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Determinants of COVID-19 vaccine-induced myocarditis

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Abstract

Background: Following the roll-out of the Pfizer-BioNTech BNT162b2, Moderna mRNA-1273, and Janssen Ad26.COV2.S coronavirus disease 2019 (COVID-19) injections in the United States, millions of individuals have reported adverse events (AEs) using the vaccine adverse events reports system (VAERS). The objective of this analysis is to describe the myocarditis data in VAERS and the COVID-19 vaccines as potential determinants of myocarditis.

Methods: We used VAERS data to examine the frequency of reporting myocarditis since the beginning of the mass vaccination campaign and compared this with historical values in VAERS and COVID-19 vaccine administration data from the Our World in Data database. We examined myocarditis reports in VAERS in the context of sex, age, and dose. Statistical analysis was done using the Student's *t*-test to determine statistically significant differences between ages among myocarditis adverse events (AEs) and the chi-square test to determine relationships between categorical variables with statistical significance.

Results: We found the number of myocarditis reports in VAERS after COVID-19 vaccination in 2021 was 223 times higher than the average of all vaccines combined for the past 30 years. This represented a 2500% increase in the absolute number of reports in the first year of the campaign when comparing historical values prior to 2021. Demographic data revealed that myocarditis occurred most in youths (50%) and males (69%). A total of 76% of cases resulted in emergency care and hospitalization. Of the total myocarditis reports, 92 individuals died (3%). Myocarditis was more likely after dose 2 ($p < 0.00001$) and individuals less than 30 years of age were more likely than individuals older than 30 to acquire myocarditis ($p < 0.00001$).

Conclusion: COVID-19 vaccination is strongly associated with a serious adverse safety signal of myocarditis, particularly in children and young adults resulting in hospitalization and death. Further investigation into the underlying mechanisms of COVID-19 vaccine-induced myocarditis is imperative to create effective mitigation strategies and ensure the safety of COVID-19 vaccination programs across populations.

Plain language summary

Using VAERS to understand myocarditis associated with COVID-19 vaccination

Why was the study done? Heart inflammation, known as myocarditis, has been previously associated with COVID-19 vaccination. After the Pfizer-BioNTech, Moderna, and Janssen COVID-19 vaccines were given in the United States, millions of people reported side effects, including myocarditis, using a system called the Vaccine Adverse Event Reporting System (VAERS). Therefore, the researchers sought to further investigate possible links between COVID-19 vaccination and myocarditis using VAERS.

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What did the researchers do? The researchers used VAERS to check the frequency of myocarditis reports after COVID-19 vaccination and compared this with past reports from other vaccines over the years. They also studied details such as the age and gender of those affected, and which dose of the vaccine they had received.

What did the researchers find? In 2021, there was a dramatic increase in the number of myocarditis reports linked to the COVID-19 vaccine, far higher than the reports from all other vaccines combined over the previous 30 years. This side effect was mostly reported in young individuals, especially males. Most of those who reported myocarditis needed emergency medical care or had to be hospitalized. Out of those affected, 92 individuals died. Myocarditis was more likely following a second dose of vaccine. Furthermore, individuals under the age of 30 were more prone to acquire myocarditis from COVID-19 vaccination compared to those aged 30 and above.

What do the findings mean? The researchers found a strong link between COVID-19 vaccination and myocarditis, especially in kids and young adults. This can lead to hospital stays and, in some cases, death. We need to study more about how the COVID-19 vaccine might cause heart inflammation to find ways to prevent it and make sure the vaccine is safe for continued use in all age groups.

Keywords: adverse events, COVID-19 vaccine, death, mortality, myocarditis, SARS-CoV-2, serious adverse events, VAERS

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Introduction

Myocarditis is inflammation of the myocardium or 'musculature' of the heart.[1,2] The myocardium is made up of many cell types; however, the greatest mass of tissue is accounted for by cardiomyocytes.[3,4] Cardiomyocytes are the principal contractile cells and are supported by specialized conduction and stromal cell types including cardiac pericytes.[5] All of these cell types can be damaged by inflammation.[6]

Myocarditis can manifest as chest pain, heart failure, or sudden death.[1,2,7–11] Myocarditis is a major risk for cardiac death among the young.[12] The high-risk age population for myocarditis is from puberty through the early 30s, and it is the third leading cause of sudden cardiac death in children and young adults. Four per million children every year were affected by myocarditis before the pandemic.[13] It has been reported that 0.05% of all pediatric hospitalizations are for myocarditis. Most cases of myocarditis are identified in young adults with males affected more often than females.[9,12,14] Multiple vaccines have been associated with myocarditis in the past including influenza and smallpox.[15]

Cases of myocarditis have been reported after Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection before the advent of coronavirus disease 2019 (COVID-19) vaccines.[16,17] In the context of COVID-19 critical illness, multiple studies have reported cardiac injury defined by clusters of International Classification of Diseases (ICD) codes related to cardiac troponin measurement.[18–20] None of these reports used clinical adjudication in addition to troponin levels or ICD codes with physician review of symptoms, electrocardiogram (ECG/EKG), echocardiography, cardiac magnetic resonance imaging (MRI), and clinical symptoms.

COVID-19 vaccine-induced myocarditis can be defined as the onset of clinical myocarditis that is temporally associated with COVID-19 mRNA or adenoviral DNA vaccine administration and in the absence of another known cause. Common clinical symptoms after vaccination include chest pain,

palpitations, and effort intolerance.[21] Thus, the clinical diagnosis calls for characteristic symptoms of cardiac arrest, elevated troponin levels, ECG changes (diffuse ST-segment elevation), and in some cases left and right ventricular dysfunction on echocardiography. In cases where the diagnosis is not secure, cardiac MRI can detect changes in tissue characterization (late gadolinium enhancement) consistent with myocardial inflammation.[22–28]

Vaccines have been instrumental in advancing immunology, paving the way for preventive measures and reducing the impact of infectious diseases. Even with effective vaccines, favorable safety profiles are not guaranteed. The vaccine adverse event reporting system (VAERS) was created and implemented in 1990 by the Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) to receive reports about adverse events (AEs) that may be associated with vaccines.[29] The primary purpose for maintaining the database is to serve as an early warning or signaling system for AEs not detected during premarket testing. In addition, the National Childhood Vaccine Injury Act of 1986, which was created because vaccines cause 'unavoidable harm', requires healthcare providers and vaccine manufacturers to report to the Department of Health and Human Services (DHHS)-specific AEs following the administration of those vaccines outlined in the Act.[30] Under-reporting is a known and serious disadvantage of the VAERS system.[30–32]

An AE is defined as any untoward or unfavorable medical occurrence in a human study participant, including any abnormal physical exam or laboratory finding, symptom, or disease, temporally associated with the participant's involvement in the research, whether or not considered related to participation in the research. A serious or severe adverse event (SAE) is defined as any AE that results in death, is life-threatening, or places the participant at immediate risk of death from the event as it occurred, requires, or prolongs hospitalization, causes persistent or significant disability or incapacity, results in congenital anomalies or birth defects, or is another condition which investigators judge to represent significant hazards.[31,33] These classifications are based on the Code of Federal Regulations. The VAERS handbook states that 10–15% of reported AEs are classified as severe for any given set of data.[29] Myocarditis qualifies as an SAE as it can be associated with hospitalization and unpredictable cardiac arrest with sudden death.

Approximately 81% of the United States population has received at least one COVID-19 shot, according to CDC data as of 10 May 2023.[34] The BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna), and Ad26.COV2.S (Janssen) products have not been fully licensed by the U.S. FDA and have instead been authorized for emergency use by the FDA under an Emergency Use Authorization to prevent COVID-19 in individuals 6 months of age and older.[35] The COVID-19 injectable products have not been approved to reduce transmission. There are no prospective, double-blind, randomized, placebo-controlled trials of COVID-19 injectable products demonstrating reductions in COVID-19 hospitalizations and deaths as primary or secondary endpoints. Thus, myocarditis resulting in hospitalization and death attributable to the COVID-19 vaccines may be viewed as an excess risk of the injection program.

The roll-out of COVID-19 injections is actively being monitored by regulatory agencies but all of the risks are not yet known.[36–39] Recently, the Israeli Ministry of Health announced that approximately 1 in 4500 men ages 16–24 who received BNT162b2 developed myocarditis.[39] In prospective cohort studies with measures before and after the second and third injections, Mansanguan *et al.*[40] and Buergin *et al.*[41] reported rates of possible myocarditis of 2.3% and 2.8%, respectively. There is great concern regarding a causal link between myocarditis and the COVID-19 injections.[42–44] Thus, we set out to describe the raw data in VAERS and the COVID-19 vaccines as potential determinants of myocarditis.

Methods

Data collection

AE data were sourced from the VAERS system, a pharmacovigilance system dedicated to monitoring vaccine safety.[45] The VAERS data are available for download in three separate comma-separated values (csv) files representing (i) general data for each report; (ii) the reported AEs or 'symptoms', and (iii) vaccine data including vaccine manufacturer and lot number, for each report. The VAERS dataset is updated once a week and has a 1-week lag time between report

updates. Upon individual reporting of vaccine side effects or AEs, a temporary VAERS ID number is assigned to the individual to preserve confidentiality, and a detailed description of the side effects is transcribed along with the individual's age, residence by state, past medical history, allergies and sex, and other details. In addition, the vaccine lot number, place of vaccination, and manufacturer details are included in the report. If the VAERS report is 'validated', a permanent VAERS ID is assigned, and the report is filed in the front-end data set available for download. We obtained the 7-day rolling average of daily new vaccine doses administered from 1 May 2020 to 3 July 2023 from the Our World in Data database[46] for illustrative purposes.

Data merging and filtering

To maximize the input variables for analysis, the three files were merged using the VAERS IDs as a linking variable. The merged data set comprises data collected pertaining to all reported AEs associated with BNT162b2, mRNA-1273, and Ad26. COV2.S products: the three primary vaccine manufacturers responsible for nCoV-2019 products currently being administered in the U.S. Data were filtered according to vaccine type [COVID19-1 (monovalent) and COVID19-2 (bivalent)] and relevant variables were sorted including VAERS ID, AEs, age, gender, state, vaccination date, date of death, death, dose series, treatment lot number, treatment manufacturer, hospitalizations, emergency department visits, and onset date of AEs. Myocarditis as a standalone AE was extracted by keyword and cardiac events were grouped by extracting multiple keywords according to Medical Dictionary for Regulatory Activities (MedDRA) nomenclature.

Data analysis

To analyze the VAERS data, we used the Language and Environment for Statistical Computing, known as R. Microsoft Excel was used to generate some graphical representations of our results. We calculated descriptive statistics to provide an overview of the dataset's myocarditis reports primary characteristics. The Student's *t*-test was used to detect significant differences, notably within different age groups concerning myocarditis AEs. Categorical variables were analyzed using the chi-square test to find any statistically significant associations. Proportions were calculated, which enabled general comparisons across variables. We compared AEs linked with COVID-19 vaccines against AE reports from VAERS spanning various vaccines over three decades. This comparison helped in assessing any potential increase in AEs following the introduction of COVID-19 vaccines. A focused subgroup analysis on myocarditis aimed to identify recurring patterns and unique characteristics by considering variables like age, gender, and outcomes, such as hospitalizations and deaths. An additional layer of analysis centered on vaccine dose to determine whether specific doses had a higher propensity for certain AEs.

Results

All-cause AEs

As of 11 August 2023, 1,566,839 AEs (962,492 domestic reports) have been reported to the VAERS system in the context of the COVID-19 injections. When comparing this number to AE reports filed to VAERS for the past 30 years for all vaccines combined, we found the number of reports in the context of the COVID-19 vaccines to be disproportionately high [Figure 1(a)]. Note that the VAERS reports for 2021 onward are for the COVID-19 injections only. The average number of AE reports per year for all vaccines combined for the past 30 years is 23,356 and during this period, the number of reports only slightly increased [Figure 1(a), gray bars]. The increase in AEs has been proportional to the increase in the number of vaccine products entering the market prior to COVID-19 vaccines (Figure 2).

In 2021, for the COVID-19 products alone, 702,466 reports were filed. Between 2020 and 2021, there was a 1322% increase in reports. This is not due to the greater number of injections administered as demonstrated by a quantitative comparison of the COVID-19 injections and only the influenza injections for a 462-day timeframe: although there were 2.3 times as many COVID-19 products compared with influenza vaccines administered in this timeframe. There were 6.2 times as many AE types reported by MedDRA code and 118 times as many AE reports. We found more than 11,000 different AE types by MedDRA code reported to date after COVID-19 vaccination. The number of types of AEs by MedDRA code reported for all other vaccines combined in 2020 is only 5000.

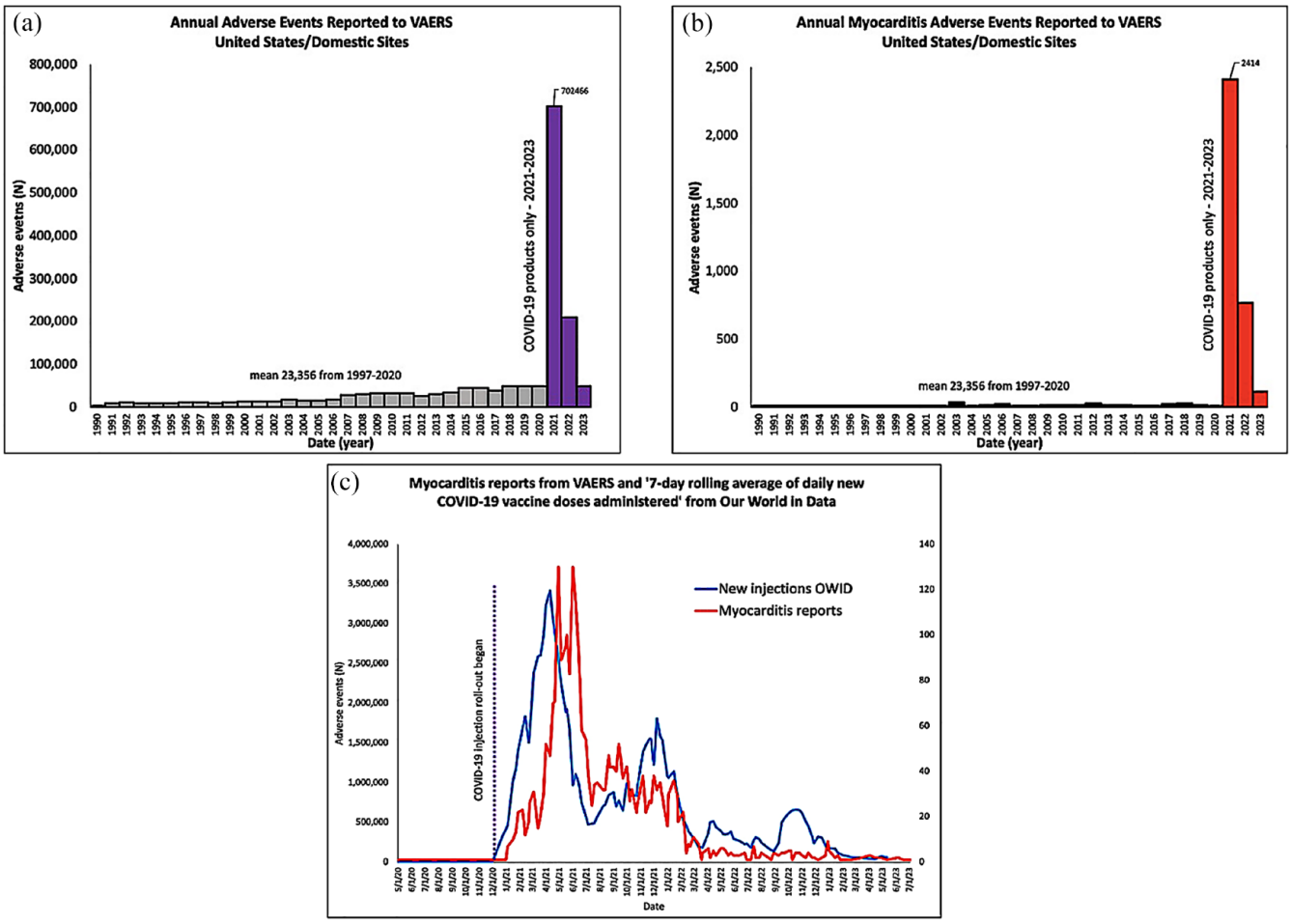

Figure 1. (a) Number of reports filed to VAERS since 1990–2020 for all vaccines combined (gray) shown with the number of reports filed to VAERS from 2021 to 11 August 2023 for only the COVID-19 injections (purple). (b) Number of reports for myocarditis filed to VAERS since 1990–2020 for all vaccines combined (black) is shown with the number of myocarditis reports filed to VAERS from 2021 to 11 August 2023 for only the COVID-19 injections (red). (c) Number of reports for myocarditis filed to VAERS (red) plotted against the number of COVID-19 injections administered (blue) from 1 May 2020 to 3 July 2023.
COVID-19, coronavirus disease 2019; VAERS, vaccine adverse events report system.

Myocarditis AEs

As of 11 August 2023, a total of 3078 reports of COVID-19 vaccine-induced myocarditis (0.3% of all AEs) have been reported to VAERS. Of these reports, 76% resulted in emergency care and hospitalization, while 3% suffered death. Among all reports, 69% of the myocarditis occurred in men.

Figure 1(b) shows the absolute numbers of myocarditis reports in VAERS U.S. Domestic Data. An average of 10.8 reports of myocarditis were filed between 1990 and 2020. Notably, 2414 reports of myocarditis were filed in 2021 alone. Figure 1(a) and (b) demonstrates that a disproportionately high number of reports were filed just shortly following the COVID-19 vaccine rollout and it follows the same pattern for general AEs.

Figure 1(c) shows the myocarditis reports from VAERS from 1 May 2020 up to and including 3 July 2023 (according to Onset Date), against Our World in Data's 7-day rolling average of daily new vaccine doses administered for the same timeframe. When comparing the trajectories of vaccine administration to the myocarditis reports in VAERS, the trajectories overlap with the same peaks and valleys.

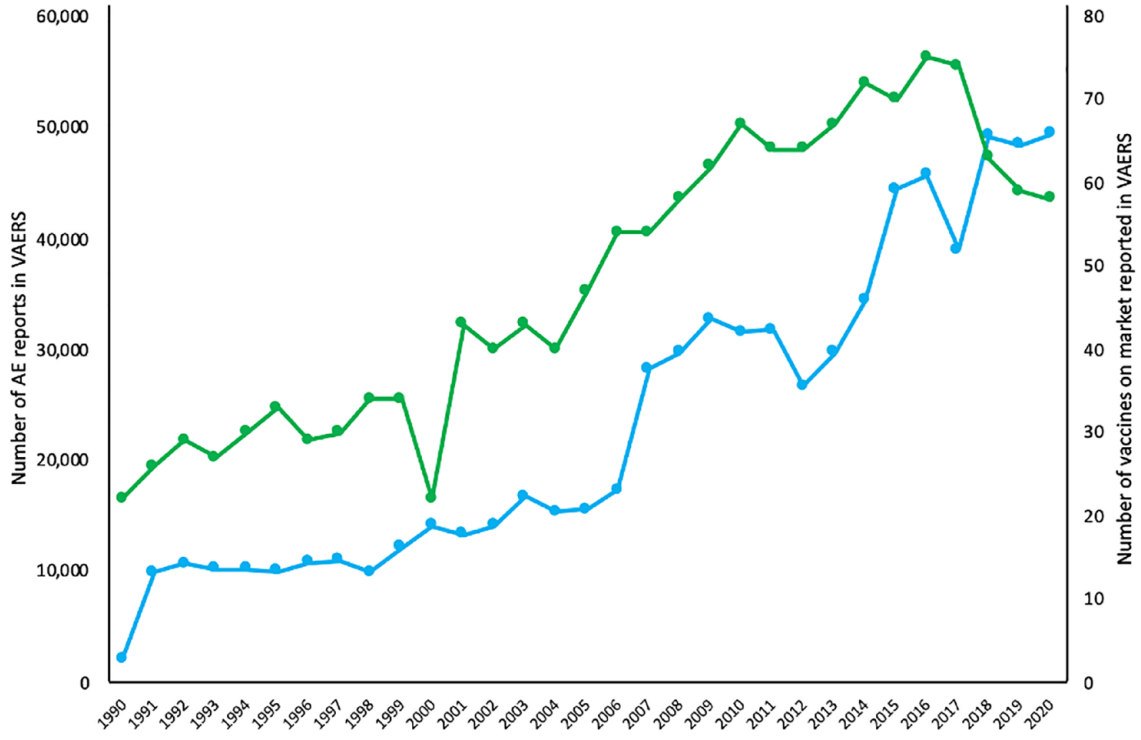

Figure 2. Comparison of the number of vaccines on the market in the United States per year (green) (according to VAERS reports) *versus* the number of VAERS AE reports (blue) from 1990 to 2020.
AE, adverse event; COVID-19, coronavirus disease 2019; VAERS, vaccine adverse events reports system.

Table 1. Characteristics of myocarditis cases in VAERS.

Vaccine type	Myocarditis cases	Age		Time to onset[a]		Sex	Died
	N (%)	Mean	SD	Mean	SD	% Male	*N* (%)
All manufacturers	3078 (100)	32	17	33	195	69	89 (2.9)
Pfizer	1924 (62.51)	29	17	33	236	72	51 (2.7)
Moderna	1014 (32.94)	38	17	28	78	67	26 (2.6)
Janssen	113 (3.67)	43	16	46	105	56	10 (8.8)
Novavax	1 (0.03)	24	–	1	–	0	0 (0)
Unknown	26 (0.85)	29	17	78	145	38	2 (7.7)

[a]Time (days) from the last vaccination to myocarditis report.
SD, standard deviation; VAERS, vaccine adverse events reports system.

Table 1 describes the characteristics of all reported myocarditis cases by vaccine type. These reports were commonly filed in tandem with reports of chest pain/discomfort (53%), elevated troponin (50%), and abnormal echocardiogram/ST-segment elevation (57%). Table 2 shows dose-wise counts and percentages of AEs and clinical tests secondary to COVID-19 vaccine-induced myocarditis.

Figure 3 shows the distribution of myocarditis cases according to CDC age grouping. In total,

Table 2. Dose-wise counts and percentages of adverse events and clinical tests secondary to COVID-19 vaccine-induced myocarditis.

Dose number	Chest pain, *N* (%)	Fatigue, *N* (%)	Troponin elevation, *N* (%)	C-reactive protein, *N* (%)	ST-segment elevation ECG abnormal, *N* (%)
Dose 1	406 (51)	98 (12)	305 (37)	101 (13)	427 (54)
Dose 2	784 (60)	128 (10)	777 (60)	224 (17)	853 (65)
Dose 3	169 (55)	32 (10)	144 (47)	48 (16)	177 (58)

COVID-19, coronavirus disease 2019; ECG, electrocardiogram.

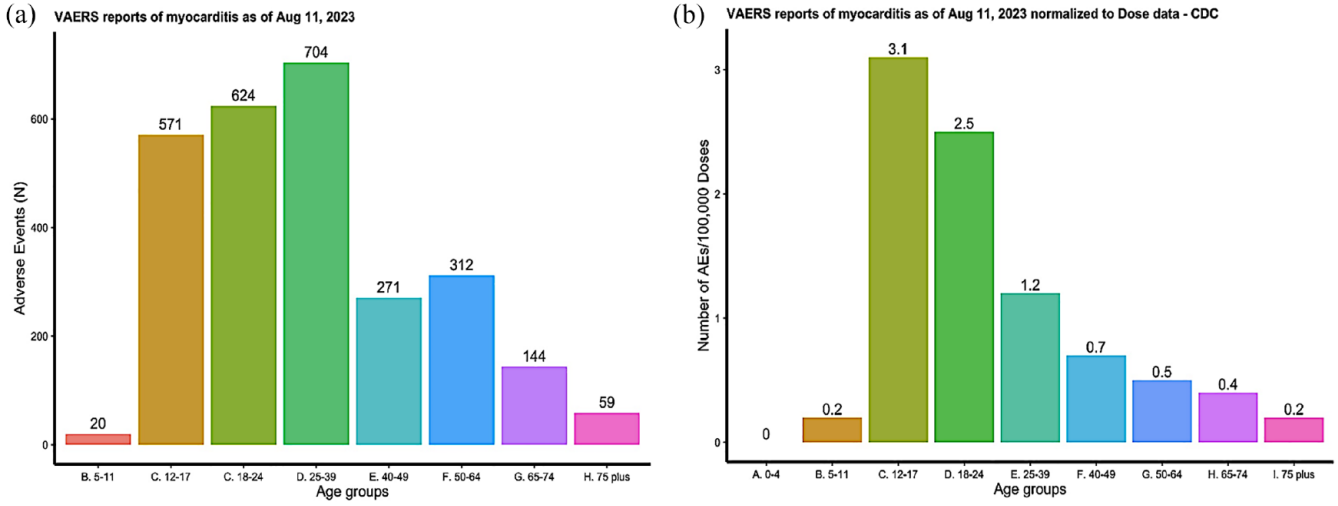

Figure 3. (a) All myocarditis reports in VAERS Domestic Data as of 11 August 2023 according to CDC age grouping. (b) All myocarditis reports filed to VAERS normalized to shot number as per CDC age grouping.
CDC, Centers for Disease Control and Prevention; VAERS, vaccine adverse events reports system.

30% of all myocarditis reports were made for children aged 0–20, and 50% of all myocarditis reports were made for young adults aged 0–30 years of age. Absolute counts were normalized to vaccine administration data by age group [Figure 3(b)]; 12- to 17-year-olds had the highest myocarditis reporting rate.

Over 731 days, we found 571 reports of myocarditis filed to VAERS for children aged 12–17 as of 11 August 2023, which represents 19% of all myocarditis reports. We found the number of myocarditis reports in VAERS after COVID-19 in 2021 was 223 times higher than the average of all vaccines combined for the past 30 years. Of the total 3078 myocarditis VAERS reports, 92 died (3%) and 7.6% of these deaths were in individuals under 20 years of age: one child was 11 years and another was 12 years.

Acute myocarditis following the second injection

The prevalence of myocarditis reports in the VAERS system was significantly higher in the context of dose 2, males, and individuals under 30 years of age. The chi-square test also revealed a relation between dose and myocarditis [χ^2 (1, 639,780) = 587.1094, $p < 0.00001$]. Men were more likely than women to suffer myocarditis [χ^2 (1, $N = 639{,}780$) = 1567.748, $p < 0.00001$]. Individuals less than 30 years of age were more likely than individuals older than 30 to get myocarditis [χ^2 (1, $N = 596{,}852$) = 1579.418, $p < 0.00001$].

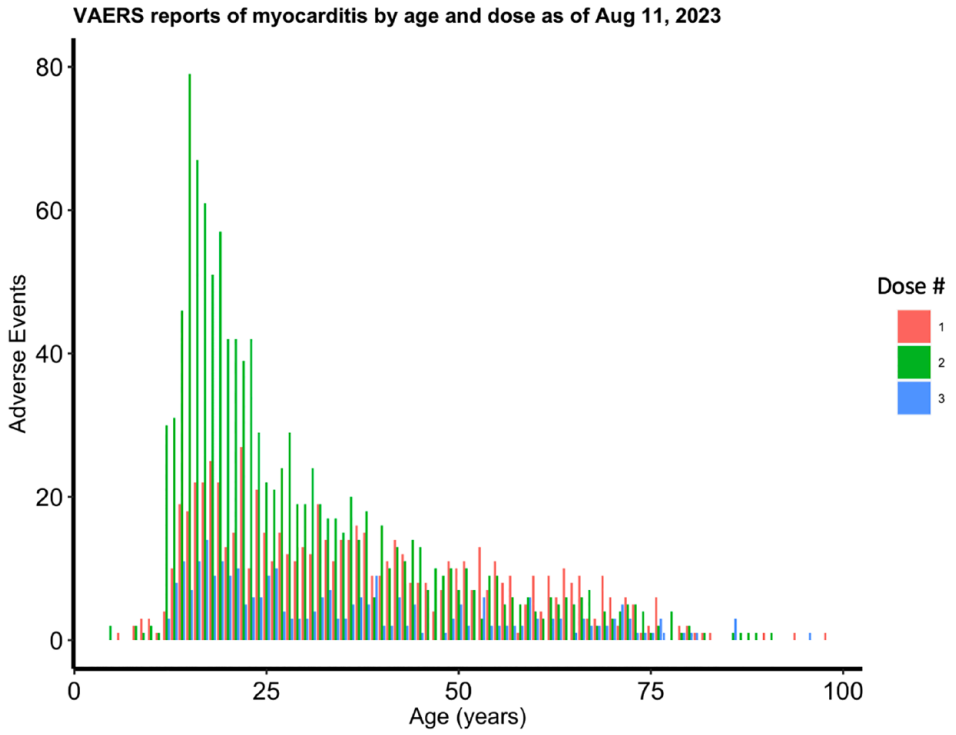

Figure 4. All myocarditis reports in VAERS Domestic Data as of 11 August 2023 are plotted according to age and dose [dose 1 (pink), dose 2 (green), and dose 3 (blue)].
VAERS, vaccine adverse events report system.

Dose 2 was generally administered 3 weeks following the first dose – assuming the individual survives dose 1 without any major complications, including death. Figure 4 reveals five times more reports of myocarditis for dose 2 in 15-year-old males and regardless of age, myocarditis cases were more frequent following dose 2.

We considered myocarditis cases could present as sudden death. An example we found from VAERS is a 33-year-old healthy man reported to have died after suffering a cardiac arrest while running 600 days following dose 2 of BNT162b2. He died in the emergency room which undoubtedly facilitated reporting. Another example retrieved was a 15-year-old healthy boy who died 358 days following dose 1 of BNT162b2 during a 1-day hospitalization for symptoms of nausea (unable to eat/drink), fever, and a headache (Table 3).

We found chest pain was a common in-tandem AE (51% of individuals who filed myocarditis reports into VAERS experienced chest pain and 12% reported fatigue following dose one). This may not be interpreted by children, adolescents, or even medical professionals, as a warning of myocarditis (Refer to VAERS_ID: 1764974).

All-cause cardiac events

There were 133,384 AEs to date (11 August 2023) directly related to clinical diagnosis of serious cardiac issues, including myocarditis. These AEs include clinical symptoms such as cardiac arrest and arrhythmia, for example, and clinical markers or diagnostic elements such as elevated troponin and ST-segment elevation that could represent myocarditis or another condition. Figure 5 shows the distribution of the absolute count [Figure 5(a)] and normalized per 100,000 injections [Figure 5(b)] of cardiac events by age group. The incidence rate was highest in individuals 75 years and older suggesting atherosclerotic cardiovascular disease.

Discussion

We found that myocarditis cases reported to VAERS had a strong and sharp rise in 2021 that coincided with the roll-out of COVID-19

Table 3. Details of two cases of COVID-19 vaccine-induced myocarditis associated with sudden death.

Case Information Terms	Person 1 (VAERS ID: 2658000)	Person 2 (VAERS ID: 2599510)
Age	33	15
Sex	M	M
Preexisting conditions	None	None
Vaccine	Pfizer	Pfizer
Vaccine lot number	FF2593	FC3184
Dose	2	1
Period[a]	600 days	358 days
Description	The patient suddenly collapsed while jogging. He was 33 y/o healthy, fit, active male with no cardiac issues, the autopsy diagnosis was myocarditis.	Started feeling significantly ill 4 days before death with complaints of nausea (unable to keep food down), weakness, and decreased food/water intake. Headache reported and sharp abdominal pain. Had a fever on admission to the hospital 1 day before death. Death 1 year after vaccine administration. Cause of death – idiopathic myocarditis.

[a]Days from the last vaccination to death.
COVID-19, coronavirus disease 2019; VAERS, vaccine adverse events reports system.

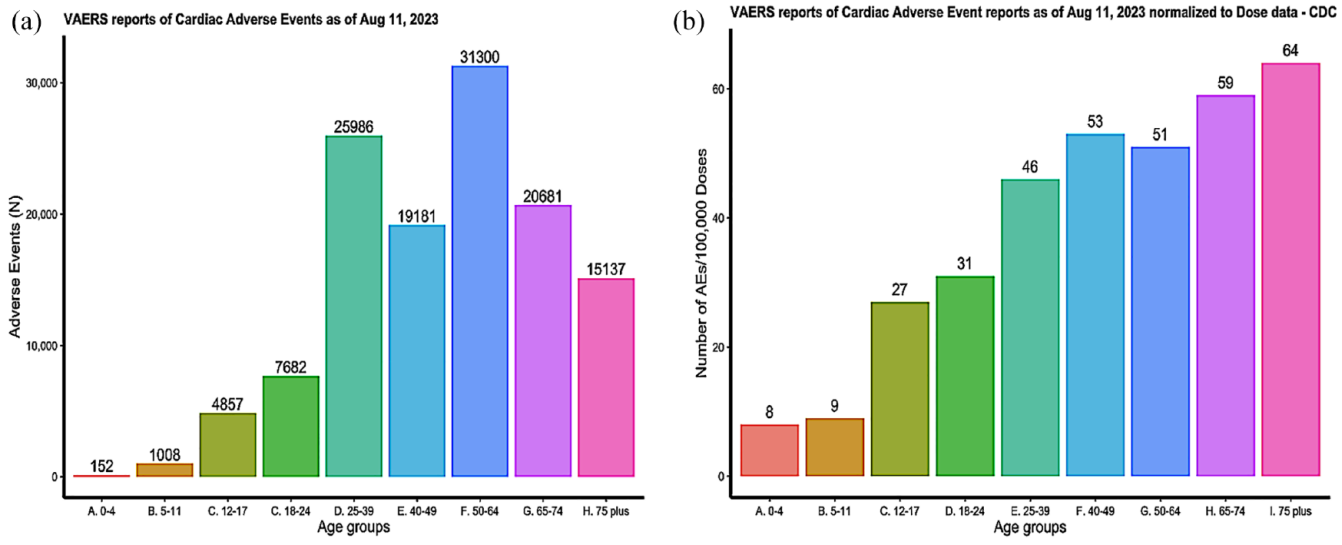

Figure 5. (a) VAERS reports of cardiac AEs by age group as of 11 August 2023. (b) VAERS reports of cardiac AEs by age group as of 11 August 2023, normalized to dose data.
AE, adverse event; VAERS, vaccine adverse events report system.

vaccines. Most reported cases in VAERS were young men with the highest incidences occurring following the second injection. There has been no alternative explanation provided for these cases other than the COVID-19 injections. Given the close temporal relationship and the context of the reporting, it seems clear that the COVID-19 vaccines are deterministic for myocarditis. These cases are reported to VAERS largely by healthcare workers who are concerned the event

happened as a result of vaccination.[47] There may be less bias in reports created by healthcare workers compared to patients who self-report.

In addition to COVID-19 vaccine-induced heart damage, there is a risk of further cardiac involvement from SARS-CoV-2 infection even in individuals deemed healthy with no preexisting medical conditions,[16–20] highlighting the need to accurately report the number of vaccine-induced myocarditis cases. A PubMed literature search for COVID-19 vaccine myocarditis yields over 800 peer-reviewed studies. Because of the spontaneous reporting of events to VAERS, we can assume that the cases reported thus far are not rare, but rather, just the tip of the iceberg. Under-reporting is a known and serious disadvantage of the VAERS system.[48] Thus, VAERS alone without adjustment cannot be used to estimate population incidence. Based on the 3078 reports of myocarditis filed to VAERS as of 11 August 2023, using an under-reporting factor of 31,[48] we estimate that the actual number of myocarditis cases in the United States and other countries that use VAERS may be around 95,418.

The strong signal of a five times higher risk of myocarditis in 15-year-olds following dose 2 is indicative of a dose–response relationship. If the effects of each dose were the same, then we would expect to see the same number of reports filed following each dose. This indicates that the effects of dosing a second time may be more damaging and cumulative with each additional dose. In such cases, it is possible that myocarditis was subclinical after dose 1 and became symptomatic after dose 2. We found 70% of all reports of myocarditis were filed within 7 days and 43% were made within 48 h. Following dose 2, 77% of reports were filed within 7 days and 48% within 48 h, thus providing more evidence of clinical concern and a temporal relationship with the injections.

The clinical implications of acute myocarditis in younger individuals as a result of uncontrolled production of the SARS-CoV-2 spike protein within cardiac myocytes and cardiac support cells are unknown. If myocarditis has developed after the first injection, then subsequent administrations should be avoided at all costs. Sustained elevations of cardiac troponin, reduction in left and right ventricular function, large areas of inflammation or scar on imaging, and cardiac arrhythmias all portend a poor prognosis for the development of heart failure and cardiac death.[49–52] Because the duration of action of genetic material coding for spike protein is unknown, long-term follow-up with cardiology consultation may be advised in cases with possible repeat imaging and biomarkers.

The modified mRNA lipid nanoparticle (LNP) platform has never before been implemented for use in human subjects on a global scale in the context of vaccination, and it has recently been shown that the LNPs bio-distribute and accumulate to transfect whichever cells are in proximity.[53] The payload-modified mRNA is translated into the foreign Spike protein which induces damage within cells, at the cell surface, and through circulation with endothelial damage and thrombosis.[54–56] Castruita *et al.*[57] have found circulating mRNA in the bloodstream for up to 28 days after injection. Swank *et al.*[58] have found circulating Spike protein among the vaccinated with post-acute sequelae for up to 1 year. Yonker *et al.*[59] have reported that the circulating Spike protein is not effectively bound by antibodies in children with myocarditis whereas those with no clinical disease have effectively bound Spike protein. Finally, Baumeier *et al.*[60] have shown the presence of Spike protein and inflammation in the myocardium of young persons suffering from COVID-19 vaccine myocarditis.

The typical timeline is up to 10 years for a proper safety and efficacy assessment of a novel genetic product.[61] The COVID-19 vaccines were rushed through phase I–III trials in about 10 months with the Operation Warp Speed initiative.[61] Safety signals emerging from VAERS were apparent in January of 2021.[45] Reports of death after product administration should prompt market withdrawal. Historically, there are many examples of biological product recalls. In 2010, rotavirus vaccines licensed in the United States were found to contain porcine circovirus type 1 and were subsequently suspended.[62] In 2010, an increased risk of narcolepsy was found following vaccination with a monovalent H1N1 influenza vaccine that was used in several European countries during the H1N1 influenza pandemic.[63] Between 2005 and 2008, a meningococcal vaccine was suspected to cause Guillain–Barré syndrome.[64] In 1998, a vaccine designed to prevent rotavirus

gastroenteritis was associated with childhood intussusception after being vaccinated.[65,66] Finally, in the early 2000s, a hepatitis B vaccine product was linked to multiple sclerosis.[67]

At the time of writing, the CDC recommends everyone 6 months and older to receive an updated COVID-19 booster.[68] However, children have a negligible risk for COVID-19,[69] and yet they are a high-risk group for myocarditis from COVID-19 vaccination as shown by our results. The World Health Organization's current vaccination advice states that healthy young people ages 6 months to 17 years are a 'low priority group' and that vaccinating this group has limited impact on public health.[70] In contradistinction from the CDC, given the very low SARS-CoV-2 infection fatality rate in children with robust natural immune responses[69,71] and the presence of effective medical treatment,[72,73] we believe COVID-19 vaccination may pose more harm to children than theoretical benefit. This corroborates actions taken by Sweden, Norway, and Finland in 2021 when health officials suspended the use of Moderna injections in young people due to the detection of safety signals for an increased risk of myocarditis.[74] Husby *et al.*[75] found a higher risk of myocarditis in those who received the Moderna product (100 mcg dose) compared to those who were injected with Pfizer (30 mcg dose), which indicates a possible dose–response relationship. Fairweather *et al.*[76] also found a higher risk of myocarditis with mRNA products, particularly with the Moderna injections. Although the CDC states that the COVID-19 products are safe and effective in all age groups,[69] Parry *et al.*[77] concluded that the COVID-19 injection program should be immediately suspended due to excess risks, including myocarditis. Moreover, Fraiman *et al.*[78] conducted a re-analysis of serious AEs reported in the phase III randomized clinical trials of Pfizer and Moderna mRNA COVID-19 products and found that there is an excess risk of AEs following vaccination. Cardiac abnormalities have been detected for at least a year after the initial diagnosis of COVID-19 vaccine-induced myocarditis, indicating the possibility of long-term effects with unknown consequences.[79] Formal risk–benefit assessments need to be conducted to clarify these findings. Also, the exact mechanisms of action for induction and progression of COVID-19 vaccine-induced myocarditis need to be elucidated to ensure appropriate management.

Limitations

Our study has all the limitations of safety databases with spontaneously reported events. There are also limitations when comparing myocarditis rates between two time periods, including less effective myocarditis detection tools in the previous period and extensive worldwide acknowledgment of myocarditis during the COVID-19 era that might skew reporting. We recognize that myocarditis has been keyed for reporting in VAERS since the 2021 U.S. FDA warnings[80] were placed on the COVID-19 mRNA products. Nonetheless, we believe VAERS data are grossly under-reported due to the lack of clinical recognition, unavailable vaccine cards, and clinician fear of professional reprisal given the emergency nature of vaccination. Despite myocarditis being the MedDRA code listed in VAERS, the diagnosis of myocarditis might be incorrect without clinical adjudication. As a general rule, the ICU cardiac injury described in COVID-19 illness is subclinical and common to many non-COVID ICU illnesses largely reflecting a minor nonspecific troponin elevation and not myocarditis. This is distinctly different than the ambulatory setting after vaccination where the presentation is obvious, and the clinical ECG laboratory and imaging findings are diagnostic of myocarditis.[21]

Conclusion

We found a very strong safety signal for COVID-19 vaccine-induced myocarditis, particularly in children and young adults, that resulted in hospitalization and death. COVID-19 vaccines induce an uncontrolled expression of potentially lethal SARS-CoV-2 spike protein within human cells, have a close temporal relationship of events, and are internally and externally consistent with emerging sources of clinical and peer-reviewed data supporting the conclusion that COVID-19 vaccines are deterministic for myocarditis, including fatal cases. Further investigation into the underlying mechanisms of COVID-19 vaccine-induced myocarditis is imperative to create effective mitigation strategies and ensure the safety of COVID-19 vaccination programs across populations.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Jessica Rose: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
All data analyzed in this study is publicly available. The data can be obtained from: https://vaers.hhs.gov and https://github.com/owid/covid-19-data/tree/master/public/data

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