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Myopericarditis following COVID-19 vaccination and non-COVID-19 vaccination: a systematic review and meta-analysis

Ryan Ruiyang Ling, Kollengode Ramanathan*, Felicia Liying Tan, Bee Choo Tai, Jyoti Somani, Dale Fisher, Graeme MacLaren*

Summary

Background Myopericarditis is a rare complication of vaccination. However, there have been increasing reports of myopericarditis following COVID-19 vaccination, especially among adolescents and young adults. We aimed to characterise the incidence of myopericarditis following COVID-19 vaccination, and compare this with non-COVID-19 vaccination.

Methods We did a systematic review and meta-analysis, searching four international databases from Jan 1, 1947, to Dec 31, 2021, for studies in English reporting on the incidence of myopericarditis following vaccination (the primary outcome). We included studies reporting on people in the general population who had myopericarditis in temporal relation to receiving vaccines, and excluded studies on a specific subpopulation of patients, non-human studies, and studies in which the number of doses was not reported. Random-effects meta-analyses (DerSimonian and Laird) were conducted, and the intra-study risk of bias (Joanna Briggs Institute checklist) and certainty of evidence (Grading of Recommendations, Assessment, Development and Evaluations approach) were assessed. We analysed the difference in incidence of myopericarditis among subpopulations, stratifying by the type of vaccine (COVID-19 *vs* non-COVID-19) and age group (adult *vs* paediatric). Among COVID-19 vaccinations, we examined the effect of the type of vaccine (mRNA or non-mRNA), sex, age, and dose on the incidence of myopericarditis. This study was registered with PROSPERO (CRD42021275477).

Findings The overall incidence of myopericarditis from 22 studies (405 272 721 vaccine doses) was 33·3 cases (95% CI 15·3–72·6) per million vaccine doses, and did not differ significantly between people who received COVID-19 vaccines (18·2 [10·9–30·3], 11 studies [395 361 933 doses], high certainty) and those who received non-COVID-19 vaccines (56·0 [10·7–293·7], 11 studies [9 910 788 doses], moderate certainty, p=0·20). Compared with COVID-19 vaccination, the incidence of myopericarditis was significantly higher following smallpox vaccinations (132·1 [81·3–214·6], p<0·0001) but was not significantly different after influenza vaccinations (1·3 [0·0–884·1], p=0·43) or in studies reporting on various other non-smallpox vaccinations (57·0 [1·1–3036·6], p=0·58). Among people who received COVID-19 vaccines, the incidence of myopericarditis was significantly higher in males (*vs* females), in people younger than 30 years (*vs* 30 years or older), after receiving an mRNA vaccine (*vs* non-mRNA vaccine), and after a second dose of vaccine (*vs* a first or third dose).

Interpretation The overall risk of myopericarditis after receiving a COVID-19 vaccine is low. However, younger males have an increased incidence of myopericarditis, particularly after receiving mRNA vaccines. Nevertheless, the risks of such rare adverse events should be balanced against the risks of COVID-19 infection (including myopericarditis).

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*Contributed equally

Yong Loo Lin School of Medicine (R R Ling, K Ramanathan MD, F L Tan, B C Tai PhD, J Somani FACP, Prof D Fisher FRACP, G MacLaren MSc) **and Saw Swee Hock School of Public Health** (B C Tai), **National University of Singapore, National University Health System, Singapore; Cardiothoracic Intensive Care Unit, National University Heart Centre** (K Ramanathan, G MacLaren) **and Division of Infectious Diseases, Department of Medicine** (J Somani, Prof D Fisher), **National University Hospital, Singapore**

Correspondence to: Dr Kollengode Ramanathan, Cardiothoracic Intensive Care Unit, National University Heart Centre, National University Hospital, Singapore 119228 **ram_ramanathan@nuhs.edu.sg**

Introduction

Globally, more than 10 billion doses of COVID-19 vaccines have been administered as of March, 2022.[1] The side-effects of vaccination are usually mild and self-limiting; however, myopericarditis is increasingly being reported after COVID-19 vaccination.[2] It has been postulated that the mRNA in the vaccine might activate aberrant innate and acquired immune responses that potentially trigger myocardial inflammation as part of a systemic reaction. Although a number of mechanisms have been suggested, the actual mechanism for the pathogenesis of post-vaccine myopericarditis has not been established.[3–9]

Myopericarditis is a rare complication of vaccination against viruses, and has previously been linked only to smallpox vaccination.[10] A study in Israel, however, suggested that mRNA COVID-19 vaccines significantly increase the risk of myocarditis, particularly in males and in people aged 16–39 years.[11] In addition, numerous case reports and series have been published on myopericarditis in people vaccinated against COVID-19.[12,13] Whether these findings reflect a true increase in incidence or merely improved reporting and recall bias remains inconclusive.[14] We conducted a systematic review and meta-analysis comparing the incidence of myopericarditis

Research in context

Evidence before this study

The risk of myopericarditis following COVID-19 vaccination has been subject to considerable scrutiny both by the scientific community and the general population given the increased reporting of such events, especially in young adults. In some studies, the risk of myopericarditis was up to three times higher than that of controls. Notably, myopericarditis has been associated with mRNA COVID-19 vaccines, and multiple immunological mechanisms have been proposed for this. We searched four international databases between Jan 1, 1947, and Dec 31, 2021, for studies reporting on myopericarditis among people receiving vaccines using the keywords "vaccines", "myocarditis", and "pericarditis", without any language restrictions. We identified 4919 studies from the search strategy, of which 22 observational studies were relevant to our study. Although we found previous systematic reviews that pooled the incident cases of myopericarditis following vaccination, we did not identify any meta-analyses evaluating the proportion of people who develop myopericarditis following vaccination.

Added value of this study

Our meta-analysis was conducted to determine if the increased reporting of myopericarditis was a true increase in incidence or a result of improved reporting systems and recall bias. Among 260 million people who received more than 405 million vaccine doses as reported in studies and databases, we found that the incidence of myopericarditis was not elevated after COVID-19 vaccination (18 cases per million vaccine doses) when compared with after non-COVID-19 vaccination (56 cases per million vaccine doses) or relative to the background pre-pandemic incidence rate of myopericarditis. In people who received a COVID-19 vaccine, a significantly higher incidence of myopericarditis was found in males (*vs* females), those younger than 30 years (*vs* those aged 30 years or older), those receiving a second dose of vaccine (*vs* a first or third dose), or those receiving an mRNA vaccine (*vs* a non-mRNA vaccine). Using robust-variance estimation methods to account for intra-study correlation, decreasing age (excluding people younger than 12 years) was associated with an increased incidence of myopericarditis.

Implications of all the available evidence

In the general population, the risk of myopericarditis after receipt of COVID-19 vaccination is low. The incidence of myopericarditis from COVID-19 vaccination also appears to be lower than that from COVID-19 infection. However, the incidence of myopericarditis for young men after mRNA COVID-19 vaccination appears higher than expected. These findings might be of interest to policy makers determining national vaccination protocols, particularly as many countries will be encouraging a booster dose of vaccination during 2022. Finally, our findings inform the general public of the rarity of myopericarditis, placing the risks into perspective and allowing for a more informed decision regarding COVID-19 vaccination.

following vaccination against COVID-19 with that following vaccination against other diseases to explore the risk of myopericarditis in subpopulations receiving COVID-19 vaccinations and to quantify the incidence of myocarditis, pericarditis, and mortality after receiving a vaccine.

Methods

Search strategy and selection criteria

This study was registered with PROSPERO (CRD42021275477) and conducted in accordance with the PRISMA statement (appendix p 3).[15] The study protocol is available online.

See Online for appendix

For the **study protocol** see https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=275477

We searched four databases (MEDLINE via Pubmed, Embase, Cochrane, and Scopus) for relevant studies, published in English, using the keywords "vaccines", "myocarditis", and "pericarditis", from Jan 1, 1947, to Dec 31, 2021 (appendix p 6). Grey literature was searched by reviewing the reference lists of included studies and review articles. Observational studies reporting on people in the general population who had myopericarditis in temporal relation to receiving vaccines were included in our review. We excluded randomised controlled trials, case reports, studies that reported on a specific subpopulation of patients, non-human studies, and studies in which the number of doses was not reported.

Data collection and risk of bias assessment

Data were collected using a prespecified data extraction form (appendix p 7). Where data were not explicit, we calculated the incidence using the reported number of patients with myopericarditis, the number of vaccine doses and types administered, and the incidence rate, as appropriate. Intra-study risk of bias was rated using the Joanna Briggs Institute (JBI) checklist for prevalence studies.[16] Overall certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach. The screening of studies, data collection, and risk of bias assessment were done independently in duplicate by RRL, FLT, and KR; disagreements were resolved by consensus.

Data synthesis

The primary outcome was the incidence of myopericarditis after any vaccination; secondary outcomes included the incidence of myocarditis, pericarditis, and mortality after any vaccination. Given the heterogeneity in reporting of individual cases of myopericarditis and pericarditis, we define in our review myopericarditis as an umbrella term describing myocarditis, pericarditis, or cases with features of both myocarditis and pericarditis, as reported in the databases or defined within the individual studies. Among studies that

reported on myocarditis and pericarditis individually, we pooled the incidence rates of both conditions accordingly. Statistical analyses were done using R version 4.0.1. We conducted random-effects meta-analyses (DerSimonian and Laird) and computed 95% CIs with the Clopper-Pearson method.[17,18] Although we initially intended to use the Freeman-Tukey double arcsine transformation, several concerns about its use in meta-analyses of rare events were raised, and hence we opted instead to use the logit transformation for our analyses.[19,20] We also did a sensitivity analysis excluding any database and preprint data and studies with high risks of bias (JBI score <7) to assess the impact of intra-study risk of bias on the reporting of myopericarditis. Publication bias was assessed by visual inspection of funnel plots as well as by Egger's test.

We analysed the difference in incidence of myopericarditis among prespecified subpopulations including the type of vaccine (COVID-19 and non-COVID-19 vaccines, and mRNA COVID-19 vaccine and non-mRNA COVID-19 vaccine) and age (paediatric [<18 years] and adult [≥18 years]) using the random-effects Q test. We further investigated the differences between individual non-COVID-19 vaccines (smallpox, influenza, and mixed [defined by the individual studies and including varicella; yellow fever; oral polio vaccine; measles, mumps, and rubella; meningococcal; and diphtheria, pertussis, and tetanus]) with COVID-19 vaccines. As there have been concerns about myopericarditis being more common in young men receiving their second dose of COVID-19 vaccination,[21] we compared its incidence by sex (male and female), age group (<30 or ≥30 years), and dose (first, second, and third) specifically for COVID-19 vaccines.

As inter-study heterogeneity between observational studies of large sample sizes tends to be overestimated by I^2 statistics, we assessed the heterogeneity as part of the GRADE approach, accounting for both quantitative heterogeneity (using I^2 statistics, exploring for sources of heterogeneity using subgroup analysis and meta-regression) and qualitative heterogeneity (distribution of the point estimates and degree of overlap of the 95% CIs of studies in the forest plots).[22,23] $p<0·05$ was considered to indicate significance in our analysis. The pooled incidence of myopericarditis and mortality are presented as cases per million vaccine doses.

Post-hoc analysis

Given the amount of attention myopericarditis in COVID-19 vaccination among younger people (particularly males) has received, we did an inverse-variance weighted meta-regression between the age and the incidence of myopericarditis among four studies that provided age-stratified data for vaccinees.[21,24–26] To account for intra-subject correlation, we estimated SEs using robust-variance estimates, incorporating a random-effects term for each study, and a moderator term for age, which was modelled as a continuous variable.[27] We clustered the pooled estimates around each unique study identifier to derive the robust-variance estimates for SE. In addition, we evaluated differences in the incidences of myocarditis and pericarditis between COVID-19 and non-COVID-19 vaccines. Finally, to estimate the baseline incidence of myopericarditis from COVID-19 infection, we did a rapid review of the literature and pooled the incidence of myopericarditis among patients with COVID-19 infection (appendix p 8). We included studies with at least ten adult patients with COVID-19 reporting on myopericarditis, and excluded any case reports, reviews, post-mortem studies or studies that did not report the number of patients with COVID-19. In the event of overlapping studies, we included the largest study and excluded other studies.

Role of the funding source

There was no funding source for this study.

Results

Of 4919 studies, 156 full-text publications were reviewed. 22 observational studies totalling 405 272 721 vaccine

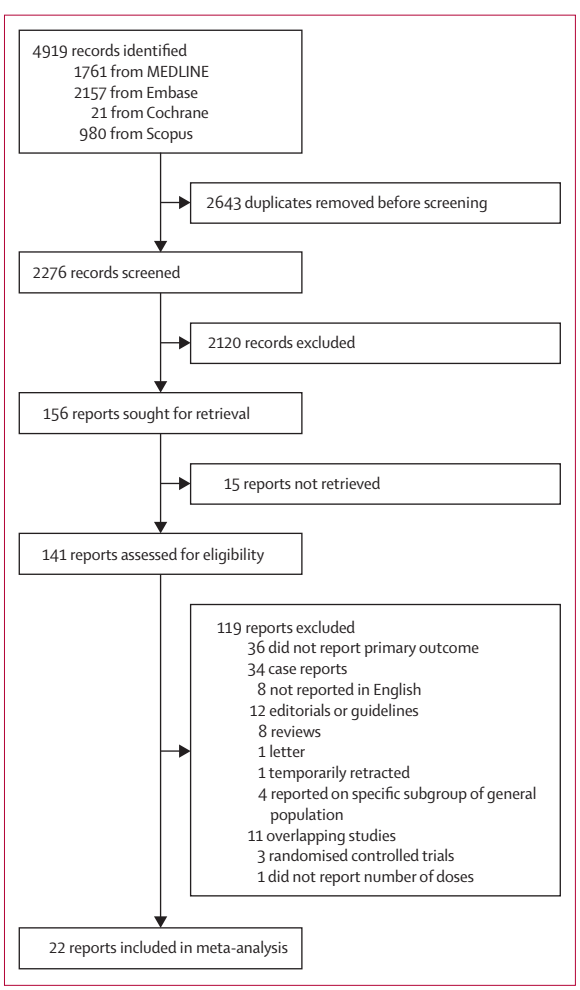

Figure 1: **Flow diagram of study identification and inclusion**

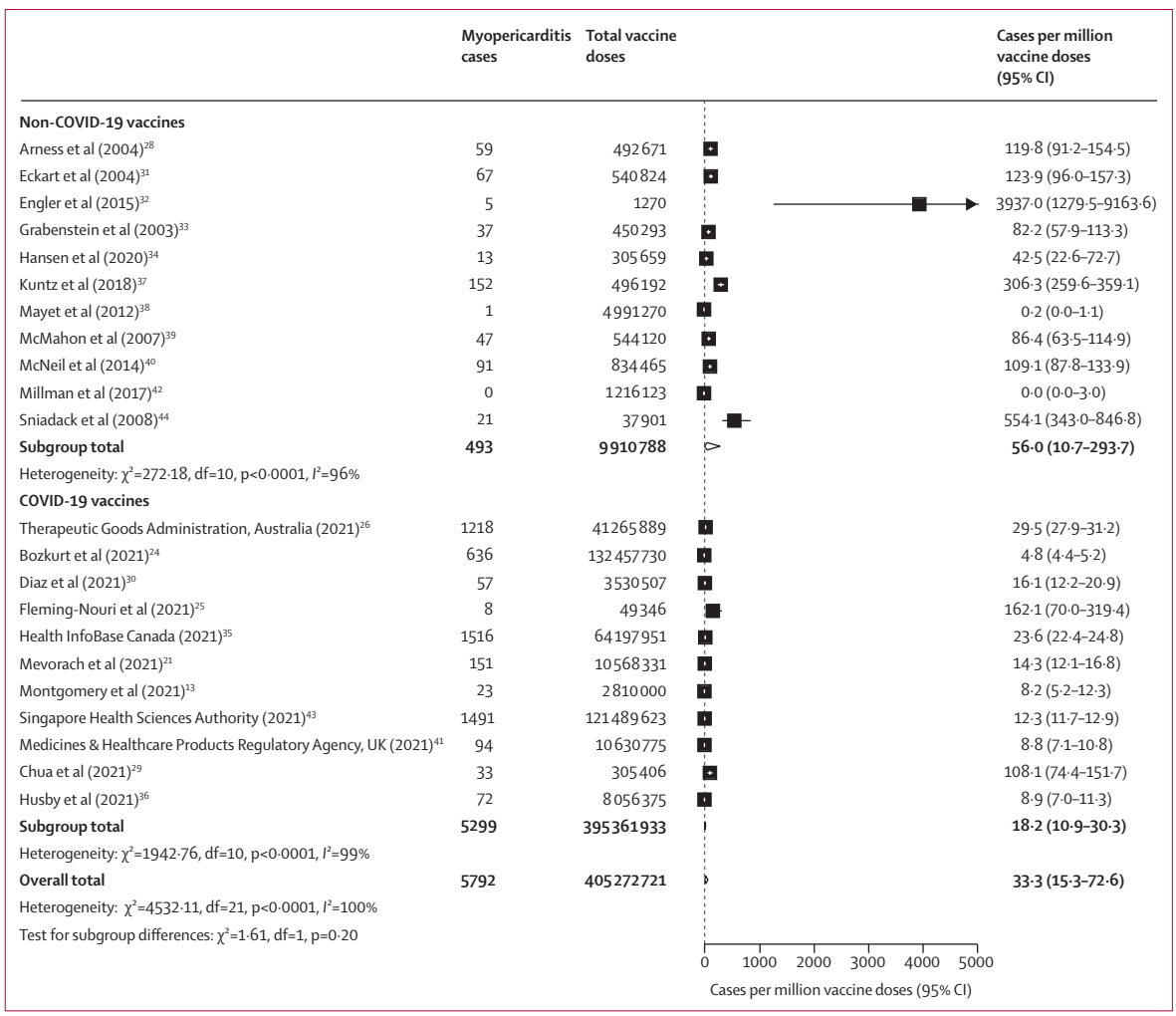

Figure 2: **Incidence of myopericarditis following vaccination in studies investigating COVID-19 and non-COVID-19 vaccines**
The pooled incidence of myopericarditis following vaccination was 18·2 cases per million doses of COVID-19 vaccine and 56·0 cases per million doses of non-COVID-19 vaccine (p=0·20).

doses were included in the meta-analysis (figure 1; appendix pp 10–17).[13,21,24–26,28–44] 11 studies reported on 395 361 933 doses of COVID-19 vaccines,[13,21,24–26,29,30,35,36,41,43] six studies reported on 2 900 274 doses of smallpox vaccines,[28,31,33,39,40,44] two studies on 1 521 782 doses of influenza vaccines,[34,42] and three studies on a variety of non-COVID-19 vaccines (such as varicella; yellow fever; oral polio vaccine; measles, mumps, and rubella; meningococcal; diphtheria, pertussis, and tetanus; BCG; hepatitis; and typhoid; 5 488 732 doses).[32,37,38] Across the nine studies that specified the type of COVID-19 vaccine, 290 730 653 doses of mRNA vaccines and 51 969 677 doses of non-mRNA vaccines were administered. Definitions of pericarditis, myocarditis, and myopericarditis in individual studies or databases are summarised in the appendix (pp 10-17). The intra-study risk of bias and GRADE assessment are also provided in the appendix (pp 18–20); apart from one study,[25] all studies were of good quality (JBI score >7).

The overall incidence of myopericarditis was 33·3 cases (95% CI 15·3–72·6) per million vaccine doses (high certainty, Egger's test p=0·12; figure 2; appendix p 21). Sensitivity analyses excluding studies with high risks of bias and databases found that the pooled incidence of myopericarditis for COVID-19 and non-COVID-19 vaccines did not change significantly (appendix p 22).

The overall incidence of myopericarditis in the general population did not differ significantly after receipt of COVID-19 vaccines (18·2 cases [10·9–30·3] per million doses, high certainty) compared with non-COVID-19 vaccines (56·0 [10·7–293·7], moderate certainty, p=0·20; figure 2). Comparing COVID-19 vaccines with each type of non-COVID-19 vaccine found a significant difference between subpopulations (global p<0·0001). The incidence of myopericarditis was 132·1 (81·3–214·6) per million doses of smallpox vaccine (p<0·0001 *vs* COVID-19 vaccines), 1·3 (0·0–884·1) per million doses of influenza vaccine (p=0·43), and 57·0 (1·1–3036·6) per million doses

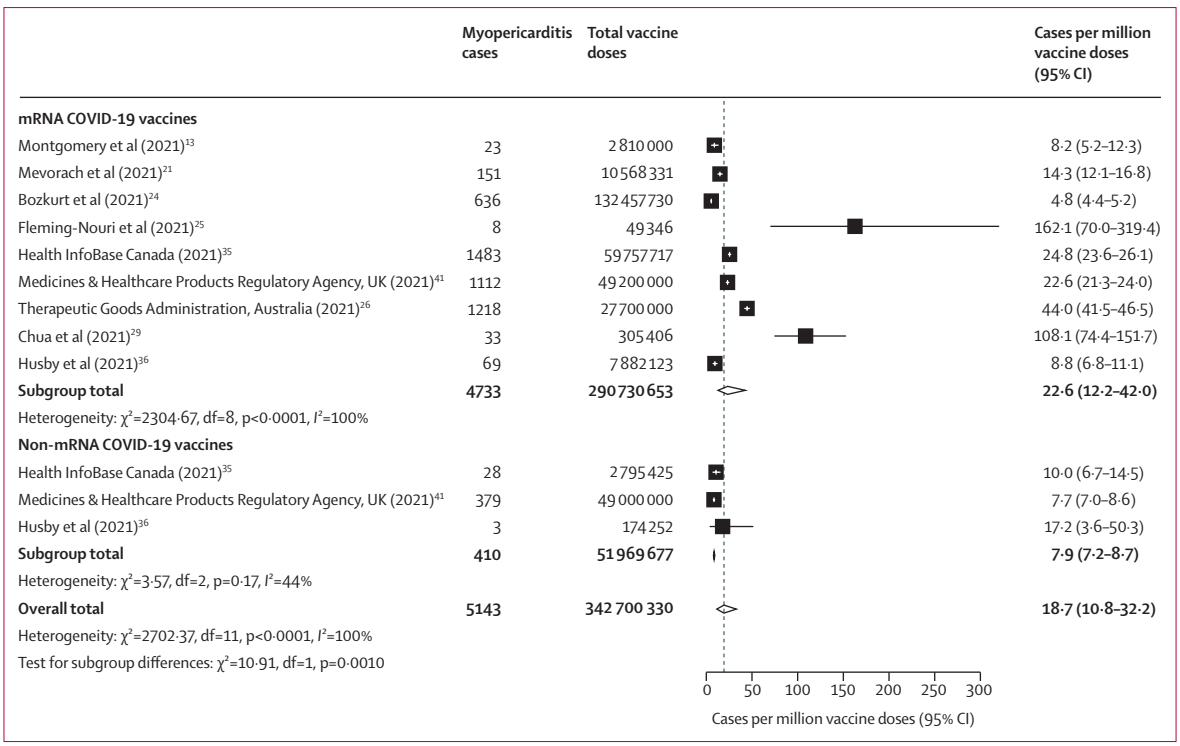

Figure 3: **Incidence of myopericarditis following vaccination in studies investigating mRNA and non-mRNA COVID-19 vaccines**
The pooled incidence of myopericarditis following COVID-19 vaccination was 22·6 cases per million doses of mRNA vaccine and 7·9 cases per million doses of non-mRNA vaccine (p=0·0010).

for studies reporting on a variety of vaccines (p=0·58; appendix p 23). Between the adult subgroup (26·0 cases [11·8–57·4] per million doses; 298 508 729 doses, 14 studies) and paediatric subgroup (18·4 [4·7–72·9]; 12 145 663 doses, six studies), the incidence of myopericarditis did not differ significantly (p=0·67; appendix p 24).

Among COVID-19 vaccines, the incidence of myopericarditis was significantly higher (p=0·0010) among those who received mRNA vaccines (22·6 cases [12·2–42·0] per million doses; 290 730 653 doses, nine studies; figure 3) than among those who received non-mRNA vaccines (7·9 [7·2–8·7]; 51 969 677 doses, three studies). Furthermore, incidence of myopericarditis was significantly higher in people younger than 30 years than in people aged 30 years or older, in those receiving a second dose of vaccination than in those receiving a first or third dose, and in males than in females (table; appendix pp 25–27). Among people younger than 30 years, the incidence of myopericarditis was approximately ten times higher in males than in females; for people older than 30 years, the incidence was around three times as high in males than in females (table; appendix pp 28–29). Further details on the demographic and clinical characteristics of patients with myopericarditis following vaccination are summarised in the appendix (pp 30–35). Time from vaccination to symptom onset was reported heterogeneously and hence these data were not pooled; nonetheless, most studies reported a window of 1–2 weeks before symptom presentation.

Meta-regression among five studies based on the age-stratified incidence of myopericarditis after COVID-19 vaccination using robust variance estimates found that age was negatively associated with myopericarditis (regression coefficient –0·069 [95% CI –0·094 to –0·045], p=0·0030, figure 4).[21,24–26,29]

A post-hoc analysis was done to investigate the incidence of myopericarditis in patients with COVID-19 (appendix pp 8–9, 36–37). Of 6181 studies, we assessed 393 full-text records and included 21 studies with 2 453 491 patients hospitalised with COVID-19 and had clinical or radiological suspicion for myopericarditis,[45–65] among whom there were 48 904 cases of myopericarditis (1·1% [95% CI 0·5–2·2]; appendix p 37).

Across all vaccines, the incidence of myocarditis was 16·0 cases (95% CI 8·2–31·2) per million doses (180 995 007 doses, seven studies, moderate certainty; appendix p 38). The incidence of myocarditis was significantly lower (p<0·0001) among those receiving COVID-19 vaccines (8·9 [6·7–11·8]; 179 664 350 doses, five studies) than those receiving non-COVID-19 vaccines (79·4 [63·6–99·0]; 1 330 657 doses, two studies).

Pericarditis had an incidence across all vaccines of 16·7 cases (5·8–48·0) per million doses (169 138 458 doses, seven studies, moderate certainty; appendix p 39), and did not differ significantly (p=0·64) between COVID-19

	Studies, n	Vaccine doses, n	Myopericarditis cases per million vaccine doses (95% CI)	p value
Type of vaccine	..	..	..	0·0010
mRNA	9[13,21,24,25,26,29,35,36,41]	290 730 653	22·6 (12·2–42·0)	..
non-mRNA	3[35,36,41]	51 969 677	7·9 (7·2–8·7)	..
Age*	..	..	..	<0·0001
≥30 years	3[21,24,26]	143 154 756	2·9 (1·8–4·7)	..
<30 years	5[21,24,25,26,29]	30 564 464	40·9 (18·4–90·9)	..
Dosing*	..	..	..	<0·0001
First dose	8[13,21,25,26,29,30,35,36]	54 971 473	7·2 (3·8–14·0)	..
Second dose	8[13,21,25,26,29,30,35,36]	46 754 686	31·3 (14·1–69·8)	..
Third dose	1[35]	2 643 203	3·0 (1·5–6·1)	..
Sex*	..	..	..	0·0019
Female	5[21,24,26,35,29]	123 336 615	5·1 (2·3–11·5)	..
Male	5[21,24,26,35,29]	110 454 182	23·0 (8·9–59·4)	..
Sex by age group*				
Age <30 years	..	..	..	<0·0001
Male	5[21,24,25,26,29]	14 532 527	59·7 (29·8–119·4)	..
Female	4[21,24,26,29]	16 161 957	5·3 (3·6–8·0)	..
Age ≥30 years	..	..	..	0·034
Male	3[21,24,26]	66 729 801	4·0 (2·4–6·8)	..
Female	3[21,24,26]	76 424 955	1·7 (0·9–3·1)	..

Forest plots of the studies included in these subgroup analyses are provided in the appendix (pp 25–29). *Data extracted from the Therapeutic Goods Administration (Australian Government Department of Health)[26] on Dec 31, 2021, were not amenable for these analyses; therefore, we opted to use data from our previous most recent update (Oct 15, 2021), in which data of sufficient granularity were provided; all other analyses were conducted on the basis of data extracted on Dec 31, 2021.

Table: **Subgroup analyses among people who received COVID-19 vaccines**

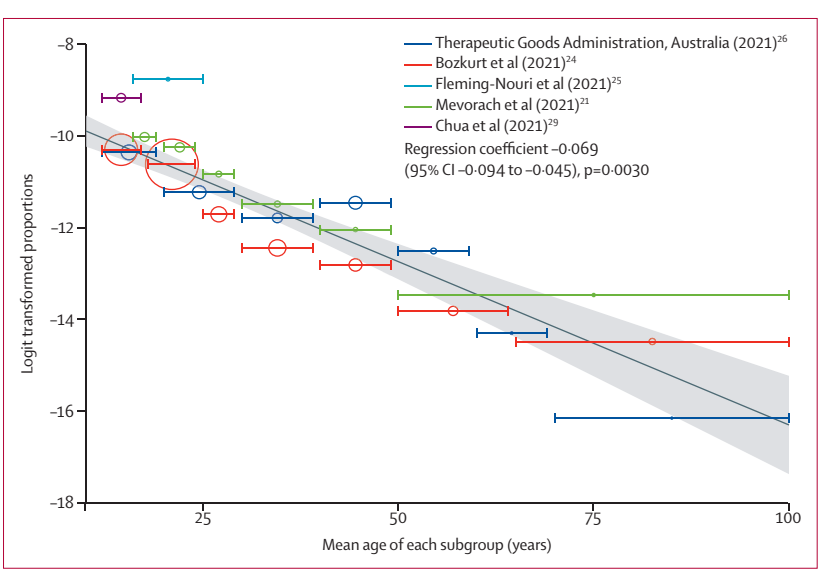

Figure 4: **Effect of age on incidence of myopericarditis following COVID-19 vaccination**
Strata-level meta-regression between age and logit-transformed robust-variance estimated incidence of myopericarditis following COVID-19 vaccination. Bubble sizes correspond to the weights of each study, which are computed as an inverse of the SE of the strata-level pooled estimate. Horizontal error bars correspond to the range of ages that each strata represents. Excluding people younger than 12 years, for whom few data were reported in the studies included, the incidence of myopericarditis increases as the mean age of each subgroup decreases.

vaccines (10·1 [5·8–17·4], 166 286 019 doses, three studies) and non-COVID-19 vaccines (20·0 [1·2–328·5]; 2 852 439 doses, four studies; appendix p 39).

The pooled all-cause mortality following vaccination was 7·8 deaths (95% CI 1·8–34·7) per million doses (240 709 487 doses, ten studies, high certainty), and overall mortality was similar (p=0·93) between COVID-19 vaccines (8·4 [2·0–35·9]; 238 540 345 doses, five studies) and non-COVID-19 vaccines (7·2 [0·2–217·5]; 2 169 142 doses, five studies; appendix p 40).

Discussion

Our systematic review and meta-analysis shows that the incidence of myopericarditis in people who received COVID-19 vaccines was not significantly different from that in people who received non-COVID-19 vaccines in general, and was lower than that in people who received smallpox vaccines. Thus, the overall risk of myopericarditis appears to be no different for this very new group of vaccines against COVID-19 than for traditional vaccines against other pathogens. We also found that young men have a higher incidence of myopericarditis than others receiving mRNA COVID-19 vaccinations.

Among the general population, the background pre-pandemic incidence of myopericarditis varies greatly depending on age and sex,[66–68] and it is possible that it has been underestimated because of the existence of subclinical myopericarditis.[69] Overall, the background incidence of myopericarditis is estimated to be between 9·5 and 21·6 per million people per month,[67,68] whereas the expected incidence of myopericarditis in vaccine recipients was 2·4 to 550 per million vaccinees.[70] In our meta-analysis, the incidence of myopericarditis following vaccination was 18·2 cases (95% CI 10·9–30·3; 8·9 cases of myocarditis and 10·1 cases of pericarditis) per million COVID-19 vaccine doses and 56·0 (10·7–293·7) per million doses of non-COVID-19 vaccines. The background incidence of myocarditis is 8·3–16·7 per million people per month[69] and of pericarditis is 4·78–21·67 per million people per month.[71,72] Notably, the specific incidence of myopericarditis after smallpox vaccination was significantly higher than after COVID-19 vaccines, and the incidence following influenza and other vaccines was similar to that following COVID-19 vaccines. The studies reporting on smallpox vaccination were primarily done in US military personnel, most of whom would be young men, and could account for the increased incidence of myopericarditis in smallpox vaccinees. The increased incidence of myopericarditis after non-COVID-19 vaccination might suggest that myopericarditis is a side-effect of the inflammatory processes induced by vaccination and is not uniquely a result of exposure to SARS-CoV-2 spike proteins through COVID-19 vaccination or infection. The risks of such infrequent adverse events are outweighed by the benefits of vaccination, which include a lower risk of infection, hospitalisation, severe disease, and death from COVID-19.[73,74] In people aged

30 years or older, the incidence of post-vaccination myopericarditis was 2·9 cases (95% CI 1·8–4·7) per million vaccine doses. Being aware of a possible association between COVID-19 vaccination and myopericarditis, clinicians might have had an inherently lower threshold for investigating a patient with non-specific chest pain after COVID-19 vaccination, eventually leading to a diagnosis of myopericarditis. Additionally, given current robust vaccine surveillance systems and the fact that COVID-19 vaccines have received a much higher degree of scrutiny than previous vaccines, the possibility of relative under-reporting of adverse events following non-COVID-19 vaccinations cannot be excluded, despite mass vaccination of more than 6 billion people in the past year.

Our analysis found that myopericarditis was more common among those who were male and under the age of 30 years. The findings of our analysis appear to be concordant with the literature: male sex and younger age groups are more susceptible to myopericarditis after COVID-19 vaccination.[11,24] Previous studies have shown that myocarditis after the second dose of an mRNA COVID-19 vaccine occurs clinically in approximately one in 10 000 young males,[75] which is approximately 50–100 times higher than expected (based on claims made in 2017–19 from the IBM MarketScan Commercial Research Database).[76] In the general population before the COVID-19 pandemic, the incidence of myocarditis was generally higher in males, and highest in young adults.[77,78] Thus far, guidelines for COVID-19 vaccine-induced myopericarditis have mainly focused on early diagnosis and treatment,[79–82] while some have recommended avoiding strenuous exercise for 2 weeks following vaccination.[83] Several national guidelines also highlight the indications and contraindications for vaccine subtypes in this context.[80,83] Although the prognosis of this self-limiting condition is generally good, long-term outcomes for affected patients after 3 months and 6 months are currently awaited.[84]

In people who received a COVID-19 vaccine, our results showed that myopericarditis was nearly four times as common in those receiving an mRNA vaccine than a non-mRNA vaccine and in those receiving their second dose of vaccine compared with a first or third dose. Similarly, a large study from Israel showed that mRNA COVID-19 vaccination was associated with a higher risk of myocarditis than the background population rate (risk ratio 3·24 [95% CI 1·55–12·44]). Over 90% of people with myocarditis after mRNA COVID-19 vaccination were male, with a median age of 25 years (IQR 20–34). The authors also highlighted an increased risk of myocarditis following COVID-19 infection (risk ratio 18·28 [95% CI 3·95–25·12]).[2] A study of cardiac MRI in young athletes recovered from COVID-19 showed a prevalence of myocarditis of 2·1%,[85] whereas our post-hoc analysis of myopericarditis in patients hospitalised with COVID-19 with radiological or clinical suspicion of myopericarditis found a prevalence of 1·1% (95% CI 0·5–2·2).

It is well recognised that such rare adverse reactions are unlikely to be identified in phase 3 trials because sample sizes are not large enough to capture these events. Following the initial publication of results from phase 3 trials of mRNA vaccines, post-marketing evaluation, including those by the US Vaccine Adverse Event Reporting System, provides opportunities to implement vaccine programmes with more precision. As of December, 2021, the omicron variant is spreading rapidly around the world and is set to be the dominant variant globally in early 2022. Consequently, vaccination and booster vaccines will be of considerable importance,[86,87] particularly for mRNA vaccines, which can be manufactured rapidly.[88] Just as different population groups have been found to be more susceptible to thrombosis with thrombocytopenia syndrome (TTS) after COVID-19 vaccination,[89] different population groups (in our analysis, those of male sex and younger age) are more susceptible to myopericarditis. Just as there are appropriate strategies to address TTS, reasonable policies—such as preferentially offering a non-mRNA vaccine to males, particularly those younger than 18 years—could be considered to manage the risk of myopericarditis, while considering the overall benefits and harms of the vaccines. These policies will become more crucial as more countries begin offering booster doses of COVID-19 vaccines to more people under the age of 30 years. However, the risk and benefit calculations on such policy-making decisions must take into account the local epidemiology (ie, the incidence rate of COVID-19 infection at the time and location that the decision is being made), whether there are other non-mRNA COVID-19 vaccines available, and the risk of morbidity from COVID-19 infection for that particular group, while recognising that such factors and decisions will be dynamic during a pandemic. It is also important to interpret the risks and benefits in the context of the background incidence of myopericarditis across subpopulations—ie, the risk of myopericarditis will depend on the prevailing prevalence of COVID-19 locally and at the time of vaccination.

There are three main strengths of our study. First, with a sample size of more than 400 million vaccine doses, to our knowledge, this study is the largest to quantify the incidence of myopericarditis post-vaccination. Second, we compared the incidence of myopericarditis between COVID-19 and non-COVID-19 vaccines, which gives an indication of whether COVID-19 vaccines increase the rate of myopericarditis compared with other routine non-COVID-19 vaccinations. Third, the analyses between subpopulations within those receiving COVID-19 vaccines help to clarify potential at-risk populations and could contribute to driving better vaccination policy-making decisions.

Nonetheless, we recognise several limitations of our analysis. Most of the studies included in our review did not report on outcomes of patients younger than 12 years receiving vaccination against COVID-19, as vaccination of

this younger age group is relatively recent. As such, the findings of our review are not generalisable to children in that age group. Additionally, the comparisons made between COVID-19 and non-COVID-19 vaccines were made indirectly across studies from different time periods. There are far more sensitive tools (eg, MRI, widespread echocardiography, or biopsy) being used currently that did not play as large a role in diagnosing myopericarditis previously in people receiving non-COVID-19 vaccines. This disparity introduces heterogeneity to the reporting and treatment of myopericarditis, which results in potential confounders within our analysis. There are other important vaccines (including, but not limited to, those against hepatitis, *Haemophilus influenzae*, pneumococcus, and diphtheria, pertussis, and tetanus) that were under-represented in our analysis, suggesting that cases of myopericarditis after these commonly used vaccines occurred very rarely. Furthermore, the 95% CIs for the pooled estimate of non-COVID-19 vaccines were relatively wide, most likely due to two main factors: heterogeneity and variability in the type of vaccine (for which we conducted a subgroup analysis of non-COVID-19 vaccine subtypes to explore as a potential source of heterogeneity), and imprecision resulting from a smaller sample size than that for COVID-19 vaccines. Because COVID-19 vaccines were developed in response to a new global pandemic, they have been administered at an unprecedented rate, with millions of doses given within a short period, unlike any of the comparator non-COVID-19 vaccines. As such, the relative incidence of myopericarditis following COVID-19 vaccination should be interpreted in this context, although it is probably more accurate than the incidence of non-COVID-19 vaccines. Our analysis is also based on study-level data, which limited our analysis of subpopulations. Although we were able to partially account for this by conducting a strata-level meta-regression analysis by age, more granular data are required to better guide the clinical decision-making process. Our analysis also uses data from registries and databases, which are inherently limited by the lack of longitudinal data, and some of the coded cases of myopericarditis might turn out to not have myopericarditis following further investigation of the symptoms. Some studies only reported the number of doses of vaccines that were administered. As a result, we had to analyse the incidence of myopericarditis by doses and not patients. Most of the studies included in our analysis did not report on myocarditis or pericarditis specifically, but grouped both complications under the umbrella term myopericarditis. Nonetheless, these remain the best data available on myopericarditis following vaccination. Additionally, myopericarditis occurring in temporal relation with COVID-19 vaccination cannot always confirm a diagnosis of vaccine-induced myopericarditis, as it is difficult to distinguish it from myopericarditis due to other causes. Finally, our review was unable to account for the disease burden or severity of myopericarditis, which, while usually mild and self-limiting, can take a more fulminant course eventually requiring mechanical circulatory support. There are also other side-effects that were not addressed in this study that might influence a person's decision to receive a vaccination.

In conclusion, this meta-analysis of more than 400 million doses of vaccines suggests that the overall incidence of myopericarditis following COVID-19 vaccination is similar to that in the published literature on its incidence after influenza vaccination, and is lower than the incidence after live smallpox vaccination. The incidence of myopericarditis in younger males after mRNA COVID-19 vaccination is higher than expected by comparison with other age groups. The scale of mass global vaccination and enhanced surveillance might account for the increased reporting of this adverse event in the context of COVID-19 vaccination. Nonetheless, certain subpopulations—those of male sex or younger age and those receiving an mRNA vaccine, particularly the second dose—appear to be at increased risk of myopericarditis following COVID-19 vaccination. These findings are important additions to the conversation when weighing the risks and benefits of COVID-19 vaccination during this pandemic. Although the results of our analysis place the risks of COVID-19 vaccination into perspective, the decision to vaccinate should be informed by appropriately weighing the benefits and harms of COVID-19 vaccination, the local risk of exposure to COVID-19 infection at the time, and the risk of myopericarditis from COVID-19 infection itself.

Contributors

KR and RRL designed the study and drafted the manuscript. RRL, KR, and FLT contributed to the search strategy, screening of articles, and data collection. RRL and FLT contributed to the risk of bias assessment and made the tables and figures. RRL, BCT, and KR contributed to data analysis and interpretation. KR, RRL, GM, JS, DF, and BCT contributed to critical revision of manuscript for intellectually important content. All authors provided critical conceptual input, interpreted the data analysis, and read and approved the final draft of the manuscript. RRL, FLT, and KR accessed and verified the data. RRL and KR were responsible for the decision to submit the manuscript for publication.

Declaration of interests

KR has received honoraria for webinars unrelated to the topic from Baxter. All other authors declare no competing interests.

Data sharing

This manuscript makes use of publicly available data from the included studies and their supplementary information files; therefore, no original data are available for sharing.

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