

Incidence, Natural History, Specific Populations and Hypothesized Mechanisms of Myocarditis and Pericarditis Following mRNA COVID-19 Vaccination: Living Evidence Synthesis

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Acknowledgments: McManus B (Context expert on hypothesized mechanisms; Department of Pathology and Laboratory Medicine, University of British Columbia); Ogunnaike-Cooke S & Abraham N (Knowledge Users; Public Health Agency of Canada) and Tricco A (Unity Health Toronto and SPOR Evidence Alliance for review of protocol; Kaitryn Campbell (McMaster University) for peer reviewing the search strategy.

10 February 2022 (Update #1)

Context

This is the first update of a living evidence synthesis conducted in November 2021 available at [COVID-END](#) and as a [pre-print](#). For this first update, the key questions were refined to focus on priority age and risk groups, to limit cases to those confirmed by medical record review and with myocarditis/myopericarditis or pericarditis rather than these outcomes in combination (when data on the outcomes separately were available), and expanded to include evidence on long-term outcomes and describe hypothesized mechanisms.

Search date

January 10, 2022

Key Questions

- KQ1: What is the incidence of myocarditis and pericarditis following mRNA COVID-19 vaccination, by age and sex, in i) people 0-4 years, 5-11 years, 12-17 years, 18-29 years ii) recipients of any age after a third dose, and iii) individuals with prior history of myocarditis following mRNA COVID-19 vaccination?
- KQ2: Among individuals of a similar age and sex, are there risk or protective factors (e.g., pre-existing conditions [e.g. cardiac diseases, immunocompromise], previous SARS-CoV-2 infection [symptomatic or asymptomatic] or other viral infections, pharmacotherapies [e.g., hormones], type of vaccine product, length of vaccine dosing interval, vaccine combination for first vs second vs booster doses) for myocarditis and pericarditis following mRNA COVID-19 vaccination?
- KQ3: What are the characteristics and short-term clinical course of myocarditis or pericarditis after COVID-19 vaccination in i) children <12 yrs, ii) recipients of any age after a third dose, and iii) individuals with prior history of myocarditis following mRNA COVID-19 vaccination?
- KQ4: Among individuals of a similar age and sex who experienced myocarditis or pericarditis after mRNA COVID-19 vaccination, what is the longer term (≥4 weeks) prognosis, and does this vary by patient or vaccine characteristics?

Contextual Question

CQ1: What are the hypothesized mechanisms involved in myocarditis and pericarditis following vaccination with mRNA COVID-19 vaccines, and do they vary by group?

Our Approach

For study eligibility for each question, see [Supplementary Table 1](#). A single reviewer completed screening and another verified 50% of exclusions, using a machine-learning program to prioritize records. For the key questions,

a second reviewer verified all exclusions at full text and data extraction, and risk of bias assessments (for KQs 1 & 2) using modified Joanna Briggs Institute tools. For KQs 1 and 2, certainty of evidence ratings were based on team consensus using GRADE. The observational evidence in KQ1 started at low certainty and in KQ2 started at high certainty; we considered rating up for a relatively large magnitude in incidence for KQ1. In the plain-language conclusions, we have used “probably”, “may” and “uncertain” to reflect level of certainty in the evidence based on GRADE of moderate, low, or very low, respectively.

For KQ1, excess incidence rates <20 per million were considered very rare. For KQ2, associations ≥ 1.5 (odds ratio/relative risk) were considered clinically relevant (i.e. OR <1.5 shows “little-to-no association”).

For CQ1, we extracted verbatim authors’ summaries of any hypotheses and, where available, findings by the authors or cited works investigating potential mechanisms (e.g., histology, gene panels, serology for innate and acquired immune system components, autoimmune antibodies, tissue biopsies, autopsy findings, etc.). We checked references used to support statements made by authors in proposing or explaining hypotheses to identify whether they provided direct empirical evidence (i.e., specific to COVID-19 mRNA vaccination). We involved three content experts to identify other potentially relevant studies and to review proposed mechanisms for comprehensiveness and interpretation; they also provided expert opinion on their impressions about the potential mechanisms. We present a summary of the results below and in descriptive tables.

Findings

[Table 1](#) and [Table 2](#) contain the Summary of Findings for KQs 1 and 2. Results for KQs 3 and 4 are presented in [Table 3](#). [Table 4](#) summarizes the hypothesized mechanisms and supporting/refuting data for myocarditis following COVID-19 mRNA vaccination. Appendix 1 contains: [eligibility criteria](#); study characteristics tables of the new [passive](#) and [active](#) reporting systems/studies contributing to KQ1 and new [studies included for KQ2](#); risk of bias assessments for [KQ 1](#) & [KQ2](#); and the [Supplementary Table for CQ1 with details about the authors’ discussion points](#). [Appendix 2](#) contains a description of our synthesis methods.

Thirty-nine studies were included in this update. We identified 33 new reports across all questions (KQ1=9¹⁻⁹, KQ2=5^{14 9-11}, KQ3=1¹², KQ4=3^{3 13 14}, CQ1=20¹⁵⁻³⁴). Findings from six studies in the previous synthesis were carried forward (KQ1=5³⁵⁻³⁹, KQ2=2^{39 40}). We excluded five studies that only reported on combined myo- and pericarditis (as we located other studies with these reported separately),⁴¹⁻⁴⁵ eight studies that did not report on confirmed cases,⁴⁶⁻⁵³ and one study⁵⁴ that reported on cases that were included in another report of more recent data.

KQ1: Incidence

Myocarditis after dose 2

- We now report on 5-11 year-old males and females and found that the incidence of myocarditis after vaccination with Pfizer may be fewer than 20 cases per million in both groups (low certainty).
- The evidence was consistent with the previous review, showing that the incidence of myocarditis after mRNA vaccine is higher in male adolescents and young adults (12-17y: range 50-139 cases per million [low certainty] and 18-29y: range 28-147 per million [moderate certainty]). The upper limit of the range in incidence increased from 99 to 147 per million for 18-29 year-old males.
- We are no longer reporting on 30-39 year-old males, because our revised criterion requiring confirmation of cases was no longer met.
- We now report on 18-39 year-old males and found that incidence of myocarditis may be between 25 to 82 cases per million (low certainty).
- Among females 18-29 years of age, the incidence of myocarditis after vaccination may be less than 20 cases per million (low certainty). We are very uncertain about the incidence of myocarditis after vaccination with mRNA vaccines in 12-17 year-old females (all data from passive reporting systems).
- Due to inconsistency and use of passive reporting systems, we are uncertain about the incidence of myocarditis after vaccination in 18-39 year old females (very low certainty).

Myocarditis after dose 3

- Among ≥ 40 year old males, the incidence of myocarditis after a third dose of an mRNA vaccines may be fewer than 20 cases per million (low certainty).

- For 13-39 year-old males or females and ≥ 40 year-old females, we are uncertain about the incidence of myocarditis after a third dose of an mRNA vaccine due to concerns about imprecision and inconsistency across studies (very low certainty).

Pericarditis

- Based on a single study only reporting across both sexes, we are uncertain about the incidence of pericarditis after Pfizer vaccination in 5-11 year old males and females (very low certainty).

Myocarditis and/or pericarditis

- We identified evidence reporting on myocarditis and pericarditis cases separately; therefore, we no longer report incidence for combined myocarditis and/or pericarditis.

KQ2: Risk Factors

Context

In KQ2 we assessed relative differences in outcomes across subgroups. It is important to note, however, that these relative results must be taken in context with KQ1 findings reporting on incidence. That is to say, the relative differences in subgroups in females and older age groups identified in the KQ2 findings should be given less weight in policy decision-making, based on the very low-to-no incidence of myocarditis after mRNA vaccination in these groups.

Myocarditis

Moderna versus Pfizer, after dose 2

- For 18-29 year-old males and females, and 18-39 year-old males the incidence of myocarditis is probably higher after vaccination with Moderna compared to Pfizer (moderate certainty).
- For 18-39 year-old females, the incidence of myocarditis may be higher after vaccination with Moderna compared to Pfizer (low certainty).
- For 30-39 year-old males and females, there may be little-to-no difference in the incidence of myocarditis after vaccination with Moderna compared to Pfizer (low certainty).
- Among ≥ 40 year-old males and females, there is probably little-to-no difference in risk of myocarditis after vaccination with Moderna compared to Pfizer (moderate certainty).

Myocarditis and/or pericarditis

Homologous vs heterologous vaccine for dose 2

- Among 18-29 and 18-39 year-old adults, and 18-29 year-old males, there may be little-to-no difference in the incidence of myocarditis/pericarditis after mRNA vaccination with a heterologous dose 2 compared to homologous dose 2 (low certainty).
- For adults ≥ 40 years old, we are uncertain about any difference in the incidence of myocarditis/pericarditis after mRNA vaccination with a heterologous dose 2 compared to homologous dose 2 (very low certainty).

Dose interval

- Among 12-17, 18-29 and 18-39 year-old individuals, the incidence of myocarditis/pericarditis after dose 2 of an mRNA vaccine may be lower when administered ≥ 31 days compared to ≤ 30 days after dose 1 (low certainty). Data specific to males 18-29 indicated that the dosing interval may need to increase to ≥ 56 days to substantially drop incidence.
- For 18-29 year-olds, the proportional decrease in incidence of myocarditis/pericarditis after dose 2 of an mRNA vaccine when administered ≥ 31 days compared to ≤ 30 days after dose 1 may be similar for Moderna compared with Pfizer. This proportional decrease may be smaller in Moderna compared to Pfizer for 18-39 year olds (low certainty).
- Among ≥ 40 year-old people, incidence of myocarditis/pericarditis after dose 2 of an mRNA vaccine may be higher when administered ≥ 31 days compared with ≤ 30 days after dose 1 (low certainty). In this group, the proportional increase in incidence of myocarditis/pericarditis after dose 2 when administered ≥ 31 days compared to ≤ 30 days after dose 1 may be greater for Moderna compared with Pfizer.

Clinical Comorbidities

- We are uncertain if people with immunocompromise or inflammatory conditions have a different risk of myocarditis after mRNA vaccination (very low certainty from single studies using passive reporting systems and having inadequate sample sizes).

KQ3: Short-term Clinical Course

- We found only one case series reporting on the short-term (<4 weeks) clinical course of cases of myocarditis after mRNA vaccination in children younger than 12 years old (mean 9 years, range 9 to 11). Among the 8 confirmed cases of myocarditis, 50% were males. All received the Pfizer vaccine product (Moderna is not authorized for younger than 18 years old).
- 75% of cases presented with symptoms after the second dose, at about 3 days (range 0 to 12) after any dose. Among tested individuals, 50% had abnormal EKG and 20% had abnormal echocardiogram. Among six patients for which outcomes were known, the symptoms resolved in five and one was still recovering.

KQ4: Longer-term Outcomes

- Three reports^{3 13 14} reported on 38 cases with follow-up approximately 90 days after diagnosis of myocarditis following vaccination with an mRNA COVID-19 vaccine.
- Among 14 patients hospitalized for myocarditis after vaccination in the two smaller case series (n=14), patients were males aged 13-19 years and followed up for ~90-105 days after diagnosis. In the case series of 5 patients,¹³ repeat cardiac MRI was undertaken in 2 patients, with both showing persistent but decreased late gadolinium enhancement similar to the distribution of the initial MRI but no new abnormalities. Further, 3 patients had self-resolving mild intermittent chest pain after discharge, 1 had recurrent chest pain after discontinuing the NSAID prescribed at discharge, and 3 had recurrent symptoms that prompted emergency department visits post-discharge. In the series of 9 patients,¹⁴ none were on heart failure medication at 90 day follow-up.
- In the larger case series (n=43),³ among cases of myocarditis and/or pericarditis (n=2) with long-term follow-up (n=24, mean follow-up time 89 days), the majority were males aged 12 to 17 years. Nine out of 18 patients receiving ECG had abnormal findings; 2 out of 17 with an echocardiogram showed abnormalities. Few (8%) patients were on medications such as NSAIDs and colchicine after discharge, and 46% had no symptoms, medications, or exercise restrictions at follow-up.

CQ1: Hypothesized Mechanisms

- We included 20 papers,¹⁵⁻³⁴ including narrative reviews, opinion pieces, letters to the editor, case reports, case series, a retrospective study, and a protocol for a prospective observational study.
- Across the included papers, we identified 16 hypotheses that are presented in Table 4. Additional details for each hypothesis are available in Supplementary Table 7.
- All hypotheses related to myocarditis rather than pericarditis. The most commonly discussed hypotheses were: hyper immune/inflammatory response; autoimmunity triggered by molecular mimicry or other mechanism; delayed hypersensitivity (serum sickness); eosinophilic myocarditis; and hypersensitivity to vaccine vehicle components (e.g., polyethylene glycol [PEG] and tromethamine; lipid nanoparticle sheath).
- A number of novel hypotheses were put forward by single papers, such as low residual levels of double-strand RNA (dsRNA), hyperviscosity inducing cardiac problems, and strenuous exercise induced secretion of proinflammatory IL-6.
- A number of papers discussed observed differences in incidence by sex (see KQ1) which could be attributed to sex steroid hormones or under-diagnosis in females.
 - Some opinions from our content experts (Drs Ian Paterson, Andrew Mackie, Bruce McManus) include:
 - The hyper immune/inflammatory response hypothesis raises the question of whether the response is systemic or specific to the heart. It is more likely systemic with concurrent subtle changes in other organs whereas the heart may be more susceptible. Further, it is easier to detect myopericarditis due to chest pain symptoms and measurable changes in cardiac biomarkers and imaging.
 - While autoimmunity triggered by molecular mimicry or other mechanism is among the more commonly discussed hypothesis, the observed response timing after the second vaccine dose (1-5 days) is considered early for this type of mechanism. If this is occurring after exposure to partial antigens (epitopes of SARs-CoV2 spike protein) being made from the mRNA vaccines, the question arises as to why this isn't the main hypothesis for myocarditis after COVID infection where there is exposure to entire SARs-CoV2 spike protein. Additionally, vaccines using adenoviral vector-based platforms produce the spike protein but have not been implicated in causing higher than background rates of myocarditis.
 - The delayed hypersensitivity hypothesis is supported by earlier work of other viruses (e.g., coxsackieviruses, echoviruses).

- Eosinophilic myocarditis is a very different entity and is not likely to be the mechanism behind all cases of post-vaccination cardiac inflammation. If this was the predominant mechanism of vaccine related myocarditis, then the rate of myocarditis would be similar to the rate of true allergic reactions to the vaccine.
- Hypersensitivity to vaccine vehicle components is among the more commonly discussed hypothesis; however, this is not likely to account for a major mechanism as allergic reactions have been very rare with the vaccines. The difference in incidence seen across sexes may point away from an allergic reaction predominating.
- The mechanism(s) may be very similar to that for myocarditis with COVID-19 infection, but at a lower incidence due to the much smaller quantity of spike protein exposure.
- One potential hypothesis that was not described in the examined articles relates to microvessel partial or complete thrombosis with multi-focal ischemic injury related to endothelial ACE2 expression and fibrin-platelet interactions in susceptible individuals.
- Several limitations exist:
 - Little direct empiric evidence was available to support or refute the proposed hypotheses. Where direct empiric evidence was available, it most often came from case reports or small series.
 - When assessing laboratory findings in case reports/series/retrospective studies, it is not clear whether any differences seen (e.g., increases in NK cells, autoantibodies) reflect a causal pathological immune response or reactive adaptive responses to the myocardial inflammation.
 - Due to the emergence of many studies since some of the articles were written, statements supporting or refuting several of the mechanisms may no longer be accurate; for example, articles stating no reports of eosinophilia are out-dated due to reports finding evidence of this.
 - A limitation to understanding the mechanism(s) of vaccine related myocarditis is the lack of invasive investigation (e.g., biopsy, tissue morphology, special studies to detect injury, immune activity, virus, etc.) given the typically mild course of the clinical conditions observed.
 - Another limitation is difficulty confirming a causal link. For example, an important proportion of cases observed or reported may not be vaccine-related and this will contribute to the heterogeneity of presentations, clinical characteristics, and resulting hypotheses.
- Choi et al.,⁵⁵ described a fatal case of myocarditis after mRNA vaccination and compared the case to another fatality reported by Verma et al.,³⁴ both of which had comprehensive clinicopathological analysis. The two cases were remarkably different, suggesting “that myocarditis after COVID-19 mRNA vaccination is heterogenous, both clinically and histologically.”⁵⁵ Moreover, there are likely multiple mechanisms leading to post-COVID-19 vaccination related myocarditis which may arise due to differences in the individuals affected.

Implications

- Adolescent and young adult males are likely at increased risk of myocarditis after an mRNA vaccination. This risk should be considered when making vaccine product recommendations for this group.
- Our findings suggest that Pfizer over Moderna and waiting more than 30 days between dose 1 and dose 2 may be preferred, especially in younger males.
- As the incidence of myocarditis after mRNA vaccination remains a rare adverse event, the findings must be considered alongside the overall benefits of vaccination and with detailed risk-benefit analyses to support policy recommendations for optimal dosing intervals and vaccine products for different populations.

Future Directions

Incidence, etc.

- As the COVID-19 pandemic enters its third year, continued surveillance of myocarditis after mRNA vaccines, especially in younger ages, after dose 3 (and subsequent doses) and in previous cases is needed to support continued decision making as regular COVID-19 boosters become a possibility for the future.
- Additional monitoring of populations with clinical comorbidities of interest (e.g., cardiac conditions, previous history of myocarditis, immunocompromised, etc.) is also needed in order to protect the already medically vulnerable.
- More longer term follow-up for vaccine related myocarditis is needed to better understand the natural history.

Hypothesized Mechanisms:

- A greater understanding of myocarditis associated with COVID-19 illness will likely yield insights into mechanisms for myocarditis associated with COVID-19 vaccines. Vaccine-related myocarditis may be a 'lesser' version of COVID-19 associated myocarditis, and exploring some of the mechanisms in the COVID-19 myocarditis literature may be valuable.
- More in-depth investigation of presenting cases is essential to understand mechanisms and confirm or refute existing hypotheses, including bloodwork, tissue biopsy, immunological analysis etc. To this end multi-center (e.g., national) prospective observational studies are required.

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Table 1: Summary of Findings for Incident Rates after Receipt of Either mRNA Vaccine (KQ1)

Sex	Age	Studies (data source and date) Country *passive surveillance	Risk interval; Confirmed cases (Y/N)	Incidence rates per million doses after dose 2 of either mRNA vaccine unless otherwise stated *weighted average across age groups ‡weighted average across products †excess incidence	Conclusions	Certainty about conclusions using GRADE
Myocarditis (after dose 2)						
M	5-11y	VAERS* Dec 19 US	7 d; Y	2.3 to 4.1† (Pfizer)	Among 5-11 year old males, the incidence of myocarditis after vaccination with the Pfizer vaccine may be fewer than 20 cases per million.	Low
		VAERS* Dec 9 US	12 d; Y	2.98 (both sexes; Pfizer)		
		VSD Dec 30 US	21 d; Y	0 myocarditis events/173,645 (both sexes; Pfizer)		
	12-17y	VAERS* Jun 18a US	Any; Y	139.5* (Pfizer)	Among 12-17 year old males, the incidence of myocarditis after vaccination with the Pfizer vaccine is probably between 50 and 139 cases per million.	Low ^{a,b}
		COVaxON* Sep 4 Canada	7 d; Y	88.1 (Pfizer)		
		VAERS* Oct 6 US	7 d; Y	49.6* (Pfizer)		
	12-39y	DVR/DPR Oct 5 Denmark	14 d; Y	87.7‡	Among 12-39y males, we are uncertain about incidence of myocarditis after vaccination with an mRNA vaccine.	Very Low ^c
	18-29y	Singapore Military	Any; Y	71.4*	Among 18-29 year old males, the incidence of myocarditis after vaccination with an mRNA vaccine is probably between 28 to 147 cases per million.	Moderate ^d
		COVaxON* Sep 4 Canada	7 d; Y	147.2‡ (18-24y)		
		Israel Defense Forces Mar 7	7 d; Y	50.7 (Pfizer; 18-24y)		
		Moderna Global Safety Database* Sep 30 Worldwide	7 d; Y	27.9*† (Ages 18-24y; Moderna)		
		VAERS* Oct 6 USA	7 d; Y	27.8*		
		Israel MOH May 31 ^e	30 d; Y	82.0†* (Pfizer)		
	18-39y	Singapore Military	Any; Y	60.2*	Among 18-39 year old males, the incidence of myocarditis after vaccination with an mRNA vaccine may be between 25 and 82 cases per million.	Low
		US Military Apr 30	4 d (all cases); Y	44 (median 25y [IQR: 20-51y])		
		Moderna Global Safety Database* Sep 30 Worldwide	7 d; Y	25.4* (Moderna)		
COVaxON* Sep 4 Canada		7 d; Y	82.2*‡			
F	5-11y	VAERS* Dec 19 US	7 d; Y	0-1.8† (Pfizer)	Among 5-11 year old females, the incidence of myocarditis after vaccination	Low

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Sex	Age	Studies (data source and date) Country *passive surveillance	Risk interval; Confirmed cases (Y/N)	Incidence rates per million doses after dose 2 of either mRNA vaccine unless otherwise stated *weighted average across age groups ‡weighted average across products †excess incidence	Conclusions	Certainty about conclusions using GRADE
		VAERS* Dec 9 US	12 d; Y	2.98 (both sexes; Pfizer)	with the Pfizer vaccine may be fewer than 20 cases per million.	
		VSD Dec 30 US	21 d; Y	0 myocarditis events/173,645 (both sexes; Pfizer)		
	12-17y	VAERS* Jun 18a US	Any; Y	13.1* (Pfizer)	Among 12-17 year old females, we are uncertain about the incidence of myocarditis after vaccination with mRNA vaccines.	Very Low ^a
		COVaxON* Sep 4 Canada	7 d; Y	9.7 (Pfizer)		
		VAERS* Oct 6 US	7 d; Y	5.2* (Pfizer)		
	18-29y	VAERS* Oct 6 US	7 d; Y	3.8*†	Among 18-29 year old females, the incidence of presenting with myocarditis after vaccination with an mRNA vaccine may be fewer than 20 cases per million.	Low
		Moderna Global Safety Database* Sep 30 Worldwide	7 d; Y	0*† (Ages 18-24; Moderna)		
		COVaxON* Sep 4 Canada	7 d; Y	34.6‡		
		Israel MOH May 31 [†]	30 d; Y	8.9*† (16-29y; Pfizer)		
	18-39y	COVaxON* Sep 4 Canada	7 d; Y	22.8*‡	Among 18-39 year old females, we are uncertain about the incidence of myocarditis after vaccination with an mRNA vaccine.	Very Low ^{a,c}
		Moderna Global Safety Database* Sep 30 Worldwide	7 d; Y	2.7* (Moderna)		
Myocarditis (after dose 3)						
M	13-39y	NIMS/NHS Nov 15 UK	28 d; Y	13 † (Pfizer)	Among 13-39 year old males, we are uncertain about the incidence of myocarditis after vaccination with mRNA vaccines.	Very Low ^{c,d}
			7 d; Y	0 †‡		
	≥40y	NIMS/NHS Nov 15 UK	28 d; Y	3 † (Pfizer)	Among ≥40 year old males, the incidence of myocarditis after vaccination with the with mRNA vaccines may be fewer than 20 cases per million.	Low
			7 d; Y	0 †‡		
F	13-39y	NIMS/NHS Nov 15 UK	28 d; Y	0 †‡	Among 13-39 year old females, we are uncertain about the incidence of myocarditis after vaccination with mRNA vaccines.	Very Low ^{c,d}
			7 d; Y	0 †‡		
	≥40y	NIMS/NHS Nov 15 UK	28 d; Y	0 †‡	Among ≥40 year old females, we are uncertain about the incidence of	Very Low ^c
			7 d; Y	0 †‡		



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Sex	Age	Studies (data source and date) Country *passive surveillance	Risk interval; Confirmed cases (Y/N)	Incidence rates per million doses after dose 2 of either mRNA vaccine unless otherwise stated *weighted average across age groups ‡weighted average across products †excess incidence	Conclusions	Certainty about conclusions using GRADE
		Mayo Clinic Oct 17 US	14d; Y	41.5‡	myocarditis after vaccination with mRNA vaccines.	
Pericarditis						
M	5-11	VSD Dec 30 US	21 d; Y	2.3 (both sexes; Pfizer)	Among 5-11 year old males, we are uncertain about the incidence of pericarditis after vaccination with Pfizer.	Very Low ^{c,e}
F	5-11	VSD Dec 30 US	21 d; Y	2.3 (both sexes; Pfizer)	Among 5-11 year old females, we are uncertain about the incidence of pericarditis after vaccination with Pfizer.	Very Low ^{c,e}

[†]Crude incident rates were converted to excess incidence rates using the estimated adjusted IRRs from the study (excess=crude incidence –(crude incidence / aIRR); for males: aIRR 16-19 y 8.96 (95% CI, 4.50 to 17.83); 20-24 y 6.13 (95% CI 3.16 to 11.88); 25-29 y 3.58 (95% CI 1.82 to 7.01); ≥30 y 1.00 (95% CI, 0.61 to 1.64) (note: for the 30-39y old data we used an average of the 25-29 and ≥30y aIRRs); for females: 16-19y 2.95 (0.42–20.91), 20-24 y 7.56 (1.47–38.96), 25-29y 0, ≥30y 0.82 (0.33–2.02)(not used)

Explanations for GRADE:

In the plain-language conclusions, we have used “probably”, “may be” and “uncertain” to reflect level of certainty in the evidence based on GRADE of moderate, low, or very low, respectively.

^aAll studies used data from passive reporting systems and were thus at high risk of bias from likely underestimation.

^bRated up for estimated incidence likely to be more than twice our clinically important threshold of 20 cases per million, highly unlikely to be seen by chance and credible to be higher than for other age categories. (Citation: Guyatt et al. 2011 <https://doi.org/10.1016/j.jclinepi.2011.06.004>)

^cRated down for inconsistency for only one study or for a large incidence range within one age/sex category

^dRated down for imprecision; sample size of 13-39 year olds getting 3rd dose was not sufficient in this UK study.

^eRated down for indirectness of findings to entire population, based on large differences in estimates in analyses for males across age groups indicating one estimate (or even a range of estimates) for all ages (for both sexes or males) is not credible.





Table 2. Summary of Findings for Possible Risk Factors for myocarditis after mRNA vaccination (KQ2)

Sex	Age	Data source & date Country *passive surveillance	Risk interval; confirmed cases (Y/N)	Incidence/reporting rate per million doses after dose 2 (95% CI) *weighted average across multiple age groups ¹	Relative measures (95% CI) aRR = adjusted risk ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
Myocarditis							
Moderna vs Pfizer (ref), dose 2							
M	18-29y	VAERS Oct 6* US	7d; Y	Moderna: 23.9* Pfizer: 26.0*		Among 18-29 year old males, there is probably a higher incidence of myocarditis following vaccination with Moderna compared with Pfizer.	Moderate ^a
		COVaxON Sep 4* Canada	Any; Y	Moderna: 299.5 (171.2, 486.4) (18-24y) Pfizer: 35.5 (7.3, 103.7) (18-24y)			
	18-39	VAERS Oct 6* US	7d; Y	Moderna: 19.2* Pfizer: 16.5*		Among 18-39 year old males, there is probably a higher incidence of myocarditis following vaccination with Moderna compared with Pfizer.	Moderate ^a
		VSD Oct 9 US	7d; Y		RD: 19.1 aRR: 2.14 (0.93 to 4.98)		
		Singapore Military	Any; Y	Moderna: 135.3* Pfizer: 0 events/27,632			
	COVaxON Sep 4* Canada	Any; Y	Moderna: 144.5* Pfizer: 19.9*				
	30-39y	VAERS Oct 6* US	7d; Y	Moderna: 6.7 Pfizer: 5.2		Among 30-39 year old males, there may be little-to-no difference in the incidence of myocarditis after vaccination with Moderna compared with Pfizer.	Low ^{a,b}
	12-39y	NIMS Nov 15 UK	7d; Y	Moderna: IRR ² = 54.65 (29.74, 100.40) Pfizer: IRR ² = 8.05 (5.37, 12.06)		Among 12-39 year old males, there may be a higher incidence of myocarditis following vaccination with Moderna compared with Pfizer.	Low ^{a,c}
		NIMS Nov 15 UK	28d; Y	Moderna: IRR ² = 16.52 (9.10, 30.00) Pfizer: IRR ² = 3.41 (2.44, 4.78)			
	≥40y	VAERS Oct 6* US	7d; Y	Moderna: 1.52* (40-64y) Pfizer: 0.98* (40-64y)		Among ≥40 year old males, there is probably little-to-no difference in risk of myocarditis after vaccination with Moderna compared with Pfizer.	Moderate ^b
NIMS Nov 15 UK		7d; Y	Moderna: 0 events Pfizer: IRR ² = 0.65 (0.27, 1.59)				
NIMS Nov 15 UK		28d; Y	Moderna: 0 events Pfizer: IRR ² = 0.79 (0.51, 1.23)				
COVaxON Sep 4* Canada		Any; Y	Moderna: 0.0 (0.0-35.6) Pfizer: 0.0 (0.0-23.3)				
F	18-29y	COVaxON Sep 4* Canada	Any; Y	Moderna: 69.1 (14.2-201.9) (18-24y) Pfizer: 0.0 (0.0-50.5) (18-24y)		Among 18-29 year old females, there is probably a	Moderate ^b



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Sex	Age	Data source & date Country *passive surveillance	Risk interval; confirmed cases (Y/N)	Incidence/reporting rate per million doses after dose 2 (95% CI) *weighted average across multiple age groups ¹	Relative measures (95% CI) aRR = adjusted risk ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
		VAERS Oct 6* US	7d; Y	Moderna: 5.5* Pfizer: 2.0*		higher incidence of myocarditis following vaccination with Moderna compared with Pfizer.	
	18-39	VAERS Oct 6* US	7d; Y	Moderna: 3.1* Pfizer: 1.4*		Among 18-39 year old females, there may be a higher incidence of myocarditis following vaccination with Moderna compared with Pfizer.	Low ^{a,c}
		COVaxON Sep 4* Canada	Any; Y	Moderna: 36.8* Pfizer: 8.9*			
	30-39y	VAERS Oct 6* US	7d; Y	Moderna: 0.4 Pfizer: 0.7		Among 30-39 year old females, there may be little-to-no difference in incidence of myocarditis after vaccination with Moderna compared with Pfizer	Low ^{a,d}
	12-39y	NIMS Nov 15 UK	7 d; Y	Moderna: IRR ² = 28.49 (6.22, 130.41) Pfizer: IRR ² = 3.11 (1.23, 7.86)		Among 12-39 year old females, there may be a higher incidence of myocarditis following vaccination with Moderna compared with Pfizer.	Low ^{a,c}
		NIMS Nov 15 UK	28d; Y	Moderna: IRR ² = 7.55 (1.67, 34.12) Pfizer: IRR ² = 1.37 (0.67, 2.80)			
	≥40y	COVaxON Sep 4* Canada	Any; Y	Moderna: 0.0 (0.0, 40.9) Pfizer: 0.0 (0.0, 23.5)		Among ≥40 year old females, there is probably little-to-no difference in the incidence of myocarditis after vaccination with Moderna compared with Pfizer.	Moderate ^u
		NIMS Nov 15 UK	7 d; Y	Moderna: 0 events Pfizer: IRR ² = 0.80 (0.33, 1.97)			
		NIMS Nov 15 UK	28d; Y	Moderna: 0 events Pfizer: IRR ² = 1.00 (0.64, 1.55)			
		VAERS Oct 6* US	7d; Y	Moderna: 0.8* (40-64y) Pfizer: 0.74* (40-64y)			
Myocarditis/pericarditis							
Homologous vs heterologous dose 2							
Both sexes	18-29y	COVaxON Sep 4* Canada	Any; Y	Mod-Mod: 162.0 (108.5, 232.6) (18-24y) Mod-Pfz: 0.0 (0.0, 218.8) (18-24y) Pfz-Mod: 203.9 (142.0, 283.6) (18-24y) Pfz-Pfz: 26.9 (14.3, 45.9) (18-24y)		Among 18-29 year old adults, there may be little-to-no difference in the incidence of myocarditis/pericarditis after vaccination with an mRNA vaccine using a heterologous dose 2 compared with homologous dose 2.	Low ^{a,c}



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Sex	Age	Data source & date Country *passive surveillance	Risk interval; confirmed cases (Y/N)	Incidence/reporting rate per million doses after dose 2 (95% CI) *weighted average across multiple age groups	Relative measures (95% CI) aRR = adjusted risk ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
	18-39y	COVaxON Sep 4* Canada	Any; Y	Mod-Mod: 72.1* Mod-Pfiz: 0.0 Pfiz-Mod: 100.3* Pfiz-Pfiz: 17.7*		Among 18-39 year old adults, there may be little-to-no difference in the incidence of myocarditis/pericarditis after vaccination with an mRNA vaccine using a heterologous dose 2 compared with homologous dose 2.	Low ^{a,c}
	≥40y	COVaxON Sep 4* Canada	Any; Y	Mod-Mod: 10.2 (4.7, 19.4) Mod-Pfiz: 12.5 (0.3, 69.7) Pfiz-Mod: 3.8 (0.8, 11.0) Pfiz-Pfiz: 5.4 (3.1, 8.6)		Among ≥40 year old adults, we are uncertain about any difference in incidence of myocarditis/pericarditis after vaccination with an mRNA vaccine using heterologous dose 2 compared with homologous dose 2.	Very Low ^{a,c}
M	18-29y	COVaxON Sep 4* Canada	Any; Y	Mod-Mod: 288.4 (18-24y) Mod-Pfiz: 0 (18-24y) Pfiz-Mod: 337.6 (18-24y) Pfiz-Pfiz: 46.6 (18-24y)		Among 18-29 year old males, there may be little-to-no difference in incidence of myocarditis/pericarditis after vaccination with an mRNA vaccine using heterologous dose 2, compared with homologous dose 2.	Low ^{a,b}
Dose interval							
Both sexes	12-17y	COVaxON Sep 4* Canada	Any; Y	<30 d: 101.9 (55.7-170.9) (Pfizer only) 31-55 d: 37.7 (21.6-61.3) (Pfizer only) ≥56 d: 55.7 (20.4-121.2) (Pfizer only)		Among 12 to 17 year old people, incidence of myocarditis/pericarditis after dose 2 of Pfizer may be lower when administered ≥31 days compared with administration ≤30 days after dose 1.	Low ^{a,c}
	18-29y	COVaxON Sep 4* Canada	Any; Y	<30 d: 199.2* (18-24y) 31-55 d: 109.4* (18-24y) ≥56 d: 56.7* (18-24y)		Among 18 to 29 year old people, incidence of myocarditis/pericarditis after dose 2 of an mRNA vaccine may be lower when administered ≥31 days compared with administration ≤30 days after dose 1.	Low ^{a,c}



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Sex	Age	Data source & date Country *passive surveillance	Risk interval; confirmed cases (Y/N)	Incidence/reporting rate per million doses after dose 2 (95% CI) *weighted average across multiple age groups ¹	Relative measures (95% CI) aRR = adjusted risk ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
	18-39y	COVaxON Sep 4* Canada	Any; Y	<30 d: 91.3* 31-55 d: 53.1* ≥56 d: 32.2*		Among 18 to 39 year old people, incidence of myocarditis/pericarditis after dose 2 of an mRNA vaccine may be lower when administered ≥31 days compared with ≤30 days after dose 1	Low ^{a,c}
	≥40y	COVaxON Sep 4* Canada	Any; Y	<30d: 0 31-55d: 4.5 ≥56 d: 7.2		Among ≥40 year old people, incidence of myocarditis/pericarditis after dose 2 of an mRNA vaccine may be higher when administered ≥31 days compared with ≤30 days after dose 1.	Low ^{a,c}
M	18-29	COVaxON Sep 4* Canada	Any; Y	≤30 d: 148.1 (18-24y) 31-55 d: 111.1 (18-24y) ≥56 d: 30.7 (18-24y)		Among 18 to 29 year old males, incidence of myocarditis/pericarditis after dose 2 of an mRNA vaccine may be lower when administered ≥56 days compared with ≤55 days after dose 1.	Low ^{a,c}
Dose interval, by Dose 2 product							
	18-29y	COVaxON Sep 4* Canada	Any; Y	<u>Moderna (18-24y)</u> <30d: 353.1 (182.4-616.8) 31-55d: 184.0 (133.7-247.0) ≥56d: 103.2 (44.5-203.3) <u>Pfizer (18-24y)</u> <30d: 45.3 (5.5-163.7) 31-55d: 34.7-15.9-66) ≥56d: 10.1 (1.2-36.5)		Among 18 to 29 year old people, the proportional decrease in incidence of myocarditis/pericarditis after dose 2 of an mRNA vaccine when administered ≥31 days compared with ≤30 days after dose 1 may be similar for Moderna compared with Pfizer.	Low ^{a,c}



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Sex	Age	Data source & date Country *passive surveillance	Risk interval; confirmed cases (Y/N)	Incidence/reporting rate per million doses after dose 2 (95% CI) *weighted average across multiple age groups ¹	Relative measures (95% CI) aRR = adjusted risk ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
	18-39y	COVaxON Sep 4* Canada	Any; Y	<u>Moderna</u> <30d: 139.3* 31-55d: 89.2* ≥56 d: 52.9 <u>Pfizer</u> <30d: 43.4* 31-55d: 17.0* ≥56d: 11.6*		Among 18 to 39 year old people, the proportional decrease in incidence of myocarditis/pericarditis after dose 2 of an mRNA vaccine when administered ≥31 days compared with ≤30 days after dose 1 may be smaller in Moderna compared with Pfizer.	Low ^{a,c}
	≥40y	COVaxON Sep 4* Canada	Any; Y	<u>Moderna</u> <30d: 0.0 (0.0-53.9) 31-55d: 7.4 (2.0-19.0) 56d: 7.5 (3.2-14.7) <u>Pfizer</u> <30d: 0.0 (0.0-34.4) 31-55d: 1.5 (0.0-8.3) 56d: 6.9 (4.0-11.1)		Among ≥40 year old people, the proportional increase in incidence of myocarditis/pericarditis after dose 2 of an mRNA vaccine when administered ≥31 days compared with ≤30 days after dose 1 may be greater for Moderna compared with Pfizer.	Low ^{a,c}
Clinical comorbidities							
Both sexes	All ages	EULAR COVAX* Europe	Any; N	Among 4025 people with inflammatory rheumatic musculoskeletal conditions (68% female) who received at least one dose of mRNA vaccine, there was one event in a young (<30y) female after dose 2 of Pfizer. There were no events in 412 people with non-inflammatory rheumatic musculoskeletal conditions who received at least one dose of mRNA vaccine.		We are uncertain if individuals with inflammatory conditions have a different risk of myocarditis/pericarditis after mRNA vaccination.	Very Low ^{a,b,d}
		VAERS Nov 30* US	Any; N	The reporting rate of myocarditis/pericarditis was higher for immunocompromised patients compared with immune competent individuals (Proportional reporting rate=1.36 [95% CI: 0.89-1.82]).		We are uncertain if individuals with immunocompromise have a difference risk of myocarditis/pericarditis after mRNA vaccination.	Very Low ^{a,b,d}

¹Weighted averages across age groups were calculated based on contribution of each age to the review-level age category.

²IRRs were calculated using a self-controlled case series design in which risk estimates are calculated within individuals, rather than across individuals.

Explanations for GRADE

In the plain-language conclusions, we have used “probably”, “may be” and “uncertain” to reflect level of certainty in the evidence based on GRADE of moderate, low, or very low, respectively.

^aRated down for inconsistency due to only one study providing estimates or from inconsistency between studies. Because of the large overlap in data between males 18-29y and 18-39y, and moderate certainty about higher incidence in the 18-39y category, we only downrated 18-29y once for inconsistency despite the large differences in effects reported between studies.

^bRated down for imprecision for small sample size (<10,000 per group) or very low event rate.

^cRated down for indirectness to whole population, based on large differences in estimates in analyses for males across age groups indicating one estimate (or even a range of estimates) for all ages (for both sexes or males) is not credible.

^dRated down for risk of bias from use of passive surveillance and lack of case verification.



Table 3. Case Series of Myocarditis, Pericarditis, or Myopericarditis after mRNA COVID-19 Vaccination (KQ3, KQ4)

Case series (country)	Characteristics and short-term clinical course (KQ3)	Characteristics and short- and long-term clinical course (KQ4)		
		Chelala 2021 (US)	Patel 2021 (US)	Klein 2022 (US)
Date of cases last updated	10 Dec 2021	14 June 2021	June 2021	25 Dec 2021
Cases, n	8	5	9	43
Confirmed cases	Diagnoses reviewed and met the CDC case definition	Clinically confirmed through review of medical records, results of biochemical laboratory testing, ECG results, and findings from echocardiography, cardiac MRI; met 2018 Lake Louise criteria	Diagnoses reviewed and met the CDC case definition and troponin elevation	ICD-10 used then diagnoses confirmed by medical record review
Case source	VAERS	Single medical centre in USA	Single medical centre in Atlanta, USA	Kaiser Permanente in Colorado, Oregon, California, and Washington; HealthPartners Institute Minnesota; Denver Health
Myocarditis, %	100%	100%	100%	53%
Pericarditis, %	0%	0%	0%	5%
Myopericarditis, %	0%	0%	0%	42%
Male, %	50%	100%	100%	86%
Median age (range), y	9 (6-11)	Mean = 17 (16-19)	15.7 (IQR 14.5-16.6)	67% = 12-15 years 33% = 16-17 years
Ages included	5-11 years			
Vaccine product, n	8 (100%) = BNT 162b2 (Pfizer)	4 (80%) = BNT 162b2 (Pfizer) 1 (20%) = mRNA-1273 (Moderna)	100% mRNA vaccine	100% = BNT 162b2 (Pfizer)
% Patients in ICU	0%	NR	22%	26%
% Hospitalized	NR	100%	100%	65%
% Patients presenting after second vaccination	75%	100%	89%	NR
% Patients with prior COVID-19 history	NR	0%	NR	5%
% Patients COVID-19 polymerase chain reaction positive	NR	0%	NR	NR
% Patients with COVID nucleocapsid antibody present (% of tested)	NR	NR	NR	NR
% Patients with SARS-CoV-2 spike antibody	NR	NR	NR	NR

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% Patients with prior myocarditis or pericarditis history	NR	0% reported significant cardiovascular risk factors or history of previous cardiovascular events	NR	5%
Presentation				
Time between last vaccine and symptom onset, median days, (range)	3 (0-12) One patient with 12 day onset had history of headache and gastrointestinal symptoms 3 or 4 days before chest pain; potential viral syndrome	4 (3-4)	Median 3 days between 2 nd vaccination and hospital admission	2 (0-20)
% Patients with chest pain on presentation	88%	100%	100%	NR
% Patients with other symptoms (eg, myalgia, fatigue, fever)	NR	NR	44% dyspnea	NR
Diagnostic evaluation				
% Patients with troponin elevation (of tested)	100% (all tested)	100% (5/5 tested)	NR	NR
Median time to troponin peak after vaccination, days	NR	NR	NR	NR
% Patients with BNP or NT-proBNP elevation (among tested)	NR	100% normal (4/5 tested)	NR	NR
% Patients with CRP elevation (among tested)	NR	80% (all tested)	NR	NR
% Patients with eosinophilia (among tested)	NR	NR	NR	NR
% Patients with abnormal ECG (among tested)	50% (6/8 tested; 2 ST elevations, 1 non-specific ST and T wave changes)	60% = normal 20% = ST segment elevation 20% = sinus bradycardia	33% = normal 67% = repolarization abnormalities	NR
% Patients with abnormal cardiac MRI (among tested)	NR	100% = no segmental wall motions abnormalities, and basilar and mid-cavity involvement; early and late gadolinium enhancement	NR	NR
% Patients with abnormal echocardiogram (among tested)	20% (5/8 tested; mitral regurgitation)	20% = LVEF mildly to moderately decreased and associated with global hypokinesis; 20% = ectasia of right coronary artery and left anterior descending artery; 80% = normal	Median (IQR) LVEF at presentation = 60 (58-67)	NR
% Patients with LVEF < 50% (among tested)	NR	20%	22% with 30-55% LVEF at presentation 78% with >55% LVEF at presentation	NR



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Outcome				
% Patients with symptoms resolved	83% resolved (5/6 reports with known outcomes)	100%	NR	100% discharged home
Fatalities, n	0	0%	0%	0%
Median hospitalization length of stay, days (range)	NR	3 (3-9)	NR	2 (0-7)
% Patients treated with medications for myocarditis	NR	Prescribed at discharge: 20% colchicine and metoprolol 20% metoprolol 20% NSAID 20% aspirin	89% Other NSAID if no aspirin 22% Vasopressors 11% IVIG 11% aspirin 0% steroids	NR
Long-term Outcomes				
Number of patients with follow-up data	NA	5/5 (100%)	9/9 (100%)	24/43 (56%)
Mean length clinical follow-up (range), days	NA	95 (92-104)	90 (NR)	88.5 (28-153)
% Repeat cardiac MRI	NA	40%	NR	4%
Characteristics of repeat cardiac MRI	NA	2 performed, both stable biventricular size and function; persistent, but decreased, LGE that was similar in distribution to the initial MRI; and an absence of new areas of abnormality	NR	Normal findings
Symptoms such as chest pain	NA	60% = mild intermittent self-resolving chest pain after discharge; in one patient recurrent symptoms occurred after discontinuation of the NSAID prescribed at discharge	NR	38% chest pain 13% shortness of breath 13% palpitations 4% fatigue 13% other (e.g., orthostatic hypotension, dizziness)
Medical visits following discharge	NA	60% = recurrent symptoms resulted in an emergency department visit	ECG findings at clinic follow up (1-2 weeks after discharge) 83% = normal 17% = repolarization abnormalities	75% electrocardiogram with 50% abnormal 71% echocardiogram with 12% abnormal
% Continued treatment with medications	NA	NR	0% on heart failure medication	8% (e.g., NSAIDs, colchicine)
% Recovered with no symptoms	NA	NR	NR	46% (no symptoms, medications, or exercise restrictions)

Abbreviations: BNP/NT-proBNP = B-type natriuretic peptide/N-terminal pro B-type natriuretic peptide; CDC = Centers for Disease Control and Prevention; CRP = c-reactive protein; ECG = echocardiogram; ICD = International Classification of Diseases; ICU = intensive care unit; IQR = interquartile range; IVIG = intravenous immune globulin; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; mRNA = messenger ribonucleic acid; NA = not applicable; NR = not reported; NSAID = non-steroidal anti-inflammatory drugs; PHAC = Public Health Agency of Canada; VAERS = vaccine adverse event reporting system



Table 4. Hypothesized mechanisms for myocarditis following mRNA COVID-19 vaccination and direct (i.e., on myocarditis after COVID-19 vaccine) supporting/refuting empirical evidence (CQ1)

Hypothesis		Citations	Direct Empirical Evidence	
			Supporting	Refuting
1	Hyper immune/inflammatory response, via exposure to spike protein, mRNA strand, or unknown trigger	N=9 Hajra et al., 2021 ²³ Tsilingiris et al., 2021 ³³ Heymans & Cooper, 2021 ²⁴ Parra-Lucare et al., 2021 ²⁹ Bozkurt et al, 2021 ¹⁷ Das et al., 2021 ²⁰ Boursier, 2021 ¹⁶ Switzer & Loeb, 2021 ³⁰ Verma et al., 2021 ³⁴	- 3 case reports: Muthukumar, Boursier, Verma - Multiple case series/reports reporting highest incidence in youth who have higher immunogenicity and reactogenicity from vaccines	- 2 case reports: Muthukumar, Larson - 1 case series: Das
2	Delayed hypersensitivity (serum sickness)	N=5 Hajra et al 2021 ²³ Tsilingiris et al., 2021 ³³ D'Angelo et al, 2021 ¹⁹ Bozkurt et al., 2021 ¹⁷ Chouchana et al., 2021 ¹⁸	- 1 case report: D'Angelo - 1 case series: Montgomery	- 6 case reports: Muthukumar, Ammirati, D'Angelo, Bautista, Mclean, Albert - 6 case series: Abu Mouch, Kim, Marshall, Rosner, Larson, Johnston
3	Eosinophilic myocarditis	N=4 Hajra et al 2021 ²³ Takeda et al. 2021 ³¹ D'Angelo et al, 2021 ¹⁹ Bozkurt et al, 2021 ¹⁷	- 1 case report: Takeda	- 6 case reports: Muthukumar, Ammirati, D'Angelo, Bautista, Mclean, Albert - 6 case series: Abu Mouch, Kim, Marshall, Rosner, Larson, Johnston
4	Hypersensitivity to vaccine vehicle components (e.g., polyethylene glycol [PEG] and tromethamine; lipid nanoparticle sheath)	N=4 Kounis et al. 2021a ²⁷ Kounis et al. 2021b ²⁶ Tsilingiris et al., 2021 ³³ Bozkurt et al., 2021 ¹⁷	- 4 case reports: Sokolska, Verma, Witberg (1 case with biopsy in series), 1 not cited - 1 cohort study: Patone	- 6 several case reports: Muthukumar, Ammirati, D'Angelo, Bautista, Mclean, Albert - 6 case series: Abu Mouch, Kim, Marshall, Rosner, Larson, Johnston

5	Response to mRNA vaccine lipid nanoparticles (direct deleterious effect; not delayed – see hypothesis 4)	N=2 Tsilingiris et al., 2021 ³³ Kadkhoda et al., 2021 ²⁵	- 1 cohort: Patone	None
6	Autoimmunity triggered by molecular mimicry or other mechanism	N=9 Hajra et al 2021 ²³ Tsilingiris et al., 2021 ³³ D'Angelo et al, 2021 ¹⁹ Heyman & Cooper, 2021 ²⁴ Bozkurt et al., 2021 ¹⁷ Chouchana et al., 2021 ¹⁸ Switzer & Loeb, 2021 ³⁰ Parra-Lucare et al., 2021 ²⁹ Ehlich et al., 2021 ²¹	Molecular mimicry: - 2 case reports: D'Angelo, Ammirati, - 1 case series: Larson - 1 in vitro study: Vojdani Other autoimmune: - 1 case report: Muthukumar	Molecular mimicry: - 3 cohorts/registry: Patone, Alberta Office of the Chief Medical Officer of Health, Australian Government - 2 case reports: Sulemankhil, Ehlich Other autoimmune: direct findings indicated but not cited
7	Low residual levels of double-strand RNA (dsRNA)	N=1 Milano et al 2021 ⁴	None	None
8	Dysregulated micro-RNA response	N=1 AbdelMassih et al. 2021 ¹⁵	None	None
9	Production of anti-idiotypic antibodies against immunogenic regions of antigen-specific antibodies	N=1 Tsilingiris et al., 2021 ³³	None	None
10	Trigger of pre-existing dysregulated immune pathways in certain individuals with predispositions (e.g., resulting in a polyclonal B-cell expansion, immune complex formation, and inflammation ¹⁷)	N=2 Bozkurt et al., 2021 ¹⁷ Switzer & Loeb, 2021 ³⁰	None	For specific predispositions: 1 - case report: Muthukumar 1 - case series: Abu Mouch
11	Antibody-dependent enhancement of immunity or other forms of immune enhancement with re-exposure to virus after vaccine	N=1 Bozkurt et al., 2021 ¹⁷	None	Multiple case reports and series reviewed and tabulated, having no evidence of acute COVID-19 infections after vaccine when presenting with myocarditis
12	Direct cell invasion via the spike protein interacting with the angiotensin-converting enzyme 2 (ACE2) widely expressed and prevalent in cardiomyocytes ¹⁸	N=2 Chouchana et al., 2021 ¹⁸ Switzer & Loeb, 2021 ³⁰	None	- 2 cases: Verma
13	Cardiac pericyte expression of ACE2 with immobilized immune complex on the	N=1 Kadkhoda et al., 2021 ²⁵	None	None

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	surface of pericytes activation of the complement system			
14	Spike-activated neutrophils (expressing ACE2) augmenting inflammatory response	N=2 Kadkhoda et al., 2021 ²⁵ Choi et al., 2021 ⁵⁵	- 1 case report: Choi	None
15	Hyperviscosity-induced cardiac problem	N=1 Mungmunpantipantip & Wiwanitkit, 2021 ⁵⁶	None	None
16	Strenuous exercise induced secretion of proinflammatory IL-6	N=1 Elkazzaz et al., 2022 ²²	None	None
Observation				
	Differences in incidence by sex could be due to sex steroid hormones or underdiagnosis in females	N=5 Tsilingiris et al., 2021 ³³ Heymans & Cooper, 2021 ²⁴ Bozkurt et al., 2021 ¹⁷ Chouchana et al., 2021 ¹⁸ Parra-Lucare et al., 2021 ²⁹	Sex hormones: None Underdiagnosis in women: CDC, Bozkurt (unpublished data)	Sex hormones: - 1 cohort: Montgomery Underdiagnosis in women: None



Appendix 1. Supplementary Tables

Supplementary Table 1. Eligibility criteria for a living evidence synthesis on myocarditis after mRNA COVID-19 vaccination.

Population/Problem	<p>People of any age; data must be reported using age categories (e.g., 0-4, 5-11, 12-17, 18-29, 30-39, ≥40 years).</p>
Intervention/Exposure	<p>KQ1: mRNA vaccines approved in Canada: BNT162b2 mRNA/PfizerBioNTech/Comirnaty, mRNA-1273/Moderna Spikevax (alternative manufacturers of same vaccine are eligible), by type of vaccine and dose. KQ2: Same as KQ1, plus potential risk/protective factors: pre-existing conditions [e.g. cardiac diseases, immunocompromise], previous SARS-CoV-2 infection (symptomatic or asymptomatic) or other viral infections, length of vaccine dosing interval. KQ3: Confirmed myocarditis or pericarditis after mRNA COVID-19 vaccination. KQ4: Confirmed myocarditis or pericarditis after mRNA COVID-19 vaccination. CQ1: Confirmed myocarditis or pericarditis after mRNA COVID-19 vaccination.</p> <p>Note: At least one dose of the vaccine needs to be with an mRNA vaccine; one or more other doses may have been with a non-mRNA vaccine.</p>
Control/Comparator	<p>KQ1: People previously vaccinated with mRNA COVID-19 vaccine but no longer at risk for outcome, previously vaccinated with other vaccines (i.e., controlling for confounders associated with vaccine uptake), or unvaccinated people; or no comparator. KQ2: People with myocarditis after vaccination with mRNA COVID-19 vaccine but without the risk/protective factor. KQ3: No comparator. KQ4: No comparator, but will include data on any comparisons with people vaccinated and not experiencing myocarditis or pericarditis. CQ1: People previously vaccinated with mRNA COVID-19 vaccine who did not experience myocarditis or pericarditis; or no comparator.</p>
Outcome	<p>KQ1: Incidence rate/cummulative risk of confirmed myocarditis (including myopericarditis) or pericarditis by dose; subgroups based on time post-vaccination (0-7d vs 8-28d vs longer. Effect measures: incidence rate/cummulative risk (may be risk difference if accounting for background rate in control group); relative/absolute effects between groups (eg. rate ratio or relative risk (RR) between vaccine types or doses). Will include rates of myocarditis or pericarditis (reported collectively) if there is no other data specific to myocarditis or pericarditis. KQ2: Ratio measures of incidence/reported events by risk/protective factor (e.g., RR or odds ratios), adjusted for key confounders (e.g., previous COVID-19 illness and severity) when reported. KQ3: Characteristics of the patients (e.g., age, sex, pre-existing conditions [e.g., cardiac diseases] and infections [e.g.,</p>

	<p>recent/past SARS-CoV-2 infection], race/ethnicity) and case presentation (e.g., timing/dose/type of vaccine, diagnostics, illness severity, treatments provided, short-term outcomes).</p> <p>KQ4: Any outcomes measured ≥ 4 weeks after onset of myocarditis or pericarditis (e.g., re-hospitalization, functional capacity, chest pain).</p> <p>CQ1: Authors' summaries of any hypotheses or findings after investigating potential mechanisms (e.g., histology, experiments with viral spike glycoprotein of SARS-CoV-2 [encoded by mRNA vaccine]), gene panels, serology for innate and acquired immune system components, autoimmune antibodies).</p>
Setting	Any setting and country.
Study design	<p>KQ1: Large (>10,000 vaccinated people) sample or multisite/health system-based observational studies; reports or databases of confirmed cases using surveillance data.</p> <p>KQ2: Observational studies (including case control studies) with $n \geq 10$ with the risk/protective factor; data for subset of people with myocarditis or pericarditis may come from passive reporting systems.</p> <p>KQ3: Case series $N > 10$; data may come from medical record review of cases reported to passive surveillance systems (if reporting more than age, sex, and dose and type of vaccine).</p> <p>KQ4: Case series $N > 10$; data may come from medical record review of cases reported to passive surveillance systems.</p> <p>CQ1: Any primary study, systematic review, or expert opinion article/letter on the topic.</p> <p>Letters and commentaries will be included if they provide sufficient data.</p>
Publication Language	English full texts.
	We will cite those excluded based on language.
Publication Year & Status	Oct 2020-onwards (vaccines were authorized mid-Sept 2020).
	Pre-prints will be included.

Supplementary Table 2. Study characteristics of active surveillance/registry studies contributing to KQ1.

Dataset Dates Country	Vaccines Studied	Sample Size; Demographics; Previous Covid-19 diagnoses	Study Group(s)	Outcome(s); Risk Interval; Case Ascertainment	Analysis	Results
Dose 3						
NIMS Dec 1 2020 to Nov 15 2021 England Patone 2021 (7268)	Pfizer-BioNTech Moderna Dose 1, 2 or 3 Interval between doses NR	21,554,158 with at least one dose, aged ≥13 y Previous COVID in 54.7% of total sample People with history of myocarditis in previous 2 years excluded	Pfizer Dose 1 n=20,391,600; Dose 2: n=17,294,004; Dose 3: n= 10,599,183 Moderna Dose 1 n=1,162,558; Dose 2: n=1,039,919; Dose 3: n= 343,716	Hospitalization due to myocarditis Risk interval: 28 d after any dose Cases identified by ICD-10 codes: I40, I400, I401, I408, I409, I41, I410-412, I418, I514	Incidence rate ratio using self-controlled case series (SCCS) method, stratified by sex and age	Excess events per 1 mil persons exposed (95% CI) 1-28d <i>Pfizer</i> <u><40y</u> Female NR NR NR Male 3 (1, 5) 12 (10, 13) 13 (7, 15) <u>≥40y</u> Female NR NR NR Male NR NR 3 (2, 4) <i>Moderna</i> <u><40 y</u> Female NR 8 (4, 9) NR Male 12 (1, 17) 101 (95, 104) <u>≥40y</u> Female NR NR NR Male NR NR NR
Mayo Clinic Enterprise Dec 1 2020 to Oct 17 2021 USA Niesen, 2021 (4913)	Pfizer-BioNTech (78%) Dose 1 & 2 18-28 d apart, Dose 3 ≥28 d after 2 nd Moderna Dose 1 & 2: 25-35 d apart; dose 3 ≥28 d after dose 2 Dose 3	47,999 receiving exactly 3 doses (78% Pfizer) Female 56.1% Mean age: Pfizer 64 y (SD 17); Moderna 65 y (SD 13) Hispanic or Latino 2%; Not Hispanic or Latino 95%; Unknown 3% Covid-19 diagnoses NR	Received 3 homologous doses Mean time dose 1 to 2: 28.6 d Mean time dose 2 to 3: 173.0 d	Myocarditis Risk interval: 0-14 d after each dose Cases identified via electronic health records using a BERT-based classification model; identified cases were manually reviewed and confirmed by two investigators	Rates	Events: 1 in female >40 years old (Moderna; 1 d after dose 3) Rate: 0.00% (95% CI 0% to 0.01%) 5,047 recipients of three doses of BNT162b2 and 558 recipients of three doses of mRNA-1273 were under 40 years of age. 33,662 recipients of three doses of BNT162b2 (57% female) and 9,582 recipients of three doses of mRNA-1273 (51% female) were 40 years of age or older.
Age 5+						

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Dataset Dates Country	Vaccines Studied	Sample Size; Demographics; Previous Covid-19 diagnoses	Study Group(s)	Outcome(s); Risk Interval; Case Ascertainment	Analysis	Results
VSD Dec 30 Thru Dec 30 2021 USA Klein 2022	Pfizer Dose 1: 587,786 Dose 2: 556035	Total doses: 1143821 5-11y: 431,485 12-15y: 750,772 16-17y: 393,049	1. Participants aged 5-11 y receiving at least 1 dose of Pfizer 2. Participants aged 12-17 y receiving at least 1 dose of Pfizer 2. Similar vaccinee in comparison interval (days 22-42) after COVID-19 vaccination.	Myocarditis, pericarditis, or myopericarditis Risk interval: 21 d Initial chart review followed with adjudication by an infectious disease clinician and/or a cardiologist to confirm cases meet CDC case definition	Excess cases based on comparison interval, adjusted for age group, sex, race/ethnicity, VSD site, and calendar date.	5-11 0 verified cases of myocarditis or myopericarditis 1 verified case of acute pericarditis in an 11 year-old. 12-17 12-15 years: 29 cases 16-17 years: 14 cases 43 validated cases among 12–17-year-olds, 0-21 days after vaccination 39 validated cases among 12–17-year-olds, 0-7 days after vaccination Interval Excess Cases 2-sided p-value 0-21 d Dose 1 0.7 0.873 Dose 2 70.8 <0.001 0-7 d Dose 1 0.3 0.836 Dose 2 70.2 <0.001
Age 12+						
Danish Vaccination Register & Danish Patient Register Oct 1 2020 to Oct 5 2021 Denmark Husby 2021 (4309)	Pfizer n=3,482,295 (98% with 2 doses) Median (IQR) 35 (24-36) days between dose 1 & dose 2 Moderna n=498,814 (96.9% with 2 doses) Excluded individuals with a positive COVID-19 test result	4,931,775 individuals contributing 4,717,464 person years Pfizer n=3,482,295 (98% with 2 doses) Moderna n=498,814 (96.9% with 2 doses) Excluded individuals with a positive COVID-19 test result	Danish residents 12y or older and either 1) receiving Pfizer 2) receiving Moderna 3) Unvaccinated (14 d pre-vaccination period)	Myocarditis or myopericarditis Risk interval: 28 d after any dose Defined myocarditis or myopericarditis as a hospital diagnosis code of myocarditis or pericarditis (ICD-10 codes listed in table S1) and co-occurrence of elevated troponin levels, with a hospital stay >24 hours	14 d pre-risk period before vaccination for each dose	Absolute rate per 100,000 vaccinated persons (95% CI) Moderna Pfizer 12-39y Males, dose 2 9.80 (4.20, 22.84) 1.54 (0.62, 3.81) Other age/sex categories NR



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Dataset Dates Country	Vaccines Studied	Sample Size; Demographics; Previous Covid-19 diagnoses	Study Group(s)	Outcome(s); Risk Interval; Case Ascertainment	Analysis	Results
Age 16+						
Singapore Military Jan 14 to Aug 3 2021 Singapore Tan 2021 (4421)	Pfizer (37,367 individuals with 1+ dose) Moderna (27,294 individuals with 1+ dose) Homologous dose 2 administered between 21 and 56 days after dose 1	127,081 doses administered to 64,661 people (96.5% with 2 doses) 92.1% male Previous or concurrent COVID-19 diagnosis NR	Singapore military personnel receiving at least 1 dose of an mRNA COVID-19 vaccine	Myocarditis Risk interval: NR Case ascertainment via military doctor or hospital diagnosis	Incidence rates and rate ratios after dose 2 versus dose 1 for both mRNA vaccines together and separately, with 95% confidence intervals	3 events; all male, 18-21y, all Moderna none with history of cardiac conditions. Overall rate: 2.4 per 100,000 doses Reporting rate per 100,000 doses administered (95% CI) <i>Any product</i> <u>18-19 y</u> Female 0/955 0/903 Male 0/11,120 2/10,521 <u>20-29 y</u> Female 0/2,819 0/2,717 Male 0/32,850 1/31,656 <u>30-39y</u> Female 0/671 0/656 Male 0/7,807 0/7,625 Note: Only male data included in report; too few females for valid estimates

AIRS = Advanced Incidence Reporting System

CAEFISS = Canadian Adverse Events Following Immunization Surveillance System is a federal system established in 1987 and includes both active and passive surveillance [19]. Adverse events following immunization (AEFI) reports are submitted to CAEFISS by provincial/territorial/federal public health authorities. AEFI reporting to public health authorities is mandatory in all provinces and territories in Canada except for the Yukon Territory and Newfoundland.

CCVCSS = Canadian COVID-19 Vaccination Coverage Surveillance System

INSPQ = Institut National de Santé Publique du Québec (INSPQ)

KPN = Kaiser Permanente Northwest

NIMS = NHS Immunisation Management Service database

VAERS = Vaccine Adverse Event Reporting System



Supplementary Table 3. Study characteristics of passive surveillance/reporting sources contributing to KQ1.

Dataset Dates of data Country of Data	Vaccines Studied	Outcome(s); Case Ascertainment & Risk Interval	Analysis	Results																														
5y+																																		
VAERS Dec 9 Nov 2 to Dec 10 2021 USA Su 2021 (7935)	Pfizer-BioNTech 7,141,428 doses Dose 1: 5,126,642 (72%) Dose 2: 2,014,786 (28%) Dose interval NR	Myocarditis in 5-11yo Risk interval: 0-12 d after any dose (VAERS) Cases reported to VAERS confirmed using CDC working case definition	Incidence	Events: VAERS: 8 (50% female); 2 after dose 1, 6 after dose 2 Crude incidence rate per million: Either dose: 8/7,141,428 = 1.12 Dose 1: 2/5,126,642 = 0.39 Dose 2: 6/2,014,786 = 2.98																														
VAERS Dec 19 Thru Dec 19 2021 USA Su 2022	Pfizer-BioNTech Dose 1 or 2 (5-17 y) 5-11 y: n=8,674,37 12-17 y: n=18,707,169 Dose 3 (16-24 y) 16-17y: n= 47,040 18-24 y: n = 929,842	Myocarditis Risk interval: 7 d Cases reported to VAERS confirmed using CDC working case definition	Reporting rate per million doses, compared to estimated background rate of 0.2 to 1.9 per 1 million person 7-day risk period	Reporting rate of myocarditis (per 1 million doses administered) <table border="1"> <thead> <tr> <th></th> <th>Dose 1</th> <th>Dose 2</th> </tr> </thead> <tbody> <tr> <td><u>5-11 y</u></td> <td></td> <td></td> </tr> <tr> <td>Male</td> <td>0.00</td> <td>4.3*</td> </tr> <tr> <td>Female</td> <td>NE</td> <td>2.0</td> </tr> <tr> <td><u>12-15 y</u></td> <td></td> <td></td> </tr> <tr> <td>Male</td> <td>4.8*</td> <td>45.7*</td> </tr> <tr> <td>Female</td> <td>1.0</td> <td>3.8*</td> </tr> <tr> <td><u>16-17 y</u></td> <td></td> <td></td> </tr> <tr> <td>Male</td> <td>6.1*</td> <td>70.2*</td> </tr> <tr> <td>Female</td> <td>0.00</td> <td>7.6*</td> </tr> </tbody> </table> *Exceeds background incidence Reporting rate per 1 million Dose 3 in adolescents and young adults Events: 4 Verified cases; 2 among 16-17y, 2 among 18-24 y 16-17y: 2/47,040 = 42.5 per million doses 18-24y: 2/929,842 = 2.2 per million doses		Dose 1	Dose 2	<u>5-11 y</u>			Male	0.00	4.3*	Female	NE	2.0	<u>12-15 y</u>			Male	4.8*	45.7*	Female	1.0	3.8*	<u>16-17 y</u>			Male	6.1*	70.2*	Female	0.00	7.6*
	Dose 1	Dose 2																																
<u>5-11 y</u>																																		
Male	0.00	4.3*																																
Female	NE	2.0																																
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Male	4.8*	45.7*																																
Female	1.0	3.8*																																
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Male	6.1*	70.2*																																
Female	0.00	7.6*																																
12y+																																		

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Dataset Dates of data Country of Data	Vaccines Studied	Outcome(s); Case Ascertainment & Risk Interval	Analysis	Results																																																																					
Moderna Global Safety Database Dec 18 2020 to Sep 30 2021 Global Strauss 2021 (4889)	Moderna (275,252,007 doses)	Myocarditis and/or myopericarditis Risk interval: 7 d after any dose Brighton Collaboration case definition and CDC working case definitions for acute myocarditis	Cumulative incidence of myocarditis/myopericarditis was assessed by calculating the reported rate after any known dose of mRNA-1273 according to age and sex, compared to population-based incidence (US Military)	Reported Rate per 100,000 doses Within 7 Days <table border="1"> <thead> <tr> <th></th> <th>Dose 1</th> <th>Dose 2</th> <th>Expected rate</th> <th>RD</th> </tr> </thead> <tbody> <tr> <td colspan="5"><18 years</td> </tr> <tr> <td>All</td> <td>0.26</td> <td>0.56</td> <td>1.67</td> <td></td> </tr> <tr> <td>Females</td> <td>0</td> <td>0.15</td> <td>1.74</td> <td>-1.59</td> </tr> <tr> <td>Males</td> <td>0.56</td> <td>1.02</td> <td>2.12</td> <td>-1.1</td> </tr> <tr> <td colspan="5">18-24y</td> </tr> <tr> <td>All</td> <td>0.65</td> <td>2.56</td> <td>1.67</td> <td></td> </tr> <tr> <td>Females</td> <td>0.20</td> <td>0.44</td> <td>1.23</td> <td>-0.79</td> </tr> <tr> <td>Males</td> <td>1.15</td> <td>4.91</td> <td>2.12</td> <td>2.79</td> </tr> <tr> <td colspan="5">25-39y</td> </tr> <tr> <td>All</td> <td>0.28</td> <td>0.78</td> <td>1.67</td> <td></td> </tr> <tr> <td>Females</td> <td>0.09</td> <td>0.19</td> <td>1.23</td> <td></td> </tr> <tr> <td>Males</td> <td>0.48</td> <td>1.44</td> <td>2.12</td> <td></td> </tr> </tbody> </table>		Dose 1	Dose 2	Expected rate	RD	<18 years					All	0.26	0.56	1.67		Females	0	0.15	1.74	-1.59	Males	0.56	1.02	2.12	-1.1	18-24y					All	0.65	2.56	1.67		Females	0.20	0.44	1.23	-0.79	Males	1.15	4.91	2.12	2.79	25-39y					All	0.28	0.78	1.67		Females	0.09	0.19	1.23		Males	0.48	1.44	2.12					
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COVaxON and Public Health Case and Contact Management Solution Jun 1 2020 to Sep 4 2021 Canada Buchan 2021 (7142)	Moderna Pfizer-BioNTech Dose 1 or dose 2 (19,740,741 doses total)	Myocarditis 7-day risk interval Group of specialized nurses and physicians classified cases according to Brighton Collaboration definition for myocarditis (level 1-2)	Crude rate per million doses, by dose	Rate per million doses (95% CI), BC level 1-2 cases on or after 1 Jun 2021 <table border="1"> <thead> <tr> <th></th> <th>Dose 1</th> <th>Dose 2</th> </tr> </thead> <tbody> <tr> <td colspan="3">Pfizer</td> </tr> <tr> <td colspan="3">12-17 y</td> </tr> <tr> <td>All</td> <td>21.5 (10.7-38.4)</td> <td>49.7 (30.8-76.0)</td> </tr> <tr> <td>Female</td> <td>8.1 (1.0-29.1)</td> <td>9.7 (1.2-35.1)</td> </tr> <tr> <td>Male</td> <td>34.2 (15.6-64.9)</td> <td>88.1 (53.0-137.5)</td> </tr> <tr> <td colspan="3">18-24 y</td> </tr> <tr> <td>All</td> <td>10.7 (2.2-31.3)</td> <td>19.0 (3.9-55.5)</td> </tr> <tr> <td>Female</td> <td>7.9 (0.2-44.1)</td> <td>0.0 (0.0-50.5)</td> </tr> <tr> <td>Male</td> <td>13.1 (1.6-47.3)</td> <td>35.5 (7.3-103.7)</td> </tr> <tr> <td colspan="3">25-39 y</td> </tr> <tr> <td>All</td> <td>9.3 (3.0-21.7)</td> <td>12.8 (3.5-32.9)</td> </tr> <tr> <td>Female</td> <td>0.0 (0.0-14.3)</td> <td>13.1 (1.6-47.5)</td> </tr> <tr> <td>Male</td> <td>17.9 (5.8-41.8)</td> <td>12.6 (1.5-45.4)</td> </tr> <tr> <td colspan="3">Moderna</td> </tr> <tr> <td colspan="3">18-24 y</td> </tr> <tr> <td>All</td> <td>0.0 (0.0-39.8)</td> <td>195.5 (117.7-305.3)</td> </tr> <tr> <td>Female</td> <td>0.0 (0.0-95.1)</td> <td>69.1 (14.2-201.9)</td> </tr> <tr> <td>Male</td> <td>0.0 (0.0-68.7)</td> <td>299.5 (171.2-486.4)</td> </tr> <tr> <td colspan="3">25-39 y</td> </tr> <tr> <td>All</td> <td>16.2 (3.3-47.3)</td> <td>48.9 (23.5-90.0)</td> </tr> <tr> <td>Female</td> <td>0.0 (0.0-45.4)</td> <td>21.5 (2.6-77.7)</td> </tr> <tr> <td>Male</td> <td>28.8 (5.9-84.3)</td> <td>72.1 (31.1-142.0)</td> </tr> </tbody> </table> <p>Note: Moderna not authorized for use in 12-17y in Canada</p>		Dose 1	Dose 2	Pfizer			12-17 y			All	21.5 (10.7-38.4)	49.7 (30.8-76.0)	Female	8.1 (1.0-29.1)	9.7 (1.2-35.1)	Male	34.2 (15.6-64.9)	88.1 (53.0-137.5)	18-24 y			All	10.7 (2.2-31.3)	19.0 (3.9-55.5)	Female	7.9 (0.2-44.1)	0.0 (0.0-50.5)	Male	13.1 (1.6-47.3)	35.5 (7.3-103.7)	25-39 y			All	9.3 (3.0-21.7)	12.8 (3.5-32.9)	Female	0.0 (0.0-14.3)	13.1 (1.6-47.5)	Male	17.9 (5.8-41.8)	12.6 (1.5-45.4)	Moderna			18-24 y			All	0.0 (0.0-39.8)	195.5 (117.7-305.3)	Female	0.0 (0.0-95.1)	69.1 (14.2-201.9)	Male	0.0 (0.0-68.7)	299.5 (171.2-486.4)	25-39 y			All	16.2 (3.3-47.3)	48.9 (23.5-90.0)	Female	0.0 (0.0-45.4)	21.5 (2.6-77.7)	Male	28.8 (5.9-84.3)	72.1 (31.1-142.0)
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*Indicates passive surveillance system with mandatory/legal reporting requirements for healthcare providers of adverse events after COVID-19 vaccines.

**Number of administered vaccine doses from European Center for Disease Control (ECDC), up to end of Week 41 2021 (Oct 16 2021). Period of vaccine doses is shorter than event reporting to account for time period between receiving vaccine and experiencing the event of interest (i.e., individuals vaccinated on October 19 are unlikely to be reporting myocarditis as an AE on that same day)



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CAEFISS: Canadian Adverse Events Following Immunization Surveillance System. Managed by PHAC, monitors the safety of marketed vaccines in Canada through both passive and active reporting strategies. Reports are submitted by public health authorities in provinces and territories, who in turn receive them from local public health units. Provincial and territorial authorities also receive reports from federal authorities that provide immunization in their jurisdictions. Active surveillance is also carried out by 12 pediatric centres across Canada, which screen all hospital admissions for potential vaccine-related adverse events.

CVP: Canada Vigilance Program. Passive surveillance program that collects reports of suspected adverse reactions to health products. Reports are submitted by health professionals and consumers on a voluntary basis either directly to Health Canada or to the market authorization holder, who in turn is required to submit reports of adverse events to Health Canada through the Canada Vigilance Program.

EudraVigilance – Passive surveillance system for the European Economic Area. Healthcare providers and patients can report any adverse effects from medical products, including vaccines. Patients, consumers and healthcare professionals report suspected side effects to either the national medicines regulatory authority or the pharmaceutical company that holds the marketing authorisation for the medicine. These reports are then transmitted electronically to EudraVigilance.

VAERS – Vaccine Adverse Events Reporting System. Passive surveillance system for the United States, to which healthcare providers and patients can report adverse events from medical products, including vaccines. Providers are required to report to VAERS adverse events (including administration errors, serious adverse events, cases of multisystem inflammatory syndrome, and cases of COVID-19 that result in hospitalization or death) that occur after receipt of any COVID-19 vaccine. Limitations include possible bias in reporting, inconsistent data quality, and incomplete information; in addition, VAERS has no direct comparison group. The VAERS system was not designed to assess causality; therefore, VAERS data generally cannot be used to determine whether a causal association between an adverse event and a vaccine exists.

Yellow Card - The Yellow Card scheme is a passive surveillance system to which anybody can voluntarily report any suspected adverse reactions or side effects to the vaccine. The reports are continually reviewed to detect possible new side effects that may require regulatory action, and to differentiate these from things that would have happened regardless of the vaccine or medicine being administered, for instance due to underlying or undiagnosed illness.



Supplementary Table 4. Study characteristics of studies/reporting systems contributing to KQ2.

Dataset Dates of data (mmm dd yyyy) Country of Data Author year (RefID)	Vaccines Studied Manufacturer Dose #	Sample Size; Demographics; Previous Covid-19 diagnoses	Outcome(s) Myo-, peri- and/or myopericarditis; Case Ascertainment & Risk Interval; Risk/protective factors considered	Outcome measures Analysis (e.g., adjustment for confounders)	Results Stratified by age and sex If required, zero cell correction proportional to the reciprocal of the size of the contrasting study arm (i.e., # events = 1/n of the other arm)																																																																																																				
Danish Vaccination Register (DVR) & Danish Patient Register (DPR) Oct 5 Oct 1 2020 to Oct 5 2021 Denmark Husby 2021 (4309)	Pfizer n=3 482 295 (98% with 2 doses) Median (IQR) 35 (24-36) days between dose 1 & dose 2 Moderna n=498 814 (96.9% with 2 doses) Median (IQR) 31 (28-35) days between dose 1 & dose 2	4 931 775 individuals contributing 4 717 464 person years Excluded individuals with a positive COVID-19 test result	Myocarditis or myopericarditis 28d risk interval Defined myocarditis or myopericarditis as a hospital diagnosis code of myocarditis or pericarditis (ICD-10 codes listed in table S1) and co-occurrence of elevated troponin levels, with a hospital stay >24 hours	Estimated crude rate ratio: Moderna compared to Pfizer	<p>Absolute rate per 100,000 vaccinated persons (95% CI)</p> <table border="1"> <thead> <tr> <th></th> <th>Moderna</th> <th>Pfizer</th> <th>cRR</th> </tr> </thead> <tbody> <tr> <td>Overall</td> <td></td> <td></td> <td></td> </tr> <tr> <td>All</td> <td>4.2 (2.6, 6.4)</td> <td>1.4 (1.0, 1.8)</td> <td>3.0</td> </tr> <tr> <td>Female</td> <td>2.0 (0.7, 4.8)</td> <td>1.3 (0.8, 1.9)</td> <td>1.54</td> </tr> <tr> <td>Male</td> <td>6.3 (3.6, 10.2)</td> <td>1.5 (1.0, 2.2)</td> <td>4.2</td> </tr> <tr> <td>12-39y</td> <td></td> <td></td> <td></td> </tr> <tr> <td>All</td> <td>5.7 (3.3, 9.3)</td> <td>1.6 (1.0, 2.6)</td> <td>3.56</td> </tr> <tr> <td>Males, dose 2</td> <td>9.80 (4.20, 22.84)</td> <td>1.54 (0.62, 3.81)</td> <td>6.36</td> </tr> </tbody> </table> <p>cRR by age</p> <table border="1"> <thead> <tr> <th></th> <th>Events</th> <th>Person years</th> <th>cRR</th> </tr> </thead> <tbody> <tr> <td>12-39y</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Moderna</td> <td>16</td> <td>40,875</td> <td>3.43</td> </tr> <tr> <td>Pfizer</td> <td>17</td> <td>149,192</td> <td></td> </tr> <tr> <td>40-59y</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Moderna</td> <td>≤3</td> <td>13,347</td> <td>3.89</td> </tr> <tr> <td>Pfizer</td> <td>10</td> <td>172,888</td> <td></td> </tr> <tr> <td>≥60y</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Moderna</td> <td>4</td> <td>20,219</td> <td>1.77</td> </tr> <tr> <td>Pfizer</td> <td>21</td> <td>187,510</td> <td></td> </tr> </tbody> </table> <p>cRR by sex</p> <table border="1"> <thead> <tr> <th></th> <th>Events</th> <th>Person years</th> <th>cRR</th> </tr> </thead> <tbody> <tr> <td>Female</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Moderna</td> <td>16</td> <td>38,088</td> <td>4.09</td> </tr> <tr> <td>Pfizer</td> <td>26</td> <td>253,135</td> <td></td> </tr> <tr> <td>Male</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Moderna</td> <td>5</td> <td>36,352</td> <td>1.60</td> </tr> <tr> <td>Pfizer</td> <td>22</td> <td>256,455</td> <td></td> </tr> </tbody> </table>		Moderna	Pfizer	cRR	Overall				All	4.2 (2.6, 6.4)	1.4 (1.0, 1.8)	3.0	Female	2.0 (0.7, 4.8)	1.3 (0.8, 1.9)	1.54	Male	6.3 (3.6, 10.2)	1.5 (1.0, 2.2)	4.2	12-39y				All	5.7 (3.3, 9.3)	1.6 (1.0, 2.6)	3.56	Males, dose 2	9.80 (4.20, 22.84)	1.54 (0.62, 3.81)	6.36		Events	Person years	cRR	12-39y				Moderna	16	40,875	3.43	Pfizer	17	149,192		40-59y				Moderna	≤3	13,347	3.89	Pfizer	10	172,888		≥60y				Moderna	4	20,219	1.77	Pfizer	21	187,510			Events	Person years	cRR	Female				Moderna	16	38,088	4.09	Pfizer	26	253,135		Male				Moderna	5	36,352	1.60	Pfizer	22	256,455	
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NIMS Dec 1 2020 to Nov 15 2021 England Patone 2021 (7268)	Pfizer or Moderna Pfizer Dose 1 n=20,391,600; Dose 2: n=17,294,004; Dose 3: n= 10,599,183 Moderna Dose 1 n=1,162,558; Dose 2: n=1,039,919; Dose 3: n= 343,716 Dosing interval NR	21,554,158 with at least one dose, aged ≥13 y Previous COVID in 54.7% of total sample. People with history of myocarditis in previous 2 years excluded	Hospitalization due to myocarditis 28d risk interval Cases identified by ICD-10 codes: I40, I400, I401, I408, I409, I41, I410-412, I418, I514 Pfizer vs. Moderna, by dose	Events per million doses IRR calculated through self- control case series method estimated crude ratio measures comparing Pfizer to Moderna by age group, by dose	<p>IRR (95% CI) - 0-28d</p> <table border="1"> <thead> <tr> <th></th> <th>Dose 1</th> <th>Dose 2</th> <th>Dose 3</th> </tr> </thead> <tbody> <tr> <td colspan="4"><i>Females</i></td> </tr> <tr> <td colspan="4"><u><40y</u></td> </tr> <tr> <td>Moderna</td> <td>2.88 (0.56, 14.74)</td> <td>7.55 (1.67, 34.12)</td> <td>NE</td> </tr> <tr> <td>Pfizer</td> <td>1.44 (0.78, 2.66)</td> <td>1.37 (0.67, 2.80)</td> <td>NE</td> </tr> <tr> <td colspan="4"><u>≥40y</u></td> </tr> <tr> <td>Moderna</td> <td>0 events</td> <td>0 events</td> <td>0 events</td> </tr> <tr> <td>Pfizer</td> <td>1.42 (0.96, 2.09)</td> <td>1.00 (0.64, 1.55)</td> <td>1.64 (0.91, 2.96)</td> </tr> <tr> <td colspan="4"><i>Males</i></td> </tr> <tr> <td colspan="4"><u><40y</u></td> </tr> <tr> <td>Moderna</td> <td>2.34 (1.03, 5.34)</td> <td>16.52 (9.10, 30.00)</td> <td>NR</td> </tr> <tr> <td>Pfizer</td> <td>1.66 (1.14, 2.41)</td> <td>3.41 (2.44, 4.78)</td> <td>7.60 (1.92, 30.15)</td> </tr> <tr> <td colspan="4"><u>≥40y</u></td> </tr> <tr> <td>Moderna</td> <td>0 events</td> <td>0 events</td> <td>0 events</td> </tr> <tr> <td>Pfizer</td> <td>0.97 (0.65, 1.47)</td> <td>0.79 (0.51, 1.23)</td> <td>2.48 (1.46, 4.19)</td> </tr> </tbody> </table> <p>IRR (95% CI) – 1-7d</p> <table border="1"> <thead> <tr> <th></th> <th>Dose 1</th> <th>Dose 2</th> <th>Dose 3</th> </tr> </thead> <tbody> <tr> <td colspan="4"><i>Females</i></td> </tr> <tr> <td colspan="4"><u><40y</u></td> </tr> <tr> <td>Moderna</td> <td>NR</td> <td>28.49 (6.22, 130.41)</td> <td>NR</td> </tr> <tr> <td>Pfizer</td> <td>1.36 (0.42, 4.39)</td> <td>3.11 (1.23, 7.86)</td> <td>NR</td> </tr> <tr> <td colspan="4"><u>≥40y</u></td> </tr> <tr> <td>Moderna</td> <td>0 events</td> <td>0 events</td> <td>0 events</td> </tr> <tr> <td>Pfizer</td> <td>1.40 (0.72, 2.74)</td> <td>0.80 (0.33, 1.97)</td> <td>2.32 (1.09, 4.94)</td> </tr> <tr> <td colspan="4"><i>Males</i></td> </tr> <tr> <td colspan="4"><u><40y</u></td> </tr> <tr> <td>Moderna</td> <td>7.97 (3.17, 20.05)</td> <td>54.65 (29.74, 100.40)</td> <td>NR</td> </tr> <tr> <td>Pfizer</td> <td>2.98 (1.75, 5.07)</td> <td>8.05 (5.37, 12.06)</td> <td>NR</td> </tr> <tr> <td colspan="4"><u>≥40y</u></td> </tr> <tr> <td>Moderna</td> <td>0 events</td> <td>0 events</td> <td>0 events</td> </tr> <tr> <td>Pfizer</td> <td>0.84 (0.37, 1.91)</td> <td>0.65 (0.27, 1.59)</td> <td>0.99 (0.31, 3.15)</td> </tr> </tbody> </table>		Dose 1	Dose 2	Dose 3	<i>Females</i>				<u><40y</u>				Moderna	2.88 (0.56, 14.74)	7.55 (1.67, 34.12)	NE	Pfizer	1.44 (0.78, 2.66)	1.37 (0.67, 2.80)	NE	<u>≥40y</u>				Moderna	0 events	0 events	0 events	Pfizer	1.42 (0.96, 2.09)	1.00 (0.64, 1.55)	1.64 (0.91, 2.96)	<i>Males</i>				<u><40y</u>				Moderna	2.34 (1.03, 5.34)	16.52 (9.10, 30.00)	NR	Pfizer	1.66 (1.14, 2.41)	3.41 (2.44, 4.78)	7.60 (1.92, 30.15)	<u>≥40y</u>				Moderna	0 events	0 events	0 events	Pfizer	0.97 (0.65, 1.47)	0.79 (0.51, 1.23)	2.48 (1.46, 4.19)		Dose 1	Dose 2	Dose 3	<i>Females</i>				<u><40y</u>				Moderna	NR	28.49 (6.22, 130.41)	NR	Pfizer	1.36 (0.42, 4.39)	3.11 (1.23, 7.86)	NR	<u>≥40y</u>				Moderna	0 events	0 events	0 events	Pfizer	1.40 (0.72, 2.74)	0.80 (0.33, 1.97)	2.32 (1.09, 4.94)	<i>Males</i>				<u><40y</u>				Moderna	7.97 (3.17, 20.05)	54.65 (29.74, 100.40)	NR	Pfizer	2.98 (1.75, 5.07)	8.05 (5.37, 12.06)	NR	<u>≥40y</u>				Moderna	0 events	0 events	0 events	Pfizer	0.84 (0.37, 1.91)	0.65 (0.27, 1.59)	0.99 (0.31, 3.15)
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LIVING EVIDENCE SYNTHESIS: UPDATE #1 SUMMARY



SPOR Evidence Alliance
Strategy for Patient-Oriented Research
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Stratégie de recherche axée sur le patient



Dataset Dates of data (mmm dd yyyy) Country of Data Author year (RefID)	Vaccines Studied Manufacturer Dose #	Sample Size; Demographics; Previous Covid-19 diagnoses	Outcome(s) Myo-, peri- and/or myopericarditis; Case Ascertainment & Risk Interval; Risk/protective factors considered	Outcome measures Analysis (e.g., adjustment for confounders)	Results Stratified by age and sex If required, zero cell correction proportional to the reciprocal of the size of the contrasting study arm (i.e., # events= 1/n of the other arm)
VAERS Oct 6 To Oct 6 2021 US Su 2021 (7936)	Pfizer or Moderna Dose 1 or Dose 2 Dosing interval NR	366,062,239 doses of mRNA vaccine (either dose 1 or dose 2) Doses NR by age/sex categories Previous COVID-19 infection NR	Myocarditis 7 day risk period Reports verified to meet case definition by provider interview or medical record review Pfizer vs. Moderna	Reporting rate of myocarditis per 1 mil doses administered Compared to background risk of 0.2 to 1.9 per 1 million person 7 day risk period estimated crude Rate Ratios (for 18+ only; Moderna not authorized in <18y)	Moderna vs. Pfizer Events per mil doses Dose 1 Dose 2 crude Risk Ratio Dose 1 Dose 2 <u>18-24</u> Female Moderna 0.6 5.3* 3.0 2.12 Pfizer 0.2 2.5* Male Moderna 6.1* 38.5* 2.65 1.05 Pfizer 2.3* 36.8* <u>25-29</u> Female Moderna 0.4 5.7* 2 4.75 Pfizer 0.2 1.2 Male Moderna 3.4* 17.2* 2.62 1.59 Pfizer 1.3 10.8 <u>30-39</u> Female Moderna 0.5 0.4 0.83 0.57 Pfizer 0.6 0.7 Male Moderna 2.3 6.7 4.6 1.29 Pfizer 0.5 5.2 <u>40-49</u> 2 1.27 Male Moderna 0.2 2.9 0.67 1.45 Pfizer 0.3 2.0 <u>50-64</u> Female Moderna 0.5 0.4 1.67 0.8 Pfizer 0.3 0.5 Male Moderna 0.5 0.6 2.5 2 Pfizer 0.2 0.3 <u>65+</u> Female Moderna 0.0 0.3 NE 1.0 Pfizer 0.1 0.3 Male Moderna 0.1 0.3 0.5 3 Pfizer 0.2 0.1



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Singapore Military Jan 14 to Aug 3 2021 Singapore Tan 2021 (4421)	Pfizer (37,367 individuals with 1+ dose) Moderna (27,294 individuals with 1+ dose) Homologous dose 2 administered between 21 and 56 days after dose 1	127,081 doses administered to 64,661 military membets (96.5% with 2 doses) 92.1% male Previous or concurrent COVID-19 diagnosis NR	Myocarditis Risk interval NR Case ascertainment via military doctor or hospital diagnosis Pfizer vs Moderna	Descriptive report only; crude numbers estimated by ARCHE	3 events; all male, 18-21y, all after dose 2 of Moderna; 0 cases with history of cardiac conditions. Overall rate: 2.4 per 100,000 doses <table border="1"> <thead> <tr> <th></th> <th>Dose 1</th> <th>Dose 2</th> <th>OR</th> </tr> </thead> <tbody> <tr> <td colspan="4">18-20 y</td> </tr> <tr> <td colspan="4">Pfizer</td> </tr> <tr> <td>Male</td> <td>0/3,789</td> <td>0/3,762</td> <td></td> </tr> <tr> <td>Female</td> <td>0/326</td> <td>0/323</td> <td></td> </tr> <tr> <td colspan="4">Moderna</td> </tr> <tr> <td>Male</td> <td>0/7,331</td> <td>2/6,759</td> <td></td> </tr> <tr> <td>Female</td> <td>0/629</td> <td>0/580</td> <td></td> </tr> <tr> <td colspan="4">20-29 y</td> </tr> <tr> <td colspan="4">Pfizer</td> </tr> <tr> <td>Male</td> <td>0/18,278</td> <td>0/18,203</td> <td></td> </tr> <tr> <td>Female</td> <td>0/1,568</td> <td>0/1,562</td> <td></td> </tr> <tr> <td colspan="4">Moderna</td> </tr> <tr> <td>Male</td> <td>0/14,572</td> <td>1/13,453</td> <td></td> </tr> <tr> <td>Female</td> <td>0/1,251</td> <td>0/1,155</td> <td></td> </tr> <tr> <td colspan="4">30-39 y</td> </tr> <tr> <td colspan="4">Pfizer</td> </tr> <tr> <td>Male</td> <td>0/5,713</td> <td>0/5,667</td> <td></td> </tr> <tr> <td>Female</td> <td>0/491</td> <td>0/487</td> <td></td> </tr> <tr> <td colspan="4">Moderna</td> </tr> <tr> <td>Male</td> <td>0/2,094</td> <td>0/1,958</td> <td></td> </tr> <tr> <td>Female</td> <td>0/180</td> <td>0/169</td> <td></td> </tr> </tbody> </table>		Dose 1	Dose 2	OR	18-20 y				Pfizer				Male	0/3,789	0/3,762		Female	0/326	0/323		Moderna				Male	0/7,331	2/6,759		Female	0/629	0/580		20-29 y				Pfizer				Male	0/18,278	0/18,203		Female	0/1,568	0/1,562		Moderna				Male	0/14,572	1/13,453		Female	0/1,251	0/1,155		30-39 y				Pfizer				Male	0/5,713	0/5,667		Female	0/491	0/487		Moderna				Male	0/2,094	0/1,958		Female	0/180	0/169	
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COVaxON and Public Health Case and Contact Management Solution (Passive) Dec 14 2020 to Sep 4 2021 Canada Buchan 2021 (7142)	Pfizer, Moderna One or two doses Dose interval NR	19,740,741 doses Demographics NR History of COVID-19 NR	Myocarditis (product type) Myocarditis/pericarditis Group of specialized nurses and physicians classified cases according to Brighton Collaboration definition (level 1-3; myocarditis meeting level 1-2); Risk interval: any time after vaccination (97.1% onset within 30 days).	Rate ratios, unadjusted (for inter-dose interval) and adjusted for dose 1 product and interval (for dose 2, Moderna vs. Pfizer)	All ages and sexes: Inter-dose interval ≤30 vs. ≥56 d (ref) , crude RR (95% CI): Moderna: 5.2 (2.6-10.0) Pfizer: 5.5 (3.1-9.6) 18-24 y, males: Dose 2: Moderna vs. Pfizer (ref) , adjusted RR (95% CI): 6.6 (3.3-13.2) Rate per million doses (95% CI), cases on or after 1 Jun 2021 (myocarditis and/or pericarditis) <table border="1"> <thead> <tr> <th></th> <th>Dose 1</th> <th>Dose 2</th> </tr> </thead> <tbody> <tr> <td><i>Pfizer</i></td> <td></td> <td></td> </tr> <tr> <td>12-17 y</td> <td>27.3 (14.9 - 45.8)</td> <td>54.4 (34.5 - 81.7)</td> </tr> <tr> <td>12-17 y, male</td> <td>34.2 (15.6 - 64.9)</td> <td>97.3 (60.3 - 148.8)</td> </tr> <tr> <td>12-17y, female</td> <td>20.1 (6.5 - 47.0)</td> <td>9.7 (1.2 - 35.1)</td> </tr> <tr> <td>18-24 y</td> <td>17.9 (5.8 - 41.7)</td> <td>44.3 (17.8 - 91.3)</td> </tr> </tbody> </table>		Dose 1	Dose 2	<i>Pfizer</i>			12-17 y	27.3 (14.9 - 45.8)	54.4 (34.5 - 81.7)	12-17 y, male	34.2 (15.6 - 64.9)	97.3 (60.3 - 148.8)	12-17y, female	20.1 (6.5 - 47.0)	9.7 (1.2 - 35.1)	18-24 y	17.9 (5.8 - 41.7)	44.3 (17.8 - 91.3)																																																																						
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SPOR
Putting Patients First

Dataset Dates of data (mmm dd yyyy) Country of Data Author year (RefID)	Vaccines Studied Manufacturer Dose #	Sample Size; Demographics; Previous Covid-19 diagnoses	Outcome(s) Myo-, peri- and/or myopericarditis; Case Ascertainment & Risk Interval; Risk/protective factors considered	Outcome measures Analysis (e.g., adjustment for confounders)	Results Stratified by age and sex If required, zero cell correction proportional to the reciprocal of the size of the contrasting study arm (i.e., # events= 1/n of the other arm)																																																																																																																														
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	<u>Pfizer-Pfizer</u>	<u>Moderna-Pfizer</u>																																																																																																																									
Male	25.0 (19.3-32.0)	14.6 (0.4-81.2)																																																																																																																									
Female	5.9 (3.5-9.5)	0.0 (0.0-58.5)																																																																																																																									
12-17 y	53.8 (37.7-74.5)	NA																																																																																																																									
18-24 y	26.9 (14.3-45.9)	0.0 (0.0-218.8)																																																																																																																									
25-39 y	13.4 (7.5-22.1)	0.0 (0.0-107.0)																																																																																																																									
≥40 y	5.4 (3.1-8.6)	12.5 (0.3-69.7)																																																																																																																									
	<u>Moderna-Moderna</u>	<u>Pfizer-Moderna</u>																																																																																																																									
Male	58.3 (42.4-78.3)	72.5 (53.8-95.6)																																																																																																																									
Female	9.5 (3.8-19.6)	13.1 (6.0-25.0)																																																																																																																									
12-17 y	NA	NA																																																																																																																									
18-24 y	162.0 (108.5-232.6)	203.9 (142.0-283.6)																																																																																																																									
25-39 y	30.1 (16.0-51.4)	52.0 (32.2-79.5)																																																																																																																									
≥40 y	10.2 (4.7-19.4)	3.8 (0.8-11.0)																																																																																																																									
	Events	Doses	Rate (95% CI)																																																																																																																								
<u>Pfizer-Pfizer</u>																																																																																																																											
Interval ≤30 d	2	21,160	94.5 (11.4-341.4)																																																																																																																								
Interval 31-55 d	8	124,235	64.4 (27.8-126.9)																																																																																																																								
Interval ≥56 d	1	90,424	11.1 (0.3-61.6)																																																																																																																								
<u>Moderna-Moderna</u>																																																																																																																											
Interval ≤30 d	4	10,623	376.5 (102.6-964.1)																																																																																																																								
Interval 31-55 d	20	60,352	331.4 (202.4-511.8)																																																																																																																								
Interval ≥56 d	3	22,641	132.5 (27.3-387.2)																																																																																																																								
<u>Moderna-Pfizer</u>																																																																																																																											
Interval ≤30 d	0	1,058	0.0 (0.0-3486.7)																																																																																																																								
Interval 31-55 d	0	5,402	0.0 (0.0-682.9)																																																																																																																								
Interval ≥56 d	0	2,393	0.0 (0.0-1541.5)																																																																																																																								
<u>Pfizer-Moderna</u>																																																																																																																											
Interval ≤30 d	6	7,720	777.2 (285.2-1691.6)																																																																																																																								
Interval 31-55 d	20	62,717	318.9 (194.8-492.5)																																																																																																																								
Interval ≥56 d	3	15,456	194.1 (40.0-567.2)																																																																																																																								
Pfizer	≤30 d	31-55 d	≥56 d																																																																																																																								

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Dataset Dates of data (mmm dd yyyy) Country of Data Author year (RefID)	Vaccines Studied Manufacturer Dose #	Sample Size; Demographics; Previous Covid-19 diagnoses	Outcome(s) Myo-, peri- and/or myopericarditis; Case Ascertainment & Risk Interval; Risk/protective factors considered	Outcome measures Analysis (e.g., adjustment for confounders)	Results Stratified by age and sex If required, zero cell correction proportional to the reciprocal of the size of the contrasting study arm (i.e., # events= 1/n of the other arm)																																								
					<table border="1"> <tr> <td>12-17 y</td> <td>101.9 (55.7-170.9)</td> <td>37.7 (21.6-61.3)</td> <td>55.7 (20.4-121.2)</td> </tr> <tr> <td>18-24 y</td> <td>45.3 (5.5-163.7)</td> <td>34.7-15.9-66)</td> <td>10.1 (1.2-36.5)</td> </tr> <tr> <td>25-39 y</td> <td>42.5 (11.6-108.7)</td> <td>8.7 (2.8-20.3)</td> <td>12.3 (4.5-26.7)</td> </tr> <tr> <td>≥40 y</td> <td>0.0 (0.0-34.4)</td> <td>1.5 (0.0-8.3)</td> <td>6.9 (4.0-11.1)</td> </tr> <tr> <td colspan="4">Moderna</td> </tr> <tr> <td></td> <td>≤30 d</td> <td>31-55 d</td> <td>≥56 d</td> </tr> <tr> <td>12-17 y</td> <td>NA</td> <td>NA</td> <td>NA</td> </tr> <tr> <td>18-24 y</td> <td>353.1 (182.4-616.8)</td> <td>184.0 (133.7-247.0)</td> <td>103.2 (44.5-203.3)</td> </tr> <tr> <td>25-39 y</td> <td>39.5 (8.1-115.4)</td> <td>45.0 (29.1-66.4)</td> <td>29.4 (10.8-64)</td> </tr> <tr> <td>≥40 y</td> <td>0.0 (0.0-53.9)</td> <td>7.4 (2.0-19.0)</td> <td>7.5 (3.2-14.7)</td> </tr> </table>	12-17 y	101.9 (55.7-170.9)	37.7 (21.6-61.3)	55.7 (20.4-121.2)	18-24 y	45.3 (5.5-163.7)	34.7-15.9-66)	10.1 (1.2-36.5)	25-39 y	42.5 (11.6-108.7)	8.7 (2.8-20.3)	12.3 (4.5-26.7)	≥40 y	0.0 (0.0-34.4)	1.5 (0.0-8.3)	6.9 (4.0-11.1)	Moderna					≤30 d	31-55 d	≥56 d	12-17 y	NA	NA	NA	18-24 y	353.1 (182.4-616.8)	184.0 (133.7-247.0)	103.2 (44.5-203.3)	25-39 y	39.5 (8.1-115.4)	45.0 (29.1-66.4)	29.4 (10.8-64)	≥40 y	0.0 (0.0-53.9)	7.4 (2.0-19.0)	7.5 (3.2-14.7)
12-17 y	101.9 (55.7-170.9)	37.7 (21.6-61.3)	55.7 (20.4-121.2)																																										
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Clinical Comorbidities																																													
EULAR COVAX Feb 5 to Jul 27 2021 Europe (30 countries) Machado 2021 (3588)	Pfizer (n=3600) Mean (SD) dose interval: 28 (12) days Moderna (n=428) Mean (SD) dose interval: 30 (8) days 74% with 2 doses; 1% with 3 doses	Reports of AEs in 4028 inflammatory (n=3218) or non-inflammatory (n=412) RMD patients. 70% female, mean age 61.6 (SD 15.2) years History of COVID-19 NR	Myocarditis or pericarditis Risk interval NR Case ascertainment not reported Inflammatory RMD vs. Non- inflammatory RMD	Crude ORs estimated from reported counts.	One event in a young (<30) female in I-RMD group with systemic lupus erythematosus after 2 nd dose of Pfizer. No events in NI-RMD group. estimated OR OR = (1/3599) / ((1/3600)/428) OR = 428.1																																								



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VAERS Nov 30 Up to Nov 30 2021 Europe, US Lane 2021 (7884)	Pfizer or Moderna At least 1 dose Dosing interval NR	3066 VAERS reports of myocarditis or pericarditis Demographics of total population not reported. The whole population had a bias of younger males experiencing myocarditis or pericarditis following COVID-19 mRNA vaccinations (20), whereas from the immunocompromised population 52.6% of these events occurred in males and 50.9% were under 60 years of age Previous COVID-19 diagnosis NR	Myocarditis/pericarditis Approximately 70% of reported events occurred within 14 days of vaccination No case validation Reports with comorbidities or concurrent medication indicative of transplantation, HIV infection, or cancer ("immunocompromised" population) were compared with each overall database population	Proportional reporting rates	3066 cases, of which 57 (1.86%) were in immunocompromised individuals PRR=1.36 [95% CI: 0.89-1.82] Myocarditis/AEs (Immunocompromised) Myocarditis/AEs (Non-immunocompromised)

CAEFISS: Canadian Adverse Events Following Immunization Surveillance System. Managed by PHAC, monitors the safety of marketed vaccines in Canada through both passive and active reporting strategies. Reports are submitted by public health authorities in provinces and territories, who in turn receive them from local public health units. Provincial and territorial authorities also receive reports from federal authorities that provide immunization in their jurisdictions. Active surveillance is also carried out by 12 pediatric centres across Canada, which screen all hospital admissions for potential vaccine-related adverse events.

CVP: Canada Vigilance Program. Passive surveillance program that collects reports of suspected adverse reactions to health products. Reports are submitted by health professionals and consumers on a voluntary basis either directly to Health Canada or to the market authorization holder, who in turn is required to submit reports of adverse events to Health Canada through the Canada Vigilance Program.

EudraVigilance – Passive surveillance system for the European Economic Area. Healthcare providers and patients can report any adverse effects from medical products, including vaccines. Patients, consumers and healthcare professionals report suspected side effects to either the national medicines regulatory authority or the pharmaceutical company that holds the marketing authorisation for the medicine. These reports are then transmitted electronically to EudraVigilance.

EULAR COVAX- The European Alliance of Associations for Rheumatology Coronavirus Vaccine physician-reported registry. Data are entered voluntarily by rheumatologists or other members of the clinical rheumatology team; patients are eligible for inclusion if they registry have a pre-existing inflammatory/rheumatic and musculoskeletal disease or non-inflammatory rheumatic and musculoskeletal disease (NI-RMD) and have received one or more doses of any vaccine against SARS-CoV-2. Data are entered directly into an online data entry system or transferred from national registries (for Portugal). Patients with NI-RMDs are included as a control group.

VAERS – Vaccine Adverse Events Reporting System. Passive surveillance system for the United States, to which healthcare providers and patients can report adverse events from medical products, including vaccines. Providers are required to report to VAERS adverse events (including administration errors, serious adverse events, cases of multisystem inflammatory syndrome, and cases of COVID-19 that result in hospitalization or death) that occur after receipt of any COVID-19 vaccine. Limitations include possible bias in reporting, inconsistent data quality, and incomplete information; in addition, VAERS has no direct comparison group. The VAERS system was not designed to assess causality; therefore, VAERS data generally cannot be used to determine whether a causal association between an adverse event and a vaccine exists.

Yellow Card - The Yellow Card scheme is a passive surveillance system to which anybody can voluntarily report any suspected adverse reactions or side effects to the vaccine. The reports are continually reviewed to detect possible new side effects that may require regulatory action, and to differentiate these from things that would have happened regardless of the vaccine or medicine being administered, for instance due to underlying or undiagnosed illness.



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Funded by the Canadian Institutes of Health Research ([CIHR](#)).



Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

Supplementary Table 5. Summary of risk of bias assessment for observational studies/surveillance data contributing to KQ1

Dataset	Were the two groups similar and recruited from the same population?		Was vaccination status measured in a reliable or valid way?	Were confounding factors identified and appropriately addressed in design or analysis?	Were the outcomes measured in a valid and reliable way?	Was the follow up time long enough for outcomes to occur?	Were the large majority of cases likely to have been identified?	Overall assessment of risk of bias
Active surveillance studies								
Husby 2021 Ref ID 4309	Y		Y	U	U	Y	U	Some risk
Klein 2022	Y		Y	U	Y	Y	Y	Some risk
Niesen 2021 Ref ID 4913	NA		Y	N	Y	Y	Y	High
Patone 2021 Ref ID 7268	Y		Y	U	N	Y	U	High
Tan 2021 Ref ID 4421	NA		Y	N	U	U	N	High
Passive surveillance studies								
Buchan 2021 Ref ID 7142	Y		Y	U	Y	N	Y	High
Strauss 2021 Ref ID 4889	NA		U	N	Y	U	U	High
Su 2021 Ref ID 7935	NA		Y	U	Y	Y	N	High
Su 2022	Y		Y	U	Y	Y	N	High

Supplementary Table 6. Summary of risk of bias assessment for observational studies/surveillance data contributing to KQ2.

Dataset	Were the two groups similar and recruited from the same population?	Were the risk/protective factors measured similarly to assign individuals to exposed and unexposed groups?	Were the risk/protective factors measured in a valid and reliable way?	Were confounding factors identified and appropriately addressed in design or analysis?	Were groups/ participants free of the outcome at the start of the study (or at time risk/protective factor was measured)?	Were the outcomes measured in a valid and reliable way?	Was the follow-up time long enough for outcome to occur?	Was follow-up complete, and if not, were reasons described and explored?	Overall assessment of risk of bias
Abraham 2021 Ref ID 7215	U	Y	Y	N	Y	Y	Y	Y	High
Buchan 2021 Ref ID 7142	U	Y	Y	N	Y	Y	N	Y	High
Husby 2021 Ref ID 4309	Y	Y	Y	Y	Y	Y	Y	Y	Low
Lane 2021 Ref ID 7884	Y	Y	N	N	U	N	U	N	High
Machado 2021 Ref ID 3588	N	Y	Y	N	U	N	N	N	High
Patone 2021 Ref ID 7268	N	Y	Y	Y	Y	N	Y	Y	High
Su 2021 Ref ID 7936	U	Y	Y	N	Y	Y	Y	N	High
Tan 2021 Ref ID 4421	Y	Y	Y	N	U	U	U	Y	High

Supplementary Table 7. Hypothesized mechanisms for myocarditis following COVID-19 vaccination and direct (myocarditis after COVID-19 vaccine) supporting/refuting empirical evidence* (CQ1)

Citation (citation type) Specific aspect of hypothesis, as applicable	Main discussion points by authors, verbatim quotes and in-text citations	Direct empiric evidence supporting/refuting hypothesis (i.e., specific to COVID-19 vaccines)*
Hypothesis 1: Hyper immune/inflammatory response		
<p>Hajra et al., 2021²³ (narrative review)</p> <p>Exposure to spike protein</p>	<ul style="list-style-type: none"> Children developed a more robust immune response than adults during SARS-CoV-2 infection, as demonstrated by multisystem inflammatory syndrome in children. In addition, mRNA vaccines produced more potent immunogenicity and reactogenicity in younger recipients and after the second dose. Similarly, the propensity of young adults to develop myocarditis following the second dose of vaccine supports the hypothesis of the vaccine-associated maladaptive immune response causing cardiac injury [35, 38, 45–47, 56, 58]. Larson et al. [38] performed a cardiac biopsy in one patient before initiating steroids, and this did not demonstrate myocardial infiltrates. Muthukumar et al. [54] demonstrated an increase in a specific natural killer (NK) cell subset and multiple autoantibodies in a 52-year-old male with COVID-19 vaccine-associated myocarditis. In contrast, the interleukin (IL)-17 level was not raised, unlike other causes of myocarditis. The authors hypothesized that such unique immune changes might be contributing to a specific subtype of vaccine-associated myocarditis with rapid recovery. This systemic immune response, when exaggerated in predisposed individuals, might cause organ damage [59]. 	<p><u>Supporting:</u> Multiple case series/reports reporting on adolescents having higher incidence after second dose. Muthukumar et al. In-depth evaluation of a case of presumed myocarditis after the second dose of COVID-19 mRNA vaccine. <i>Circulation</i>. 2021;144:487–98. Case report; increase in NK cells (lymphocytes)</p> <p><u>Refuting:</u> Larson et al. Myocarditis after BNT162b2 and mRNA-1273 Vaccination. <i>Circulation</i>. 2021 ;144:506–508. Case report; no myocardial infiltrates. Muthukumar et al. (see above). Case report; no IL-17 cytokine release (hence different cytokines possibly involved than with other types of myocarditis).</p>
<p>Tsilingiris et al., 2021³³ (article)</p> <p>Exposure to mRNA strand</p>	<ul style="list-style-type: none"> mRNA strands are immunogenic and may themselves trigger an immune response directed against cardiomyocyte epitopes or adversely influence the myocardium in the frame of an exaggerated systemic reaction [22]. 	None
<p>Heymans & Cooper, 2021²⁴ (letter)</p> <p>Exposure to mRNA strand</p>	<ul style="list-style-type: none"> The immune system might detect the mRNA in the vaccine as an antigen, resulting in the activation of proinflammatory cascades and immunological pathways in the heart. Although nucleoside modifications of mRNA reduce their innate immunogenicity, the immune response to mRNA might still drive the activation of an aberrant innate and acquired immune response, which can explain the stronger immune response seen with mRNA vaccines than with other 	None

	types of COVID-19 vaccine. However, this hypothesis is not supported by the lack of immune-related adverse effects in other organs in which the mRNA vaccine is being uptaken.	
Parra-Lucares et al., 2021 ²⁹ (case report and narrative review) Exposure to mRNA strand	<ul style="list-style-type: none"> This [mRNA] exogenous nucleotide material can be immunogenic and stimulate an innate immune response in organisms, generating an abnormal response with the potential to affect tissues other than the target cells of the therapy. To prevent this, nucleoside modifications are made to the mRNA used to decrease this unwanted immune response [55,59]. However, in patients with a genetic predisposition, it may not be sufficient to prevent it. The activation of cells that express the Toll-like receptor and dendritic cells exposed to mRNA can activate pro-inflammatory cascades [59–61], which may have effects at the myocardial level. An exhaustive study of immunological mediators was conducted in one case [Muthukumar et al.]. Elevated plasma levels of interleukin-1 receptor (IL-1R) antagonist, interleukin 5 (IL-5), and interleukin 16 (IL-16) were observed, with no changes in interleukin 6 (IL-6), tumor necrosis factor (TNF), interleukin 1 beta (IL-1), interleukin 2 (IL-2), or interferon gamma (IFN). This patient also had increased plasma levels of natural killer (NK) cells, which destroy infected cells and participate in the innate immune response [65–67]. These preliminary data suggest a role for the abnormal activation of innate immunity in the development of vaccine-associated myocardial compromise. 	<p>Supporting: Muthukumar A et al. In-depth evaluation of a case of presumed myocarditis after the second dose of COVID-19 mRNA vaccine. Circulation. 2021;144:487–498. Case report (52 year-old) data with panel of 48 cytokines and chemokines; elevated levels of some cytokines and NK cells.</p>
Bozkurt et al, 2021 ¹⁷ (narrative review) Exposure to mRNA strand or spike protein or unknown trigger	<ul style="list-style-type: none"> Exposure to mRNA strand: The immune system may therefore detect the mRNA in the vaccine as an antigen, resulting in activation of proinflammatory cascades and immunologic pathways that may play a role in the development of myocarditis as part of a systemic reaction in certain individuals. Exposure to spike protein: By 1 case report, SARS-CoV-2 spike IgM and IgG neutralizing antibody levels were not significantly different in the patient with myocarditis than in individuals without myocarditis post-COVID-19 mRNA vaccination.[17](Muthukumar et al.) arguing against a hyperimmune response. Unspecified trigger: Surge in NK cells - Same patient had a 2-fold increase in the frequency of NK cells [17], which are the classical population of innate lymphoid cells, expressing a heterogeneous repertoire of germline encoded receptors that allows them to destroy cells that are infected by viruses, cancer cells, or cells that are rejected. The surge in NK cells may have either contributed to the pathology or the disease resolution process. Unspecified trigger: Dysregulated cytokine expression: (A) patient with myocarditis had elevated levels of IL-1 (interleukin 1) receptor antagonist, IL-5, IL-16, but not proinflammatory cytokines such as IL-6, tumor necrosis factor, IL-1B, IL-2, or interferon-γ levels. However, the patient had diminished levels of leukemia inhibitory factor, varying bidirectional profiles for IL-10, macrophage migration inhibitory factor, and vascular endothelial growth factor relative to an unvaccinated individual or a vaccinated individual without myocarditis.[17] <i>Bozkurt notes: It is not clear whether the differences seen in this patient regarding relative increases in NK cells, autoantibodies, and a dysregulated cytokine profile reflect a causal pathological immune response or reactive adaptive responses to myocardial inflammation</i> 	<p>Supporting: Unknown trigger, with surge in NK cells & dysregulated cytokine expression: Muthukumar A et al. In-depth evaluation of a case of presumed myocarditis after the second dose of COVID-19 mRNA vaccine. Circulation. 2021;144:487–498. Case report data with panel of 48 cytokines and chemokines; elevated levels of some cytokines and NK cells</p> <p>Refuting: Exposure to spike protein: Muthukumar A et al. In-depth evaluation of a case of presumed myocarditis after the second dose of COVID-19 mRNA vaccine. Circulation. 2021;144:487–498. Case report data; similar spike IgM and IgG neutralizing antibody levels</p>
Das et al., 2021 ²⁰ (case series)	<ul style="list-style-type: none"> Exposure to spike protein: Anti-spike IgG antibody titers in a small subset of our patients were variable (data not shown) and did not correlate with the extent of cardiac injury. Exposure to unknown trigger: Furthermore, Muthukumar et al. conducted detailed immunologic investigation in a 52-year-old man who developed myocarditis 3 days after receiving the second dose of Moderna mRNA COVID-19 vaccine and reported that his 	<p>Refuting: Exposure to spike protein or other unknown trigger, with antibody response: Their case series data (n=25, 12-18 years)(Das)</p>

<p>Exposure to spike protein and other unknown trigger</p>	<p>antibody responses to 18 different SARS-CoV-2 antigens did not differ from (and were lower for some antigens) vaccinated controls who did not develop complications.[16]</p>	<p>Muthukumar A et al. In-depth evaluation of a case of presumed myocarditis after the second dose of COVID-19 mRNA vaccine. <i>Circulation</i>. 2021;144:487–498. Case report data; antibody responses to 18 different SARS-CoV-2 antigens same as controls.</p>
<p>Boursier et al., 2021¹⁶ (case reports) Exposure to unknown trigger</p>	<ul style="list-style-type: none"> The DOTATOC-PET images showed an increase in myocardial uptake relative to blood activity, predominantly in the lateral and inferior walls. Myocardial/blood SUVmax ratio was >2.2 in both cases and, thus, higher than what we commonly observe in non-myocarditis patients. This likely reflects a myocardial infiltrate of inflammatory cells overexpressing somatostatin receptors (lymphocytes, macrophages, activated monocytes) [1–4], presumably within specific antigenic sites. 	<p><u>Supporting:</u> Two cases (18 and 21-year old males) with PET findings supporting myocardial infiltrate.</p>
<p>Switzer & Loeb, 2021³⁰ (narrative review) Exposure to unknown trigger</p>	<ul style="list-style-type: none"> A potential avenue for vaccine-associated myocarditis may be a nonspecific innate inflammatory immune response. 	<p>None</p>
<p>Verma et al., 2021³⁴ (letter to the editor describing 2 cases) Exposure to unknown trigger</p>	<ul style="list-style-type: none"> Case 1: 45 year old woman; endomyocardial biopsy specimen showed an inflammatory infiltrate predominantly composed of T-cells and macrophages, admixed with eosinophils, B cells, and plasma cells. Case 2: 42 year old man; autopsy revealed biventricular myocarditis...An inflammatory infiltrate admixed with macrophages, T-cells, eosinophils, and B cells was observed. 	<p><u>Supporting:</u> Biopsy and autopsy findings from their two cases; showing inflammatory infiltrate.</p>
<p>Hypothesis 2: Delayed hypersensitivity (serum sickness)</p>		
<p>Hajra et al., 2021²³ (article)</p>	<ul style="list-style-type: none"> The development of symptoms within 1–4 days of the second dose of vaccine could be explained by a delayed hypersensitivity or serum sickness-like reaction. Additionally, patients who developed myocarditis following the first dose had a history of COVID-19 infection. In both cases, initial exposure caused sensitization to viral antigen with subsequent exposure forming antigen-antibody complexes and eventual damage to cardiac myocytes [33, 40, 55, 60]. 	<p><u>Supporting:</u> 3 case series/reports reporting highest incidence after second dose, or history of previous COVID if experiencing myocarditis after first dose: D'Angelo T et al. Myocarditis after SARS-CoV-2 vaccination: a vaccine-induced reaction? <i>Can J Cardiol</i>. 2021 Montgomery J et al. Myocarditis Following Immunization With mRNA COVID-19 Vaccines in Members of the US Military. <i>JAMA Cardiol</i>. 2021 Shay DK et al. Myocarditis Occurring After Immunization With mRNA-Based</p>

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		COVID-19 Vaccines. JAMA Cardiol [Internet]. 2021 [cited 2021 Sep 16]
Tsilingiris et al., 2021 ³³ (article)	<ul style="list-style-type: none"> In the foreground stand immune or autoimmune mediated processes as possible mechanisms, and the highest frequency of occurrence after the second vaccine dose (after allowing for a presumed sensitization process to take place after the first dose) seems to strengthen this notion. 	None
D'Angelo et al, 2021 ¹⁹ (case report)	<ul style="list-style-type: none"> In fact, the first vaccine dose may have presumably acquired sensitization. Moreover, the hypothesis of a delayed hypersensitivity after the second dose would be concordant either with the timing of symptoms, and with the mild peripheral eosinophilia seen in our case. 	<u>Supporting:</u> Case report data; 30 year-old male after second dose.
Bozkurt et al., 2021 ¹⁷ (narrative review)	<ul style="list-style-type: none"> Reports to date do not suggest a delayed hypersensitivity reaction, such as serum sickness-like reaction or eosinophilic myocarditis as a cause for myocarditis after mRNA COVID-19 vaccination.[15](D'Angelo et al.) Although rare, delayed localized skin hypersensitivity reactions have been described with mRNA COVID-19 vaccination with a median latency of 7 days,[59](Johnson et al.) unlike myocarditis emerging earlier within 3 to 4 days after vaccination. None of the case reports published to date had evidence of eosinophilia in peripheral blood or immune complex deposition or eosinophilic infiltrates in endomyocardial biopsy samples arguing against hypersensitivity, allergic or eosinophilic myocarditis.[8–17] 	<u>Refuting:</u> Several case reports and series; no eosinophilia: Marshall M et al. Symptomatic acute myocarditis in seven adolescents following Pfizer-BioNTech COVID-19 vaccination. Pediatrics. Published online June 4, 2021. Rosner CM et al. Myocarditis temporally associated with COVID-19 vaccination. Circulation. 2021;144:503–506. Abu Mouch S et al. Myocarditis following COVID-19 mRNA vaccination. Vaccine. 2021;39:3790–3793. Larson KF et al. Myocarditis after BNT162b2 and mRNA-1273 vaccination. Circulation. 2021;144:507–509. Ammirati E et al. Temporal relation between second dose BNT162b2 mRNA Covid-19 vaccine and cardiac involvement in a patient with previous SARS-COV-2 infection. Int J Cardiol Heart Vasc. 2021;34:100774. Bautista GJ et al. Acute myocarditis after administration of the BNT162b2 vaccine against COVID-19. Rev Esp Cardiol (Engl Ed). Published online April 27, 2021;S1885-5857(21)00133-X. Mclean K, Johnson T. Myopericarditis in a previously healthy adolescent male following COVID-19 vaccination: a case report. Acad Emerg Med. Published online June 16, 2021.



		<p>D'Angelo T et al. Myocarditis after SARS-CoV-2 vaccination: a vaccine induced reaction? Can J Cardiol. Published online June 9, 2021;S0828-282X(21)00286-5.</p> <p>Albert E et al. Myocarditis following COVID-19 vaccination. Radiol Case Rep. 2021;16:2142–2145.</p> <p>Muthukumar A et al. In-depth evaluation of a case of presumed myocarditis after the second dose of COVID-19 mRNA vaccine. Circulation. 2021;144:487–498.</p> <p>Johnston MS et al. Delayed localized hypersensitivity reactions to the Moderna COVID-19 vaccine: a case series. JAMA Dermatol. 2021;157:716–720. Skin reactions rare and delayed more than myocarditis.</p>
Chouchana et al., 2021 ¹⁸ (retrospective study on Vigibase case and discussion)	<ul style="list-style-type: none"> This may be related to greater adaptive immune response in younger individuals, which may lead to greater increases of CD4+ Th17+ cell populations, predisposing individuals to developing myocarditis. It would be interesting to see if the recently reported mRNA diagnostic of Th17 activation in myocarditis is also positive in these patients.[41] 	None
Hypothesis 3: Eosinophilic myocarditis		
Hajra et al 2021 ²³ (narrative review)	<ul style="list-style-type: none"> Small pox vaccine and tetanus toxoid vaccine have been found to cause myocardial damage following immunization. Endomyocardial biopsy has demonstrated evidence of eosinophilic myocarditis in such cases [62, 63]. Increased circulating eosinophils produced following immunization infiltrate cardiac tissue. Degranulation of eosinophils causes direct myocardial injury [64]. A similar mechanism might exist in the case of mRNA COVID-19 vaccine-associated myocarditis. However, the lack of peripheral eosinophilia in a few instances renders this mechanism unlikely [45, 58]. 	None in this review; authors of cited reports [45, 58] did not examine eosinophilia.
Takeda et al. 2021 ³¹ (case report)	<ul style="list-style-type: none"> Case report data: Interventricular septal biopsies obtained from the right ventricle revealed diffuse eosinophilic infiltration of the myocardial interstitium. Eosinophilic infiltration, as well as eosinophil degranulation between the myocardial fibers, was observed. 	<u>Supporting:</u> Case report biopsy data, 53 year-old male; no data on whether from exposure to spike protein epitope.
D'Angelo et al, 2021 ¹⁹ (case report and discussion)	<ul style="list-style-type: none"> Case report data: White blood cells were $10.4 \times 10^3/\mu\text{L}$ (normal 4.0-10.0), with mild eosinophilia ($0.9 \times 10^3/\mu\text{L}$, normal 0.0-0.5 $\times 10^3$). A further hypothesis can be represented by eosinophilic myocarditis directly after immunisation, which has been reported as an extremely rare event, despite the possible underdiagnosis due to its delayed development.[5] 	<u>Refuting:</u> Case report laboratory data (only mild eosinophilia), 30 year-old male; no data on whether from exposure to spike protein epitope.
Bozkurt et al, 2021 ¹⁷	<ul style="list-style-type: none"> (In a case report and series (n=4), there was also no evidence of leukocytosis, eosinophilia, anemia, thrombocytopenia, or transaminase elevation.[19,12](Ammirati et al. and Kim et al.) 	<u>Refuting:</u>

(narrative review)	<ul style="list-style-type: none"> • Reports to date do not suggest a delayed hypersensitivity reaction, such as serum sickness–like reaction or eosinophilic myocarditis as a cause for myocarditis after mRNA COVID-19 vaccination.[15](D'Angelo T et al.) Although rare, delayed localized skin hypersensitivity reactions have been described with mRNA COVID-19 vaccination with a median latency of 7 days,[59](Johnson et al.) unlike myocarditis emerging earlier within 3 to 4 days after vaccination. None of the case reports published to date had evidence of eosinophilia in peripheral blood or immune complex deposition or eosinophilic infiltrates in endomyocardial biopsy samples arguing against hypersensitivity, allergic or eosinophilic myocarditis.[8–17] 	<p>Ammirati E et al. Temporal relation between second dose BNT162b2 mRNA Covid-19 vaccine and cardiac involvement in a patient with previous SARS-COV-2 infection. <i>Int J Cardiol Heart Vasc.</i> 2021;34:100774. doi: 10.1016/j.ijcha.2021.100774: Case report with no eosinophilia</p> <p>Kim HW et al. Patients with acute myocarditis following mRNA COVID-19 vaccination. <i>JAMA Cardiol.</i> Published online June 29, 2021. doi: 10.1001/jamacardio.2021.2828. Case series n=3 without eosinophilia</p> <p>D'Angelo T et al. Myocarditis after SARS-CoV-2 vaccination: a vaccine induced reaction? <i>Can J Cardiol.</i> Published online June 9, 2021;S0828-282X(21)00286-5.</p> <p>Johnston MS et al. Delayed localized hypersensitivity reactions to the Moderna COVID-19 vaccine: a case series. <i>JAMA Dermatol.</i> 2021;157:716–720. doi: 10.1001/jamadermatol.2021.1214. Skin reactions rare and delayed more than myocarditis.</p> <p>Several case reports and series; no eosinophilia: (see Hypothesis 2)</p>
Hypothesis 4: Hypersensitivity to vaccine vehicle components (e.g., polyethylene glycol [PEG] and tromethamine; lipid nanoparticle sheath)		
<p>Kounis et al. 2021a²⁷ (letter)</p> <p>Hypersensitivity to PEG and tromethamine</p>	<ul style="list-style-type: none"> • Sokolska et al. described young patient [1] had an atopic diathesis due to his previous history of atopic asthma, pollen and pet allergy and, therefore, the induced myocarditis was presumably hypersensitivity myocarditis. • In 2 cases of myocarditis following COVID-19 vaccination in the USA and in 1 in Israel, the endomyocardial biopsies revealed eosinophils and other interacting and interrelated inflammatory cells such as macrophages, T-cells, and B cells compatible with hypersensitivity myocarditis [2](Witberg et al.) • This type of myocarditis is particularly difficult to recognise because the clinical features characteristic of a drug hypersensitivity reaction — including non-specific skin rash, malaise, fever, and eosinophilia — are absent in most cases [not specific to COVID vaccine cases] [3]. 	<p><u>Supporting:</u></p> <p>Sokolska JM et al. Every rose has its thorns — acute myocarditis following COVID-19 vaccination. <i>Kardiol Pol.</i> 2021; 79(10): 1153–1154, doi: 10.33963/KP.a2021.0075. 1 case with allergy</p> <p>Witberg G et al. Myocarditis after COVID-19 vaccination in a large health care organization. <i>N Engl J Med.</i> 2021 [Epub ahead of print], doi: 10.1056/NEJMoa2110737. 1 case with biopsy of 54 in series</p>

		No references for 2 cases in the USA with eosinophilia.
Kounis et al. 2021b ²⁶ (letter) Hypersensitivity to PEG and tromethamine	<ul style="list-style-type: none"> Hypersensitivity or drug induced myocarditis occurs after hypersensitivity reactions to drugs or substances and is neither necrotizing nor fibrotic [7,8]. One third of patients may demonstrate no peripheral eosinophilia and most patients respond well to steroids and drug cessation [9]. Drugs and substances that can cause hypersensitivity myocarditis include vaccines, antibiotics, central nervous system drugs, antitubercular agents and a variety of other undetermined drugs [10]. Hypersensitivity myocarditis can occur in 3% to 10% of cardiac explants and in patients with a ventricular assist device. Two cases after mRNA vaccination described [by Verma et al.] had endomyocardial biopsies revealing eosinophils and other interacting inflammatory cells such as macrophages, T-cells, and B cells [11]. Lymphocytic myocarditis with presence of macrophages and T cells has been diagnosed after BNT162b2 COVID-19 vaccination, but staining with hematoxylin-eosin to identify eosinophils was not performed [12]. 	<u>Supporting:</u> Verma AK, Lavine KJ, Lin CY. Myocarditis after Covid-19 mRNA vaccination. N Engl J Med. 2021;30(385):1332–4. Two cases with eosinophilia on biopsy.
Tsilingiris et al., 2021 ³³ (article) Hypersensitivity to PEG and lipid nanoparticle sheath	<ul style="list-style-type: none"> The polyethylene glycol (PEG) component and several other ingredients of the lipid nanoparticle sheath have been implicated in other hypersensitivity reactions, most notably in extremely rare but potentially life-threatening immediate cases of anaphylaxis following mRNA vaccine administration [28,29]. It should be noted that in this report and in stark contrast to other available observations a small overall increase in myocarditis risk was observed after the first dose of ChAdOx1 vaccine [34].(Patone et al.) 	<u>Supporting:</u> Patone et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. Nat Med 2021. https://doi.org/10.1038/s41591-021-01630-0 .
Bozkurt et al., 2021 ¹⁷ (narrative review) Hypersensitivity: excipients not mentioned	<ul style="list-style-type: none"> Reports to date do not suggest a delayed hypersensitivity reaction, such as serum sickness–like reaction or eosinophilic myocarditis as a cause for myocarditis after mRNA COVID-19 vaccination.[15] Although rare, delayed localized skin hypersensitivity reactions have been described with mRNA COVID-19 vaccination with a median latency of 7 days,[59](Johnson et al.) unlike myocarditis emerging earlier within 3 to 4 days after vaccination. None of the case reports published to date had evidence of eosinophilia in peripheral blood or immune complex deposition or eosinophilic infiltrates in endomyocardial biopsy samples arguing against hypersensitivity, allergic or eosinophilic myocarditis.[8–17] Lipid nanoparticles or adjuvants used in mRNA vaccines have not been shown to result in an immune or inflammatory response and have not been associated with myocarditis either. 	<u>Refuting:</u> Several case reports and series (see Hypothesis 2). Johnston MS et al. Delayed localized hypersensitivity reactions to the Moderna COVID-19 vaccine: a case series. JAMA Dermatol. 2021;157:716–720. doi: 10.1001/jamadermatol.2021.1214. Skin reactions rare and delayed more than myocarditis
Hypothesis 5: Response to mRNA vaccine lipid nanoparticles (direct deleterious effect; not delayed – see Hypothesis 4)		

<p>Tsilingiris et al., 2021³³ (article)</p>	<ul style="list-style-type: none"> To counter the inherent instability of free mRNA and facilitate its entry into selected host cells, a lipid nanoparticle sheath is used as a delivery vehicle; the most crucial element of the lipid nanoparticles is the variable ionizable lipid (SM-102 for Moderna and ALC-0315 for Pfizer/BioNTech). The recent observation of a similar adverse event in a recipient of the non-mRNA, peptide-based NVX-CoV2373 in the frame of a phase III clinical trial with 7020 participants in the active treatment arm raises the question whether the lipid nanoparticle sheath, which is a common structural component of these platforms could be implicated in the pathogenesis of vaccine-induced myocarditis.[30] The case of myocarditis within the NVX-CoV2373 clinical trial was reviewed by an independent safety monitoring which determined that it was likely of viral origin and not related to the vaccination itself. It should be noted that in this report (Patone et al.) and in stark contrast to other available observations a small overall increase in myocarditis risk was observed after the first dose of ChAdOx1 vaccine [34]. One could argue that there have been up until now essentially no reports of a similar clinical picture among receivers of other non-vaccine, LPN-containing treatments. This could be a mere result of the rarity of this adverse event combined with the massive vaccination programs, which could have allowed for the clustering and recognition of such cases. 	<p>Supporting: Patone et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. Nat Med 2021. https://doi.org/10.1038/s41591-021-01630-0.</p>
<p>Kadkhoda, 2021²⁵ (letter)</p>	<ul style="list-style-type: none"> A more likely mechanism [than Hypothesis 13 of pericyte expression] is where the vaccine lipid nanoparticles leak from the injection site and enter circulation where clinical injection practices are not very well observed [7]. Then the nanoparticles reach the heart and can be endocytosed by cardiac tissue including cardiac muscle, pericytes, endothelial cells, and macrophages. 	<p>None</p>
<p>Hypothesis 6: Autoimmunity triggered by molecular mimicry*** or other mechanism</p>		
<p>Hajra et al 2021²³ (narrative review) Molecular mimicry</p>	<ul style="list-style-type: none"> Molecular mimicry: The high prevalence of myocardial damage in COVID-19 [where there is exposure to entire spike protein], combined with a tiny proportion of myocarditis in mRNA COVID-19 vaccine recipients [exposure to partial antigen i.e. small epitope of spike protein], indicates the possibility of molecular mimicry between SARS-CoV-2 spike protein and an unknown myocardial protein [33, 38, 58, 61]. 	<p>Supporting: 3 case series/reports of myocarditis after mRNA vaccination, indicating lower rates than due to COVID-19: D'Angelo T et al. Myocarditis after SARS-CoV-2 vaccination: a vaccine-induced reaction? Can J Cardiol. 2021 Larson KF, Ammirati E, Adler ED, Cooper LT, Hong KN, Saponara G, et al. Myocarditis after BNT162b2 and mRNA-1273 Vaccination. Circulation. 2021 Ammirati E et al. Temporal relation between second dose BNT162b2 mRNA Covid-19 vaccine and cardiac involvement in a patient with previous SARS-COV-2 infection. IJC Heart Vasc. 2021;34:100774.</p>

<p>Tsilingiris et al., 2021³³ (article)</p> <p>Molecular mimicry and other autoimmune</p>	<ul style="list-style-type: none"> • Molecular mimicry: Among others, supported by the relatively frequent occurrence of myocardial damage and myocarditis in the frame of SARS-CoV-2 infection, a mechanism of molecular mimicry between the viral S-protein and various self-antigens (i.e., α-myosin) has been suggested [22]. In this case, relatively similar rates of myocarditis occurrence would be expected among receivers of adenoviral vector-based platforms. The currently available evidence presents a rather solid counterargument against this scenario; while cases of myocarditis/pericarditis in association with administration of the ChAdOx1 vaccine (Vaxzevria, Astra-Zeneca) have also been reported [34](Patone et al.), they do not seem to occur more frequently than expected in the absence of vaccination according to most available evidence [23,24](Alberta; Australian Government), while there is so far one published only 1 case reported after Janssen Ad26.COVS.2 [25].(Sulemankhil et al.) • Other autoimmune: In the foreground stand immune or autoimmune mediated processes as possible mechanisms, and the highest frequency of occurrence after the second vaccine dose (after allowing for a presumed sensitization process to take place after the first dose) seems to strengthen this notion. mRNA vaccines have been already causally implicated in a number of immune-mediated adverse events such as autoimmune thrombocytopenia and thyroiditis [11,21]. 	<p><u>Refuting:</u> Molecular mimicry: More cases should occur in non-mRNA vaccines, which introduce spike protein, than have been reported: Patone et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. Nat Med 2021. https://doi.org/10.1038/s41591-021-01630-0. Alberta. Office of the chief medical officer of health. Myocarditis and/or Pericarditis following COVID-19 Vaccines 2021. https://www.alberta.ca/assets/documents/health-myocarditis-and-pericarditis-following-covid.pdf. Australian Government. Department of Health. COVID-19 vaccination – guidance on myocarditis and pericarditis after mRNA COVID-19 vaccines. 2021. Sulemankhil I, Abdelrahman M, Negi SI. Temporal association between the COVID-19 Ad26.COVS.2 vaccine and acute myocarditis: a case report and literature review. Cardiovasc Revascularization Med : Mol Interv 2021. https://doi.org/10.1016/j.carrev.2021.08.012.</p>
<p>D'Angelo et al, 2021¹⁹ (case report and discussion)</p> <p>Molecular mimicry</p>	<ul style="list-style-type: none"> • The pathophysiology of our case was more likely related to an autoimmune phenomenon. Although the exact trigger for autoimmune myocarditis is unknown, literature evidence suggests a “molecular mimicry” when the viral antigen resembles proteins on the myocardium. When autoreactive sensitisation occurs, cytokines and lymphocytes migrate into the myocardial interstitial space, inducing an inflammatory response.[3] 	<p>None; nothing from case report to support & reference to influenza vaccine-induced fulminant myocarditis.</p>
<p>Heyman & Cooper, 2021²⁴ (letter)</p> <p>Molecular mimicry</p>	<ul style="list-style-type: none"> • Antibodies directed to SARS- CoV-2 spike glycoproteins might cross-react with structurally similar human protein sequences, including myocardial α- myosin heavy chain. These autoantibodies might be innocent bystanders resulting from myocardial inflammation and injury, or might reflect a certain immune-genetic background that predisposes to developing hyperimmunity and myocarditis upon any trigger.[9] 	<p><u>Supporting:</u> Vojdani, A. & Kharrazian, D. Potential antigenic cross-reactivity between SARS- CoV-2 and human tissue with a possible link to an increase in autoimmune diseases. Clin. Immunol. 2020;217: 108480. In vitro study.**</p>

<p>Bozkurt et al., 2021¹⁷ (narrative review)</p> <p>Molecular mimicry and other autoimmune</p>	<ul style="list-style-type: none"> • Molecular mimicry: Another important potential mechanism for myocarditis is molecular mimicry between the spike protein of SARS-CoV-2 and self-antigens.[50] Antibodies against SARS-CoV-2 spike glycoproteins have been experimentally shown to cross-react with structurally similar human peptide protein sequences, including α-myosin.[50](Vojdani et al.) However, severe adverse events or autoimmune reactions have been very rare.[46,47](Polack et al. and Baden et al.) • Other autoimmune: (One case) had higher levels of antibodies against some self-antigens such as aquaporin 4, endothelial cell antigen, and proteolipid protein 1.[17](Muthukumar A et al) In the patient studied, autoantibody levels peaked on day 2 along with symptoms, but they did not recede as expected, as the clinical condition improved, although the follow-up was rather short. Also, the autoantibodies may not be pathogenic and could also be seen as a result of myocardial inflammation. (Historically, circulating heart-reactive autoantibodies have been reported at a higher frequency in patients with myocarditis and have been implicated in pathogenesis. These autoantibodies are usually directed against multiple antigens, some of which may have functional effects on cardiac myocytes.[49]) Autoantibodies are found more frequently in first-degree relatives of patients with cardiomyopathy than in the healthy population, raising the possibility that myocarditis may develop in a subgroup of patients with the appropriate genetic background. 	<p><u>Supporting:</u> Molecular mimicry: Vojdani, A. & Kharrazian, D. Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases. Clin. Immunol. 2020;217: 108480. In vitro study (see row immediately above for details). Other autoimmunity: Muthukumar A et al. In-depth evaluation of a case of presumed myocarditis after the second dose of COVID-19 mRNA vaccine. Circulation. 2021;144:487–498.</p>
<p>Chouchana et al., 2021¹⁸ (retrospective study on Vigibase case and discussion)</p> <p>Molecular mimicry</p>	<ul style="list-style-type: none"> • The mRNA is known to be a self-adjuvant for innate immune responses, and this may help to explain their immunogenicity, and trigger excessive immune responses in some individuals, especially when there may be presence of a cross-reacting antigen. 	<p>None</p>
<p>Switzer & Loeb, 2021³⁰ (narrative review)</p> <p>Molecular mimicry and other autoimmune</p>	<ul style="list-style-type: none"> • Molecular mimicry: A potential avenue for vaccine-associated myocarditis may be a nonspecific innate inflammatory immune response, or perhaps an interaction between the encoded viral spike protein of the mRNA and an as-yet undetermined cardiac protein [21,56]. Studies have hypothesized that the antibodies generated in response to the mRNA spike protein may react with surface antibodies of the cardiomyocytes of susceptible hosts, provoking an inflammatory reaction and associated tissue damage [21,57]. • Other autoimmune: Heart-reactive auto-antibodies have been reported at elevated levels in patients with myocarditis [2,57,64]. These antibodies may target multiple antigens, possibly having functional effects on cardiac myocytes and contributing to the pathogenesis of vaccine-induced. 	<p>None</p>
<p>Parra-Lucarets et al., 2021²⁹ (case report and narrative review)</p> <p>Molecular mimicry and other autoimmune</p>	<ul style="list-style-type: none"> • Molecular mimicry: The presence of mimicry between the spike protein and cardiac autoantigens (e.g., myosin) generates anti-SARS-CoV-2 antibodies with affinity to cardiac proteins, inducing an autoimmune humoral response. In in vitro studies [68] (Vojdani et al), anti-SARS-CoV-2 antibodies have been shown to cross-react with human proteins, such as alpha-myosin, a structural protein of cardiomyocytes involved in myocardial muscle contraction. <i>However, to date, it has not been shown that these antibodies can generate an autoimmune response in tissues that express these proteins, both in animal models and in patients.</i> 	<p><u>Supporting:</u> Molecular mimicry: Vojdani, A. & Kharrazian, D. Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases. Clin. Immunol. 2020;217: 108480. In vitro study showing</p>

	<ul style="list-style-type: none"> • Other autoimmune: The presence of antibodies against self-antigens was evaluated in the clinical case described above [64](Muthukumar A et al.). Autoantibodies such as anti-aquaporin 4, anti-endothelial antigen, or anti-proteolipid protein 1 were detected. These autoantibodies have been previously reported in patients with myocarditis [69] and first-degree relatives of patients with myocarditis, which supports the existence of a myocarditis mechanism mediated by autoantibody formation. <i>However, it has not been demonstrated that these autoantibodies can cause an autoimmune response in organisms, both in the heart and other tissues, so it could only be a non-causal correlation.</i> • Other autoimmune: In most cases [of patients with clinical and laboratory findings of myocarditis associated with anti-SARS-CoV-2 vaccination], significant alterations in autoimmune parameters observed in other pathologies were not detected, including rheumatoid factor (RF), antinuclear antibodies (ANA), or elevation of inflammatory parameters (C-reactive protein or erythrocyte sedimentation rate). 	<p>cross-reactivity with at least one protein in muscle, i.e. α-myosin (see above); caution about unknown implications.</p> <p>Other autoimmune: Muthukumar A et al. In-depth evaluation of a case of presumed myocarditis after the second dose of COVID-19 mRNA vaccine. <i>Circulation</i>. 2021;144:487–498. Case report with detected autoantibodies; caution about unknown implications.</p> <p><u>Refuting:</u> Other autoimmune: Indicative of direct data but no citations</p>
<p>Ehlich et al., 2021²¹ (case report in 40 year-old male after first dose, with biopsy)</p> <p>Molecular mimicry</p>	<ul style="list-style-type: none"> • Case report of biopsy-proven (left ventricular endomyocardial) lymphocytic myocarditis in 40-year male after first dose. Histology and immuno-histology of the biopsies revealed acute lymphocytic myocarditis. As the patient developed myocarditis a few days after the first vaccination in absence of anti-SARS-CoV-2-antibodies, the pathogenesis of mRNA COVID-19 vaccine associated myocarditis does not appear to depend on anti-SARS CoV-2 spike protein antibodies. Thus, the hypothesis of cross-reactivity of antibodies induced by mRNA vaccination with myocardial antigens (molecular mimicry [7]) is not corroborated by our case. Rather, the quick cardiac infiltration of immune cells after vaccination suggests that myocarditis may be caused by other mechanisms. 	<p><u>Refuting:</u> Molecular mimicry (after first dose): Their case report data, due to lack of anti-SARS-CoV-2-antibodies</p>
<p>Hypothesis 7: Low residual levels of double-strand RNA (dsRNA)</p>		
<p>Milano et al 2021²⁸ (special report)</p>	<ul style="list-style-type: none"> • The presence of low residual levels of double-strand RNA (dsRNA) has been reported in mRNA COVID-19 vaccine preparations...dsRNA is known to be a strong exogenous inducer of immune-inflammatory reactions involving well-identified intracellular signaling cascades and mediators.²⁸ • The current methods used to purify IVT mRNA vaccine preparations vary in terms of technical performance and, at best, allow the removal of 90% of dsRNA when using HPLC, as reported by the developers of mRNA vaccines [17]. • dsRNA is detected by antigen-presenting cells, endothelial cells and the airway epithelium [18], and gives rise to dose-related innate immune activation [17]. When packaged in lipid nanoparticles, dsRNA is preferentially transferred to phagocytic monocytic-derived cells, such as macrophages and dendritic cells, which are key actors in immunity [24]. • However, a relatively low level of clinical evidence is currently available in this [COVID-19 mRNA vaccines] context to be taken as hypothesis-generating. 	<p>None</p>
<p>Hypothesis 8: Dysregulated micro-RNA response</p>		

<p>AbdelMassih et al. 2021¹⁵ (literature review)</p>	<ul style="list-style-type: none"> • MicroRNAs are short non-coding RNAs that play a crucial role in the regulation of gene expression during cellular processes. It is now established that some of the host-generated miRNAs are known to modulate the antiviral defense during viral infection. Recently, multiple DNA and RNA viruses have been shown to produce miRNAs known as viral miRNAs (v-miRNAs). viral RNA can either alter the expression of host miRNA or use cellular machinery to form viral miRNAs. We hypothesize that mRNA vaccines can either trigger the release of host miRNAs or contain themselves some miRNAs that can trigger [myocarditis]. • [In conclusion] the evidence reveals that the micro-RNAs implicated in myocarditis in general are as well implicated in the pathogenesis of severe COVID-19, this can explain why patients having a first dose with a history of COVID-19 can develop myocarditis from mRNA vaccines, also the relatively higher likelihood of this complication in males and younger aged individuals can be explained by the upregulation of key myocarditis related miRNAs in those two strata, due to higher muscle mass and suggests performing a sarcopenia index in recipients of the vaccine to correlate it with the likelihood of this complication. 	<p>None</p>
<p>Hypothesis 9: Production of anti-idiotypic antibodies against immunogenic regions of antigen-specific antibodies</p>		
<p>Tsilingiris et al., 2021³³ (article)</p>	<ul style="list-style-type: none"> • This process could in theory lead to tissue-specific adverse events through the formation of immune complexes, activation, blockade and/or down-regulation of membrane receptors (e.g. ACE2), as well as complement- or immune cell-mediated cellular damage [26]. 	<p>None</p>
<p>Hypothesis 10: Trigger of pre-existing dysregulated immune pathways in certain individuals with predispositions (e.g., resulting in a polyclonal B-cell expansion, immune complex formation, and inflammation¹⁷)</p>		
<p>Bozkurt et al., 2021¹⁷ (narrative review)</p>	<ul style="list-style-type: none"> • Although nucleoside modifications of mRNA have been shown to reduce their innate immunogenicity,⁴⁵ in certain individuals with genetic predisposition,⁴⁸ the immune response to mRNA may not be turned down and may drive the activation of an aberrant innate and acquired immune response. The dendritic cells or Toll-like receptor expressing cells exposed to RNA may still have the capacity to express cytokines and activation markers in certain individuals, although this may be markedly less when exposed to mRNA with nucleoside modifications than when treated with unmodified RNA. The immune system may therefore detect the mRNA in the vaccine as an antigen, resulting in activation of proinflammatory cascades and immunologic pathways that may play a role in the development of myocarditis as part of a systemic reaction in certain individuals.[45,48] • [In 6 male cases of COVID mRNA vaccine myocarditis in Israel], serology for autoimmune disorders with antinuclear antibodies and rheumatoid factor were negative, with no evidence of predilection to individuals with pre-existing autoimmune disorders.[10](Abu Mounch et al.) • In 1 case report (Muthukumar et al.), a panel testing for variants in 121 genes potentially linked to cardiomyopathy was negative,[17] arguing against an existing predisposition to cardiomyopathy attributable to known gene variants in that case. 	<p><u>Refuting:</u> For specific predispositions: Abu Mounch S et al. Myocarditis following COVID-19 mRNA vaccination. Vaccine. 2021;39:3790–3793. Case series n=6 Muthukumar A et al. In-depth evaluation of a case of presumed myocarditis after the second dose of COVID-19 mRNA vaccine. Circulation. 2021;144:487–498.</p>
<p>Switzer & Loeb, 2021³⁰ (narrative review)</p>	<ul style="list-style-type: none"> • It is possible that genetic factors regulating the inflammasome activation, or interferon-signaling cascade, may contribute to an individual's risk of developing the cytokine storm responsible for triggering auto-reactive cell activity after exposure to the mRNA vaccine [58, 61, 63]. 	<p>None</p>

Hypothesis 11: Antibody-dependent enhancement of immunity or other forms of immune enhancement with re-exposure to virus after vaccine		
Bozkurt et al., 2021 ¹⁷ (narrative review)	<ul style="list-style-type: none"> No evidence of either cellular immune enhancement or antibody-dependent enhancement of immunity was observed in non-human primate studies after SARS-CoV-2 virus challenge, either after vaccination [not specific to approved mRNA vaccines] or previous infection.[58] These findings led a National Institutes of Health ACTIV study (Accelerating COVID-19 Therapeutic Interventions and Vaccines) panel to conclude that the risk of immune enhancement after COVID-19 immunizations was low, but required ongoing pharmacovigilance and monitoring.[58] To date, neither COVID-19 disease nor the new COVID-19 vaccines have shown evidence of causing antibody-dependent enhancement of immunity or other forms of immune enhancement with re-exposure. People infected with SARS-CoV-2 have not been reported to develop antibody-dependent enhancement of immunity on repeat exposure, and vaccine breakthrough COVID-19 cases are rare and mild. There is no evidence of acute COVID-19 infection during presentation with myocarditis cases after COVID-19 vaccination, arguing against a breakthrough infection as a cause (Table 4 review of available cases reports and series) 	Refuting: Multiple case reports and series reviewed and tabulated, having no evidence of acute COVID-19 infections after vaccine when presenting with myocarditis.
Hypothesis 12: Direct cell invasion via the spike protein interacting with the angiotensin-converting enzyme 2 (ACE2) widely expressed and prevalent in cardiomyocytes¹⁸		
Chouchana et al., 2021 ¹⁸ (retrospective study on Vigibase case and discussion)	<ul style="list-style-type: none"> In two recently reported cases of myocarditis following mRNA vaccination, only inflammatory infiltration was assessed in the myocardium, suggesting that the ACE2 hypothesis is probably not relevant.[46] 	Refuting: Verma, A.K et al., Myocarditis after Covid-19 mRNA Vaccination. N. Engl. J. Med. 385, 1332–1334 (2021). Data from 2 case reports; only inflammatory infiltration was assessed in the myocardium
Switzer & Loeb, 2021 ³⁰ (narrative review)	<ul style="list-style-type: none"> Encoded viral surface spike protein of the mRNA vaccine, which triggers the immune response, may interact with ACE2 receptors in the host, increasing the likelihood of cardiac sensitivity or inflammatory reactions [38,39]. Possible host genetic factors in ACE2 receptors, which vary across ethnic groups, may drive increased susceptibility to elevated cardiovascular symptoms or the development of an inflammatory response triggering symptom onset [39,52,58]. 	None
Hypothesis 13: Cardiac pericyte expression of ACE2 with immobilized immune complex on the surface of pericytes activation of the complement system		
Kadkhoda et al., 2021 ²⁵ (letter)	<ul style="list-style-type: none"> The role of pericytes in susceptibility to COVID-19 through the expression of SARS-CoV-2 receptor, i.e., angiotensin-converting enzyme 2 (ACE2) has been demonstrated [4]. It has also been shown that after infection with SARS-CoV-2, anamnestic humoral immune responses to previously-encountered common coronaviruses (CoVs) is augmented significantly [6]. Anti-spike antibodies elicited as a result of past exposure to common CoVs and/or to SARS-CoV-2 spike (be it through prior infection or vaccination), may elicit anti-idiotypic antibodies, that is, antibodies directed against the paratope region of anti-spike antibodies. Since the latter is the mirror image of the anti-spike antibodies, it may mimic the spike protein itself and bind ACE2 expressed on cardiac pericytes that express ACE2. This forms an immobilized immune 	None

	complex on the surface of pericytes. This localized immune complex, in turn, may lead to activation of the complement system through its classical pathway and damage to the target cell.	
Hypothesis 14: Spike-activated neutrophils (expressing ACE2) augmenting inflammatory response		
Kadkhoda et al., 2021 ²⁵ (letter)	<ul style="list-style-type: none"> Local production of spike protein on the surface of cardiac cells and/or its shedding along with detached cell membranes may recruit neutrophils that also express ACE2 on their surface. Spike-activated neutrophils produce neutrophil extracellular traps [8] that subsequently activate alternative pathway of complement in situ, damaging cardiac endothelial cells. 	None
Choi et al., 2021 ⁵⁵ (case report)	<ul style="list-style-type: none"> There were three main histological findings in the heart: 1) myocarditis predominantly involving the atrial wall, with neutrophil and histiocyte predominance; 2) non-inflammatory single-cell necrosis; and 3) diffuse CBN [contraction band necrosis] throughout the myocardium, predominantly in the left ventricle... In this case, the myocarditis was histologically different from viral or immune-mediated myocarditis in that the inflammatory infiltrates were predominantly neutrophils and histiocytes, rather than lymphocytes...The underlying mechanism of myocardial injury in this case is unclear, but it may have involved cytokine-mediated or histiocyte-linked immunologic injury to the myocardium. 	<u>Supporting:</u> Autopsy findings from Choi case report (22 year-old male); inflammatory infiltrates were predominantly neutrophils and histiocytes, rather than lymphocytes.
Hypothesis 15: Hyperviscosity-induced cardiac problem		
Mungmunpantipantip & Wiwanitkit, 2021 ⁵⁶ (letter to the editor)	The underlying mechanism of post COVID-19 vaccination hyperviscosity is a change of antibody level in plasma after vaccine stimulation. In the case of underlying high blood viscosity or previous COVID-19, the excessive increasing of antibody level might occur and can result in excessive blood viscosity and hyperviscosity.[2,3]	None
Hypothesis 16: Strenuous exercise induced secretion of proinflammatory IL-6		
Elkazzaz et al., 2022 ²² (protocol for retrospective and prospective observational study)	<ul style="list-style-type: none"> Cytokine storm is suggested as one of the major pathological characteristics of SARS-CoV-2 infection, it was found that the presence of SARS-CoV-2 spike protein in epithelial cells promotes IL-6 trans-signaling by activation of the AT1 axis to initiate coordination of a hyper-inflammatory response [17]. Also, it was shown that increase of TNF-α and IL-6 was found after the 1st vaccination in individuals with pre-existing COVID-19 immunity(18) and also, IL-6 were significantly higher after the second COVID vaccination dose of S-Protein Based Vaccines for COVID-19 at day 23 than those at day 2 [18]. Compared to the DNA vaccine, the mRNA vaccine induced a more robust production of IL-5, IL-6 [19]. Pro-inflammatory cytokines IL-6, TNF-α, a heterodimeric cytokine belonging to the IL-12 family were increased early upon vaccine administration [20]. Exercise causes skeletal muscle cells to release IL-6, and it raises the plasma concentration of IL-6 100 times higher than at rest [23]. Strenuous exercise raises levels of a variety of pro- and anti-inflammatory cytokines. The concentration of IL-6 increases up to 100-fold after strenuous exercise, such as a marathon race [3,4]. 	None

	<ul style="list-style-type: none"> In addition to the induction effect of COVID-19 vaccine on IL-6, strenuous exercise (and muscle contraction) could boost the effect of IL-6 leading to myocarditis. 	
Differences in incidence by sex could be due to sex steroid hormones or underdiagnosis in females		
Tsilingiris et al., 2021 ³³ (article)	<ul style="list-style-type: none"> In order to explain the skewed gender distribution of cases, the influence of sex steroid hormones (estrogen, testosterone) has been suggested [34]. 	None; cited reference does not refer to or investigate sex hormones
Heymans & Cooper, 2021 ²⁴ (letter)	<ul style="list-style-type: none"> Differences in hormone signalling might be involved in the pathophysiology of COVID-19 mRNA- vaccination- related myocarditis. Testosterone can inhibit anti- inflammatory immune cells and promote a more aggressive T helper 1 cell- type immune response. By contrast, oestrogen has inhibitory effects on pro- inflammatory T cells, resulting in a decrease in cell-mediated immune responses.[1] 	None
Bozkurt et al., 2021 ¹⁷ (narrative review)	<ul style="list-style-type: none"> Sex hormones: An important possible explanation relates to sex hormone differences.3,65,66 Testosterone is thought to play a role, by a combined mechanism of inhibition of anti-inflammatory cells [3,65–67] and commitment to a Th1-type immune response.[68] Estrogen has inhibitory effects on proinflammatory T cells, resulting in a decrease in cell-mediated immune responses; and pericarditis incidence is higher in women during the postmenopausal period.[69] Underdiagnosed in women: Another contributing factor could be underdiagnosis in women. By our analysis of the VAERS database, as of June 6, 2021, there were 6235 reported cases of chest pain, 69% of which were in women, versus 30% in men.[70] Despite a higher prevalence of chest pain in women, diagnostic evaluation, including ECG, laboratory biomarkers, echocardiography, and MRI, was performed and reported more often in male than in female patients presenting with chest pain after COVID vaccination (Bozkurt, unpublished data, 2021). 	<p><u>Supporting:</u> Sex hormones: None</p> <p>Underdiagnosis in women: Centers for Disease Control and Prevention. The Vaccine Adverse Event Reporting System (VAERS) results. June 6, 2021. Accessed July 6, 2021. https://wonder.cdc.gov/vaers.html. Mor chest pain complaints in females. Bozkurt, unpublished data, 2021. Fewer investigations in females.</p>
Chouchana et al., 2021 ¹⁸ (retrospective study on Vigibase case and discussion)	<ul style="list-style-type: none"> Although, female patients usually generate higher overall antibody levels and more adverse events following vaccination, male patients have increased enhanced type-1 immune responses.[47] These differences may be driven by sex hormone differences and testosterone is thought to play a role in commitment to a Th1 response.[38] 	None
Parra-Lucarens et al., 2021 ²⁹ (case report and narrative review)	<ul style="list-style-type: none"> Testosterone has been observed to exhibit inhibitory effects on anti-inflammatory cells, increased activity of pro-inflammatory M1 macrophages, and increased CD4+ type 1 (Th1) T lymphocyte response [70]. In turn, estrogens have an inhibitory effect on pro-inflammatory T lymphocytes, causing a decrease in the cellular immune response. This fact explains the observation that the highest incidence of myocarditis or pericarditis (not specific to mRNA COVID) in women occurs in those of postmenopausal age [72]. However, given the characteristics of the published reports (several of these coming from studies carried out in soldiers, for example) [39,73], there is a significant selection bias, so it is not yet possible to confirm whether this complication is more frequent in the male population. 	<p><u>Refuting:</u> Montgomery J et al. Myocarditis Following Immunization with MRNA COVID-19 Vaccines in Members of the US Military. JAMA Cardiol. 2021, 6, 1202–1206. Source population biased towards males (but many other population-based studies exist now).</p>

Appendix 2. Evidence synthesis methods

Search strategy

We worked with an experienced medical information specialist (Becky Skidmore) to develop the search strategies. The initial search was peer-reviewed Oct 5, 2021, with slight modifications made in Dec 2021. Searches combine concepts for COVID-19, vaccines, and myocarditis/pericarditis/cardiovascular manifestations/adverse events/surveillance. The original search was limited to articles published since October 2020. We ran the searches for the first iteration of this review on October 6, 2021 and ran the update on Jan 10, 2022. We did not add limits for language, country or study design. We have since removed the limits for human (not animal only) studies (to enable generation of a list of references to potentially relevant animal studies), as well as letters to the editor and commentaries. We added a limit to exclude case reports. We used Endnote for citation management.

Study Selection

In our original review we conducted 2 pilot rounds in Excel, using 200 records, with all team members involved in screening. Instead of redoing this step we provided an in-depth training session on the changes of scope to all review team members. We then conducted screening and selection in DistillerSR using structured forms. Title and abstract review used DistillerSR's machine learning tool (DAISY) which calculates the likelihood of inclusion for each unreviewed record based on those already screened and continually re-prioritizes records during screening. A single reviewer screened all titles/abstracts, and another reviewer verified exclusions for the first 50% records, where a large majority of relevant studies were located. For full text selection, a single reviewer reviewed all records, with exclusions verified by another reviewer and additional verification of included studies during data extraction.

Data Extraction

We extracted all data into structured tables and conducted a pilot exercise with 2 studies for each new question (KQ2 & 4; CQ1). Thereafter, one reviewer extracted all data and a second reviewer verified the extracted data. Discrepancies were resolved by discussion or by a review lead. Specific equity-related populations of interest for study results were sex, age, and race/ethnicity.

For KQs 1 and 2, we distinguished between estimates of incidence compared with an unexposed group (excess incidence/risk differences) versus without a control, and extracted data on incident rates per person-years and per doses of vaccine/people vaccinated (dose 2). We extracted data on any stratified or subgroup analyses based on age, sex, different vaccine types, and different risk intervals. Effect measures included: incidence rate/cumulative risk (including excess risk [risk difference] when using a control group) and relative and absolute effects between groups (e.g., incidence rate ratio (IRR) or risk difference), adjusted for key confounders (i.e., age, sex, infection status, cardiac and immunodeficiency/autoimmune conditions) when reported.

Risk of Bias Assessment

One review lead and all other reviewers piloted each risk of bias tool with 10% (or 2 whichever is higher) papers. Assessments were then completed by one reviewer and verified by another. Discrepancies were resolved by discussion or by a review lead. We used the JBI checklist for cohort studies, with focus on valid and reliable outcome ascertainment and, for KQ2, accounting for key confounders including pre-existing health conditions and prior COVID-19 exposure (including during long-term follow-up). The findings of the risk of bias assessments were used when undertaking Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessments of the certainty of the evidence.

We did not assess risk of bias for included studies in KQs 3 or 4 or for CQ1.

Synthesis

We analyzed data on myocarditis (including myopericarditis) and pericarditis separately, when able. Data are summarized in a descriptive way and the results were contextualized for the Canadian context. For KQs 1 and 2, we did not pool results from the included studies due to heterogeneity in dosing and risk intervals, case ascertainment, populations (age and sex). We tabulated all results and compared and contrasted findings between studies based on the major differentiating population, vaccine and methodologic variables. We reached consensus on a best estimate of the incidence or a range. Based on clinical input we developed primary age categories (12-17y, 18-29y, 30-39y, ≥ 40 y) to rely on when possible. If a study contributed more than one result within these (e.g., 20-24y and 25-29y, results for each mRNA vaccine) we took the weighted average of the incident rates. When a study reported an incidence rate (or data to calculate this) and an IRR compared with a control/background rate, but not the difference in incidence (excess incidence over background rate), we calculated the excess incidence (i.e., crude incidence – [crude incidence/IRR]). Summary of findings tables were developed with GRADE applied to results for KQs 1 and 2. Descriptive tables were created for KQs 3 and 4, and CQ1.

For KQs 1 and 2, we assessed the certainty for each of our conclusion statements using GRADE. For KQ1, observational studies started at Low certainty; for KQ2, studies started at High certainty. We rated down based on serious concerns about risk of bias, inconsistency, indirectness, imprecision, and/or reporting biases. For KQ1, we considered incidence rates < 20 per million to be “little-to-none”; for KQ2, associations ≥ 1.5 (OR/RR) were considered clinically relevant (i.e., OR < 1.5 shows “little-to-no association”). For KQ1, we rated down for indirectness for comparisons across both sexes, due to the large heterogeneity in incidence rates across ages (for males) and sexes. We considered rating up for observational studies due to large incidence rates when no other major limitations were evident, as recommended in the GRADE guidance.(Guyatt et al, <https://doi.org/10.1016/j.jclinepi.2011.06.004>).