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SYSTEMATIC REVIEW

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COVID-19 vaccine induced myocarditis in young males: A systematic review

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Abstract

Background: Myocarditis is a rare but significant adverse event associated with COVID-19 vaccination, especially for men under 40. If the risk of myocarditis is not stratified by pertinent risk factors, it may be diluted for high-risk and inflated for low-risk groups. We sought to assess how the risk of myocarditis is reported in the literature.

Methods: In accordance with PRISMA standards, we reviewed primary publications in PubMed, Embase, Google Scholar and MedRxiv (through 3/2022) and included studies that estimated the incidence of myocarditis/pericarditis after receiving either the BNT162b2 (Pfizer), mRNA-1273 (Moderna) or Ad26COVS1 (Janssen) vaccine. The main outcome was the percentage of studies using 4, 3, 2, 1 or 0 stratifiers (i.e. sex, age, dose number and manufacturer) when reporting the highest risk of myocarditis. Secondary outcomes included the incidence of myocarditis in males after dose 1 and 2 of the BNT162b2 (Pfizer) or mRNA-1273 (Moderna) vaccine.

Results: The 29 included studies originated in North America, Europe, Asia, or were Worldwide. Of them, 28% (8/29) used all four stratifiers, and 45% (13/29) used 1 or 0 stratifiers. The highest incidence of myocarditis ranged from 8.1—39 cases per 100,000 persons (or doses) in studies using four stratifiers. Six studies reported an incidence greater than 15 cases per 100,000 persons (or doses) in males aged 12–24 after dose 2 of an mRNA-based vaccine.

Conclusions: Only one in four articles reporting myocarditis used four stratifiers, and men younger than 40 receiving a second dose of an mRNA vaccine are at greatest risk.

KEYWORDS

COVID-19 vaccination, epidemiology, health policy, myocarditis

1 | INTRODUCTION

Myocarditis and/or pericarditis may be a serious safety signal associated with COVID-19 vaccination.[1] Early data from Israel estimated the excess risk of myocarditis from the BNT162b2 (Pfizer) vaccine to be 2.7 events per 100,000 persons across people of all demographics.[2] Since then, however, reports have emerged finding the risk of myocarditis to be much higher in certain subsets of people. In an analysis by the Centers for Disease Control (CDC) of 1626 myocarditis cases reported to the Vaccine Adverse Reporting System (VAERS) after mRNA-based COVID-19 vaccination, 1195 (73%) were younger than 30, 82% (1265/1538) occurred after the second dose and 82% (1334/1625) were males.[3] Additional published analyses have supported this data by showing that those at highest risk of myocarditis are men under age 30 who receive a second mRNA vaccine dose.[4–10]

The CDC and Food and Drug Administration (FDA) monitor COVID-19 vaccine safety which informs policy recommendations regarding the optimal vaccination schedule. In a meeting on June 7th, the CDC reported that among all demographics, adolescent men receiving the second dose of the Pfizer vaccine had the highest incidence of myocarditis.[11] The CDC has already recommended an extended delay of 3 or 4—8 weeks (from an initial recommendation of 3—4 weeks) between dose 1 and 2 of the primary mRNA COVID-19 vaccination series for healthy individuals to reduce the risk of myocarditis.[12] It is likely that they will continue to update their recommendations as more data emerges to minimise the risk and maximize the benefit of vaccination.

We performed a review of the literature to estimate the population-level incidence of myocarditis after COVID-19 vaccination. We specifically looked at studies that stratified the risk by sex, age, dose number and manufacturer to identify the subset of people at greatest risk. This information may empower policymakers and public health agencies to make prudent decisions about how to vaccinate against COVID-19 safely.

2 | METHODS

2.1 | Objective

We sought to find articles that estimate the risk of post-COVID-19 vaccine induced myocarditis broken down by sex, age, dose number and manufacturer.

The primary outcome was the percentage of studies using 4, 3, 2, 1 or 0 stratifiers (i.e. sex, age, dose number and manufacturer) when reporting the highest risk of myocarditis.

The secondary outcome was the incidence of myocarditis in men after dose 1 and 2 of the BNT162b2 (Pfizer) or mRNA-1273 (Moderna) vaccine. The Pfizer and Moderna vaccine carry the greatest risk of myocarditis. We aimed at comparing the risk of myocarditis between dose 1 and dose 2 within the same vaccine and between the two vaccines.

2.2 | Literature search

Articles discussing COVID-19 vaccination and myocarditis in relation to the BNT162b2 (Pfizer), mRNA-1273 (Moderna) and Ad26COVS1 (Janssen), COVID-19 vaccine was identified in PubMed, Embase, Google Scholar and MedRxiv through 3/2022 using the following general search terms: 'myocarditis', 'pericarditis', 'COVID-19 vaccine', 'BNT162b2', 'mRNA-1273', and 'Adv26' through 03/2022. The full search query can be found in the appendix (Table S1).

We limited our search to the three FDA approved or authorised COVID-19 vaccines: BNT162b2 (Pfizer), mRNA-1273 (Moderna) and Ad26COV21 (Janssen). The ChAdOx1 (AstraZeneca) vaccine was excluded because only case reports of myocarditis after vaccination were found in the literature, and some nations suspended in younger people (e.g. Germany March 2021) (Table S1).

2.3 | PRISMA guidelines/ article inclusion

The review article was in accordance with the standards of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement. All articles initially found were screened by a single reviewer via title/abstract, and all case reports/series, review papers and unrelated reports (i.e. myocarditis related to SARS-CoV-2 and adverse events other than myocarditis) were removed. The remaining selection was reassessed, and all reports that did not provide a population-level incidence estimate of myocarditis, pericarditis and/or myopericarditis were removed. Additionally, all estimates presented only as presentation, duplicates and unrelated articles were eliminated. Articles were excluded if they were not full-length original articles (i.e. >2500 words), as these often-lacked sufficient explanation of methods for categorization (Figure S1). All articles reporting an incidence risk of myocarditis/pericarditis after COVID-19 vaccination were included. A second researcher was consulted whether there was uncertainty about including a report.

2.4 | Data abstraction

All included articles were read completely by a single reviewer, and the following data points were extracted for the primary analysis: title, author, myocarditis risk estimates, number of stratifiers used for the highest incidence estimate, database/cohort used to derive the incidence, study country of origin, time frame postvaccination considered, myocarditis diagnosis method, journal and impact factor, accrued citations in Google Scholar and Altmetric score. The accrued citations in Google Scholar and the Altmetric score were noted on 6/6/2022 and were used to investigate the correlation between the magnitude of myocarditis risk estimates and the accrued citations in Google Scholar or Altmetric score.

The following data points were extracted, and descriptive statistics were compiled (if available in the manuscript): average age of patients with myocarditis, total number of vaccine doses administered, total number of myocarditis cases, number of myocarditis cases in males, number of myocarditis cases in females, the time frame considered and if the paper was peer reviewed and published or if it was a preprint.

The stratifiers we prespecified were: sex, age, dose number and manufacturer. These stratifiers were chosen because emerging reports suggested that the incidence of myocarditis varied among vaccine recipients of different sexes and ages, the dose received and the vaccine manufacturer. Additionally, although there are many other stratification factors to consider the ones selected were the most prevalent and were readily accessible. The time between dose 1 and 2 is another relevant stratification factor, but this was only considered in one study by Buchan et al.[10] Articles were grouped according to the number of stratifiers used to estimate the incidence of myocarditis.

In this analysis, myocarditis was considered synonymous with pericarditis and myo/pericarditis. Thus, myocarditis includes myocarditis, pericarditis and myo/pericarditis.

2.5 | Data analysis

Statistical analysis was performed in R version 4.2.2. The Kruskal–Wallis test was used to compare a difference in the distribution of the highest myocarditis risk by stratified groups. A univariate meta-regression was used to assess how stratification is related to the rate of myocarditis. We sought to identify if factors, such as journal impact factor, industry funding or study location, were predictors of the degree of stratify a study utilised. We used a Kruskal–Wallis test to determine whether impact factor was a predictor of the degree of stratification. The Fisher's Exact test was used to evaluate whether either industry funding or study location was a predictor of the degree of stratification.

2.6 | Ethics approval

In accordance with 45 CFR §46.102(f), this study was not submitted for institutional review board approval because it involved publicly available data and did not involve individual patient data.

3 | RESULTS

A total of 758 articles were obtained after literature search. Of those, 89% (674/758) were removed from the initial screen as they were case reports/ series, review papers or unrelated articles. Of the remaining 84 articles, 30% (25/84) were duplicates, 6% (5/84) were presentations or not full-length articles, 8% (7/84) did not provided a population-level incidence of myocarditis and 21% (18/84) were unrelated. This left 29 articles for the final analysis.

The analysis contained cases of myocarditis from males and females of all age groups. The studies came from a diverse group of countries: Hong Kong, Canada, US, Israel, UK, Denmark, South Korea, Singapore and some were worldwide.

We found 28% (eight of 29) of studies utilised four stratifiers (Table 1) and Table 2. The incidence of myocarditis ranged from 8.1 to 39 cases per 100,000 persons (or doses) when four stratifiers were examined (Figure 1). All were in men under age 40 after dose 2 of an mRNA-based vaccine.

The highest two estimates when examining four stratifiers, 39 and 37.3 cases per 100,000 persons were in males aged 12–17 after dose 2 of the Pfizer vaccine (Figure 2). The two studies reporting rates after the Moderna vaccine found a risk of 30 cases per 100,000 doses in males aged 18–24 after dose 2 and 10.1 cases per 100,000 persons in males under age 40 after dose 2 (Figure 3).

We found 17% (five of 29) of studies utilised three stratifiers (Table 1). The incidence of myocarditis ranged from 4.3 to 53.7 cases per 100,000 persons (or doses) when only three stratifiers were examined (Figure 1). The highest incidence of myocarditis across all 29 articles was found in this group. Sharff et al estimated a risk of 53.7 cases per 100,000 doses in males aged 18–24 after dose 2 of either the Pfizer or Moderna vaccine[9] (Figure 2). The lowest estimate in this group by Choe. et al, 4.3 cases per 100,000 persons, did not stratify by sex.

We noted that 10% (three of 29) of studies utilised two stratifiers (Table 1). The incidence of myocarditis ranged

TABLE 1 Studies included in the analysis are organised by the number (not type) of stratifiers utilised (sex, age, dose number and manufacturer)

# Of Stratifiers	Title (Author)	Highest Risk Estimate/100,000 Persons or Doses (sex; age; dose #; manufacturer)	Database or Cohort (country)	Time Frame Postvaccine Considered	Diagnosis Method (Diagnosis used)	Journal (IF)	Citations accrued as of 6/6/22	Altmetric Score As of 6/6/22
4 Stratifiers (sex, age, dose #, manufacturer)	Myocarditis Following COVID-19 BNT162b2 Vaccination among Adolescents in Hong Kong[4] (Li, et al)	39.02 (Male; 12–17; D2; Pfizer)	Hong Kong territory wide electronic health record database (Hong Kong)	Not reported	Inpatient cases identified via ICD-9 codes: 422.x and 429.0 (myocarditis)	JAMA Paediatrics (26.8)	4	954
	Epidemiology of Acute Myocarditis/Pericarditis in Hong Kong Adolescents Following Comirnaty Vaccination[5] (Chua, et al)	37.32 (Male; 12–17; D2; Pfizer)	Hospital Authority Clinical Data Analysis and Reporting System – Hong Kong (Hong Kong)	14d after D1 or D2	Hong Kong Paediatric Investigation Protocol for Comirnaty-related Myocarditis/Pericarditis (Cardiovascular Injury-Coalition for Epidemic Preparedness Innovations & Brighton Collaboration Criteria) (myocarditis/pericarditis)	Oxford Academic Clinical Infectious Diseases (9.1)	35	n/a
	Epidemiology of myocarditis and pericarditis following mRNA vaccines in Ontario, Canada: by vaccine product, schedule and interval[10] (Buchan, et al)	29.95 (Male; 18–24; D2; Moderna)	Public Health Case and Contact Management Solution—Ontario (Canada)	All reports following vaccination, regardless of time since vaccination	Brighton Collaboration Criteria level 1–3 (myocarditis/pericarditis)	medRxiv	9	n/a
	BNT162b2 Vaccine-Associated Myo/Pericarditis in Adolescents: A Stratified Risk–Benefit Analysis[6] (Krug, et al)	16.2 (Male; 12–15; D2; Pfizer)	VAERS (US)	Not reported	CDC working definition for probably acute myocarditis (myo/pericarditis)	European Journal of Clinical Investigation (4.7)	6	2180
	Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel[7] (Mevorach, et al)	15.07 (Male; 16–19; D2; Pfizer)	Ministry of Health database—Israel (Israel)	21d after D1 or D2	ICD-9422.0-9x and 429.0x for screening. Review by physicians and Brighton Collaboration Criteria (myocarditis)	NEJM (176)	194	6640
	Myocarditis Cases Reported After mRNA-Based COVID-19 Vaccination in the US From December 2020 to August 2021[3] (Oster, et al)	10.59 (Male; 16–17; D2; Pfizer)	VAERS (US)	7d after D1 or D2	CDC case definition for probable or confirmed myocarditis and review by CDC physicians (myocarditis)	JAMA (157.3)	104	9933

TABLE 1 (Continued)

# Of Stratifiers	Title (Author)	Highest Risk Estimate/100,000 Persons or Doses (sex; age; dose #; manufacturer)	Database or Cohort (country)	Time Frame Postvaccine Considered	Diagnosis Method (Diagnosis used)	Journal (IF)	Citations accrued as of 6/6/22	Altmetric Score As of 6/6/22
	Risk of myocarditis following sequential COVID-19 vaccinations by age and sex[18] (Patone, et al)	10.1 (Male; <40; D2; Moderna)	National Data for Hospital Admission—England (UK)	28d after D1 or D2	ICD-10 codes: I40, I400, I401, I408, I409, I41, I410, I411, I412, I418, I514 (myocarditis)	medRxiv	6	n/a
	Myocarditis after BNT162b2 Vaccination in Israeli Adolescents[8] (Mevorach (2), et al)	8.09 (Male; 12–15; D2; Pfizer)	Ministry of Health database—Israel (Israel)	21d after D1 or D2	ICD 422.0-9x and 429.0x for screening. Review by physicians and Brighton Collaboration Criteria. (myocarditis)	NEJM (176)	13	664
3 Stratifiers	Risk of Myopericarditis following COVID-19 mRNA vaccination in a Large Integrated Health System: A Comparison of Completeness and Timeliness of Two Methods[9] (Sharff, et al)	53.7 (Male; 18–24; D2; mRNA)	Kaiser Permanente Northwest (US)	30d after D2	ICD-10 Codes and text description of all KPNW encounters with 'myocarditis' or 'pericarditis'. (myocarditis/pericarditis)	Pharmacoepidemiology and Drug Safety (2.89)	6	338
	Myocarditis after Covid-19 Vaccination in a Large Health Care Organization[19] (Witberg, et al)	10.69 (Male; 16–29; D1/2; Pfizer)	Clalit Health Services—Israel (Israel)	21d after D1 and D2	ICD-9 Codes: 422, 429.0, 398.0, 391.2 (and subcodes) (myocarditis)	NEJM (176)	196	5271
	Population-based Incidence of Myopericarditis After COVID-19 Vaccination in Danish Adolescents[20] (Nygaard, et al)	9.7 (Male; 12–17; D1/2; Pfizer)	18 Danish Paediatric Depts. And Danish VAERS (Denmark)	4wks after D1	Clinical Diagnosis (myopericarditis)	Paediatric Infectious Disease (1.7)	12	360
	Myocarditis After mRNA-1273 Vaccination: A Population-Based Analysis of 151 Million Vaccine Recipients Worldwide[21] (Straus, et al)	7.40 (Male; 18–24; D1/2; Moderna)	Moderna global safety database (Worldwide)	Not reported	Brighton Collaboration; CDC working case definitions (myopericarditis)	medRxiv	2	n/a
	Safety and effectiveness of BNT162b2 mRNA Covid-19 vaccine in adolescents[22] (Choe, et al)	4.3 (Male/Female; 16–18; D2; Pfizer)	COVID-19 Vaccination Adverse Events Management Guideline—Korea (South Korea)	30d after D2	COVID-19 Vaccination Adverse Events Management Guideline. Hand reported (myocarditis/pericarditis)	Vaccine (3.64)	6	7

(Continues)

TABLE 1 (Continued)

# Of Stratifiers	Title (Author)	Highest Risk Estimate/100,000 Persons or Doses (sex; age; dose #; manufacturer)	Database or Cohort (country)	Time Frame Postvaccine Considered	Diagnosis Method (Diagnosis used)	Journal (IF)	Citations accrued as of 6/6/22	Altmetric Score As of 6/6/22
2 Stratifiers	SARS-CoV-2 vaccination and myocarditis or myopericarditis: population-based cohort study[23] (Husby, et al)	6.3 (Males; All ages; D1/2; Moderna)	Hospital-Based Diagnoses from Danish National Patient Register (Denmark)	28d after D1 or D2	ICD-10 codes & increased troponin & hospital stay >24 hrs (myocarditis or myopericarditis)	BMJ (93.3)	58	2514
	Myocarditis Following Immunization With mRNA COVID-19 Vaccines in Members of the US Military[24] (Montgomery, et al)	4.36 (Male; 21–50; D2; mRNA)	US Military—Referrals to Defence Health Agency—VAERS (US)	Not reported	Adjudication process and CDC case definition (myocarditis)	JAMA Cardiology (30.15)	298	4342
	Carditis After COVID-19 Vaccination With a Messenger RNA Vaccine and an Inactivated Virus Vaccine: A Case–Control Study[25] (Lai, et al)	1.00 (Male/Female; All ages; D2; Pfizer)	Hospital Authority of Hong Kong (Hong Kong)	Not reported	ICD-9-CM codes: 420.9, 422.x, 423.9, 429.0 (myocarditis/pericarditis)	Annals of Internal Medicine (51.6)	13	826
1 Stratifier	Features of Inflammatory Heart Reactions Following mRNA COVID-19 Vaccination at a Global Level[26] (Chouchana, et al)	7.82 (Male/Female; 18–29; D1/2; mRNA)	VigiBase (WHO global database of individual case safety reports) (US)	Not reported	Coded via Medical Dictionary for Regulatory Activities (myocarditis)	ASCPT (6.87)	7	288
	Incidence of Myopericarditis and Myocardial Injury in Coronavirus Disease 2019 Vaccinated Subjects[27] (Farahmand, et al)	7.3 (Male; all ages; D1/2; COVID-19 Vaccine)	Beth Israel Deaconess Medical Center (US)	Not reported	ICD-10 codes: I010, I011, I012, I090, I092, I30, I31, I32, I33, I38, I39, I40, I41, I514, and I21A1 (myopericarditis)	American Journal of Cardiology (2.78)	4	39
	Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting[2] (Barda, et al)	2.7 (Male/Female; All ages; D1/2; Pfizer)	Clalit Health Service (Israel)	21d after D1 and D2	Diagnostic codes and free-text phrases that accompany diagnoses (myocarditis)	NEJM (176)	357	12,240
	Myocarditis and Pericarditis following COVID-19 Vaccination: Inequalities in Age and Vaccine Types[28] (Li, et al)	2.09 (Male/Female; 12–17; D1/2; COVID-19 Vaccines)	VAERS (US)	Not reported	Preferred terms (myocarditis, pericarditis) coded in VAERS (myocarditis/pericarditis)	Journal of Personalized Medicine (1.01)	20	263

TABLE 1 (Continued)

# Of Stratifiers	Title (Author)	Highest Risk Estimate/100,000 Persons or Doses (sex; age; dose #; manufacturer)	Database or Cohort (country)	Time Frame Postvaccine Considered	Diagnosis Method (Diagnosis used)	Journal (IF)	Citations accrued as of 6/6/22	Altmetric Score As of 6/6/22
	The Safety of mRNA-1273, BNT162b2 and JNJ-78436735 COVID-19 Vaccines: Safety Monitoring for Adverse Events Using Real-World Data[29] (Sa, et al)	0.62 (Male/Female; All ages; D1/2; Janssen)	VAERS (US)	Not reported	Not reported (myocarditis/pericarditis)	Vaccines (3.6)	1	n/a
	Acute Myocarditis Following COVID-19 mRNA Vaccination in Adults Aged 18 Years or Older[30] (Simone, et al)	0.58 (Male/Female; >18; D2; mRNA)	Kaiser Permanente Southern California (US)	10d after D1 or D2	Independent review by 2 cardiologists (myocarditis)	JAMA Internal Medicine (44.41)	42	1823
	Safety Monitoring of mRNA Vaccines Administered During the Initial 6 Months of the U.S. COVID-19 Vaccination Program: Reports to Vaccine Adverse Events Reporting System (VAERS) and v-safe[31] (Rosenblum, et al)	0.49 (Male/Female; All ages; D1/2; Pfizer)	VAERS & V-safe (US)	Not reported	Not reported (myopericarditis)	The Lancet Infectious Diseases (71.42)	11	3126
	The safety profile of COVID-19 vaccinations in the United States[32] (Singh, et al)	0.182 (Male/Female; All ages; D1/2; Janssen)	VAERS (US)	Not reported	Not reported (myocarditis/pericarditis)	American Journal of Infection Control (3.64)	9	32
	Myocarditis Following COVID-19 mRNA Vaccine: A Case Series and Incidence Rate Determination[33] (Perez, et al)	109.52/100,000 person years (Male; All ages; D1/2; mRNA)	Mayo Clinic Health System (US)	14d after D1 or D2	ICD-10 codes: I40.0, I40.1, I40.8, I40.9, I41, I51.4, B33.22 (myocarditis)	Oxford Academic Clinical Infectious Diseases (9.1)	21	75
0 Stratifiers	Adverse reactions and safety profile of the mRNA COVID-19 vaccines among Asian military personnel[34] (Tan, et al)	2.4 (Male/Female; All ages; D1/2; mRNA)	Singapore military personnel (Singapore)	Not reported	Hand classified by physician (myocarditis/pericarditis)	Annals Academy of Medicine, Singapore (2.47)	1	n/a
	A Small but Significantly Greater Incidence of Inflammatory Heart Disease Identified after Vaccination for Severe Acute Respiratory Syndrome Coronavirus 2[35] (Knowlton, et al)	2.30 (Male/Female; All ages; D1/2; COVID-19 vaccines)	Intermountain Healthcare (US)	60d after D1	Brighton Collaboration criteria of definitive and probably myocarditis and pericarditis; Clinician review (myocarditis, pericarditis, or myopericarditis)	Oxford Academic Open Forum Infectious Diseases (3.8)	1	14

(Continues)

TABLE 1 (Continued)

# Of Stratifiers	Title (Author)	Highest Risk Estimate/100,000 Persons or Doses (sex; age; dose #; manufacturer)	Database or Cohort (country)	Time Frame Postvaccine Considered	Diagnosis Method (Diagnosis used)	Journal (IF)	Citations accrued as of 6/6/22	Altmetric Score As of 6/6/22
	Myocarditis and Pericarditis After Vaccination for COVID-19[36] (Diaz, et al)	1.0 (Male/Female; All ages; D1/2; COVID-19 Vaccine)	Providence Health Care System (US)	Not reported	Clinical diagnosis from EMR; Abnormal troponin or cardiac MRI with evidence of myocarditis. (myocarditis)	JAMA (157)	186	5610
	Comparisons of the risk of myopericarditis between COVID-19 patients and individuals receiving COVID-19 vaccines: a population-based study[37] (Chou, et al)	0.55 (Male/Female; All ages; D1/2; COVID-19 Vaccine)	Hospital Authority Hong Kong West Cluster (Hong Kong)	Not reported	Expert panel review; ICD codes 420.9, 422.x, 423.9, and 429.0 (myopericarditis)	Clinical Research in Cardiology (5.46)	1	50

Note: The highest population-level myocarditis risk estimate from each article is presented for simplicity. Male/Female—Male and Female. D1/2—Dose 1 and 2. mRNA—Pfizer and Moderna. COVID-19 Vaccines—Combination of multiple COVID-19 vaccines. ICD—International Disease Classification. d = days.

from 1 to 6.3 cases per 100,000 persons (or doses) when only two stratifiers were examined (Figure 1).

We found 45% (13 of 29) of studies utilised either 1 or 0 stratifiers (Table 1). The incidence of myocarditis ranged from 0.2 to 7.8 cases per 100,000 persons (or doses) when 1 and 0 stratifiers were examined (Figure 1). 85% (11 of 13) studies in this group did not separate out the risk between males from females.

The rates of myocarditis decline across groups (groups = 4, 3, 2, 1, or 0 stratifiers) using fewer stratification factors ($p = 0.0007$) (Figure 1). In other words, when myocarditis is reported more granularly, rates are highest.

The univariate meta-regression showed a significant association between the risk of myocarditis and the number of stratification factors. The comparator for the analysis was the group with 0 stratifiers. The group with four stratifiers had a beta coefficient of 2.6 ($p < 0.0001$), the group with three stratifiers had a beta coefficient of 2.4 ($p < 0.0001$), the group with two stratifiers has a beta coefficient of 0.91 ($p = 0.06$) and the group with one stratifier was not significant.

The median journal impact factor in among 4, 3, 2, 1 and 0 stratifier groups was 92.1, 3.3, 51.6, 6.9 and 4.6, respectively. The journal impact factor was not a predictor of the degree of stratification ($p = 0.257$).

Only one study was funded by industry. Industry funding was not a predictor of the degree of stratification ($p = 0.414$).

The percentage of studies conducted in the United States among 4, 3, 2, 1 and 0 stratifier groups was 50%, 11%, 67%, 20% and 75%, respectively. US or Non-US study origin was a predictor of the degree of stratification ($p = 0.02$).

The incidence of myocarditis after dose 1 of the Pfizer vaccine in men under age 40 ranged from 0.2 to 5.6 cases per 100,000 persons (or doses) (Figure 2). The incidence of myocarditis after dose 2 of the Pfizer vaccine in males under age 40 was considerably higher and ranged from 1.2 to 39 cases per 100,000 persons (or doses) (Figure 2).

The incidence of myocarditis after dose 1 of the Moderna vaccine in men under age 40 ranged from 0.5 to 3.7 cases per 100,000 persons (or doses) (Figure 3). The incidence of myocarditis after dose 2 of the Moderna vaccine in men under age 40 ranged from 2.4 to 30 cases per 100,000 persons (or doses) (Figure 3).

There were five studies with Altimetric scores greater than 5000 and Google Scholar citations greater than 100 (Table 1). Two of these studies used all four stratifiers (incidence: 15.1 and 10.6 cases per 100,000 persons (or doses)), one of the studies used three stratifiers (incidence: 10.7 cases per 100,000 persons), one of the studies used one stratifier (incidence: 2.7 cases per 100,000 persons) and one of the studies 0 stratifiers (incidence: 1.0 cases per 100,000 persons).

TABLE 2 Descriptive statistics of all studies included in the analysis

Descriptor	Studies using 4 stratifiers ($N = 8$)	Studies using 3 stratifiers ($N = 5$)	Studies using 2 stratifiers ($N = 3$)	Studies using 1 stratifier ($N = 9$)	Studies using 0 stratifiers ($N = 4$)
Average age of patients with myocarditis, median (range)	15.25 (13.69–24)	21.5 (16–27)	25	38 (25–44)	36 (22–48)
Total number of vaccine doses administered, median (range)	9,931,875 (305,406-354,100,845)	2,923,182 (261,334-275,252,007)	2,800,000	240,000,000 (268,320-298,792,852)	1,457,474 (127,081-7,588,200)
Total number of myocarditis cases, median (range)	194.5 (13–1626)	35 (15–1439)	27 (23–269)	21 (7–1956)	31 (3–67)
Number of myocarditis cases in males, median (range)	118 (12–1334)	32.5 (13–1117)	109.5 (23–196)	6 (6–15)	15 (3–15)
Number of myocarditis cases in females, median (range)	18 (1–296)	2.5 (2–292)	36.5 (0–73)	1 (0–6)	5 (0–6)
Study Period, median weeks, (range)	27.85 (20–38)	31.52 (17.6–43.4)	22.9 (17–52.7)	31.14 (17–41.6)	29.87 (25–33.6)
Full length/peer reviewed, *n* (%)	6 (75)	4 (80)	3 (100)	9 (100)	4 (100)
Preprint, *n* (%)	2 (25)	1 (20)	0 (0)	0 (0)	0 (0)

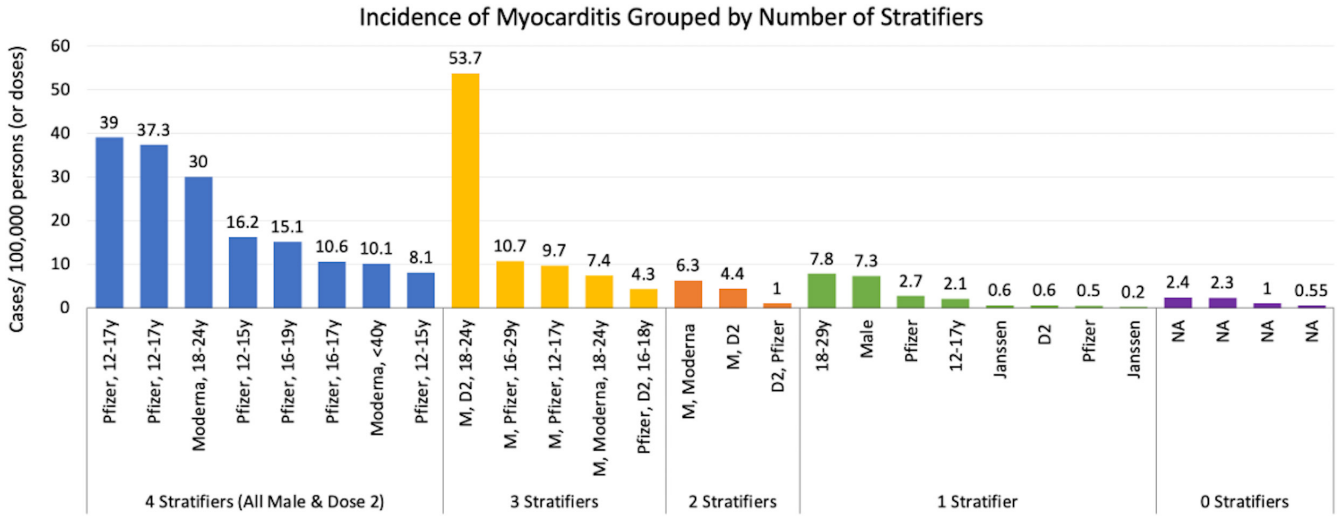

FIGURE 1 Highest myocarditis incidence from each study. Each bar represents a unique study. Data are grouped according to the number of stratifiers used. Stratifiers are sex, age, dose number and manufacturer. Each bar is labelled on the x-axis with the stratifiers unique to the study that the estimate was obtained from. The number above each bar represents the myocarditis incidence. Male (M), Dose 2 (D2), Not Applicable (NA). In studies using four stratifiers, the stratifiers Male and Dose 2 were universally applicable

4 | DISCUSSION

We performed a review to identify articles that estimated the incidence of COVID-19 vaccine induced myocarditis in young males. Our analysis was broad which identified both published and unpublished literature. We found 29 articles that met the inclusion criteria and categorised them based on how the incidence of myocarditis was reported.

Overall, we found that higher incidences of myocarditis were correlated with more granular data. In other words, studies that stratified by all four (sex, age, dose number and manufacturer) or even three risk factors reported the highest rates of myocarditis, with few exceptions. This was supported by the univariate meta-regression which showed a significant association between the degree of stratification and the myocarditis risk. In studies that did not stratify appropriately, the risk estimate is likely diluted for subgroups of people at higher risk (young men) and inflated for people at lower risk (older women). In an era of precision medicine, it seems inappropriate to use a nonstratified or

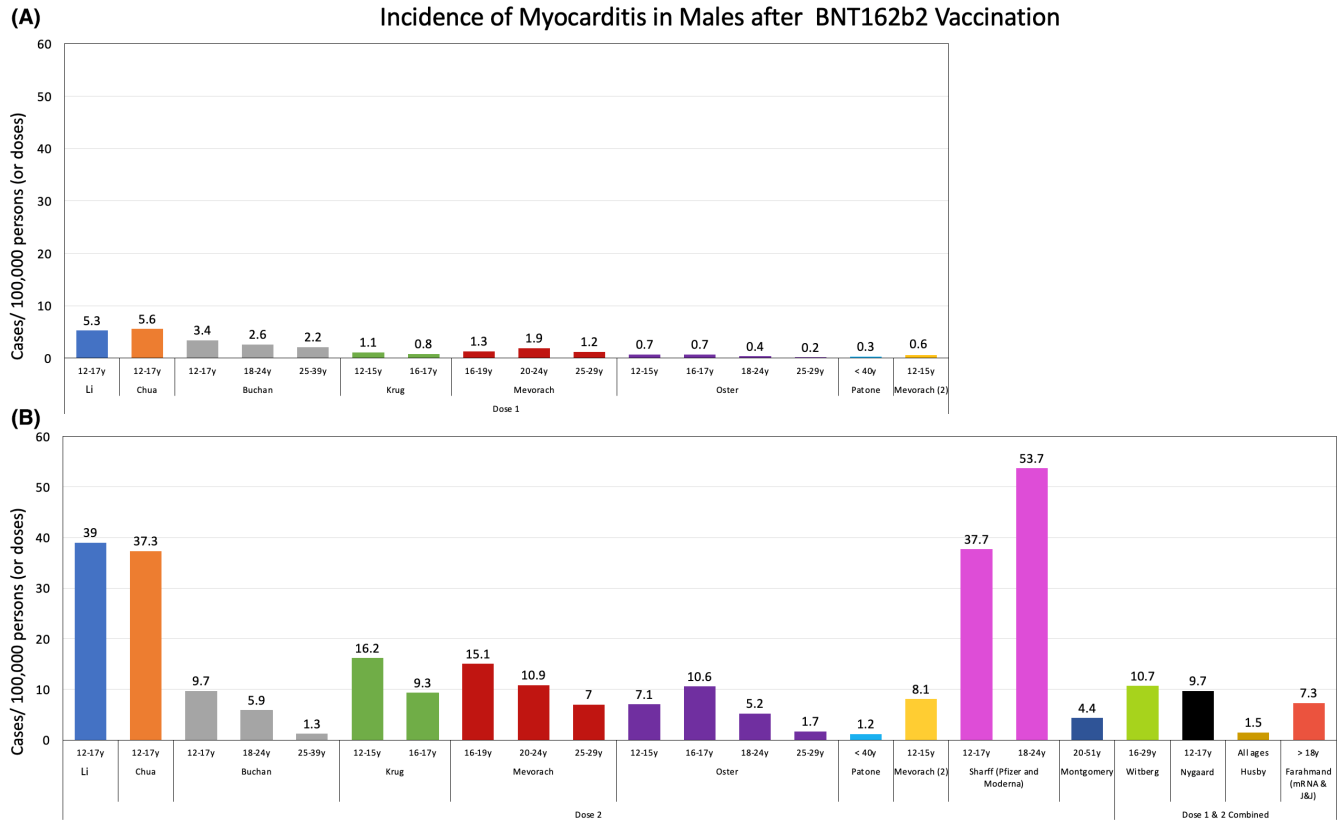

FIGURE 2 Myocarditis incidence in males after of BNT162b2 (Pfizer) vaccination. (A) Incidence of myocarditis after dose 1 of BNT162b2 vaccination. (B) Incidence of myocarditis after dose 2 (left) or after either dose 1 or 2 (right) of BNT162b2 vaccination. Sharff et al is an exception and combines data from Pfizer and Moderna vaccination. Estimates are grouped by the study they were collected from—indicated by the author listed on the x-axis. Bars of the same colour are estimates from the same study but from a different age group. Incidence estimates were only included from studies that separated men from women and provided an estimate of the incidence of myocarditis in males after BNT162b2 vaccination

broad myocarditis incidence estimates when forming policy around vaccinating young men, a category easily identifiable.

Consistently, we found that men under the age of 40 who received a second dose of either the Pfizer or Moderna vaccine had the highest incidence of myocarditis. Our review covered the time of the initial vaccine roll-out and the months that followed. During this period, adverse events associated with COVID-19 vaccination, such as myocarditis, were first being identified. Given that as high as 70% of studies reporting adverse events associated with COVID-19 vaccination did not stratify enough to calculate the incidence in the demographic at highest risk, public health officials may have overlooked or minimised this complication, delaying the opportunity for risk mitigation.

Our analysis showed higher rates of myocarditis than reported by the CDC through the Vaccine Adverse Events Reporting System (VAERS). As of a 7 June 2022, presentation, VAERS documented 4.64 cases per 100,000 doses for those aged 12–15 and 7.59 cases per 100,000 doses for those aged 16–17 after dose 2 of the Pfizer vaccine.[11] However, data from Vaccine Safety Datalink (VSD) aligns better with our report. Vaccine Safety Datalink reports 15.3 cases per 100,000 doses for those aged 12–15 and 13.9 cases per 100,000 doses for those aged 16–17 after dose 2 of the Pfizer vaccine.[11] Notably, Sharff et al found that VSD undercounts cases of myocarditis. Her analysis using encounter text description keyword searching identified five additional cases of myocarditis that were missed using VSD methodology.[9]

Furthermore, we found that for both Pfizer and Moderna vaccines, the risk of myocarditis is orders of magnitude greater after the second dose compared to the first dose, especially for age groups under 25. There are five studies reporting an incidence greater than 10 cases per 100,000 persons (or doses) in men aged 12–19 after dose 2 of the Pfizer vaccine. The risk of myocarditis across those five studies ranges from 1/2562 to 1/9442 persons. The Moderna COVID-19 vaccine was approved later than Pfizer's; thus, there are less data on the incidence of myocarditis. However, we found that men aged <40 who receive the second dose are at highest risk.

To contextualise the incidence of myocarditis after COVID-19 vaccination, it is helpful to compare the risk to

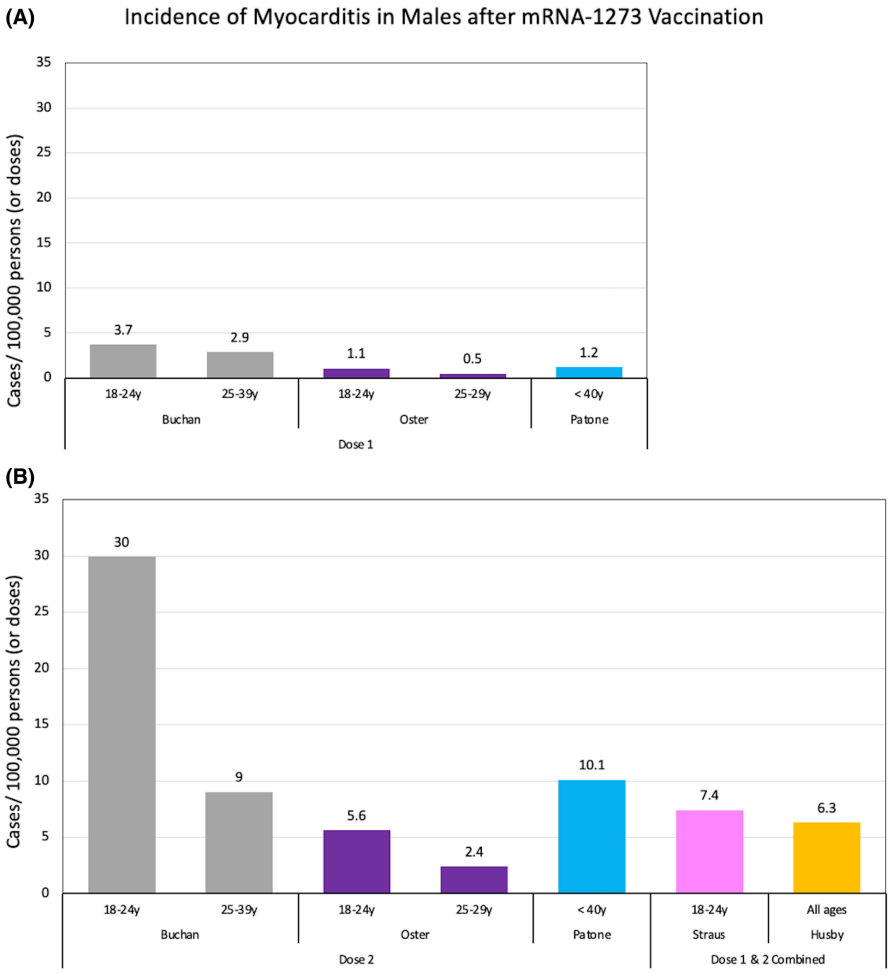

FIGURE 3 Myocarditis incidence estimates in males after mRNA-1273 (Moderna) vaccination. (A) Incidence of myocarditis after dose 1 of mRNA-1273 vaccination. (B) Incidence of myocarditis after dose 2 (left) or after either dose 1 or 2 (right) of mRNA-1273 vaccination. Estimates are grouped by the study they were collected from—indicated by the author listed on the x-axis. Bars of the same colour are estimates from the same study but from a different age group. Incidence estimates were only included from studies that separated males from females and provided an estimate of the incidence of myocarditis in men after mRNA-1273 vaccination

the incidence of myocarditis after influenza vaccination or SARS-CoV-2 infection. Myocarditis is typically not associated with influenza vaccination; thus, there are few, if any reports describing the incidence. On the contrary, myocarditis is a known cardiovascular sequala of COVID-19.[13] The CDC estimated that among men 12–17 and 18–29, the incidence of myocarditis and myocarditis or pericarditis was 50.1–64.9 and 55.3–100.6 cases per 100,000, respectively.[13] The incidence of myocarditis found for young men after SARS-CoV-2 infection is larger than what we found for myocarditis following COVID-19 vaccination. Moreover, Patone et al showed that the number of excess myocarditis events after SARS-CoV-2 infection was at least four times larger than after either dose 1 or 2 of the AstraZeneca, Pfizer or Moderna vaccine among people of all ages.[14] However, when Patone's analysis was limited to those under 40, the number of excess myocarditis events after dose 2 of the Moderna vaccine outnumbered those having had a SARS-CoV-2 infection.[14] Furthermore, calculating the incidence of myocarditis after vaccination is relatively precise given that the two inputs, cases of myocarditis and vaccine doses administered, are known. The calculation for estimating the incidence of myocarditis after SARS-CoV-2 infection is more challenging to obtain because the total number of people who have had an infection is likely unknown and unattainable. Studies typically rely on documented infections, which likely suffers the flaw of undercounting the total number of infections because not everyone with the infection has a documented positive test. Thus, the incidence may be inflated and inaccurate. Using seroprevalence data as opposed to documented infections would better capture the total number of infections in a given population, and would more accurately estimate myocarditis post infection.

There is variability between the rates of myocarditis across studies, even within the same stratifying bin. This is likely due to multiple factors. One being the time-frame postvaccine dedicated to capturing adverse events is not uniform across all studies (Table 1). Some have wider windows than others, which affects the number of myocarditis cases attributed to vaccination. Additionally, across studies, there was variability between the diagnostic criteria used to evaluate whether a patient was experiencing myocarditis (Table 1). Some criteria may be more strict or lenient leading to less or more cases of myocarditis meeting inclusion, respectively. Finally, we included studies performed in multiple countries and across various health systems or databases dedicated to recording

adverse events attributed to vaccination. There is inherent variability between the collection methods used by each system. For example, some use active surveillance while others use passive recording. We acknowledge that the pitfalls in uniformity make myocarditis incidence estimates less certain; however, the available data are still valuable and helps distil who is at greatest risk.

We did not find a correlation between the magnitude of myocarditis risk estimates and either the accrued citations in Google Scholar or the Altmetric score. The accrued citations in Google Scholar and the Altmetric score are both crude and early estimates of the publicity an article receives. The number of citations or Altmetric score was more correlated with the prestige of the journal publishing the article than the myocarditis risk estimate.

We attempted to identify characteristics of either the study or the journal that would correlate with the degree of stratification utilised by a particular study. We found that impact factor and industry funding was not significantly associated with the degree of stratification. However, we did find that the country origin of either US or non-US was significantly associated with the degree of stratification.

4.1 | Strengths and limitations

This study has at least two strengths and four limitations. To our knowledge, ours is the largest and most comprehensive review on this topic. Previous systematic reviews on adverse events associated with COVID-19 vaccination focus on describing the clinical course and outcomes of vaccine induced injury gathered from case reports or series[15,16,17] or limit their analysis to reports from vaccine safety surveillance databases.[17] Rather than describing clinical sequalae, ours is the first to summarise the predicted incidence of postvaccine myocarditis across unpublished and published literature. We are also the first to document the phenomenon where the number of stratification factors by which myocarditis is reported correlates with aggregate risk results. Yet, we have four limitations. Since our initial literature search (03/2022), additional data have been collected and published on the incidence of postvaccine myocarditis. Our manuscript does not include these reports, but on crude observation, the new estimates agree with the data presented here. Second, we did not score each study according to its quality of data and therefore viewed each study equally. If a study utilised poor data, we did not account for this in our analysis. Additionally, our analysis is limited by the data presented in each study. For example, we were not able to present myocarditis incidence estimates in young men from studies that did not stratify data by sex and age. Finally, due to heterogeneity of data sources, definitions and lack of complete stratification, we did not pursue meta-analytic or pooled estimate, and merely chose to describe our results. Pooled estimates would suffer from missing data.

5 | CONCLUSION

Myocarditis is a serious adverse event that disproportionately affects men under 40, with highest risk among men aged 12–24 who receive a second dose of a COVID-19 mRNA vaccine. We show that when investigators present the risk of myocarditis stratified by sex, age, dose number and manufacturer, it is much larger than without stratification. An important safety signal may have been ignored or minimised by failure to stratify appropriately.

AUTHOR CONTRIBUTIONS

BK and VP conceptualised study design. BK reviewed and abstracted data. VP reviewed and confirmed abstracted data. BK wrote first draft of manuscript. BK and VP reviewed and revised subsequent and finalised draft of manuscript.

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CONFLICT OF INTEREST

All other authors have no financial nor nonfinancial conflicts of interest to report.

DATA AVAILABILITY STATEMENT

No additional data outside of the manuscript will be available.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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