LIVING EVIDENCE SYNTHESIS: UPDATE #2 SUMMARY

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, Erika Lingohr, Rachelle Janicki (Knowledge Users; Public Health Agency of Canada) and Tricco A (Unity Health Toronto and SPOR Evidence Alliance for review of protocol and/or this report; Kaitryn Campbell (McMaster University) for peer reviewing the search strategy.

Funding: To help Canadian decision-makers as they respond to unprecedented challenges related to the COVID-19 pandemic, COVID-END in Canada is preparing evidence responses like this one. The development and continued updating of this living evidence synthesis has been funded by the Canadian Institutes of Health Research (CIHR) and the Public Health Agency of Canada. The opinions, results, and conclusions are those of the team that prepared the living evidence synthesis, and independent of the Government of Canada, CIHR and the Public Health Agency of Canada. No endorsement by the Government of Canada, CIHR or Public Health Agency of Canada is intended or should be inferred.

17 May 2022 (Update #2)

Context

This is the second update of a living evidence synthesis conducted in November 2021 available at COVID-END and as a pre-print. This second update continues to focus on evidence for priority age and risk groups, cases confirmed by medical record review, and myocarditis/myopericarditis or pericarditis reported separately rather than in combination.

Search date

April 11, 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?

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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 key 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 we considered rating up for a relatively large magnitude in incidence. In KQ2 evidence started at high certainty. In the plain-language conclusions, we have used "probably", "may" and "uncertain" to reflect our 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 and Table 4. Table 5 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 passive and active reporting systems/studies contributing to KQ1 and studies included for KQ2; risk of bias assessments for studies 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.

Sixty-five studies were included in this update. We identified 28 new reports across all questions (KQ1=9[1-9], KQ2=5[5 6 10-12], KQ3=1[4], KQ4=7[8 13-18], CQ1=10[19-28]). Findings from 37 of 40 studies in the previous synthesis were carried forward (KQ1=12[29-40], KQ2=6[29 35 38 40-42]; KQ3=1[37]; KQ4=3[31 43 44]; CQ1=21[45-65]). Three reports from the previous synthesis were replaced by reports of data that were either more recent [66 67] or more detailed[68] (i.e., reported by narrower age categories). The green font indicates changes to conclusions and/or the certainty in the evidence since the last update.

KQ1: Incidence

Myocarditis after dose 2

- Overall, the evidence was quite consistent with the previous update.
- We identified 1 new report in 5-11 year-old males and females which supported the conclusion that the incidence of myocarditis after vaccination with Pfizer may be fewer than 20 cases per million in both groups (low certainty).
- We identified 4 new studies reporting on 12-17 year-old males and females. In males, we have increased certainty for an incidence in the range of 40-390 cases per million of myocarditis after vaccination with an mRNA vaccine (moderate certainty). Among 12-17 year-old females, we are uncertain about the incidence of myocarditis after vaccination with an mRNA vaccine due to large inconsistency across studies (very low certainty).

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- We identified 3 new studies reporting on 18-29 year-old males and females. Among 18-29 year-old males, the incidence of myocarditis after vaccination with an mRNA vaccine is probably between 28 and 147 cases per million (moderate certainty). 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 certainty).
- We identified 2 new studies reporting on 18-39 year-old males and females. Among 18-39 year-old males, the incidence of myocarditis after vaccination with an mRNA vaccine is probably between 21 and 82 cases per million (moderate certainty). Among females, we have increased certainty in the evidence compared to the last synthesis: the incidence of myocarditis after vaccination with an mRNA vaccine may be fewer than 20 cases per million (low certainty).

Myocarditis after dose 3

- We identified 4 new reports of myocarditis after a third dose of an mRNA vaccine.
- Among 12-17 year-old males, the incidence of myocarditis after vaccination with a third dose of a mRNA vaccine may be fewer than 20 cases per million (low certainty). Among 12-17 year-old females, we are uncertain about the incidence of myocarditis after vaccination with a third dose of an mRNA vaccine, as only 1 study reporting zero events contributed evidence to this outcome.
- Among 18-29 year-old females, the incidence of myocarditis after vaccination with a third dose of an mRNA vaccine may be fewer than 20 cases per million (low certainty).
- For 18-29 year-old males and 30-39 year-old males or females, we are uncertain about the incidence of myocarditis after a third dose of an mRNA vaccine due to evidence from only 1 study that relied on passive reporting systems (very low certainty).
- For ≥40 year-old females, we identified an additional report. We now conclude that among this group the incidence of myocarditis after vaccination with a third dose of an mRNA vaccine may be fewer than 20 cases per million (low certainty). Our conclusions for ≥40 year-old males remain unchanged; the incidence of myocarditis after a third dose of an mRNA vaccine in this group may be fewer than 20 cases per million (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).
- Based on a single study reporting 12-15 year-old males and females, 16-24 year-old males and females, and 25-39 year-old males and females, we are uncertain about the incidence of pericarditis after vaccination with an mRNA vaccine in these groups (very low certainty).

KQ2: Risk Factors

Context

In KQ2 we assessed relative differences in outcomes across subgroups. It is important to consider these relative results in the context of the KQ1 findings reporting on incidence. That is, the relative differences between 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).
- Among 12-39 year-old females, there may be a higher incidence of myocarditis following vaccination with Moderna compared with Pfizer (low certainty). For 18-39 year-old females, we now have increased certainty that the incidence of myocarditis is probably higher after vaccination with Moderna compared to Pfizer (moderate 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 may be a higher incidence of myocarditis after vaccination with Moderna compared to Pfizer (low certainty).

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Moderna versus Pfizer, after dose 3

- Among 18-29 year-old males, there may be a higher incidence of myocarditis after vaccination with a third dose of Moderna compared with Pfizer (low certainty).
- Among 18-29 year-old females, 30-39 year-old males and females, and ≥40 year-old males and females, we are uncertain whether the incidence of myocarditis differs after vaccination with a third dose of Moderna compared with Pfizer.

Homologous vs heterologous vaccine for dose 2

- Among 16-24 year-old males and females, 25-39 year-old males, and ≥40 year-old males and females, the incidence of myocarditis may be higher after mRNA vaccination with a heterologous dose 2 compared to homologous dose 2 (low certainty).
- For females 25-39 years-old, we are uncertain about any difference in the incidence of myocarditis after mRNA vaccination with a heterologous dose 2 compared to homologous dose 2 (very low certainty).

Clinical comorbidities: With vs without a positive COVID-19 test before vaccination, dose 1 or 2

- Among individuals with a history of COVID-19 infection, we are uncertain whether the incidence of myocarditis differs after vaccination with dose 1 or dose 2 of an mRNA vaccine compared to those without a history of COVID-19 infection (very low certainty for each dose).

Myocarditis and/or pericarditis

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 aged 18-29 years indicated that the dosing interval may need to increase to ≥56 days to substantially drop incidence.
- For 18-29 year-old individuals, 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

- In addition to the 2 studies from the prior update, a study using active surveillance from Italy (n=2.8 million) reported on incidence within subgroups based on clinical comorbidities (see Table 4 for listings of what is included in each category). The only usable data was across both sexes and all ages, as well as for myo- or pericarditis, such that the applicability to myocarditis in certain individuals such as males 12-29 years of age (where few individuals may have the condition e.g. hypertension or cardiovascular disease) is uncertain.
- There may be a higher incidence of myocarditis or pericarditis after vaccination with an MRNA vaccine (low certainty) in individuals with the following: taking anti-inflammatory medications, cancer, cardiovascular conditions, hematologic conditions, previous infection (other than COVID-19), and rheumatic conditions.
- We are uncertain about whether there is an association with higher incidence for individuals with immunocompromised or pulmonary conditions.

Pericarditis

Moderna versus Pfizer, after dose 2

- Among 18-39 year-old males and females and ≥40 year-old males and females, there is probably a higher incidence of pericarditis after vaccination with Moderna compared with Pfizer (moderate certainty).

Homologous vs heterologous vaccine for dose 2

- For 16-24, 25-39, and ≥40 year-old males and females we are uncertain whether the incidence of pericarditis differs after vaccination with a heterologous dose 2 of Moderna compared with homologous Moderna or Pfizer (very low certainty).

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KQ3: Short-term Clinical Course

Children younger than 12 years

- We found no additional case series reporting on the short-term clinical course of myocarditis after mRNA vaccination in children younger than 12 years old
- One case series reported on the short-term (<4 weeks) clinical course 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.

After third dose

- We found one case series reporting on myocarditis after the third dose/booster in adolescent boys. Among the 32 cases, all received the Pfizer vaccine and had been hospitalized. All were discharged at follow-up.

KQ4: Longer-term Outcomes

- In addition to 3 reports[31 43 44] from the previous synthesis, seven additional reports were included for longer-term outcomes
- In total, 478 cases were included representing 440 cases of myocarditis and 36 of myopericarditis (one report also included 2 cases of pericarditis) in predominantly male samples. Follow-up data were available for 9% (n=44) at approximately 3 months and 84% (n=401) at 4 to 6 months.
- Among 24 patients with follow-up electrocardiogram, 42% had abnormal findings. Abnormal echocardiogram findings were found in 12% of 17 patients followed up with this imaging.
- Ongoing chest pain was reported by 32% of 416 patients reporting this outcome. Of 384 patients reporting other symptoms, these included shortness of breath 21.4% (n=82), palpitations 21.4% (n=82), and fatigue 24% (n=91).
- At follow-up (n=38), 18% of patients were still taking medications related to myocarditis.
- At follow-up (n=55), 69% were recovered with no symptoms.
- Among 360 cases followed (median 4.8 months) in the larger case series, 4% (n=13) were readmitted to hospital following myocarditis diagnosis, and 20% (n=71) were prescribed heart medications. Cardiac MRI abnormalities were detected in 54% (n=79) of 147 re-tested. Missed school and work due to myocarditis was reported in 2.8% (n=10) and 2% (n=7), respectively. Sixty-seven percent (n=242) of those followed-up completed the health-related quality of life tool EuroQol 5D-5L, with 45% (n=109) reporting problems with anxiety/depression and 29% (n=70) with pain.

CQ1: Hypothesized Mechanisms

- We included 30 papers,[19-28 45-47 49-65] including narrative reviews, opinion pieces, letters to the editor, case series, two cross-sectional studies, a retrospective cohort study, and a protocol for a prospective observational study.
- Across the included papers, we identified 19 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, strenuous exercise induced secretion of proinflammatory IL-6, oxidative stress reaction, elevated histamine with pericyte induced vasoconstrictions, and IL-18-mediated immune responses and cardiotoxicity.
- 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:

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- 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.,[48] described a fatal case of myocarditis after mRNA vaccination and compared the case to another fatality reported by Verma et al.,[65] 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."[48] 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, though the incidence remains very low and the prognosis is favorable. Some evidence suggests that a third dose is safe for 12 to 17 year-old males not having experienced myocarditis from the first or second dose; data from active surveillance is required to increase certainty for other ages of males and for females.
- Our findings suggest that Pfizer over Moderna, getting homologous doses, and waiting more than 30 days between dose 1 and dose 2 may be preferred, especially in younger males.

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- As the incidence of myocarditis after mRNA vaccination remains a rare and usually self-limiting adverse event, the overall benefits of vaccination and with detailed risk-benefit analyses should be considered with policy recommendations for optimal dosing intervals and vaccine products for different populations.

Future Directions

- 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., previous history of myocarditis, immunocompromised, etc.) is also needed in order to protect the already medically vulnerable. For potential impact from clinical comorbidities, data reported by age group and sex is necessary to understand whether risk may differ in all groups and to determine the absolute risk difference.
- Studies having more than 6 months' follow-up for vaccine-related myocarditis are needed to better understand the natural history. Multi-site, prospective registries would be good to inform on long-term outcomes given that this is a rare event.

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.
- Studying mechanisms in patients having myocarditis should restrict inclusion to patients/tissue samples with confirmed/definitive myocarditis through elevated troponin and MRI findings in order to avoid findings that may explain other cardiac involvement.

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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 across age groups ‡weighted 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**
		PCORnet Jan 31 US	7 d; Y	0 events (Pfizer)		
		PCORnet Jan 31 US	21 d; Y	0 events (Pfizer)		
		VSD Dec 30 US	21 d; Y	0 events (myo or pericarditis; Pfizer)		
	12-17y	VAERS* Jun 18a US	Any; Y	139.5* (Pfizer)	Among 12-17 year old males, the incidence myocarditis after vaccination with the Pfizer vaccine is probably between 40 and 390 cases per million.	**Moderate**[a]
		COVaxON* Sep 4 Canada	7 d; Y	88.1 (Pfizer)		
		VAERS* Oct 6 US	7 d; Y	49.6* (Pfizer)		
		PCORnet Jan 31 US	7 d; Y	220 (Pfizer)		
		PCORnet Jan 31 US	21 d; Y	267 (Pfizer)		
		Israeli MOH Oct 20 Israel	30 d; Y	80.9 (Pfizer)		
		eHRSS Oct 18 Hong Kong	NR; Y	390.2 (Pfizer)		
		Nordic cohort Oct 5 Nordic countries	7 d; Y	39.4*†‡		
		Nordic cohort Oct 5 Nordic countries	28d; Y	49.2*†‡		
	18-29y	Singapore Military Singapore	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**[a]
		COVaxON* Sep 4 Canada	7 d; Y	147.2‡ (18-24y)		
		IDF Mar 7 Israel	7d; Y	50.7 (Pfizer; 18-24y)		
		Moderna Global Safety Database* Sep 30 Worldwide	7 d; Y	27.9*† (Ages 18-24y; Moderna)		
		VAERS* Jan 13 USA	7 d; Y	30.9*		

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 across age groups ‡weighted across products †excess incidence	Conclusions	Certainty about conclusions using GRADE
		PCORnet Jan 31 US	7 d; Y	65		
		PCORnet Jan 31 US	21 d; Y	84		
		Israeli MOH Oct 10 Israel	30 d; Y	106.2*		
	18-39y	Singapore Military Singapore	Any; Y	60.2*	Among 18-39 year old males, the incidence of myocarditis after vaccination with an mRNA vaccine is probably between 21 and 82 cases per million.	**Moderate**[a]
		US Military Apr 30 US	4 d (all cases); Y	44 (median 25y [IQR: 20 to 51y])		
		Moderna Global Safety Database* Sep 30 Worldwide	7 d; Y	25.4* (Moderna)		
		COVaxON* Sep 4 Canada	7 d; Y	82.2*‡		
		VAERS* Jan 13 US	7 d; Y	20.7* (Moderna)		
		Nordic cohort Oct 5 Nordic countries	7d; Y	39.4*†‡		
		Nordic cohort Oct 5 Nordic countries	28d; Y	47.7*†‡		
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 with the Pfizer vaccine may be fewer than 20 cases per million.	**Low**
		PCORnet Jan 31 US	7 d; Y	0 events (Pfizer)		
		PCORnet Jan 31 US	21 d; Y	0 events (Pfizer)		
		VAERS* Dec 9 US	12 d; Y	2.98 (both sexes; Pfizer)		
		VSD Dec 30 US	21 d; Y	2.3* (both sexes; myo- or pericarditis; 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 an mRNA vaccine.	**Very Low** [b]
		COVaxON* Sep 4 Canada	7 d; Y	9.7 (Pfizer)		
		VAERS* Oct 6 US	7 d; Y	5.2* (Pfizer		
		eHRSS Oct 18 Hong Kong	NR; Y	49.7 (13.5 to 127.2) (Pfizer)		

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 across age groups ‡weighted across products †excess incidence	Conclusions	Certainty about conclusions using GRADE
		PCORnet Jan 31 US	7 d; Y	11		
		PCORnet Jan 31 US	21 d; Y	32		
		Israeli MOH Oct 20 Israel	30 d; Y	6.9 (Pfizer)		
		Nordic cohort Oct 5 Nordic countries	7 d; Y	1.5*†‡		
		Nordic cohort Oct 5 Nordic countries	28d; Y	10.9*†‡		
	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
		VAERS* Jan 13 US	7 d; Y	5.6* (Moderna)		
		Moderna Global Safety Database* Sep 30 Worldwide	7 d; Y	0*† (Ages 18-24; Moderna)		
		COVaxON* Sep 4 Canada	7 d; Y	34.6‡		
		PCORnet Jan 31 US	7 d; Y	16		
		PCORnet Jan 31 US	21 d; Y	21		
		Israeli MOH Oct 10 Israel	30 d; Y	13.7*		
	18-39y	COVaxON* Sep 4 Canada	7 d; Y	22.8*‡	Among 18-39 year old females, the incidence of myocarditis after vaccination with an mRNA vaccine may be below 20 cases per million.	Low
		Moderna Global Safety Database* Sep 30 Worldwide	7 d; Y	2.7* (Moderna)		
		VAERS* Jan 13 US	7 d; Y	3.3*		
		Nordic cohort Oct 5 Nordic countries	7d; Y	3.3*†‡		
		Nordic cohort Oct 5 Nordic countries	28d; Y	4.0*†‡		
Myocarditis (after dose 3)						
M	12-17y	Israeli MOH Oct 10 Israel	30 d; Y	17.3*	Among 12-17 year old males, the incidence of myocarditis	Low

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 across age groups ‡weighted across products †excess incidence	Conclusions	Certainty about conclusions using GRADE
		VAERS* Feb 20 US	NR; Y	11.4	after vaccination with a third dose of a mRNA vaccine may be fewer than 20 cases per million.	
	18-29y	Israeli MOH Oct 10 Israel	30 d; Y	26.5	Among 18-29 year old males, we are uncertain about the incidence of myocarditis after vaccination with a third dose of an mRNA vaccine.	**Very Low** [b,c]
		IDF Sep 30 Israel	7 d; Y	64 (18-24 y)		
		IDF Sep 30 Israel	14 d; Y	112.5 (18-24 y)		
		VAERS* Feb 6 US	6 d; Y	4.6*‡		
	30-39y	VAERS* Feb 6 US	6d; Y	1.35‡	Among 30-39 year old males, we are uncertain about the incidence of myocarditis after vaccination with a third dose of an mRNA vaccine.	**Very Low** [b,d]
	≥40y	NIMS/NHS Nov 15 UK	28 d; Y	3† (Pfizer) 0 events/143,066 (Moderna)	Among ≥40 year old males, the incidence of myocarditis after vaccination with a third dose of an mRNA vaccine may be fewer than 20 cases per million.	**Low**
		NIMS/NHS Nov 15 UK	7 d; Y	0†‡		
		Israeli MOH Oct 10 Israel	30 d; Y	4.1 (≥30y)		
F	12-17y	Israeli MOH Oct 10 Israel	30 d; Y	0 events* (Pfizer)	Among 12-17 year old females, we are uncertain about the incidence of myocarditis after vaccination with a third dose of an mRNA vaccine.	**Very Low** [b,e]
	18-29y	VAERS* Feb 6 US	6d; Y	~1‡	Among 18-29 year old females, the incidence of myocarditis after vaccination with a third dose of an mRNA vaccine may be fewer than 20 cases per million.	**Low**
		Israeli MOH Oct 10 Israel	30 d; Y	0 events*		
	30-39y	VAERS* Feb 6 US	6d; Y	~1‡	Among 30-39 year old females, we are uncertain about the incidence of myocarditis after vaccination with a third dose of an mRNA vaccine.	**Very Low** [b,d]

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 across age groups ‡weighted across products †excess incidence	Conclusions	Certainty about conclusions using GRADE
	≥40y	NIMS/NHS Nov 15 UK	28 d; Y	0†‡	Among ≥40 year old females, the incidence of myocarditis after vaccination with a third dose of an mRNA vaccine may be fewer than 20 cases per million.	Low[2]
		NIMS/NHS Nov 15 UK	7 d; Y	0†‡		
		Mayo Clinic Oct 17 US	14d; Y	41.5‡		
		Israeli MOH Oct 10	30 d; Y	0 events/1,542,142 doses (≥30y)		
Pericarditis						
M	5-11y	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** [b,c]
	12-15y	Nordic cohort Oct 5 Nordic countries	28d; Y	0 events†‡	Among 12-15 year old males, we are uncertain about the incidence of pericarditis after vaccination with an mRNA vaccine.	**Very Low** [b,c]
	16-24y	Nordic cohort Oct 5 Nordic countries	28d; Y	21.0†‡	Among 16-24 year old males, we are uncertain about the incidence of pericarditis after vaccination with an mRNA vaccine.	**Very Low** [b,c]
	25-39y	Nordic cohort Oct 5 Nordic countries	28d; Y	13.9†‡	Among 25-39 year old males, we are uncertain about the incidence of pericarditis after vaccination with an mRNA vaccine.	**Very Low** [b,c]
F	5-11y	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** [b,c]
	12-15y	Nordic cohort Oct 5 Nordic countries	28d; Y	0 events*†‡	Among 12-15 year old females, we are uncertain about the incidence of pericarditis after vaccination with an mRNA vaccine.	**Very Low** [b,c]

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 across age groups ‡weighted across products †excess incidence	Conclusions	Certainty about conclusions using GRADE
	16-24y	Nordic cohort Oct 5 Nordic countries	28d; Y	8.1†‡	Among 16-24 year old females, we are uncertain about the incidence of pericarditis after vaccination with an mRNA vaccine.	**Very Low** [b,c]
	25-39y	Nordic cohort Oct 5 Nordic countries	28d; Y	5.4†‡	Among 25-39 year old females, we are uncertain about the incidence of pericarditis after vaccination with an mRNA vaccine.	**Very Low** [b,c]

Green text = evidence identified by April 2022 update

[1]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)

[2] Although there was some inconsistency, the Mayo Clinic did not weight heavily into our certainty because of its relatively small sample size compared to the other studies

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. GRADE certainty in blue text indicates increased certainty over the previous synthesis; red text indicates decreased certainty compared with the previous synthesis.

[a] Rated 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)

[b] Rated down for inconsistency for only one study or for a large incidence range within one age/sex category

[c] Rated 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.

[d] Rated down for risk of bias from reliance of estimate on passive surveillance

[e] Rated down for imprecision for small sample size (<10,000 per group) or very low event rate.

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 (95% CI) *weighted average across multiple age groups[3]	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	7 d; 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,c]
		COVaxON* Sep 4 Canada	Any; Y	Moderna: 299.5 (171.2, 486.4) Pfizer: 35.5 (7.3, 103.7)			
	18-39y	VAERS* Oct 6 US	7 d; 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 Jan 15 US	7 d; Y		RD: 13.6 aRR: 1.31 (0.73 to 2.31)		
		Nordic cohort Oct 5	7 d; Y	Moderna: 113.3* Pfizer: 18.39*			
		Nordic cohort Oct 5	28 d; Y	Moderna: 140.3* Pfizer:31.1*			
		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	7 d; 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]
	≥40y	VAERS* Oct 6 US	7 d; Y	Moderna: 1.52* (40-64y) Pfizer: 0.98* (40-64y)		Among ≥40 year old males, the may be a higher incidence of myocarditis after vaccination with Moderna compared with Pfizer.	**Low** [a,b]
		NIMS Nov 15 [†] UK	7 d; Y	Moderna: 0 events Pfizer: IRR = 0.65 (0.27, 1.59)			
		NIMS Nov 15 [†] UK	28 d; Y	Moderna: 0 events Pfizer: IRR = 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)			
		Nordic cohort Oct 5	7 d; Y	Moderna: 5.4 Pfizer: 1.4			
		Nordic cohort Oct 5	28 d; Y	Moderna: 18.9 Pfizer: 6.5			
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]

Sex	Age	Data source & date Country *passive surveillance	Risk interval; confirmed cases (Y/N)	Incidence/reporting rate per million doses (95% CI) *weighted average across multiple age groups[3]	Relative measures (95% CI) aRR = adjusted risk ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
		VAERS* Oct 6 US	7 d; Y	Moderna: 5.5* Pfizer: 2.0*		higher incidence of myocarditis following vaccination with Moderna compared with Pfizer.	
	18-39y	VAERS* Oct 6 US	7 d; Y	Moderna: 3.1* Pfizer: 1.4*		Among 18-39 year old females, there is probably a higher incidence of myocarditis following vaccination with Moderna compared with Pfizer.	Moderate[a]
		COVaxON* Sep 4 Canada	Any; Y	Moderna:36.8* Pfizer: 8.9*			
		VSD Jan 15 US	7 d; Y		RD: -1.8 aRR: 0.53 (0.02 to 5.81)		
		Nordic cohort Oct 5	7 d; Y	Moderna: 7.3* Pfizer: 3.1*			
		Nordic cohort Oct 5	28 d; Y	Moderna: 10.4* Pfizer: 5.9*			
	30-39y	VAERS* Oct 6 US	7 d; 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,b]
	≥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 may be a higher incidence of myocarditis after vaccination with Moderna compared with Pfizer.	Low [a,b]
		NIMS Nov 15[1] UK	7 d; Y	Moderna: 0 events Pfizer: IRR= 0.80 (0.33, 1.97)			
		NIMS Nov 15[1] UK	28 d; Y	Moderna: 0 events Pfizer: IRR = 1.00 (0.64, 1.55)			
		VAERS* Oct 6 US	7 d; Y	Moderna: 0.8* (40-64y) Pfizer: 0.74* (40-64y)			
		Nordic cohort Oct 5	7 d; Y	Moderna: 5.4 Pfizer: 1.4			
		Nordic cohort Oct 5	28 d; Y	Moderna: 8.9 Pfizer: 4.0			
Moderna vs Pfizer (ref), dose 3							
M	18-29y	VAERS* Feb 6 US	6 d; Y	Moderna: 6.4* Pfizer: 2.9*		Among 18-29 year old males, there may be a higher incidence of myocarditis after vaccination with a third dose of Moderna compared with Pfizer.	Low [a,d]

Sex	Age	Data source & date Country *passive surveillance	Risk interval; confirmed cases (Y/N)	Incidence/reporting rate per million doses (95% CI) *weighted average across multiple age groups[3]	Relative measures (95% CI) aRR = adjusted risk ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
	30-39y	VAERS* Feb 6 US	6 d; Y	Moderna: <1.0 Pfizer: 1.7		Among 30-39 year old males, we are uncertain whether the incidence of myocarditis differs after vaccination with a third dose of Moderna compared with Pfizer.	**Very Low** [a,b,d]
	≥40y	VAERS* Feb 6 US	6 d; Y	Moderna: <1.0* Pfizer: <2.0*		Among ≥40 year old males, we are uncertain whether the incidence of myocarditis differs after vaccination with a third dose of Moderna compared with Pfizer.	**Very Low** [a,b,d]
F	18-29y	VAERS* Feb 6 US	6 d; Y	Moderna: 1.1* Pfizer: 0.5*		Among 18-29 year old males, we are uncertain whether the incidence of myocarditis differs after vaccination with a third dose of Moderna compared with Pfizer.	**Very Low** [a,b,d]
	30-39y	VAERS* Feb 6 US	6 d; Y	Moderna: 1.5 Pfizer: <1.0		Among 30-39 year old females, we are uncertain whether the incidence of myocarditis differs after vaccination with a third dose of Moderna compared with Pfizer.	**Very Low** [a,b,d]
	≥40y	VAERS* Feb 6 US	6 d; Y	Moderna: <2.0* Pfizer: 0 events*		Among ≥40 year old females, we are uncertain whether the incidence of myocarditis differs after vaccination with a third dose of Moderna compared with Pfizer.	**Very Low** [a,b,d]
Heterologous vs Homologous (ref) dose 2							
M	16-24	Nordic cohort Oct 5	7 d; Y	Mod-Mod: 141.2 Pfiz-Mod: 250.6 Pfiz-Pfiz: 42.1		Among 16-24y males, the incidence of myocarditis may be higher after vaccination with a heterologous dose 2 of Moderna compared with homologous Moderna or Pfizer.	**Low** [a,b]
		Nordic cohort Oct 5	28 d; Y	Mod-Mod: 198.3 Pfiz-Mod: 283.3 Pfiz-Pfiz: 68.3			

Sex	Age	Data source & date Country *passive surveillance	Risk interval; confirmed cases (Y/N)	Incidence/reporting rate per million doses (95% CI) *weighted average across multiple age groups[3]	Relative measures (95% CI) aRR = adjusted risk ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
		COVaxON* Sep 4 Canada	Any; Y	Mod-Mod: 288.4 (18-24y; myo- or pericarditis) Mod-Pfiz: 0 (18-24y; myo- or pericarditis) Pfiz-Mod: 337.6 (18-24y; myo- or pericarditis) Pfiz-Pfiz: 46.6 (18-24y; myo- or pericarditis)			
	25-39y	Nordic cohort Oct 5	7 d; Y	Mod-Mod: 74.4 Pfiz-Mod: 92.3 Pfiz-Pfiz: 7.3		Among 25-39y males, the risk of myocarditis may be higher after vaccination with a heterologous dose 2 of Moderna compared with homologous Moderna or Pfizer.	Low [a,b]
		Nordic cohort Oct 5	28 d; Y	Mod-Mod: 86.6 Pfiz-Mod: 118.5 Pfiz-Pfiz: 13.7			
	≥40y	Nordic cohort Oct 5	7 d; Y	Mod-Mod: 5.8 Pfiz-Mod: 10.2 Pfiz-Pfiz: 3.2		Among ≥40y males, the incidence of myocarditis may be higher after vaccination with a heterologous dose 2 of Moderna compared with homologous Moderna or Pfizer.	Low [a,b]
		Nordic cohort Oct 5	28 d; Y	Mod-Mod: 19.5 Pfiz-Mod: 40.8 Pfiz-Pfiz: 6.5			
F	16-24y	Nordic cohort Oct 5	7 d; Y	Mod-Mod: 0 events/99,139 vaccinees Pfiz-Mod: 87.1 Pfiz-Pfiz: 7.5		Among 16-24y females, the incidence of myocarditis may be higher after vaccination with a heterologous dose 2 of Moderna compared with homologous Moderna or Pfizer.	Low [a,b]
		Nordic cohort Oct 5	28 d; Y	Mod-Mod: 0 events/99,139 vaccinees Pfiz-Mod: 95.8 Pfiz-Pfiz: 8.7			
	25-39y	Nordic cohort Oct 5	7 d; Y	Mod-Mod: 15.7 Pfiz-Mod: 0 events/109,575 vaccinees Pfiz-Pfiz: 4.1		Among 25-39y females, we are uncertain whether the incidence of myocarditis differs after vaccination with a heterologous dose 2 of Moderna compared with homologous Moderna or Pfizer.	Very Low [A,b]
		Nordic cohort Oct 5	28 d; Y	Mod-Mod: 18.3 Pfiz-Mod: 0 events/97,835 vaccinees Pfiz-Pfiz: 4.5			
	≥40y	Nordic cohort Oct 5	7 d; Y	Mod-Mod: 3.0 Pfiz-Mod: 12.8 Pfiz-Pfiz: 1.9		Among ≥40y females, the incidence of myocarditis may be higher after vaccination with a heterologous dose 2 of Moderna compared with homologous Moderna or Pfizer.	Low [a,b]
		Nordic cohort Oct 5	28 d; Y	Mod-Mod: 8.6 Pfiz-Mod: 51.1 Pfiz-Pfiz: 4.0			
Clinical comorbidities – With vs without (ref) positive COVID-19 test before vaccination, dose 1							

Sex	Age	Data source & date Country *passive surveillance	Risk interval; confirmed cases (Y/N)	Incidence/reporting rate per million doses (95% CI) *weighted average across multiple age groups[3]	Relative measures (95% CI) aRR = adjusted risk ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
Both sexes	All ages	NIMS Aug 24 UK	28 d; Y		aRR = 0.72 (Pfizer)	Among individuals with a history of COVID-19 infection, we are uncertain about the incidence of myocarditis after vaccination with dose 1 of an mRNA vaccine compared to those without a history of COVID-19 infection.	**Very Low** [a,b,c]
Clinical comorbidities – With vs without (ref) positive COVID-19 test before vaccination, dose 2							
Both sexes	All ages	NIMS Aug 24 UK	28 d; Y		aRR = 0.58 (Pfizer)	Among individuals with a history of COVID-19 infection we are uncertain about the incidence of myocarditis after vaccination with dose 2 of an mRNA vaccine compared to those without a history of COVID-19 infection.	**Very Low** [A,c]
		ISS/AIFA Sep 30 Italy	21 d; Y		cRR=1.83 (myo- or pericarditis)		
Myocarditis/pericarditis							
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 or 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]
	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 or 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]
	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 or 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]

Sex	Age	Data source & date Country *passive surveillance	Risk interval; confirmed cases (Y/N)	Incidence/reporting rate per million doses (95% CI) *weighted average across multiple age groups[3]	Relative measures (95% CI) aRR = adjusted risk ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
	≥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 or 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 or 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							
Both sexes	18-29y	COVaxON* Sep 4 Canada	Any; Y	Moderna (18-24y) <30d: 353.1 (182.4-616.8) 31-55d: 184.0 (133.7-247.0) ≥56d: 103.2 (44.5-203.3) Pfizer (18-24y) <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 or 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]
	18-39y	COVaxON* Sep 4 Canada	Any; Y	Moderna <30d: 139.3* 31-55d: 89.2* ≥56 d: 52.9 Pfizer <30d: 43.4* 31-55d: 17.0* ≥56d: 11.6*		Among 18 to 39 year old people, the proportional decrease in incidence of myocarditis or 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]

Sex	Age	Data source & date Country *passive surveillance	Risk interval; confirmed cases (Y/N)	Incidence/reporting rate per million doses (95% CI) *weighted average across multiple age groups[3]	Relative measures (95% CI) aRR = adjusted risk ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
	≥40y	COVaxON* Sep 4 Canada	Any; Y	Moderna <30d: 0.0 (0.0-53.9) 31-55d: 7.4 (2.0-19.0) 56d: 7.5 (3.2-14.7) Pfizer <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 or 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 – Anti-inflammatory medications							
Both sexes	All ages	ISS/AIFA Sep 30 Italy	21 d; Y	NSAID use cRR=13.27 Systemic corticosteroid use cRR=4.10		Among individuals taking anti-inflammatory medications, there may be a higher incidence of myocarditis or pericarditis after vaccination with an mRNA vaccine compared to individuals without.	**Low** [a,c]
Clinical comorbidities – Cancer							
Both sexes	All ages	ISS/AIFA Sep 30 Italy	21 d; Y	Neoplasm cRR=2.95 *Includes malignant neoplasms or personal history of malignant neoplasm*		Among individuals with cancer, there may be a higher incidence of myocarditis or pericarditis after mRNA vaccination compared to those without.	**Low** [a,c]
Clinical comorbidities – Cardiovascular conditions							
Both sexes	All ages	ISS/AIFA Sep 30 Italy	21 d; Y	Cardiovascular and cerebrovascular diseases cRR=33.54 *Includes: all diseases of the circulatory system; excluding hypertensive diseases* Hypertension cRR=13.38		Among individuals with cardiovascular conditions, there may be a higher incidence of myocarditis or pericarditis after vaccination with an mRNA vaccine compared to individuals without cardiovascular conditions.	**Low** [a,c]
Clinical comorbidities – Hematologic conditions							

Sex	Age	Data source & date Country *passive surveillance	Risk interval; confirmed cases (Y/N)	Incidence/reporting rate per million doses (95% CI) *weighted average across multiple age groups[3]	Relative measures (95% CI) aRR = adjusted risk ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
Both sexes	All ages	ISS/AIFA Sep 30 Italy	21 d; Y	Hematologic dx cRR=2.34 *Includes: Iron deficiency anemias; other deficiency anemias, hereditary hemolytic anemias, acquired hemolytic anemias, aplastic anemia and other bone marrow failure syndromes; Other and unspecified anemias; Coagulation defects; Purpura and other hemorrhagic conditions; (280-284;285 (excl.285.1); diseases of white blood cells; Other diseases of blood and blood-forming organs)*		Among individuals with hematologic conditions, there may be a higher incidence of myocarditis or pericarditis after mRNA vaccination compared to those without.	**Low** [a,c]
Clinical comorbidities - Immunocompromise							
Both sexes	All ages	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]).		Among individuals with immunocompromised, we are uncertain whether the incidence of myocarditis or pericarditis after vaccination with an mRNA vaccine differs compared to immunocompetent individuals.	**Very Low** [a,b,c]
Clinical comorbidities –Infection (other than COVID-19)							
Both sexes	All ages	ISS/AIFA Sep 30 Italy	21 d; Y	Infection in last 12 mos cRR=2.43 *Includes: Urinary tract infection, site not specified; Tuberculosis; Diseases due to other mycobacteria; Cytomegaloviral disease; chickenpox; Herpes zoster; Herpes simplex; Pneumocystosis; Cryptococcosis*		Among individuals with a recent history of non-COVID-19 infection, there may be a higher incidence of myocarditis or pericarditis after mRNA vaccination compared to those without.	**Low** [a,c]
Clinical comorbidities – Pulmonary conditions							
Both sexes	All ages	ISS/AIFA Sep 30 Italy	21 d; Y	COPD cRR=1.29 *Includes: bronchitis, not specified as acute or chronic; emphysema; Asthma; Bronchiectasis; Extrinsic allergic alveolitis* Chronic Pulmonary Disease cRR=10.32 *Includes: pneumonia and influenza; Chronic bronchitis; Extrinsic allergic alveolitis; Other diseases of lung*		Among individuals with pulmonary conditions, we are uncertain whether the incidence of myocarditis or pericarditis after vaccination with an mRNA vaccine differs compared to those without.	**Very Low** [a,c]
Clinical comorbidities – Rheumatic conditions							
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.		Among individuals with rheumatic conditions, there may be a higher incidence of myocarditis or pericarditis after mRNA vaccination compared	**Low** [b,c]

Sex	Age	Data source & date Country *passive surveillance	Risk interval; confirmed cases (Y/N)	Incidence/reporting rate per million doses (95% CI) *weighted average across multiple age groups[3]	Relative measures (95% CI) aRR = adjusted risk ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
		ISS/AIFA Sep 30 Italy	21 d; Y	Rheumatic dx cRR=6.02 *Includes Giant cell arteritis; Diffuse diseases of connective tissue; Rheumatoid arthritis and other inflammatory polyarthropathies; Ankylosing spondylitis and other inflammatory spondylopathies; Polymyalgia rheumatica; Psoriasis and similar disorders OR pharmacy claim for immunosuppressants in past 12 mos*		to individuals without inflammatory conditions.	
Pericarditis							
Moderna vs Pfizer (ref), dose 2							
M	18-39y	Nordic cohort Oct 5	28 d; Y	Moderna: 40.3* Pfizer: 16.5*		Among 18-39 year old males, there is probably a higher incidence of pericarditis after vaccination with Moderna compared with Pfizer.	**Moderate**[a,4]
	≥40y	Nordic cohort Oct 5	28 d; Y	Moderna: 21.8 Pfizer: 12.8		Among ≥40 year old males, there is probably a higher incidence of pericarditis after vaccination with Moderna compared with Pfizer.	**Moderate**[a]
F	18-39y	Nordic cohort Oct 5	28 d; Y	Moderna: 26.6* Pfizer: 3.0*		Among 18-39 year old females, there is probably a higher incidence of pericarditis after vaccination with Moderna compared with Pfizer.	**Moderate**[a,4]
	≥40y	Nordic cohort Oct 5	28 d; Y	Moderna: 11.8 Pfizer: 7.5		Among ≥40 year old females, there is probably a higher incidence of vaccination with Moderna compared with Pfizer.	**Moderate**[a]
Heterologous vs Homologous (ref), dose 2							
M	16-24	Nordic cohort Oct 5	28 d; Y	Mod-Mod: 79.3 Pfiz-Mod: 50.0 Pfiz-Pfiz: 16.6		Among 16-24y males, we are uncertain whether the incidence of pericarditis differs after vaccination with a heterologous dose 2 of Moderna compared with homologous Moderna or Pfizer.	**Very Low**[A,b]
	25-39y	Nordic cohort Oct 5	28 d; Y	Mod-Mod: 23.3 Pfiz-Mod: 39.5 Pfiz-Pfiz: 16.5		Among 25-39y males, we are uncertain about the incidence of pericarditis after vaccination with a heterologous dose 2 of Moderna compared with homologous Moderna or Pfizer.	**Very Low**[A,b]

Sex	Age	Data source & date Country *passive surveillance	Risk interval; confirmed cases (Y/N)	Incidence/reporting rate per million doses (95% CI) *weighted average across multiple age groups[3]	Relative measures (95% CI) aRR = adjusted risk ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
	≥40y	Nordic cohort Oct 5	28 d; Y	Mod-Mod: 23.0 Pfiz-Mod: 16.3 Pfiz-Pfiz: 12.8		Among ≥40y males, we are uncertain about the incidence of pericarditis after vaccination with a heterologous dose 2 of Moderna compared with homologous Moderna or Pfizer.	**Very Low** [A,B]
F	16-24y	Nordic cohort Oct 5	28 d; Y	Mod-Mod:51.1 Pfiz-Mod: 38.3 Pfiz-Pfiz: 1.8		Among 16-24y females, we are uncertain about the incidence of pericarditis after vaccination with a heterologous dose 2 of Moderna compared with homologous Moderna or Pfizer.	**Very Low** [A,B]
	25-39y	Nordic cohort Oct 5	28 d; Y	Mod-Mod: 15.7 Pfiz-Mod: 0 events/109,575 vaccinees Pfiz-Pfiz: 4.1		Among 25-39y females, we are uncertain about the incidence of pericarditis after vaccination with a heterologous dose 2 of Moderna compared with homologous Moderna or Pfizer.	**Very Low** [A,B]
	≥40y	Nordic cohort Oct 5	28 d; Y	Mod-Mod: 3.0 Pfiz-Mod: 12.8 Pfiz-Pfiz: 1.9		Among ≥40y females, we are uncertain about the incidence of pericarditis differs vaccination with a heterologous dose 2 of Moderna compared with homologous Moderna or Pfizer.	**Very Low** [A,B]

Green text = evidence identified by April 2022 update

[1]this study reported IRRs calculated using a self-controlled case series design. In this study design, individuals serve as their own controls and risk estimates in pre- and post-intervention intervals are calculated within individuals.

[2]Because of the large overlap in data between males 18-29y and 18-39y, we only downrated 18-29y once for inconsistency despite the large differences in effects reported between studies.

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

[4] We did not rate down for indirectness because the incidence of pericarditis differs less across age groups than myocarditis.

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. GRADE certainty in blue text indicates increased certainty over the previous synthesis; red text indicates decreased certainty compared with the previous synthesis.

[a] Rated down for inconsistency or due to only one study providing estimates
[b] Rated down for imprecision for small sample size (<10,000 per group) or very low event rate.
[c] Rated 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.
[d] Rated down for risk of bias from use of passive surveillance

Table 3. Case Series of Myocarditis, Pericarditis, or Myopericarditis after mRNA COVID-19 Vaccination in 5-11 year-olds or after a third dose (KQ3)

	Characteristics and short-term clinical course	
Case series (country)	**Su 2021[37] (US)**	**Hause 2022[4] (US)**
Date of cases last updated	10 Dec 2021	20 Feb 2022
Cases, n	8	32
Confirmed cases	Diagnoses reviewed and met the CDC case definition	Diagnoses reviewed and met the CDC case definition
Case source	VAERS	VAERS
Myocarditis, n	8 (100%)	32 (100%)
Pericarditis, n	0	0
Myopericarditis, n	0	0
Male, n	4 (50%)	32 (100%)
Median age (range), y **Ages included**	9 (6-11) 5-11 years	NR (12-17) 12-17 years
Vaccine product, n	8 (100%) = BNT162b2 (Pfizer)	32 (100%) = BNT162b2 (Pfizer) third dose
Patients in ICU	0	NR
Hospitalized, n	NR	32 (100%)
Patients presenting after dose 2	6 (75%)	NR
Patients with prior COVID-19 history	NR	NR
Patients COVID-19 polymerase chain reaction positive	NR	NR
Patients with COVID nucleocapsid antibody present (among tested)	NR	NR
Patients with SARS-CoV-2 spike antibody	NR	NR
Patients with prior myocarditis or pericarditis history	NR	NR
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	NR
Patients with chest pain on presentation	7 (88%)	NR
Patients with other symptoms (eg, myalgia, fatigue, fever)	NR	NR
Diagnostic evaluation		
Patients with troponin elevation (among tested)	8 (100%, all tested)	NR
Median time to troponin peak after vaccination, days	NR	NR
Patients with BNP or NT-proBNP elevation (among tested)	NR	NR
Patients with CRP elevation (among tested)	NR	NR
Patients with eosinophilia (among tested)	NR	NR

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Patients with abnormal ECG (among tested)	3 (50%, 6/8 tested); ST elevation (2 patients), non-specific ST and T wave changes (1 patient)	NR
Patients with abnormal cardiac MRI (among tested)	NR	NR
Patients with abnormal echocardiogram (among tested)	1 (20%, 5/8 tested) mitral regurgitation	NR
Patients with LVEF<50% (among tested)	NR	NR
Outcome		
Patients with symptoms resolved	5 (83% resolved, 6/8 with known outcomes)	32 (100%) discharged, 18 (56%) recovered, 9 (28%) recovering
Fatalities, n	0	0
Median hospitalization length of stay, days (range)	NR	NR
Patients treated with medications for myocarditis	NR	NR

Green text = evidence identified by April 2022 update

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

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Table 4. Case Series of Myocarditis and Myopericarditis after mRNA Vaccination reporting longer-term outcomes (at least 4 weeks of follow-up).

Case series	Chelala 2021[43] (US)	Patel 2021[44] (US)	Klein 2022[31] (US)	Amir 2022[13] (Israel)	Manfredi[15] (Italy)	Rosner 2022[17] (US)	Puchalski 2022[16] (Poland)	Schauer[18] 2022 (US)	Mevorach[9] 2022 (Israel)	Kracalik 2022[14] (US)
Date of cases last updated	14 June 2021	June 2021	25 Dec 2021	15 March 2022 (publication date)	30 Dec 2021	5 April 2022 (publication date)	August 2021	7 Jan 2022	20 Oct 2021	Jan 2022
Cases, n	5	9	43	15	6	6	5	16	13	360
Confirmed cases	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	Defined clinically, based on the presence of two or more of the following: (1) signs and symptoms of acute myocardial involvement (e.g., chest pain, arrhythmia); (2) elevated troponin; (3) echocardiographic evidence of ventricular dysfunction without an alternative explanation; and (4) (ST-T) changes in the ECG.	Myocarditis was defined by the presence of an LGE typical pattern (subepicardial or patchy associated with hyperenhancement in T2W images). Myopericarditis was defined by the presence of the CMR findings mentioned above, associated with pericardial effusion	Confirmed via diagnostic testing	2018 Lake Louise Myocarditis Criteria	Confirmed via diagnostic testing	Brighton Collaboration criteria	Confirmed via diagnostic testing
Case source	Single medical centre in USA	Single medical centre in Atlanta, USA	Kaiser Permanente in Colorado, Oregon, California, and Washington; HealthPartners Institute Minnesota; Denver Health	Clalit Health Services	Marche, Italy region database	VAERS (2 U.S. medical centers in Falls Church, Virginia, and Dallas, Texas)	Medical University of Warsaw	Seattle Children's Hospital	Israel Ministry of Health	VAERS
Myocarditis, %	100%	100%	53%	15 (100%)	4 (67%)	6 (100%)	5 (100%)	0%	13 (100%)	360 (100%)
Pericarditis, %	0%	0%	5%	0%	0%	0%	0%	0%	0%	0%
Myopericarditis, %	0%	0%	42%	0%	2 (33%)	0%	0%	16 (100%)	0%	0%
Male, %	100%	100%	86%	15 (100%)	4 (67%)	6 (100%)	100%	15 (94%)	12 (92%)	308 (86%)
Median age (range), y Ages included	Mean = 17 (16-19) NR	15.7 (IQR 14.5-16.6) NR	67% = 12-15 years 33% = 16-17 years NR	17.2 (14.9-19) NR	16.5 (14-25) NR	28 (19-39) all ages	17 (15-17) NR	15 (12-17) <18 years	14 (12-15) 12 – 16 years	18 (IQR 15-22) 12-29 years
Vaccine type, n	4 (80%) = BNT162b2 (Pfizer) 1 (20%) = mRNA-1273 (Moderna)	100% mRNA vaccine	100% = BNT162b2 (Pfizer)	15 (100%) = BNT162b2 (Pfizer)	4 (67%) = BNT162b2 (Pfizer) 2 (33%) = mRNA-1273 (Moderna)	6 (100%) = BNT162b2 (Pfizer)	5 (100%) = BNT162b2 (Pfizer)	16 (100%) = BNT162b2 (Pfizer)	13 (100%) = BNT162b2 (Pfizer)	100% mRNA
% Patients in ICU	NR	22%	26%	7 (47%)	NR	NR	NR	0%	0%	NR
% Hospitalized	100%	100%	65%	15 (100%)	6 (100%)	6 (100%)	5 (100%)	16 (100%)	13 (100%)	324 (90%)
% Patients presenting after dose 2	100%	89%	NR	14 (93%)	100%	6 (100%) (other presentation after single dose J&J)	2 (40%)	16 (100%)	12 (93%)	307 (85%)

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Case series	Chelala 2021[45] (US)	Patel 2021[46] (US)	Klein 2022[31] (US)	Amir 2022[15] (Israel)	Manfredi[15] (Italy)	Rosner 2022[17] (US)	Puchalski 2022[16] (Poland)	Schauer[18] 2022 (US)	Mevorach[9] 2022 (Israel)	Kracalik 2022[14] (US)
% Patients with prior COVID-19 history	0%	NR	5%	NR	NR	0%	0%	NR	0%	31 (9%)
% Patients COVID-19 polymerase chain reaction positive	0%	NR	NR	0% (all tested)	NR	NR	0%	NR	0% (9/13 tested)	NR
% Patients with COVID nucleocapsid antibody present (% of tested)	NR	NR	NR	0% (all tested)	NR	NR	NR	NR	NR	NR
% Patients with SARS-CoV-2 spike antibody	NR	NR	NR	0% (all tested)	NR	NR	NR	NR	NR	NR
% Patients with prior myocarditis or pericarditis history	0% reported significant cardiovascular risk factors or history of previous cardiovascular events	NR	5%	NR	NR	NR	NR	NR	NR	6 (2%)
Presentation										
Time between last vaccine and symptom onset, median days, (range)	4 (3-4)	Median 3 days between dose 2 and hospital admission	2 (0-20)	3 (0-28)	3-4 days	3 (2-5)	2 (2-23)	3 (2-4)	NR	NR
% Patients with chest pain on presentation	100%	100%	NR	100%	NR	NR	100%	16 (100%)	13 (100%)	NR
% Patients with other symptoms (eg, myalgia, fatigue, fever)	NR	44% dyspnea	NR	4 (27%) fever	100% fever 1 (17%) atrial tachycardia	NR	4 (80%) fever	6 (38%) fever 6 (38%) shortness of breath	4 (31%) fever 1 (31%) dyspnea 2 (15%) palpitations	NR
Diagnostic evaluation										
% Patients with troponin elevation (of tested)	100% (5/5 tested)	NR	NR	4 (93%; 15/15 tested)	100% (6/6 tested)	100% (6/6 tested)	100% (5/5 tested)	100% (16/16 tested)	100% (13/13 tested)	NR
Median time to troponin peak after vaccination, days	NR	NR	NR	NR	NR	NR	3 (3-4)	NR	NR	NR
% Patients with BNP or NT pro BNP elevation (among tested)	100% normal (4/5 tested)	NR	NR	NR	No BNP increment was acutely found	100% normal (6/6 tested)	2 (40%, 5/5 tested) moderate rise	NR	NR	NR
% Patients with CRP elevation (among tested)	80% (all tested)	NR	NR	13 (87%; 15/15 tested)	100% (all tested)	NR	4 (80%, 5/5 tested) moderate rise	median 3.45 mg/dL, range 0-6.5 mg/dL (12/16 tested)	12 (92%)	NR
% Patients with eosinophilia (among tested)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
% Patients with abnormal ECG (among tested)	60% = normal 20% = ST segment elevation	33% = normal	NR	11 (73%) = ST changes	no significant ECG abnormalities were found at	3 (50%) = ST segment elevation	5 (100%) ST elevation	10 (63%) = abnormal, commonly diffuse	6 (46%, all tested): 5 (395) ST elevation	NR

Case series	Chelala 2021[45] (US)	Patel 2021[46] (US)	Klein 2022[31] (US)	Amir 2022[13] (Israel)	Manfredi[15] (Italy)	Rosner 2022[17] (US)	Puchalski 2022[16] (Poland)	Schauer[18] 2022 (US)	Mevorach[9] 2022 (Israel)	Kracalik 2022[14] (US)
	20% = sinus bradycardia	67% = repolarization abnormalities		1 (7%) = borderline ST changes 2 (13%) = normal	presentation	1 (17%) = PR depression	1 (20%) ST depression	ST segment elevation	2 (15%) diffuse 3 (23%) nondiffuse 2 (15%) T-wave change	
% Patients with abnormal cardiac MRI (among tested)	100% = no segmental wall motions abnormalities, and basilar and mid-cavity Involvement; early and late gadolinium enhancement	NR	NR	15 (100%, all tested) mid-myocardial subepicardial left ventricle involvement, without right ventricular involvement and sub-endocardium unaffected; 4 (27%) hyper enhancement on T2 sequences (representing edema); and 14 (93%) abnormal late enhancement (representing inflammation and necrosis)	6 (100%, all tested) 4 (67%) Myocarditis characterized by myocardial edema (T2w hyperenhancement) and LGE in the lateral wall of the left ventricle; 1 (17%) isolated ventricular involvement; 6 (100%) preserved LV ejection	6 (100%, all tested) no regional wall motion abnormalities; evidence of late gadolinium enhancement 2 (33%) evidence of pericardial inflammation	5 (100%,all tested) hyperintense signal of oedema partly overlapping with LGE in particular LV segments	16 (100%, all tested); 16 (100%) edema; 15 (94%) LGE in a patchy subepicardial to transmural pattern with predilection for the inferior LV free wall; 2 (13%) LV regional wall motion abnormalities	NR (1/13 tested)	NR
% Patients with abnormal echocardiogram (among tested)	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	1 (7%) = shortening fraction 28%, mild mitral regurgitation; 1 (7%) = mild mitral; regurgitation 1 (7%) = effusion; 2 (13%) = mild LV	0%	NR	5 (100%, all tested) no changed to regional wall motion and pericardial effusions	2 (13%) mildly reduced LV systolic function with no dilation; 14 (88%) normal LV systolic function	2 (15%, 13/13 tested) abnormal 3 (23%) pericardial effusion 2 (15%) abnormal LV function 100% EF normal or mildly reduced	NR
% Patients with LVEF<50% (among tested)	20%	22% = 30-55% LVEF at presentation 78% >55% LVEF at presentation	NR	1 (7%) LVEF 45%	0%	0%	0%	Median LVEF 59% (range 45-69%)	NR (13/13 tested)	NR
Short-term Outcome										
% Patients with symptoms resolved	100%	NR	100% discharged home	15 (100%) after 6 months	NR	6 (100%)	NR	16 (100%)	NR	NR
Fatalities, n	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Median hospitalization length of stay, days (range)	3 (3-9)	NR	2 (0-7)	5 (3-9)	7 (SD 2)	NR	13 (10-16)	2 (1-4)	Mean 3.1 (1-6)	NR

LIVING EVIDENCE SYNTHESIS UPDATE #2 SUMMARY

Case series	Chelala 2021[45] (US)	Patel 2021[46] (US)	Klein 2022[31] (US)	Amir 2022[15] (Israel)	Manfredi[19] (Italy)	Rosner 2022[17] (US)	Puchalski 2022[16] (Poland)	Schauer[18] 2022 (US)	Mevorach[9] 2022 (Israel)	Kracalik 2022[14] (US)
% Patients treated with medications for myocarditis	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	9 (60%) NSAID 2 (13%) Aspirin 3 (20%) Colchicine 2 (13%) steroids 1 (7%) IVIG	6 (100%) colchicine 6 (100%) ibuprofen 1 (17%) metoprolol	NR	6 (100%) ACEI 3 (60%) Ramipril 1 (20%) Lisinopril 1 (20%) Enalapril	16 (100%) NSAID 2 (19%) IVIG and corticosteroid 1 (6%) IVIG	10 (77%) NSAID 1 (8%) cortico-steroids	NR
Long-term Outcomes										
Number of patients with follow-up data	5/5 (100%)	9/9 (100%)	24/43 (56%)	14/15 (93%)	6/6 (100%)	6/6 (100%)	5/5 (100%)	16/16 (100%)	NR	360 (100%)
Mean length clinical follow-up (range), days	95 (92-104)	90 (NR)	88.5 (28-153)	5-6 months	Median 3 months (SD 5)	Median 189 (164-322)	117 (106-134)	Median 3.7 (range 2.8-8.1 months)	30 days	Median 143 (IQR 131, 162)
% Repeat cardiac MRI	40%	NR	4%	9 (64%)	6 (100%)	6 (100%)	5 (100%)	16 (100%)	NR	147 (41%)
Characteristics of repeat cardiac MRI	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	7 (50%) = positive LGE (4 [29%] significant mid-myocardial and sub-epicardial patchy lage enhancement); 2 (14%) = negative LGE; 1 (7%) persistent mild myocardial dysfunction	Cardiac MRIs did not present persistent cardiac involvement	4 (67%) = resolved or near resolved LGE 1 (17%) = Improved with LGE in the basal/mid L/IL segments 1 (17%) = Improved with LGE in A/I segments	3 (60%) no oedema 1 (20%) Mid: anterolateral inferolateral 1 (20%) Basal inferolateral	LVEF% = 57.7 ± 2.7 (none with regional wall motion abnormalities); LGE % = 7.7 ± 5.7; 11 (69%) persistent LGE; Global longitudinal strain 75% -16.4 ± 2.1; 1 (6%) edema	NR	79 (54% abnormal (n=380, from provider data)
Symptoms such as chest pain	60% = mild intermittent self-resolving chest pain after discharge; in one patient recurrent symptoms occurred after discontinuation of the NSAID prescribed at discharged	NR	38% chest pain 13% shortness of breath 13% palpitations 4% fatigue 13% other (e.g., orthostatic hypotension, dizziness)	NR	NR	0%	1 (20%)	4 (25%)	NR	115 (32%) chest pain 90 (25%) fatigue 79 (22%) shortness of breath 79 (22%) palpitations
Medical visits following discharge	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	NR	NR	NR	1 (20%) follow-up appointment postponed for one month due to moderate infectious symptoms	NR	No hospital admission after discharge	13 (4%) readmitted to hospital following myocarditis
% Continued treatment with medications	NR	0% on heart failure medication	8% (e.g., NSAIDs, colchicine)	NR	NR	NR	5 (100%) ACEI	NR	NR	71 (20%) prescribed medication for heart

Case series	Chelala 2021[45] (US)	Patel 2021[46] (US)	Klein 2022[31] (US)	Amir 2022[13] (Israel)	Manfredi[15] (Italy)	Rosner 2022[17] (US)	Puchalski 2022[16] (Poland)	Schauer[18] 2022 (US)	Mevorach[9] 2022 (Israel)	Kracalik 2022[14] (US)
% Recovered with no symptoms	NR	NR	46% (no symptoms, medications, or exercise restrictions)	100% after 6 months	100%	100%	1 (20%) moderate infectious symptoms	NR	NR	NR
Other outcomes	NR	NR	NR	NR	NR	NR	NR	NR	NR	46 (8%) Missed school; 10 (37%) of these believed due to myocarditis 19 (5%) Missed work; 7 (37%) of these believed due to myocarditis HRQL (EuroQol-5D-5L) problems after myocarditis (n=242) • 5 (2%) self-care • 12 (5%) Mobility • 51 (21%) Usual activities • 70 (29%) Pain -•109 (45%) Anxiety/depression

Green text = evidence identified by April 2022 update

Abbreviations: **CDC** = Centers for Disease Control and Prevention; **CMR** = cardiovascular magnetic resonance imaging; **ECG** = echocardiogram; **ICD** = International Classification of Diseases; **ICU** = intensive care unit; **IQR** = interquartile range; **LVEF** = left ventricular ejection fraction; **MRI** = magnetic resonance imaging; **NR** = not reported; **NSAID** = non-steroidal anti-inflammatory drugs; **PHAC** = Public Health Agency of Canada; **VAERS** = vaccine adverse event reporting system

Table 5. 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=13 Hajra et al., 2021[54] Tsilingiris et al., 2021[64] Heymans & Cooper, 2021[55] Parra-Lucares et al., 2021[61] Bozkurt et al, 2021[47] Das et al., 2021[51] Boursier, 2021[69] Switzer & Loeb, 2021[62] Verma et al., 2021[65] Gnanenthiran & Limaye 2022 Dursun et al. 2022 Mormile 2022 Frustaci et al. 2022	- 4 case reports: Muthukumar, Boursier, Verma, Nguyen -1 case series of authors: Frustaci - 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=6 Hajra et al., 2021[54] Tsilingiris et al., 2021[64] D'Angelo et al, 2021[50] Bozkurt et al., 2021[47] Chouchana et al., 2021[49] Gnanenthiran & Limaye 2022	- 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[54] Takeda et al. 2021[63] D'Angelo et al, 2021[50] Bozkurt et al, 2021[47] Kounis et al., 2022	- 3 case reports: Takeda, Witberg, Choi -1 case series: Verma	- 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=6 Kounis et al. 2021a[58] Kounis et al. 2021b[57] Tsilingiris et al., 2021[64] Bozkurt et al., 2021[47] Kounis et al., 2022 Al-Ali et al., 2022	- 4 case reports: Sokolska, Verma, Witberg (1 case with biopsy in series), 1 not cited -1 case series: Warren - 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

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Hypothesis		Citations	Direct Empirical Evidence	
			Supporting	Refuting
5	Response to mRNA vaccine lipid nanoparticles (direct deleterious effect; not delayed – see hypothesis 4)	N=2 Tsilingiris et al., 2021[64] Kadkhoda et al., 2021[56]	- 1 cohort: Patone	None
6	Autoimmunity triggered by molecular mimicry or other mechanism	N=13 Hajra et al., 2021[54] Tsilingiris et al., 2021[64] D'Angelo et al., 2021[50] Heyman & Cooper, 2021[55] Bozkurt et al., 2021[47] Chouchana et al., 2021[49] Switzer & Loeb, 2021[62] Parra-Lucares et al., 2021[61] Ehlrich et al., 2021[52] Gnanenthiran & Limaye, 2022 Chin et al., 2022 Mormile, 2022 Marrama et al., 2022	Molecular mimicry: - 2 case reports: D'Angelo, Ammirati, - 1 case series: Larson - 2 in vitro studies Vojdani. Marrama 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, Ehlrich 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[70]	None	None
9	Production of anti-idiotype antibodies against immunogenic regions of antigen-specific antibodies	N=1 Tsilingiris et al., 2021[64]	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[47])	N=2 Bozkurt et al., 2021[47] Switzer & Loeb, 2021[62]	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[47]	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[49]	N=2 Chouchana et al., 2021[49] Switzer & Loeb, 2021[62]	None	- 2 cases: Verma
13	Cardiac pericyte expression of ACE2 with immobilized immune complex on the surface of pericytes activation of the complement system	N=1 Kadkhoda et al., 2021[56]	None	None

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Hypothesis		Citations	Direct Empirical Evidence	
			Supporting	Refuting
14	Spike-activated neutrophils (expressing ACE2) augmenting inflammatory response	N=2 Kadkhoda et al., 2021[56] Choi et al., 2021[48]	- 1 case report: Choi	None
15	Hyperviscosity-induced cardiac problem	N=1 Mungmunpuntipantip & Wiwanitkit, 2021[60]	None	None
16	Strenuous exercise induced secretion of proinflammatory IL-6	N=1 Elkazzaz et al., 2022[71]	None	None
17	Oxidative stress reaction	N=1 Dursun et al., 2022	Author's cross sectional study	None
18	Elevated histamine with pericyte induced vasoconstrictions	N=1 Ricke 2022	CDC data on temporal nature of cases	None
19	IL-18-mediated immune responses and cardiotoxicity	N=1 Won et al., 2022	Author's cross sectional study with controls	None
Observation				
	Differences in incidence by sex could be due to sex steroid hormones or under-diagnosis in females	N=6 Tsilingiris et al., 2021[64] Heymans & Cooper, 2021[55] Bozkurt et al., 2021[47] Chouchana et al., 2021[49] Parra-Lucares et al., 2021[61] Mormile, 2022	Sex hormones: None Underdiagnosis in women: CDC, Bozkurt (unpublished data)	Sex hormones: - 1 cohort: Montgomery Underdiagnosis in women: None
	Supportive of the autoimmune mechanism from genetic variants of T-bet, age-related lower levels of T-bet (T helper cell transcription factor) and PD-1, leading to release of autoreactive CD8+ CTL cells, there is upregulation of T-Bet and PD-1 by estrogen and this might explain the higher incidence of men developing myocarditis or pericarditis in comparison to women.	N=1 Mormile, 2022	None	None

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Appendix 1. Supplementary Tables

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

Population/Problem	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).
Intervention/Exposure	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. Note: At least one dose of the vaccine needs to be with an mRNA vaccine; one or more other doses may be a non-mRNA vaccine.
Control/Comparator	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.
Outcome	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 specifc 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., 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). KQ4: Any outcomes measured ≥4 weeks after onset of myocarditis or pericarditis (e.g., re-hospitalization, functional capacity, chest pain). 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).

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LIVING EVIDENCE SYNTHESIS UPDATE #2 SUMMARY

Setting	Any setting and country.
Study design	KQ1: Large (>10,000 vaccinated people) sample or multisite/health system-based observational studies; reports or databases of confirmed cases using surveillance data. KQ2: Observational studies (including case control studies) with n ≥10 with the risk/protective factor; data for subset of people with myocarditis or pericarditis may come from passive reporting systems. KQ3: Case series N>10; data may come from medical record review of cases reported to passive suveillance systems (if reporting more than age, sex, and dose and type of vaccine). KQ4: Case series N>10; data may come from medical record review of cases reported to passive suveillance systems. CQ1: Any primary study, systematic review, or expert opinion article/letter on the topic. Letters and commentaries will be included if they provide sufficient data.
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.

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

Dataset Dates Country Study	Vaccines Studied	Sample Size; Demographics; Previous Covid-19 diagnoses	Study Group(s)	Outcome(s); Case Ascertainment; Risk Interval	Analysis	Results
Nordic Cohort Oct 5 **Dec 27 2020 to Oct 5 2021** **Denmark, Finland, Norway, Sweden** **Karlstadt 2022**[6]	Pfizer-BioNTech 15,064,585 Dose 1 or 2 Moderna 2,390,870 Dose 1 or 2 Homologous or heterologous dose 2 Interval between doses NR	Surveillance population: 23,122,522 Nordic residents ≥12 y Demographics NR Previous covid-19 infection NR but accounted for in analysis	1. At least Pfizer Dose 1 (n=15,064,585) 2. At least Moderna Dose 1 (n=2,390,870) 3. Unvaccinated at end of follow-up (n=4,308,454)	Myocarditis inpatient stay; Myo- or pericarditis inpatient or outpatient stay ICD-10 codes: I400 I401 I408 I409 I411 I418 I514 in primary or secondary diagnosis field (Myocarditis) ICD-10 codes: I400 I401 I408 I409 I411 I418 I514 I300 I301 I308 I309 I328 in primary or secondary diagnosis field (Myo- or pericarditis) Blinding of assessors NR Risk interval: 0-7d or 0-28d after any dose	Poisson regression for the number of events to estimate incidence rate ratios (IRRs) with 95% CIs comparing rates in the risk periods after vaccination with rates in unvaccinated periods, adjusted for age group, sex, previous SARS-CoV-2 infection, healthcare worker, nursing home resident, comorbidity variables	**Incidence of myocarditis hospitalizations, per 1000 person-years** *28d risk period* Events / 1000 PY / IR / IRR / Excess events in 28d Males, ages ≥12 y Pfiz/Pfiz 85 495.0 0.172 2.04 (1.61 to 2.58) 0.67 (0.46 to 0.88) Pfiz/Mod 34 23.7 1.433 16.99 (11.51 to 25.07) 10.34 (6.86 to 13.83) Mod/Mod 53 72.3 0.733 8.55 (6.40 to 11.41) 4.97 (3.62 to 6.32) Males, ages 16-24 y Pfiz/Pfiz 37 41.5 0.891 5.31 (3.68 to 7.68) 5.55 (3.70 to 7.39) Pfiz/Mod 17 4.6 3.687 35.6 (18.9 to 67.3) 27.5 (14.4 to 40.6) Mod/Mod 15 5.8 2.584 13.8 (8.08 to 23.7) 18.4 (9.05 to 27.7) Males, ages 25-39 y Pfiz/Pfiz 15 83.9 0.179 1.75 (1.03 to 2.99) 0.59 (0.07 to 1.10) Pfiz/Mod 15 9.7 1.543 23.2 (12.6 to 42.6) 11.3 (5.59 to 17.1) Mod/Mod 26 23.0 1.132 13.0 (8.23 to 20.4) 8.01 (4.92 to 11.1) Males, ages ≥40 y Pfiz/Pfiz 27 363.6 0.085 1.08 (0.74 to 1.57) 0.05 (−0.19 to 0.28) Pfiz/Mod ≤5 9.4 ND 3.54 (0.85 to 14.79) 1.17 (−0.58 to 2.93) Mod/Mod 26 23.0 1.132 3.45 (1.87 to 6.35) 1.38 (0.50 to 2.27) Females, ages ≥12 y Pfiz/Pfiz 30 522.7 0.057 1.25 (0.77 to 2.05) 0.09 (−0.09 to 0.26) Pfiz/Mod ≤5 19.1 ND 9.62 (3.11 to 29.77) 1.44 (0.02 to 2.87) Mod/Mod 7 71.6 0.098 2.73 (1.27 to 5.87) 0.48 (0.07 to 0.89) Females, ages 16-24 y Pfiz/Pfiz ≤5 43.9 ND 2.86 (1.10 to 7.48) 0.57 (−0.01 to 1.15) Pfiz/Mod ≤5 4 ND 71.7 (15.1 to 340) 3.74 (−1.45 to 8.93) Mod/Mod 0 6 ND ND ND Females, ages 25-39 y Pfiz/Pfiz ≤5 85 ND 2.35 (0.89 to 6.25) 0.26 (−0.04 to 0.55) Pfiz/Mod 0 7.5 ND ND ND

Karlstadt 2022 cont.						

Mod/Mod ≤5 21 ND 7.31 (2.16 to 24.8) 0.95 (−0.14 to 2.03)

Females, ages ≥40 y

Pfiz/Pfiz 20 388.1 0.052 1.02 (0.63 to 1.65) 0.01 (−0.18 to 0.20)

Pfiz/Mod ≤5 7.5 ND 8.12 (1.83 to 36.00) 1.79 (−0.72 to 4.29)

Mod/Mod ≤5 44.4 ND 3.03 (1.10 to 8.31) 0.46 (−0.05 to 0.97)

Incidence of myocarditis hospitalizations, per 1000 person-years

7-day risk period

	Events	1000 PY	IRR (95% CI)	Excess events in 7d per 100,000 (95% CI)
Males, ages ≥12 y				
Pfiz/Pfiz	45	134.5	4.13 (3.02-5.64)	0.49 (0.34-0.64)
Pfiz/Mod	31	6.5	54.57 (36.29-82.06)	8.95 (5.8-12.1)
Mod/Mod	44	20.3	25.09 (17.09-36.84)	3.99 (2.81-5.16)
Males, 16-24				
Pfiz/Pfiz	27	12.3	12.5 (8.2 to 19.0)	3.86 (2.4 to 5.3)
Pfiz/Mod	17	1.3	120.1 (63.5 to 227.1)	24.77 (13 to 36.6)
Mod/Mod	14	1.9	38.3 (22.0 to 66.8)	13.8 (6.6 to 21)
Males, 25-39y				
Pfiz/Pfiz	9	23.5	3.8 (1.9 to 7.4)	0.5 (0.2 to 0.9)
Mod/Mod	26	6.7	44.3 (26.9 to 73.0)	7.3 (4.5 to 10.1)
Pfiz/Mod	13	2.7	67.0 (34.9 to 128.6)	9.0 (4.1 to 13.9)
Males, ≥40 y				
Pfiz/Pfiz	7	96.8	1.50 (0.7-3.2)	0.05 (-0.03-0.1)
Mod/Mod	≤5	11.6	5.7 (1.8-17.9)	0.4 (-0.1-0.9)
Pfiz/Mod	≤5	2.5	7.0 (1.0-51.0)	0.7 (-0.7-2.0)
Females, ages ≥12 y				
Pfiz/Pfiz	10	141.1	2.15 (1.06-4.34)	0.07 (0.01-0.14)
Pfiz/Mod	≤5	5.2	28.69 (4.24-194.38)	0.71 (-0.28-1.69)
Mod/Mod	≤5	20	4.18 (1.33-13.1)	0.22 (-0.04-0.48)
Females, 16-24y				
Pfiz/Pfiz	≤5	12.8	7.9 (2.3 to 26.8)	0.4 (-0.1 to 0.8)
Pfiz/Mod	≤5	1.1	210.81 (44.45-999.75)	3.34 (-1.29-7.97)
Mod/Mod	0	1.9	NE	NE
Females, 25-39y				
Pfiz/Pfiz	≤5	23.6	11.1 (2.6 to 46.7)	0.2 (-0.03 to 0.5)
Pfiz/Mod	0	2.1	NE	NE
Mod/Mod	≤5	6.1	25.12 (5.78-109.14)	0.6 (-0.23-1.44)

Karlstadt 2022 cont.						Females, ≥40 y Pfiz/Pfiz ≤5 103 1.3 (0.5-3.6) 0.02 (-0.04-0.1) Pfiz/Mod 0 2 NE NE Mod/Mod ≤5 11.9 6.2 (0.9-45.6) 0.1 (-0.1-0.4)
NIMS/NHS Nov 15 Dec 1 2020 to Nov 15 2021 England Patone 2021[35]	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 3: n= 10,599,183 Moderna 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 receiving dose 3 (95% CI)** 1-28d Dose 1 Dose 2 Dose 3 *Pfizer* <40y Female NR NR NR Male 3 (1, 5) 12 (10, 13) 13 (7, 15) ≥40y Female NR NR NR Male NR NR 3 (2, 4) *Moderna* <40 y Female NR 8 (4, 9) NR Male 12 (1, 17) 101 (95, 104) ≥40y Female NR NR NR Male NR NR NR
eHRSS Oct 18 **Mar 10 to Oct 18 2021** **Hong Kong** **Li 2022**[7]	Pfizer Dose 1 or 2 Dose interval: 21 days	Dose 1 n=224,560 Dose 2 n=162,518 Demographics NR Previous COVID-19 infection NR	Adolescents who received at least 1 dose of BNT162b2 Adolescents with a history of myocarditis were excluded	Inpatient myocarditis ICD codes: 422.x, 429.0 Risk interval NR Blinding of outcome assessor NR	Cumulative incidence with exact 95% confidence interval (CI) were estimated based on Poisson distribution.	**Incidence of myocarditis hospitalizations, per 100,000 persons** Males dose 1: 5.27 (1.94-11.48) dose 2: 39.02 (26.69-55.08) Females: dose 1: 0.90 (0.023-5.03) dose 2: 4.97 (1.35-12.72)
IDF Sep 30 **Aug 15 to Sep 30 2021** **Israel** **Friedensohn 2022**[3]	Pfizer Dose 3 Dose interval NR	N=126,029 Demographics NR 1 case with positive covid-19 test excluded	All military personnel vaccinated with a third dose of Pfizer	Myocarditis Diagnosed with myocarditis based on laboratory, electrocardiogram, echocardiography and cardiac MRI findings, confirmed by an independent cardiologist. Risk intervals: 0-7d, 0-14d	Incidence of myocarditis.	**Incidence of myocarditis per 100,000 3rd doses given** All members (≥18y, both sexes): 0-7d Interval: 3.17 (95% CI, 0.64-6.28) 0-14d Interval: 5.55 (95% CI, 1.44-9.67) Males, 18-24y 0-7d interval: 6.43 (95% CI, 0.13-12.73) 0-14d interval: 11.25 (95% CI, 2.92-19.59)
IDF May 7 Dec 28 2020 to Mar 7 2021 Israel Levin 2021[32]	Pfizer-BioNTech 138,000 military personnel receiving 2 doses	138,000 NR NR	Vaccinated with 2 doses (n=138,000) Interval between doses NR	Myocarditis Medical record review, requiring ECG, echocardiography, or MRI findings Risk interval: 7 d after dose 2 Not blinded	Crude cumulative incidence	Events: 7 confirmed in risk interval (100% male; Age 18-24) Incidence: 5.07 per 100,000 people

LIVING EVIDENCE SYNTHESIS: UPDATE #2 SUMMARY

Israeli MOH Oct 20 **Jun 2 to Oct 20 2021** **Israel** **Mevorach 2022** [8]	Pfizer Dose 1 or 2 Dose interval NR	Adolescents (12-15y) receiving at least dose 1 dose 1: n=404,407 dose 2: 326,463 52% female Previous covid-19 infection NR	1) Adolescents receiving dose 1 2) Adolescents receiving dose 2	Myocarditis hospitalizations ICD-10 codes 422.0-9x and 429.0x; cases confirmed by cardiologist according to the Brighton collaboration case definition for myocarditis. Risk intervals: 0-21d after dose 1; 0-30d after dose 2	Reported incidence of myocarditis per 100,000 doses	Males dose 1: 0.56 cases per 100,000 dose 2: 8.09 cases per 100,000 Females dose 1: 0 cases per 100,000 dose 2: 0.69 cases per 100,000
Israeli MOH Oct 10 **Dec 2020 to Oct 10 2021** **Alroy-Preis 2021** [1]	Pfizer or Moderna, Dose 1, 2 or 3 Dose interval NR	N= ~4 million	All vaccinated Israelis	Myocarditis ICD-10 codes 422.0-9x and 429.0x; cases confirmed by cardiologist according to the Brighton collaboration case definition for myocarditis. Risk intervals: 0-21d (dose 1), 0-30d (dose 2, 3)	Raw numbers of doses and cases.	Females 12-15y: Dose 1 —; Dose 2 —; Dose 3 0 cases / 279 vaccinees 16-19y: Dose 1 0 / 248,881; Dose 2 2 / 222,067; Dose 3 0 / 97,807 20-24y: Dose 1 1 / 263,845; Dose 2 6 / 242,697; Dose 3 0 / 141,910 25-29y: Dose 1 0 / 247,365; Dose 2 1 / 229,189; Dose 3 0 / 130,283 ≥30y: Dose 1 3 / 2,127,538; Dose 2 7 / 2,029,074; Dose 3 0 / 1,542,142 Males 12-15y: Dose 1 —; Dose 2 —; Dose 3 0 cases / 292 vaccinees 16-19y: Dose 1 3 / 254,497; Dose 2 36 / 223,079; Dose 3 5 / 96,238 20-24y: Dose 1 6 / 275,235; Dose 2 26 / 251,672; Dose 3 5 / 139,015 25-29y: Dose 1 3 / 257,713; Dose 2 20 / 239,319; Dose 3 1 / 133,650 ≥30y: Dose 1 10 / 1,983,230; Dose 2 32 / 1,897,067; Dose 3 6 / 1,448,745
Singapore Military Aug 3 Jan 14 to Aug 3 2021 Singapore Tan 2021 [40]	Pfizer (37,367 individuals with 1+ dose) Moderna (27,294 individuals with 1+ dose) Homologous dose 2 administered 21-56 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 after Moderna, none with cardiac history. Reporting rate per 100,000 doses administered (95% CI) *Any product* — Dose 1 — Dose 2 18-19 y Female: 0/955 — 0/903 Male: 0/11,120 — 2/10,521 20-29 y Female: 0/2,819 — 0/2,717 Male: 0/32,850 — 1/31,656 30-39y 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
PCORnet Jan 31 **Jan 1 2021 to Jan 31 2022** **United States** **Block 2022** [2]	Any mRNA vaccine* Dose 1 or 2 Dose interval NR *Moderna not approved for <18y	15,215,178 persons aged ≥5 years Dose 1 n=2,548,334 Dose 2 n=2,483,597 Previous covid-19 infection NR	1) Infection 2) Dose 1 3) Dose 2 4) Unspecified dose 5) Any dose cohort	Myocarditis Cases identified by ICD-10-CM codes B33.22, I40, I40.0, I40.1, I40.8, I40.9, or I51.4 Risk interval: 0-7d, 0-21d Blinding of outcome assessor NR	The sex- and age-stratified incidences of the cardiac outcomes (cases per 100,000 persons) were calculated within 7- or 21--day risk windows.	**Incidence of myocarditis, per 100,000 persons** 7d risk interval: Dose 1 — Dose 2; 21d risk interval: Dose 1 — Dose 2 Males 5-11 y: 0 — 0 — 4.0 — 0 12-17 y: 2.2 — 22.0 — 3.3 — 26.7 18-29 y: 0.9 — 6.5 — 3.6 — 8.4 ≥30 y: 0.9 — 0.5 — 1.9 — 1.2 Females 5-11 y: 0 — 0 — 0 — 0

						12-17 y 1.0 1.1 1.0 3.2 18-29 y 0.5 1.6 1.0 2.1 ≥30 y 0.8 0.5 1.4 0.9
VSD Dec 30 Thru Dec 30 2021 United States Klein 2022[31]	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 3. 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 per 1 million doses / 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
Mayo Clinic Enterprise Dec 1 2020 to Oct 17 2021 United States Niesen, 2021[34]	Pfizer-BioNTech (78%) Dose 1 & 2 18-28 d apart, Dose 3 ≥28 d after 2nd 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	Cumulative incidence	Events: 1 in female >40 years old (Moderna; 1 d after dose 3) Cumulative incidence: 0.00% (95% CI 0% to 0.01%) 5,047 recipients of three doses of BNT 162b2 and 558 recipients of three doses of mRNA-1273 were under 40 years of age. 33,662 recipients of three doses of BNT 162b2 (57% female) and 9,582 recipients of three doses of mRNA-1273 (51% female) were 40 years of age or older.
US Military Apr 30 Jan 1 to Apr 30 2021 United States Montgomery 2021[33]	Pfizer-BioNTech or Moderna	2,810,00 doses (38% dose 2) Males 100% Median age 25 (20-51) Tested cases for Covid-19 n=0 but all cases after dose 2 (n=3) had previous Covid-19	1. Vaccinated Expected numbers within 30 d after vaccination	Myocarditis Cases identified via referrals to Defense Health Agency clinical specialists and through review of VAERS reports; each cases adjudicated using CDC definition for probable Risk interval: all presented within 4 d	Incidence in vaccinated Observed vs expected cases: expected number based on an expected annual incidence ranging from 1-10 per 100 000 person-years (US) to 22 per 100 000 person-years (internationally); presenting within a 30-day period after vaccination.	Events: 23 (20 after dose 2) **Observed vs expected:** Total doses: 23 v vs 2 to 52 Dose 2: 20 vs 1 to 20 Dose 2 to military members: 19 vs 0 to 10 Dose 2 to male military members: 19 vs 0 to 8 **Incidence:** Total doses: 0.8 per 100,000 doses Dose 2: 1.9 per 100,000 doses Dose 2 to military members: 3.5 per 100,000 doses Dose 2 to male military members: 4.4 per 100,000 doses

LIVING EVIDENCE SYNTHESIS: UPDATE #2 SUMMARY

Green text = evidence identified by April 2022 update
DVR/DPR = Danish Vaccination Register & Danish Patient Register
eHRSS - The Electronic Health Record Sharing System (eHRSS) is a territory-wide, patient-oriented electronic sharing platform which enables authorised healthcare providing organisations in the public and private sectors to access and share participating patients' electronic health records (eHR) for healthcare purposes.
IDF – Israeli Defense Forces
NHS = National Health Service, which is the single-payer national health system in the UK.
NIMS = NHS Immunisation Management Service database
PCORnet - the National Patient-Centered Clinical Research Network, a national network of networks that facilitates access to health care data and interoperability through use of a common data model across participating health care systems (https://pcornet.org/data). The PCORnet Common Data Model contains information captured from EHRs and other health care data sources (e.g., health insurance claims), including demographic characteristics, diagnoses, prescriptions, procedures, and laboratory test results, among other elements.
VSD = Vaccine Safety DatalinkMOH – Ministry of Health

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

Dataset Dates of data Country of Data Study	Vaccines Studied	Outcome(s); Case Ascertainment & Risk Interval	Analysis	Results
COVaxON and Public Health Case and Contact Management Solution* Jun 1 2020 to Sep 4 2021 Canada Buchan 2021[29]	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 Jun 1 2021** *Pfizer* Dose 1 Dose 2 12-17 y 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 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 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* Dose 1 Dose 2 18-24 y 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 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) Note: Moderna not authorized for use in 12-17y in Canada
Moderna Global Safety Database Sep 30 Dec 18 2020 to Sep 30 2021 Global Strauss 2021 [36]	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** Dose 1 Dose 2 Expected rate RD <18 years Females 0 0.15 1.74 -1.59 Males 0.56 1.02 2.12 -1.1 18-24y Females 0.20 0.44 1.23 -0.79 Males 1.15 4.91 2.12 2.79 25-39y Females 0.09 0.19 1.23 Males 0.48 1.44 2.12
VAERS Feb 20 **Dec 9 2021 to Feb 20 2022** **United States**	Pfizer Dose 3 Boost interval: (≥2 months after dose 1 of Janssen or ≥5	Myocarditis Confirmed to meet CDC working definition Risk interval NR	Crude reporting rate per million doses administered	Males, 12-17y: 11.4 per million booster doses administered

Hause 2022a [4]	months after dose 2 of an mRNA vaccine			
VAERS Feb 6 **Sep 22 2021 to Feb 6 2022** **United States** **Hause 2022b**[5]	Pfizer or Moderna Dose 3 Boost interval: ≥5 months after dose 2 of an mRNA vaccine	Myocarditis Confirmed to meet CDC working definition Risk interval: 0-6d	Crude reporting rate per million doses administered	**Crude reporting rate per million booster doses** Males — Pfizer — Moderna — Average 18-24 y — 4.1 — 8.7 — 6.4 25-29 y — 1.1 — 3.2 — 2.15 30-39 y — 1.7 — 1.0 — 1.35 Females — Pfizer — Moderna — Average 18-24 y — <1.0 — 1.1 — ~1.0 25-29 y — NE — 1.2 — <1 30-39 y — <1.0 — 1.5 — ~1.0
VAERS Jan 13 **Through Jan 13 2022** **United States** **Shimabukuro 2022**[9]	Moderna Dose 1 or 2 Dose interval NR	Myocarditis Verified to meet CDC case definition Risk interval: 0-7d	Crude reporting rate per million doses	**Reporting rate, per million doses (95% CI)** Dose 1 — Dose 2 Males 18-24 y — 5.8* — 40.0* 25-29 y — 2.9* — 18.3* 30-39 y — 3.3* — 8.4* Females 18-24 y — 0.5 — 5.5* 25-29 y — 0.3 — 5.8* 30-39 y — 0.6 — 0.6 *Reporting rate exceeds background incidence
VAERS Dec 19 Thru Dec 19 2021 United States Su 2022[39]	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** Dose 1 — Dose 2 5-11 y Male — 0.00 — 4.3* Female — NE — 2.0 12-15 y Male — 4.8* — 45.7* Female — 1.0 — 3.8* 16-17 y Male — 6.1* — 70.2* Female — 0.00 — 7.6* *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
VAERS Dec 9	Pfizer-BioNTech 7,141,428 doses	Myocarditis in 5-11yo	Reporting rate per million doses (estimated)	Events: VAERS: 8 (50% female); 2 after dose 1, 6 after dose 2

Nov 2 to Dec 10 2021 United States Su 2021a [37]	Dose 1: 5,126,642 (72%) Dose 2: 2,014,786 (28%) Dose interval NR	Risk interval: 0-12 d after any dose (VAERS) Cases reported to VAERS confirmed using CDC working case definition		**Crude reporting rate per 1 million doses administered** 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 Oct 6 Up to Oct 6, 2021 United States Su 2021b [38]	Pfizer-BioNTech, Moderna and Janssen	Myopericarditis (myocarditis +/- pericardtis); pericarditis Risk interval: 7 d Screening via 30 MedDRA terms and ICD-10; all analyzed reports verified to meet CDC case definition by provider interview or medical record review	Crude reporting rates of confirmed cases of myopericarditis after each dose	For myopericarditis: 67% Pfizer; 29% Moderna; 76% after dose 2 (50 preliminary reports after Janssen not in analysis) **Events: 935 verified cases; 797 in males; 138 in females.** **Reporting rate of myopericarditis per 1 million doses administered** Pfizer / Moderna Males — Dose 1 / Dose 2 / Dose 1 / Dose 2 12-15y: **4.2** / **39.9** / 0.0 / not calculated 16-17y: **5.7** / **69.1** / 0.0 / not calculated 18-24y: **2.3** / **36.8** / **6.1** / **38.5** 25-29y: 1.3 / **10.8** / **3.4** / **17.2** 30-39y: 0.5 / **5.2** / **2.3** / **6.7** Females 12-15y: 0.4 / **3.9** / 0.0 / 0.0 16-17y: 0.0 / **7.9** / 0.0 / 0.0 18-24y: 0.2 / **2.5** / 0.6 / **5.3** 25-29y: 0.2 / 1.2 / 0.4 / **5.7** 30-39y: 0.6 / 0.7 / 0.5 / 0.4 *Reporting rates exceed background incidence (bolded data above)) An estimated 1–10 cases of myocarditis per 100,000 person years occurs among people in the United States, regardless of vaccination status; adjusted for the 7-day risk period, this estimated background is 0.2 to 1.9 per 1 million person 7-day risk period
VAERS Jun 18 Jan 1 to Jun 18 2021 United States Høeg 2021[30]	Pfizer-BioNTech Moderna (only 1 of 257 cases; not approved for <18y) Dose schedule NR	Myocarditis "Myocarditis," "pericarditis," "myopericarditis" or "chest pain" in the symptom notes; "troponin" required element in the laboratory data; cases meeting CDC working case definition of probable myocarditis. Risk interval: Any timing	Crude rates per million vaccinees Cases with an unknown dose number were assigned to dose 1 or dose 2 in the same proportion as the known doses: 15% occurred following dose 1 and 85% occurred following dose 2	Events: 257 (92% within 5 d; 90% males) **Crude reporting rate of myocarditis cases per million vaccinees** Dose 2 Males 12-15 y: 162.2 Males 16-17 y: 94.0 Females 12-15 y: 13.0 Females 16-17 y: 13.4

Green text = evidence identified by April 2022 update

*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 (EDCD), 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)

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

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

Dataset **Dates of data** *(mmm dd yyyy)* **Country of Data** **Author year**	**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)
COVaxON and Public Health Case and Contact Management Solution* Dec 14 2020 to Sep 4 2021 Canada Buchan 2021[29]	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). Inter-dose interval ≤30 vs. ≥56 d; Moderna dose 2 vs. Pfizer dose 2	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), BC level 1-2 Myocarditis cases on or after 1 Jun 2021** *Pfizer* — Dose 1 — Dose 2 12-17 y, male — 34.2 (15.6-64.9) — 88.1 (53.0-137.5) 12-17 y, female — 8.1 (1.0-29.1) — 9.7 (1.2-35.1) 18-24 y, male — 13.1 (1.6-47.3) — 35.5 (7.3-103.7) 18-24 y, female — 7.9 (0.2-44.1) — 0.0 (0.0-50.5) 25-39 y, male — 17.9 (5.8-41.8) — 12.6 (1.5-45.4) 25-39 y, female — 0.0 (0.0-14.3) — 13.1 (1.6-47.5) ≥40 y, male — 0.0 (0.0-14.4) — 0.0 (0.0-23.3) ≥40 y, female — 0.0 (0.0-14.8) — 0.0 (0.0 - 23.5) *Moderna* — Dose 1 — Dose 2 12-17 y — NA — NA 18-24 y, male — 0.0 (0.0-68.7) — 299.5 (171.2-486.4) 18-24 y, female — 0.0 (0.0-95.1) — 69.1 (14.2-201.9) 25-39 y, male — 28.8 (5.9-84.3) — 72.1 (31.1-142.0) 25-39 y, female — 0.0 (0.0 - 45.4) — 21.5 (2.6 - 77.7) ≥40 y, male — 18.3 (2.2-66.2) — 0.0 (0.0-35.6) ≥40 y, female — 0.0 (0.0 - 40.5) — 0.0 (0.0 - 40.9) **Rate per million (95% CI), by product (dose1-dose2)** Pfizer-Pfizer — Moderna-Pfizer 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) Moderna-Moderna — Pfizer-Moderna 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) **Rate per million doses (95% CI), males 18-24 y, 2 doses by interval and product** Events — Doses — Rate (95% CI) Pfizer-Pfizer

Buchan 2021 cont					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) Moderna-Moderna 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) Moderna-Pfizer 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) Pfizer-Moderna 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) **Rate per million doses (95% CI), dose 2 by product and interval** Pfizer ≤30 d 31-55 d ≥56 d 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)
EULAR COVAX* Feb 5 to Jul 27 2021 Europe (30 countries) Machado 2021[42]	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 2nd dose of Pfizer. No events in NI-RMD group. estimated OR OR = (1/3599) / ((1/3600)/428) OR = 428.1
ISS/AIFA Sep 30 **Dec 27 2020 to Sep 30 2021** **Italy** **Massari 2022[11]**	Pfizer-BioNTech (84%) or Moderna (16%)	Total doses 5,109,231 to 2,861,809 people 49% females Median age 26 y (range 12-39) 8% (14% of cases) with COVID-19 diagnosis before vaccination	Myocarditis/pericarditis ICD codes: myocarditis: 391.2| 398.0| 422| 429.0; pericarditis: 391.0| 393| 420| 423.1| 423.2| 423.9 Risk interval: 0-7 d, 7-14 d & 14-21 d	Self-controlled case series (within-person comparison of different time-periods) Relative incidence estimated by Poisson regression	Myocarditis/pericarditis: 441 events (95 Moderna and 346 Pfizer) **Relative Risk of Myocarditis/pericarditis in individuals vaccinated with mRNA vaccines with compared to without risk factors of interest.** **Risk factor any mRNA Pfizer* Moderna*** Prev. COVID 1.83 1.80 1.48 COPD/Asthma 1.29 1.43 NE CPD 10.32 12.46 NE Neoplasm 2.95 3.22 NE Hematologic dx 2.34 2.62 NE CVD 33.54 34.94 29.57

			Risk factors: Previous COVID Infection; COPD/Asthma; Chronic pulmonary disease CPD); Neoplasm; Hematological disease (dx); cardiovascular and cerebrovascular diseases (CVD); Hypertension; Rheumatic diseases; Neurological diseases; Peptic ulcer; Infection (non-covid) in past 12 mos; Corticosteroids for systemic use; NSAID use	adjusted for seasonal effect; Subgroup analyses by age group (12-17, 18-29, and 30-39 y) and vaccine type Sensitivity analyses: excluding people without a positive SARS-CoV-2 test before and during study period (n=378); excluding people with heterologous vaccine combinations (n=440)	Hypertension 13.38 13.72 12.28 Rheumatic dx 6.02 5.88 NE Neurological dx 1.48 1.45 NE Peptic ulcer 11.66 12.17 9.83 Infection 2.43 2.55 2.02 Corticosteroids 4.10 4.55 NE NSAID 13.27 14.41 NE NE = not estimated due to <10 cases with risk factor
NIMS Nov 15 Dec 1 2020 to Nov 15 2021 England Patone 2021[35]	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 scheduled 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	**IRR (95% CI) - 0-28d** ≥40y Dose 1 Dose 2 Dose 3 *Females* 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) *Males* 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) **IRR (95% CI) – 1-7d** ≥40y Dose 1 Dose 2 Dose 3 *Females* 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) *Males* 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
NIMS Aug 24 **Dec 1 2020 to Aug 24 2021** **England**	Pfizer Moderna Either dose	Adults ≥16 y vaccinated with at least one dose of Pfizer (n = 16,993,389; 70.5% with two doses) or Moderna (n = 1,006,191; 36.7% with two doses)	Myocarditis; pericarditis ICD-10 codes Risk interval: 1-7d, 1-28d	Incidence rate ratios estimated using self-controlled case series methodology	**Incidence rate ratios (IRR 95% CI) for Myocarditis in vaccinated individuals with, or without a +ve COVID-19 test prior to vaccination** *1-28d risk period* With +ve Without cRR Pfizer, dose1 0.96 (0.42, 2.20) 1.34 (1.03, 1.74) 0.716 Pfizer, dose 2 0.52 (0.12, 2.23) 1.35 (1.00, 1.82) 0.385 Moderna, dose 1 NR 2.37 (0.98, 5.75) NE Moderna, dose 2 NR 8.70 (2.35, 32.11) NE

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Patone 2022[12]			Risk factors considered: positive COVID-19 test before vaccination		**Incidence rate ratios (IRR 95% CI) for Pericarditis in vaccinated individuals with, or without a +ve COVID-19 test prior to vaccination** *1-28d risk period* — With +ve: — Without: — cRR: Pfizer, dose 1: 1.43 (0.61, 3.36) — 0.68 (0.50, 0.93) — 2.10 Pfizer, dose 2: NE — 0.90 (0.69, 1.18) — NE
Nordic cohort Oct 5 2021 **Dec 27 2020 to Oct 5 2021** **Denmark, Finland, Norway, Sweden** **Karlstadt 2022**[6]	Pfizer-BioNTech 15,064,585 Dose 1 or 2 Moderna 2,390,870 Dose 1 or 2 Homologous or heterologous dose 2 Interval between doses NR	Surveillance population: 23,122,522 nordic residents ≥12 y 50% males Previous covid-19 infection NR but accounted for in analysis	Myocarditis inpatient stay; Myo- or pericarditis inpatient or outpatient stay ICD-10 codes: I400 I401 I408 I409 I411 I418 I514 in primary or secondary diagnosis field (Myocarditis) Risk interval: 0-7 d or 0-28 d after any dose Risk factors: Moderna vs Pfizer; Homologous vs. heterologous dose 2.	Crude incident rate; Incidence rate ratio, adjusted Poisson regression comparing rates (vs unvaccinated individuals) in risk periods after vaccination; adjusted for age group, sex, SARS-CoV-2 infection before Dec 27, 2020, healthcare worker status, nursing home resident, and comorbidities (pulmonary disease, kidney disease, autoimmune disease, cardiovascular disease or diabetes, and cancer), and calendar period Stratified by age groups and sex, vaccine combinations (heterologous vs. homologous)	**Myocarditis, 0-7 d interval, Moderna vs Pfizer** **Myocarditis, 0-28 d risk interval, Moderna vs Pfizer** **Pericarditis, 0-28 d risk interval, Moderna vs Pfizer** **Myocarditis, 0-28 d interval, Homologous vs. Heterologous Dose 2**

Myocarditis, 0-28 d risk interval, Moderna vs Pfizer

	Dose 1						Dose 2					
	Male			Female			Male			Female		
	events	IR	cRR	events	IR	cRR	events	IR	cRR	events	IR	cRR
12-15 y												
Moderna	13	0.139	1.1	≤5	ND	-	87			≤12	0.	
Pfizer	70	0.125		35	0.061		85	0.172		30	0.057	
16-24 y												
Moderna	≤5	ND	-	0	ND	-	32			ND	ND	-
Pfizer	24	0.376		≤5	ND		37	0.891		≤5	ND	
25-39 y												
Moderna	≤5	ND	-	0	ND	-	41			ND	ND	-
Pfizer	17	0.156		≤5	ND		15	0.179		≤5	ND	
40+ y												
Moderna	6	0.125	1.7	≤5	ND	-	≤16	0.		ND	ND	
Pfizer	27	0.072		27	0.069		31	0.085		20	0.052	

Pericarditis, 0-28 d risk interval, Moderna vs Pfizer

	Dose 1						Dose 2					
	Male			Female			Male			Female		
	events	IR	cRR	events	IR	cRR	events	IR	cRR	events	IR	cRR
12-15 y												
Moderna	10	0.421	2.5	12	0.133	1.8	36			20		
Pfizer	93	0.166		43	0.075		88	0.178		43	0.082	
16-24 y												
Moderna	≤5	ND	-	≤5	ND	-	≤11			≤10	ND	-
Pfizer	≤5	ND		≤5	ND		9	0.217		≤5	ND	
25-39 y												
Moderna	≤5	ND	-	≤5	ND	-	≤11			≤10	ND	-
Pfizer	17	0.156		≤5	ND		18	0.215		≤5	ND	
40+ y												
Moderna	≤5	ND	-	7	0.144	1.5	≤18			≤12		
Pfizer	72	0.192		38	0.097		61	0.168		38	0.098	

					cIR per 1000 person-years (95% CI), by product *Males* Pfiz-Pfiz Pfiz-Mod cRR Mod-Mod Mod-Pfiz cRR 16-24 y 0.891 3.687 2.584 NR NE 25-39 y 0.179 1.543 1.132 NR NE ≥40 y 0.085 NE 0.254 NR NE *Females* 16-24 y NE NE 71.7/2.86 NE NE NE 25-39 y NE NE NE NE NE ≥40 y NE NE 8.12/1.02 NE NE NE **Myocarditis, 0-7 d interval, Homologous vs. Heterologous Dose 2** **cIR per 1000 person-years (95% CI), by product** *Males* Pfiz-Pfiz Pfiz-Mod cRR Mod-Mod Mod-Pfiz cRR 16-24 y 2.190 13.028 7.379 NR NE 25-39 y 0.383 4.767 3.898 NR NE ≥40 y 0.072 NE 6.95/1.50 NE NR NE *Females* 16-24 y NE NE 210.81/7.88 NE NR NE 25-39 y NE NE NE NE NR NE ≥40 y NE NE NE NE NR NE **Pericarditis, 0-28 d interval, Homologous vs. Heterologous Dose 2** **cIR per 1000 person-years (95% CI), by product** *Males* Pfiz-Pfiz Pfiz-Mod cRR Mod-Mod Mod-Pfiz cRR 16-24 y 0.217 NE 6.36/2.85 1.034 NR NE 25-39 y 0.215 NE 4.33/2.95 0.305 NR NE ≥40 y 0.168 NE 1.32/1.09 0.30 NR NE *Females* 16-24 y NE NE 3.43/2.47 NE NR NE 25-39 y NE NE 23.21/3.34 NE NR NE ≥40 y 0.098 NE 1.61/1.39 NE NR NE IR: crude incident rate per 1,000 person-years ND: not determined
Singapore Military Aug 3 Jan 14 to Aug 3 2021 Singapore Tan 2021[40]	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 Dose 1 Dose 2 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
VSD Jan 15 **Dec 14 2020 to Jan 15 2022** **United States** **Goddard 2022**[10]	Pfizer-BioNTech 2,891,498 Dose 1: 1,479,596 Dose 2: 1,411,902 Moderna 1,803,267 Dose 1: 923,711 Dose 2: 879,556	Total 4,694,765 doses 18-39 y Among cases, 17% (n=7) Pfizer and 13% (n=5) Moderna with COVID-19 infection >30 d prior to myocarditis/pericarditis; individuals with COVID-19 infection ≤30 d prior to myocarditis/pericarditis were excluded	Myocarditis or pericarditis Cases with ICD-10 codes (B33.22, B33.23, I30.*, I31.9, I40.*, and I51.4) and meeting the CDC case definition of confirmed or probable myocarditis, pericarditis, or myopericarditis Risk interval: 0-7d, 0-42d	Adjusted rate ratio of mRNA-1273 compared to Pfizer Poisson regression, conditioned on strata defined by calendar date, age group, sex, race/ethnicity, and VSD site Excess cases in risk period per 1M doses of mRNA-1273 vs BNT162b2	**Myocarditis 0-7 d after Moderna compared with Pfizer** Adjusted rate ratio — Excess cases per 1M doses Males, 18-39 y Either dose 1.32 (0.78 to 2.22) 8.1 Dose 2 1.31 (0.73 to 2.31) 13.6 Females, 18-39 y Either dose 1.57 (0.27 to 8.12) 1.1 Dose 2 0.53 (0.02 to 5.81) -1.8 **Myocarditis and pericarditis 0-7 d after Modern compared with Pfizer** Adjusted rate ratio — Excess cases per 1M doses Males, 18-39 y Either dose 1.52 (0.93 to 2.48) 13.4 Dose 2 1.50 (0.86 to 2.61) 21.9 Females, 18-39 y Either dose 2.34 (0.65 to 8.71) 3.5 Dose 2 1.35 (0.23 to 7.15) 1.6
VAERS* Feb 6 **Sep 22 2021 to Feb 6 2022** **United States** **Hause 2022b**[5]	Pfizer-BioNTech or Moderna Dose 3	721,562 ≥18 y Pfizer primary series: 349,545 Moderna primary series: 327,464 89% with homologous mRNA vaccination Previous COVID-19 infection NR	Myocarditis CDC case definition by clinician interview with healthcare provider, or clinician review of medical record Risk interval: 0-6 d	Crude rate Stratified by sex and age group	**Myocarditis, Moderna vs Pfizer** Rate per 1M doses — cRR Moderna — Pfizer **18-24 y** Males 8.7 4.1 2.1 Females 1.1 <1.0 1.1 **25-29 y** Males 3.2 1.1 2.9 Females 1.2 - ND **30-39 y** Males <1.0 1.7 0.58 Females 1.5 <1.0 1.5 **40-49 y**

					Males - - ND Females <1.0 - ND **50-64 y** Males - <1.0 ND Females <1.0 - ND **≥65 y** Males <1.0 <1.0 1.0 Females - - ND
VAERS* Nov 30 Up to Nov 30 2021 United States Lane 2021[41]	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]
VAERS* Oct 6 To Oct 6 2021 United States Su 2021 [38]	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 1 mil doses: Dose 1 / Dose 2; crude Risk Ratio: Dose 1 / Dose 2 18-24 y 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* 25-29 y 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 30-39 y 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		
					40-49 y					
					Female	Moderna	0.2	1.4	2	1.27
						Pfizer	0.1	1.1		
					Male	Moderna	0.2	2.9	0.67	1.45
						Pfizer	0.3	2.0		
					50-64 y					
					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		
					65y+					
					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		

Green text = evidence identified by April 2022 update

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.

COVaxON - Covid-19 Vaccinations Ontario is a central data repository for COVID-19 vaccine data and reporting in Ontario, administered by the Ontario Ministry of Health.

NIMS - The English National Immunisation (NIMS) Database of COVID-19 vaccination includes data on vaccine type, date and doses for all people vaccinated in England.

ISS/AIFA - an active surveillance database, based on Regional health care claims, was set up by the Italian National Institute of Health (ISS) and the Italian Medicines Agency (AIFA) to provide real-world data on SARS-CoV-2 vaccine safety.

COVaxON - Covid-19 Vaccinations Ontario is a central data repository for COVID-19 vaccine data and reporting in Ontario, administered by the Ontario Ministry of Health

VSD - Vaccine Safety Datalink

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

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

Study Dataset	Were the two groups similar and recruited from the same population?	Was vaccination status measured in a reliable or valid way?	Were all key confounding factors (age, sex, Covid-19 infection, pre-existing conditions) identified and appropriately addressed in design or analysis?	Were the outcomes measured in a valid and reliable way (medical record review)?	Was the follow up time long enough for outcomes to occur (7-30 days)?	Were the large majority of cases likely to have been identified?	Overall assessment of risk of bias
Active surveillance studies							
Alroy-Preis 2021 Israeli MOH Oct 10	Y	Y	N	Y	Y	U	High risk
Block 2022 PCORnet Jan 31	Y	Y	Y	N (ICD codes only)	Y	Y	High risk
Friedensohn 2022 IDF Sep 30	Y	Y	Y	U	Y	Y	Some risk
Karlstadt 2022 Nordic Cohort Oct 5	Y	Y	Y	N (ICD codes only)	Y	U	High risk
Klein 2022 VSD Dec 30	Y	Y	U	Y	Y	Y	Some risk
Levin 2021 IDF May 7	NA	Y	N	Y	Y	Y	High risk
Li 2022 eHRSS Oct 18	Y	Y	U	N (ICD codes only)	U	U	High risk
Montgomery 2021 US Military Apr 30	NA	U	N (potential confounders only reported for cases; no adjustment in analysis)	U	U	U	High Risk
Mevorach 2022 Israel MOH Oct 20	Y	Y	N (no confounders considered)	Y	Y	U	High risk
Niesen 2021 Mayo Clinic Enterprise Oct 17	NA	Y	N (age [only < vs > 40; sex)	Y	Y	Y	High risk
Patone 2021 NIMS/NHS Nov 15	Y	Y	U	N (ICD codes only)	Y	U	High risk

Tan 2021 Singapore Military Aug 3	NA	Y	N (age and sex only)	U	U	N	High risk
Passive surveillance studies							
Buchan 2021 COVaxON and Public Health Case and Contact Management Solution Sep 4	Y	Y	U	Y	N	Y	High risk
Hause 2022a VAERS Feb 20	NA	U	N (age and sex only)	Y	U	N	High risk
Hause 2022b VAERS Feb 6	NA	U	N (age and sex only)	Y	Y	N	High risk
Høeg 2021 VAERS Jun 18	NA	N	N	U	U	N	High risk
Shimabukuro 2022 VAERS Jan 13	NA	U	N (age and sex only)	Y	Y	N	High risk
Strauss 2021 Moderna Global Safety Database Sep 30	NA	U	N	Y	U	U	High risk
Su 2021a VAERS Dec 9	NA	Y	U	Y	Y	N	High risk
Su 2021b VAERS Oct 6	NA	N	N	Y	Y	N	High risk
Su 2022 VAERS Dec 19	Y	Y	U	Y	Y	N	High risk

Green text = evidence identified by April 2022 update

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

Study 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
Buchan 2021 COVaxON and Public Health Case and Contact Management Solution	U	Y	Y	N	Y	Y	N	Y	High risk
Goddard 2022 VSD Jan 15	Y	Y	Y	Y	Y	Y	Y	Y	Low risk
Hause 2022b VAERS Feb 6	Y	Y	U	N	U	Y	Y	N	High risk
Karlstadt 2022 Nordic Cohort Oct 5	Y	Y	Y	N	Y	N (ICD codes only)	Y	Y	High risk
Lane 2021 VAERS Nov 30	Y	Y	N	N	U	N	U	N	High risk
Machado 2021 EULAR COVAX	N	Y	Y	N	U	N	N	N	High risk
Massari 2022 ISS/AIFA Sep 30	Y	Y	Y	Y	U	N (ICD codes only)	Y	Y	High risk
Patone 2021 NIMS Nov 15	N	Y	Y	Y	Y	N	Y	Y	High risk
Patone 2022 NIMS Aug 24	Y	Y	U	Y	U	N (ICD codes only)	Y	Y	High risk
Su 2021 VAERS Oct 6	U	Y	Y	N	Y	Y	Y	N	High risk
Tan 2021 Singapore Military Aug 31	Y	Y	Y	N	U	U	U	Y	High risk

Green text = evidence identified by April 2022 update

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		
Hajra et al., 2021[54] (narrative review) Exposure to spike protein	• 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].	Supporting: 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. Circulation. 2021;144:487–98. Case report; increase in NK cells (lymphocytes) Refuting: Larson et al. Myocarditis after BNT162b2 and mRNA-1273 Vaccination. Circulation. 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).
Tsilingiris et al., 2021[64] (article) Exposure to mRNA strand	• 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
Heymans & Cooper, 2021[55] (letter)	• 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

Exposure to mRNA strand	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[61] (case report and narrative review) Exposure to mRNA strand	• 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.	<u>Supporting</u>: 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.
Bozkurt et al, 2021[47] (narrative review) Exposure to mRNA strand or spike protein or unknown trigger	• 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](Mathukumar 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] • *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*	<u>Supporting:</u> 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 <u>Refuting:</u> 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
Das et al., 2021[51] (case series)	• 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	<u>Refuting:</u> Exposure to spike protein or other unknown trigger, with antibody response: Their case series data (n=25, 12-18 years)(Das)

Exposure to spike protein and other unknown trigger	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]	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; antibody responses to 18 different SARS-CoV-2 antigens same as controls.
Boursier et al.,, 2021[69] (case reports) Exposure to unknown trigger	• 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.	Supporting: Two cases (18 and 21-year old males) with PET findings supporting myocardial infiltrate.
Switzer & Loeb, 2021[62] (narrative review) Exposure to unknown trigger	• A potential avenue for vaccine-associated myocarditis may be a nonspecific innate inflammatory immune response.	None
Verma et al., 2021[65] (letter to the editor describing 2 cases) Exposure to unknown trigger	• Case 1: 45 year old women; 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.	Supporting: Biopsy and autopsy findings from their two cases; showing inflammatory infiltrate.
Gnanenthiran & Limaye, 2022 (narrative review)	• The exact processes underlying mRNA vaccine-induced myopericarditis have not been elucidated, but a number of hypotheses are proposed.4,9 These include a hyperimmune response similar to the multi-system inflammatory response seen in children with COVID-19 (MIS-C), although this is not supported by measurement of vaccine-induced antibody levels in affected patients.9 (Das)	Refuting: -1 case series: Das, B.B. et al. Myocarditis and Pericarditis Following mRNA COVID-19 Vaccination: What Do We Know So Far? Children 2021, 8, 607. https://doi.org/10.3390/children8070607
Dursun et al. 2022 (cross section study)	• After mRNA vaccination, the immune system may perceive the mRNA as an antigen and start activation of proinflammatory and immunologic reaction.6,7 The innate immunogenicity and genetic position in certain individuals may be responsible for this.8	None
Mormile 2022 (expert opinion)	• The immune system may identify the mRNA in the vaccine as an antigen eliciting a pro-inflammatory cascade and immunologic signaling pathways resulting in myocarditis as a part of a systemic reaction in certain subjects [1,3,5,8].This conjecture appears to be corroborated by the fact that endomyocardial biopsy specimens from patients with myocarditis after COVID-19 mRNA vaccination show similar inflammatory infiltrate predominantly composed of T-cells and a substantial CD-68-positive macrophages, CD3-positive T-lymphocytes admixed with eosinophils, B-cells and plasma cells [11,12].	Supporting: Nguyen TD et al. Acute myocarditis after COVID-19 vaccination with mRNA-1273 in a patient with former SARS-CoV-2 infection. In: ESC Heart Fail. Sep 18; 2020.

		Verma AK et al. Myocarditis after Covid-19 mRNA Vaccination. N Engl J Med. 2021;385(14):1332–1334. 30.
Frustaci et al. 2022 (case series)	• Case series with 3 patients (39F, 78M, 52M) with severe myocarditis after dose 2. Biopsy and immunohistochemistry. The histological findings obtained by left ventricular endomyocardial biopsy were characterized in all instances by presence in the myocardium of prevalent eosinophilic infiltrates (Figure 2G), associated with degranulation of crystalloids and elevation in the circulatory blood of cationic protein. This last protein is known in patients with eosinophilic endomyocardial disease to induce myocardial and coronary vessel damage (Churg–Strauss syndrome), as well as endocarditis with thrombus formation (Loeffler disease) because of parallel activation of factor X of coagulation. Post-vax inflammatory lesions observed in our patients demonstrate myocarditis hypersensitivity and the formation of new antigens from macromolecules of cardiomyocytes and some component (spike protein?) of the BNT162b2 vaccine. Interestingly, all three patients described in our report were affected by allergic disorders that would indicate some predisposition to allergic reactions to new antigens.	Supporting: Authors' 3 cases with biopsy and immunohistochemistry
Hypothesis 2: Delayed hypersensitivity (serum sickness)		
Hajra et al., 2021[54] (article)	• 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].	Supporting: 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? Can J Cardiol. 2021 Montgomery J et al. Myocarditis Following Immunization With mRNA COVID-19 Vaccines in Members of the US Military. JAMA Cardiol. 2021 Shay DK et al. Myocarditis Occurring After Immunization With mRNA-Based COVID-19 Vaccines. JAMA Cardiol [Internet]. 2021 [cited 2021 Sep 16]
Tsilingiris et al., 2021[64] (article)	• 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[50] (case report)	• 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.	Supporting: Case report data; 30 year-old male after second dose.
Bozkurt et al., 2021[47] (narrative review)	• 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	Refuting: Several case reports and series; no eosinophilia: Marshall M et al. Symptomatic

	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]	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. 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. Albert E et al. Myocarditis following COVID-19 vaccination. Radiol Case Rep. 2021;16:2142–2145. 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. 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.
Chouchana et al., 2021[49] (retrospective study on Vigibase case and discussion)	• 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
Gnanenthiran & Limaye, 2022 (narrative review)	• Presentation after 2-3 days is earlier than would be expected for delayed-type hypersensitivity, and patients do not demonstrate eosinophilia, nor features of thrombosis or mast cell activation syndrome.	None
Hypothesis 3: Eosinophilic myocarditis		
Hajra et al 2021[54] (narrative review)	• 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[63] (case report)	• 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.	Supporting: Case report biopsy data, 53 year-old male; no data on whether from exposure to spike protein epitope.
D'Angelo et al, 2021[50] (case report and discussion)	• Case report data: White blood cells were 10.4 x 10^3/μL (normal 4.0-10.0), with **mild** eosinophilia (0.9 x 10^3/μL, normal 0.0-0.5 x 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]	Refuting: 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[47] (narrative review)	• (In a case report and series (n=4), there was also no evidence of leukocytosis, eosinophilia, anemia, thrombocytopenia, or transaminase elevation.[19,12](Ammirarti et al. and Kim et al.) • 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]	Refuting: 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. doi: 10.1016/j.ijcha.2021.100774: Case report with no eosinophilia Kim HW et al. Patients with acute myocarditis following mRNA COVID-19 vaccination. JAMA Cardiol. Published online June 29, 2021. doi:

		10.1001/jamacardio.2021.2828. Case series n=3 without eosinophilia 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. 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. Several case reports and series; no eosinophilia: (see Hypothesis 2)
Kounis et al. 2022 (commentary)	• So far, myocardial biopsies have been performed and reported only in 8 patients worldwide with myocarditis following COVID-19 vaccine. In 3 patients, the biopsy and in the 4th patient the autopsy demonstrated eosinophic myocardial infiltration. These reports were 2 from the USA [13], one from Israel [14] and a fatal case from Korea [15] respectively. All 4 cases had received BNT162b2 COVID-19 vaccines. The rest 4 patients had undetermined causes of myocarditis. Previous history of atopic childhood asthma, pollen and pet allergy [16] could be aggravating factor for myocarditis. All above support our view that COVID-19 vaccine-associated myocarditis seems similar to hypersensitivity myocarditis	Supporting : Isaak A et al. Myocarditis Following COVID-19 Vaccination. Radiology. 2021; 301: E378-E379. Verma AK, et al. Myocarditis after Covid-19 mRNA Vaccination. N Engl J Med. 2021; 385: 1332-1334 Witberg G, et al. Myocarditis after Covid-19 Vaccination in a Large Health Care Organization. N Engl J Med. 2021; 385: 2132-2139 Choi S et al. Myocarditis-induced Sudden Death after BNT162b2 mRNA COVID-19 Vaccination in Korea: Case Report Focusing on Histopathological Findings. J Korean Med Sci. 2021; 36: e286.
Hypothesis 4: Hypersensitivity to vaccine vehicle components (e.g., polyethylene glycol [PEG] and tromethamine; lipid nanoparticle sheath)		
Kounis et al. 2021a[58] (letter) Hypersensitivity to PEG and tromethamine	• 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].	Supporting: Sokolska JM et al. Every rose has its thorns — acute myocarditis following COVID-19 vaccination. Kardiol Pol. 2021; 79(10): 1153–1154, doi: 10.33963/KP.a2021.0075. 1 case with allergy Witberg G et al. Myocarditis after COVID-19 vaccination in a large health care organization. N Engl J Med. 2021 [Epub ahead of print], doi:

		10.1056/NEJMoa2110737. 1 case with biopsy of 54 in series No references for 2 cases in the USA with eosinophilia.
Kounis et al. 2021b[57] (letter) Hypersensitivity to PEG and tromethamine	• 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].	Supporting: 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[64] (article) Hypersensitivity to PEG and lipid nanoparticle sheath	• 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.)	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.
Bozkurt et al., 2021[47] (narrative review) Hypersensitivity: excipients not mentioned	• 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.	Refuting: 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
Kounis et al. 2022 (commentary)	• BNT162b2 COVID-19 vaccines contain the excipient polyethylene glycol also known as macrogol or PEG that could potentially induce hypersentitivity reactions [17]. Creams, ointments, lotions, cosmetics that are used frequently by females and young individuals and dental materials contain also PEG that is able to sensitize its users. Indeed, 1–5.4% of the	None

Hypersensitivity to PEG	general population is sensitized to cosmetics or dental materials [18] and 2% to 5% of the population, in USA, have experienced hypersensitivity or anaphylaxis, to drugs, food, or insect stings [19]. Therefore, hypersensitivity myocarditis could be induced by the vaccine excipient. However, recent reports [20] have demonstrated that most individuals after first-dose mRNA COVID-19 vaccine reactions, regardless of excipient skin testing result, were able to receive the second mRNA COVID-19 vaccine dose safely. Others [19] have suggested alternative excipients in vaccine manufacturing if vaccine component-induced hypersensitivity is confirmed by systematic future investigations. In a recent report [21] the authors concluded that hypersensitivity to such excipients constitutes risk to patients with allergy to PEG or polysorbates. After diagnostic evaluation, safe COVID-19 vaccines could be offered to most patients, "the remainders will await new vaccines containing different excipients".	
Al-Ali et al 2022 (systematic review) Hypersensitivity to PEG	• PEG is historically safe, with one meta-analysis reporting on 37 case reports of anaphylaxis following exposure to PEG in different forms.[108] It is possible that people who are allergic to PEG may develop an inflammatory response which may lead to myocarditis secondary to the allergic reaction. This may also explain the lower prevalence of myocarditis post AstraZeneca, J&J and Sinovac vaccines as they are devoid of PEG.	None
Hypothesis 5: Response to mRNA vaccine lipid nanoparticles (direct deleterious effect; not delayed – see Hypothesis 4)		
Tsilingiris et al., 2021[64] (article)	• 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.	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.
Kadkhoda, 2021[56] (letter)	• 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.	None

Hypothesis 6: Autoimmunity triggered by molecular mimicry*** or other mechanism		
Hajra et al 2021[54] (narrative review) Molecular mimicry	• 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].	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, Sapon- ara G, et al. Myocarditis after BNT162b2 and mRNA-1273 Vac- cination. 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.
Tsilingiris et al., 2021[64] (article) Molecular mimicry and other autoimmune	• 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.COV2.S [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].	Refuting: 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.COV2.S 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.
D'Angelo et al, 2021[50] (case report and discussion) Molecular mimicry	• 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]	None; nothing from case report to support & reference to influenza vaccine-induced fulminant myocarditis.
Heyman & Cooper, 2021[55] (letter) Molecular mimicry	• 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]	Supporting: 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.**
Bozkurt et al., 2021[47] (narrative review) Molecular mimicry and other autoimmune	• 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.	Supporting: 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.
Chouchana et al., 2021[49] (retrospective study on Vigibase case and discussion)	• 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.	None

Molecular mimicry		
Switzer & Loeb, 2021[62] (narrative review) Molecular mimicry and other autoimmune	• 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.	None
Parra-Lucares et al., 2021[61] (case report and narrative review) Molecular mimicry and other autoimmune	• 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 crosstalk with human proteins, such as alpha-myosin, a structural protein of cardiomyocytes involved in myocardial muscle contraction. *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*. • 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. *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*. • 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).	<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 cross-reactivity with at least one protein in muscle, i.e. α-myosin (see above); caution about unknown implications. Other autoimmune: 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 with detected autoantibodies; caution about unknown implications. <u>Refuting</u>: Other autoimmune: Indicative of direct data but no citations
Ehlrich et al., 2021[52] (case report in 40 year-old male after first dose, with biopsy) Molecular mimicry	• Case report of biopsy-proven (left ventricular endomyocardial) lymphocytic myocarditis in 40-yr 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.	<u>Refuting</u>: Molecular mimicry (after first dose): Their case report data, due to lack of anti-SARS-CoV-2-antibodies

Gnanenthiran & Limaye, 2022 (narrative review)	• Other possibilities include molecular mimicry between antibodies generated against SARS-CoV2 spike protein and a self-antigen, or aberrant induction of apoptosis with subsequent inflammation.9	None
Chin et al. 2022 (narrative review) Other autoimmune	• Elevated heart-reactive autoantibodies, which are found in patients susceptible to myocarditis, may attack the cardiac myocytes after vaccination [41].	None
Mormile 2022 (expert opinion) Other autoimmune	• May be connected with age-related lower levels of T-bet (T helper cell transcription factor) and PD-1 in predisposed individulas with T-bet polymorphisms by the release of autoreactive CD8+CTL. the first vaccination might initially function as an antigen-driven autoreactive effector CD8+ CTLs cell by genetic variants of T-Bet producing an overly aggressive immune system response with the second dose as a booster shot for strong autoimmune reactions against the heart resulting in rapidly evolving form of acute myocarditis or pericarditis in predisposed individuals.	None
Marrama et al. 2022 (cross-sectional study)	• We performed a sequence identity comparison between SARS-CoV-2 spike protein-derived peptides and (not vaccine associated) myocarditis-associated antigens. We also performed a structural analysis of these antigens and the SARS-CoV-2 spike protein to identify potential discontinuous 3-D epitope similarities. We found no significant enrichment in the frequency of spike-derived peptides similar to myocarditis-associated antigens (cardiac proteins) as compared to several controls	Supporting: Cross sectional study with sequencing but not in case of vaccine-associated myocarditis
Hypothesis 7: Low residual levels of double-strand RNA (dsRNA)		
Milano et al 2021[59] (special report)	• 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.[59] • 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.	None
Hypothesis 8: Dysregulated micro-RNA response		
AbdelMassih et al. 2021[70] (literature review)	• 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	None

	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.	
Hypothesis 9: Production of anti-idiotype antibodies against immunogenic regions of antigen-specific antibodies		
Tsilingiris et al., 2021[64] (article)	• 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].	None
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 inflammation[47])		
Bozkurt et al., 2021[47] (narrative review)	• 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 (Mathukumar 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.	<u>Refuting</u>: For specific predispositions: Abu Mouch 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.
Switzer & Loeb, 2021[62] (narrative review)	• 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].	None
Hypothesis 11: Antibody-dependent enhancement of immunity or other forms of immune enhancement with re-exposure to virus after vaccine		
Bozkurt et al., 2021[47] (narrative review)	• 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	<u>Refuting:</u> Multiple case reports and series reviewed and tabulated, having no evidence of

	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)	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 cardiomyocytes[49]		
Chouchana et al., 2021[49] (retrospective study on Vigibase case and discussion)	• 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[62] (narrative review)	• 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[56] (letter)	• 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-idiotype 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 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.	None
Hypothesis 14: Spike-activated neutrophils (expressing ACE2) augmenting inflammatory response		

Kadkhoda et al., 2021[56] (letter)	• 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
Hypothesis 15: Hyperviscosity-induced cardiac problem		
Mungmunpuntipantip & Wiwanitkit, 2021[60] (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[71] (protocol for retrospective and prospective observational study)	• 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 showed that increase of TNF-a 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]. • 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.	None
Hypothesis 17: Oxidative stress reaction		
Dursun et al. 2022 (cross-sectional study)	• Studied pericarditis n=10, mycarditis n=3, controls n=10; Serum nitric oxide levels and OSI (total oxidant status, H2O2/total antioxidant status) were lower (abnormal) in myopericarditis group than the control and acute pericarditis group ($p < 0.05$). This shows inflammatory and procoagulant state.	Author's study
Hypothesis 18: Elevated histamine levels with pericyte induced vasoconstrictions		
Ricke 2022 (short report)	• Innate immune responses to vaccines cause elevated histamine levels post vaccination; the histamine level reached may exceed the vaccinees' histamine tolerance level for several days.	Supporting: CDC reports on temporal nature of cases

	This article proposes that the elevated histamine level is causative for the reported cardiac adverse events. For myocarditis reported adverse events, this article proposes that elevated histamine levels induce cardiac capillary pericyte induced vasoconstrictions followed by localized ischemia and anoxia; this is followed by the release of troponin from myocyte cells affected by anoxia. This hypothesis is supported by the temporal onset timing of adverse events. In COVID-19 patients with myocarditis, vasoconstrictions associated with clamped pericyte cells has been proposed as the initial step in myocarditis [22]. Pericyte cell clamping was proposed to be caused possibly by either direct SARS-CoV-2 infection or by elevated histamine levels [22].	Fremont-Smith Int J Infect Dis. 2021 Dec;113:331-335. Autopsies in COVID cases implicating histamine but not in myocarditis
Hypothesis 19: IL-18-mediated immune responses and cardiotoxicity		
Won et al. 2022 (cross-sectional study with 1 case and 10 controls)	• A case of myopericarditis following the first dose of the mRNA-1273 COVID-19 vaccine in a young man who had a history of mild COVID-19 three months before vaccination. Biopsy and immune profile compared with 5 healthy controls and 5 vaccinated controls. • Endomyocardial biopsy revealed diffuse CD68+ cell infiltration with neither substantial inflammatory cell infiltration nor acute cardiomyocyte necrosis. • IL-18 and IL-27, Th1-type cytokines, were highly increased in the patient with COVID-19 vaccine-related myopericarditis compared with vaccinated controls who experienced no cardiac complications. In the patient, circulating NK cells and T cells showed an activated phenotype and mRNA profile, and monocytes expressed increased levels of IL-18 and its upstream NLRP3 inflammasome. • Plasma levels of Th2-related soluble factors such as IL-4, IL-5, IL-13, and CCL22 were comparable between the patient with COVID-19 mRNA vaccine related myopericarditis and healthy controls.	Supporting: Author's study
Differences in incidence by sex could be due to sex steroid hormones, underdiagnosis in females, or upregulation of		
Tsilingiris et al., 2021[64] (article)	• 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[55] (letter)	• 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[47] (narrative review)	• 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]	Supporting: Sex hormones: None Underdiagnosis in women: Centers for Disease Control and Prevention. The Vaccine Adverse Event Reporting System (VAERS) results. June

	• 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).	6, 2021. Accessed July 6, 2021. https://wonder.cdc.gov/vaers.html. More chest pain complaints in females. Bozkurt, unpublished data, 2021. Fewer investigations in females.
Chouchana et al., 2021[49] (retrospective study on Vigibase case and discussion)	• 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-Lucares et al., 2021[61] (case report and narrative review)	• 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.	Refuting: 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).
Mormile, 2022 (expert review)	• Supportive of the autoimmune mechanism (see Hypothesis 6) from genetic variants of T-bet, age-related lower levels of T-bet (T helper cell transcription factor) and PD-1, leading to release of autoreactive CD8+ CTL cells, there is upregulation of T-Bet and PD-1 by estrogen and this might explain the higher incidence of men developing myocarditis or pericarditis in comparison to women.	None

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, ≥40y) 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).

LIVING EVIDENCE SYNTHESIS: UPDATE #2 SUMMARY

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