recent FDA study reported that approximately 60% of young individuals hospitalized with myocarditis following mRNA vaccines exhibited persistent signs of myocardial injury about six months post-vaccination [230]. Nevertheless, throughout the pandemic, public health officials and healthcare leaders routinely dismissed any possibility of long-term sequelae from mRNA-induced myocarditis (Table 6).

Severe or fulminant myocarditis is more likely to lead to long-term complications (see Table 6). Fulminant cases are characterized by a rapid decline in cardiac function and carry a high mortality rate. Studies have reported mortality rates ranging from 20% to as high as 75%, depending on factors such as the underlying cause and the timeliness of treatment [231,232]. Regarding long-term myocardial damage, the prognosis varies. Some studies suggest that patients who survive the acute phase of fulminant myocarditis may experience significant recovery of cardiac function, with long-term survival rates comparable to the general population; however, other research indicates that a subset of patients may suffer from persistent cardiac dysfunction or develop dilated cardiomyopathy, leading to ongoing health challenges [233]. The variability in outcomes underscores the importance of early recognition and aggressive management of fulminant myocarditis to improve survival rates and reduce the risk of long-term cardiac sequelae. Regular follow-up with cardiac imaging and functional testing is crucial in detecting and managing long-term sequelae of myocarditis.

Mounting evidence supports the assertion that the COVID-19 mRNA vaccines can induce severe and sometimes fatal myocarditis [126,204,234,235]. As noted previously, 96% of the myocarditis cases initially reported to VAERS prior to June 11, 2021 and meeting the CDC's case definition were hospitalized [39]. Using a case-finding method in VAERS, Krug et al., identified 253 cases of myocarditis among boys ages 12-17 and observed an 87% hospitalization rate following the primary series of BNT162b2 [74].

Table 6. Potential sequelae of COVID-19 mRNA vaccine-related myocarditis.

Short-term Sequelae	
Heart Failure (Acute or Fulminant)	Severe inflammation and myocardial injury can cause a sudden decline in the heart's ability to pump blood effectively. Symptoms include sudden severe apnea, chest pain or fainting.
Arrhythmias	Myocarditis can disrupt the electrical conduction system and cause various arrhythmias: ventricular tachycardia or fibrillation (life-threatening); atrial fibrillation or flutter; and heart block (first-degree to complete).
Cardiogenic Shock	This severe reduction in cardiac output can result in systemic hypoperfusion and organ failure.
Thromboembolic Events	Inflammation and impaired myocardial contractility can increase the risk of intracardiac thrombus formation, leading to stroke or pulmonary embolism.
Pericarditis and Pericardial Effusion	Myocarditis can be associated with concurrent inflammation of the pericardium, potentially leading to tamponade.
Long-term Sequelae	
Dilated Cardiomyopathy	Persistent myocardial damage and scarring can lead to ventricular dilation and systolic dysfunction.
Chronic Heart Failure	Progressive decline in cardiac function due to ongoing myocardial remodeling and fibrosis.
Persistent Arrhythmias	Scarring and electrical instability can result in chronic arrhythmias, increasing the risk of sudden cardiac death.
Sudden Cardiac Arrest	Due to ventricular arrhythmias or significant pump failure.
Chronic Thromboembolic Risk	Especially in patients with reduced ejection fraction or atrial fibrillation.
Restrictive Cardiomyopathy	In rare cases, severe fibrosis may lead to a stiffened myocardium, impairing diastolic filling.
Post-Myocarditis Syndrome	Persistent chest pain, fatigue, and functional limitations due to incomplete resolution of inflammation or scar formation.
Autoimmune Cardiac Disorders	Myocarditis can sometimes trigger chronic autoimmune processes, further damaging cardiac tissue.

Clinical notes: In terms of management, early diagnosis, anti-inflammatory treatments, and appropriate cardiac support can significantly improve outcomes. Following the COVID-19 mRNA vaccines, it is conceivable that mRNA-induced myocarditis may overlap or interact with viral myocarditis, as well as autoimmune and toxin-induced etiologies, all of which may influence the prognostic outlook.

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The most significant elevations in troponin levels were observed in adolescents aged 16–17 years, in both male and female patients. The authors note that elevated troponin levels are strongly indicative of underlying cardiac disease in pediatric populations presenting with symptoms, and that the threshold for normal troponin levels in children may be lower than the adult standard of 0.1 ng/mL [236].

Watanabe and Hama reported a significantly elevated myocarditis mortality rate ratio (MMRR) in individuals vaccinated against COVID-19 when compared to the general population during the three years preceding the pandemic, with the highest increase observed in young adults (MMRR: 7.80 for individuals in their 30s), mostly males [235]. Choi et al. reported a case of fatal myocarditis associated with mRNA injection in a 22-year-old male military recruit [148]. This man developed symptoms five days after the first dose of the BNT162b2 product and died only seven hours later, with autopsy showing isolated atrial myocarditis with neutrophil and histiocyte predominance. Verma et al. documented the case of a 42-year-old man who presented with chest pain and dyspnea two weeks after the second dose of mRNA-1273, dying three days after symptom onset [237]. Shime et al. presented a case report of a 15-year-old boy who had recovered from myocarditis associated with COVID-19, but then developed near-fatal myocarditis seven months later, upon receiving a single dose of BNT162b2 [238]. Given that all three males were healthy prior to the injections, each case offers a clear temporal basis for establishing causality.

The common refrain from the vaccine industry is that such cases are rare and that the benefits outweigh the risks; however, substantial epidemiological evidence now contradicts this view. Previously we discussed Patone et al.'s large study and its findings (see Table 1). The authors identified 617 cases of myocarditis occurring 1 to 28 days after any dose of the COVID-19 gene-based injections, of which 97 resulted in fatal outcomes, yielding a case fatality rate of 16.2% [(97/617) × 100] [68]. Notably, all fatalities occurred in individuals over the age of 40, among whom 381 cases of myocarditis were reported, corresponding to a mortality rate of approximately 25.46% [(97/381) × 100] within this subgroup. These extraordinary case fatality rates could also be related to high background rates of comorbid cardiovascular disease in the British population, with rates roughly comparable to those of the U.S. population.

In a population study in Japan, Takada et al. confirmed 919 cases of mRNA vaccine-related myocarditis and 321 cases of mRNA vaccine-related pericarditis [239]. The reporting odds ratio (ROR) was statistically significant for both conditions: myocarditis (ROR: 30.51; 95% CI: 27.82–33.45) and pericarditis (ROR: 21.99; 95% CI: 19.03–25.40). Approximately 9.6% (about 1 out of every 10) individuals who were diagnosed with myocarditis or pericarditis following the COVID-19 mRNA vaccines died afterward, a high case fatality rate for a relatively healthy population. More modest rates have been reported by other authors. Rose et al. estimated a case fatality rate of 2.9% based on 3078 VAERS reports of mRNA vaccine-induced myocarditis [47].

Other investigators contend, however, that the risk of life-threatening myocarditis is still greater post-infection than post-injection. In a population-based cohort study (n=23 million) utilizing nationwide register data from four Nordic countries (Denmark, Finland, Norway, and Sweden), Husby et al. analyzed clinical outcomes of myocarditis associated with the COVID-19 mRNA products compared with other types of myocarditis [240]. They identified 7292 individuals aged ≥12 years who had an incident diagnosis of myocarditis as a main or secondary diagnosis. The main outcome measures were heart failure or death from any cause within 90 days of hospital admission for new onset myocarditis, as well as hospital readmission for new onset myocarditis within 90 days of hospital discharge. In individuals aged 12–39 years without pre-existing comorbidities, the RR of heart failure or mortality was significantly greater for myocarditis linked to COVID-19 infection compared to mRNA-associated myocarditis (RR 5.78, 95% CI: 1.84–18.20).

Table 2 of Husby et al., indicates there were 22 heart-failure cases post mRNA injection, and 12 cases post SARS-CoV2 infection. However, the total number of patients was 530 for the post-injection versus 109 for the post-infection group. This explains the higher incidence rates and RR's for heart failure and death (from any cause) for the post-infection group. Compared with conventional myocarditis, the RR of heart failure within 90 days was 0.56 (95% confidence interval 0.37 to 0.85) and 1.48 (95% CI: 0.86 to 2.54) for myocarditis associated with either mRNA injections or COVID-19 disease, respectively; the relative risk of death was 0.48 (95% CI: 0.21 to 1.09) and 2.35 (1.06 to 5.19), respectively. As with the Patone et al., study, however, there was no adjudication of these hospital myocarditis cases, and therefore all of our previous arguments apply as to why the estimates are likely distorted. Moreover, the authors fail to indicate whether those with COVID-19 had been previously vaccinated: serious cardiac AEs seemingly linked with the infection plausibly could have been due to an interaction between the vaccines and the infections, especially given the very long persistence of spike protein following the mRNA injections. (We have a paper currently undergoing peer-review that explains how the temporality of this interaction would make the infections appear to be the cause of serious AEs, when it is more likely that the mRNA vaccines are "priming" the individual for the serious cardiac events post infection.)

For their conclusion, Husby et al. state: "Compared with myocarditis associated with COVID-19 disease and conventional myocarditis, myocarditis after vaccination with SARS-CoV-2 mRNA vaccines was associated with better clinical outcomes within 90 days of admission to hospital." However, these "better clinical outcomes" for cases of mRNA vaccine-related myocarditis may bear no relationship to any intrinsic difference in severity of post-injection versus post-infection myocarditis. The age breakdown in Table 1 reveals that the percentages of cases among individuals >40 years old are as follows: 35.8% for the post-injection group, 56% for the post-infection group, and 50% for the post-conventional group. This substantial difference in age distribution between the mRNA-injected and SARS-CoV-2-infected myocarditis groups (with the latter comprised of approximately 56.4% more individuals >40) may partially explain the findings from Husby et al. Although the authors state that they excluded patients with

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predisposing comorbidities (malignancy, cardiovascular disease, or autoimmune diseases), they did not exclude those with comorbid obesity, diabetes, and hypertension, conditions that may significantly increase the risk of myocarditis and other severe COVID-19 outcomes [241]. Individuals over age 40 are more likely to experience obesity, diabetes, and hypertension, as evidenced by higher prevalence rates in this age group compared to younger adults [242,243]. Any patient with a positive RT-PCR test result (a COVID-19 "case") with these comorbidities is more likely to experience severe complications due to metabolic and inflammatory dysregulation associated with these comorbidities [244,245]. The predictable result of such an imbalanced age distribution between the injected and infected myocarditis groups in Husby et al.'s study is increased rates of heart failure and deaths among the post-infection myocarditis group.

On a related note, it is difficult to understand why Husby et al., did not exclude younger individuals (aged 12-39) with obesity, diabetes, or compromised immunity. The authors imply that the 47 individuals from this younger age bracket who were hospitalized for COVID-19 were healthy prior to their contracting COVID-19, as they had "no predisposing comorbidities". However, this exclusion did not apply to diabetic, obese, or immune-compromised individuals in this younger age cohort, all of whom would have been at greater risk of severe cardiac events. During the pandemic, younger adults without these comorbidities very rarely died from, or were hospitalized for, COVID-19 [246,247].

As we documented previously, postmortem findings have revealed substantial post-injection cardiac damage, including sudden cardiac arrest and death, following the COVID-19 mRNA vaccines [125,126]. Myocarditis is a leading cause of sudden death in young people, occurring twice as often in males as in females and being especially common among athletes [209,214,248]. A comprehensive study in Germany concluded that premature CAD, SADS, and myocarditis are the three leading causes of sports-related sudden cardiac arrest in younger athletes, ≤ 35 years of age [249]. Given that these high-performing individuals are usually considered to be among the healthiest people in the world, it is difficult to see how their greater risk of experiencing the life-threatening aspects of myocarditis could justify calling this a "mild" condition.

The myocardial damage associated with these vaccines seems to result in sudden death due to the added stress of intensive physical exertion (or exercise intolerance) as a byproduct of the elevated catecholamine levels commonly seen in male athletes and further exacerbated by the mRNA product's components [147]. Biodistribution studies have revealed that the adrenal glands are among the major target sites for accumulation of the SARS-CoV-2 spike protein generated by either the infection or the injection [250,251]. Further amplification of the hypercatecholaminergic state appears to be due to the mRNA-generated spike protein's activity in adrenal chromaffin cells, which overexpresses enzymes driving noradrenaline production and increased myocarditis risk [147]. In the context of this exercise-mRNA interaction, the combination of stress responses and androgen sensitivity may explain the heightened potential for sudden death in male athletes.

In the heavily mRNA-vaccinated nation of Australia, there has been a noteworthy increase in sudden cardiac deaths, particularly in terms of the number of deaths from sudden arrhythmic death syndrome (SADS), which is commonly referred to as "Sudden Adult Death Syndrome". Myocarditis is a well-documented risk factor for SADS due to its potential to cause electrical instability and fatal arrhythmias [252]. A recent study showed that SADS in Australia has increased to 25 (7.2%) in 2018, 26 (7.5%) in 2019, 18 (5.3%) in 2020, 52 (13.2%) in 2021, and 80 (19.4%) in 2022 (p=0.0001) [253]. Thus the largest increases occurred in the years in which the COVID-19 mRNA products were aggressively introduced to the nation on a massive scale. In the most recent Australian study, 98% of the 206 myocarditis cases analyzed were attributed to the mRNA injections (mostly second dose), the remaining 2% of cases being linked with the AstraZeneca adenoviral vector vaccines [254]. The majority of patients presented to emergency departments with clinical symptoms. Among these, 129 individuals (62% of all cases) required hospital admission, including five cases necessitating intensive care and one fatality [254].

The long-term risks associated with COVID-19 mRNA products could potentially contribute to premature mortality. Conditions such as strokes and myocarditis linked to the mRNA vaccines may result in early death, years after the initial onset. Research on stroke outcomes indicates a mortality rate of 28% within the first 28 days, increasing to 41% at one year and 60% at five years [255]. Furthermore, undiagnosed cardiac and clotting disorders may persist silently for extended periods. Upon autopsy, nearly two-thirds of sudden unexplained death cases show non-diagnostic cardiac findings, notably ventricular hypertrophy, coronary atheromatosis, and myocardial fibrosis (scarring) [256]. These findings may serve as precursors or early markers for underlying structural cardiac disorders that had remained undiagnosed during the individual's lifetime. Therefore, what is "mild" in the short term could prove to be a fatal event in the long term.

One factor that may have contributed to the misperception that COVID-related myocarditis tends to be more severe than mRNA vaccine-related myocarditis is the drug known as Remdesivir (brand name, Veklury). This nucleotide analog prodrug inhibits the RNA-dependent RNA polymerase of SARS-CoV-2, thereby interfering with viral replication [257]. Originally proved to be ineffective for the treatment of Ebola, Remdesivir gained EUA status during the pandemic for severe COVID-19 disease after early studies indicated a reduction in recovery time, particularly in patients requiring supplemental oxygen (but not mechanical ventilation) [257]. Remdesivir became the primary COVID-19 drug approved for use in U.S. hospitals, with the U.S. government paying hospitals a 20% bonus incentive for utilizing the Remdesivir protocol [258]. Eventually, however, a controlled clinical trial showed that Remdesivir failed to provide any significant clinical benefit [259]. Part of this failure was due to the drug's poor safety profile and its ability to induce persistent mitochondrial and structural damage in human cardiomyocytes [260]. Clinically,

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Remdesivir can have significant cardiotoxic effects, potentially leading to prolonged QT intervals and torsade de pointes, which in turn can result in ventricular arrhythmias and sudden cardiac arrest [261-263]. The drug was also linked with sinus bradycardia (slow heart rate), which can cause serious complications, notably heart failure and cardiac arrest [263,264]. Remdesivir's cardiotoxic impact may be heightened in patients with pre-existing cardiovascular conditions.

In terms of biological plausibility for the more serious cardiac sequelae, both the synthetic, modified mRNA and mRNA-derived spike protein have been detected in the hearts of individuals who died following the COVID-19 mRNA vaccines and in cases of mRNA vaccine-related myocarditis, respectively [265,266]. In contrast, autopsy findings from individuals who died following SARS-CoV-2 infection suggest that any incidental myocarditis is not associated with direct cardiac infection with the coronavirus [234]. Direct cardiotoxicity of the BNT162b2 and mRNA-1273 injections on rat cardiomyocytes has been observed 48 hours following the injection, resulting in specific pathophysiological dysfunctions associated with cardiomyopathy [267]. No such direct cardiotoxicity has been demonstrated with the SARS-CoV-2 or Omicron variant infections. Therefore, there appears to be a more direct causal pathway between the COVID-19 mRNA vaccines and myocarditis when compared to the coronavirus infections. This reinforces the biological plausibility of our argument that COVID-19 mRNA vaccines are far more likely to cause myocarditis when compared to the SARS-CoV-2 infections.

In conclusion, rare viral myocarditis, pericarditis, and myocarditis can often present with mild clinical symptomology. Acute vaccine-induced myocarditis, presents with acute symptoms, arrhythmias, and heart failure warranting hospitalization. Despite hospitalization, vaccine myocarditis has led to death. Even minimal inflammation or scarring of the cardiac musculature—often indicated by elevated cardiac troponin levels—can predispose young individuals to a lifelong increased risk of heart failure and sudden cardiac arrest. Even cases classified as mild myocarditis may result in persistent cardiovascular complications, including chronic cardiac dysfunction and arrhythmias. Given these potential outcomes, the COVID-19 mRNA vaccine products warrant a black box warning to highlight myocarditis, pericarditis, and myocarditis as potentially life-threatening adverse effects.

Misconception 3. Risk-Benefit Analyses Favor the COVID-19 mRNA "Vaccines"

Vaccination programs, often implemented across large populations, require rigorous risk-benefit assessments to ensure a highly favorable balance of outcomes and justify aggressive public health policies, notably mandates. A key regulatory question for public health authorities is whether the risks of COVID-19 vaccination outweigh the benefits for specific target populations, taking into account pandemic uncertainties such as fluctuations in disease incidence and emergence of new variants. As we have seen, multiple studies identified an increased risk of myopericarditis following the COVID-19 mRNA injections, particularly among young males aged 12–24 years receiving two doses of the Moderna product, mRNA-1273. Risk-benefit analyses should first prioritize modeling within narrow age bands, especially in population subgroups at higher risk for mRNA-associated myocarditis (younger males in particular). Such an approach ensures a sufficient number of myocarditis/pericarditis cases within these groups to generate reliable rate estimates. Published evidence suggests that young males in these subgroups may exhibit a less favorable risk-benefit profile compared to females and older individuals, emphasizing the need for targeted evaluation in regulatory decision-making.

As a basic starting point for our risk-benefit discussion, let us consider Fraiman et al.'s comprehensive re-analysis of registrational trial data. This re-analysis revealed alarming rates of serious AEs, about one for every 800 vaccine recipients (1,250 serious adverse events per million) for the more extensive Pfizer trial [103]. The official serious AE rate for other vaccines is only 1-2 per million, according to U.S. Department of Health & Human Services [268]. The Fraiman et al. findings surpassed this benchmark by over 600-fold, indicating a much greater degree of mRNA vaccine-related harm than had been observed with traditional vaccines. In addition, according to the Fraiman et al. report, data from the Pfizer trial indicated a greater than four-fold higher risk of AEs of special interest following the BNT162b2 injections compared to the risk of COVID-19 hospitalizations (10.1 AEs of special interest vs. 2.3 hospitalizations per 10,000 participants, respectively). Moderna's trial showed more than a two-fold higher risk (15.1 AEs of special interest vs. 6.4 hospitalizations per 10,000 participants, respectively). These findings raise questions about the net benefit of the mRNA vaccines, particularly for populations at low risk of severe COVID-19. While the products may help prevent COVID-19 cases in the short term, the higher-than-expected AE rates emphasize the need for careful consideration of individual risk profiles and transparent communication about potential risks and benefits.

Public health authorities have commonly asserted that the risk of cardiac complications is higher among individuals infected with SARS-CoV-2 than among those receiving the COVID-19 mRNA vaccines. In a previous section ("Misconception #1: Coronavirus infections cause more myocarditis than COVID-19 vaccinations"), we delineated the various erroneous assumptions that underlie this assertion, which are based largely on observational studies that suffer from flawed methodologies and misreporting issues. In contrast, data from rigorously controlled prospective studies evaluating myocardial injury indicate that the incidence of myocarditis following administration of BNT162b2 or mRNA-1273 vaccines in young adults is approximately 2.5% (2,500 per 100,000) after the second or third dose [118,122]. As illustrated in Figure 7, the estimated 2.2% risk of myocarditis among adolescents (ages 13-18) following mRNA vaccination is substantially higher than the 0.06% myocarditis risk associated with SARS-CoV-2 infection in the same age group [269]. The observed disparity in myocarditis risk, with a higher incidence following mRNA vaccines compared to SARS-CoV-2 infections in adolescents, highlights the need to critically reevaluate the ongoing recommendation of COVID-19 mRNA vaccines for this demographic.

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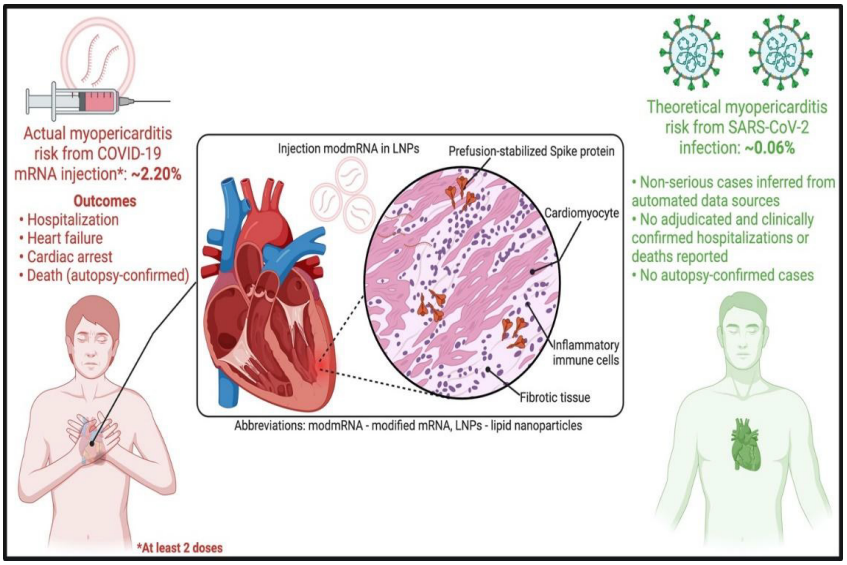

Figure 7. Prospective studies that use clinical testing to detect asymptomatic myocarditis cases provide the most reliable data for assessing myocarditis risk in adolescents, the group at highest risk. Based on this research, the actual risk of myocarditis in these younger mRNA-injected individuals (2.2%) significantly surpasses the theoretical risk of myocarditis in those infected by the wild-type SARS-CoV-2 (0.06%).

The FDA conducted two risk-benefit analyses of primary series mRNA vaccinations: the first by Funk et al. for BNT162b2, the second by Yogurtcu et al. for mRNA-1273 [270,271]. Both studies were based on simulated population-based scenarios, a choice most likely made on the basis of speed †, resource efficiency, and ability to model scenarios in the context of relatively limited real-world data. It is important to note, however, that simulation studies are easily exploited by choosing assumptions, models, and input parameters that align with a particular set of biases and desired outcomes. Uncertainties in key parameters, such as myocarditis incidence, vaccine efficacy, and AE rates, can lead to overly optimistic results. Researcher's intent on validating a public health policy such as mass vaccination would tend to overestimate vaccine efficacy while underestimating myocarditis risks. They would also tend to construct pandemic scenarios that amplify the perceived benefits, such as higher infection rates or more severe outcomes in unvaccinated populations. Sensitivity analyses in this context can be designed to focus on favorable outcomes while downplaying worst-case scenarios. The inherent flexibility and reliance on assumptions in simulation studies make them particularly susceptible to subjective interpretation, enabling (biased) researchers to subtly skew results while maintaining the appearance of scientific rigor.

Such concerns are appropriate to mention in this context given the FDA's long-standing conflicts of interest with respect to the pharmaceutical industry [272,273]. The FDA is a regulatory agency funded by the federal government to oversee the safety and efficacy of medical products, including gene-based prodrugs such as BNT162b2 and mRNA-1273. During the development of the COVID-19 mRNA products, drug companies received substantial funding from U.S. government initiatives. For instance, Moderna was awarded up to $483 million by the Biomedical Advanced Research and Development Authority (BARDA) in April 2020 to accelerate the development of its COVID-19 mRNA candidate [274]. The company then received another $1.53 billion in August 2020 [275]. This funding was part of the government's efforts to expedite the EUA. By the summer of 2020, the U.S. government had already pre-purchased hundreds of millions of mRNA doses, alongside direct financial support for the clinical trials and the expansion of Moderna's manufacturing capabilities [275]. After devoting so much of taxpayers' dollars to financing these projects and accelerating the EUA process, one would expect government agencies such as the FDA to have a strong a priori bias toward favorable risk-benefit conclusions of any analysis of the mRNA products.

For the two FDA risk-benefit analyses, investigators employed a range of modeling scenarios to address uncertainties surrounding pandemic dynamics and vaccination outcomes. To quantify benefits, the agency estimated reductions in COVID-19 cases, hospitalizations, intensive care unit (ICU) admissions, and deaths attributable to vaccination. COVID-19 mRNA vaccine-related risks, including cases of mRNA-attributable myocarditis/pericarditis, along with associated hospitalizations, ICU admissions, and deaths, were also evaluated. The FDA concluded that the benefits of the mRNA vaccines outweighed the risks of mRNA-attributable myocarditis/pericarditis, even among males within the highest-risk age groups: 16-17 years for BNT162b2 and 18-25 years for mRNA-1273.

For example, with regard to the Moderna product, mRNA-1273, Yogurtcu et al., state in their abstract: "Remarkably, we predicted vaccinating one million 18-25 year-old males would prevent 82,484 cases, 4,766 hospitalizations, 1,144 ICU admissions, and 51 deaths due to COVID-19, comparing to 128 vaccine-attributable myocarditis/pericarditis cases, 110 hospitalizations, zero ICU admissions, and zero deaths" [271]. Let us consider the authors' myo-pericarditis "remarkable" estimate of 12.8 cases per 100,000 (0.0128%) mRNA-1273 inoculations (second dose) for younger males in the 18-25 age group. This estimate appears to reflect strong bias, given the published observational study findings for males from this same age group. For example, in a cohort study for Kaiser Permanente, Sharff et al., estimated 53.7 cases per 100,000 doses in males aged 18–24 after the second dose, a fourfold increase compared to the FDA's estimate for simulation purposes [70]. Buchan et al., estimated about 30 cases per 100,000 doses for this same population subgroup after the second mRNA-1273 dose [69].

† In 2020, the development initiatives for Moderna's and Pfizer-BioNTech's products were named Operation Warp Speed and Project Lightspeed, respectively. The names were subsequently changed due to concerns that they might encourage vaccine hesitancy, amplifying the perception that the products were rushed to market without sufficient testing for safety.

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Bourdon et al. reanalyzed the FDA's benefit-risk assessment of Modern's mRNA-1273 product, focusing on males aged 18–25 years and utilizing data available up to the third week of January 2022 [86]. The authors identified notable flaws and limitations in the FDA's analyses, particularly regarding inputs and assumptions for hospitalization benefits and mRNA vaccine-related myocarditis risks. The pivotal flaw was the FDA's exclusion of prior-infection protection, despite ample evidence suggesting it provides significant immunity. To justify this exclusion, FDA cited insufficient understanding (at the time) of prior-infection protection's degree, impact, and time-dependency. However, Bourdon and colleagues noted that the protection conferred by mRNA-1273 vaccination against the Omicron variant was similarly uncertain during the same period. Despite this uncertainty, the FDA assumed the mRNA vaccines would provide 72% effectiveness against hospitalization and 30% effectiveness against cases for at least five months. By contrast, prior-infection protection was assigned zero effectiveness in all Omicron-based scenarios, despite evidence indicating its superiority to vaccine-induced protection for both the Delta and Omicron variants.

Bourdon and colleagues argued that the FDA could have reasonably assumed prior-infection protection to be at least equivalent to vaccine-induced protection, which would have significantly altered the benefit-risk calculations. Moreover, they noted that COVID-19 hospitalization rate for males aged 18-25 was overestimated by equating it with the rate for males aged 18-45. Bourdon et al., criticized the FDA for failing to request CDC data on incidental COVID-19 hospitalizations (hospital admissions where patients tested positive for COVID-19 but were treated for unrelated conditions), disaggregated hospitalization data for age subranges (e.g., 18-25), and age/sex-specific mRNA vaccine-related myocarditis data from the CDC's Vaccine Safety Datalink (VSD) system. These omissions, along with inconsistent use of international data, further undermined the rigor of the FDA's analyses.

Employing the FDA's analytic framework, Bourdon et al., addressed the various limitations mentioned above and enhanced the model by incorporating additional factors: (1) immunity conferred by prior COVID-19 infection; (2) more granular age stratification in COVID-19 hospitalization rates, and (3) the impact of incidental hospitalizations. The analysis also incorporated more realistic estimates of rates of Omicron-variant infection and of mRNA vaccine-related myopericarditis. Using hospitalizations as the primary outcome measure-comparing those prevented by vaccination with those caused by mRNA vaccine-related myopericarditis/pericarditis-Bourdon et al. identified a net harm associated with the vaccines among 18–25-year-old males, except under scenarios involving unrealistically high Omicron infection prevalence.

When comparing their projections with the FDA's "most likely scenario," the benefit-risk ratio projected by Bourdon et al. was 0.67, 60 times lower than the FDA's estimate of 43.33. The authors' reanalysis suggests that, over the FDA's assumed five-month vaccination protection period, the mRNA-1273 injections resulted in 16% to 63% more hospitalizations attributable to myocarditis or pericarditis than hospitalizations prevented due to COVID-19. These conclusions are based on data and assumptions that were available as of January 22, 2022. The FDA's underestimation of risk may have been due, in part, to the agency's reliance on a small internal dataset of 21 second-dose mRNA vaccine-related myocarditis events to estimate mRNA-1273-associated risk, disregarding findings from international regulatory agencies, the VSD, and some of the earlier large-scale observational studies we listed in Table 1.

Krug et al. conducted a comprehensive risk-benefit analysis to evaluate the risk of myo/pericarditis following COVID-19 mRNA vaccines in adolescent boys (aged 12-17), stratified by health status and history of SARS-CoV-2 infection [74]. Using data from VAERS, they identified cases of myo/pericarditis meeting CDC diagnostic criteria. The authors considered various scenarios in their analysis, including sex, prior infection, comorbidities, and variant-specific risks. For adolescent boys without comorbidities, the primary outcomes included: (1) the crude incidence of myo/pericarditis post-vaccination in adolescents aged 12-15 and 16-17 years, and (2) risk-benefit analyses considering variables such as age, sex, comorbidities, SARS-CoV-2 variants (Delta and Omicron), and vaccination history.

Krug et al. identified a total of 253 cases of myo/pericarditis, with 129 cases occurring after the first COVID-19 mRNA dose and 124 after the second dose, of which 86.9% required hospitalization. The incidence of myo/pericarditis per million after the second dose in male adolescents aged 12-15 and 16-17 years was 162.2 and 93.0, respectively. Using a 120-day COVID-19 hospitalization rate as a comparator to vaccination-related risks, Krug et al. estimated that the risk of myo/pericarditis in 12-15-year-old boys without comorbidities after the second mRNA dose was 2.8 times higher than their 120-day risk of COVID-19 hospitalization, while this risk was 1.6 times higher for older boys in the same cohort. During the Delta variant surge, the risk-benefit analysis indicated that primary mRNA series was favorable primarily for non-immune girls with comorbidities. Conversely, for boys with prior SARS-CoV-2 infection and no comorbidities, even a single modRNA dose posed greater risks than benefits, according to international estimates. For boys with comorbidities, COVID-19 hospitalization rates exceeded the risk of myo/pericarditis during periods of moderate to high disease incidence, even when accounting for potential overestimates of hospitalization rates due to incidental admissions [276-279]. During the Omicron wave, the dynamics shifted: a single dose appeared protective for non-immune children, while the second dose did not confer additional benefit at the population level. However, among boys with comorbidities, the 120-day hospitalization risk remained 1.7-3 times higher than the risk of vaccine-associated myo/pericarditis, though these risks were roughly equivalent when adjusted for incidental admissions [74].

To summarize, the five key findings from the Krug et al., risk-benefit analysis were as follows:

- Overall, the risk of myo/pericarditis following the second mRNA dose exceeded the risk of COVID-19 hospitalization during the Delta variant wave after the first dose.
- During Omicron, the additional benefit of a second dose was minimal due to reduced vaccine effectiveness against

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hospitalization.

- The analysis provides grounds for discouraging COVID-19 vaccination in boys aged 12–17 with a history of prior infection.
- For girls, with or without comorbidities, two doses were not beneficial if there was a history of SARS-CoV-2 infection.
- In some estimates, even a single dose was not advantageous for girls in this age group without comorbidities after prior infection.

The study also highlighted that incidental hospitalization rates likely increased during Omicron, even among unvaccinated adolescents, due to the variant's lower intrinsic virulence. As depicted in Figure 5 of the Krug et al. study, surges in disease incidence can elevate hospitalization rates despite reduced severity.

Evidence suggests that previous SARS-CoV-2 infection affords natural-immune protection against hospitalization in children. Data from Qatar, Israel, the United Kingdom, and the United States indicate that prior infection provides at least equivalent protection against severe COVID-19 compared to the COVID-19 mRNA vaccines [280-283]. However, the extent and durability of this protection remain unclear. Before the Omicron wave, seroprevalence in some U.S. regions exceeded 80% with CDC estimates indicating at least 40% among children aged 12-17 [74]. This figure likely increased substantially during the winter of 2021-2022.

If an immunocompetent child or young adult has successfully eliminated or inactivated SARS-CoV-2, whether through mucosal immunity or systemic immune responses, it is less likely that the virus itself could directly contribute to subsequent AEs like myocarditis. The vast majority of infections in young healthy people would likely result in benign outcomes. This assertion is further reinforced by the minuscule, near-zero IFR in children and young adults (0.0003% at 0-19 years, 0.002% at 20-29 years) [284]. In Sweden, 1.8 million children were allowed to freely attend school in 2020, and yet there were zero "COVID-19 deaths" in this pediatric population by summer of 2021 [285]. Intriguingly, in countries that showed excess mortality in 2020, mortality rates among children and young adults were extremely low [286]. For individuals under age 40, SARS-CoV-2 infection severity and fatality rates beginning in 2020 were comparable to those of influenza [287].

The biological basis for infection-induced immune protection against COVID-19 is well established. Following recovery from COVID-19, the immune system retains long-lived memory cells, suggesting a durable capacity to respond to subsequent infections, potentially lasting for several years [288]. Evidence indicates that repeated exposure to SARS-CoV-2, particularly through natural infection with the Omicron variant, enhances antibody affinity maturation and T-cell memory, thereby contributing to improved mitigation of future infections [289,290]. A recent cohort study demonstrated that children with prior SARS-CoV-2 infection exhibited sustained protection against reinfection for at least 18 months [291]. Specifically, children aged 5-11 years maintained stable levels of protection throughout the study period, whereas adolescents aged 12-18 years experienced a modest but measurable decline over time. These findings suggest that natural immunity, particularly in younger populations, provides robust and durable protection, potentially with a more favorable safety profile compared to modRNA-based products. In terms of COVID-19 risk, as noted earlier, younger men and women in 2021-2022 had an extremely low IFR, ranging from 0.0003% at <19 years, to 0.035% at 40-49 years [284]. This IFR approaches absolute zero with the more recent Omicron variants. In contrast, there is substantial evidence highlighting a concerning prevalence and incidence of cardiac injury in younger populations following the injections-injuries that could translate into premature death in both the short and long terms [15,16,292-294].

With the implementation of "vaccine mandates" in the U.S. university setting, the exposure of millions of young adults to the experimental COVID-19 mRNA vaccines resulted in a unique research opportunity from a risk-benefit perspective. Bardosh et al., estimated that the implementation of bivalent booster mandates in universities may result in a net harm for younger adults, projecting at least 18.5 serious adverse events for every COVID-19 hospitalization averted [295]. This projection includes an estimated 1.5 to 4.6 cases of booster-associated myocarditis in males, often necessitating hospitalization. In this section, we have therefore presented several risk-benefit analyses of the COVID-19 mRNA products based on data from real-world populations indicating the potential risks outweigh the benefits for younger populations. Although the majority of published risk-benefit analyses to date present a favorable assessment for the COVID-19 mRNA products, we found most of these analyses to be inadequate.

Perhaps the most important example is the "benefit-risk assessment framework" created by Wallace and colleagues, which was used to inform the Advisory Committee for Immunization Practices (ACIP) COVID-19 vaccine policy decisions [296]. The authors used the framework to inform seven different ACIP policy decisions, asserting that the framework "allowed for rapid and direct comparison of the benefits and potential harms of vaccination, which may be helpful in informing other vaccine policy decisions." For their analysis, Wallace et al., estimated mRNA vaccine-related myocarditis risk using VAERS data. Cases of myocarditis with symptom onset within seven days post-vaccination were identified and cross-referenced with mRNA dose data from the CDC repository. Reports of myocarditis among individuals under 30 years of age were reviewed and validated by the CDC to confirm adherence to a standardized case definition. The risk was quantified as the number of cases per million doses administered, stratified by age, sex, and dose number. As expected, Wallace et al., observed the highest incidence of myocarditis following the second mRNA dose, particularly among young males aged 12-29 years. Nevertheless, in the "benefits" side, the authors also made some highly optimistic projections: For every 1 million second doses of mRNA administered to males aged 12-29 years, the vaccines were projected to prevent 11,000 COVID-19 cases, 560 hospitalizations, 138 intensive care unit admissions, and six deaths, compared with an expected 39-47 cases of myocarditis.

Based on the Wallace et al., report, the ACIP concluded on June 23, 2021 that the benefits of COVID-19 mRNA vaccination

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outweighed the risk of myocarditis across all demographic groups analyzed. However, the risk-benefit balance varied by age and sex, reflecting the predominance of myocarditis cases in males under 30 years and the increasing risk of severe outcomes from COVID-19 with advancing age. More importantly, due to smaller sample sizes and limited case counts, the VSD was unable to analyze narrower age groups as in the VAERS data. Instead, broader age group rates in the VSD were compared with VAERS findings to evaluate concordance between the two surveillance systems. As we noted previously, the use of VAERS, a passive surveillance system, may greatly underreport myocarditis cases (by a factor of 56; see our previous calculation of VAERS underreporting, in the section, "Warning Signs from Diverse Epidemiological Sources"), potentially missing milder, subclinical or undiagnosed cases. The less granular analysis necessitated by broader age groupings in the VSD likely masked age-specific variations in risk, particularly in younger males, where the myocarditis incidence was highest. Together, these factors probably resulted in Wallace et al.'s substantial underestimation of the true myocarditis risk following mRNA COVID-19 vaccines.

Lastly, as alluded to before, many of the published risk-benefit studies are fraught with conflicts of interest. For example, the risk-benefit analysis by Shiri et al., was funded by Moderna, and two of the authors were Moderna employees [297]. Many of the observational studies cited in this review have suffered from conflicts of interest as well, including Stowe et al., which states: "The authors have declared that no competing interests exist." However, three of the four authors work for the United Kingdom (UK) Health Security Agency. Similarly, the study by Patone et al. was funded by the UK government, which may have influenced the authors' choice not to provide post-vaccination myocarditis incidence rates for males at highest risk, e.g., those 16-24 years old. Instead, despite the large size of the authors' study population (≥ 42.8 million), males under 40 constitute Patone et al.'s group at highest risk of mRNA vaccine-related myocarditis. A more striking example is the PCORNet analysis of data from over 15 million patients across 40 healthcare systems, concluding that young males face a 1.8 to 5.6 times greater risk of adverse cardiac events, including myopericarditis, following COVID-19 infection compared to the risk after a second mRNA dose [298]. The study was published in the *Morbidity and Mortality Weekly Report*, a CDC publication that does not adhere to the external peer-review process used by academic journals. Several of the authors have strong ties to multiple drug companies, including Pfizer and Janssen. Moreover, 10 of the authors have professional relationships with the CDC's COVID-19 Emergency Response Team. This entity drives the mass vaccination program by strategizing distribution and promoting access and public trust in the COVID-19 mRNA products. With such extensive conflicts of interest and lack of peer review, it is difficult to consider the authors' risk-benefit claim to be valid. (We omitted most papers with strong conflicts of interest in making our selections for this review).

A qualitative assessment of the risk-benefit profile of the Moderna product, mRNA-1273, highlights contrasting outcomes and concerns. Large observational and passive surveillance studies have reported a higher incidence of clinical myocarditis-associated hospitalizations with mRNA-1273 compared to BNT162b2 [68,123,299,300]. However, data from observational studies indicates that mRNA-1273 induces stronger immunogenicity and may afford greater protection against COVID-19 relative to BNT162b2 [286,301]. Is the added protection truly necessary for relatively healthy, younger segments of the population? The answer is most likely no, particularly since the increased immunogenicity of the mRNA-1273 is itself associated with more adverse impacts. More specifically, the enhanced humoral response induced by mRNA injections (both mRNA-1273 and BNT162b2), characterized by elevated antibody titers, has been associated with an increased risk of immunopathology, heightened reactogenicity, and a range of AEs [302-310]. For younger age groups, the additional protection against COVID-19 theoretically afforded by mRNA-1273 may not translate into a real benefit, given their lower baseline risk of severe disease and hospitalization. In this demographic, the elevated risk of mRNA-attributable myocarditis becomes a far more significant concern, outweighing the theoretical increment in protection.

There is yet another qualitative reason why the risk-benefit calculus is highly unfavorable for the COVID-19 mRNA vaccines in the younger segment of the population. This relates to the fact that myocarditis incidence shows a very different pattern in patients with COVID-19, exponentially increasing with age [311]. The logical basis for this age-related relationship is that older adults are more likely to experience severe systemic inflammation, immune dysfunction (along with higher viral loads), and pre-existing comorbidities, notably diabetes and hypertension [242,312]. All of these factors predispose these older individuals to both COVID-19 and cardiovascular complications, including myocarditis [241]. Conversely, younger individuals are less likely to experience myocarditis from COVID-19 itself except in the rare situation of severe COVID-19 [311]. At the same time, as we documented earlier, mRNA vaccine-related myocarditis incidence is markedly higher in these younger age groups. Given the low risk of severe COVID-19 and COVID-related myocarditis in younger individuals, the markedly higher incidence of mRNA vaccine-related myocarditis strongly undermines the justification for continuing these vaccinations in this age group. For the younger segment of the population in particular, this risk-benefit perspective supports a firm non-use policy along with reasonable risk-reducing alternatives such as vitamin D supplementation and lifestyle habits conducive to stronger immunocompetence.

Note: The effects of age and gender on the occurrence of clinically suspected myocarditis showed a different demographic pattern prior to the COVID-19 era. Male patients were notably younger than female patients, with an average age of 34.1±15.1 years compared to 49.0±18.7 years ($p<0.0001$) [313]. Among males, the highest incidence occurred between 16 and 20 years of age, followed by a steady decline with increasing age ($r=-0.95$, $p<0.0001$). In contrast, myocarditis in females was more evenly distributed across all age groups, with the peak incidence observed between 56 and 60 years. This distribution among males and females may have led to the assumption that myocarditis always tends to occur more primarily among younger males. The pattern shifted markedly in the context of COVID-19, perhaps in part due to differing diagnostic criteria

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pre- and post-2020. As discussed under Misconception #1, there is ample reason to suggest that viral myocarditis has been overdiagnosed and often misclassified since 2020.

To summarize, two important risk-benefit analyses indicate an unfavorable risk-benefit calculus for the COVID-19 mRNA products. Bourdon and colleagues demonstrated that extending the FDA's risk-benefit model to include prior-infection protection, incidental hospitalizations, and evidence-based assumptions reversed the conclusion that the mRNA-1273 injections provided overwhelming benefit to males aged 18-25 years [86]. Instead, the Bourdon et al. reanalysis revealed that vaccination posed an excessive risk of hospitalizations for mRNA vaccine-related myocarditis in this demographic. The failure of the FDA's analysis to account for these critical factors contributed to guidelines that disproportionately placed certain subgroups at increased risk of serious adverse cardiac outcomes. While the absolute differences in risk were small, the implications for public health policy and institutional accountability are substantial. Similarly, Krug et al. estimated that the risk of myo/pericarditis following the second mRNA dose exceeded the risk of COVID-19 hospitalization during the Delta variant wave after the first dose. The myo/pericarditis risk in 12–15-year-old boys without comorbidities after the second mRNA dose was nearly 3 times higher than their 120-day risk of COVID-19 hospitalization; this risk was nearly twice as high for older boys in the same cohort. The precautionary principle dictates that when any medical product is distributed on a population-wide basis and demonstrates an unfavorable risk-benefit balance, it should be seriously reconsidered and/or removed from the market to prevent further harm. This approach prioritizes safety, acknowledging that the burden of proof lies in demonstrating its safety and efficacy rather than waiting for additional harms to manifest.

Discussion

This narrative review has presented diverse evidence and perspectives highlighting the relatively large contribution of COVID-19 mRNA vaccinations to elevated myocarditis rates during the COVID-19 pandemic. Various sources of epidemiological and clinical data collectively highlight an emerging pattern suggesting that the risks of myopericarditis (either specifically defined myocarditis or pericarditis or most often both conditions) associated with COVID-19 vaccination were significantly underreported and/ or underestimated by regulatory agencies due to the lack of large-scale prospective cohort studies with baseline and post vaccination assessments (history, ECG, laboratories, cardiac imaging).

Figure 8 depicts the pathophysiology, risk factors, and misconceptions surrounding myocarditis following COVID-19 mRNA-based vaccinations. In terms of pathophysiology (top-left panel), the myocarditis induced by modified mRNA vaccines is marked by the infiltration of inflammatory immune cells, cardiomyocyte damage, and the presence of fibrotic tissue. The lipid nanoparticle (LNP)-encapsulated modified mRNA is delivered into cells, leading to the production of prefusion-stabilized spike protein, which may contribute to immune-mediated myocardial injury. In terms of the high-risk groups (top-right panel), young males (ages 12–24) are at greatest risk of developing myocarditis post-vaccination, with rates up to seven times higher than their female counterparts. Contributing to this elevated risk are inflammatory and hormonal factors, vaccine type-and dose-related effects, and genetic/immune predisposition. Next, in terms of clinical outcomes (bottom-left panel), we synopsize key statistics on post-vaccine myocarditis. Finally, we list and debunk the key misconceptions (bottom-right panel) regarding myocarditis and COVID-19 mRNA vaccinations.

Epidemiological observations

The founding clinical trials and postmarketing surveillance studies provided the first compelling evidence of a signal for serious cardiac events. Prospective cardiac studies subsequently identified subtle myocardial changes post-injection, even without overt symptoms. Autopsy findings provide direct pathological evidence of fatal mRNA- and Spike protein-related heart inflammation inflammation. Military health system data reveal statistically significant increases in myocarditis cases following the vaccines. Life insurance company analyses show excess mortality trends correlating with the mass vaccination campaigns. VAERS data, despite passive reporting limitations, consistently report elevated myopericarditis cases, particularly in young males after successive doses. Case reports and athletic monitoring offer real-world examples of severe cardiac events following the COVID-19 mRNA vaccines.

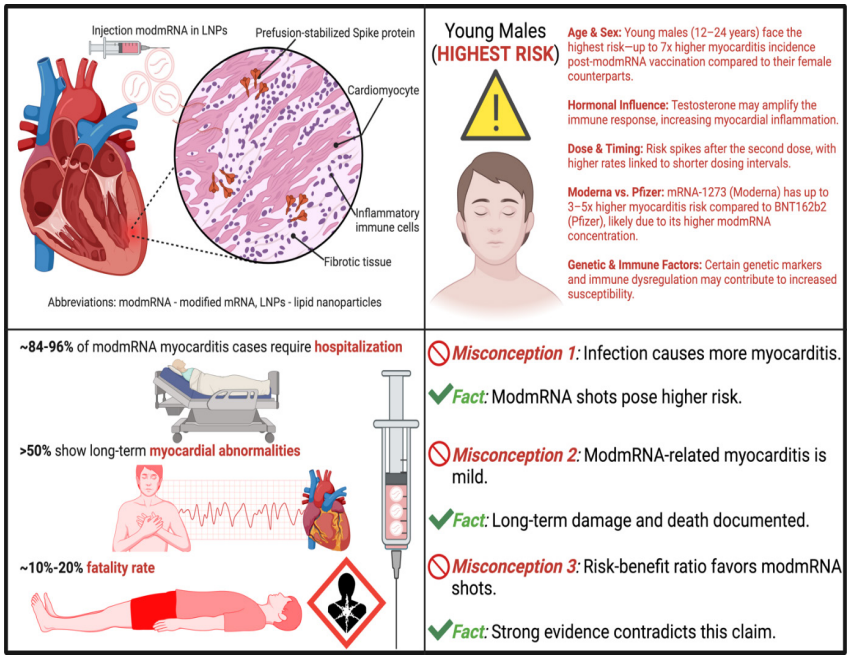

Figure 8. Myocarditis and COVID-19 mRNA-Based Vaccinations: Risks, Misconceptions, and Revelations. This figure illustrates the pathophysiology, risk factors, and misconceptions surrounding myocarditis following COVID-19 mRNA-based vaccinations. See text for details.

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Most of the post-marketing studies of the COVID-19 mRNA vaccines in younger individuals (notably adolescents) did not conduct multivariable adjusted analyses to evaluate the specific myocarditis risks associated with these products. Studies that do not stratify by age and gender are unable to adequately assess risk in adolescent males, the segment of the population known to be at greatest risk. Ideally, more prospective studies such as the Mansanguan et al. study would be conducted, with long-term follow-up observations. Such studies, utilizing a combination of cardiac imaging and biomarkers, provide a reliable method of detecting subclinical myocarditis. Large-scale surveys passive surveillance are wholly inadequate. Any large scale study that examines the effect of COVID-19 mRNA vaccines on myocarditis must take into account age, gender, number of doses (second dose being most important), and specific "vaccine" type, with the Moderna product, mRNA-1273, having the strongest adverse impact.

For hospitalized acute COVID-19, it is possible that Remdesivir contributed to myocarditis. Remdesivir-induced mitochondrial and structural damage observed in human cardiomyocytes could theoretically result in myocardial inflammation, fibrosis, and dysfunction [260]. Given its controversial safety profile and widespread use during the pandemic, it is reasonable to speculate that overuse of Remdesivir within the heavily incentivized U.S. hospital system may have been responsible in part for elevations is cardiac troponin and serious cardiac events in the context of COVID-19, thus reinforcing the misconception that the coronavirus infection was causing more cases.

The claim that SARS-CoV-2 infection causes more myocarditis than the COVID-19 mRNA vaccines lacks robust evidence and is largely based on biased and flawed research methodologies. As discussed earlier, reliance on ICD-10 coding and troponin levels in hospitalized patients has led to widespread misclassification of infection-related myocarditis. Autopsy studies of fatal COVID-19 cases have failed to detect direct viral damage to the heart, further challenging the accuracy of these diagnoses. Amid the pandemic, the Myocarditis Research Foundation, in collaboration with the Helix Research Network, launched a study ostensibly exploring myocarditis after infection or mRNA vaccines [314]. However, its methodology is deeply flawed, relying on ICD-10 codes, unequal post-exposure recruitment windows (14 days after injection versus 8 weeks after infection), and a lack of clinical confirmation or independent adjudication. This, combined with a focus on genetic predisposition without measuring mRNA or spike protein levels, perpetuates a narrative of vaccine safety while diverting attention from vaccine-associated increases in myocarditis, heart failure, and cardiac arrest. These methodological issues, coupled with inflated "infection-related myocarditis" numbers during COVID-19, underscore the need for rigorous clinical confirmation in assessing myocarditis prevalence and incidence.

These and many other major methodological flaws have led to incorrect assumptions that SARS-CoV-2 infection, rather than recent COVID-19 mRNA injection, was the primary cause. Additional issues, including lack of stratification, over-reliance on PCR testing, and failure to detect subclinical myocarditis in large studies, have further reinforced the erroneous view that coronavirus infection outweighs mRNA vaccination as a determinant of myocarditis. Ideally prospective cohort studies should have implemented precise patient classification methods, ensured equal and extended observation periods, and incorporated comprehensive clinical adjudication using physical examination, electrocardiography (ECG), blood biomarkers, and cardiac imaging. Reliance solely on automated, simulated data sources for comparative analyses is inadvisable, as this approach is prone to investigator bias and may produce misleading conclusions.

Despite these facts, published reviews, editorials and commentaries on myocarditis during the COVID-19 era continue to assert that the condition is more strongly associated with SARS-CoV-2 infection than with the COVID-19 mRNA vaccines. This assertion has been used to justify ongoing mRNA vaccines despite myocarditis being recognized as a safety signal by many authorities. This claim has received the bulk of its reinforcement from the passive surveillance data primarily managed by the CDC. The propagation of this narrative helped crystallize the public health assertion that SARS-CoV-2 infection was responsible for more cases of myocarditis than the COVID-19 mRNA vaccinations.

COVID-19 mRNA-associated risk estimates for myocarditis use well-defined denominators, often the total numbers of injected individuals, ensuring an accurate measure of exposure. In contrast, the infection risk denominator typically represents a subset, not the full infected population. Additionally, surveillance biases differ: infections are often identified reactively (e.g., symptomatic individuals seeking testing), while mRNA vaccine-related AEs are systematically monitored post-injection. These divergent methodologies make direct comparisons inherently flawed. Stowe et al.'s assertion that "the attributable risk estimates for COVID-19 used laboratory confirmed cases as the denominator and will be affected by the proportion of all SARS-CoV-2 infections captured by testing, precluding a direct comparison with vaccine-associated attributable risks," underscores the importance of contextualizing attributable risk estimates within their methodological frameworks [71].

Individuals with mildly symptomatic COVID-19 are less likely to seek testing, especially outside structured surveillance studies. This bias inflates the observed incidence rate of myocarditis per detected infection because the denominator (total infections) underrepresents the true infection burden, while the numerator (hospitalized myocarditis cases) remains accurate. Seroprevalence studies have consistently shown far higher infection rates than routine testing data suggest, and the true infection-to-case ratio could be at least two- to four-fold higher [86,315,316]. The observed incidence reflects a subset of infections skewed toward higher severity, making it an overestimate when extrapolated to all SARS-CoV-2 infections in the community. (Moreover, based on the previously mentioned ONS data, it is reasonable to assume that well over 50% of Stowe et al.'s study population, which is similar to that of the Patone al. study described below, became infected during the study period. Based on positive-test numbers reported at the bottom of Table 4 of Stowe paper, this would suggest the number of infections is at least twice the number of positive tests.) Accurate comparisons

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would require infection risk estimates based on seroprevalence data, reflecting the total infected population, rather than laboratory-confirmed cases alone [71].

Biological Plausibility of COVID-19 Vaccine-Related Cardiac Events

Initially, the administration of COVID-19 mRNA products was based on the assertion that the synthetic mRNA, encapsulated within the lipid nanoparticle (LNP) vehicle, would remain localized at the site of injection in the deltoid muscle. However, subsequent biodistribution studies contradicted this claim, revealing widespread distribution of the mRNA throughout the body, followed by systemic production of the spike protein [317]. Once spike protein enters the bloodstream, it circulates systemically and can persist for 6-8 months (187-245 days) post-injection [318,319]. This persistence was enabled during the development of the Pfizer and Moderna mRNA products by the replacement of uridine nitrogen bases with N1-methylpseudouridine, a less immunogenic but more stable nitrogen base [320].

While the extended half-life of this pseudouridinated mRNA in the body was originally seen as a benefit, given that the technology was intended to deliver immunogenic proteins, it has become clear that the injected mRNA may also convert transfected cells into "viral protein factories" without an inherent mechanism to halt or regulate this ongoing production. As a result, spike protein can be continually produced, circulating in the body for extended periods, contributing to chronic, systemic inflammation, immune dysregulation, and diverse immune-related pathologies [94,321-326]. Spike protein has been associated with chronic inflammation and damage in organs such as the heart, liver, spleen, ovaries, and nervous system [266,321,327-330]. Several single nucleotide polymorphisms have been identified that may predispose individuals to adverse events following the COVID-19 mRNA vaccines, and these same genetic variants have been associated with autoimmune diseases and several cancer types as well [66].

The release of inflammatory cytokines, such as interleukin-6 and interleukin-1β, has been associated with the COVID-19 mRNA vaccine-related AEs, including the emergence of new-onset autoimmune-inflammatory diseases [331-333]. The autoimmune effects of the mRNA-generated spike protein may be due to molecular mimicry with human proteins [321,326]. These observations may explain the emergence of long-term serious AEs linked to the mRNA vaccines, some of which have only recently been recognized and characterized [334].

One significant concern regarding the extended systemic presence of the mRNA is the use of N1-methylpseudouridine to help stabilize the mRNA sequences. This modification has been shown to enhance error rates during reverse transcription, potentially leading to harmful genetic alterations [335]. Even minor transcriptional errors may have serious biological consequences, and when these effects are amplified across a large population, the results could be disastrous. Additionally, the manufacturing process has been shown to introduce billions of bacterial DNA fragments into each dose of COVID-19 mRNA vaccine [98,99]. Recent data reveal that the Pfizer mRNA product, Comirnaty, contains DNA impurities that surpass the permitted threshold by several hundred times, and in some instances, by over 500-fold [336]. The DNA impurities are integrated into the lipid nanoparticles and directly transported along with the mRNA into the cells of the vaccine recipient. The most serious concern that arises from such impurities, is the possibility that this could lead to integration of the bacterial DNA into the human genome via insertional mutagenesis. Such genetic disruptions could theoretically trigger immune dysregulation and autoimmune responses, potentially prompting the production of circulating heart-reactive autoantibodies to target the cardiomyocytes, resulting in cardiac muscle inflammation and damage [5,322].

Several mechanisms have been proposed to explain the association between COVID-19 mRNA vaccines and myocarditis. Some hypotheses include an aberrant immune or hyperimmune response to the spike protein produced by the mRNA, molecular mimicry, or direct inflammatory stimulation by the vaccine components [194,321,322]. The hyperimmune or inflammatory response hypothesis raises the question of whether the condition arises from a systemic inflammatory process or is confined to the myocardium. While systemic inflammation often results in multi-organ injury, myocarditis associated with mRNA vaccines is more likely an isolated cardiac phenomenon [26]. This is supported by the predominant presentation of chest pain, along with measurable changes in cardiac biomarkers and imaging findings. Among the proposed mechanisms, autoimmunity-potentially triggered by molecular mimicry or other pathways-has been widely discussed. However, the typical onset of symptoms within one to five days following the second vaccine dose is considered too rapid to be explained solely by autoimmune mechanisms. An allergic or hyperergic (hyperimmune) mechanism may underlie the occurrence of acute myocardial infarction shortly after mRNA administration. The phenomenon, referred to as Kounis syndrome, has been documented in the context of acute coronary syndrome triggered by allergic reactions to foods, medications, or environmental agents [337]. A case of Kounis syndrome and "hypersensitivity myocarditis" following COVID-19 mRNA vaccines has also been reported in the literature [338].

If myocarditis following mRNA vaccines results from exposure to partial antigens, such as epitopes of the SARS-CoV-2 spike protein, this pathway would also need to account for myocarditis occurring after SARS-CoV-2 infection [26]. The potential interaction between mRNA injection and subsequent infection was mentioned earlier in this paper. (Note: COVID-19 mRNA-induced myocarditis is associated with isolated spike protein presence without nucleocapsid protein, as the mRNA products encode only the spike protein. In contrast, SARS-CoV-2 infection induces the presence of both spike and nucleocapsid proteins in the bloodstream).

In terms of the pathogenesis of myocarditis, the biological plausibility for a causal link between the COVID-19 mRNA vaccines and adverse effects is now well-supported by several key findings:

- Spike protein and active inflammation were observed in

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biopsied myocardial samples from young individuals hospitalized with mRNA vaccine-related myocarditis [266].
- COVID-19 mRNA was found in the heart at autopsy up to 30 days post-injection [265]. In principle, the mRNA could have resulted in ongoing spike protein production, along with the associated inflammatory effects.
- Spike protein has been detected in circulation in young adults who developed myocarditis following a COVID-19 mRNA injection, but not in those injected individuals who did not develop myocarditis (suggesting susceptibility based on an immunologic inability to remove spike protein from the blood) [339].

Recent *in vivo* animal studies have shown that both mRNA-1273 and BNT162b2 induce specific dysfunctions in isolated cardiomyocytes, which are pathophysiologically linked to cardiomyopathy [267]. Direct cardiotoxic effects of the Pfizer and Moderna mRNA vaccines on rat cardiomyocytes were observed 48 hours post-injection, showing dysfunctions linked to cardiomyopathy. This suggests that cardiomyocytes are not exempt from the biodistribution of lipid nanoparticle-modified mRNA, and thus, each new mRNA product may pose the risk of severe heart issues, such as cardiomyopathy and cardiac arrest. Among the more plausible cardiotoxic mechanisms is the downregulation of the angiotensin-converting enzyme 2 (ACE2) receptor following spike protein binding. This can result in unopposed ACE activity, leading to elevated angiotensin-2 levels, inflammation, and apoptosis of cardiac cells [340]. Angiotensin-2 elevation contributes to inflammation and oxidative stress, both of which are critical in the development of cardiomyopathy [341].

Finally, the aforementioned immunological impacts of repeated COVID-19 mRNA vaccines, notably T-cell exhaustion and the IgG4 antibody class switch, may also be linked to various adverse cardiac events via autoimmunity. This raises concerns that the policy of ongoing boosters may contribute to the increases in autoimmune-inflammatory processes that help fuel the pathogenesis of mRNA vaccine-related myocarditis, pericarditis, heart failure, and other serious cardiac events.

In summary, myocarditis following COVID-19 mRNA vaccination has been linked to several potential immunopathogenic mechanisms. A key consideration is whether the condition arises from a systemic inflammatory response or remains confined to the myocardium. Unlike systemic inflammation, which typically involves multi-organ injury, mRNA vaccine-related myocarditis predominantly presents as isolated cardiac inflammation, evidenced by chest pain, elevated cardiac biomarkers, and characteristic imaging findings. Autoimmunity, particularly through molecular mimicry, has been proposed as a mechanism; however, the rapid onset of symptoms within one to five days post-vaccination suggests that autoimmunity alone is unlikely to be the primary driver [26]. An alternative hypothesis implicates immune activation by SARS-CoV-2 spike protein epitopes present in both the mRNA product and the coronavirus, raising the question of whether myocarditis following the infection and mRNA injection shares a common antigenic trigger. This has implications for mRNA product safety and the various cardiac sequelae.

Conclusions

Myocarditis remains one of the most significant cardiac adverse events linked to the COVID-19 mRNA vaccines manufactured by Pfizer and Moderna. This review critically evaluated the relationship between mRNA vaccines and myocarditis using evidence from reanalyses of clinical trials, postmarketing data, prospective cardiac-monitoring studies, and large observational studies. Despite consistent safety signals showing a relatively high risk of myocarditis and its sequelae in younger age groups, public health authorities have defended the continued use of these products with claims that myocarditis from SARS-CoV-2 infections, including Omicron, is more frequent; that vaccine-related myocarditis is rare, mild, and transient (without long term sequelae); and that the benefits outweigh the risks. However, our critique, grounded in epidemiological, clinical, and immunological evidence, challenges these assertions. The combination of low risk of severe COVID-19 and a higher likelihood of mRNA vaccine-related myocarditis in younger people makes it difficult to rationalize a policy of ongoing mRNA vaccines in this population.

The theoretical absolute benefit of COVID-19 mRNA vaccination is largely contingent on an individual's baseline risk of severe COVID-19 disease, prior natural immunity, current SARS-CoV-2 and access to early ambulatory treatment protocols. For healthy individuals under the age of 20, 30, or 40, the upper bound of absolute benefits has consistently been negligible across all strains, often approaching zero. Furthermore, no robust studies to date have reliably established a benefit of the COVID-19 vaccination in infants, children and young adults. Even relatively rare safety signals (on a population-wide basis) can substantially alter the overall risk-benefit analysis in younger populations. The analyses by Krug et al., and Bourdon et al., both substantiate an unfavorable risk-benefit calculus. Specifically, for young males, the risk associated with COVID-19 mRNA vaccine-related myocarditis following the second dose exceeds the potential upper-bound reduction in severe COVID-19 outcomes. This underscores the critical need for age- and risk-stratified evaluations to better inform public health policy and to ensure that the harms do not consistently outweigh the theoretical benefits. Given the substantial evidence presented here concerning cardiotoxicity and serious cardiac events in younger generations, we strongly recommend the immediate withdrawal of COVID-19 mRNA products from the market.

Disclosure statement

The authors declare that they have no competing interests.

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