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

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To help Canadian decision-makers as they respond to unprecedented challenges related to the COVID-19 pandemic, COVID-END in Canada is preparing rapid 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

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Context

This is the third update of a living evidence synthesis initiated in November 2021 available at COVID-END and published in BMJ[1]. This third 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

August 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?
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?

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Our Approach

For study eligibility for each question, see Supplementary Table 1. A single reviewer completed screening and another verified 50% of exclusions, using a machine-learning program to prioritize records. For the key questions, a second reviewer verified all exclusions at full text and data extraction stages. Risk of bias assessments (for KQs 1 & 2) using modified Joanna Briggs Institute tools were also verified by a second reviewer. 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, ratio measures ≥1.5 (e.g., odds ratio, relative risk) were considered clinically relevant (e.g., 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.

Seventy-four studies were included in this update. We identified 21 new reports across all questions (KQ1=7[2-8], KQ2=5[4 5 8-10], KQ3=0, KQ4=9[2 6 11-17], CQ1=5[18-23]). Findings from 62 of 64 studies in the previous synthesis were carried forward (KQ1=18[24-41], KQ2=11[28 29 33 39 41-47]; KQ3=2[27 40]; KQ4=10[31 35 48-55]; CQ1=30[23 56-84]). Two reports from the previous synthesis were replaced by reports of more recent data [85 86]. Three studies previously included as pre-prints [33 34 45] have been published since their inclusion[87-89]. The data tables have been updated to reflect the published reports; the updated data from these studies was either identical between pre-print and publication or would not have changed our conclusions in the previous updates.

In the findings below, green font indicates changes to conclusions or certainty in the evidence since the last update.

We identified two cross sectional studies that were not eligible due lack of a comparator group, but examined the occurrence of myocarditis or pericarditis after vaccination with an mRNA vaccine in individuals with a history of these conditions [90 91]. Among 95 individuals with a history of myocarditis, 79 participants were fully vaccinated with either Pfizer or Moderna with no reoccurrence of myocarditis; the remaining 16 refused vaccination mainly due to concerns about the risk of myocarditis [91]. Two of 64 individuals with a history of pericarditis experienced mild recurrence after mRNA vaccination [90].

KQ1: Incidence

Myocarditis after dose 2

- Overall, the evidence remained consistent with the previous updates.
- We included 3 new reports 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).

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- We identified 5 new studies reporting on 12-17 year-old males and females. In males, we remain moderately certain about a higher incidence (range 15-390 cases per million) of myocarditis after vaccination with an mRNA vaccine (moderate certainty). Among 12-17 year old females, the incidence of presenting with myocarditis after vaccination with an mRNA vaccine may be 4 to 37 cases per million (low certainty.
- We identified 5 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 29 and 157 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 1 to 50 cases per million (low certainty).
- We identified 4 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 104 cases per million (moderate certainty). Among females, we continue to have low certainty about the incidence of myocarditis after vaccination with an mRNA vaccine (may be fewer than 20 cases per million).

Myocarditis after dose 3

- We identified 4 new reports of myocarditis after a third dose of an mRNA vaccine.
- We identified one new report on booster doses among 5-11 year old males and females. Based on only one report using data from passive surveillance/spontaneous reporting, we are uncertain about the incidence of myocarditis after vaccination with a third dose of mRNA vaccine for this age group.
- We identified two new studies reporting on 12-17 year-olds. 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). All 3 studies reporting on 12-17 year-old females reported zero events, giving us increased certainty that the incidence of myocarditis after vaccination with a third dose of an mRNA vaccine in this group may be fewer than 20 cases per million (low certainty).
- We Identified two new studies reporting on 18-29 year-olds. Among 18-29 year-old males, we remain uncertain about the incidence of myocarditis after a third dose of an mRNA vaccine due to large inconsistency across studies (very low certainty). 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).
- We identified two new studies reporting on 30-39 year-old males and females. Among both 30-39 year old males and 30-39 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 both).
- This update did not search for studies in ≥40 year-olds for KQ1. We continue to conclude that among both ≥40 year-old males and ≥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 certainty for both).

Myocarditis after dose 4

We identified one new study reporting on myocarditis after a fourth dose of an mRNA vaccine in individuals ≥12 years old of either sex and presumed to be immunocompromised. We are uncertain about the incidence of myocarditis after vaccination with a fourth dose of an mRNA vaccine in this group due to indirectness from reporting outcomes across age and sex groups, from all evidence coming from a single study using only data from passive surveillance/spontaneous reporting.

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 for both males and females).
- We identified one new study reporting 12-17 year-old males and females. For both males and females we now have increased certainty that the incidence of pericarditis after vaccination with dose 2 of an mRNA vaccine may be fewer than 20 cases per million (low certainty for both males and females).
- We identified one new study reporting 18-24 year-old males and females. For 18-24 year-old males we remain uncertain about the incidence of pericarditis after vaccination with dose 2 of an mRNA vaccine due to inconsistency in estimates across studies. For 18-24 year old females, we have increased certainty that the incidence of pericarditis after vaccination with dose 2 of an mRNA vaccine may be fewer than 20 cases per million.

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- We identified one new study reporting on 25-39 year-old males and females. We now have increased certainty for 25-39y old males that the incidence of pericarditis after vaccination with dose 2 of an mRNA vaccine may be fewer than 20 cases per million (low certainty). For 25-39 year-old females, we remain uncertain about the incidence of pericarditis after vaccination with dose 2 of an mRNA vaccine due to inconsistency across studies.

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

- We identified one new study reporting on 12-17 year old males and females and now report on this age category. Among 12-17 year-old males, there may be a higher incidence of myocarditis following vaccination with Moderna compared with Pfizer (low certainty). Among 12-17 year-old females, we are uncertain about the incidence of myocarditis following vaccination with Moderna compared with Pfizer (very low certainty), due to inconsistency from a single study reporting findings that are contradictory to the evidence across all other age/sex categories.
- With the identification of a study reporting on 12-17 year old males and females, we are no longer reporting on the 12-39 year old age category.
- We identified 3 new studies reporting on 18-29 year-old males and females and 2 new studies reporting on 18-39 year old males and females. We now have enough confidence to quantify the difference between vaccines in these groups and conclude that among 18-29 year old males and females and 18-39 year-old males and females, the incidence of myocarditis is probably at least 2-3 times higher after vaccination with Moderna compared to Pfizer (moderate certainty).
- We identified 2 new studies reporting on 30-39 year-old males and females. We now conclude that among 30-39 year old males, there is probably a higher incidence of myocarditis after vaccination with Moderna compared to Pfizer (moderate certainty). Among 30-39 year old females, we are now uncertain about the incidence of myocarditis after vaccination with Moderna compared with Pfizer, due to large inconsistency in findings across studies (very low certainty).
- We identified one new study reporting on ≥40 year-old males and females. There may be a higher incidence of myocarditis after vaccination with Moderna compared to Pfizer in both groups (low certainty).

Moderna versus Pfizer, after dose 3

- We did not identify any new studies reporting on Moderna vs 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

- We did not identify any new studies reporting on homologous vs heterologous dosing regimens.
- 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

- We did not identify any new studies comparing individuals with vs without a positive COVID-19 test before vaccination. 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).

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Dose interval: Dose 1 to Dose 2

- We identified one new study reporting on dose interval between dose 1 and dose 2 for Pfizer and Moderna, in 12-29 year-olds and in ≥30 year-olds (both sexes combined).
- In both 12-29 year olds and ≥30 year-olds, the incidence of myocarditis after dose 2 of an mRNA vaccine may be lower when administered ≥27 days compared with <27 days after dose 1 (low certainty).

Dose interval: Dose 2 to Dose 3

- We identified one new study reporting on dose interval between dose 2 and dose 3 for Pfizer and Moderna, in 12-29 year-olds and in ≥30 year-olds (both sexes combined).
- In 12-29 year olds receiving dose 3 of Pfizer and ≥30 year-olds receiving dose 3 of Moderna, the incidence of myocarditis after dose 3 of may be lower when administered ≥170 days after dose 2 compared with <170 days after dose 2 (low certainty).
- In ≥30 year-olds receiving dose 3 of Pfizer, we are undertain about whether incidence of myocarditis after dose 3 may be different across different dose timings due to evidence from a single study that contradicts the findings in dose timing across other age groups, doses, and mRNA products (very low certainty).

Myocarditis and/or pericarditis

Dose interval

- We no longer report on associations between dose interval and myo/pericarditis because we identified one study reporting on dose interval for myocarditis alone (see previous section).

Clinical Comorbidities

- We identified no new studies reporting on clinical comorbidies and myocarditis and/or pericarditis.
- Studies reporting on these associations only reported across both sexes and all ages; therefore 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.

Race

- We identified one new study reporting on myocarditis and pericarditis combined in black and in white US military members. There may not be a higher incidence of myocarditis or pericarditis after vaccination with an mRNA vaccine in black individuals compared with white (low certainty).

Pericarditis

Moderna versus Pfizer, after dose 2

- We identified one new study reporting on pericarditis after Moderna compared with Pfizer in 18-29 year old males and now report findings for this group, for whom there is probably a higher incidence of pericarditis after vaccination with Moderna compared with Pfizer (moderate certainty).
- We identified one new study reporting on 18-39 year-old males, and our conclusions for this groups has not changed. We continue to have moderate certainty that 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).
- We identified one new study reporting on 30-39 year-old males and females and now report on these groups. Among 30-39 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 ≥40y 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

- Similar to the previous update, 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 no additional case series reporting on the short-term clinical course of myocarditis after a third (or fourth) dose of an mRNA vaccine.
- Among the 32 cases previously identified, all received the Pfizer vaccine and had been hospitalized. All were discharged at follow-up.

KQ4: Longer-term Outcomes

- In addition to 10 reports from the previous synthesis, nine new reports[2 6 11-17] were included for longer-term outcomes.
- Across 17 studies with unique patients, 243 cases were followed up at least 4 weeks (medians ranged from 4 to 23 weeks; longer than 12 weeks in all but 2[2 31] reports). Two reports[6 49] from at least 12-week follow-up of more than 390 cases reported to the national surveillance system in the US (VAERS) may overlap in coverage with the other nine reports from distinct sites in the US. Sixteen (84%) studies had follow-up data for ≥90% of their patients with myocarditis; three studies had lower rates of follow-up (38-62%)[13 15 35]. Follow-up for completion of health-related quality of life questionnaires was suboptimal (67%) in one study of patients with myocarditis reported to VAERS[49]. No deaths were reported in the included studies reporting on longer term outcomes.
- Among nine reports[12-15 48-50 52 53] of MRI findings at follow-up (n=233 of 461 [51%] followed up), although improvements were seen in late gadolinium enhancement, positive findings persisted in many patients (n=approximately 165 of 233 [71%]) indicating some residual fibrosis.
- Ongoing chest pain was reported by 29% of 532 patients reporting this outcome[2 11 12 14 16 35 49 51-54]. Of 464 patients reporting on other symptoms, these included shortness of breath 18% (n=152), palpitations 17% (n=152), and fatigue 22% (n=171).
- At follow-up (n=418)[12 35 49 51 55], 20% of patients were still taking medications related to myocarditis.
- At follow-up in studies with unique patients (n=84)[11 13 14 35 48 50-52], 82% were recovered with no symptoms. Among 398 patients 12 to 29 years of age from the VAERS database with follow-up data from healthcare providers after at least 90 days[6], 16% had not fully recovered, 67% had fully recovered, and 15% had probably recovered but further information was required.
- Among 360 VAERS cases followed (median 4.8 months)[49], 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 35 papers: 5 new reports[18-22] and 30 from the previous update[23 56-84] 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. New papers that did not add any new hypotheses or data (e.g. case series) were not charted for this update[92-98].

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- Across the included papers, we identified 22 hypotheses that are presented in Table 5. 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 "Spike effect" with Angiotensin II accumulation without protection (in younger people) by over-expression of some angiotensinases (PRCP, and POP), SARS-CoV-2 spike glycoprotein injuring cardiac pericytes which support the capillaries and the cardiomyocytes, exosomes released by macrophages that have taken up the mRNA nanoparticles and the specific microRNAs found in those exosomes, 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.
- Findings of a case series of 15 patients who underwent endomyocardial biopsy suggest an autoimmune response, because nine patients had hearts expressing SARS-CoV2 spike protein and a dominance of CD4+ T cell infiltrates[20].
- One new experimental study examined whether the components of the mRNA vaccine formulations elicited PEG-specific antibody responses in serum by enzyme linked immunosorbent assay (ELISA), and detected an increase in the reactivity to mRNA vaccine formulations in Moderna but not Pfizer vaccinees' (n=10) sera in a prime-boost dependent manner[21]. Although there was an increase in the anti-PEG antibodies in several Moderna vaccinees who experienced adverse effects, there was no obvious association between PEG antibodies and the adverse reactions (n=9). The authors' suggest that perhaps anti-formulation immune responses are contributing to the higher reactogenicity sometimes observed with the Moderna compared with Pfizer vaccine.
- A number of papers discussed observed differences in incidence by sex (see KQ1) which could be attributed to sex steroid hormones or under-diagnosis in females.
- Some opinions from our content experts (Drs Ian Paterson, Andrew Mackie, Bruce McManus) include:
  - The hyper immune/inflammatory response hypothesis raises the question of whether the response is systemic or specific to the heart. It is more likely systemic with concurrent subtle changes in other organs whereas the heart may be more susceptible. Further, it is easier to detect myopericarditis due to chest pain symptoms and measurable changes in cardiac biomarkers and imaging.
  - While autoimmunity triggered by molecular mimicry or other mechanism is among the more commonly discussed hypothesis, the observed response timing after the second vaccine dose (1-5 days) is considered early for this type of mechanism. If this is occurring after exposure to partial antigens (epitopes of SARS-CoV2 spike protein) being made from the mRNA vaccines, the question arises as to why this isn't the main hypothesis for myocarditis after COVID infection where there is exposure to entire SARS-CoV2 spike protein. Additionally, vaccines using adenoviral vector-based platforms produce the spike protein but have not been implicated in causing higher than background rates of myocarditis.
  - The delayed hypersensitivity hypothesis is supported by earlier work of other viruses (e.g., coxsackieviruses, echoviruses).
  - Eosinophilic myocarditis is a very different entity and is not likely to be the mechanism behind all cases of post-vaccination cardiac inflammation. If this was the predominant mechanism of vaccine related myocarditis, then the rate of myocarditis would be similar to the rate of true allergic reactions to the vaccine.
  - Hypersensitivity to vaccine vehicle components is among the more commonly discussed hypothesis; however, this is not likely to account for a major mechanism as allergic reactions have been very rare with the vaccines. The difference in incidence seen across sexes may point away from an allergic reaction predominating.
  - The mechanism(s) may be very similar to that for myocarditis with COVID-19 infection, but at a lower incidence due to the much smaller quantity of spike protein exposure.
  - One potential hypothesis that was not described in the examined articles relates to microvessel partial or complete thrombosis with multi-focal ischemic injury related to endothelial ACE2 expression and fibrin-platelet interactions in susceptible individuals.

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- 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.,[99] described a fatal case of myocarditis after mRNA vaccination and compared the case to another fatality reported by Verma et al.,[84] 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."[99] 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 absolute risk is extremely low and is outweighed by the benefits of protection against COVID-19 of conferred by vaccination. 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.
- Our findings suggest that Pfizer over Moderna, getting homologous doses, and waiting more than 27 days between dose 1 and dose 2 may be preferred, especially in younger males.
- At approximately 3 months follow-up, it appears that about 70-80% of patients have fully recovered in terms of their myocarditis symptoms. Positive late gadolinium enhancement findings may persist in a majority of patients, indicating some residual fibrosis. A substantial proportion of patients may experience other problems, such as anxiety/depression or unspecified pain, but low follow-up rates and the lack of control data limit this finding. One large case series in the US found few (2-3% of affected) individuals missed school or work due to myocarditis.
- As the incidence of myocarditis after mRNA vaccination remains a rare adverse event, the findings must be considered alongside the overall benefits of vaccination and with detailed risk-benefit analyses to support policy recommendations for optimal dosing intervals and vaccine products for different populations.

Future Directions

Incidence, etc.

- As regular COVID-19 boosters become a reality, continued surveillance of myocarditis after mRNA vaccines is needed to support continued decision making, especially after dose 3 and subsequent doses and with the forthcoming distribution of updated bivalent vaccines to be used as booster doses.
- 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. Data reported by age group and sex is necessary to understand whether risk may differ across 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 and long-term impacts of these events.

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

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'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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Tables

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

Sex	Age	Studies (data source and date) Country *passive surveillance	Risk interval; Confirmed cases (Y/N)	Incidence rates per million doses after dose 2 of either mRNA vaccine unless otherwise stated *weighted average across age groups ‡weighted average across products †excess incidence	Conclusions	Certainty about conclusions using GRADE
Myocarditis (after dose 2)						
M	5-11y	VAERS* May 26 US	7 d; Y	2.6 (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 (range: 0 to 2.6).	**Low**
		PCORnet Jan 31 US	7 d; Y	0 events (Pfizer)		
		Moderna global safety database* Feb 15 Worldwide	7 d; Y	0 (Moderna)		
		PCORnet Jan 31 US	21 d; Y	0 events (Pfizer)		
		VSD Dec 30 US	21 d; Y	0 events (myo or pericarditis; Pfizer)		
		TGA* Aug 21 Australia	Any; Y	2 (Pfizer)		
	12-17y	VAERS* Jun 18a US	Any; Y	118.7 (Pfizer)	Among 12-17 year old males, the incidence myocarditis after vaccination with an mRNA vaccine is probably between 15 and 390 cases per million.	**Moderate**[a]
		COVaxON* Sep 4 Canada	7 d; Y	88.1 (Pfizer)		
		VAERS* May 26 US	7 d; Y	58.2* (Pfizer)		
		SNDS Oct 31 France	7 d; Y	19.3† (Pfizer)		
		PCORnet Jan 31 US	7 d; Y	220 (Pfizer)		
		Moderna global safety database* Feb 15 Worldwide	7 d; Y	14.6 (Moderna)		
		PCORnet Jan 31 US	21 d; Y	267 (Pfizer)		
		Israeli MOH Oct 20 Israel	30 d; Y	80.9 (Pfizer)		
		SAEFVIC* Feb 22 Australia	Any; Y	242		
		TGA* Aug 21 Australia	Any; Y	172‡		
		eHRSS Oct 18 Hong Kong	Any; Y	390.2 (Pfizer)		

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Sex	Age	Studies (data source and date) Country *passive surveillance	Risk interval; Confirmed cases (Y/N)	Incidence rates per million doses after dose 2 of either mRNA vaccine unless otherwise stated *weighted average across age groups ‡weighted average across products †excess incidence	Conclusions	Certainty about conclusions using GRADE
		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 29 and 157 cases per million.	**Moderate**[a]
		COVaxON* Sep 4 Canada	7 d; Y	147.2‡ (18-24y)		
		SNDS Oct 31 France	7 d; Y	61.9†‡ (18-24y)		
		IDF Mar 7 Israel	7d; Y	50.7 (18-24y; Pfizer)		
		Moderna global safety database* Feb 15 Worldwide	7 d; Y	42.3 (18-24y; Moderna)		
		VAERS* May 26 US	7 d; Y	29.0*		
		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*		
		TGA* Aug 21 Australia	Any; Y	156.5‡		
		BNPV* Sep 30 France	Any; Y	72*‡		
	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 19 and 104 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* Feb 15 Worldwide	7 d; Y	23.0* (Moderna)		
		COVaxON* Sep 4 Canada	7 d; Y	82.2*‡		
		SNDS Oct 31 France	7 d; Y	34.3*†‡		
		VAERS* Jan 13 US	7 d; Y	20.7* (Moderna)		
		VAERS* May 26 US	7 d; Y	19.2*		
		Nordic cohort Oct 5	7d; Y	39.4*†‡		

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Sex	Age	Studies (data source and date) Country *passive surveillance	Risk interval; Confirmed cases (Y/N)	Incidence rates per million doses after dose 2 of either mRNA vaccine unless otherwise stated *weighted average across age groups ‡weighted average across products †excess incidence	Conclusions	Certainty about conclusions using GRADE
		Nordic countries				
		Nordic cohort Oct 5 Nordic countries	28d; Y	47.7*†‡		
		TGA* Aug 21 Australia	Any; Y	103.5*‡		
F	5-11y	VAERS* May 26	7 d; Y	0.7 (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 (range: 0 to 3).	**Low**
		PCORnet Jan 31 US	7 d; Y	0 events (Pfizer)		
		Moderna global safety database* Feb 15 Worldwide	7 d; Y	0 (Moderna)		
		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)		
		TGA* Aug 21 Australia	Any; Y	0 (Pfizer)		
	12-17y	VAERS* Jun 18a US	Any; Y	12.7 (Pfizer)	Among 12-17 year old females, the incidence of presenting with myocarditis after vaccination with an mRNA may be 1 to 50 cases per million.	**Low**
		COVaxON* Sep 4 Canada	7 d; Y	9.7 (Pfizer)		
		VAERS* May 26 US	7 d; Y	5.5* (Pfizer)		
		eHRSS Oct 18 Hong Kong	Any; Y	49.7 (13.5 to 127.2) (Pfizer)		
		SNDS Oct 31 France	7 d; Y	2.6† (Pfizer)		
		PCORnet Jan 31 US	7 d; Y	11		
		Moderna global safety database* Feb 15 Worldwide	7 d; Y	1.3 (Moderna)		
		PCORnet Jan 31 US	21 d; Y	32		
		Israeli MOH Oct 20 Israel	30 d; Y	6.9 (Pfizer)		
		SAEFVIC* Feb 22 Australia	Any; Y	43		
		TGA* Aug 21 Australia	Any; Y	39‡		

Funded by the Canadian Institutes of Health Research (CIHR) and PHAC.

Sex	Age	Studies (data source and date) Country *passive surveillance	Risk interval; Confirmed cases (Y/N)	Incidence rates per million doses after dose 2 of either mRNA vaccine unless otherwise stated *weighted average across age groups ‡weighted average across products †excess incidence	Conclusions	Certainty about conclusions using GRADE
		Nordic cohort Oct 5 Nordic countries	7 d; Y	1.5*†‡		
		Nordic cohort Oct 5 Nordic countries	28 d; Y	10.9*†‡		
	18-29y	VAERS* May 26 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 4 to 37 cases per million.	**Low**
		VAERS* Jan 13 US	7 d; Y	5.6* (Moderna)		
		TGA* Aug 21 Australia	Any; Y	37‡		
		Moderna global safety database* Feb 15 Worldwide	7 d; Y	3.8 (18-24y; Moderna)		
		COVaxON* Sep 4 Canada	7 d; Y	34.6‡		
		SNDS Oct 31 France	7 d; Y	11.4†‡ (18-24y)		
		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 (range: 2.3 to 23).	**Low**
		Moderna global safety database* Feb 15 Worldwide	7 d; Y	2.3* (Moderna)		
		VAERS* May 26 US	7 d; Y	2.5*		
		SNDS Oct 31 France	7 d; Y	5.7*†‡		
		Nordic cohort Oct 5 Nordic countries	7 d; Y	3.3*†‡		
		Nordic cohort Oct 5 Nordic countries	28 d; Y	4.0*†‡		
		TGA* Aug 21 Australia	Any; Y	22.5*‡		
Myocarditis (after dose 3)						
M	5-11y	VAERS* May 26 US	7 d; Y	0	Among 5-11 year old males, we are uncertain about the incidence of	**Very Low** [b,c]

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Sex	Age	Studies (data source and date) Country *passive surveillance	Risk interval; Confirmed cases (Y/N)	Incidence rates per million doses after dose 2 of either mRNA vaccine unless otherwise stated *weighted average across age groups ‡weighted average across products †excess incidence	Conclusions	Certainty about conclusions using GRADE
					myocarditis after vaccination with a third dose of an mRNA vaccine.	
	12-17y	Moderna global safety database* Feb 15 Worldwide	7 d; Y	0 (Moderna)	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 (range: 0 to 18.8).	**Low**
		Israeli MOH Oct 10 Israel	30 d; Y	17.3*		
		VAERS* May 26 US	7 d; Y	18.8* (Pfizer)		
		VAERS* Feb 20 US	Any; Y	11.4		
	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 (range: 4 to 112.5).	**Very Low** [b,c]
		Moderna global safety database* Feb 15 Worldwide	7 d; Y	4.0 (18-24y; Moderna)		
		IDF Sep 30 Israel	7 d; Y	64 (18-24 y)		
		VAERS* May 26 US	7 d; Y	6.1*		
		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	1.4‡	Among 30-39 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 (range: 1 to 4.2).	**Low**
		VAERS* May 26	7 d; Y	4.2*		
		Moderna global safety database* Feb 15 Worldwide	7 d; Y	3.3 (25-39y; Moderna)		
	≥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 (range: 0 to 4.1).	**Low**
		NIMS/NHS Nov 15 UK	7 d; Y	0†‡		
		Israeli MOH Oct 10 Israel	30 d; Y	4.1 (≥30y)		
F	5-11y	VAERS* May 26	7 d; Y	0	Among 5-11 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]
	12-17y	Israeli MOH Oct 10 Israel	30 d; Y	0 events* (Pfizer)	Among 12-17 year old females, the incidence of myocarditis after vaccination	**Low**

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Sex	Age	Studies (data source and date) Country *passive surveillance	Risk interval; Confirmed cases (Y/N)	Incidence rates per million doses after dose 2 of either mRNA vaccine unless otherwise stated *weighted average across age groups ‡weighted average across products †excess incidence	Conclusions	Certainty about conclusions using GRADE
		VAERS* May 26 US	7 d; Y	0*	with a third dose of an mRNA vaccine may be fewer than 20 cases per million (range: 0 to 0).	
		Moderna global safety database* Feb 15 Worldwide	7 d; Y	0 (Moderna)		
	18-29y	VAERS* Feb 6 US	6 d; 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 (range: 0 to 1.2)	**Low**
		VAERS* May 26 US	7 d; Y	1.2*		
		Moderna global safety database* Feb 15 Worldwide	7 d; Y	0.6 (18-24y; Moderna)		
		Israeli MOH Oct 10 Israel	30 d; Y	0 events*		
	30-39y	VAERS* Feb 6 US	6 d; Y	~1‡	Among 30-39 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 (range: 0.6 to 1.4).	Low
		VAERS* May 26 US	7 d; Y	0.6		
		Moderna global safety database* Feb 15 Worldwide	7 d; Y	1.4 (25-39y; Moderna)		
	≥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 (range: 0 to 41.5).	**Low**[2]
			7 d; Y	0†‡		
		Mayo Clinic Oct 17 US	14 d; Y	41.5‡		
		Israeli MOH Oct 10	30 d; Y	0 events/1,542,142 doses (≥30y)		
Myocarditis (after dose 4)						
Both	≥12y	VAERS Mar 28 US	Any; Y	0/518,113 doses	In people ≥12 years old, we are uncertain about the incidence of myocarditis after vaccination with a fourth dose of an mRNA vaccine.	**Very Low** [b,c]
Pericarditis (after dose 2)						
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]
	12-17y	Nordic cohort Oct 5 Nordic countries	28 d; Y	8.4*†‡	Among 12-17 year old males, the incidence of pericarditis after vaccination with an mRNA vaccine may be fewer than 20 cases per million (range: 6.8 to 8.4).	Low
		SNDS Oct 31 France	7 d; Y	6.8† (Pfizer)		
	18-24y	Nordic cohort Oct 5 Nordic countries	28 d; Y	21.0*†‡ (16-24y)	Among 18-24 year old males, we are uncertain about the incidence of pericarditis	**Very Low** [b]

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Sex	Age	Studies (data source and date) Country *passive surveillance	Risk interval; Confirmed cases (Y/N)	Incidence rates per million doses after dose 2 of either mRNA vaccine unless otherwise stated *weighted average across age groups ‡weighted average across products †excess incidence	Conclusions	Certainty about conclusions using GRADE
		SNDS Oct 31 France	7 d; Y	12.9†‡	after vaccination with an mRNA vaccine(range: 12.9 to 21)	
	25-39y	Nordic cohort Oct 5 Nordic countries	28 d; Y	13.9†‡	Among 25-39 year old males, the incidence of pericarditis after vaccination with an mRNA vaccine may be fewer than 20 cases per million (range: 3.7 to 13.9).	Low
		SNDS Oct 31 France	7 d; Y	3.7*†‡		
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]
	12-17y	Nordic cohort Oct 5 Nordic countries	28 d; Y	3.2 *†‡	Among 12-17 year old females, the incidence of pericarditis after vaccination with an mRNA vaccine may be fewer than 20 cases per million (range: 3.2 to 6.8).	Low
		SNDS Oct 31 France	7 d; Y	6.8† (Pfizer)		
	18-24y	Nordic cohort Oct 5 Nordic countries	28 d; Y	8.1†‡ (16-24)	Among 18-24 year old females, the incidence of pericarditis after vaccination with an mRNA vaccine may be fewer than 20 cases per million (range: 8.1 to 13.5).	Low
		SNDS Oct 31 France	7 d; Y	13.5† (Pfizer)		
	25-39y	Nordic cohort Oct 5 Nordic countries	28 d; Y	5.4†‡	Among 25-39 year old females, we are uncertain about the incidence of pericarditis after vaccination with an mRNA vaccine (range: 5.4 to 22.4).	Very Low [b,c]
		SNDS Oct 31 France	7 d; Y	22.4*†‡		

Green text = evidence identified by Aug 2022 update.

Purple text indicates updated evidence from previously included pre-prints that have been peer-reviewed and published since their inclusion.

BNPV - Base Nationale de Pharmacovigilance is the French national spontaneous reporting database.

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.

HSA – Health Science Authority of Singapore

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.

SAEFVIC - Surveillance of Adverse Events Following Vaccination in the Community (SAEFVIC) is the state-wide vaccine safety service for the Australian state of Victoria. SAEFVIC comprises central reporting enhanced passive and active surveillance systems integrated with clinical services and has been operating since 2007.

SNDS - French National Health Data System (Système National des Données de Santé)

TGA - The Therapeutic Goods Administration is the medicine and therapeutic regulatory agency of the Australian Government. As part of the Department of Health, the TGA regulates the quality, supply and advertising of medicines, pathology devices, medical devices, blood products and most other therapeutics.

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VAERS – Vaccine Adverse Events Reporting System is a passive surveillance system inr 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 that occur after receipt of any COVID-19 vaccine. 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

VSD - Vaccine Safety Datalink is a collaborative project between CDC's Immunization Safety Office and nine health care organizations to monitor safety of vaccines and conduct studies about rare and serious adverse events following immunization. VSD uses electronic health data from each participating site including the kind of vaccine given to each patient, date of vaccination, and other vaccinations given on the same day, and information on medical illnesses that have been diagnosed at doctors' offices, urgent care visits, emergency department visits, and hospital stays.

Notes:

[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

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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 aOR = adjusted odds ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
Myocarditis							
Moderna vs Pfizer (ref), dose 2							
M	12-17y	TGA* Aug 21 Australia	NR; Y	Moderna: 213 Pfizer:131		Among 12-17 year old males, there may be a higher incidence of myocarditis following vaccination with Moderna compared with Pfizer.	**Low** [a,b]
	18-29y	VAERS* Oct 6 US	7 d; Y	Moderna: 23.9* Pfizer: 26.0*		Among 18-29 year old males, there is probably at least 2-3 times higher incidence of myocarditis following vaccination with Moderna compared with Pfizer.	**Moderate** [c,2]
		SNDS Oct 31 France	7 d; Y	Moderna: 146.3* Pfizer:40.4*	Ratio of aORs: 3.19		
		TGA* Aug 21 Australia	NR; Y	Moderna: 223 Pfizer: 90			
		BNPV* Sep 30 France	NR; Y	Moderna: 110.3* Pfizer: 33.0*			
		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 at least a 2-3 times higher incidence of myocarditis following vaccination with Moderna compared with Pfizer.	**Moderate** [c]
		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*			
		SNDS Oct 31 France	7 d; Y	Moderna: 105.6* Pfizer: 26.6*	Ratio of aORs: 4.65		
		Nordic cohort Oct 5	28 d; Y	Moderna: 140.3* Pfizer:31.1*			
		TGA* Aug 21 Australia	NR; Y	Moderna: 144.4* Pfizer: 62.7*			
		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 is probably a higher	**Moderate** [a]

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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 aOR = adjusted odds ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
		SNDS Oct 31 France	7 d; Y	Moderna: 64.5 Pfizer: 10.3	Ratio of aORs:7.89	incidence of myocarditis following vaccination with Moderna compared with Pfizer.	
		TGA* Aug 21 Australia	NR; Y	Moderna: 50 Pfizer: 30			
	≥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,c]
		NIMS Nov 15[1] UK	7 d; Y	Moderna: 0 events Pfizer: IRR = 0.65 (0.27, 1.59)			
		NIMS Nov 15[1] 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			
		TGA* Aug 21 Australia	NR; Y	Moderna: 9* Pfizer: 6.25*			
F	12-17y	TGA* Aug 21 Australia	NR; Y	Moderna: 5 Pfizer: 28		Among 12-17 year-old females, we are uncertain about any difference in incidence of myocarditis following vaccination with Moderna compared with Pfizer.	**Very Low** [A,b]
	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 at least a 2-3 times higher incidence of myocarditis following vaccination with Moderna compared with Pfizer.	**Moderate** [c]
		VAERS* Oct 6 US	7 d; Y	Moderna: 5.5* Pfizer: 2.0*			
		SNDS Oct 31 France	7 d; Y	Moderna: 37.4* Pfizer: 5.6*	Ratio of aORs:3.43		
		TGA* Aug 21 Australia	NR; Y	Moderna: 48 Pfizer: 26			
	18-39y	VAERS* Oct 6 US	7 d; Y	Moderna: 3.1* Pfizer: 1.4*		Among 18-39 year old females, there is probably at least a 2-3 times 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*			

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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 aOR = adjusted odds ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
		SNDS Oct 31 France	7 d; Y	Moderna: 19.7* Pfizer: 4.0*	Ratio of aORs:2.65		
		Nordic cohort Oct 5	28 d; Y	Moderna: 10.4* Pfizer: 5.9*			
		TGA* Aug 21 Australia	NR; Y	Moderna: 26.2* Pfizer: 18.7*			
	30-39y	VAERS* Oct 6 US	7 d; Y	Moderna: 0.4 Pfizer: 0.7		Among 30-39 year old females, we are uncertain about the difference in incidence of myocarditis after vaccination with Moderna compared with Pfizer	Very Low [a,b,c]
		SNDS Oct 31 France	7 d; Y	Moderna: 2.7 Pfizer: 2.1	Ratio of aORs: 0.35		
		TGA* Aug 21 Australia	NR; Y	Moderna: 0 Pfizer: 10			
	≥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,c]
		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			
		TGA* Aug 21 Australia	NR; Y	Moderna: 17.5* Pfizer: 7*			
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,b]
	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,c]

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Sex	Age	Data source & date Country *passive surveillance	Risk interval; confirmed cases (Y/N)	Incidence/reporting rate per million doses (95% CI) *weighted average across multiple age groups[3]	Relative measures (95% CI) aRR = adjusted risk ratio aOR = adjusted odds ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
	≥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,c]
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,c]
	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,c]
	≥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,c]
Heterologous vs Homologous (ref) dose 2							
M	16-24y	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,c]
		Nordic cohort Oct 5	28 d; Y	Mod-Mod: 198.3 Pfiz-Mod: 283.3 Pfiz-Pfiz: 68.3			
		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)			

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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 aOR = adjusted odds ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
	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,c]
		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,c]
		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,c]
		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,c]
		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,c]
		Nordic cohort Oct 5	28 d; Y	Mod-Mod: 8.6 Pfiz-Mod: 51.1 Pfiz-Pfiz: 4.0			
Dose interval, dose 1 to dose 2							

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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 aOR = adjusted odds ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
Both sexes	12-29y	SNDS Jan 31 France	7d; Y	Pfizer <27 d: 11 (9.0-14) 27-39 d: 8.7 (5.7-13) >39d: 5 (3.1-8.0) Moderna <27 d: 82 (34-200) 27-39 d: 25 (12-55) >39 d: 39 (17-86)		Among person 12-29 years old, incidence of myocarditis after dose 2 of an mRNA vaccine may be lower when administered ≥27 days compared with <27 days after dose 1.	**Low** [a,d]
	≥30y	SNDS Jan 31 France	7d; Y	Pfizer <27d: 4.8 (3.1-7.3) 27-39d: 0.77 (0.36-1.6) >39d: 1.9 (1.1-3.2) Moderna <29d: 31 (13-73) 29-39d: 9.9 (4.9-20) >39d: 4.8 (2.4-9.6)		Among persons ≥30 years old, incidence of myocarditis after dose 2 of an mRNA vaccine may be lower when administered ≥27 days compared with <27 days after dose 1.	**Low** [a,d]
Dose interval, dose 2 to dose 3, Pfizer							
Both sexes	12-29y	SNDS Jan 31 France	7d; Y	Pfizer <170 d: 6 (3.3-11) 170-193 d: 3.9 (1.8-8.5) >193 d: 3.3 (0.86-13)		Among person 12-29 years old, incidence of myocarditis after dose 3 of Pfizer may be lower when administered ≥170 days after dose 2 compared with <170 days after dose 2.	**Low** [a,d]
	≥30y	SNDS Jan 31 France	7d; Y	Pfizer <170 d: 2.1 (0.90-4.7) 170-193 d: 3.4 (1.8-6.6) >193 d: 1.9 (0.91-3.9)		Among persons ≥30 years old, we are uncertain about whether incidence of myocarditis after dose 3 of Pfizer may be different with different dose timing.	**Very Low** [A,d]
Dose interval, dose 2 to dose 3, Moderna							
Both sexes	≥30y	SNDS Jan 31 France	7d; Y	Moderna <170 d: 6.5 (3.3-13) 170-193 d: 3 (1.2-8.0) >193 d: 2.6 (1.0-6.6)		Among persons ≥30 years old, incidence of myocarditis after dose 3 of Moderna may be lower when administered ≥170 days after dose 2 compared with <170 days after dose 2.	**Low** [a,d]
Clinical comorbidities – With vs without (ref) positive COVID-19 test before vaccination, dose 1							

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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 aOR = adjusted odds 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 whether the incidence of myocarditis differs after vaccination with dose 1 of an mRNA vaccine compared to those without a history of COVID-19 infection.	**Very Low** [a,c,d]
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 risk of myocarditis after vaccination with dose 2 of an mRNA vaccine compared to those without a history of COVID-19 infection.	**Very Low** [A,d]
		ISS/AIFA Sep 30 Italy	21 d; Y		cRR=1.83 (myo- or pericarditis)		
Myocarditis/pericarditis							
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,d]
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,d]
Clinical comorbidities – Cardiovascular conditions							

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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 aOR = adjusted odds ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
Both sexes	All ages	ISS/AIFA Sep 30 Italy	21 d; Y	Cardiovascular and cerebrovascular diseases *Includes: all diseases of the circulatory system; excluding hypertensive diseases* Hypertension	cRR=33.54 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,d]
Clinical comorbidities – Hematologic conditions							
Both sexes	All ages	ISS/AIFA Sep 30 Italy	21 d; Y	Hematologic dx *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*)	cRR=2.34	Among individuals with hematologic conditions, there may be a higher incidence of myocarditis or pericarditis after mRNA vaccination compared to those without.	**Low** [a,d]
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,c,d]
Clinical comorbidities –Infection (other than COVID-19)							
Both sexes	All ages	ISS/AIFA Sep 30 Italy	21 d; Y	Infection in last 12 mos *Includes: Urinary tract infection, site not specified; Tuberculosis; Diseases due to other mycobacteria; Cytomegaloviral disease; chickenpox; Herpes zoster; Herpes simplex; Pneumocystosis; Cryptococcosis*	cRR=2.43	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,d]
Clinical comorbidities – Pulmonary conditions							
Both sexes	All ages	ISS/AIFA Sep 30 Italy	21 d; Y	COPD *Includes: bronchitis, not specified as acute or chronic; emphysema; Asthma; Bronchiectasis; Extrinsic allergic alveolitis* Chronic Pulmonary Disease *Includes: pneumonia and influenza; Chronic bronchitis*; *Extrinsic allergic alveolitis; Other diseases of lung*	cRR=1.29 cRR=10.32	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,d]

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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 aOR = adjusted odds ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
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 to individuals without rheumatic conditions.	**Low** [c,d]
		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*			
Race - Black vs white (ref)							
Both sexes	≥18y	VHA Oct 5 US	Any; Y	Black: 340 White: 360		Among adults, there may not be higher incidence of myocarditis or pericarditis after mRNA vaccination in Black individuals compared to white individuals.	**Low** [a,d]
Pericarditis							
Moderna vs Pfizer (ref), dose 2							
M	18-29	SNDS Oct 31 France	7 d; Y	Moderna: 26.6* Pfizer: 9.0*	Ratio of aORs: 2.93*	Among 18-29 year old males, there is probably a higher incidence of pericarditis after vaccination with Moderna compared with Pfizer	**Moderate** [a]
	18-39y	Nordic cohort Oct 5	28 d; Y	Moderna: 40.3* Pfizer: 16.5*		Among 18-39 year old males, there is probably at least 2 times higher incidence of pericarditis after vaccination with Moderna compared with Pfizer.	**Moderate** [c;4]
		SNDS Oct 31 France	7 d; Y	Moderna: 17.4* Pfizer: 7.4*			
	30-39y	SNDS Oct 31 France	7 d; Y	Moderna: 8.1 Pfizer: 5.4	Ratio of aORs: 1.5	Among 30-39 year old males, there is probably a higher incidence of pericarditis after vaccination with Moderna compared with Pfizer	**Moderate** [a]
	≥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]

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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 aOR = adjusted odds ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
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]
	30-39y	SNDS Oct 31 France	7 d; Y	Moderna: 13.7 Pfizer: 3.7	Ratio of aORs: 10	Among 30-39 year old females, there is probably a higher incidence of pericarditis after vaccination with Moderna compared with Pfizer	**Moderate** [a]
	≥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 pericarditis after vaccination with Moderna compared with Pfizer.	**Moderate** [a]
Heterologous vs Homologous (ref), dose 2							
M	16-24y	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,c]
	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 whether the incidence of pericarditis differs after vaccination with a heterologous dose 2 of Moderna compared with homologous Moderna or Pfizer.	**Very Low** [A,c]
	≥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 whether the incidence of pericarditis differs after vaccination with a heterologous dose 2 of Moderna compared with homologous Moderna or Pfizer.	**Very Low** [A,c]
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 whether the incidence of pericarditis differs after vaccination with a heterologous dose 2 of Moderna compared with homologous Moderna or Pfizer.	**Very Low** [A,c]

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Sex	Age	Data source & date Country *passive surveillance	Risk interval; confirmed cases (Y/N)	Incidence/reporting rate per million doses (95% CI) *weighted average across multiple age groups[3]	Relative measures (95% CI) aRR = adjusted risk ratio aOR = adjusted odds ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
	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 whether the incidence of pericarditis differs after vaccination with a heterologous dose 2 of Moderna compared with homologous Moderna or Pfizer.	**Very Low** [A,c]
	≥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 whether the incidence of pericarditis differs after vaccination with a heterologous dose 2 of Moderna compared with homologous Moderna or Pfizer.	**Very Low** [A,c]

Green text = evidence identified by Aug 2022 update

BNPV - Base Nationale de Pharmacovigilance is the French national spontaneous reporting database for drug products including vaccines.

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.

EULAR COVAX- The European Alliance of Associations for Rheumatology Coronavirus Vaccine is a 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.

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.

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.

SAEFVIC - Surveillance of Adverse Events Following Vaccination in the Community (SAEFVIC) is the state-wide vaccine safety service for the Australian state of Victoria. SAEFVIC comprises central reporting enhanced passive and active surveillance systems integrated with clinical services.

SNDS - the French administrative health care database covers around 99% of the French population and includes anonymized data on socio-demographics, medical characteristics, ambulatory care, hospitalizations, diagnosis, drugs and procedures, mortality, and costs.

VHA - Veteran's Health Administration is a nationalized healthcare service in the United States that provides healthcare and healthcare-adjacent services to Veterans through the administration and operation of healthcare facilities including inpatient, outpatient, and care home facilities.

VAERS – Vaccine Adverse Events Reporting System is a passive surveillance system inr 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 that occur after receipt of any COVID-19 vaccine. 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

VSD - Vaccine Safety Datalink is a collaborative project between CDC's Immunization Safety Office and nine health care organizations to monitor safety of vaccines and conduct studies about rare and serious adverse events following immunization. VSD uses electronic health data from each participating site including the kind of vaccine given to each patient, date of vaccination, and other vaccinations given on the same day, and information on medical illnesses that have been diagnosed at doctors' offices, urgent care visits, emergency department visits, and hospital stays.

Notes:

[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.

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[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. Upper-case superscripts indicate rating down twice for that domain.

[a] Rated down for inconsistency or due to only one study providing estimates
[b] Rated down for risk of bias from reliance on passive surveillance/spontaneous reporting
[c] Rated down for imprecision for large range over conclusion threshold, small sample size (<10,000 per group), and/or very low event rate.
[d] 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.

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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[40] (US)	Hause 2022[27] (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

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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
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

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 4a. Case Series of Myocarditis and Myopericarditis after mRNA Vaccination reporting longer-term outcomes (at least 4 weeks of follow-up), from previous updates.

Case series	Chelala 2021[54] (US)	Patel 2021[55] (US)	Klein 2022[35] (US)	Amir 2022[48] (Israel)	Manfredi[50] (Italy)	Rosner 2022[52] (US)	Puchalski 2022[51] (Poland)	Schauer[53] 2022 (US)	Mevorach[31] 2022 (Israel)	Kracalik 2022[49] (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, %	5 (100%)	9 (100%)	23 (53%)	15 (100%)	4 (67%)	6 (100%)	5 (100%)	0%	13 (100%)	360 (100%)
Pericarditis, %	0%	0%	2 (5%)	0%	0%	0%	0%	0%	0%	0%
Myopericarditis, %	0%	0%	18 (42%)	0%	2 (33%)	0%	0%	16 (100%)	0%	0%
Male, %	5 (100%)	9 (100%)	37 (86%)	15 (100%)	4 (67%)	6 (100%)	5 (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

Funded by the Canadian Institutes of Health Research (CIHR) and PHAC.

Case series	Chelala 2021[54] (US)	Patel 2021[55] (US)	Klein 2022[35] (US)	Amir 2022[48] (Israel)	Manfredi[50] (Italy)	Rosner 2022[52] (US)	Puchalski 2022[51] (Poland)	Schauer[53] 2022 (US)	Mevorach[31] 2022 (Israel)	Kracalik 2022[49] (US)
% Patients in ICU	NR	2 (22%)	11 (26%)	7 (47%)	NR	NR	NR	0%	0%	NR
% Hospitalized	5 (100%)	9 (100%)	28 (65%)	15 (100%)	6 (100%)	6 (100%)	5 (100%)	16 (100%)	13 (100%)	324 (90%)
% Patients presenting after dose 2	5 (100%)	8 (89%)	NR	14 (93%)	6 (100%)	6 (100%) (other presentation after single dose J&J)	2 (40%)	16 (100%)	12 (93%)	307 (85%)
% 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%	NR	NR	0%	NR	0% (9/13 tested)	NR
% Patients with COVID nucleocapsid antibody present (% of tested)	NR	NR	NR	0%	NR	NR	NR	NR	NR	NR
% Patients with SARS-CoV-2 spike antibody	NR	NR	NR	0%	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

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Case series	Chelala 2021[54] (US)	Patel 2021[55] (US)	Klein 2022[35] (US)	Amir 2022[48] (Israel)	Manfredi[50] (Italy)	Rosner 2022[52] (US)	Puchalski 2022[51] (Poland)	Schauer[53] 2022 (US)	Mevorach[31] 2022 (Israel)	Kracalik 2022[49] (US)
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 20% = sinus bradycardia	33% = normal 67% = repolarization abnormalities	NR	11 (73%) = ST changes 1 (7%) = borderline ST changes 2 (13%) = normal	no significant ECG abnormalities were found at presentation	3 (50%) = ST segment elevation 1 (17%) = PR depression	5 (100%) ST elevation 1 (20%) ST depression	10 (63%) = abnormal, commonly diffuse ST segment elevation	6 (46%,all tested): 5 (395) ST elevation 2 (15%) diffuse 3 (23%) nondiffuse 2 (15%) T-wave change	NR

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Case series	Chelala 2021[54] (US)	Patel 2021[55] (US)	Klein 2022[35] (US)	Amir 2022[48] (Israel)	Manfredi[50] (Italy)	Rosner 2022[52] (US)	Puchalski 2022[51] (Poland)	Schauer[53] 2022 (US)	Mevorach[31] 2022 (Israel)	Kracalik 2022[49] (US)
% 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

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Case series	Chelala 2021[54] (US)	Patel 2021[55] (US)	Klein 2022[35] (US)	Amir 2022[48] (Israel)	Manfredi[50] (Italy)	Rosner 2022[52] (US)	Puchalski 2022[51] (Poland)	Schauer[53] 2022 (US)	Mevorach[31] 2022 (Israel)	Kracalik 2022[49] (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	2 (40%)	NR	2 (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

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Case series	Chelala 2021[54] (US)	Patel 2021[55] (US)	Klein 2022[35] (US)	Amir 2022[48] (Israel)	Manfredi[50] (Italy)	Rosner 2022[52] (US)	Puchalski 2022[51] (Poland)	Schauer[53] 2022 (US)	Mevorach[31] 2022 (Israel)	Kracalik 2022[49] (US)
% 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
% 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

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; LGE = late gadolinium enhancement; **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
;

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Table 4b. Series of Myocarditis and Myopericarditis after mRNA Vaccination reporting longer-term outcomes (at least 4 weeks of follow-up): new studies from August 2022 search.

Case series	Alhussein 2022[12] (Canada)	Ahmed 2022[11] (US)	Hadley 2022[14] (US)	Patel, Y 2022[17] (US)	Montarello 2022[15] (Australia)	Cheng 2022[2] (Australia)	Fronza 2022[13] (Canada)	Pareek 2022[16] (US)	Shimabukuro[6] 2022 (US)
Date of cases last updated	01 Dec 2021	26 Jan 2022 (pub received)	01 July 2021	01 Sept 2021	01 March 2022	22 Feb 2022	01 Nov 2021	24 Sept 2021 (pub received)	19 July 2022
Cases, n	20	6	15	14	21	70 (extra 5 cases considered to have alternative cause for myocarditis; ** indicates out of 75)	13 (of 21, referred for MRI at follow-up)	10	1321
Confirmed cases	High clinical suspicion based upon the European Society of Cardiology Diagnostic Criteria; CMR-based diagnostic criteria by the updated Lake Louise Criteria; all within 10 days of vaccination	Lake Louise Criteria (83% undergoing cardiac MRI)	Centers for Disease Control and Prevention case definition (with elevated troponin level and frequently abnormal ECG)	Clinical presentation (typical chest pain symptoms, electrocardiography findings, and elevated cardiac biomarkers) and presence of Lake Louise criteria on T1- and/or T2-weighted cardiac MRI studies when available	NR (all hospitalized)	Brighton Collaboration Criteria	Clinical presentation and diagnostic testing criteria of the European Society of Cardiology, and revised Lake Louise criteria for MRI	NR (all hospitalized with MRI findings)	Centers for Disease Control and Prevention case definition
Case source	Single centre in Alberta	Single centre in Kentucky	Single centre in Boston, Massachusetts	Single centre in East Providence, RI	Central Adelaide Local Health Network	Surveillance of Adverse Events Following Vaccination in the Community in Victoria	Tertiary hospital network in Ontario	Single centre in New Haven, CT	VAERS
Myocarditis, %	20 (100%)	6 (100%)	15 (100%)	14 (100%)	21 (100%)	44 (59%)**	13 (100%)	3 (30%)	1321 (100%) (or myopericarditis)
Pericarditis, %	0	0	0	0	0	0	0	0	0
Myopericarditis, %	0	0	0	0	0	31 (41%)**	0	7 (70%)	NR
Male, %	17 (85%)	6 (100%)	14 (93%)	14 (100%)	20 (93%)	62 (82%)	10 (77%)	9 (90%)	960 (73%)
Median age (range), y Ages included	23 (IQR 20 – 29) ≥18	16 (IQR 14 – 18) 12 - 20	15 (12 – 18) < 19	19 (IQR 16 – 24) NR	Mean 26 (SD 8) NR	NR 12 - 17	Mean 33 (SD 14) ≥18	19 (16 – 38) NR	28 (IQR 21-42) ≥18
Vaccine type, n	6 (30%) = BNT162b2 (Pfizer) 14 (70%) = mRNA-1273 (Moderna)	6 (100%) = BNT162b2 (Pfizer)	15 (100%) = BNT162b2 (Pfizer)	12 (86%) = BNT162b2 (Pfizer) 2 (14%) = mRNA-1273 (Moderna)	21 (100%) = BNT162b2 (Pfizer)	63 (84%) = BNT162b2 (Pfizer) 12 (16%) = mRNA-1273 (Moderna)**	4 (31%) = BNT162b2 (Pfizer) 9 (69%) = mRNA-1273 (Moderna)	9 (90%) = BNT162b2 (Pfizer) 1 (10%) = mRNA-1273 (Moderna)	1321 (100%) = mRNA
% Patients in ICU	3 (15%)	NR	0	3 (21%)	NR	0	0	NR	NR
% Hospitalized	18 (90%)	6 (100%)	15 (100%)	14 (100%)	21 (100%)	51 (77%)	6 (46%)	10 (100%)	NR
% Patients presenting after second vaccination	16 (80%)	6 (100%)	14 (93%)	14 (100%)	19 (91%)	61 (81%)	NR	NR	962 (73%) (102 [7.7%] after 3rd dose)
% Patients with prior COVID-19 history	4 (20%)	1 (17%)	0	0	NR	NR	NR	NR	NR

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Case series	Alhussein 2022[12] (Canada)	Ahmed 2022[11] (US)	Hadley 2022[14] (US)	Patel, Y 2022[17] (US)	Montarello 2022[15] (Australia)	Cheng 2022[2] (Australia)	Fronza 2022[13] (Canada)	Pareek 2022[16] (US)	Shimabukuro[6] 2022 (US)
% Patients COVID-19 polymerase chain reaction positive	0	NR	NR	NR	NR	NR	NR	NR	NR
% Patients with COVID nucleocapsid antibody present (% of tested)	NR	NR	1 (7%)	NR	NR	NR	NR	NR	NR
% Patients with SARS-CoV-2 spike antibody	NR	1 (17%)	NR	NR	NR	NR	NR	NR	NR
% Patients with prior myocarditis or pericarditis history	1 (5%) myocarditis	0	NR	NR	NR	NR	NR	NR	NR
Presentation									
Time between last vaccine and symptom onset, median days, (range)	After 2nd dose (80%): within 6 days (2-6) After 1st dose (20%); within 10 days (2-10)	Range 2 – 5 days after 2nd dose	3 (1 – 6)	Mean 3 (SD 0.5) (4 days eligibility criteria)	NR	2 (0 – 49)	NR	Within 14 days	3 (IQR 2-5)
% Patients with chest pain on presentation	19 (95%)	6 (100%)	15 (100%)	NR	21 (100%)	70 (100%)	13 (100%)	10 (100%)	NR
% Patients with other symptoms (eg, myalgia, fatigue, fever)	2 (10%) dyspnea 1 (5%) myalgia 1 (5%) epigastric discomfort	1 (17%) fever	10 (67%) fever 8 (53%) myalgia 6 (40%) headache 6 (40%) fatigue	NR	13 (62%) fever 7 (33%) dyspnea 10 (48%) myalgia	14 (20%) palpitations 21 (30%) dyspnoea 6 (9%) diaphoresis 33 (47%) non-specific symptoms (dizziness, vomiting, fatigue)	NR	3 (30%) myalgia 6 (60%) fever 1 (10%) dyspnea 2 (20%) palpitations	NR
Diagnostic evaluation									
% Patients with troponin elevation (of tested)	20 (100%)	6 (100%)	15 (100%)	Mean 18.9 (SD 17.6) peak serum cardiac troponin I level (ng/mL) (all tested)	Mean 864 (range 72 – 4532) ng/mL (all tested)	138.3 (IQR 57 -315) median fold increase (all tested)	NR	NR	NR
Median time to troponin peak after vaccination, days	NR	NR	NR (0.1-2.3 days after admission)	NR	NR	NR	NR	NR	NR
% Patients with BNP or NT pro BNP elevation (among tested)	Median (IQR) = 576 (211 – 931) peak NT-proBNP (4 tested)	NR	15 (100%)	Mean 55.5 (SD 43.4) BNP level (pg/mL) (8 tested)	Mean 531 (range 52 – 1686) ng/mL (all tested)	NR	NR	NR	NR

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Case series	Alhussein 2022[12] (Canada)	Ahmed 2022[11] (US)	Hadley 2022[14] (US)	Patel, Y 2022[17] (US)	Montarello 2022[15] (Australia)	Cheng 2022[2] (Australia)	Fronza 2022[13] (Canada)	Pareek 2022[16] (US)	Shimabukuro[6] 2022 (US)
% Patients with CRP elevation (among tested)	18 (90%) (all tested)	6 (100%) (all tested)	15 (100%)	Mean 50.6 (SD 41.6) CRP level (mg/L) (11 tested)	Mean 47 (range 2.7 – 160) mg/L (all tested)	NR	NR	NR	NR
% Patients with eosinophilia (among tested)	NR	NR	NR	NR	NR	NR	NR	NR	NR
% Patients with abnormal ECG (among tested)	9 (45%) normal 11 (55%) ST-elevation 4 (20%) PR depression (all tested)	4 (67%) patterns varied with ST-elevations being most common (all tested)	9 (60%) ST elevation	NR	14 (67%) widespread ST segment elevation (all tested) 3 (14%) PR depression (all tested)	49 (70%) (all tested)	NR	NR	NR
% Patients with abnormal cardiac MRI (among tested)	5 of 10 (50%)	5 (100%) extensive LGE (83% tested)	13 (87%); 12 (80% with LGE)	Mean 85.4 (SD 13.5) LVEDVi (mL/m^2) (all tested)	19 (100%) myocardial oedema 18 (95%) LGE predominantly sub-epicardial involving inferolateral segments (19 tested)	33 (92%) (36 tested) 32 (97%) LGE 20 (61%) edema	11 (85%) LGE presence (all tested)	1 (10%) edema 2 (20%) patchy edema 1 (10%) localized edema 2 (20%) thickening and enhancement of pericardium (all tested)	NR
% Patients with abnormal echocardiogram (among tested)	NR	1 (17%) depressed LVEF of 35% (all tested)	NR	NR	6 (26%) LVEF was reduced 1 (5%) extensive myocardial LGE (all tested)	8 (9%) (68 tested)	NR	NR	NR
% Patients with LVEF<50% (among tested)	5 (25%) (all tested)	1 (17%) (all tested)	2 (13%) (all tested)	Mean 59 (SD 3.2) (all tested)	Mean 52 (SD 4.7) (all tested)	NR	Mean 56 (SD 4) LVEF % (all tested)	0 (all tested)	NR
Short-term outcomes									
% Patients with symptoms resolved	20 (100%)	6 (100%)	11 (73%)	NR	NR	NR	NR	NR	NR
Fatalities, n	0	0	0	NR	NR	0	0	0	NR
Median hospitalization length of stay, days (range)	3 (IQR 2 – 3)	3.5 (IQR 3 – 4)	2 (1 – 5)	2 (IQR 1 – 3)	NR	2 (NR)	NR	Range 1 - 8	NR
% Patients treated with medications for myocarditis	19 (95%) colchicine 15 (75%) NSAID 5 (25%) ACEi 4 (20%) beta blocker 1 (5%) spironolactone	6 (100%) ibuprofen	7 (47%) treated with immunoglobulins and methylprednisolone	NR	NR	NR	6 (46%) colchicine 3 (23%) aspirin 3 (23%) ibuprofen	NR	NR
Longer term outcomes									
Number of patients with follow-up data	20 (100%)	6 (100%)	10 (67%)	14 (100%)	8 (38%)	64 (91%)	13 (100%) referred for MRI at follow-up	10 (100%)	Focus on 12-29 year-olds: 398
Mean length clinical follow-up (range), days	Median 111 (IQR 92 – 224)	Median 159 (IQR 46 – 178)	Median 92 (76–119)	NR (6 months for cardiac events)	NR	NR (approximately 30)	Median 100 (IQR 74 – 237)	Median 90 (30-120)	At least 90 days post-myocarditis

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Case series	Alhussein 2022[12] (Canada)	Ahmed 2022[11] (US)	Hadley 2022[14] (US)	Patel, Y 2022[17] (US)	Montarello 2022[15] (Australia)	Cheng 2022[2] (Australia)	Fronza 2022[13] (Canada)	Pareek 2022[16] (US)	Shimabukuro[6] 2022 (US)
% Repeat cardiac MRI	20 (100%)	6 (100%) at median 117 days (IQR 88 – 188)	10 (100%)	NR	8 (100%)	NR	13 (100%)	7 (70%)	NR
Characteristics of repeat cardiac MRI	Significant reductions in LVEDV (end-diastolic volume) and LVESV (end-systolic volume), associated with 3% absolute increase in mean LVEF Mean (SD) = 57.7 (3.48 LVEF, % 18 (90%) patients showed persistence of abnormal LGE (residual fibrosis) although mean fibrosis burden was <5% of LV mass in 85% of cases. Of 5 with ≤50% LVEF at baseline, all recovered to above this threshold.	Significant reduction in LGE burden Normalization of T1 and T2 parameters Patient with LVEF <50% remained	Extracellular volume remained elevated in 1 (10%) and borderline in 3 (30%) 8 (80%) persistent LGE	NR	8 (100%) significant reduction in LGE compared to baseline	NR	3 (13%) LGE resolved 8 (62%) decreased 2 (15%) remained negative LVEF increased and was normal in all at follow-up (56±4% vs. 60±3%)	CMR findings had generally improved, though not resolved completely 6 (86%) no edema 0 LVEF <50%	NR
Symptoms such as chest pain	4 (20%) chest pain	0	2 (20%) chest pain (but with acute Covid-19 infection) 1 (10%) fatigue	NR	NR	32 (50%) symptoms remained 17 (27%) chest pain 15 (23%) fatigue 9 (14%) palpitations 9 (14%) dyspnoea	NR	2 (20%) varying degrees of chest discomfort 8 (80%) asymptomatic	NR
Medical visits following discharge	NR	NR	2 (20%) from chest pain & acute Covid-19	NR	NR	NR	NR	NR	NR
% Continued treatment with medications	4 (20%) extended colchicine and NSAIDs without steroids	NR	NR	NR	NR	NR	NR	NR	NR
% Recovered with no symptoms	NR	6 (100%)	8 (80%)	NR	NR	NR	13 (100%)	NR	4 (1%) no improvement 61 (15%) improved, but not fully recovered 60 (15%) probably fully recovered, awaiting additional information 265 (67%) fully recovered

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Case series	Alhussein 2022[12] (Canada)	Ahmed 2022[11] (US)	Hadley 2022[14] (US)	Patel, Y 2022[17] (US)	Montarello 2022[15] (Australia)	Cheng 2022[2] (Australia)	Fronza 2022[13] (Canada)	Pareek 2022[16] (US)	Shimabukuro[6] 2022 (US)
Other outcomes	No patient experienced major clinical outcomes (i.e. cardiac hospitalization, new-onset heart failure requiring diuretic use, atrial fibrillation, or ventricular arrhythmia).	ECG performed in 5/6 (83%), 4 (80%) normal, 1 (20%) nonspecific early repolarization changes	3 (30%) elevated troponin 10 (100%) BNP and CRP normal LVEF normal in 100%	14 (100%) no cardiac event at 6 months	NR	NR	13 (100%) resolved myocardial edema 13 (100%) asymptomatic with normal troponin levels and no adverse cardiac events at median 159 (IQR 107 – 232) days	NR	Most patients who were reached reported no impact on their quality of life, and most did not report missing school or work

Abbreviations: **BNP** = B-type natriuretic peptide; **CDC** = Centers for Disease Control and Prevention; **CMR** = cardiovascular magnetic resonance imaging; **CRP**: c-reactive protein; **ECG** = echocardiogram; **ICD** = International Classification of Diseases; **ICU** = intensive care unit; **IQR** = interquartile range; **LGE** = late gadolinium enhancement; **LVEF** = left ventricular ejection fraction; **MRI** = magnetic resonance imaging; **NR** = not reported; **NSAID** = non-steroidal anti-inflammatory drugs; **PHAC** = Public Health Agency of Canada; **SD** = standard deviation; **VAERS** = vaccine adverse event reporting system; **yr** = years

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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[74] Tsilingiris et al., 2021[83] Heymans & Cooper, 2021[75] Parra-Lucares et al., 2021[81] Bozkurt et al, 2021[68] Das et al., 2021[71] Boursier, 2021[100] Switzer & Loeb, 2022[23] Verma et al., 2021[84] Gnanenthiran & Limaye 2022[60] Dursun et al. 2022[58] Mormile 2022[63] Frustaci et al. 2022[59] Amemiya et al. 2022[18]	- 4 case reports: Muthukumar, Boursier, Verma, Nguyen -2 case series of authors: Frustaci, Amemiya - 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[74] Tsilingiris et al., 2021[83] D'Angelo et al, 2021[70] Bozkurt et al., 2021[68] Chouchana et al., 2021[69] Gnanenthiran & Limaye 2022[60]	- 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[74] Takeda et al. 2021[82] D'Angelo et al, 2021[70] Bozkurt et al, 2021[68] Kounis et al., 2022 [61]	- 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=7 Kounis et al. 2021a[78] Kounis et al. 2021b[77] Tsilingiris et al., 2021[83] Bozkurt et al., 2021[68] Kounis et al., 2022[61] Al-Ali et al., 2022[56] Carreno et al. 2022[21]	- 4 case reports: Sokolska, Verma, Witberg (1 case with biopsy in series), 1 not cited -1 case series: Warren - 1 cohort study: Patone - 1 experimental study: Carreno	- 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[83] Kadkhoda et al., 2021[76]	- 1 cohort: Patone	None
6	Autoimmunity triggered by molecular mimicry or other mechanism	N=14 Hajra et al., 2021[74] Tsilingiris et al., 2021[83] D'Angelo et al., 2021[70] Heyman & Cooper, 2021[75] Bozkurt et al., 2021[68] Chouchana et al., 2021[69] Switzer & Loeb, 2021[23] Parra-Lucares et al., 2021[81] Ehlrich et al., 2021[72] Gnanenthiran & Limaye, 2022[60] Chin et al., 2022[57] Mormile, 2022[63] Marrama et al., 2022[62] Baumeier et al. 2022[20]	Molecular mimicry: - 2 case reports: D'Angelo, Ammirati, - 2 case series: Larson, Baumeier - 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[101]	None	None
9	Production of anti-idiotype antibodies against immunogenic regions of antigen-specific antibodies	N=1 Tsilingiris et al., 2021[83]	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[68])	N=2 Bozkurt et al., 2021[68] Switzer & Loeb, 2022[23]	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[68]	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[69]	N=3 Chouchana et al., 2021[69] Switzer & Loeb, 2022[23] Seneff et al, 2022[22]	None	- 2 cases: Verma

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Hypothesis		Citations	Direct Empirical Evidence	
			Supporting	Refuting
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[76]	None	None
14	Spike-activated neutrophils (expressing ACE2) augmenting inflammatory response	N=2 Kadkhoda et al., 2021[76] Choi et al., 2021[99]	- 1 case report: Choi	None
15	Hyperviscosity-induced cardiac problem	N=1 Mungmunpuntipantip & Wiwanitkit, 2021[80]	None	None
16	Strenuous exercise induced secretion of proinflammatory IL-6	N=1 Elkazzaz et al., 2022[102]	None	None
17	Oxidative stress reaction	N=1 Dursun et al., 2022[58]	Author's cross sectional study	None
18	Elevated histamine with pericyte induced vasoconstrictions	N=1 Ricke 2022[64]	CDC data on temporal nature of cases	None
19	IL-18-mediated immune responses and cardiotoxicity	N=1 Won et al., 2022[65]	Author's cross sectional study with controls	None
20	SARS-CoV-2 spike glycoprotein injuring cardiac pericytes, which support the capillaries and the cardiomyocytes	N=1 Seneff et al 2022[22]	None	None
21	Exosomes released by macrophages that have taken up the mRNA nanoparticles, and the specific microRNAs found in those exosomes	N=1 Seneff et al 2022[22]	None	None
22	"Spike effect" with Angiotensin II accumulation in the blood without protection (in younger people) by over-expression of some angiotensinases (PRCP, and POP) as developed in older people or those with comorbidities	N=1 Angeli et al. 2022[19]	VAERS data and 1 case series (Simone) about age suscepibiity	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[83] Heymans & Cooper, 2021[75] Bozkurt et al., 2021[68] Chouchana et al., 2021[69] Parra-Lucares et al., 2021[81] Mormile, 2022[63]	Sex hormones: None Underdiagnosis in women: CDC, Bozkurt (unpublished data)	Sex hormones: - 1 cohort: Montgomery Underdiagnosis in women: None

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Hypothesis		Citations	Direct Empirical Evidence	
			Supporting	Refuting
	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[63]	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 vaccinated 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).
Setting	Any setting and country.

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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 S	Sample Size; Demographics; Previous Covid-1 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[29]	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 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)

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Karlstadt 2022 cont.						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) 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)

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NIMS/NHS Nov 15 Dec 1 2020 to Nov 15 2021 England Patone 2021[39]	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 million 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[30]	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)
SNDS Oct 31 May 12 to Oct 31 2021 France Le Vu 2022a[4]	Pfizer or Moderna Dose 1 or Dose 2 Dose timing NR	46,011,449 total doses 49% female 12-17y: 6,745,593 18-24y: 8,344,300 25-29y:5,419,714 30-39y:11,697,444 40-50y: 13,804,398	French residents vaccinated with 1 or 2 doses of an mRNA vaccine.	Myocarditis admitted to hospital Cases identified from hospital records using ICD-10 codes for myocarditis (I40.x, I41.x, and I51.4) and pericarditis (I30.x and I32.x) Risk interval: 1-7d, 8-21d	Excess incidence per 100,00 vaccines was calculated by taking the inverse of the estimated number of doses required for the occurrence of a vaccine-associated case, estimated as the ratio of doses administered to the number of attributable cases. Primary analysis (for KQ2): OR of admission for myocarditis in those exposed to an mRNA vaccine within 7 days prior to admission compared to no mRNA vaccination or	**Excess incidence of myocarditis per million vaccinees, by age and sex for 7days follc vaccination** *(extracted from Figure 3)* BNT162b2 **mRNA-1273** **Total** Sex Age **Dose 2** **Dose 2** **Dose 2** Female 12-17 2.6 (0.3 to 6.6) '- 2.6 (0.3 to 6.6) 18-24 6.4 (2.8 to 11.3) 53.3 (29.5 to 91.3) 11.4 (6.4 to 16.4) 25-29 3.3 (0.6 to 8.9) 13.8 (2.8 to 50.2) 4.5 (0.0 to 9.1) 30-39 1.9 (0.1 to 5.1) ns NE Male 12-17 19.3 (12.1 to 27.1) - 19.3 (12.1 to 27.1) 18-24 47.9 (37.1 to 58.9) 171.1 (123.9 to 230.7) 61.9 (50.5 to 73.3) 25-29 21.4 (12.9 to 32.5) 107.1 (64.3 to 169.6) 31.6 (20.9 to 42.3) 30-39 8.9 (4.6 to 14.6) 64.3 (42.1 to 94.3) 16.3 (10.7 to 21.8) *Crude incidence data also available, see Calculations spreadsheet* *NE=Not estimated* **Excess incidence of pericarditis per million vaccinees, by age and sex for 7days follo vaccination** *(extracted from Figure 3)*

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					vaccination >7days before admission.	<table><tr><th></th><th></th><th>BNT162b2</th><th>mRNA-1273</th><th>Total</th></tr><tr><th>Sex</th><th>Age</th><th>Dose 2</th><th>Dose 2</th><th>Dose 2</th></tr><tr><td>Female</td><td>12-17</td><td>6.786</td><td>ns</td><td>6.786</td></tr><tr><td></td><td>18-24</td><td>13.482</td><td>ns</td><td>13.482</td></tr><tr><td></td><td>25-29</td><td>9.911</td><td>ns</td><td>9.911</td></tr><tr><td></td><td>30-39</td><td>Ns</td><td>28.661</td><td>28.661</td></tr><tr><td></td><td>40-50</td><td>Ns</td><td>20.982</td><td>20.982</td></tr><tr><td>Male</td><td>12-17</td><td>4.018</td><td>-</td><td>4.018</td></tr><tr><td></td><td>18-24</td><td>10.268</td><td>33.482</td><td>12.903</td></tr><tr><td></td><td>25-29</td><td>2.946</td><td>11.339</td><td>3.945</td></tr><tr><td></td><td>30-39</td><td>3.125</td><td>6.518</td><td>3.576</td></tr><tr><td></td><td>40-50</td><td>ns</td><td>ns</td><td>NE</td></tr></table> *Crude incidence data also available, see Calculations spreadsheet* *NE=Not estimated*
IDF Sep 30 Aug 15 to Sep 30 2021 Israel Friedensohn 2022[26]	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[36]	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

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Israeli MOH Oct 20 Jun 2 to Oct 20 2021 Israel Mevorach 2022 [31]	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	Adolescents receiving dose 1 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 [24]	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 Cases 0, Vaccinees 248,881; Dose 2 Cases 2, Vaccinees 222,067; Dose 3 Cases 0, Vaccinees 279 16-19y: Dose 1 Cases 0, Vaccinees 248,881; Dose 2 Cases 2, Vaccinees 222,067; Dose 3 Cases 0, Vaccinees 97,807 20-24y: Dose 1 Cases 1, Vaccinees 263,845; Dose 2 Cases 6, Vaccinees 242,697; Dose 3 Cases 0, Vaccinees 141,910 25-29y: Dose 1 Cases 0, Vaccinees 247,365; Dose 2 Cases 1, Vaccinees 229,189; Dose 3 Cases 0, Vaccinees 130,283 ≥30y: Dose 1 Cases 3, Vaccinees 2,127,538; Dose 2 Cases 7, Vaccinees 2,029,074; Dose 3 Cases 0, Vaccinees 1,542,142 Males 12-15y: Dose 1 Cases 0, Vaccinees 292; Dose 2 Cases 0, Vaccinees 279; Dose 3 Cases 0, Vaccinees 292 16-19y: Dose 1 Cases 3, Vaccinees 254,497; Dose 2 Cases 36, Vaccinees 223,079; Dose 3 Cases 5, Vaccinees 96,238 20-24y: Dose 1 Cases 6, Vaccinees 275,235; Dose 2 Cases 26, Vaccinees 251,672; Dose 3 Cases 5, Vaccinees 139,015 25-29y: Dose 1 Cases 3, Vaccinees 257,713; Dose 2 Cases 20, Vaccinees 239,319; Dose 3 Cases 1, Vaccinees 133,650 ≥30y: Dose 1 Cases 10, Vaccinees 1,983,230; Dose 2 Cases 32, Vaccinees 1,897,067; Dose 3 Cases 6, Vaccinees 1,448,745
Singapore Military Aug 3 Jan 14 to Aug 3 2021 Singapore Tan 2021 [41]	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

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PCORnet Jan 31 Jan 1 2021 to Jan 31 2 United States Block2022[25]	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	Infection Dose 1 Dose 2 Unspecified dose 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 / 21d risk interval Dose 1 / Dose 2 / 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[35]	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 United States Niesen, 2021[38]	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 BNT162b2 and 558 recipients of three doses of mRNA-1273 were under 40 years of age. 33,662 recipients of three doses of BNT162b2 (57% female) and 9,582 recipients of three doses of mRNA-1273 (51% female) were 40 years of age or older.

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US Military Apr 30 Jan 1 to Apr 30 2021 United States Montgomery 2021[37]	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 al cases after dose 2 (n=3) had previous Covid-19	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

Green text = evidence identified by August 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.
SNDS= French National Health Data System (Système National des Données de Santé)
VSD = Vaccine Safety Datalink MOH – Ministry of Health

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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 Interva	Analysis	Results
TGA Aug 21 Up to Aug 21 2022 Australia Therapeutic Goods Administration 2022[8]	Pfizer-BioNTech or Moderna Dose 1 Dose 2	Myocarditis (including myopericarditis) Reports are reviewed reports against an internationally accepted criteria to classify the likelihood of myocarditis. Risk interval NR	Crude reporting rate of likely myocarditis cases per million doses	Table 3. Rates of likely myocarditis cases following mRNA vaccination **Age (years)** / **Moderna Dose 2** / **Pfizer Dose 2** Rate per million doses / Rate per million doses Male / Female / Male / Female **5-11y**: NE / NE / 2 / 0 **12-17**: 213 / 50 / 131 / 28 **18-29**: 223 / 48 / 90 / 26 **30-39**: 50 / 0 / 30 / 10
SAEFVIC Feb 22 Feb 22 2021 to Feb 22 2022 Australia Cheng 2022[2]	Pfizer-BioNTech or Moderna Dose 1 or Dose 2 871 689 doses (782,964 Pfizer and 88,725 Moderna).	Myocarditis or myopericarditis Each case was categorised by at least two independent experts utilising the Brighton Collaboration definition with graded levels of certainty. Risk interval NR	Crude reporting rate per million doses	**Count and reporting rate of cases by sex and dose number** Total / Dose / Count / Rate per million doses (90% CI) **Males,** 12-17y: 1 / 10 / 44 (24 to 75) 2 / 52 / 242 (190 to 305) **Females,** 12-17y: 1 / **4** / **18 (6 to 42)** 2 / **9** / **43 (23 to 75)**
COVaxON and Public Health Case and Contact Management Solution* Jun 1 2020 to Sep 4 2021 Canada Buchan 2022[33 89]	Pfizer-BioNTech or Moderna 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 events Male: 13.1 (1.6-47.3) / 35.5 (7.3-103.7) 25-39 y Female: 0 events / 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 events / 69.1 (14.2-201.9) Male: 0 events / 299.5 (171.2-486.4)

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<table>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>25-39 y
Female 0 events 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 at time of study</td>
</tr>
<tr>
<td>BNPV Sep 30

Up to Sep 30 2021

France

Salvo 2022[5]</td>
<td>Pfizer-BioNTech or Moderna ~83 million total doses (Dose 1 and Dose 2 combined; 73 million BNT162b2 and 10 million mRNA-1273)</td>
<td>Myocarditis

All cases were routinely evaluated by drug safety medical professionals and repeated at national level in the context of an intensive pharmacovigilance monitoring.

Risk interval NR</td>
<td>Reporting rates (Rr) per 100.000 injections were calculated according to age, gender and injection rank (converted to per million doses); Poisson distribution was used to compute Rrs 95% Confidence Interval (95% CI).</td>
<td>Reporting rate of confirmed cases of myocarditis per million doses
Dose 2 Moderna Pfizer Both
Males
18–24 years 139 (92 to 201) 43 (34 to 55) 91 (63 to 128)
25–29 years 70 (34 to 129) 19 (12 to 29) 44.5 (23 to 79)</td>
</tr>
<tr>
<td>Moderna global safety database Feb 15

Dec 18 2020 to Feb 15 2022

Global

Strauss 2022[7]</td>
<td>Moderna (568,668,391 doses administered to ~252 million people)

Any dose

Dose schedule NR</td>
<td>Myocarditis and myopericarditis

Brighton Collaboration case definition for myocarditis

Risk interval: 0-21d</td>
<td>The reporting rate was calculated as the number of reported cases per 100 000 person-years according to age group and sex (converted to per million doses). Person-years of follow-up were estimated by assigning a 21-day risk window following each estimated dose administered.

The observed reporting rate was compared with an expected rate from a population-based data estimate derived from individuals without a diagnosis of COVID-19 between March 2020 and January 2021 from the US Premier Healthcare Database.</td>
<td>Reported Rates of Myocarditis and Myopericarditis Within 7 Days of mRNA-1273 According to Age and Dose Number (per million Doses Administered)
<table>
<tr><th></th><th>Dose 1</th><th>Dose 2</th><th>Dose 3</th></tr>
<tr><td>Male recipients</td><td></td><td></td><td></td></tr>
<tr><td><12 y</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>12-17y</td><td>2.6</td><td>14.6</td><td>0</td></tr>
<tr><td>18-24y</td><td>8.2</td><td>42.3</td><td>4.0</td></tr>
<tr><td>25-39y</td><td>4.1</td><td>14.0</td><td>3.3</td></tr>
<tr><td>Female recipients</td><td></td><td></td><td></td></tr>
<tr><td><12 y</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>12-17y</td><td>0.5</td><td>1.3</td><td>0</td></tr>
<tr><td>18-24y</td><td>1.5</td><td>3.8</td><td>0.6</td></tr>
<tr><td>25-39y</td><td>1.2</td><td>1.6</td><td>1.4</td></tr>
</table>
Rate ratios of Observed vs Expected rates of myocarditis and Myopericarditis Within 7 Days of mRNA-1273 According to Age and Dose Number (per million Doses Administered)
<table>
<tr><th></th><th>Dose 1</th><th>Dose 2</th><th>Dose 3</th></tr>
<tr><td>Male recipients</td><td></td><td></td><td></td></tr>
<tr><td><12 y</td><td>NA</td><td>NA</td><td>NA</td></tr>
<tr><td>12-17y</td><td>7.9 (3.3 to 19)</td><td>44.1 (21.6 to 89.9)</td><td>NA</td></tr>
<tr><td>18-24y</td><td>24.8 (16.8 to 36.5)</td><td>127.4 (87.5 to 185.4)</td><td>12.1 (6.2 to 23.7)</td></tr>
<tr><td>25-39y</td><td>16.1 (11.9 to 21.9)</td><td>54.9 (41.2 to 73.1)</td><td>12.9 (8.0 to 20.9)</td></tr>
<tr><td>Female recipients</td><td></td><td></td><td></td></tr>
<tr><td><12 y</td><td>NA</td><td>NA</td><td>NA</td></tr>
</table>
</td>
</tr>
</table>

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<table>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>12-17y</td><td>3.2 (0.7 to 15.7)</td><td>7.8 (2.1 to 28.9)</td><td>NA</td></tr>
<tr><td>18-24y</td><td>9.1 (4.8 to 17.2)</td><td>22.9 (12.8 to 41.1)</td><td>3.5 (0.9 to 13)</td></tr>
<tr><td>25-39y</td><td>9.7 (6.1 to 15.3)</td><td>12.8 (8.0 to 20.6)</td><td>11.1 (5.7 to 21.7)</td></tr>
</table>
</td></tr>
<tr><td>VAERS May 26

Dec 14 2020 to May 26 2022

United States

Shimabukuro 2022a[6]</td><td>Pfizer-BioNTech (all ages) or Moderna (≥18y only)
Dose 1
Dose 2
Dose 3</td><td>Myocarditis

Adjudicated after healthcare provider interview and/or medical record review to meet CDC myocarditis case definition

Risk interval: 0-7d</td><td>Reporting rate per million doses.

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 days 0–7 risk interval, this estimated background is 0.2 to 2.2 per 1 million person-day 0–7 risk interval</td><td>Reporting rate, per 1 million doses administered
<table>
<tr><td></td><td colspan="3">Males, 0-7d</td><td colspan="3">Females, 0-7d</td></tr>
<tr><td>Age (yrs)</td><td>Dose 1</td><td>Dose 2</td><td>Dose 3</td><td>Dose 1</td><td>Dose 2</td><td>Dose 3</td></tr>
<tr><td>5–11</td><td>0.2</td><td>2.6</td><td>0</td><td>0.2</td><td>0.7</td><td>0</td></tr>
<tr><td>12–15</td><td>5.3</td><td>46.4</td><td>15.3</td><td>0.7</td><td>4.1</td><td>0</td></tr>
<tr><td>16–17</td><td>7.2</td><td>75.9</td><td>24.1</td><td>0</td><td>7.5</td><td>0</td></tr>
<tr><td>18–24*</td><td>4.2</td><td>38.9</td><td>9.9</td><td>0.6</td><td>4</td><td>0.6</td></tr>
<tr><td>25–29*</td><td>1.8</td><td>15.2</td><td>4.8</td><td>0.4</td><td>3.5</td><td>2</td></tr>
<tr><td>30–39*</td><td>1.9</td><td>7.5</td><td>1.8</td><td>0.6</td><td>0.9</td><td>0.6</td></tr>
</table>
peach shaded cells indicate that reporting rate exceeded estimated background incidence for the period
*Pfizer and Moderna combined for ages ≥18y</td></tr>
<tr><td>VAERS Mar 28

Jan 12 to Mar 28 2022

United States

Hause 2022[3]</td><td>Pfizer or Moderna
Dose 4 (n=518,113)</td><td>Myocarditis

verified by medical record review and met the CDC case definition for myocarditis

Risk interval NR</td><td>Crude reporting rate</td><td>No verified cases of myocarditis reported out of 518,113 fourth doses

“One nonserious, preliminary report of myocarditis remains under review.”</td></tr>
<tr><td>VAERS Feb 20

Dec 9 2021 to Feb 20 2022

United States

Hause 2022a[27]</td><td>Pfizer-BioNTech

Dose 3

Boost interval: (≥2 months after dose 1 of Janssen or ≥5 months after dose 2 of an mRNA vaccine</td><td>Myocarditis

Confirmed to meet CDC working definition

Risk interval NR</td><td>Crude reporting rate per million doses administered</td><td>Males, 12-17y: 11.4 per million booster doses administered</td></tr>
<tr><td>VAERS Feb 6

Sep 22 2021 to Feb 6 2022

United States

Hause 2022b[28]</td><td>Pfizer-BioNTech or Moderna

Dose 3

Boost interval: ≥5 months after dose 2 of an mRNA vaccine</td><td>Myocarditis

Confirmed to meet CDC working definition

Risk interval: 0-6d</td><td>Crude reporting rate per million doses administered</td><td>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</td></tr>
<tr><td>VAERS Jan 13</td><td>Moderna</td><td>Myocarditis</td><td>Crude reporting rate per million doses</td><td>Reporting rate, per million doses (95% CI)
Dose 1 Dose 2</td></tr>
</table>

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Through Jan 13 2022 United States Shimabukuro 2022b[32]	Dose 1 or 2 Dose interval NR	Verified to meet CDC case definition Risk interval: 0-7d		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 9 Nov 2 to Dec 10 2021 United States Su 2021a[40]	Pfizer-BioNTech 7,141,428 doses Dose 1: 5,126,642 (72%) Dose 2: 2,014,786 (28%) Dose interval NR	Myocarditis in 5-11yo Risk interval: 0-12 d after any dose (VAERS) Cases reported to VAERS confirmed using CDC working case definition	Reporting rate per million doses (estimated)	Events: VAERS: 8 (50% female); 2 after dose 1, 6 after dose 2 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 Jun 18 Jan 1 to Jun 18 2021 United States Krug 2022[34 88]	Pfizer-BioNTech or Moderna (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	Crude reporting rate of myocarditis cases per million vaccinees Dose 2 Males 12-15 y: 162.2 Males 16-17 y: 93.0 Males 12-17 y: 118.7 Females 12-15 y: 13.0 Females 16-17 y: 12.5 Females 12-17 y: 12.7

Green text = evidence identified by August 2022 update.
Purple text indicates updated evidence from previously included pre-prints that have been peer-reviewed and published since their inclusion.
NE = not estimated
NR = not reported
*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)
BNPV - Base Nationale de Pharmacovigilance is the French national spontaneous reporting database.
HSA – Health Science Authority of Singapore
SAEFVIC - Surveillance of Adverse Events Following Vaccination in the Community (SAEFVIC) is the state-wide vaccine safety service for the Australian state of Victoria. SAEFVIC comprises central reporting enhanced passive and active surveillance systems integrated with clinical services and has been operating since 2007.
TGA - The Therapeutic Goods Administration is the medicine and therapeutic regulatory agency of the Australian Government. As part of the Department of Health, the TGA regulates the quality, supply and advertising of medicines, pathology devices, medical devices, blood products and most other therapeutics.
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

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

<table>
<tr><th>Dataset
Dates of data
(mmm dd yyyy)
Country of Data
Author year</th><th>Vaccines Stu
Manufacturer
Dose #</th><th>Sample Size; Demographics; Previous Covid-19 diagnoses</th><th>Outcome(s)
Myo-, peri- and/or myopericarditis; Case Ascertainment & Risk Interval; Risk/protective factors considered</th><th>Outcome measures Analysis (e.g., adjustment for confounders)</th><th>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)</th></tr>
<tr><td>TGA Aug 21

Up to Aug 21 2022

Australia

Therapeutic Goods Administration 2022[8]</td><td>Pfizer or Moderna
Dose 1, Dose 2, or Dose 3</td><td>49,000,000 total doses (43.7 million Pfizer and 5.3 million Moderna)

Demographics NR

Previous Covid-19 Diagnoses NR</td><td>Myocarditis (including myopericarditis)

Reports are reviewed against an internationally accepted criteria to classify the likelihood of myocarditis.

Risk interval NR</td><td>Crude reporting rate of likely myocarditis cases per 100,000 doses administered (converted to per million doses)</td><td>Crude incidence rate ratio for occurrence of myocarditis after vaccination with Dose 2 of Moderna compared with Dose 2 of Pfizer.
<table>
<tr><th>Age (years)</th><th>Moderna, Dose 2</th><th>Pfizer Dose 2</th><th>Incidence rate ratio</th></tr>
<tr><td>Males</td><td colspan="2">Rate* per million doses</td><td></td></tr>
<tr><td>12-17</td><td>213</td><td>131</td><td>1.626</td></tr>
<tr><td>18-29</td><td>223</td><td>90</td><td>2.478</td></tr>
<tr><td>30-39</td><td>50</td><td>30</td><td>1.667</td></tr>
<tr><td>40-49</td><td>16</td><td>14</td><td>1.143</td></tr>
<tr><td>50-59</td><td>20</td><td>7</td><td>2.857</td></tr>
<tr><td>60-69</td><td>0</td><td>4</td><td>0.000</td></tr>
<tr><td>70+</td><td>0</td><td>0</td><td>NE</td></tr>
<tr><td>Females</td><td></td><td></td><td></td></tr>
<tr><td>12-17</td><td>5</td><td>28</td><td>0.1786</td></tr>
<tr><td>18-29</td><td>48</td><td>26</td><td>1.846</td></tr>
<tr><td>30-39</td><td>0</td><td>10</td><td>0.000</td></tr>
<tr><td>40-49</td><td>20</td><td>17</td><td>1.176</td></tr>
<tr><td>50-59</td><td>50</td><td>3</td><td>16.667</td></tr>
<tr><td>60-69</td><td>0</td><td>4</td><td>0.000</td></tr>
<tr><td>70+</td><td>0</td><td>4</td><td>0.000</td></tr>
</table></td></tr>
<tr><td>COVaxON and Public Health Case and Contact Management Solution*

Dec 14 2020 to Sep 4 2021</td><td>Pfizer, Moderna

One or two doses

Dose interval NR</td><td>19,740,741 doses

Demographics NR

History of COVID-19 NR</td><td>Myocarditis (product type)
Myocarditis/pericarditis

Group of specialized nurses and physicians classified cases according to Brighton Collaboration</td><td>Rate ratios, unadjusted (for inter-dose interval) and adjusted for dose 1 product and interval (for dose 2, Moderna vs. Pfizer)</td><td>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)</td></tr>
</table>

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Canada Buchan 2022[33 89] Buchan 2022 cont			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		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 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)

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					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[46]	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[43]	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 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	Self-controlled case series (within-person comparison of different time-periods) Relative incidence estimated by Poisson regression 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	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 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

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			mos; Corticosteroids for systemic use; NSAID use	SARS-CoV-2 test before and during study period (n=378); excluding people with heterologous vaccine combinations (n=440)	
NIMS Nov 15 Dec 1 2020 to Nov 15 2021 England Patone 2021[39]	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 Patone 2022[44]	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 Risk factors considered: positive COVID-19 test before vaccination	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 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	Pfizer-BioNTech 15,064,585 Dose 1 or 2	Surveillance population: 23,122,522 nordic residents ≥12 y	Myocarditis inpatient stay; Myo- or pericarditis inpatient or outpatient stay	Crude incident rate; Incidence rate ratio, adjusted	Myocarditis, 0-28 d risk interval, Moderna vs Pfizer Dose 1 | Dose 2 Male | Female | Male | Female

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Dec 27 2020 to Oct 5 2021 Denmark, Finland, Norway, Sweden Karlstadt 2022[29]	Moderna 2,390,870 Dose 1 or 2 Homologous or heterologous dose 2 Interval between doses NR	50% males Previous covid-19 infection NR but accounted for in analysis	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.	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)	

	event s	IR	cR R	event s	IR	cR R	event s	IR	cR R	event s	IR	cR R
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		
	event s	IR	cR R	event s	IR	cR R	event s	IR	cR R	event s	IR	cR R
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	

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<td></td>
<td></td>
<td>
Myocarditis, 0-28 d interval, Homologous vs. Heterologous Dose 2
cIR per 1000 person-years (95% CI), by product
<table>
<tr><th>Males</th><th>Pfiz-Pfiz</th><th>Pfiz-Mod cRR</th><th>Mod-Mod</th><th>Mod-Pfiz cRR</th></tr>
<tr><td>16-24 y</td><td>0.891</td><td>3.687</td><td>2.584</td><td>NR</td><td>NE</td></tr>
<tr><td>25-39 y</td><td>0.179</td><td>1.543</td><td>1.132</td><td>NR</td><td>NE</td></tr>
<tr><td>≥40 y</td><td>0.085</td><td>NE</td><td>0.254</td><td>NR</td><td>NE</td></tr>
<tr><td>Females</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>16-24 y</td><td>NE</td><td>NE</td><td>71.7/2.86</td><td>NE</td><td>NE</td><td>NE</td></tr>
<tr><td>25-39 y</td><td>NE</td><td>NE</td><td>NE</td><td>NE</td><td>NE</td></tr>
<tr><td>≥40 y</td><td>NE</td><td>NE</td><td>8.12/1.02</td><td>NE</td><td>NE</td><td>NE</td></tr>
</table>

Myocarditis, 0-7 d interval, Homologous vs. Heterologous Dose 2
cIR per 1000 person-years (95% CI), by product
<table>
<tr><th>Males</th><th>Pfiz-Pfiz</th><th>Pfiz-Mod cRR</th><th>Mod-Mod</th><th>Mod-Pfiz cRR</th></tr>
<tr><td>16-24 y</td><td>2.190</td><td>13.028</td><td>7.379</td><td>NR</td><td>NE</td></tr>
<tr><td>25-39 y</td><td>0.383</td><td>4.767</td><td>3.898</td><td>NR</td><td>NE</td></tr>
<tr><td>≥40 y</td><td>0.072</td><td>NE</td><td>6.95/1.50</td><td>NE</td><td>NR</td><td>NE</td></tr>
<tr><td>Females</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>16-24 y</td><td>NE</td><td>NE</td><td>210.81/7.88</td><td>NE</td><td>NR</td><td>NE</td></tr>
<tr><td>25-39 y</td><td>NE</td><td>NE</td><td>NE</td><td>NE</td><td>NR</td><td>NE</td></tr>
<tr><td>≥40 y</td><td>NE</td><td>NE</td><td>NE</td><td>NE</td><td>NR</td><td>NE</td></tr>
</table>

Pericarditis, 0-28 d interval, Homologous vs. Heterologous Dose 2
cIR per 1000 person-years (95% CI), by product
<table>
<tr><th>Males</th><th>Pfiz-Pfiz</th><th>Pfiz-Mod cRR</th><th>Mod-Mod</th><th>Mod-Pfiz cRR</th></tr>
<tr><td>16-24 y</td><td>0.217</td><td>NE</td><td>6.36/2.85</td><td>1.034</td><td>NR</td><td>NE</td></tr>
<tr><td>25-39 y</td><td>0.215</td><td>NE</td><td>4.33/2.95</td><td>0.305</td><td>NR</td><td>NE</td></tr>
<tr><td>≥40 y</td><td>0.168</td><td>NE</td><td>1.32/1.09</td><td>0.30</td><td>NR</td><td>NE</td></tr>
<tr><td>Females</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>16-24 y</td><td>NE</td><td>NE</td><td>3.43/2.47</td><td>NE</td><td>NR</td><td>NE</td></tr>
<tr><td>25-39 y</td><td>NE</td><td>NE</td><td>23.21/3.34</td><td></td><td>NE</td><td>NR</td><td>NE</td></tr>
<tr><td>≥40 y</td><td>0.098</td><td>NE</td><td>1.61/1.39</td><td>NE</td><td>NR</td><td>NE</td></tr>
</table>

IR: crude incident rate per 1,000 person-years
ND: not determined
</td>
</tr>
<tr>
<td>SNDS Jan 31

Dec 27 2020 to Jan 31 2022

France

Le Vu 2022b[9]</td>
<td>Pfizer or Moderna

Dose 1 or Dose 2

Dose timing NR</td>
<td>N=53,790
4,890 cases admitted to hospital for myocarditis and 48,900 controls of the general population matched for gender, age, and area of residency.</td>
<td>Myocarditis admitted to hospital

Cases identified from hospital records using ICD-10 codes for myocarditis (I40.x, I41.x, and I51.4) and pericarditis (I30.x and I32.x)

Risk interval: 1-7d, 8-21d</td>
<td>Case-Control study

Odds ratio of admission for myocarditis in those exposed to an mRNA vaccine within 7 days prior to admission compared to no mRNA vaccination or vaccination</td>
<td>
Odds of myocarditis within 7 days of dose, compared to unexposed (unvaccinated or >21days since last dose), by dose number and interval for each mRNA vaccine

12-29y, Dose 2
<table>
<tr><th></th><th>BNT162b2</th><th>mRNA-1273</th></tr>
<tr><td>Interval</td><td>OR (95%CI)</td><td>OR (95%CI)</td></tr>
<tr><td><27d</td><td>11 (9.0-14)</td><td>82 (34-200)</td></tr>
<tr><td>27-39d</td><td>8.7 (5.7-13)</td><td>25 (12-55)</td></tr>
<tr><td>>39d</td><td>5 (3.1-8.0)</td><td>39 (17-86)</td></tr>
</table>

12-29y, Dose 3*
<table>
<tr><th></th><th>BNT162b2</th></tr>
</table>
</td>
</tr>
</table>

Funded by the Canadian Institutes of Health Research (CIHR) and PHAC.

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>>21days before admission.

Ratio of aORs used by this review to compare Moderna to Pfizer.</td>
<td>
<table>
<tr><th>Interval</th><th>OR (95%CI)</th></tr>
<tr><td><170d</td><td>6 (3.3-11)</td></tr>
<tr><td>170-193d</td><td>3.9 (1.8-8.5)</td></tr>
<tr><td>>193d</td><td>3.3 (0.86-13)</td></tr>
</table>
*Estimates could not be obtained for the third dose of the mRNA-1273 (Moderna) vaccine as France recommended against the use of this vaccine for boosters in persons younger than 30 years

≥30y, Dose 2
<table>
<tr><th></th><th>BNT162b2</th><th>mRNA-1273</th></tr>
<tr><th>Interval</th><th>OR (95%CI)</th><th>OR (95%CI)</th></tr>
<tr><td><27d</td><td>4.8 (3.1-7.3)</td><td>31 (13-73)</td></tr>
<tr><td>27-39d</td><td>0.77 (0.36-1.6)</td><td>9.9 (4.9-20)</td></tr>
<tr><td>>39d</td><td>1.9 (1.1-3.2)</td><td>4.8 (2.4-9.6)</td></tr>
</table>
≥30y, Dose 3
<table>
<tr><th></th><th>BNT162b2</th><th>mRNA-1273</th></tr>
<tr><th>Interval</th><th>OR (95%CI)</th><th>OR (95%CI)</th></tr>
<tr><td><170</td><td>2.1 (0.90-4.7)</td><td>6.5 (3.3-13)</td></tr>
<tr><td>170-193</td><td>3.4 (1.8-6.6)</td><td>3 (1.2-8.0)</td></tr>
<tr><td>>193</td><td>1.9 (0.91-3.9)</td><td>2.6 (1.0-6.6)</td></tr>
</table>
</td>
</tr>
<tr>
<td>SNDS Oct 31

May 12 to Oct 31 2021

France

Le Vu 2022a[4]</td>
<td>Pfizer or Moderna

Dose 1 & Dose 2

Dose timing NR</td>
<td>1612 cases of myocarditis and 1613 cases of pericarditis, matched with 16,120 and 16,130 control subjects, respectively.</td>
<td>Myocarditis admitted to hospital

Cases identified from hospital records using ICD-10 codes for myocarditis (I40.x, I41.x, and I51.4) and pericarditis (I30.x and I32.x)

Risk interval: 1-7d, 8-21d</td>
<td>Matched case-Control study

Odds ratio of admission for myocarditis in those exposed to an mRNA vaccine within 7 days prior to admission compared to no mRNA vaccination or vaccination >21days before admission.

Ratio of aORs used by this review to</td>
<td>
Association between myocarditis and exposure to mRNA vaccines within 7 days, according to sex and age group
<table>
<tr><th></th><th>mRNA-1273, Dose 2</th><th>BNT162b2, Dose 2</th><th>Ratio of aORs (Ratio of 95% CIs)</th></tr>
<tr><th>Age</th><th>aOR (95% CI)</th><th>aOR (95% CI)</th><th></th></tr>
<tr><td>Males</td><td></td><td></td><td></td></tr>
<tr><td>12-17y</td><td>NA</td><td>18 (9-35)</td><td>NA</td></tr>
<tr><td>18-24y</td><td>44 (22-88)</td><td>13 (9.2-19)</td><td>3.38 (2.39 to 4.63)</td></tr>
<tr><td>25-29y</td><td>19 (8.3-43)</td><td>7.1 (4.2-12)</td><td>2.67 (1.98 to 3.58)</td></tr>
<tr><td>30-39y</td><td>45 (19-110)</td><td>5.7 (3.4-9.5)</td><td>7.89 (5.59 to 11.58)</td></tr>
<tr><td>Females</td><td></td><td></td><td></td></tr>
<tr><td>12-17y</td><td>NA</td><td>7.1 (1.5-33)</td><td>NA</td></tr>
<tr><td>18-24y</td><td>41 (12-140)</td><td>9.6 (4.3-22)</td><td>4.27 (2.79 to 6.36)</td></tr>
<tr><td>25-29y</td><td>23 (2.1-270)</td><td>10 (2.1-47)</td><td>2.3 (1 to 5.74)</td></tr>
<tr><td>30-39y</td><td>1.4 (0.11-18)</td><td>4 (1.4-11)</td><td>0.35 (0.08 to 1.64)</td></tr>
</table>
</td>
</tr>
</table>

Funded by the Canadian Institutes of Health Research (CIHR) and PHAC.

<table>
<tr>
<td></td><td></td><td></td><td></td><td>compare Moderna to Pfizer.</td>
<td>
Incidence of pericarditis per million vaccinees, by age and sex for 7days following vaccinatio
<table>
<tr><td></td><td></td><td colspan="2">BNT162b2</td><td colspan="2">mRNA-1273</td></tr>
<tr><td></td><td></td><td colspan="2">Dose 2</td><td colspan="2">Dose 2</td></tr>
<tr><td>Sex</td><td>Age</td><td>IR</td><td>aOR</td><td>IR</td><td>aOR</td></tr>
<tr><td>Female</td><td>12-17</td><td>3.43</td><td>10 (2.5-41)</td><td>0.0</td><td>NE</td></tr>
<tr><td></td><td>18-24</td><td>7.54</td><td>5.9 (2.9-12)</td><td>0.0</td><td>NE</td></tr>
<tr><td></td><td>25-29</td><td>5.36</td><td>6.4 (2.3-18)</td><td>0.0</td><td>NE</td></tr>
<tr><td></td><td>18-29</td><td>6.68</td><td></td><td>0.0</td><td>NE</td></tr>
<tr><td></td><td>30-39</td><td>3.69</td><td>2 (0.9-4.6)</td><td>13.7</td><td>20 (3.5-110)</td></tr>
<tr><td></td><td>18-39y</td><td>5.30</td><td></td><td>7.0</td><td>NE</td></tr>
<tr><td>Male</td><td>12-17</td><td>4.61</td><td>6.8 (2.3-20)</td><td>0.0</td><td>NE</td></tr>
<tr><td></td><td>18-24</td><td>12.1</td><td>6.3 (3.5-11)</td><td>36.0</td><td>11 (4.1-32)</td></tr>
<tr><td></td><td>25-29</td><td>4.39</td><td>2.9 (1.1-8)</td><td>13.0</td><td>7.5 (1.2-45)</td></tr>
<tr><td></td><td>18-29y</td><td>9.05</td><td>4.8</td><td>26.6</td><td>26.41</td></tr>
<tr><td></td><td>30-39</td><td>5.35</td><td>2.4 (1.2-4.6)</td><td>8.1</td><td>4.9 (1.3-19)</td></tr>
<tr><td></td><td>18-39y</td><td>7.36</td><td></td><td>17.4</td><td></td></tr>
</table>
</td>
</tr>
<tr>
<td>BNPV Sep 30

Up to Sep 30 2021

France

Salvo 2022[5]</td>
<td>Pfizer or Moderna

Dose 1 or Dose 2

Dose timing NR</td>
<td>~83 million total doses (73 million BNT162b2 and 10 million mRNA-1273 doses)

Demographics NR</td>
<td>Myocarditis

All cases were routinely evaluated by drug safety medical professionals and repeated at national level in the context of an intensive pharmacovigilance monitoring.

Risk interval NR</td>
<td>Reporting rates (Rr) per 100.000 injections were calculated according to age, gender and injection rank; Poisson distribution was used to compute Rrs 95% Confidence Interval (95% CI). (converted to per million doses)</td>
<td>
Reporting rate of confirmed cases of myocarditis per million doses
<table>
<tr><td></td><td>Moderna, Dose 2</td><td>Pfizer, Dose 2</td></tr>
<tr><td><u>Males</u></td><td></td><td></td></tr>
<tr><td>18–24 years</td><td>139 (92 to 201)</td><td>43 (34 to 55)</td></tr>
<tr><td>25–29 years</td><td>70 (34 to 129)</td><td>19 (12 to 29)</td></tr>
<tr><td>18-29 years</td><td>110.25</td><td>33.00</td></tr>
</table>
</td>
</tr>
<tr>
<td>Singapore Military Aug 3

Jan 14 to Aug 3 2021

Singapore</td>
<td>Pfizer (37,367 individuals with 1+ dose)

Moderna (27,294 individuals with 1+ dose)</td>
<td>127,081 doses administered to 64,661 military membets (96.5% with 2 doses)

92.1% male</td>
<td>Myocarditis

Risk interval NR

Case ascertainment via military doctor or hospital diagnosis

Pfizer vs Moderna</td>
<td>Descriptive report only; crude numbers estimated by ARCHE</td>
<td>
3 events; all male, 18-21y, all after dose 2 of Moderna; 0 cases with history of cardiac conditions.

Overall rate: 2.4 per 100,000 doses
<table>
<tr><td></td><td>Dose 1</td><td>Dose 2</td></tr>
<tr><td>18-20 y</td><td></td><td></td></tr>
<tr><td>Pfizer</td><td></td><td></td></tr>
<tr><td>Male</td><td>0/3,789</td><td>0/3,762</td></tr>
<tr><td>Female</td><td>0/326</td><td>0/323</td></tr>
</table>
</td>
</tr>
</table>

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Tan 2021[41]	Homologous dose 2 administered between 21 and 56 days after dose 1	Previous or concurrent COVID-19 diagnosis NR			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[42]	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	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	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 Moderna / Pfizer / cRR 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

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Hause 2022b[28]		Previous COVID-19 infection NR			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[45] [87]	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	3063 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[47]	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	Moderna vs. Pfizer Events per 1 mil doses: Dose 1 / Dose 2 (Moderna / Pfizer); 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

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				estimated crude Rate Ratios (for 18+ only; Moderna not authorized in <18y)	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
VHA Oct 5 Jan 4 to Oct 5 2021 United States Dickerman 2022 14096	Pfizer Dose 2 scheduled 21 days after Dose 1 Moderna Dose 2 scheduled 28 days after Dose 1	N=429564 7% Female 18-39y: 4% 40-49y: 6% 50-59y: 14% 60-69y: 27% 70-79y: 39% ≥80y: 10% 20% Black	Myocarditis or pericarditis The adverse events were defined using diagnosis codes recorded in inpatient and outpatient domains as well as fee domains (claims for out-of-network care) to capture diagnoses documented both inside and outside the VA health care system. Risk interval: 0-14 d Race (Black vs. White)	Cumulative incidence (risk) curves for the vaccination groups were estimated using the Kaplan-Meier estimator.	**Exclude – No comparisons of interest** 14-day risk of myo- or pericarditis no. of events/million persons (95% CI) Pfizer / Moderna / Total Black race: 340 (1.3, 5.0) / 340 (150, 660) / 340 White race: 430 (3.3, 5.8) / 290 (190, 370) / 360

Green text = evidence identified by August 2022 update

BNPV - Base Nationale de Pharmacovigilance is the French national spontaneous reporting database.

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

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.

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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.

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.

SAEFVIC - Surveillance of Adverse Events Following Vaccination in the Community (SAEFVIC) is the state-wide vaccine safety service for the Australian state of Victoria. SAEFVIC comprises central reporting enhanced passive and active surveillance systems integrated with clinical services and has been operating since 2007.

SNDS - the French administrative health care database covers around 99% of the French population, and includes anonymized data on socio-demographics, medical characteristics, ambulatory care, hospitalizations, diagnosis, drugs and procedures, mortality, and costs.

VHA = Veteran's Health Administration is a nationalized healthcare service in the United States that provides healthcare and healthcare-adjacent services to Veterans through the administration and operation of healthcare facilities including inpatient, outpatient, and care home facilities.

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

VSD - Vaccine Safety Datalink

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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
Le Vu 2022a SNDS Oct 31	NA	Y	Y	Y	U	N	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

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Cheng 2022 SAEFVIC Feb 22	NA	U	N	Y	N	N	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
Krug 2022 VAERS Jun 18	NA	N	N	U	U	N	High risk
Salvo 2022 14846 BNPV Sep 30	NA	U	N (age and sex only)	U	N	N	High risk
Shimabukuro 2022a VAERS May 26	NA	U	N (age and sex only)	Y	Y	N	High risk
Shimabukuro 2022b VAERS Jan 13	NA	U	N (age and sex only)	Y	Y	N	High risk
Strauss 2022 Moderna global safety database Feb 15	Y	Y	N (age and sex only)	Y	U	N	High risk
Su 2021a VAERS Dec 9	NA	Y	U	Y	Y	N	High risk
Australian Therapeutic Goods Agency 2022 TGA Aug 21	NA	U	N	Y	N	N	High risk

Green text = evidence identified by Aug 2022 update

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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 2022 COVaxON and Public Health Case and Contact Management Solution	U	Y	Y	N	Y	Y	N	Y	High risk
Dickerman 2022 VHA Oct 5	Y	Y	Y	Y	Y	U – diagnoses defined using medical records (not otherwise specified)	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
Le Vu 2022a SNDS Oct 31	U	Y	Y	Y	Y	U	Y	Y	Moderate risk
Le Vu 2022b SNDS Jan 31	U	Y	Y	Y	Y	U	Y	Y	Moderate 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
Salvo 2022 BNPV Sep 30	U	Y	Y	N	U	U	U	N	High Risk
Su 2021 VAERS Oct 6	U	Y	Y	N	Y	Y	Y	N	High risk
Tan 2021	Y	Y	Y	N	U	U	U	Y	High risk

Funded by the Canadian Institutes of Health Research (CIHR) and PHAC.

Singapore Military Aug 31									
Therapeutic Goods Administration 2022 TGA Aug 7	U	Y	Y	U	U	Y	U	N	High risk

Green text = evidence identified by Aug 2022 update

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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		
Amemiya et al. 2022[18] (case series)	• Case series of 3 patients who underwent biopsy: All three patients showed similar histological findings of mild interstitial inflammatory infiltrates that were predominantly composed of macrophages admixed with a few T-cells without adjacency to cardiomyocyte necrosis. Eosinophils were either absent or rarely found. Immunohistochemical expression of tenascin-C (TN-C) was observed in the (sub)endocardium and partially in the interstitium. Human leukocyte antigen (HLA)-DR antigens were diffusely positive on capillary endothelial cells and interstitial infiltrating cells compared with that in other nonmyocarditis cases. Moderate endomyocardial fibrous thickening and mild interstitial fibrosis of the myocardium were also observed. No viral genomes including SARS-CoV-2 were detected in the myocardium of all EMB specimens by a multivirus real-time PCR system.	Supporting; Primary data collected
Hajra et al., 2021[74] (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.

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		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[83] (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[75] (letter) Exposure to mRNA strand	• 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 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.	None
Parra-Lucares et al., 2021[81] (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.	Supporting: Muthukumar A et al. In-depth evaluation of a case of presumed myocarditis after the second dose of COVID-19 mRNA vaccine. Circulation. 2021;144:487–498. Case report (52 year-old) data with panel of 48 cytokines and chemokines; elevated levels of some cytokines and NK cells.
Bozkurt et al, 2021[68]	• Exposure to mRNA strand: The immune system may therefore detect the mRNA in the vaccine as an antigen, resulting in activation of proinflammatory	Supporting:

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(narrative review) Exposure to mRNA strand or spike protein or unknown trigger	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	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 Refuting: Exposure to spike protein: Muthukumar A et al. In-depth evaluation of a case of presumed myocarditis after the second dose of COVID-19 mRNA vaccine. Circulation. 2021;144:487–498. Case report data; similar spike IgM and IgG neutralizing antibody levels
Das et al., 2021[71] (case series) Exposure to spike protein and other unknown trigger	• 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 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]	Refuting: Exposure to spike protein or other unknown trigger, with antibody response: Their case series data (n=25, 12-18 years)(Das) 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.

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Boursier et al.,, 2021[100] (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[23] (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[84] (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	Supporting: Nguyen TD et al. Acute myocarditis after COVID-19 vaccination with mRNA-1273 in a patient with former SARS-

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	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].	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[74] (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]

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Tsilingiris et al., 2021[83] (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[70] (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[68] (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 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: Several case reports and series; no eosinophilia: Marshall M et al. Symptomatic acute myocarditis in seven adolescents following Pfizer-BioNTech COVID-19 vaccination. Pediatrics. Published online June 4, 2021. Rosner CM et al. Myocarditis temporally associated with COVID-19 vaccination. Circulation. 2021;144:503–506. Abu Mouch S et al. Myocarditis following COVID-19 mRNA vaccination. Vaccine. 2021;39:3790–3793. Larson KF et al. Myocarditis after BNT162b2 and mRNA-1273 vaccination. Circulation. 2021;144:507–509. Ammirati E et al. Temporal relation between second dose BNT162b2 mRNA Covid-19 vaccine and cardiac involvement in a patient with previous SARS-COV-2 infection. Int J Cardiol Heart Vasc. 2021;34:100774. Bautista GJ et al. Acute myocarditis after administration of the BNT162b2 vaccine against COVID-19. Rev Esp

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		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[69] (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		

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Hajra et al 2021[74] (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[82] (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[70] (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[68] (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

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		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)		
Carreno et al. 2022[21] (experimental study)	• This experimental study examined whether the components of the mRNA vaccine formulations elicited PEG-specific antibody responses in serum by enzyme linked immunosorbent assay (ELISA), and detected an increase in the reactivity to mRNA vaccine formulations in Moderna but not Pfizer vaccinees' (n=10) sera in a prime-boost dependent manner. Although there was an increase in the anti-PEG antibodies in several mRNA-1273 vaccinees who experienced adverse effects, there was no obvious association between PEG antibodies and the adverse reactions (n=9). The authors' suggest that perhaps anti-formulation immune responses are contributing to the higher reactogenicity sometimes observed with the Moderna compared with Pfizer vaccine.	Supporting: Primary data collection

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Kounis et al. 2021a[78] (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[77] (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[83] (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.

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Bozkurt et al., 2021[68] (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) Hypersensitivity to PEG	• 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 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".	None
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)		

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Tsilingiris et al., 2021[83] (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[76] (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		
Baumeier et al. 2022[20] (case series)	• Molecular mimicry: This case series of 15 patients who underwent endomyocaridal biopsy suggests an autoimmune response, because of nine hearts expressing SARS-CoV2 spike protein and a dominace of CD4+ T cell infiltrates.	Supporting: Primary data collection
Hajra et al 2021[74] (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

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		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[83] (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

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		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[70] (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[75] (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[68] (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	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.

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	healthy population, raising the possibility that myocarditis may develop in a subgroup of patients with the appropriate genetic background.	
Chouchana et al., 2021[69] (retrospective study on Vigibase case and discussion) Molecular mimicry	• 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
Switzer & Loeb, 2022[23] (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[81] (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*	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 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.

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	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).	Circulation. 2021;144:487–498. Case report with detected autoantibodies; caution about unknown implications. Refuting: Other autoimmune: Indicative of direct data but no citations
Ehlrich et al., 2021[72] (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.	Refuting: 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	Supporting:

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	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	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[79] (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.[79] • 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[101] (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 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.	None

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Hypothesis 9: Production of anti-idiotype antibodies against immunogenic regions of antigen-specific antibodies		
Tsilingiris et al., 2021[83] (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[68])		
Bozkurt et al., 2021[68] (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.	Refuting: 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, 2022[23] (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[68] (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 Therapeutic Interventions and Vaccines) panel to conclude that the risk of immune enhancement after COVID-19 immunizations was low, but required	Refuting: Multiple case reports and series reviewed and tabulated, having no evidence of acute COVID-19 infections after vaccine when presenting with myocarditis.

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	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)	
Hypothesis 12: Direct cell invasion via the spike protein interacting with the angiotensin-converting enzyme 2 (ACE2) widely expressed and prevalent in cardiomyocytes[69]		
Chouchana et al., 2021[69] (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, 2022[23] (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[76] (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	None

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	immune complex, in turn, may lead to activation of the complement system through its classical pathway and damage to the target cell.	
Hypothesis 14: Spike-activated neutrophils (expressing ACE2) augmenting inflammatory response		
Kadkhoda et al., 2021[76] (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[80] (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[102] (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	Author's study

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	pericarditis group ($p < 0.05$). This shows inflammatory and procoagulant state.	
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. 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].	Supporting: CDC reports on temporal nature of cases 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
Hypothesis 20: SARS-CoV-2 spike glycoprotein injuring cardiac pericytes, which support the capillaries and the cardiomyocytes		
Seneff et al. 2022[22] (narrative review)	• Vaccination induces a profound impairment in type I interferon signaling, which has diverse adverse consequences to human health. • The SARS-CoV-2 spike glycoprotein has been demonstrated to injure cardiac pericytes, which support the capillaries and the cardiomyocytes.	Supporting: None

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Hypothesis 21: Exosomes released by macrophages that have taken up the mRNA nanoparticles, and the specific microRNAs found in those exosomes		
Seneff et al. 2022[22] (narrative review)	• Immune cells that have taken up the vaccine nanoparticles release into circulation large numbers of exosomes containing spike protein along with critical microRNAs that induce a signaling response in recipient cells at distant sites. • A study involving patients suffering from severe COVID-19 disease looked specifically at the expression of circulating microRNAs compared to patients suffering from influenza and to healthy controls. One microRNA that was consistently upregulated in association with COVID-19 was miR-155, and the authors suggested that it might be a predictor of chronic myocardial damage and inflammation. By contrast, influenza infection was not associated with increased miR-155 expression. • Other studies shwing reevance of miR-155 to cardiovascualr disease and inflammation.	None (directly in patients with myocarditis
Hypothesis 22: "Spike effect" with Angiotensin II accumulation in the blood without protection (in younger people) by over-expression of some angiotensinases (PRCP, and POP) as developed in older people or those with comorbidities		
Angeli et al. 2022[19] (narrative review)	• COVID-19 vaccines increase the endogenous synthesis of SARS-CoV-2 spike proteins. Once synthetized, the free-floating spike proteins circulate in the blood, interact with ACE2 receptors and resemble the pathological features of SARS-CoV-2 ("Spike effect" of COVID-19 vaccines). It has been noted that an increased catalytic activity of (other angiotensinases) POP/PRCP is typical in elderly individuals with comorbidities or previous cardiovascular events, but not in younger people. Thus, the adverse reactions to COVID-19 vaccination associated with Ang II accumulation are generally more common in younger and healthy subjects.	Supporting: Case series (Simone et al 2021) and VAERS data of myocarditis mainly in young men
Differences in incidence by sex could be due to sex steroid hormones or underdiagnosis in females		
Tsilingiris et al., 2021[83] (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[75] (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[68] (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	Supporting: Sex hormones: None Underdiagnosis in women:

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	to a Th1-type immune response.[68] Estrogen has inhibitory effects on proinflammatory T cells, resulting in a decrease in cell-mediated immune responses; and pericarditis incidence is higher in women during the postmenopausal period.[69] • Underdiagnosed in women: Another contributing factor could be underdiagnosis in women. By our analysis of the VAERS database, as of June 6, 2021, there were 6235 reported cases of chest pain, 69% of which were in women, versus 30% in men.[70] Despite a higher prevalence of chest pain in women, diagnostic evaluation, including ECG, laboratory biomarkers, echocardiography, and MRI, was performed and reported more often in male than in female patients presenting with chest pain after COVID vaccination (Bozkurt, unpublished data, 2021).	Centers for Disease Control and Prevention. The Vaccine Adverse Event Reporting System (VAERS) results. June 6, 2021. Accessed July 6, 2021. https://wonder.cdc.gov/vaers.html. Mor chest pain complaints in females. Bozkurt, unpublished data, 2021. Fewer investigations in females.
Chouchana et al., 2021[69] (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[81] (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

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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 first update on Jan 10, 2022. The second search update was run on April 11, 2022. We did not add limits for language, country or study design. After the first search, we 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 question. After the pilot, one reviewer extracted all data and a second reviewer verified it. 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. We 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. When both incidence rates and excess incidence were reported, we prioritized the latter for synthesis.

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 studies included in KQs 3 or 4 or for CQ1.

Synthesis

We analyzed data on myocarditis (including myopericarditis) and pericarditis separately, when able. Data are summarized descriptively 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, and case ascertainment methods. 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 (5-11y, 12-17y,

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18-29y, 30-39y, ≥40y) to report 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).

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