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 fourth update of a living evidence synthesis initiated in November 2021 available at COVID-END and published in BMJ[1]. This 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. For the contextual question on biological mechanisms, the focus is on empirical evidence from studies of patients with myocarditis following COVID-19 vaccination.

Throughout the report below, green font indicates new data or changes to conclusions or certainty in the evidence since the last update.

Key Messages

- 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 conferred by vaccination. Evidence suggests that the risk of myocarditis after booster doses is low for 12 to 17 year old males not having experienced myocarditis from the first or second dose.
- In this update, we identified the possibility of higher incidence in females after a 2nd dose and 30-39 year-old males than previously reported. This may be due in part to an "infamy bias" from public media reporting on myocarditis after mRNA vaccination which may have increased reports of myocarditis or led to patients with less severe symptoms seeking care when they may not have otherwise.[2] The higher observed incidence in new evidence compared to earlier reports may also be driven by the higher rate of myocarditis after Moderna compared with Pfizer, especially in the 30-39 year old age group.
- Newer studies report higher incidence than previously, leading to reduced certainty in the incidence estimates of myocarditis after an mRNA vaccination in 12-17year-old and 30-39 year old males after a 3rd dose. This may be driven by limitations in reporting in earlier studies (i.e., reliance on passive surveillance systems), and/or by the aforementioned "infamy bias"
- Our findings suggest that receiving Pfizer (compared to 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 6 months follow-up, it appears that about 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 notable proportion of patients may experience other problems, such as

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anxiety/depression, pain, or difficulties with usual activities, but low follow-up rates and the lack of control data limit this finding. One large case series in the US found few (6% of affected) individuals missed school or work in the 2 weeks before follow-up due to myocarditis.

- The available studies on biological mechanisms appear to suggest that a humoral immune response (with antigen-specific antibodies) is not a major contributor. The cellular immune response (T-cell/CD4) may play a central role in mRNA vaccine associated myocarditis. Furthermore, increased expression of HLA-DR and increased anti-IL-1RA activity are consistent with an autoimmune mechanism. Elevated levels of spike proteins have been identified in the plasma and in cardiomyocytes of patients with vaccine associated myocarditis. They are potential modulators of the immune response and have correlated with cardiac troponin T levels and cytokine mediated innate immune activation. Firm conclusions are limited due to diverse study designs and populations. When assessing findings, it is not clear whether observed differences (e.g., increases in CD4+ T cells, cytokines) between myocarditis cases vs. vaccinated controls reflect a causal pathological immune response or reactive adaptive responses to the myocardial inflammation. In the clinical setting, endomyocardial biopsy is infrequently performed in individuals with suspected myocarditis. Accordingly, there is limited tissue data upon which to draw mechanistic conclusions.

Search date

February 4, 2023

Key Questions

KQ1: What is the incidence of myocarditis and pericarditis following mRNA COVID-19 vaccination, by age, sex and dose, in i) people 0-4 years, 5-11 years, 12-17 years, 18-29 years ii) recipients of any age after any booster 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 years, ii) recipients of any age after any booster 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 (≥12 weeks) prognosis, and does this vary by patient or vaccine characteristics?

Contextual Question

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

Our Approach

For study eligibility for each question, see Supplementary Table 1. A single reviewer completed screening and another verified 50% of exclusions, using a machine-learning program to prioritize records. For the key questions, a second reviewer verified all exclusions at full text and data extraction 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 or highly consistent and very low (i.e., zero or near-zero) incidences across multiple studies. 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, one reviewer extracted data on the study population(s), methods and findings as well as authors’ conclusions. We wrote a narrative for each study and attempted to draw any inferences of findings across studies.

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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 Tables 4A and 4B. Table 5 provides details on the studies investigating biological mechanisms in patients experiencing myocarditis following COVID-19 vaccination, as well as any control groups. Appendix 1 contains: eligibility criteria; study characteristics tables of the passive and active reporting systems/studies contributing to KQ1 and studies included for KQ2 and risk of bias assessments for studies for KQ 1 & KQ2. Appendix 2 contains details of our synthesis methods.

58 studies were included in this update. We identified 17 new reports across all questions (KQ1=8[3-10], KQ2=5[5-8 10], KQ3=0, KQ4=3[11-13], CQ1=6[14-19]). Findings from 40 of 83 studies in the previous synthesis were carried forward (KQ1=25[20-44], KQ2=16[22 23 26 31 32 36 42 44-52]; KQ3=2[30 43]; KQ4=9[24 38 53-59]; CQ1=1[60]). Three studies with <12 weeks of follow-up[20 34 61] and six studies with N<10[62-67] previously included in KQ4 no longer met our updated eligibility criteria. A presentation to the American Committee on Immunization Practices[68] previously included in KQ4 was superseded by a peer-reviewed publication reporting more detailed data.[12] Thirty-four studies previously included in CQ1 on hypothesized mechanisms did not reported any empirical data and were therefore excluded from this update.[69-102]

KQ1: Incidence

Myocarditis after dose 2

- Overall, the evidence remained consistent with the previous updates.
- We identified 1 new report on myocarditis after primary series of Moderna or Pfizer in children 6 months to 4 years old. The incidence of myocarditis after vaccination with an mRNA vaccine may be fewer than 20 cases per million. (low certainty).
- We included no new reports in 5-11-year-old males and females. The incidence of myocarditis after vaccination with Pfizer is probably fewer than 20 cases per million in both groups (moderate certainty).
- We identified 2 new studies reporting on 12-17-year-old males and females. In males, we remain moderately certain about a higher incidence (range 13 to 390 cases per million) of myocarditis after vaccination with an mRNA vaccine (moderate certainty). Among 12-17-year-old females, we remain uncertain about the incidence of presenting with myocarditis after vaccination with an mRNA (very low certainty, range: 1 to 50 cases per million).
- We identified 2 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, we remain uncertain about the incidence of presenting with myocarditis after vaccination with an mRNA vaccine (very low certainty, range: 2 to 37 cases per million).
- We identified 2 new studies reporting on 18-39-year-old males and females. Among 18-39-year-old males, the incidence of myocarditis after vaccination with an mRNA vaccine is probably between 8 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 monovalent booster doses

- We identified 4 new reports of myocarditis after a third dose of monovalent mRNA vaccine.
- We identified 1 additional report on monovalent booster doses among 5-11-year-old males and females. Based on two reports with data only from one passive surveillance/spontaneous reporting source, we are uncertain about the incidence of myocarditis after vaccination with a third dose of mRNA vaccine for this age group (very low certainty).
- We identified 1 new study reporting on monovalent booster doses among 12-17-year-olds. Among 12-17-year-old males, we are now uncertain about the incidence of myocarditis after vaccination with a third dose of a monovalent mRNA vaccine because of increased inconsistency in reported incidence across studies (very low certainty, range: 0 to 90 cases per million). In 12-17-year-old females, all 4 studies reported zero events, giving us increased certainty that the incidence of myocarditis after vaccination with a third dose of a monovalent mRNA vaccine in this group is probably fewer than 20 cases per million (moderate certainty).
- We identified 2 new studies reporting on monovalent booster doses among 18-29-year-olds. Among 18-29-year-old males, we remain uncertain about the incidence of myocarditis after a third dose of a monovalent mRNA vaccine due to large inconsistency across studies (very low certainty, range: 4 to 113 cases per million). Among

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18-29-year-old females, we now have increased certainty that the incidence of myocarditis after vaccination with a third dose of a monovalent mRNA vaccine is probably fewer than 20 cases per million (moderate certainty).

- We identified three 3 studies reporting on monovalent booster doses among 30-39-year-old males and females. Among 30-39-year-old males, we are now uncertain about the incidence of myocarditis after a third dose of a monovalent mRNA vaccine (very low certainty, range: 1 to 48 cases per million). Among 30-39-year-old females, we continue to have low certainty that the incidence of myocarditis after vaccination with a third dose of a monovalent mRNA vaccine may be fewer than 20 cases per million.
- We identified one new study reporting on monovalent booster doses among ≥40-year-olds. 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).
- We identified no new studies reporting on myocarditis after a fourth dose of a monovalent mRNA vaccine. We remain uncertain about the incidence of myocarditis after vaccination with a fourth dose of a monovalent mRNA vaccine in ≥12-year-olds due to indirectness from reporting outcomes across age and sex groups, and from all evidence coming from a single study using only data from passive surveillance/spontaneous reporting.

Myocarditis after bivalent booster doses

- We now refer to any dose after dose 2 (or dose 3 for immunocompromised individuals) as “booster doses” because of changes around the nomenclature being used to refer to COVID-19 vaccine dosing.
- We identified 3 reports on myocarditis after any booster dose of a bivalent mRNA vaccine. No two studies reported on the same age and sex group.
- Among children 5-11 years old we are uncertain about the incidence of myocarditis after a booster dose of bivalent mRNA vaccine due to evidence from a single report using data from passive surveillance/spontaneous reporting (very low certainty).
- Among individuals ≥12 years old we are uncertain about the incidence of myocarditis after a booster dose of bivalent mRNA vaccine due to evidence a single report using data from passive surveillance/spontaneous reporting (very low certainty).
- Among males ≥50 years old, we are uncertain about the incidence of myocarditis after a booster dose of bivalent mRNA vaccine due to evidence from a single report (very low certainty).
- Among females ≥50 years old we are uncertain about the incidence of myocarditis after a booster dose of bivalent mRNA vaccine due to evidence from a single report (very low certainty).

Pericarditis

- We identified no new studies reporting on 5-11-year-olds. 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 no new studies reporting on 12-17-year-olds. For both 12-17 year old males and females, 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).
- We identified no new studies reporting 18-24-year-olds. 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 (very low certainty). For 18-24 year old females, we continue to conclude that the incidence of pericarditis after vaccination with dose 2 of an mRNA vaccine may be fewer than 20 cases per million (low certainty).
- We identified no new studies reporting on 25-39-year-olds. We continue to conclude that 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.
- We identified no new reports on pericarditis after any booster dose of a monovalent mRNA vaccine.
- We identified 2 new reports on pericarditis after any booster dose of a bivalent mRNA vaccine.
- Among individuals ≥12 years old we are uncertain about the incidence of pericarditis after a booster dose of bivalent mRNA vaccine due to evidence a single report using data from passive surveillance/spontaneous reporting (very low certainty).
- Among males ≥50 years old, we are uncertain about the incidence of pericarditis after a booster dose of bivalent mRNA vaccine due to evidence from a single report (very low certainty).
- Among females ≥50 years old we are uncertain about the incidence of pericarditis after a booster dose of bivalent mRNA vaccine due to evidence from a single report (very low certainty).

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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 1 new study reporting on Moderna versus Pfizer in children 6 months to 4 years old. Among individuals 6 months to 4 years old, the incidence of myocarditis may not differ following primary series vaccination with Moderna compared with Pfizer (low certainty)
- We identified no new studies reporting on 12-17-year-old males and females. 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.
- We identified 1 new study reporting on 18-29-year-old males and females and 2 new studies reporting on 18-39-year-old males and females. We continue to conclude that among 18-29-year-old males and females and 18-39-year-old females, the incidence of myocarditis is probably at least 2-3 times higher after vaccination with Moderna compared to Pfizer (moderate certainty). Among 18-39-year-old males we now conclude that the incidence of myocarditis is probably 2-5 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, providing increased certainty for these groups. In 30-39-year-old males we are now certain that there is a higher incidence of myocarditis after vaccination with Moderna compared to Pfizer (high certainty). Among 30-39-year-old females, we now conclude that the incidence of myocarditis may be higher after vaccination with Moderna compared to Pfizer (low certainty).
- We identified 1 new study reporting on ≥40-year-old males and females. In ≥40-year-old males we are now uncertain about the incidence of myocarditis after Moderna compared to Pfizer. We continue to conclude that there may be a higher incidence of myocarditis after vaccination with Moderna compared to Pfizer in ≥40-year-old females (low certainty).

Moderna versus Pfizer, after dose 3 (monovalent)

- We identified 1 new study reporting on Moderna vs Pfizer after a monovalent dose 3.
- Among 18-29-year-old males, there may be a higher incidence of myocarditis after vaccination with a third monovalent dose of Moderna compared with Pfizer (low certainty).
- Among 18-29-year-old females, there may be no difference in the incidence of myocarditis after vaccination with a third monovalent dose of Moderna compared to Pfizer (low certainty).
- Among 30-39-year-old males, there may be a lower incidence of myocarditis after vaccination with a third monovalent dose of Moderna compared to Pfizer (low certainty).
- Among 30-39-year-old females there may be a higher incidence of myocarditis after vaccination with a third monovalent dose of Moderna compared to Pfizer (low certainty).
- Among ≥40-year-old males, we continue to conclude that the incidence of myocarditis may be higher after vaccination with a third monovalent dose of Moderna compared with Pfizer (low certainty). Among ≥40-year-old females we remain uncertain about any difference in incidence after vaccination with a third monovalent dose of Moderna compared to Pfizer (very low certainty).

Moderna versus Pfizer, bivalent booster doses

- We identified 2 new studies reporting on Moderna vs Pfizer after a bivalent booster dose.
- In both 5-11-year-olds (both sexes) and ≥12-year-olds (both sexes), there may be no difference in the incidence of myocarditis after a bivalent booster dose of Moderna compared to Pfizer (low certainty).

Homologous vs heterologous vaccine for dose 2

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

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- 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).

Dose interval: Dose 1 to Dose 2

- We did not identify any new studies reporting on dose interval between dose 1 and dose 2.
- In both 12-29-year-olds and ≥30-year-olds (both sexes combined), 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 did not identify any new studies reporting on dose interval between dose 2 and dose 3.
- In 12-29-year-olds (both sexes combined) 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 uncertain 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

Clinical Comorbidities

- We identified no new studies reporting on clinical comorbidities 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 no new studies reporting on myocarditis and/or pericarditis by race. There may be no difference in 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 no new studies reporting on pericarditis after Moderna compared with Pfizer in 18-29-year-old males and continue to conclude there is probably a higher incidence of pericarditis after vaccination with Moderna compared with Pfizer (moderate certainty).
- We identified no new studies reporting on 18-39-year-old males, and our conclusions for this groups have 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 no new studies reporting on 30-39-year-old males and females continue to conclude there is probably a higher incidence of pericarditis after vaccination with Moderna compared with Pfizer (moderate certainty).

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Moderna versus Pfizer, after bivalent booster doses

- We identified 1 new study reporting on Moderna vs Pfizer after a bivalent booster dose.
- In ≥12-year-olds (both sexes), there may be no difference in the incidence of pericarditis after a bivalent booster dose of Moderna compared to Pfizer (low certainty).

Homologous vs heterologous vaccine for dose 2

- We identified no new studies reporting on pericarditis by homologous vs. heterologous vaccine dosing. 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).

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. The lack of new case series in this age group is perhaps not surprising, given the very low incidence of myocarditis after mRNA vaccination identified in KQ1 for this age group.
- 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 subsequent) 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 nine reports from the previous synthesis,[24 38 53-59] three new reports were included for longer-term (≥12 weeks) outcomes.[11-13] Overall, findings were similar to the previous update.
- Across 10 studies with unique patients, 278 cases were followed up at least 12 weeks (medians ranged from 13 to 27 weeks). Two reports with at least 12-week follow-up of at least 519 cases reported to Vaccine Adverse Events Reporting System (VAERS) in the US may include cases that overlap with the other reports from the five distinct samples in the other US-based reports.[12 24] Eight (67%) studies had follow-up data for ≥90% of patients with myocarditis;[11 13 53-55 57-59] four studies had lower rates of follow-up (30-76%).[12 24 38 56] Follow-up for completion of health-related quality of life questionnaires was suboptimal (71%) in one study of patients with myocarditis reported to VAERS.[12 68] One death was reported in one study.[13]
- Eight reports presented follow-up MRI findings for 228/651 (35%) patients followed up) with a range of median follow-up from 13 to 27 weeks.[12 38 53-57 59] Improvements were seen in late gadolinium enhancement, positive findings persisted in many patients (139/228, 61%) indicating some residual fibrosis. At follow-up, LVEF% was >50% for all patients in which it was reported (41/41, 100%).[53 55 57 59]
- Ongoing chest pain during follow up (range in medians: 13 to 27 weeks) was reported by 139/481 (29%) patients reporting this outcome.[11 12 38 53 56 57 59] Other symptoms commonly reported by patients included fatigue (91/455, 20%), shortness of breath (85/455, 19%), and palpitations (80/455, 18%).
- At follow-up,[12 38 53] 110/437 patients (25%) were still taking medications related to myocarditis after 13 to 27 weeks or at last healthcare provider encounter.
- 72% of unique patients (72/99) were recovered with no symptoms after 13 to 24 weeks median follow-up. Among 393 patients 12 to 29 years old identified from the VAERS database for whom healthcare providers reported follow-up outcomes after a median of 191 days (~27 weeks),[12] 81% were considered

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fully recovered by their provider based on their clinical assessment and testing information. Cardiac MRI abnormalities were detected in 81/151 (54%) of those re-tested.

- Among 357 VAERS cases completing self-report follow-up questionnaires (median 191 days),[12] 6 patients (2%) reported readmission to hospital. EuroQol 5D-5L, which measures health-related quality of life, was completed by 249/357 (71%) patients who reported problems with anxiety/depression (114/249, 46%), 30% (n=74) pain (74/249, 30%), and ongoing problems participating in their usual activities (49/249, 21%). Few (15/267, 6%) of affected individuals missed school or work in the 2 weeks before follow-up due to myocarditis

CQ1: Hypothesized Mechanisms

The previous version of this report has details of papers describing many hypothesized mechanisms for SARS-CoV-2 vaccine-associated myocarditis. For this version, only studies reporting empirical data on 5 or more patients with suspected myocarditis after SARS-CoV-2 vaccination were included; one study carried forward from the earlier versions[60] and six new studies were found.[14-19] A narrative summarizing each study is presented below, and Table 5 includes details and findings of the included studies. We have not used green font for this section which is all new.

Studies involving biopsy (n=4)

- Two studies examined patients with and without suspected myocarditis after vaccination. One study from Germany evaluated neutralizing autoantibodies targeting the endogenous interleukin-1 receptor antagonist (IL-1RA), which inhibits interleukin-1 signaling and inflammation, and progranulin, which inhibits tumor necrosis factor signaling.[16] Among 61 patients (80% male; 17-79 years of age) with suspected myocarditis having biopsy (timing not reported), 40 had confirmed myocarditis (criteria not reported), among which anti–IL-1RA antibodies were found in 9 of 12 patients (75%) younger than 21 years of age, compared with 3 of 28 patients (11%) 21 years of age or older. Anti–IL-1RA antibodies were not detectable in the 21 patients in whom biopsy ruled out the diagnosis of myocarditis, and were observed in only 2 of 214 vaccinated control participants (1%) and in 2 of 125 participants (2%) who had histologically proven myocarditis that had been diagnosed before the Covid-19 pandemic. IL-1RA plasma levels correlated with markers of cardiac damage (troponin T, creatine kinase, creatine kinase MB, or pro–B-type natriuretic peptide), cardiac-tissue infiltration of CD3+ T cells and CD68+ macrophages, and systemic inflammation (C-reactive protein). These antibodies impaired IL-1RA bioactivity in vitro, were associated with low circulating levels of IL-1RA. A hyperphosphorylated IL-1RA isoform was observed in young male patients with biopsy-confirmed myocarditis after vaccination. The authors suggest that the evidence points toward a transient hyperphosphorylation of IL-1RA preceding a breakdown of peripheral immune tolerance.
- Another study from Germany performed autopsy in 5 deceased patients (mean age 58 years) with confirmed (Dallas criteria) myocarditis, 4-10 days after vaccination mainly (4 of 5) after their first dose.[15] All cases showed a consistent phenotype with: i) focal interstitial lymphocytic myocardial infiltration, in three cases accompanied by demonstrable microfocal myocyte destruction, ii) T-cell dominant infiltrate with CD4 positive T-cells outnumbering CD8 positive T-cells by far, and iii) frequently associated with T-cell infiltration of epicardium and subepicardial fat tissue revealing a similar immune phenotype (CD4 > > CD8). Similar (epi-)myocardial T-cell infiltration was not found among either 20 autopsies performed on bodies found dead within 20 days following an anti-SARS-CoV-2 vaccination or age- and sex matched cohorts from three independent periods from the authors' autopsy-files. Autopsy findings suggested death due to an arrhythmic cause. An inflammatory foci, predominantly in the right heart, which may suggest a gradual blood-stream derived dilution effect, allowed some speculation that inadvertent intravascular vaccine injection may have contributed.
- A US study conducted histopathology and gene expression (rapid turnaround reverse-transcription quantitative polymerase chain reaction) in patients with myocardial injury (6 with suspected post-vaccination myocarditis, 7 with post-COVID-19 myocardial injury and 95 age and sex-matched biobanked control heart samples) for mRNA expression of 7 candidate genes including ACE2, ACE, and other genes whose protein products could be involved in myocardial dysfunction, inflammation, and coagulopathy.[14] None of the 5 patients with suspected post-vaccination myocarditis having biopsy had myocardial inflammatory infiltrate; proinflammatory biomarkers were normal and 3 cases demonstrated no evidence of an inflammatory infiltrate or microthrombi, and only nonspecific abnormalities with no evidence of loss of contractile elements. Further, only 1 of 7 patients with injury post-COVID-19 had definitive myocarditis. These findings may have been from recovery from inflammation or biopsy sampling error. Myocardial gene expression (i.e., down-regulation in ACE2, ACE2/ACE ratio, AGTR1 [encoding type 1 receptor and a biosensor of angiotensin II generation], and ITGA5 [possible CoV-2 co-receptor whose encoded protein binds to and is co-regulated with ACE2 in eccentric remodeling] and upregulation in ACE and F3

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[tissue factor]) was altered to predispose to inflammation, thrombosis, and contractile dysfunction. Changes noted up to 137 or 182 days post-infection diagnosis, reflecting ongoing injury process, or sustained S protein levels. The authors propose that COVID-19 and post–mRNA vaccine myocardial injury may have a common molecular pathology, and that if translated into protein changes, the adjustments in ACE2 and ACE mRNA expression would have negative implications for cardiac myocyte and endothelial cell function as well as for promoting a procoagulant state and predisposing to inflammation. Upregulation of F3 gene may promote thrombosis and inflammation.

- Lacking any control group, another study from Germany performed immunohistochemical analyses from biopsies (timing not reported) in 15 patients (60% male, mean age 38 years) with suspected myocarditis after COVID-19 vaccination (11 after Pfizer [9 after second dose], 4 after non-mRNA) and reduced ejection fraction (mean LVEF 30%).[60] Analyses revealed myocardial inflammation in 14 of 15 patients, with active myocarditis according the Dallas criteria (n = 2), severe giant cell myocarditis (n = 2) and inflammatory cardiomyopathy (DCMi; n = 10). When used, cMRI was able to detect myocardial inflammation in only 33.3% (2/6) of the cases. The SARS-CoV-2 spike protein was found in sparse cells (cardiomyocytes) in 9 of 15 cases. Except the cases with active myocarditis, giant cell myocarditis, and one case of DCMi, CD4+-T-cell-to-CD8+-T-cell ratio was ≥1, suggesting a predominantly autoimmunological origin of the observed inflammation. The expression of SARS-CoV-2 spike protein within the heart and the dominance of CD4+ lymphocytic infiltrates (considered a major driver of autoimmune myocarditis) indicate an autoimmunological response to the vaccination. Expression of HLA-DR (associated strongly several autoimmune diseases) was increased in 11 of 14 (79%) patients, supporting an autoimmunological contribution to myocardial inflammation after vaccination. No patient had increased perforin+ cells, indicating no contribution of cytotoxic events following the COVID-19 vaccination.

Studies involving immunoprofiling (n=3)

- Three studies performed various immunological tests in patients with and without suspected myocarditis after vaccination. Among 16 hospitalized patients with myocarditis (81% male, 88% after 2nd or 3rd dose, mean age 16 years [range 12-21]) and 45 healthy age-matched mRNA vaccinated controls, authors of a US study performed extensive antibody profiling, including tests for SARS-CoV-2–specific humoral responses and assessment for autoantibodies or antibodies against the human-relevant virome, SARS-CoV-2–specific T-cell analysis, and cytokine and SARS-CoV-2 antigen profiling (mean 4 [exposed] and 14 days [controls] after vaccination).[18] Most responses for antibody profiling (i.e. humoral responses of anti-spike or anti-receptor binding protein, IgM, IgG, or IgA levels, self-antibodies) and T-cell analysis were essentially indistinguishable between the individuals who did and did not develop postvaccine myocarditis; there was a modest increase in cytokine production (i.e., interleukin (IL)-8, IL-6, tumor necrosis factor-α, IL-10, interferon-γ, and IL-1β) suggesting likely innate inflammatory activation. Total leukocytes, specifically neutrophils, were significantly increased in individuals with postvaccine myocarditis. There were markedly elevated levels of full-length spike protein (33.9±22.4 pg/mL), unbound by antibodies, in the plasma of individuals with postvaccine myocarditis, whereas no free spike was detected in asymptomatic vaccinated control subjects. No significant differences were found in antibody neutralization capacities. These results suggest that postvaccine myocarditis is associated with normal adaptive and T-cell immunity but modest innate activation. Elevated levels of free spike protein in circulation, unbound by anti-spike antibodies, appear to correlate with cardiac troponin T levels and innate immune activation with cytokine release. The spike antigen itself, which appears to evade antibody recognition rather than invoking immune hyperactivation, may contribute to myocarditis in these individuals.
- A study in Hungary performed routine laboratory testing and testing of humoral and cellular immune response to COVID-19 vaccination in 12 males (22 ± 7 years old, 81% after second dose) with suspected post-vaccine myocarditis and 23 age- and sex-matched controls with similar vaccine exposure.[17] 25% versus 91% had previous COVID-19 infection but anti-NCP (IgG, IgM) testing showed no difference between the two groups. Findings indicated no difference in the humoral immune response (i.e., anti-SARS-CoV-2 modified nucleocapsid protein (NCP)-IgG, anti-SARS-CoV-2 NCP-IgM, SARS-CoV-2 spike (S) protein receptor-binding domain (RBD) Ig, IgG or IgA) but an increased T-cell response. There was no correlation between the humoral immune response (S Ig, SP1 IgG, SP1 IgA) and LVEF, whereas the T-cell response parameters showed a negative correlation with the marker of systolic function. An amplified cellular immune response was found in acute myocarditis cases occurring 4 days after COVID-19 vaccination and it appeared that a T-cell response was sustained for several months after infection and appears to be more prolonged than the antibody response.
- A US study enrolled 23 patients with post-vaccine myocarditis (13 at 2-5 days after vaccination [100% males, mean age 14.6 years] and 10 during 2-5 weeks after resolution of myocarditis) and 10 healthy controls 2-4 weeks after their second dose of mRNA vaccine, both groups with no history of COVID-19, to examine serum samples

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for qualified SARS-CoV-2 pseudovirion neutralization assay using SARS-CoV-2 WA-1 strain, the five variants of concern (Alpha, Gamma, Beta, Delta, and Omicron) and two variants of interest (Lambda and Mu, and seroreactivity to SARS-CoV-2 recombinant spike- receptor binding domain from WA-1 and Omicron.[19] Among those with myocarditis, there was an increase in neutralizing values of 2 to 8-fold from the acute to post-acute time-point across all SARS-CoV-2 variants; neutralization of Omicron was reduced by 31.8-fold compared with the vaccine homologous WA1/2020 and the end-point titer of serum IgG binding to WA1/2020-RBD was 13.7-fold higher than to Omicron. In the healthy controls, neutralizing antibody response was reduced against SARS-CoV-2 variants ranging from 1.2-fold for Alpha to 3.3-fold against Beta compared with vaccine-homologous WA1/2020 and neutralization titers against Omicron were reduced by 27.2-fold with 50% having no measurable neutralization titers compared with vaccine-homologous WA1/2020. In summary, post-vaccination neutralization titers were significantly higher for children with vaccination-induced myocarditis (2–5 weeks post-vaccination) compared with healthy control children (2–4 weeks post-vaccination) against vaccine-homologous WA1/2020 as well as trended higher for Omicron (not statistically significant), possibly suggesting higher immunogenicity of mRNA vaccines in the vaccine-induced myocarditis children. Children with vaccination-induced myocarditis made a robust antibody response that trended higher than healthy children.

Future Directions

- As regular COVID-19 boosters become a reality, continued surveillance of myocarditis after mRNA vaccines is needed to support continued decision making, especially for monovalent booster doses and bivalent vaccines.
- 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 with 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.
- The available studies on biological mechanisms are diverse in their methods and populations, such that additional work is required to better enable comparisons across studies and thus further support any proposed mechanisms.

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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 per million doses 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 primary series)						
Both	6 mo-4y	VAERS* Aug 21/22 US	NR; Y	0/599,457 (Pfizer) 0/440,773 (Moderna)	Among children 6 months to 4 years old, the incidence of myocarditis after vaccination with an mRNA vaccine may be fewer than 20 cases per million.	**Low** *Note: we did not rate down for inconsistency or ROB because this single, passive surveillance study agrees with the Low certainty 5-11 y dose 2 data and we would not expect cases to be higher in this age group.*
Myocarditis (after dose 2)						
M	5-11y	VAERS* May 26/22 US	7 d; Y	2.6 (Pfizer)	Among 5-11-year-old males, the incidence of myocarditis after vaccination with the Pfizer vaccine is probably fewer than 20 cases per million.	**Moderate** [a]
		PCORnet Jan 31/22 US	7 d; Y	0 events (Pfizer)		
		Moderna Global Safety Database* Feb 15/22 Worldwide	7 d; Y	0 (Moderna)		
		PCORnet Jan 31/22 US	21 d; Y	0 events (Pfizer)		
		VSD Dec 30/21 US	21 d; Y	0 events (myo- or pericarditis; Pfizer)		
		TGA* Aug 21/22 Australia	Any; Y	2 (Pfizer)		
	12-17y	VAERS* Jun 18/21 US	Any; Y	118.7 (Pfizer)	Among 12-17-year-old males, the incidence myocarditis after vaccination with an mRNA vaccine is probably between 13 and 390 cases per million.	**Moderate** [a]
		COVaxON* Sep 4/21 Canada	7 d; Y	88.1 (Pfizer)		
		VAERS* May 26/22 US	7 d; Y	58.2* (Pfizer)		
		SNDS Oct 31/21 France	7 d; Y	19.3† (Pfizer)		
		PCORnet Jan 31/22 US	7 d; Y	220 (Pfizer)		

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Sex	Age	Studies (data source and date) Country *passive surveillance	Risk interval; Confirmed cases (Y/N)	Incidence per million doses of either mRNA vaccine unless otherwise stated *weighted average across age groups ‡weighted average across products †excess incidence	Conclusions	Certainty about conclusions using GRADE
		Moderna Global Safety Database* Feb 15/22 Worldwide	7 d; Y	14.6 (Moderna)		
		BC COVID-19 Cohort Mar 10/22 Canada	7 d; Y	67.3 (Pfizer)		
		PCORnet Jan 31/22 US	21 d; Y	267 (Pfizer)		
		BC COVID-19 Cohort Mar 10/22 Canada	21 d; Y	67.3 (Pfizer)		
		Israeli MOH Oct 20/21 Israel	30 d; Y	80.9 (Pfizer)		
		SAEFVIC* Feb 22/22 Australia	Any; Y	242		
		TGA* Aug 21/22 Australia	Any; Y	172‡		
		eHRSS Oct 18/21 Hong Kong	Any; Y	390.2 (Pfizer)		
		Nordic cohort Oct 5/21 Nordic countries	7 d; Y	39.4*†‡		
		Nordic Cohort Sep 1/22 Nordic countries	28 d; Y	12.7*† (Pfizer)		
		Nordic cohort Oct 5/21 Nordic countries	28d; Y	49.2*†‡		
	18-29y	Singapore Military Aug 3/21 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 to 157 cases per million.	**Moderate** [a]
		COVaxON* Sep 4/21 Canada	7 d; Y	147.2‡ (18-24y)		
		SNDS Oct 31/21 France	7 d; Y	61.9†‡ (18-24y)		
		IDF Mar 7/21 Israel	7d; Y	50.7 (18-24y; Pfizer)		
		Moderna Global Safety Database* Feb 15/22 Worldwide	7 d; Y	42.3 (18-24y; Moderna)		
		VAERS* May 26/22 US	7 d; Y	29.0*		
		PCORnet Jan 31/22 US	7 d; Y	65		

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Sex	Age	Studies (data source and date) Country *passive surveillance	Risk interval; Confirmed cases (Y/N)	Incidence per million doses of either mRNA vaccine unless otherwise stated *weighted average across age groups ‡weighted average across products †excess incidence	Conclusions	Certainty about conclusions using GRADE
		BC COVID-19 Cohort Mar 10/22 Canada	7 d; Y	135.3‡		
		PCORnet Jan 31/22 US	21 d; Y	84		
		BC COVID-19 Cohort Mar 10/22 Canada	21 d; Y	143.7‡		
		Nordic Cohort Sep 1/22 Nordic countries	28 d; Y	55.2*†‡		
		Israeli MOH Oct 10/21 Israel	30 d; Y	106.2*		
		TGA* Aug 21/22 Australia	NR; Y	156.5‡		
		BNPV* Sep 30/21 France	NR; 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 8 and 104 cases per million.	**Moderate** [a]
		US Military Apr 30/21 US	4 d (all cases); Y	44 (median 25y [IQR: 20 to 51y])		
		Moderna Global Safety Database* Feb 15/22 Worldwide	7 d; Y	23.0* (Moderna)		
		COVaxON* Sep 4/21 Canada	7 d; Y	82.2*‡		
		SNDS Oct 31/21 France	7 d; Y	34.3*†‡		
		VAERS* Jan 13/22 US	7 d; Y	20.7* (Moderna)		
		VAERS* May 26/22 US	7 d; Y	19.2*		
		Nordic cohort Oct 5/21 Nordic countries	7d; Y	39.4*†‡		
		BC COVID-19 Cohort Mar 10/22 Canada	7 d; Y	90.7*‡		
			21 d; Y	97.4*‡		
		Nordic cohort Oct 5/21 Nordic countries	28d; Y	47.7*†‡		
		Nordic Cohort Sep 1/22 Nordic countries	28 d; Y	8.4*† (Pfizer)		

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Sex	Age	Studies (data source and date) Country *passive surveillance	Risk interval; Confirmed cases (Y/N)	Incidence per million doses of either mRNA vaccine unless otherwise stated *weighted average across age groups ‡weighted average across products †excess incidence	Conclusions	Certainty about conclusions using GRADE
		TGA* Aug 21/22 Australia	NR; Y	103.5*‡		
F	5-11y	VAERS* May 26/22 US	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.	**Low**
		PCORnet Jan 31/22 US	7 d; Y	0 events (Pfizer)		
		Moderna Global Safety Database* Feb 15/22 Worldwide	7 d; Y	0 (Moderna)		
		PCORnet Jan 31/22 US	21 d; Y	0 events (Pfizer)		
		VAERS* Dec 9/21 US	12 d; Y	2.98 (both sexes; Pfizer)		
		VSD Dec 30/21 US	21 d; Y	2.3* (both sexes; myo- or pericarditis; Pfizer)		
		TGA* Aug 21/22 Australia	NR; Y	0 (Pfizer)		
	12-17y	VAERS* Jun 18/21 US	Any; Y	12.7 (Pfizer)	Among 12-17-year-old females, we are uncertain whether the incidence of presenting with myocarditis after vaccination with an mRNA vaccine is fewer than 20 cases per million (range: 1 to 50).	**Very Low** [b]
		COVaxON* Sep 4/21 Canada	7 d; Y	9.7 (Pfizer)		
		VAERS* May 26/22 US	7 d; Y	5.5* (Pfizer)		
		eHRSS Oct 18/21 Hong Kong	NR; Y	49.7 (13.5 to 127.2) (Pfizer)		
		SNDS Oct 31/21 France	7 d; Y	2.6† (Pfizer)		
		PCORnet Jan 31/22 US	7 d; Y	11		
		Moderna Global Safety Database* Feb 15/22 Worldwide	7 d; Y	1.3 (Moderna)		
		BC COVID-19 Cohort Mar 10/22 Canada	7 d; Y	15.3 (1.9 to 55.3) (Pfizer)		
		PCORnet Jan 31/22 US	21 d; Y	32		
		BC COVID-19 Cohort Mar 10/22 Canada	21 d; Y	15.3 (1.9 to 55.3) (Pfizer)		
		Israeli MOH Oct 20/21 Israel	30 d; Y	6.9 (Pfizer)		

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Sex	Age	Studies (data source and date) Country *passive surveillance	Risk interval; Confirmed cases (Y/N)	Incidence per million doses of either mRNA vaccine unless otherwise stated *weighted average across age groups ‡weighted average across products †excess incidence	Conclusions	Certainty about conclusions using GRADE
		SAEFVIC* Feb 22/22 Australia	NR; Y	43		
		TGA* Aug 21/22 Australia	NR; Y	39‡		
		Nordic cohort Oct 5/21 Nordic countries	7 d; Y	1.5*†‡		
		Nordic cohort Oct 5/21 Nordic countries	28d; Y	10.9*†‡		
		Nordic Cohort Sep 1/22 Nordic countries	28 d; Y	2.53*† (Pfizer)		
	18-29y	VAERS* May 26/22 US	7 d; Y	3.8*	Among 18-29-year-old females, we are uncertain whether the incidence of presenting with myocarditis after vaccination with an mRNA vaccine is fewer than 20 cases per million (range: 2 to 37).	**Very Low** [b]
		VAERS* Jan 13/22 US	7 d; Y	5.6* (Moderna)		
		TGA* Aug 21/22 Australia	NR; Y	37‡		
		Moderna Global Safety Database* Feb 15/22 Worldwide	7 d; Y	3.8 (18-24y; Moderna)		
		COVaxON* Sep 4/21 Canada	7 d; Y	34.6‡		
		SNDS Oct 31/21 France	7 d; Y	11.4†‡ (18-24y)		
		PCORnet Jan 31/22 US	7 d; Y	16		
		BC COVID-19 Cohort Mar 10/22 Canada	7 d; Y	10.7‡		
		PCORnet Jan 31/22 US	21 d; Y	21		
		BC COVID-19 Cohort Mar 10/22 Canada	21 d; Y	15.7‡		
		Nordic Cohort Sep 1/22 Nordic countries	28 d; Y	2.0*† (Pfizer)		
		Israeli MOH Oct 10/21 Israel	30 d; Y	13.7*		
	18-39y	COVaxON* Sep 4/21 Canada	7 d; Y	22.8*‡	Among 18-39-year-old females, the incidence of myocarditis after vaccination with an mRNA vaccine may be below 20 cases per million.	**Low**
		Moderna Global Safety Database* Feb 15/22 Worldwide	7 d; Y	2.3* (Moderna)		

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Sex	Age	Studies (data source and date) Country *passive surveillance	Risk interval; Confirmed cases (Y/N)	Incidence per million doses 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 26/22 US	7 d; Y	2.5*		
		SNDS Oct 31/21 France	7 d; Y	5.7*†‡		
		Nordic cohort Oct 5/21 Nordic countries	7d; Y	3.3*†‡		
		BC COVID-19 Cohort Mar 10/22 Canada	7 d; Y	10.8*‡		
			21 d; Y	16.9*‡		
		Nordic cohort Oct 5/21 Nordic countries	28d; Y	4.0*†‡		
		Nordic Cohort Sep 1/22 Nordic countries	28 d; Y	1.7*† (Pfizer)		
		TGA* Aug 21/22 Australia	NR; Y	22.5*‡		
Myocarditis (after dose 3, monovalent)						
M	5-11y	VAERS* May 26/22 US	7 d; Y	0	Among 5-11-year-old males, we are uncertain about the incidence of myocarditis after vaccination with a third dose of a monovalent mRNA vaccine (range: 0 to 0 cases).	**Very Low** [d]
		VAERS* Jul 31/22 US	NR; Y	0/657,302 (both sexes; Pfizer)		
	12-17y	Moderna Global Safety Database* Feb 15/22 Worldwide	7 d; Y	0 (Moderna)	Among 12-17-year-old males, we are uncertain about the incidence of myocarditis after vaccination with a third dose of a monovalent mRNA vaccine (range: 0 to 94 cases per million).	**Very Low** [b]
		Israeli MOH Oct 10/21 Israel	30 d; Y	17.3*		
		VAERS* May 26/22 US	7 d; Y	18.8* (Pfizer)		
		BC COVID-19 Cohort Mar 10/22 Canada	7 d; Y	70.1 (14.5 to 204.9) (Pfizer)		
			21 d; Y	93.5 (25.5 to 239.3) (Pfizer)		
		VAERS* Feb 20/22 US	NR; Y	11.4		
	18-29y	Israeli MOH Nov 5/21 Israel	30 d; Y	35.7* (Pfizer)	Among 18-29-year-old males, we are uncertain about the incidence of myocarditis after vaccination with a third dose of a monovalent mRNA vaccine (range: 4 to 113 cases per million).	**Very Low** [b,c]
		Israeli MOH Oct 10/21 Israel	30 d; Y	26.5		
		Moderna Global Safety Database* Feb 15/22 Worldwide	7 d; Y	4.0 (18-24y; Moderna)		

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Sex	Age	Studies (data source and date) Country *passive surveillance	Risk interval; Confirmed cases (Y/N)	Incidence per million doses of either mRNA vaccine unless otherwise stated *weighted average across age groups ‡weighted average across products †excess incidence	Conclusions	Certainty about conclusions using GRADE
		BC COVID-19 Cohort Mar 10/22 Canada	7 d; Y	34.7‡		
		IDF Sep 30/21 Israel	7 d; Y	64 (18-24 y)		
		VAERS* May 26/22 US	7 d; Y	6.1*		
		IDF Sep 30/21 Israel	14 d; Y	112.5 (18-24 y)		
		BC COVID-19 Cohort Mar 10/22 Canada	21 d; Y	34.7‡		
		VAERS* Feb 6/22 US	6 d; Y	4.6*‡		
	30-39y	VAERS* Feb 6/22 US	6d; Y	1.35‡	Among 30-39-year-old males, we are uncertain about the incidence of myocarditis after vaccination with a third dose of a monovalent mRNA vaccine (range: 1 to 48 cases per million).	**Very Low** [b]
		VAERS* May 26/22 US	7 d; Y	4.2*		
		Moderna Global Safety Database* Feb 15/22 Worldwide	7 d; Y	3.3 (25-39y; Moderna)		
		Israeli MOH Nov 5/21 Israel	30 d; Y	18.1 (Pfizer)		
		Nordic Cohort Sep 1/22 Nordic countries	28 d; Y	48.1*† (25-39y; Pfizer)		
		BC COVID-19 Cohort Mar 10/22 Canada	7 d; Y	14.0 ‡		
			21 d; Y	22.1 ‡		
	≥40y	NIMS/NHS Nov 15/21 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 a monovalent mRNA vaccine may be fewer than 20 cases per million.	**Low**
		NIMS/NHS Nov 15/21 UK	7 d; Y	0†‡		
		BC COVID-19 Cohort Mar 10/22 Canada	7 d; Y	3.69 *‡		
			21 d; Y	9.3*‡		
		Israeli MOH Oct 10/21 Israel	30 d; Y	4.1 (≥30y)		
F	5-11y	VAERS* May 26/22 US	7 d; Y	0	Among 5-11-year-old females, the incidence of myocarditis after vaccination	**Low**

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Sex	Age	Studies (data source and date) Country *passive surveillance	Risk interval; Confirmed cases (Y/N)	Incidence per million doses 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* Jul 31/22 US	NR; Y	0/657,302 (both sexes)	with a third dose of an mRNA vaccine may be fewer than 20 cases per million.	*Note: we did not rate down for ROB because findings are similar to the Moderate certainty findings in 12-17 year olds*
	12-17y	Israeli MOH Oct 10/21 Israel	30 d; Y	0 events* (Pfizer)	Among 12-17-year-old females, the incidence of myocarditis after vaccination with a third dose of an mRNA vaccine is probably fewer than 20 cases per million.	**Moderate** [a]
		VAERS* May 26/22 US	7 d; Y	0*		
		Moderna Global Safety Database* Feb 15/22 Worldwide	7 d; Y	0 (Moderna)		
		BC COVID-19 Cohort Mar 10/22 Canada	7 d; Y	0‡ (Pfizer)		
			21 d; Y	0‡ (Pfizer)		
	18-29y	VAERS* Feb 6/22 US	6d; Y	~1‡	Among 18-29-year-old females, the incidence of myocarditis after vaccination with a third dose of an mRNA vaccine is probably fewer than 20 cases per million.	**Moderate** [a]
		VAERS* May 26/22 US	7 d; Y	1.2*		
		Moderna Global Safety Database* Feb 15/22 Worldwide	7 d; Y	0.6 (18-24y; Moderna)		
		BC COVID-19 Cohort Mar 10/22 Canada	7 d; Y	0‡		
			21 d; Y	0‡		
		Israeli MOH Oct 10/21 Israel	30 d; Y	0 events*		
		Israeli MOH Nov 5/21 Israel	30 d; Y	1.8* (Pfizer)		
	30-39y	VAERS* Feb 6/22 US	6d; 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.	**Low**
		VAERS* May 26/22 US	7 d; Y	0.6		
		Moderna Global Safety Database* Feb 15/22 Worldwide	7 d; Y	1.4 (25-39y; Moderna)		
		BC COVID-19 Cohort Mar 10/22 Canada	7 d; Y	5‡		
			21 d; Y	5‡		

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Sex	Age	Studies (data source and date) Country *passive surveillance	Risk interval; Confirmed cases (Y/N)	Incidence per million doses 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 Sep 1/22 Nordic countries	28 d; Y	4.1*† (25-39y; Pfizer)		
		Israeli MOH Nov 5/21 Israel	30 d; Y	3.7 (Pfizer)		
	≥40y	NIMS/NHS Nov 15/21 UK	28 d; Y	0†‡	Among ≥40-year-old females, the incidence of myocarditis after vaccination with a third dose of an mRNA vaccine may be fewer than 20 cases per million.	**Low** *Note: 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*
			7 d; Y	0†‡		
		Mayo Clinic Oct 17/21 US	14d; Y	41.5‡		
		BC COVID-19 Cohort Mar 10/22 Canada	7 d; Y	5.0*‡		
			21 d; Y	9.3*‡		
		Israeli MOH Oct 10/21	30 d; Y	0 events/1,542,142 doses (≥30y)		
Myocarditis(after dose 4, monovalent)						
Both	≥12y	VAERS* Mar 28/22 US	NR; Y	0/518,113 doses	In all ages and sexes, we are uncertain about the incidence of myocarditis after vaccination with a fourth dose of an mRNA vaccine.	**Very Low** [b,c]
Myocarditis(any booster dose, bivalent)						
Both	5-11y	VAERS* Jan 1/23 US	NR; Y	0/861,251 doses (Pfizer) 0/92,108 doses (6-11y; Moderna)	Among 5-11-year-olds, we are uncertain about the incidence of myocarditis after a booster dose of bivalent mRNA vaccine.	**Very Low** [b,d]
	≥12y	VAERS* Oct 23/22 US	NR; Y	0.21 (Pfizer) 0.24 (≥18y; Moderna)	Among individuals ≥12 years old, we are uncertain about the incidence of myocarditis after a booster dose of bivalent mRNA vaccine.	**Very Low** [b,c,d]
M	≥50y	Danish Health Data Authority Dec 10/22 Denmark	28d; Y	0.8†	Among males ≥50 years old, we are uncertain about the incidence of myocarditis after a booster dose of bivalent mRNA vaccine	**Very Low** [b]
F	≥50y	Danish Health Data Authority Dec 10/22 Denmark	28d; Y	4.5†	Among females ≥50 years old, we are uncertain about the incidence of myocarditis after a booster dose of bivalent mRNA vaccine	**Very Low** [b]
Pericarditis (after dose 2, monovalent)						
M	5-11y	VSD Dec 30/21 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]
	12-17y	Nordic cohort Oct 5/21 Nordic countries	28d; 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.	**Low**
		SNDS Oct 31/21 France	7d; Y	6.8† (Pfizer)		

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Sex	Age	Studies (data source and date) Country *passive surveillance	Risk interval; Confirmed cases (Y/N)	Incidence per million doses of either mRNA vaccine unless otherwise stated *weighted average across age groups ‡weighted average across products †excess incidence	Conclusions	Certainty about conclusions using GRADE
	18-24y	Nordic cohort Oct 5/21 Nordic countries	28d; Y	21.0*†‡ (16-24y)	Among 18-24-year-old males, we are uncertain about the incidence of pericarditis after vaccination with a n mRNA vaccine.	**Very Low** [b]
		SNDS Oct 31/21 France	7d; Y	12.9†‡		
	25-39y	Nordic cohort Oct 5/21 Nordic countries	28d; 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.	**Low**
		SNDS Oct 31/21 France	7d; Y	3.7*†‡		
F	5-11y	VSD Dec 30/21 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]
	12-17y	Nordic cohort Oct 5/21 Nordic countries	28d; 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.	**Low**
		SNDS Oct 31/21 France	7d; Y	6.8† (Pfizer)		
	18-24y	Nordic cohort Oct 5/21 Nordic countries	28d; 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.	**Low**
		SNDS Oct 31/21 France	7d; Y	13.5† (Pfizer)		
	25-39y	Nordic cohort Oct 5/21 Nordic countries	28d; Y	5.4†‡	Among 25-39-year-old females, we are uncertain about the incidence of pericarditis after vaccination with an mRNA vaccine.	**Very Low** [b,c]
		SNDS Oct 31/21 France	7d; Y	22.4*†‡		
Pericarditis (any booster dose, bivalent)						
Both	≥12y	VAERS* Oct 23/22 US	NR; Y	0.07 (Pfizer) 0.37 (≥18y; Moderna)	Among individuals ≥12 years old, we are uncertain about the incidence of pericarditis after a booster dose of a bivalent mRNA vaccine.	**Very Low** [b,c,d]
M	≥50y	Danish Health Data Authority Dec 10/22 Denmark	28d; Y	0.1†	Among males ≥50 years old, we are uncertain about the incidence of pericarditis after a booster dose of a bivalent mRNA vaccine	**Very Low** [b]
F	≥50y	Danish Health Data Authority Dec 10/22 Denmark	28d; Y	4.2†	Among females ≥50 years old, we are uncertain about the incidence of pericarditis after a booster dose of a bivalent mRNA vaccine	**Very Low** [b]

Green text = new evidence identified by Feb 2023 update. Blue text = increased certainty since last report; red text = decreased certainty since last report.
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.

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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.
VAERS – Vaccine Adverse Events Reporting System is a passive surveillance system in 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)

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/spontaneous reporting

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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[2]	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), primary series							
Both	6mo-4y	VAERS* Aug 21/22	NR; Y	Moderna: 0 events (6mo to 5y) Pfizer: 0 events		Among individuals 6 months to 4 years old, the incidence of myocarditis may not differ following primary series vaccination with Moderna compared with Pfizer.	**Low** [a,b]
Moderna vs Pfizer (ref), dose 2							
M	12-17	TGA* Aug 21/22/22 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,c]
	18-29y	VAERS* Oct 6/21 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** [d]
		SNDS Oct 31/21 France	7 d; Y	Moderna: 146.3* Pfizer:40.4*	Ratio of aORs: 3.19		
		BC COVID-19 Cohort Mar 10/22 Canada	7 d; Y	Moderna: 220.5 (141.3–328.1) Pfizer: 50.6 (27.0–86.6)			
			21 d; Y	Moderna: 229.7 (148.7–339.1) Pfizer: 58.4 (32.7–96.3)			
		TGA* Aug 21/22 Australia	NR; Y	Moderna: 223 Pfizer: 90			
		BNPV* Sep 30/21 France	NR; Y	Moderna: 110.3* Pfizer: 33.0*			
		COVaxON* Sep 4/21 Canada	Any; Y	Moderna: 299.5 (171.2, 486.4) Pfizer: 35.5 (7.3, 103.7)			
	18-39y	VAERS* Oct 6/21 US	7 d; Y	Moderna: 19.2* Pfizer:16.5*		Among 18-39-year-old males, there is probably at least a 2-5 times higher incidence of myocarditis following	**Moderate** [d]
		VSD Jan 15/22 US	7 d; Y		RD: 13.6 aRR: 1.31 (0.73 to 2.31)		

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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[2]	Relative measures (95% CI) aRR = adjusted risk ratio aOR = adjusted odds ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
		Nordic cohort Oct 5/21 Nordic countries	7 d; Y	Moderna: 113.3* Pfizer: 18.39*		vaccination with Moderna compared with Pfizer.	
		SNDS Oct 31/21 France	7 d; Y	Moderna: 105.6* Pfizer: 26.6*	Ratio of aORs: 4.65		
		BC COVID-19 Cohort Mar 10/22 Canada	7 d; Y	Moderna: 152.0* Pfizer: 29.7*			
		BC COVID-19 Cohort Mar 10/22 Canada	21 d; Y	Moderna: 157.1* Pfizer: 38.1*			
		Nordic Cohort Sep 1/22 Nordic countries	28 d; Y	Moderna: 85.6* Pfizer: 13.9*			
		TGA* Aug 21/22 Australia	NR; Y	Moderna: 144.4* Pfizer: 62.7*			
		Singapore Military Aug 3/21 Singapore	Any; Y	Moderna: 135.3* Pfizer: 0 events/27,632			
		COVaxON* Sep 4/21 Canada	Any; Y	Moderna: 144.5* Pfizer: 19.9*			
	30-39y	VAERS* Oct 6/21 US	7 d; Y	Moderna: 6.7 Pfizer: 5.2		Among 30-39-year-old males, there is a higher incidence of myocarditis following vaccination with Moderna compared with Pfizer.	**High**
		SNDS Oct 31/21 France	7 d; Y	Moderna: 64.5 Pfizer: 10.3	Ratio of aORs:7.89		
		BC COVID-19 Cohort Mar 10/22 Canada	7 d; Y	Moderna: 69.9 (28.1–144.0) Pfizer: 4.6 (0.1–25.7)			
			21 d; Y	Moderna: 69.9 (28.1–144.0) Pfizer: 13.8 (2.9–40.5)			
		Nordic Cohort Sep 1/22 Nordic countries	28 d; Y	Moderna: 53.4 (24-39y) Pfizer: 6.4 (24-39y)			
		TGA* Aug 21/22 Australia	NR; Y	Moderna: 50 Pfizer: 30			
	≥40y	VAERS* Oct 6/21 US	7 d; Y	Moderna: 1.52* (40-64y) Pfizer: 0.98* (40-64y)		Among ≥40-year-old males, we are uncertain about a difference in incidence of myocarditis after vaccination with Moderna compared with Pfizer.	**Very Low** [A,c]
		NIMS Nov 15/21[1] UK	7 d; Y	Moderna: 0 events Pfizer: IRR = 0.65 (0.27, 1.59)			
		BC COVID-19 Cohort Mar 10/22 Canada	7 d; Y	Moderna: 2.6* Pfizer: 10.3*			
			21 d; Y	Moderna: 2.6* Pfizer: 11.5*			

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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[2]	Relative measures (95% CI) aRR = adjusted risk ratio aOR = adjusted odds ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
		NIMS Nov 15/21[1] UK	28 d; Y	Moderna: 0 events Pfizer: IRR = 0.79 (0.51, 1.23)			
		COVaxON* Sep 4/21 Canada	Any; Y	Moderna: 0.0 (0.0-35.6) Pfizer: 0.0 (0.0-23.3)			
		Nordic cohort Oct 5/21 Nordic countries	7 d; Y	Moderna: 5.4 Pfizer: 1.4			
			28 d; Y	Moderna: 18.9 Pfizer: 6.5			
		TGA* Aug 21/22 Australia	NR; Y	Moderna: 9* Pfizer: 6.25*			
F	12-17y	TGA* Aug 21/22 Australia	NR; Y	Moderna: 5 Pfizer: 28		Among 12-17y females, we are uncertain about a difference in incidence of myocarditis following vaccination with Moderna compared with Pfizer.	**Very Low** [A,c]
	18-29y	COVaxON* Sep 4/21 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** [d]
		VAERS* Oct 6/21 US	7 d; Y	Moderna: 5.5* Pfizer: 2.0*			
		SNDS Oct 31/21 France	7 d; Y	Moderna: 37.4* Pfizer: 5.6*	Ratio of aORs:3.43		
		BC COVID-19 Cohort Mar 10/22 Canada	7 d; Y	Moderna: 10.0 (0.3–55.8) Pfizer: 11.3 (2.3–33.0)			
			21 d; Y	Moderna: 20.0 (2.4–72.3) Pfizer: 11.3 (2.3–33.0)			
		TGA* Aug 21/22 Australia	NR; Y	Moderna: 48 Pfizer: 26			
	18-39y	VAERS* Oct 6/21 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** [c]
		COVaxON* Sep 4/21 Canada	Any; Y	Moderna:36.8* Pfizer: 8.9*			
		VSD Jan 15/22 US	7 d; Y		RD: -1.8 aRR: 0.53 (0.02 to 5.81)		
		Nordic cohort Oct 5/21 Nordic countries	7 d; Y	Moderna: 7.3* Pfizer: 3.1*			
		SNDS Oct 31/21 France	7 d; Y	Moderna: 19.7* Pfizer: 4.0*	Ratio of aORs:2.65		
		BC COVID-19 Cohort Mar 10/22	7 d; Y	Moderna: 15.4* Pfizer: 6.2*			

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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[2]	Relative measures (95% CI) aRR = adjusted risk ratio aOR = adjusted odds ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
		Canada	21 d; Y	Moderna: 25.8* Pfizer: 8.1*			
		Nordic cohort Oct 5/21 Nordic countries	28 d; Y	Moderna: 10.4* Pfizer: 5.9*			
		TGA* Aug 21/22 Australia	NR; Y	Moderna: 26.2* Pfizer: 18.7*			
	30-39y	VAERS* Oct 6/21 US	7 d; Y	Moderna: 0.4 Pfizer: 0.7		Among 30-39-year-old females, there may be a higher incidence of myocarditis after vaccination with Moderna compared with Pfizer.	**Low** [a,d]
		SNDS Oct 31/21 France	7 d; Y	Moderna: 2.7 Pfizer: 2.1	Ratio of aORs: 0.35		
		BC COVID-19 Cohort Mar 10/22 Canada	7 d; Y	Moderna: 21.8 (2.6–78.7) Pfizer: 0.0 (0.0–15.8)			
			21 d; Y	Moderna: 32.7 (6.7–95.5) Pfizer: 4.3 (0.1–23.9)			
		Nordic Cohort Sep 1/22 Nordic countries	28 d; Y	Moderna: 5.5 Pfizer: 2.4			
		TGA* Aug 21/22 Australia	NR; Y	Moderna: 0 Pfizer: 10			
	≥40y	COVaxON* Sep 4/21 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]
		NIMS Nov 15/21[1] UK	7 d; Y	Moderna: 0 events Pfizer: IRR= 0.80 (0.33, 1.97)			
		NIMS Nov 15/21[1] UK	28 d; Y	Moderna: 0 events Pfizer: IRR = 1.00 (0.64, 1.55)			
		VAERS* Oct 6/21 US	7 d; Y	Moderna: 0.8* (40-64y) Pfizer: 0.74* (40-64y)			
		Nordic cohort Oct 5/21 Nordic countries	7 d; Y	Moderna: 5.4 Pfizer: 1.4			
		BC COVID-19 Cohort Mar 10/22 Canada	7 d; Y	Moderna: 6.1* Pfizer: 3.0*			
			21 d; Y	Moderna: 6.1* Pfizer: 9.4*			
		Nordic cohort Oct 5/21 Nordic countries	28 d; Y	Moderna: 8.9 Pfizer: 4.0			
		TGA* Aug 21/22 Australia	NR; Y	Moderna: 17.5* Pfizer: 7*			
Moderna vs Pfizer (ref), dose 3 (monovalent)							

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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[2]	Relative measures (95% CI) aRR = adjusted risk ratio aOR = adjusted odds ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
M	18-29y	VAERS* Feb 6/22 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 monovalent dose of Moderna compared with Pfizer.	**Low** [a,c]
		BC COVID-19 Cohort Mar 10/22 Canada	7 d; Y	Moderna: 39.5 (1.0–220.2) Pfizer: 29.8 (6.1–87.0)			
			21 d; Y	Moderna: 39.5 (1.0–220.2) Pfizer: 29.8 (6.1–87.0)			
	30-39y	VAERS* Feb 6/22 US	6 d; Y	Moderna: <1.0 Pfizer: 1.7		Among 30-39-year-old males, there may be a lower incidence of myocarditis after vaccination with a third monovalent dose of Moderna compared with Pfizer.	**Low** [c,d]
		BC COVID-19 Cohort Mar 10/22 Canada	7 d; Y	Moderna: 11.6 (0.3–64.8) Pfizer: 16.3 (0.4–90.8)			
			21 d; Y	Moderna: 11.6 (0.3–64.8) Pfizer: 32.6 (3.9–117.7)			
	≥40y	VAERS* Feb 6/22 US	6 d; Y	Moderna: <1.0* Pfizer: <2.0*		Among ≥40-year-old males, the incidence of myocarditis may not differ after vaccination with a third monovalent dose of Moderna compared with Pfizer.	**Low** [a,b]
		BC COVID-19 Cohort Mar 10/22 Canada	7 d; Y	Moderna: 3.7* Pfizer: 3.7*			
			21 d; Y	Moderna: 9.0* Pfizer: 9.6*			
F	18-29y	VAERS* Feb 6/22 US	6 d; Y	Moderna: 1.1* Pfizer: 0.5*		Among 18-29-year-old females, incidence of myocarditis may not differ after vaccination with a third monovalent dose of Moderna compared with Pfizer.	**Low** [c,d]
		BC COVID-19 Cohort Mar 10/22 Canada	7 d; Y	Moderna: 0.00 (0.0–95.9) Pfizer: 0.00 (0.0–29.6)			
		BC COVID-19 Cohort Mar 10/22 Canada	21 d; Y	Moderna: 0.00 (0.0–95.9) Pfizer: 0.00 (0.0–29.6)			
	30-39y	VAERS* Feb 6/22 US	6 d; Y	Moderna: 1.5 Pfizer: <1.0		Among 30-39-year-old females, there may be a higher incidence of myocarditis after vaccination with a third monovalent dose of Moderna compared with Pfizer.	**Low** [c,d]
		BC COVID-19 Cohort Mar 10/22 Canada	7 d; Y	Moderna: 10.0 (0.3–55.4) Pfizer: 0.0 (0.0–50.4)			
		BC COVID-19 Cohort Mar 10/22 Canada	21 d; Y	Moderna: 10.0 (0.3–55.4) Pfizer: 0.0 (0.0–50.4)			
	≥40y	VAERS* Feb 6/22 US	6 d; Y	Moderna: <2.0* Pfizer: 0 events*		Among ≥40-year-old females, we are uncertain about a difference in incidence of myocarditis after vaccination with a third monovalent dose of Moderna compared with Pfizer.	**Very Low** [A,c]
		BC COVID-19 Cohort Mar 10/22 Canada	7 d; Y	Moderna: 5.5* Pfizer: 4.5*			
			21 d; Y	Moderna: 6.9* Pfizer: 11.8*			
Moderna vs Pfizer (ref), bivalent booster dose							

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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[2]	Relative measures (95% CI) aRR = adjusted risk ratio aOR = adjusted odds ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
Both	5-11y	VAERS* Jan 1/23 US	NR; Y	Moderna: 0/92,108 (6–11 y, only approved for ≥6 y) Pfizer: 0/861,251		Among 5-11-year-old children, the incidence of myocarditis may not differ after a bivalent booster dose of Moderna compared with Pfizer.	**Low** [a,b]
	≥12y	VAERS* Oct 23/22 US	NR; Y	Moderna: 0.24 (≥18 y) Pfizer: 0.21		Among individuals aged 12 years and older, the incidence of myocarditis may not differ after a bivalent booster dose of Moderna compared with Pfizer.	**Low** [a,b]
Heterologous vs Homologous (ref) dose 2							
M	16-24y	Nordic cohort Oct 5/21 Nordic countries	7 d; Y	Mod-Mod: 141.2 Pfiz-Mod: 250.6 Pfiz-Pfiz: 42.1		Among 16-24-year-old 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,d]
		Nordic cohort Oct 5/21 Nordic countries	28 d; Y	Mod-Mod: 198.3 Pfiz-Mod: 283.3 Pfiz-Pfiz: 68.3			
		COVaxON* Sep 4/21 Canada	Any; Y	Mod-Mod: 288.4 (18-24y; myo- or pericarditis) Mod-Pfiz: 0 (18-24y; myo- or pericarditis) Pfiz-Mod: 337.6 (18-24y; myo- or pericarditis) Pfiz-Pfiz: 46.6 (18-24y; myo- or pericarditis)			
	25-39y	Nordic cohort Oct 5/21 Nordic countries	7 d; Y	Mod-Mod: 74.4 Pfiz-Mod: 92.3 Pfiz-Pfiz: 7.3		Among 25-39y 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,d]
		Nordic cohort Oct 5/21 Nordic countries	28 d; Y	Mod-Mod: 86.6 Pfiz-Mod: 118.5 Pfiz-Pfiz: 13.7			
	≥40y	Nordic cohort Oct 5/21 Nordic countries	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,d]
		Nordic cohort Oct 5/21 Nordic countries	28 d; Y	Mod-Mod: 19.5 Pfiz-Mod: 40.8 Pfiz-Pfiz: 6.5			

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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[2]	Relative measures (95% CI) aRR = adjusted risk ratio aOR = adjusted odds ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
F	16-24y	Nordic cohort Oct 5/21 Nordic countries	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,d]
		Nordic cohort Oct 5/21 Nordic countries	28 d; Y	Mod-Mod: 0 events/99,139 vaccinees Pfiz-Mod: 95.8 Pfiz-Pfiz: 8.7			
	25-39y	Nordic cohort Oct 5/21 Nordic countries	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 about a difference in incidence of myocarditis after vaccination with a heterologous dose 2 of Moderna compared with homologous Moderna or Pfizer.	**Very Low** [A,d]
		Nordic cohort Oct 5/21 Nordic countries	28 d; Y	Mod-Mod: 18.3 Pfiz-Mod: 0 events/97,835 vaccinees Pfiz-Pfiz: 4.5			
	≥40y	Nordic cohort Oct 5/21 Nordic countries	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,d]
		Nordic cohort Oct 5/21 Nordic countries	28 d; Y	Mod-Mod: 8.6 Pfiz-Mod: 51.1 Pfiz-Pfiz: 4.0			
Dose interval, dose 1 to dose 2							
Both	12-29y	SNDS Jan 31/22 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, 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** [a,b]
	≥30y	SNDS Jan 31/22 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,b]
Dose interval, dose 2 to dose 3, Pfizer							

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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[2]	Relative measures (95% CI) aRR = adjusted risk ratio aOR = adjusted odds ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
Both	12-29y	SNDS Jan 31/22 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,b]
	≥30y	SNDS Jan 31/22 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,b]
Dose interval, dose 2 to dose 3, Moderna							
Both	≥30y	SNDS Jan 31/22 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,b]
Clinical comorbidities – With vs without (ref) positive COVID-19 test before vaccination, dose 1							
Both	All ages	NIMS Aug 24/21 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,b,d]
Clinical comorbidities – With vs without (ref) positive COVID-19 test before vaccination, dose 2							
Both	All ages	NIMS Aug 24/21 UK	28 d; Y		aRR = 0.58 (Pfizer)	Among individuals with a history of COVID-19 infection we are uncertain whether the incidence of myocarditis differs after vaccination with dose 2 of an mRNA vaccine compared to those without a history of COVID-19 infection.	**Very Low** [A,b]
		ISS/AIFA Sep 30/21 Italy	21 d; Y		cRR=1.83 (myo- or pericarditis)		
Myocarditis/pericarditis							
Clinical comorbidities – Anti-inflammatory medications							

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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[2]	Relative measures (95% CI) aRR = adjusted risk ratio aOR = adjusted odds ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
Both		ISS/AIFA Sep 30/21 Italy	21 d; Y	NSAID use Systemic corticosteroid use	cRR=13.27 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 those without.	**Low** [a,b]
Clinical comorbidities – Cancer							
Both	All ages	ISS/AIFA Sep 30/21 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,b]
Clinical comorbidities – Cardiovascular conditions							
Both	All ages	ISS/AIFA Sep 30/21 Italy	21 d; Y	Cardiovascular and cerebrovascular diseases cRR=33.54 *Includes: all diseases of the circulatory system; excluding hypertensive diseases* Hypertension cRR=13.38		Among individuals with cardiovascular conditions, there may be a higher incidence of myocarditis or pericarditis after vaccination with an mRNA vaccine compared to individuals without cardiovascular conditions.	**Low** [a,b]
Clinical comorbidities – Hematologic conditions							
Both	All ages	ISS/AIFA Sep 30/21 Italy	21 d; Y	Hematologic dx cRR=2.34 *Includes: Iron deficiency anemias; other deficiency anemias, hereditary hemolytic anemias, acquired hemolytic anemias, aplastic anemia and other bone marrow failure syndromes; Other and unspecified anemias; Coagulation defects; Purpura and other hemorrhagic conditions;* (280-284; 285 (excl.285.1); *diseases of white blood cells*; *Other diseases of blood and blood-forming organs*)		Among individuals with hematologic conditions, there may be a higher incidence of myocarditis or pericarditis after mRNA vaccination compared to those without.	**Low** [a,b]
Clinical comorbidities – Immunocompromise							
Both	All ages	VAERS* Nov 30/21 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 immunocompromise, we are uncertain whether the incidence of myocarditis or pericarditis after vaccination with an mRNA vaccine differs compared to immunocompetent individuals.	**Very Low** [a,b,d]
Clinical comorbidities –Infection (other than COVID-19)							

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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[2]	Relative measures (95% CI) aRR = adjusted risk ratio aOR = adjusted odds ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
Both	All ages	ISS/AIFA Sep 30/21 Italy	21 d; Y	Infection in last 12 months cRR=2.43 *Includes: Urinary tract infection, site not specified; Tuberculosis; Diseases due to other mycobacteria; Cytomegaloviral disease; chickenpox; Herpes zoster; Herpes simplex; Pneumocystosis; Cryptococcosis*		Among individuals with a recent history of infection other than SARS-CoV-2, there may be a higher incidence of myocarditis or pericarditis after mRNA vaccination compared to those without.	**Low** [a,b]
Clinical comorbidities – Pulmonary conditions							
Both	All ages	ISS/AIFA Sep 30/21 Italy	21 d; Y	COPD cRR=1.29 *Includes: bronchitis, not specified as acute or chronic; emphysema; Asthma; Bronchiectasis; Extrinsic allergic alveolitis* Chronic Pulmonary Disease cRR=10.32 *Includes: pneumonia and influenza; Chronic bronchitis; Extrinsic allergic alveolitis; Other diseases of lung*		Among individuals with pulmonary conditions, we are uncertain whether the incidence of myocarditis or pericarditis after vaccination with an mRNA vaccine differs compared to those without.	**Very Low** [A,b]
Clinical comorbidities – Rheumatic conditions							
Both	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 inflammatory conditions.	**Low** [b,d]
		ISS/AIFA Sep 30/21 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 months*			
Pericarditis							
Moderna vs Pfizer (ref), dose 2							
M	18-29	SNDS Oct 31/21 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 5/21 Nordic countries	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** [d] *Note: We did not rate down for indirectness because the incidence of pericarditis differs less across age groups than myocarditis.*
		SNDS Oct 31/21 France	7 d; Y	Moderna: 17.4* Pfizer: 7.4*			

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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[2]	Relative measures (95% CI) aRR = adjusted risk ratio aOR = adjusted odds ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
	30-39y	SNDS Oct 31/21 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 5/21 Nordic countries	28 d; Y	Moderna: 21.8 Pfizer: 12.8		Among ≥40-year-old males, there is probably a higher incidence of pericarditis after vaccination with Moderna compared with Pfizer.	**Moderate** [a]
F	18-39y	Nordic cohort Oct 5/21 Nordic countries	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] *Note: We did not rate down for indirectness because the incidence of pericarditis differs less across age groups than myocarditis.*
	30-39y	SNDS Oct 31/21 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 5/21 Nordic countries	28 d; Y	Moderna: 11.8 Pfizer: 7.5		Among ≥40-year-old females, there is probably a higher incidence of vaccination with Moderna compared with Pfizer.	**Moderate** [a]
Moderna vs Pfizer (ref), bivalent booster dose							
Both	≥12y	VAERS* Oct 23/22 US	NR; Y	Moderna: 0.37 (≥18y) Pfizer: 0.07		Among individuals aged 12 years and older, the incidence of pericarditis may be higher after a bivalent booster dose of Moderna compared with Pfizer.	**Low** [a,b]
Heterologous vs Homologous (ref), 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[2]	Relative measures (95% CI) aRR = adjusted risk ratio aOR = adjusted odds ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
M	16-24	Nordic cohort Oct 5/21 Nordic countries	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,d]
	25-39y	Nordic cohort Oct 5/21 Nordic countries	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,d]
	≥40y	Nordic cohort Oct 5/21 Nordic countries	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,d]
F	16-24y	Nordic cohort Oct 5/21 Nordic countries	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,d]
	25-39y	Nordic cohort Oct 5/21 Nordic countries	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,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[2]	Relative measures (95% CI) aRR = adjusted risk ratio aOR = adjusted odds ratio RD = risk difference	Conclusions	Certainty about conclusions using GRADE
	≥40y	Nordic cohort Oct 5/21 Nordic countries	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,d]

Green text = new evidence identified by Feb 2023 update. Blue text = increased certainty since last report; red text = decreased certainty since last report.

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.

[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

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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[43] (US)	Hause 2022[30] (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 a history of headache and gastrointestinal symptoms 3 or 4 days before chest pain; potential viral syndrome	NR

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Patients with chest pain on presentation	7 (88%)	NR
Patients with other symptoms (e.g., 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

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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 (≥12 weeks of follow-up), from previous updates.

Case series	Klein 2022 (US) [38]	Amir 2022 (Israel) [54]	Schauer 2022 (US) [59]	Alhussein 2022 (Canada) [53]	Hadley 2022 (US) [56]	Patel 2022 (US) [58]	Fronza 2022 (Canada) [55]	Pareek 2022 (US) [57]	Shimabukuro 2022 (US) [24]
Date cases last updated	25 Dec 2021	15 March 2022 (publication date)	7 Jan 2022	01 Dec 2021	01 July 2021	01 Sept 2021	01 Nov 2021	24 Sept 2021 (pub received)	19 July 2022
Cases, n	43	15	16	20	15	14	13 (of 21 referred for CMR at follow-up)	10	1321
Confirmed cases	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. 4 (26%) met Lake Louise criteria for myocarditis	Confirmed via diagnostic testing	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	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 CMR studies when available	Clinical presentation and diagnostic testing criteria of the European Society of Cardiology, and revised Lake Louise criteria for CMR	NR (all hospitalized with CMR findings)	Centers for Disease Control and Prevention case definition
Case source	Kaiser Permanente in Colorado, Oregon, California, and Washington; HealthPartners Institute Minnesota; Denver Health	Clalit Health Services	Seattle Children's Hospital	Single centre in Alberta	Single centre in Boston, MA	Single centre in East Providence, RI	Tertiary hospital network in Ontario	Single centre in New Haven, CT	VAERS
Myocarditis, %	53%	15 (100%)	0%	20 (100%)	15 (100%)	14 (100%)	13 (100%)	3 (30%)	1321 (100%) (or myopericarditis)
Pericarditis, %	5%	0%	0%	0%	0%	0%	0%	0%	0%
Myopericarditis, %	42%	0%	16 (100%)	0%	0%	0%	0%	7 (70%)	NR
Male, %	86%	15 (100%)	15 (94%)	17 (85%)	14 (93%)	14 (100%)	10 (77%)	9 (90%)	960 (73%)
Median age (range), y Ages included	67% = 12-15 years 33% = 16-17 years NR	17.2 (14.9-19) NR	15 (12-17) Younger than 18 years	23 (IQR 20 – 29) ≥18	15 (12 – 18) < 19	19 (IQR 16 – 24) NR	Mean 33 (SD 14) ≥18	19 (16 – 38) NR	28 (IQR 21-42) ≥18
Vaccine type, n	100% = BNT162b2 (Pfizer)	15 (100%) = BNT162b2 (Pfizer)	16 (100%) = BNT162b2 (Pfizer)	6 (30%) = BNT162b2 (Pfizer) 14 (70%) = mRNA-1273 (Moderna)	15 (100%) = BNT162b2 (Pfizer)	12 (86%) = BNT162b2 (Pfizer) 2 (14%) = 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	26%	7 (47%)	0%	3 (15%)	0%	3 (21%)	0%	NR	NR

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Case series	Klein 2022 (US) [38]	Amir 2022 (Israel) [54]	Schauer 2022 (US) [59]	Alhussein 2022 (Canada) [53]	Hadley 2022 (US) [56]	Patel 2022 (US) [58]	Fronza 2022 (Canada) [55]	Pareek 2022 (US) [57]	Shimabukuro 2022 (US)[24]
% Hospitalized	65%	15 (100%)	16 (100%)	18 (90%)	15 (100%)	14 (100%)	6 (46%)	10 (100%)	NR
% Patients presenting after second vaccination	NR	14 (93%)	16 (100%)	16 (80%)	14 (93%)	14 (100%)	NR	NR	962 (73%) (102 [7.7%] after 3rd dose)
% Patients with prior COVID-19 history	5%	NR	NR	4 (20%)	0	0	NR	NR	NR
% Patients COVID-19 polymerase chain reaction positive	NR	0% (all tested)	NR	0	NR	NR	NR	NR	NR
% Patients with COVID nucleocapsid antibody present (% of tested)	NR	0% (all tested)	NR	NR	1 (7%)	NR	NR	NR	NR
% Patients with SARS-CoV-2 spike antibody	NR	0% (all tested)	NR	NR	NR	NR	NR	NR	NR
% Patients with prior myocarditis or pericarditis history	5%	NR	NR	1 (5%) myocarditis	NR	NR	NR	NR	NR
Time between last vaccine and symptom onset, median days, (range)	2 (0-20)	3 (0-28)	3 (2-4)	After 2nd dose (80%): within 6 days (2-6) days After 1st dose (20%); within 10 days (2-10)	3 (1 – 6)	Mean 3 (SD 0.5) (4 days eligibility criteria)	NR	Within 14 days	3 (IQR 2-5)
% Patients with chest pain on presentation	NR	100%	16 (100%)	19 (95%)	15 (100%)	NR	13 (100%)	10 (100%)	NR
% Patients with other symptoms (e.g., myalgia, fatigue, fever)	NR	4 (27%) fever	6 (38%) fever 6 (38%) shortness of breath	2 (10%) dyspnea 1 (5%) myalgia 1 (5%) epigastric discomfort	10 (67%) fever 8 (53%) myalgia 6 (40%) headache 6 (40%) fatigue	NR	NR	3 (30%) myalgia 6 (60%) fever 1 (10%) dyspnea 2 (20%) palpitations	NR
% Patients with troponin elevation (of tested)	NR	4 (93%; 15/15 tested)	100% (16/16 tested)	20 (100%)	15 (100%)	Mean 18.9 (SD 17.6) peak serum cardiac troponin I level (ng/mL) (all tested)	NR	NR	NR
Median time to troponin peak	NR	NR	NR	NR	NR (0.1-2.3 days after admission)	NR	NR	NR	NR

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Case series	Klein 2022 (US) [38]	Amir 2022 (Israel) [54]	Schauer 2022 (US) [59]	Alhussein 2022 (Canada) [53]	Hadley 2022 (US) [56]	Patel 2022 (US) [58]	Fronza 2022 (Canada) [55]	Pareek 2022 (US) [57]	Shimabukuro 2022 (US) [24]
after vaccination, days									
% Patients with BNP or NT pro BNP elevation (among tested)	NR	NR	NR	Median (IQR) = 576 (211 – 931) peak NT-proBNP (4 tested)	15 (100%)	Mean 55.5 (SD 43.4) BNP level (pg/mL) (8 tested)	NR	NR	NR
% Patients with CRP elevation (among tested)	NR	13 (87%; 15/15 tested)	median 3.45 mg/dL, range 0-6.5 mg/dL (12/16 tested)	18 (90%) (all tested)	15 (100%)	Mean 50.6 (SD 41.6) CRP level (mg/L) (11 tested)	NR	NR	NR
% Patients with eosinophilia (among tested)	NR	NR	NR	NR	NR	NR	NR	NR	NR
% Patients with abnormal ECG (among tested)	NR	11 (73%) = ST changes 1 (7%) = borderline ST changes 2 (13%) = normal	10 (63%) = abnormal, commonly diffuse ST segment elevation	9 (45%) normal 11 (55%) ST-elevation 4 (20%) PR depression (all tested)	9 (60%) ST elevation	NR	NR	NR	NR
% Patients with abnormal CMR (among tested)	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)	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	5 of 10 (50%)	13 (87%); 12 (80% with LGE)	Mean 85.4 (SD 13.5) LVEDVi (mL/m^2) (all tested)	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 (7%) = shortening fraction 28%, mild mitral regurgitation; 1 (7%) = mild mitral; regurgitation 1 (7%) = effusion; 2 (13%) = mild LV	2 (13%) mildly reduced LV systolic function with no dilation; 14 (88%) normal LV systolic function	NR	NR	NR	NR	NR	NR
% Patients with	NR	1 (7%) LVEF 45%	Median LVEF 59% (range 45-69%)	5 (25%) (all tested)	2 (13%) (all tested)	Mean 59 (SD 3.2) (all tested)	Mean 56 (SD 4) LVEF % (all tested)	0 (all tested)	NR

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Case series	Klein 2022 (US) [38]	Amir 2022 (Israel) [54]	Schauer 2022 (US) [59]	Alhussein 2022 (Canada) [53]	Hadley 2022 (US) [56]	Patel 2022 (US) [58]	Fronza 2022 (Canada) [55]	Pareek 2022 (US) [57]	Shimabukuro 2022 (US) [24]
LVEF<50% (among tested)									
% Patients with symptoms resolved	100% discharged home	15 (100%) after 6 months	16 (100%)	20 (100%)	11 (73%)	NR	NR	NR	NR
Fatalities, n	0%	0%	0%	0	0	NR	0	0	NR
Median hospitalization length of stay, days (range)	2 (0-7)	5 (3-9)	2 (1-4)	3 (IQR 2 – 3)	2 (1 – 5)	2 (IQR 1 – 3)	NR	Range 1 - 8	NR
% Patients treated with medications for myocarditis	NR	9 (60%) NSAID 2 (13%) Aspirin 3 (20%) Colchicine 2 (13%) steroids 1 (7%) IVIG	16 (100%) NSAID 2 (19%) IVIG and corticosteroid 1 (6%) IVIG	19 (95%) colchicine 15 (75%) NSAID 5 (25%) ACEi 4 (20%) beta blocker 1 (5%) spironolactone	7 (47%) treated with immunoglobulins and methylprednisolone	NR	6 (46%) colchicine 3 (23%) aspirin 3 (23%) ibuprofen	NR	NR
Number of patients with follow-up data	24 (56%)	14 (93%)	16 (100%)	20 (100%)	10 (67%)	14 (100%)	13 (100%) referred for CMR at follow-up	10 (100%)	Focus on 12-29-year-olds: 398
Mean length clinical follow-up (range), days	88.5 (28-153)	5-6 months	Median 3.7 (range 2.8-8.1) months	Median 111 (IQR 92 – 224)	Median 92 (76–119)	NR (6 months for cardiac events)	Median 100 (IQR 74 – 237)	Median 90 (30-120)	At least 90 days post-myocarditis
% Repeat CMR	4%	9 (64%)	16 (100%)	20 (100%)	10 (100%)	NR	13 (100%)	7 (70%)	NR
Characteristics of repeat CMR	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	LGE % = 7.7 ± 5.7; 11 (69%) persistent LGE; LVEF% 57.7 ± 2.7 (none with regional wall motion abnormalities); Global longitudinal strain 75% -16.4 ± 2.1; 1 (6%) edema	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.	Extracellular volume remained elevated in 1 (10%) and borderline in 3 (30%) 8 (80%) persistent LGE	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

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Case series	Klein 2022 (US) [38]	Amir 2022 (Israel) [54]	Schauer 2022 (US) [59]	Alhussein 2022 (Canada) [53]	Hadley 2022 (US) [56]	Patel 2022 (US) [58]	Fronza 2022 (Canada) [55]	Pareek 2022 (US) [57]	Shimabukuro 2022 (US) [24]
Symptoms such as chest pain	38% chest pain 13% shortness of breath 13% palpitations 4% fatigue 13% other (e.g., orthostatic hypotension, dizziness)	NR	4 (25%) chest pain	4 (20%) chest pain	2 (20%) chest pain (but with acute Covid-19 infection) 1 (10%) fatigue	NR	NR	2 (20%) varying degrees of chest discomfort	NR
Medical visits following discharge	75% electrocardiogram with 50% abnormal 71% echocardiogram with 12% abnormal	NR	NR	NR	2 (20%) from chest pain & acute Covid-19	NR	NR	NR	NR
% Continued treatment with medications	8% (e.g., NSAIDs, colchicine)	NR	NR	4 (20%) extended colchicine and NSAIDs without steroids	NR	NR	NR	NR	NR
% Recovered with no symptoms	46% (no symptoms, medications, or exercise restrictions)	14 (100%, after 6 months)	NR	NR	8 (80%)	NR	13 (100%)	8 (80%) asymptomatic	4 (1%) no improvement 61 (15%) improved, but not fully recovered 60 (15%) probably fully recovered, awaiting additional information 265 (67%) fully recovered
Other outcomes	NR	NR	NR	No patient experienced major clinical outcomes (i.e. cardiac hospitalization, new-onset heart failure requiring diuretic use, atrial fibrillation, or ventricular arrhythmia).	3 (30%) elevated troponin 10 (100%) BNP and CRP normal LVEF normal in 100%	14 (100%) no cardiac event at 6 months	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: **CDC** = Centers for Disease Control and Prevention; **CMR** = cardiovascular magnetic resonance imaging; **ECG** = echocardiogram; **FU** = follow-up; **ICD** = International Classification of Diseases; **ICU** = intensive care unit; **IQR** = interquartile range; **LGE** = late gadolinium enhancement; **LVEF** = left ventricular ejection fraction; **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. Case series of Myocarditis and Myopericarditis after mRNA Vaccination reporting longer-term outcomes (≥12 weeks of follow-up): new studies from Feb 2023 search.

Case series	Chua 2022 (China) [11]	Kracalik 2022 (US) [12]	Lai 2022 (Hong Kong) [13]
Date cases last updated	16 Feb 2022	12 Jan 2022	31 March 2022
Cases, n	28	519	104
Confirmed cases	Cardiovascular Injury-Coalition for Epidemic Preparedness Innovations (CEPI) and the Brighton Working Group criteria	Centers for Disease Control and Prevention case definition	Cases without elevated troponin levels during indexed hospitalization were excluded Diagnoses in database made and entered by registered hospital doctors based on standard clinical work-up, including CMR
Case source	Single centre	VAERS	Hospital Authority of Hong Kong and Department of Health
Myocarditis, %	17 (60%)	519 (100%)	104 (100%)
Pericarditis, %	0	0	0
Myopericarditis, %	11 (39%)	0	0
Male, %	24 (86%)	457 (88%)	82 (79%)
Median age (range), y Ages included	Mean 14 (12-17) 12-18	17 (IQR 15 – 22) 12-29	Mean 26 (SD 15) ≥12
Vaccine type, n	28 (100%) = BNT162b2 (Pfizer)	393 (76%) = BNT162b2 (Pfizer) 126 (24%) = mRNA-1273 (Moderna)	104 (100%) = BNT162b2 (Pfizer)
% Patients in ICU	NR	99/393 (25%)	NR
% Hospitalized	100%	484/519 (93%)	104 (100%)
% Patients presenting after second vaccination	20 (71%)	448 (86%)	68 (65%) 8 (8%) after booster dose
% Patients with prior COVID-19 history	NR	48 (9%) determined by positive laboratory-confirmed test	0 (prior infection excluded)
% Patients COVID-19 polymerase chain reaction positive	0	NR	0
% Patients with COVID nucleocapsid antibody present (% of tested)	0	NR	0

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

Case series	Chua 2022 (China) [11]	Kracalik 2022 (US) [12]	Lai 2022 (Hong Kong) [13]
% Patients with SARS-CoV-2 spike antibody	NR	NR	0
% Patients with prior myocarditis or pericarditis history	NR	7 (1%)	0
Time between last vaccine and symptom onset, median days, (range)	NR	NR 360/393 (92%) within 7 days	Within 28 days
% Patients with chest pain on presentation	28 (100%)	NR	NR
% Patients with other symptoms (e.g., myalgia, fatigue, fever)	NR	NR	NR
% Patients with troponin elevation (of tested)	NR	19/200 (10%)	104 (100%)
Median time to troponin peak after vaccination, days	NR	NR	NR
% Patients with BNP or NT pro BNP elevation (among tested)	NR	NR	NR
% Patients with CRP elevation (among tested)	NR	NR	NR
% Patients with eosinophilia (among tested)	NR	NR	NR
% Patients with abnormal ECG (among tested)	18 (67%) elevated ST segment 10 (36%) sinus tachycardia 3 (11%) normal 1 (4%) not available	71/311 (23%) ST-elevation abnormal in 18 (6%)	NR
% Patients with abnormal CMR (among tested)	26 (93%) (27, 96% tested) With myocarditis (n = 16) 1 (6%) borderline LV function, 1 (6%) borderline RV function, and 1 (6%) borderline biventricular function	81/151 (54%) presence of LGE and oedema on CMR was uncommon at 20 (13%)	Data unavailable

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Case series	Chua 2022 (China) [11]	Kracalik 2022 (US) [12]	Lai 2022 (Hong Kong) [13]
	With peri-myocarditis (n = 11) 3 (27%) borderline biventricular functions and 1 (9%) borderline LV function		
% Patients with abnormal echocardiogram (among tested)	Normal cardiac function in 16 (94%) out of 17 with myocarditis and in nine (82%) out of 11 with perimyocarditis	17/279 (6%)	NR
% Patients with LVEF<50% (among tested)	17 (61%) >50% 11 (39%) not reported	33/100 (33%)	NR
% Patients with symptoms resolved	18 (64%)	NR	NR
Fatalities, n	NR	0	1 (1%)
Median hospitalization length of stay, days (range)	NR	NR	NR
% Patients treated with medications for myocarditis	NR	48 (12%) colchicine 42 (11%) beta blocker 31 (8%) NSAID 15 (4%) aspirin 14 (4%) ACE inhibitor 9 (2%) Angiotensin II receptor blocker 6 (2%) diuretic 6 (2%) other medication 4 (1%) corticosteroid	NR
Number of patients with FU data	28 (100%)	393 (76%)	104 (100%)
Mean length clinical FU (range), days	Median 100 (61-178)	Median 191 (IQR 170 – 216)	Median 169 (IQR 54.5 – 159.5)
% Repeat CMR	0	151 (38%)	NR
Characteristics of repeat CMR	NR	Median 91 days (IQR 24-143) from myocarditis onset to FU imaging 81 (54%) any abnormality 47 (31%) LGE only 20 (13%) LGE and edema 7 (5%) abnormality or abnormal finding not provided 3 (2%) wall motion abnormality and LGE 2 (1%) wall motion abnormality only 1 (<1%) edema only 1 (<1%) wall motion abnormality, LGE and edema	NR

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Case series	Chua 2022 (China) [11]	Kracalik 2022 (US) [12]	Lai 2022 (Hong Kong) [13]
Symptoms such as chest pain	10 (36%) non-specific symptoms 5 (18%) chest pain 2 (7%) occasional shortness of breath 1 (6%) reduced exercise tolerance 1 (6%) recurrent vasovagal near-syncope	In the 2 weeks before FU survey (of 357 reporting): 178 (50%) at least one symptom 113 (32%) chest pain 89 (25%) fatigue 80 (22%) shortness of breath 77 (22%) heart palpitations	NR
Medical visits following discharge	NR	6/357 (2%) self-reported re-admission (adverse reactions to intravenous immune globulin n=3; any cardiac abnormality n=3)	33 (32%) subsequent hospitalizations 21 (20%) subsequent A&E attendance 1 (1%) subsequent ICU admission
% Continued treatment with medications	NR	104/393 (26%) prescribed daily medications at last health care provider encounter (median 92 d from onset)	NR
% Recovered with no symptoms	18 (64%)	125 (39%) self-reported asymptomatic 320/393 (81%) considered fully or probably fully recovered by health care provider	NR
Other outcomes	Significant mean bodyweight gain of 1.81 kg (95%CI 0.47-3.1 kg)	249/357 (71%) completed both the EQ-5D-5L and EQ-VAS Any problem on EQ-5D: 114 (46%) anxiety or depression 74 (30%) pain 49 (21%) problems performing usual activities 13 (5%) mobility problems 4 (2%) problems with self-care Overall, reported having good health, by high median weighted index score (0·94; IQR 0·88–1·00) and median overall health status (EQ-VAS) score 15/267 (6%) reporting missing school or work due to myocarditis in the 2 weeks before the survey date.	2 (2%) heart failure 1 (1%) dilated cardiomyopathy 0 (0%) heart transplant surgery

Abbreviations: **BNP** = B-type natriuretic peptide; **CDC** = Centers for Disease Control and Prevention; **CMR** = cardiovascular magnetic resonance imaging; **CRP**: c-reactive protein; **ECG** = echocardiogram; **FU** = follow-up; **ICD** = International Classification of Diseases; **ICU** = intensive care unit; **IQR** = interquartile range; **LGE** = late gadolinium enhancement; **LVEF** = left ventricular ejection fraction; **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. Studies on mechanisms of myocarditis after vaccination (CQ1)

Author; Citation; Country	Methods	Sample(s): E: exposed to myocarditis after vaccination NEV: no myocarditis after vaccine NE: other, as described	Findings	Authors' Conclusions
Thurner et al. IL-1RA antibodies in myocarditis after SARS-CoV-2 vaccination. *N Engl J Med* 387;16. doi: 10.1056/NEJMc2205667 Germany	Evaluated neutralizing autoantibodies targeting the endogenous interleukin-1 receptor antagonist (IL-1RA), which inhibits interleukin-1 signaling and inflammation, and progranulin, which inhibits tumor necrosis factor signaling. Endomyocardial biopsy to confirm myocarditis.	E: 69 (80% male; 14 to 79 years of age) who had clinically suspected myocarditis; 40 of 61 with endomyocardial biopsy had histologically confirmed myocarditis (criteria not reported) NEV: 214 healthy adults who had samples obtained 1 week after receipt of the second dose of SARS-CoV-2 vaccine NE: 127 patients with myocarditis whose samples were obtained before 2020	E: in 40 with confirmed myocarditis: anti–IL-1RA antibodies were found in 9 of 12 patients (75%) younger than 21 years of age, as compared with 3 of 28 patients (11%) 21 years of age or older. Anti–IL-1RA antibodies were not detectable in the 21 patients in whom biopsy ruled out the diagnosis of myocarditis. IL-1RA antibody–positive patients with biopsy-confirmed myocarditis had an early onset of symptoms, which occurred mostly after receipt of the second vaccine dose, and a milder course of myocarditis than patients with biopsy-confirmed myocarditis but without anti–IL-1RA autoantibodies. NEV and NE: IL-1RA antibodies were observed in 2 of 214 vaccinated control participants (1%) and in 2 of 125 participants (2%) who had histologically proven myocarditis that had been diagnosed before the Covid-19 pandemic.	Neutralizing antibodies against IL-1RA and a hyperphosphorylated IL-1RA isoform were observed in young male patients with biopsy-confirmed myocarditis after the receipt of SARS-CoV-2 mRNA vaccine. These antibodies impaired IL-1RA bioactivity in vitro, were associated with low circulating levels of IL-1RA, and were found in patients with biomarker evidence of cardiac damage and inflammation. Previous data that had been obtained from patients with critical Covid-19 did not support the cross-reactivity of purified IL-1RA antibodies with structural proteins of SARS-CoV-2, including the spike protein, which argues against virus- or vaccine driven molecular mimicry. Current evidence points toward a transient hyperphosphorylation of IL-1RA preceding a breakdown of peripheral immune tolerance. In Western blots of total plasma protein, antibodies to IL-1RA coincided with weaker bands of free IL-1RA, but prominent immune (IgM or IgG)–complexed protein with an atypical IL-1RA isoform occurred exclusively in patients who were seropositive for anti–IL-1RA antibodies. This additional IL-1RA isoform was hyperphosphorylated at threonine position 111, which had been observed previously in adult patients with critical Covid-19 and in patients with MIS-C. In contrast to our observations in patients with myocarditis after SARS-CoV-2 vaccination, IL-1RA was not hyperphosphorylated in any of the samples that had been obtained from control participants. IL-1RA plasma levels correlated with markers of cardiac damage (troponin T, creatine kinase, creatine kinase MB, or pro–B-type natriuretic peptide), cardiac-tissue infiltration of CD3+ T cells and CD68+ macrophages, and systemic inflammation (C-reactive protein).

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Author; Citation; Country	Methods	Sample(s): E: exposed to myocarditis after vaccination NEV: no myocarditis after vaccine NE: other, as described	Findings	Authors' Conclusions
Schwab et al. Autopsy-based histopathological characterization of myocarditis after anti-SARS -CoV-2-vaccination. *Clinical Research in Cardiology* https://doi.org/10.1007/s00392-022-02129-5 Germany	Autopsy-based histopathological characterization, including immunohistochemistry	E: 5 patients (40% male; mean age 58 years [46-75]; 80% after first dose; 0% with previous COVID-19) with post vaccine myocarditis via Dallas criteria, assessed 4-10 days after vaccination NEV: 20 persons who had died unexpectedly and within 20 days after anti-SARS-CoV-2 vaccination but not having myocarditis NE: Three age- and sex matched cohorts from autopsy files (covering the years 2005/2006, 2010/2011 and 2015/2016) were retrieved and the myocardial samples were evaluated for the presence and phenotype of inflammatory infiltrates.	Histology showed patchy interstitial myocardial T-lymphocytic infiltration, predominantly of the CD4 positive subset, associated with mild myocyte damage. CD3-positive T-cells by far outnumbered the few CD20-positive B-cells detected, and most T-cells belonged to the CD4-positive subset. T cells were negative for Tbet as a marker for Th1 cells, GATA3 as a marker for Th2 cells, D2-40, as a marker for Th17 cells. Microfocal myocyte injury was demonstrable in three cases. In 4 cases, an inflammatory infiltration of the epicardium and the subepicardial fat tissue was concomitantly found and revealed an identical immunophenotype. (T-cell dominant; CD4 > > CD8). Autopsy findings suggested death due to acute arrhythmogenic cardiac failure. All cases lacked significant coronary heart disease, acute or chronic manifestations of ischaemic heart disease, manifestations of cardiomyopathy or other signs of a pre-existing, clinically relevant heart disease. One case had detection of human herpes virus 6 (HHV6) which may have caused the myocarditis.	All cases showed a consistent phenotype: (A) focal interstitial lymphocytic myocardial infiltration, in three cases accompanied by demonstrable microfocal myocyte destruction. (B) T-cell dominant infiltrate with CD4 positive T-cells outnumbering CD8 positive T-cells by far; (C) frequently associated with T-cell infiltration of epicardium and subepicardial fat tissue revealing a similar immune phenotype (CD4 > > CD8). A comparable (epi-)myocardial (T-cell) infiltration was neither found in any of the other 20 autopsies performed on bodies found dead within 20 days following an anti-SARS-CoV-2 vaccination nor in the age- and sex matched cohorts from three independent periods from our autopsy-files. We recorded inflammatory foci predominantly in the right heart, which may suggest a gradual blood-stream derived dilution effect and based on this finding it is at least tempting to speculate that inadvertent intravascular vaccine injection may be contributive. Further studies and extended registry are needed to identify persons at risk for this potentially fatal AEFI and may be aided by detailed clinical, serological, and molecular analyses which were beyond the scope of this study.
Altman et al. Myocardial injury and altered gene	Endomyocardial biopsy, histopathology and gene expression (rapid turnaround	E: 6 patients (4 males; 36 ± 13 years; no previous cardiac history in 5); with myocardial injury after	E: 1 of 6 had myocarditis and no biopsy Biopsy – none had myocardial inflammatory infiltrate; proinflammatory biomarkers were normal and 3 cases demonstrated no evidence of an	COVID-19 and post–mRNA vaccine myocardial injury may have a common molecular pathology. Myocardial gene expression was altered to predispose to inflammation, thrombosis, and

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Author; Citation; Country	Methods	Sample(s): E: exposed to myocarditis after vaccination NEV: no myocarditis after vaccine NE: other, as described	Findings	Authors' Conclusions
expression associated with SARS-CoV-2 infection or mRNA vaccination. *Am Coll Cardiol Basic Trans Science*. 2022. https://doi.org/10.1016/j.jacbts.2022.08.005 US	reverse-transcription quantitative polymerase chain reaction for mRNA expression of 7 candidate genes including ACE2, ACE, and other genes whose protein products could be involved in myocardial dysfunction, inflammation, and coagulopathy)	mRNA vaccination, presenting with a clinical diagnosis of myocarditis (n=4 with gene expression 13, 32, 40, and 182 days after vaccination) NE1: 7 patients with myocardial injury ≤6 months after SARS-CoV-2 infection (n=6 with gene expression); all treated with remdesivir and dexamethasone, and anticoagulated and/or received antiplatelet agents, NE2: 95 control samples from both nonfailing (LVEF ≥0.50) and failing (LVEF <0.35) LVs, using biobanked mid-distal interventricular septum samples from explanted organ donor or cardiac transplant recipient hearts (age -and sex-matched to NE1 group) and other controls from another biopsy study	inflammatory infiltrate or microthrombi, and only nonspecific abnormalities with no evidence of loss of contractile elements Gene expression - mRNA abundance values that were similar to the COVID-19 data (NE1): none of the individual gene mRNA abundances had P values <0.10 (range 0.12-0.44) between the NE1 and E groups and same directionality and statistically significant differences between E and controls as seen for NE1 NE: Multiple protocol designated proinflammatory cytokines were within normal limits at the time of biopsy; Biopsy - 1 of 7 had definitive myocarditis and evidence of myocyte injury (myocytolysis and loss of contractile elements); 4 had other and 2 had no abnormalities Gene expression - compared with controls: - decreased ACE2 mRNA (-2.7 to -3.4-fold; P<0.01), ACE2/ACE expression ratio (-6.1 to -9.0-fold; P<0.01), AGTR1 (low-abundance mRNA that encodes the type 1 receptor and a biosensor of angiotensin II generation) (-2.7 to 4.4-fold; P<0.05), ITGA5 mRNA (a possible CoV-2 co-receptor whose encoded protein binds to and is co-regulated with ACE2 in eccentric remodeling (-1.7 to 1.8-fold; P=0.01), full-length transcript (flTF) of the F3 or tissue factor (TF) gene - increased ACE mRNA (2.1 to 2.8-fold; P<0.05) - no significant differences in angiotensinogen (AGT) mRNA	contractile dysfunction. Changes were durable, noted up to 137- or 182-days post-infection diagnosis, reflecting ongoing injury process, or sustained S protein levels. Lack of biopsy & histology-confirmed myocarditis in E group possibly due to recovery from inflammation or EmBx sampling error. mRNA expression of candidate genes, selected for protein gene product likelihood of producing myocardial dysfunction, inflammation, or a prothrombotic state in response to Spike protein, exhibited similar changes, consisting of down-regulation in ACE2, ACE2/ACE ratio, AGTR1, and ITGA5 and upregulation in ACE and F3 (tissue factor). If translated into protein changes the adjustments in ACE2 and ACE mRNA expression would lead to much higher myocardial concentrations of angiotensin II, and lack of changes in AGT would indicate the myocardial renin-angiotensin system in COVID-19 patients was functionally imbalanced toward angiotensin II production, having negative implications for cardiac myocyte and endothelial cell function as well as for promoting a procoagulant state and predisposing to inflammation. Upregulation of F3 gene may promote thrombosis and inflammation. Targeted therapies could include intensive angiotensin II inhibitory and/or anticoagulation strategies including tissue factor inhibition.
Baumeier et al. Intramyocardial inflammation after COVID-19 vaccination: an endomyocardial biopsy-proven case	Endomyocardial biopsy with histopathology and immunohistochemical analysis	E: 15 patients (60% male, mean 38 years) with reduced ejection fraction (LVEF = 30 (14–39)%) and suspected myocarditis after COVID-19 vaccination (11	Immunohistochemical EMB analyses revealed myocardial inflammation in 14 of 15 patients, with active myocarditis according the Dallas criteria (n = 2), severe giant cell myocarditis (n = 2) and inflammatory cardiomyopathy (DCMi; n = 10). 11 of 15 had received Pfizer, 9 after dose 2.	The expression of SARS-CoV-2 spike protein within the heart and the dominance of CD4+ lymphocytic infiltrates (considered a major driver of autoimmune myocarditis) indicate an autoimmunological response to the vaccination.

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Author; Citation; Country	Methods	Sample(s): E: exposed to myocarditis after vaccination NEV: no myocarditis after vaccine NE: other, as described	Findings	Authors' Conclusions
series. *Int J Mol Sci*. 2022, 23, 6940. https://doi.org/10.3390/ijms23136940 Germany		after Pfizer, 4 after non-mRNA)	No viral pathogens detected. Diverse pattern of inflammatory markers, ranging from mild to severe degree of inflammation. When used, cMRI was able to detect myocardial inflammation in only 33.3% (2/6) of the cases From 14 patients with inflammation, 9 (64%) showed elevated infiltration of CD3+ T cells, 12 (86%) showed increased levels of CD45R0+ T-memory cells and LFA-1+ lymphocytes, 11 (79%) showed increased numbers of MAC-1+ macrophages and HLADR+- presenting cells, and none showed augmented levels of perforin+ cytotoxic cells. Cellular adhesion molecules ICAM-1 and VCAM-1 were normal in 12 patients. The SARS-CoV-2 spike protein was found in sparse cells (cardiomyocytes) in 9 of 15 cases. Except the cases with active myocarditis, giant cell myocarditis, and one case of DCMi, CD4+-T-cell-to-CD8+-T-cell ratio was ≥1, suggesting a predominantly autoimmunological origin of the observed inflammation.	Expression of HLA-DR was increased in 11 of 14 (79%) patients with evident inflammation. Due to the fact that HLA class II regions strongly associate with several autoimmune diseases, induction of HLA-DR in response to the vaccination supports an autoimmunological contribution to myocardial inflammation after vaccination. None of the patients showed increased presence of perforin+ cells, indicating no contribution of cytotoxic events following the COVID-19 vaccination.
Yonker et al. Circulating spike protein detected in post–COVID-19 mRNA vaccine myocarditis. *Circulation*. 2023;147:00–00. DOI: 10.1161/CIRCULATIONAHA.122.061025 US	Antibody profiling, including tests for SARS-CoV-2–specific humoral responses and assessment for autoantibodies or antibodies against the human-relevant virome, SARS-CoV-2–specific T-cell analysis, and cytokine and SARS-CoV-2 antigen profiling	E: 16 patients (81% male; 88% after 2nd or 3rd dose; mean 16 y [range 12-21]) who were hospitalized for myocarditis after mRNA SARS-CoV-2 vaccination (confirmed and probable via CDC criteria), sample collected mean 4 (1-19 d after vaccination) NEV: 45 healthy, asymptomatic, age-matched vaccinated control subjects, sample collected mean 14 (4-21) days after 2nd dose	Antibody profiling (adaptive immunity i.e. anti-spike or anti-receptor binding protein, IgM, IgG, or IgA levels, self-antibodies) and T-cell responses (naive, effector, memory, SARS-CoV-2 spike–specific CD4+ T cells) in E group essentially indistinguishable from NE. Only noticeable difference in the T-cell signature was a higher frequency of PD-1–expressing bulk CD4+ T cells (P=0.02), likely reflecting variability in expansion after immunization but potentially also suggesting a higher level of exhaustion in this cell subset. E group had modest increase in cytokine production, with distinct cytokine profiles reminiscent of the profile seen in MIS-C, with significantly elevated levels of interleukin (IL)-8, IL-6, tumor necrosis factor-α, IL-10, interferon-γ, and IL-1β and lower IL-4 levels compared with NEV, with no notable differences in IL-5, IL-12p70, or IL-22.	mRNA vaccine–induced immune responses did not differ between individuals who developed myocarditis and individuals who did not. However, free spike antigen was detected in the blood of adolescents and young adults who developed post-mRNA vaccine myocarditis. These results suggest that postvaccine myocarditis is associated with normal adaptive and T-cell immunity but modest innate activation. Elevated levels of free spike protein in circulation, unbound by anti-spike antibodies, appear to correlate with cardiac troponin T levels and innate immune activation with cytokine release. Whether the circulating spike protein in the setting of mRNA vaccination was pathogenic is unclear. Spike protein appears to evade antibody recognition because the anti-spike antibodies that are generated are produced in adequate quantities with normal

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			Complete blood count results: total leukocytes, specifically neutrophils, were significantly increased in E (P=0.007 and P=0.01, respectively), whereas platelet counts were decreased (P=0.03). Markedly elevated levels of full-length spike protein, unbound by antibodies in E, whereas no free spike was detected in NEV (P<0.0001). Free and antibody-bound spike, which was detectable only in E, remained detectable up to 3 weeks after vaccination, but no significant differences in antibody neutralization capacities were observed between groups.	functional and neutralization capacity. There is growing in vitro evidence that spike itself can stimulate cardiac pericytes dysfunction or inflame the endothelium, potentially by downregulating angiotensin-converting enzyme 2 expression, by impairing endothelial nitric oxide bioavailability, or by activating integrin-mediated inflammation with hyperpermeability of the endothelial cell layer. Thus, the spike antigen itself, which evades antibody recognition rather than invoking immune hyperactivation, may contribute to myocarditis in these individuals.
Vago et al. Immunological response and temporal associations in myocarditis after COVID-19 vaccination using cardiac magnetic resonance imaging: An amplified T-cell response at the heart of it? *Front Cardiovasc Med.* 9:961031. doi: 10.3389/fcvm.2022.961031 Hungary	After identification via CMR-based registry, routine laboratory testing and testing of humoral and cellular immune response to COVID-19 vaccination. Acute myocarditis was defined as per the modified Lake Louise criteria. Clinical and CMR follow-up was performed after 3–6 months in E and NE. Immune responses compared between E (mean of 109 and 86 days after the first and second doses) and NEV (matched by timing).	E: 16 (100% male; 22 ±7 years; 19% prior COVID-19) with CMR confirmed and clinical suspicion of acute myocarditis, frequently with predisposing factors such as immune-mediated disease (n=4) and previous myocarditis (n=2); 12 after mRNA vaccine; 81% after 2nd dose, presented 4 ±2 days after vaccine. N=12 for immunologic response, NEV (no myocarditis but similar vaccination exposure; 91% previous COVID-19): 23, age- and sex-matched to E with similar doses and type of anti-SARS-CoV-2 vaccine and the time elapsed since their vaccination NE (myocarditis unrelated to COVID-19 or vaccination): 10 with CMR <2 weeks after the acute presentation	E: white blood cell count, eosinophil count, and other markers remained in the normal range E vs NE: No difference in CMR metrics; marginal difference in T1 mapping. E vs NEV: 25% vs 91% previous COVID-19 but anti-NCP (IgG, IgM) testing showed no difference between the two groups. No difference in the humoral immune response i.e. Anti-SARS-CoV-2 modified nucleocapsid protein (NCP)-IgG, Anti-SARS-CoV-2 NCP-IgM, SARS-CoV-2 spike (S) protein receptor-binding domain (RBD) Ig, IgG or IgA. - S1 IgG and IgA values negatively correlated with the time elapsed since the first vaccination. - Markers of the humoral immune response showed higher values after the mRNA vaccine than after the vector vaccine. Increased T-cell response ($p < 0.01$). - No difference in cellular immune response between mRNA and vector vaccinated No difference in the immune response of myocarditis patients with or without predisposing factors (but small sample). No correlation between the humoral	An amplified cellular immune response was found in acute myocarditis cases occurring 4 days after COVID-19 vaccination. It seems that a T-cell response is sustained for several months after infection and appears to be more prolonged than the antibody response. It has also been suggested that the T-cell response to different COVID-19 vaccines differs among age groups.

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			immune response (S Ig, SP1 IgG, SP1 IgA) and LVEF, whereas the T-cell response parameters showed a negative correlation with the marker of systolic function.	
Zahra et al. Neutralization of severe acute respiratory syndrome Coronavirus 2 Omicron and other variants in serum from children with vaccination-induced myocarditis. Clinical Infectious Diseases 2022;75(9):1645–8. https://doi.org/10.1093/cid/ciac323 US	Serum samples for qualified SARS-CoV-2 pseudovirion neutralization assay using SARS-CoV-2 WA-1 strain and the 5 variants of concern (Alpha, Gamma, Beta, Delta, and Omicron) and 2 variants of interest (Lambda and Mu), and seroreactivity to SARS-CoV-2 recombinant spike-receptor binding domain from byWA-1 and Omicron	E: 13 (12 after 2nd dose) acute (2–5 days post-mRNA vaccination) (100% male; 14.6 [13.8-15.7] years) and 10 post-acute (2-5 weeks after resolution of myocarditis) with no history of COVID-19 NEV: 10 healthy controls, 2-4 weeks after 2nd dose of mRNA vaccine with no history of COVID-19	E: demonstrated neutralizing antibodies early (2–5 days) post-vaccination against WA1/2020; post-acute, the neutralizing antibody response increased by 5-fold; similar trend for increase in neutralizing values of 2 to 8-fold from acute to post-acute time-point was observed across all SARS-CoV-2 variants; neutralization of Omicron was reduced by 31.8-fold compared with the vaccine homologous WA1/2020. End-point titer of serum IgG binding to WA1/2020-RBD was 13.7-fold higher than to Omicron NEV: highest neutralizing antibody response against vaccine homologous WA1/2020; response was reduced against SARS-CoV-2 variants ranging from 1.2-fold for Alpha to 3.3-fold against Beta. Neutralization titers against Omicron were reduced by 27.2-fold and 50% had no measurable neutralization titers. End-point titer of serum IgG binding to WA1/2020-RBD was 55-fold higher than to Omicron	Post-vaccination neutralization titers were significantly higher for children with vaccination-induced myocarditis (2–5 weeks post-vaccination) compared with healthy control children (2–4 weeks post-vaccination) against vaccine-homologous WA1/2020 as well as trended higher for Omicron (not statistically significant), possibly suggesting higher immunogenicity of mRNA vaccines in the vaccine-induced myocarditis children. Children with vaccination-induced myocarditis made a robust antibody response that trended higher than healthy children.

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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 (including bivalent versions and alternative manufacturers of same vaccine), 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/cumulative 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/cumulative risk (may be risk difference if accounting for background rate in control group); relative/absolute effects between groups (e.g., rate ratio or relative risk (RR) between vaccine types or doses). Will include rates of myocarditis or pericarditis (reported collectively) if there is no other data specific to myocarditis or pericarditis. Includes recurrence for people previously having mRNA vaccine-associated 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 ≥12 weeks after onset of myocarditis or pericarditis (e.g., re-hospitalization, functional capacity, chest pain). CQ1: Data from investigations related to potential mechanisms (e.g., histology, experiments with viral spike glycoprotein of SARS-CoV-2 [encoded by mRNA vaccine]), gene panels, serology for innate and acquired immune system components, autoimmune antibodies).

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Setting	Any setting and country.
Study design	KQ1: Large (>10,000 vaccinated people) sample or multisite/health system-based observational studies; reports or databases of confirmed cases using surveillance data. KQ2: Observational studies (including case control studies) with n ≥10 with the risk/protective factor; data for subset of people with myocarditis or pericarditis may come from passive reporting systems. KQ3: Case series N>10; data may come from medical record review of cases reported to passive surveillance 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 surveillance systems. CQ1: Any primary study with N≥5 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 (refID)	Vaccines Studied	Sample Size; Demographics; Previous Covid-19 diagnoses	Study Group(s)	Outcome(s); Case Ascertainment; Risk Interval	Analysis	Results
BC COVID-19 Cohort Mar 10/22 Dec 15 2020 to Mar 10 2022 Canada Naveed 2022[10]	Pfizer-BioNTech 6,989,921 total doses Moderna 3,265,464 total doses Interval between doses NR	3,994,380 individuals receiving at least Pfizer dose 1 or Moderna dose 1 Demographics NR Previous Covid-19 NR	Individuals receiving at least dose 1 of Pfizer Individuals receiving at least dose 1 of Moderna Historical background rates from 2019	Emergency department visit or hospitalization for myocarditis; Emergency department visit or hospitalization for myopericarditis ICD-10 codes for myocarditis (I40.1, I40.8, I51.4), myopericarditis (I30.0, I30.8, I30.9) Blinding of assessors NR Risk interval: 0-7d, 0-21d	observed-to-expected analyses using background (expected) rates from 2019. Calculated rates of myocarditis per 100 000 mRNA vaccines by sex, age, vaccine type and dose number and 95% confidence intervals (CIs) for rates using the exact method.	**Incidence rate of myocarditis per 100 000 doses (95% CI)** *Incidence rate of myocarditis per 100 000 doses (95% CI)* **7 day risk interval, Pfizer+Moderna** *Males* — Dose 1 — Dose 2 — Dose 3 12–17* — 2.13 (0.44 to 6.24) — 6.73 (3.08 to 12.78) — 7.01 (1.45 to 20.49) 18–29 — 0.63 (0.015 to 3.535) — 13.53 (8.4 to 20.735) — 3.465 (0.355 to 15.36) 30–39 — 0.215 (0.005 to 3.11) — 3.725 (1.41 to 8.485) — 1.395 (0.035 to 7.78) 40–49 — 0 (0 to 3.61) — 0.955 (0.02 to 5.3) — 0.93 (0.025 to 7.49) 50–59 — 0.705 (0.02 to 4.92) — 0.6 (0.07 to 4.41) — 0 (0 to 4.895) 60–69 — 0 (0 to 3.685) — 0.29 (0.005 to 3.725) — 0 (0 to 3.91) 70–79 — 0 (0 to 5.7) — 0 (0 to 4.71) — 0.915 (0.11 to 5.785) ≥ 80 — 0 (0 to 11.56) — 1.39 (0.17 to 12.45) — 0 (0 to 8.58) *Females* 12–17* — 0.00 (0.00 to 2.69) — 1.53 (0.19 to 5.53) — 0.00 (0.00 to 8.20) 18–29 — 0 (0 to 2.555) — 1.065 (0.13 to 4.44) — 0 (0 to 6.275) 30–39 — 0 (0 to 2.9) — 1.09 (0.13 to 4.725) — 0.5 (0.015 to 5.29) 40–49 — 0 (0 to 3.715) — 0.255 (0.005 to 3.955) — 0 (0 to 4.64) 50–59 — 0 (0 to 3.525) — 0.865 (0.02 to 4.805) — 0 (0 to 4.015) 60–69 — 0 (0 to 3.475) — 0.25 (0.005 to 3.4) — 1.805 (0.22 to 6.52) 70–79 — 0 (0 to 5.555) — 0.925 (0.025 to 6.265) — 0 (0 to 3.79) ≥ 80 — 0 (0 to 8.545) — 0 (0 to 7.535) — 0.685 (0.015 to 7.895) **21 day risk interval, Pfizer + Moderna** *Males* — Dose 1 — Dose 2 — Dose 3 12–17* — 2.85 (0.78 to 7.29) — 6.73 (3.08 to 12.78) — 9.35 (2.55 to 23.93) 18–29 — 0.815 (0.055 to 3.835) — 14.37 (9.035 to 21.77) — 3.465 (0.355 to 15.36) 30–39 — 2.33 (0.6 to 6.555) — 4.185 (1.55 to 9.225) — 2.21 (0.21 to 9.125) 40–49 — 0.27 (0.005 to 4.12) — 1.245 (0.085 to 5.78) — 0.93 (0.025 to 7.49) 50–59 — 1.95 (0.235 to 7.035) — 0.6 (0.07 to 4.41) — 0.815 (0.02 to 6.43) 60–69 — 0 (0 to 3.685) — 0.29 (0.005 to 3.725) — 1.06 (0.025 to 5.905) 70–79 — 0 (0 to 5.7) — 0 (0 to 4.71) — 0.915 (0.11 to 5.785) ≥ 80 — 0 (0 to 11.56) — 1.39 (0.17 to 12.45) — 0.93 (0.025 to 10.325) *Females* 12–17* — 0.00 (0.00–2.69) — 1.53 (0.19 to 5.53) — 0.00 (0.00 to 8.20) 18–29 — 0.175 (0.005 to 2.89) — 1.565 (0.235 to 5.265) — 0 (0 to 6.275) 30–39 — 0.405 (0.05 to 3.615) — 1.85 (0.34 to 5.97) — 0.5 (0.015 to 5.29) 40–49 — 0 (0 to 3.715) — 0.255 (0.005 to 3.955) — 0.73 (0.02 to 6.015) 50–59 — 0 (0 to 3.525) — 1.37 (0.17 to 5.615) — 0 (0 to 4.015) 60–69 — 0.22 (0.005 to 3.89) — 0.5 (0.06 to 3.81) — 2.145 (0.35 to 7.05) 70–79 — 1.225 (0.03 to 7.865) — 1.23 (0.035 to 6.835) — 0 (0 to 3.79) ≥ 80 — 0.49 (0.01 to 9.47) — 0.52 (0.015 to 8.515) — 1.79 (0.045 to 9.98) *12-17 y rates are Pfizer only; Moderna was not approved for this age group during the study period. **Ratio of observed-to-expected rates of myocarditis among males following mRNA SARS-CoV-2 vaccination** OE ratio (95% CI) Age (y) — **Dose 1** — **Dose 2** — **Dose 3** *Pfizer, 7 day risk interval* 12–17 — 42.56 (8.78–124.38) — 134.29 (61.41–254.93) — 139.80 (28.83–408.55)

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Dataset Dates Country Study (refID)	Vaccines Studied	Sample Size; Demographics; Previous Covid-19 diagnoses	Study Group(s)	Outcome(s); Case Ascertainment; Risk Interval	Analysis	Results
						18–29 2.45 (0.06–13.66) 34.05 (18.13–58.23) 20.02 (4.13–58.50) 30–39 3.13 (0.08–17.45) 3.35 (0.08–18.68) 11.84 (0.30–65.95) 40–49 0.00 (0.00–27.54) 8.05 (0.20–44.85) 25.51 (0.65–142.11) 50–59 0.00 (0.00–33.4) 20.05 (2.43–72.45) 0.00 (0.00–100.90) 60–69 0.00 (0.00–38.59) 12.10 (0.31–67.40) 0.00 (0.00–102.01) 70–79 0.00 (0.00–29.43) 0.00 (0.00–32.29) 0.00 (0.00–64.13) ≥ 80 0.00 (0.00–61.02) 35.25 (4.27–127.32) 0.00 (0.00–130.95) Moderna, *7 day risk interval* 12–17 NA NA NA 18–29 6.08 (0.15–33.87) 148.32 (95.03–220.69) 26.58 (0.67–148.11) 30–39 0.00 (0.00–27.75) 50.77 (20.41–104.6) 8.45 (0.21–47.06) 40–49 0.00 (0.00–71.62) 18.08 (0.46–100.73) 0.00 (0.00–63.56) 50–59 23.61 (0.60–131.53) 0.00 (0.00–75.52) 0.00 (0.00–63.26) 60–69 0.00 (0.00–114.68) 0.00 (0.00–87.46) 0.00 (0.00–60.58) 70–79 0.00 (0.00–118.33) 0.00 (0.00–89.82) 23.74 (2.88–85.77) ≥ 80 0.00 (0.00–232.48) 0.00 (0.00–188.82) 0.00 (0.00–86.93) *Pfizer, 21 day risk interval* 12–17 18.92 (5.15–48.43) 44.76 (20.47–84.98) 62.13 (16.93–159.08) 18–29 1.63 (0.20–5.91) 13.10 (7.33–21.60) 6.67 (1.38–19.50) 30–39 6.26 (2.30–13.63) 3.35 (0.69–9.80) 7.89 (0.96–28.50) 40–49 2.49 (0.06–13.87) 5.37 (0.65–19.38) 8.50 (0.22–47.37) 50–59 6.04 (0.73–21.8) 6.68 (0.81–24.15) 9.12 (0.23–50.80) 60–69 0.00 (0.00–12.86) 4.03 (0.10–22.47) 9.22 (0.23–51.36) 70–79 0.00 (0.00–9.81) 0.00 (0.00–10.76) 0.00 (0.00–21.38) ≥ 80 0.00 (0.00–20.34) 11.75 (1.42–42.44) 0.00 (0.00–43.65) *Moderna, 21 day risk interval* 12–17 NA NA NA 18–29 2.03 (0.05–11.29) 51.50 (33.33–76.03) 8.86 (0.22–49.37) 30–39 5.01 (0.61–18.11) 16.92 (6.80–34.87) 2.82 (0.07–15.69) 40–49 0.00 (0.00–23.87) 6.03 (0.15–33.58) 0.00 (0.00–21.19) 50–59 15.74 (1.91–56.85) 0.00 (0.00–25.17) 0.00 (0.00–21.09) 60–69 0.00 (0.00–38.23) 0.00 (0.00–29.15) 5.47 (0.14–30.50) 70–79 0.00 (0.00–39.44) 0.00 (0.00–29.94) 7.91 (0.96–28.59) ≥ 80 0.00 (0.00–77.49) 0.00 (0.00–62.94) 7.86 (0.20–43.77) **Ratio of observed versus expected rates of myocarditis among females following mRNA Covid-19 vaccination in British Columbia*** OE Ratio (95% CI) 7-DAY RISK WINDOW Pfizer Dose 1 Dose 2 Dose 3 12-17 0.00 (0.00-103.41) 58.92 (7.14-212.84) 0.00 (0.00-315.53) 18-29 0.00 (0.00-26.93) 23.35 (4.81-68.23) 0.00 (0.00-61.19) 30-39 0.00 (0.00-31.01) 0.00 (0.00-32.92) 0.00 (0.00-104.73) 40-49 0.00 (0.00-30.51) 8.82 (0.22-49.13) 0.00 (0.00-92.92) 50-59 0.00 (0.00-36.80) 10.91 (0.28-60.81) 0.00 (0.00-104.20) 60-69 0.00 (0.00-31.92) 9.86 (0.25-54.94) 44.23 (5.36-159.78) 70-79 0.00 (0.00-20.90) 0.00 (0.00-22.76) 0.00 (0.00-45.22) 80+ 0.00 (0.00-124.44) 0.00 (0.00-132.10) 0.00 (0.00-280.33) Moderna Dose 1 Dose 2 Dose 3 12-17 NA NA NA

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Dataset Dates Country Study (refID)	Vaccines Studied	Sample Size; Demographics; Previous Covid-19 diagnoses	Study Group(s)	Outcome(s); Case Ascertainment; Risk Interval	Analysis	Results
						18-29 0.00 (0.00-78.82) 20.69 (0.52-115.28) 0.00 (0.00-198.13) 30-39 0.00 (0.00-89.60) 45.30 (5.49-163.65) 20.68 (0.52-115.24) 40-49 0.00 (0.00-98.04) 0.00 (0.00-87.73) 0.00 (0.00-67.68) 50-59 0.00 (0.00-114.96) 26.25 (0.66-146.23) 0.00 (0.00-68.68) 60-69 0.00 (0.00-105.71) 0.00 (0.00-79.52) 27.25 (3.30-98.43) 70-79 0.00 (0.00-92.35) 18.86 (0.48-105.07) 0.00 (0.00-32.09) 80+ 0.00 (0.00-463.01) 0.00 (0.00-386.02) 47.13 (1.19-262.57) 21-DAY RISK WINDOW Pfizer Dose 1 Dose 2 Dose 3 12-17 0.00 (0.00-34.47) 19.64 (2.38-70.95) 0.00 (0.00-105.18) 18-29 2.43 (0.06-13.56) 7.78 (1.60-22.74) 0.00 (0.00-20.40) 30-39 5.61 (0.68-20.25) 2.97 (0.08-16.58) 0.00 (0.00-34.91) 40-49 0.00 (0.00-10.17) 2.94 (0.07-16.38) 8.40 (0.21-46.78) 50-59 0.00 (0.00-12.27) 10.91 (2.25-31.90) 0.00 (0.00-34.73) 60-69 2.88 (0.07-16.07) 6.57 (0.80-23.75) 14.74 (1.79-53.26) 70-79 0.00 (0.00-6.97) 2.06 (0.05-11.46) 0.00 (0.00-15.07) 80+ 11.24 (0.28-62.65) 11.94 (0.30-66.51) 25.33 (0.64-141.13) Moderna Dose 1 Dose 2 Dose 3 12-17 NA NA NA 18-29 0.00 (0.00-26.27) 13.79 (1.67-49.83) 0.00 (0.00-66.04) 30-39 0.00 (0.00-29.87) 22.65 (4.67-66.20) 6.89 (0.17-38.41) 40-49 0.00 (0.00-32.68) 0.00 (0.00-29.24) 0.00 (0.00-22.56) 50-59 0.00 (0.00-38.32) 8.75 (0.22-48.74) 0.00 (0.00-22.89) 60-69 0.00 (0.00-35.24) 0.00 (0.00-26.51) 13.62 (2.81-39.82) 70-79 8.35 (0.21-46.50) 6.29 (0.16-35.02) 0.00 (0.00-10.70) 80+ 0.00 (0.00-154.34) 0.00 (0.00-128.67) 15.71 (0.40-87.52)
Danish Health Data Authority **Dec 10/22** Jan 1 2021 to Dec 10 2022 Denmark Andersson 2023[3]	Pfizer-BioNTech (bivalent) Dose 4 Moderna (bivalent) Dose 4	1,740,417 Danish residents born in 1972 or earlier Mean (SD) age 67.8 (10.7) years Previous COVID-19 NR	Receiving Pfizer (bivalent) as dose 4 Receiving Moderna (bivalent) as dose 4	Myocarditis, pericarditis Physician-assigned diagnoses, identified by ICD-10 codes (myocarditis: I401, I408, I409, I418, I514; pericarditis: I300, I308, I309, I328) Blinding of assessors NR Risk interval: 0-28d	Poisson regression estimated adjusted incidence rate ratios (IRRs), with corresponding 95% confidence intervals (CI), comparing the outcome rates during the risk period to the reference period rates, adjusted for sex, age groups, ethnicity, region of residence, calendar, and number of comorbidities.	*Events of myocarditis or pericarditis in Danish residents ≥50y receiving a bivalent dose 4* Bivalent boosters: Events per person years; Rate per million Reference period: Events per person years; Rate per million IRR Excess rate *Myocarditis* Females 6/69066 6.7 29/991433 2.2 3.89 (1.05-14.50) 4.5 Males 3/61223 3.8 35/901972 3 1.60 (0.36-7.07) 0.8 *Pericarditis* Females 11/69036 12.2 104/991018 8 1.20 (0.57-2.50) 4.2 Males 11/61179 13.8 161/901332 13.7 1.22 (0.59-2.53) 0.1
Nordic Cohort **Sep 1/22**	Pfizer-BioNTech Dose 2 or 3	Surveillance population: 8,859,339 12-to-39-year-olds	Individuals receiving 2 doses of Pfizer	Myocarditis	Poisson regression estimated adjusted incidence rate ratios (IRRs) of myocarditis, with	Incidence rate per 100,000 and IRR of myocarditis within 28 days

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Dataset Dates Country Study (refID)	Vaccines Studied	Sample Size; Demographics; Previous Covid-19 diagnoses	Study Group(s)	Outcome(s); Case Ascertainment; Risk Interval	Analysis	Results
Dec 27 2020 to Sep 1 2022 Denmark, Finland, Norway, Sweden Hviid 2022[8]	Moderna Dose 2 or 3 Homologous Dose 3 Interval between doses NR	48% female Previous Covid-19 NR	Individuals receiving 2 doses of Moderna Individuals receiving 3 doses of Pfizer Individuals receiving 3 doses of Moderna	First occurrence of a main or secondary myocarditis diagnosis (ICD-10 codes: I40.0, I40.1, I40.8, I40.9, I41.1, I41.8, or I51.4) at discharge from inpatient hospital care. Blinding of assessors NR Risk interval: 0-28d	associated 95% confidence intervals (CIs). IRRs compare the 28-day period after booster dose to unvaccinated follow-up, adjusted for age, calendar period, and vaccination priority group (e.g., frontline personnel and high-risk individuals).	**Incidence of myocarditis hospitalizations, per 1000 person-years** *28d risk period* Events 1000 PY IR IRR Excess events in 28d <u>Males, ages ≥12 y</u> 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) <u>Males, ages 16-24 y</u> 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) <u>Males, ages 25-39 y</u> 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) <u>Males, ages ≥40 y</u> 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) <u>Females, ages ≥12 y</u> 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) <u>Females, ages 16-24 y</u> 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
Nordic Cohort Oct 5/21 Dec 27 2020 to Oct 5 2021 Denmark, Finland, Norway, Sweden Karlstadt 2022[32]	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	At least Pfizer Dose 1 (n=15,064,585) At least Moderna Dose 1 (n=2,390,870) 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	

Sex, Age	Events	Person-years of follow-up	Incidence per 100,000 vaccinees	Adjusted incidence rate ratio (95% CI)	Excess incidence per 100,000 vaccinees
BNT1BNT2 acute 28-day risk period vs unvaccinated follow-up (Dose 2)					
Females, 12-15 y	2	45827.46	0.28	12.56 (1.67 to 94.22)	0.25770701
Females, 16-24 y	8	160806.33	0.36	3.12 (1.36 to 7.17)	0.24461538
Females, 25-39 y	10	307206.31	0.24	2.20 (1.09 to 4.46)	0.13090909
Males, 12-15 y	9	55890.23	1.22	3.59 (1.52 to 8.51)	0.88016713
Males, 16-24 y	60	170560.15	2.70	4.13 (2.90 to 5.88)	2.04624697
Males, 25-39 y	27	323930.60	0.64	1.77 (1.14 to 2.76)	0.27841808
MOD1MOD2 acute 28-day risk period vs unvaccinated follow-up					
Females, 25-39 y	4	55866.20	0.55	4.22 (1.47 to 12.12)	0.41966825
Males, 16-24	29	15655.35	14.20	15.04 (9.57 to 23.63)	13.2558511
Males, 25-39	38	54509.16	5.34	10.21 (6.78 to 15.38)	4.81698335

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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)

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				

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						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)
NIMS/NHS Nov 15/21/21 Dec 1 2020 to Nov 15 2021 England Patone 2021[42]	Pfizer-BioNTech Moderna Dose 1, 2 or 3 Interval between doses NR	21,554,158 with at least one dose, aged ≥13 y Previous COVID in 54.7% of total sample People with history of myocarditis in previous 2 years excluded	Pfizer Dose 3: n= 10,599,183 Moderna Dose 3: n= 343,716	Hospitalization due to myocarditis Risk interval: 28 d after any dose Cases identified by ICD-10 codes: I40, I400, I401, I408, I409, I41, I410-412, I418, I514	Incidence rate ratio using self-controlled case series (SCCS) method, stratified by sex and age	**Excess events per 1 mil persons receiving dose 3 (95% CI)** 1-28d Dose 1 Dose 2 Dose 3 *Pfizer* <u><40y</u> Female NR NR NR Male 3 (1, 5) 12 (10, 13) 13 (7, 15) <u>≥40y</u> Female NR NR NR Male NR NR 3 (2, 4) *Moderna* <u><40 y</u> Female NR 8 (4, 9) NR Male 12 (1, 17) 101 (95, 104) <u>≥40y</u> Female NR NR NR Male NR NR NR
SNDS Oct 31/21 May 12 to Oct 31 2021 France Le Vu 2022[22]	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 vaccination >7days before admission.	**Excess incidence of myocarditis per million vaccinees, by age and sex for 7days following vaccination** *(extracted from Figure 3)* Sex Age BNT162b2 **Dose 2** **mRNA-1273 Dose 2** **Total Dose 2** Femal e 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*

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Dataset Dates Country Study (refID)	Vaccines Studied	Sample Size; Demographics; Previous Covid-19 diagnoses	Study Group(s)	Outcome(s); Case Ascertainment; Risk Interval	Analysis	Results
						Excess incidence of pericarditis per million vaccinees, by age and sex for 7days following vaccination *(extracted from Figure 3)* Sex / Age / BNT162b2 Dose 2 / mRNA-1273 Dose 2 / Total Dose 2 Female 12-17: 6.786 / ns / 6.786 Female 18-24: 13.482 / ns / 13.482 Female 25-29: 9.911 / ns / 9.911 Female 30-39: Ns / 28.661 / 28.661 Female 40-50: Ns / 20.982 / 20.982 Male 12-17: 4.018 / - / 4.018 Male 18-24: 10.268 / 33.482 / 12.903 Male 25-29: 2.946 / 11.339 / 3.945 Male 30-39: 3.125 / 6.518 / 3.576 Male 40-50: ns / ns / NE *Crude incidence data also available, see Calculations spreadsheet* *NE=Not estimated*
eHRSS Oct 18/21 Mar 10 to Oct 18 2021 Hong Kong Li 2022 [33]	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)
Israeli MOH Nov 5/21 Jul 30 2021 to Nov 5 2021 Israel Mevorach 2022[9]	Pfizer-BioNTech Dose 3 (20-24 weeks after dose 2) Interval between doses NR	N = 3,944,797 Demographics NR Previous COVID-19 NR	Individuals receiving dose 3 of Pfizer	Myocarditis Definite/probably cases based on the Brighton Collaboration Myocarditis Case Definition Blinding of assessors NR Risk interval: 0-30 d	Myocarditis risk for definite/probable cases after the booster dose was computed	**Incidence of myocarditis per 100,000 vaccinees receiving dose 3** **Pfizer** / **Dose 3** *Male* 16-19 y: 6.44 20-24 y: 5.21 25–29 y: 0.79 30–39 y: 1.81 *Female* 16-19 y: 1.06 20-24 y: 0.00 25–29 y: 0.00

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Dataset Dates Country Study (refID)	Vaccines Studied	Sample Size; Demographics; Previous Covid-19 diagnoses	Study Group(s)	Outcome(s); Case Ascertainment; Risk Interval	Analysis	Results
						30–39 y 0.37
IDF Sep 30/21 Aug 15 to Sep 30 2021 Israel Friedensohn 2022 [29]	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 Mar 7/21 Dec 28 2020 to Mar 7 2021 Israel Levin 2021[39]	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
Israeli MOH Oct 20/21 Jun 2 to Oct 20 2021 Israel Mevorach 2022[34]	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 10/21 Dec 2020 to Oct 10 2021 Israel Alroy-Preis 2021[27]	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 Dose 1: 12-15y; 16-19y 0 cases / 248,881 vaccinees; 20-24y 1 / 263,845; 25-29y 0 / 247,365; ≥30y 3 / 2,127,538 Dose 2: 16-19y 2 / 222,067; 20-24y 6 / 242,697; 25-29y 1 / 229,189; ≥30y 7 / 2,029,074 Dose 3: 12-15y 0 / 279; 16-19y 0 / 97,807; 20-24y 0 / 141,910; 25-29y 0 / 130,283; ≥30y 0 / 1,542,142 Males Dose 1: 12-15y; 16-19y 3 / 254,497; 20-24y 6 / 275,235; 25-29y 3 / 257,713 Dose 2: 16-19y 36 / 223,079; 20-24y 26 / 251,672; 25-29y 20 / 239,319 Dose 3: 12-15y 0 / 292; 16-19y 5 / 96,238; 20-24y 5 / 139,015; 25-29y 1 / 133,650

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Dataset Dates Country Study (refID)	Vaccines Studied	Sample Size; Demographics; Previous Covid-19 diagnoses	Study Group(s)	Outcome(s); Case Ascertainment; Risk Interval	Analysis	Results
						≥30y 10 1,983,230 32 1,897,067 6 1,448,745
Singapore Military Aug 3/21 Jan 14 to Aug 3 2021 Singapore Tan 2021 [44]	Pfizer (37,367 individuals with 1+ dose) Moderna (27,294 individuals with 1+ dose) Homologous dose 2 administered between 21 and 56 days after dose 1	127,081 doses administered to 64,661 people (96.5% with 2 doses) 92.1% male Previous or concurrent COVID-19 diagnosis NR	Singapore military personnel receiving at least 1 dose of an mRNA COVID-19 vaccine	Myocarditis Risk interval: NR Case ascertainment via military doctor or hospital diagnosis	Incidence rates and rate ratios after dose 2 versus dose 1 for both mRNA vaccines together and separately, with 95% confidence intervals	3 events; all male, 18-21y, all after Moderna, none with cardiac history. Reporting rate per 100,000 doses administered (95% CI) *Any product* Dose 1 Dose 2 18-19 y Female 0/955 0/903 Male 0/11,120 2/10,521 20-29 y Female 0/2,819 0/2,717 Male 0/32,850 1/31,656 30-39y Female 0/671 0/656 Male 0/7,807 0/7,625 Note: Only male data included in report; too few females for valid estimates
PCORnet Jan 31/22 **Jan 1 2021 to Jan 31 2022** United States Block 2022 [28]	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 30/21 Thru Dec 30 2021 United States Klein 2022[38]	Pfizer Dose 1: 587,786 Dose 2: 556035	Total doses: 1143821 5-11y: 431,485 12-15y: 750,772 16-17y: 393,049	1. Participants aged 5-11 y receiving at least 1 dose of Pfizer 2. Participants aged 12-17 y receiving at least 1 dose of Pfizer 2. Similar vaccinee in comparison interval (days 22-42) after COVID-19 vaccination.	Myocarditis, pericarditis, or myopericarditis Risk interval: 21 d Initial chart review followed with adjudication by an infectious disease clinician and/or a cardiologist to confirm cases meet CDC case definition	Excess cases based on comparison interval, adjusted for age group, sex, race/ethnicity, VSD site, and calendar date.	**5-11** 0 verified cases of myocarditis or myopericarditis 1 verified case of acute pericarditis in an 11 year-old. **12-17** 12-15 years: 29 cases 16-17 years: 14 cases 43 validated cases among 12–17-year-olds, 0-21 days after vaccination 39 validated cases among 12–17-year-olds, 0-7 days after vaccination Interval Excess Cases per 1 million doses 2-sided p-value 0-21 d Dose 1 0.7 0.873 Dose 2 70.8 <0.001

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Dataset Dates Country Study (refID)	Vaccines Studied	Sample Size; Demographics; Previous Covid-19 diagnoses	Study Group(s)	Outcome(s); Case Ascertainment; Risk Interval	Analysis	Results
						0-7 d Dose 1 0.3 0.836 Dose 2 70.2 <0.001
Mayo Clinic Enterprise Oct 17/21 Dec 1 2020 to Oct 17 2021 United States Niesen 2021[41]	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.
US Military Apr 30/21 Jan 1 to Apr 30 2021 United States Montgomery 2021[40]	Pfizer-BioNTech or Moderna	2,810,00 doses (38% dose 2) Males 100% Median age 25 (20-51) Tested cases for Covid-19 n=0 but all cases after dose 2 (n=3) had previous Covid-19	1. Vaccinated 2. 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 February 2023 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 Defence 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 DatalinkMOH – Ministry of Health

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

<table>
<tr><th>Dataset
Dates of data
Country of Data
Study (RefID)</th><th>Vaccines Studied</th><th>Outcome(s); Case Ascertainment & Risk Interval</th><th>Analysis</th><th>Results</th></tr>
<tr>
<td>TGA Aug 21/22

Up to Aug 21 2022

Australia

Therapeutic Goods Administration 2022[26]</td>
<td>Pfizer and Moderna
Dose 1
Dose 2</td>
<td>Myocarditis (including myopericarditis)

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

Risk interval NR</td>
<td>Crude reporting rate of likely myocarditis cases</td>
<td>Table 3. Rates of likely myocarditis cases following mRNA vaccination
<table>
<tr><th rowspan="2">Age (years)</th><th colspan="2">Moderna Dose 2</th><th colspan="2">Pfizer Dose 2</th></tr>
<tr><th colspan="2">Rate per million doses</th><th colspan="2">Rate per million doses</th></tr>
<tr><th></th><th>Male</th><th>Female</th><th>Male</th><th>Female</th></tr>
<tr><td>5-11y</td><td>NE</td><td>NE</td><td>2</td><td>0</td></tr>
<tr><td>12-17</td><td>213</td><td>50</td><td>131</td><td>28</td></tr>
<tr><td>18-29</td><td>223</td><td>48</td><td>90</td><td>26</td></tr>
<tr><td>30-39</td><td>50</td><td>0</td><td>30</td><td>10</td></tr>
</table>
</td>
</tr>
<tr>
<td>SAEFVIC Feb 22/22

Feb 22 2021 to Feb 22 2022

Australia

Cheng 2022[20]</td>
<td>Pfizer or Moderna
Dose 1 or Dose 2
871 689 doses (782,964 Pfizer and 88,725 Moderna).</td>
<td>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</td>
<td>Crude reporting rate</td>
<td>Count and reporting rate of cases by sex and dose number
<table>
<tr><th></th><th></th><th>Count</th><th>Rate per million doses (90% CI)</th></tr>
<tr><td>Total</td><td>Dose</td><td></td><td></td></tr>
<tr><td>Males, 12-17y</td><td>1</td><td>10</td><td>44 (24 to 75)</td></tr>
<tr><td></td><td>2</td><td>52</td><td>242 (190 to 305)</td></tr>
<tr><td>Females, 12-17y</td><td>1</td><td>4</td><td>18 (6 to 42)</td></tr>
<tr><td></td><td>2</td><td>9</td><td>43 (23 to 75)</td></tr>
</table>
</td>
</tr>
</table>

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Dataset Dates of data Country of Data Study (RefID)	Vaccines Studied	Outcome(s); Case Ascertainment & Risk Interval	Analysis	Results
COVaxON* Sept 4/21 Dec 14 2020 to Sep 4 2021 Canada Buchan 2022[36]	Moderna Pfizer-BioNTech Dose 1 or dose 2 (19,740,741 doses total)	Myocarditis 7-day risk interval Group of specialized nurses and physicians classified cases according to Brighton Collaboration definition for myocarditis (level 1-2)	Crude rate per million doses, by dose	**Rate per million doses (95% CI), BC level 1-2 cases on or after Jun 1 2021** *Pfizer* Dose 1 Dose 2 12-17 y Female 8.1 (1.0-29.1) 9.7 (1.2-35.1) Male 34.2 (15.6-64.9) 88.1 (53.0-137.5) 18-24 y Female 7.9 (0.2-44.1) 0 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) 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
BNPV Sep 30/21 Up to Sep 30 2021 France Salvo 2022[23]	Pfizer or Moderna ~83 million total doses (Dose 1 and Dose 2 combined; 73 million BNT162b2 and 10 million mRNA-1273)	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	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).	**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)
VAERS Jan 1/23 Oct 12 2022 to Jan 1 2023 United States Hause 2023[7]	Moderna (bivalent) Pfizer-BioNTech (bivalent) Dose 3+	Myocarditis Confirmed to meet CDC working definition Risk interval NR	Crude reporting rate per million doses	Pfizer-BioNTech bivalent: 0 events in 861,251 children aged 5–11 years Moderna bivalent: 0 events in 92,108 children aged 6–11 years* *Moderna only approved for ≥6 y

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Dataset Dates of data Country of Data Study (RefID)	Vaccines Studied	Outcome(s); Case Ascertainment & Risk Interval	Analysis	Results
VAERS Oct 23/22 Aug 31 to Oct 23 2022 United States Hause 2022a[5]	Pfizer-BioNTech (bivalent) Booster dose (14.4 million vaccinees) Moderna (bivalent) Booster dose (8.2 million vaccinees)	Myocarditis; Pericarditis Confirmed to meet CDC working definition Risk interval NR	Crude reporting rate per million vaccinees	**Myocarditis (Age range 12-78 years)** Pfizer: 3 cases among 14.4 million vaccinees = 0.21 cases per million vaccinees Moderna 2 cases among 8.2 million vaccinees = 0.24 cases per million vaccinees **Pericarditis (Age range 46-78 years)** Pfizer: 1 case among 14.4 million persons aged ≥12 y = 0.07 cases per million vaccinees Moderna: 3 cases among 8.2 million persons aged ≥18 y = 0.37 cases per million vaccinees
VAERS Aug 21/22 Jun 18 to Aug 21 2022 United States Hause 2022b[6]	Pfizer-BioNTech 3 doses at 3 week intervals (599457 vaccinnees) Moderna 2 doses 4 weeks apart (440,773 vaccinnees)	Myocarditis Confirmed to meet CDC working definition Risk interval NR	Crude reporting rate per million vaccinees	Pfizer: 0 events in children aged 6 mos to 4 years. Moderna: 0 events in children aged 6 mos to 5 years.
VAERS Jul 31/22 May 17 to July 31 2022 United States Hause 2022c[4]	Pfizer-BioNTech Dose 3 (657,302 doses)	Myocarditis Confirmed to meet CDC working definition Risk interval NR	Crude reporting rate per million doses	Dose 3: 0 events in 657,302 children aged 5–11 years
VAERS May 26/22 Dec 14 2020 to May 26 2022 United States Shimabukuro 2022a[35]	Pfizer (all ages) or Moderna (≥18y only) Dose 1 Dose 2 Dose 3	Myocarditis Adjudicated after healthcare provider interview and/or medical record review to meet CDC myocarditis case definition Risk interval: 0-7d	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	Reporting rate, per 1 million doses administered Males, 0-7d | Females, 0-7d Age (yrs) | Dose 1 | Dose 2 | Booster | Dose 1 | Dose 2 | Booster 5–11 | 0.2 | 2.6 | 0 | 0.2 | 0.7 | 0 12–15 | 5.3 | 46.4 | 15.3 | 0.7 | 4.1 | 0 16–17 | 7.2 | 75.9 | 24.1 | 0 | 7.5 | 0 18–24* | 4.2 | 38.9 | 9.9 | 0.6 | 4 | 0.6 25–29* | 1.8 | 15.2 | 4.8 | 0.4 | 3.5 | 2 30–39* | 1.9 | 7.5 | 1.8 | 0.6 | 0.9 | 0.6 *peach shaded cells indicate that reporting rate exceeded estimated background incidence for the period* *Pfizer and Moderna combined for ages ≥18y

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Dataset Dates of data Country of Data Study (RefID)	Vaccines Studied	Outcome(s); Case Ascertainment & Risk Interval	Analysis	Results
VAERS Mar 28/22 Jan 12 to Mar 28 2022 United States Hause 2022d[21]	Pfizer or Moderna Dose 4 (n=518,113)	Myocarditis verified by medical record review and met the CDC case definition for myocarditis Risk interval NR	Crude reporting rate	No verified cases of myocarditis reported out of 518,113 fourth doses "One nonserious, preliminary report of myocarditis remains under review."
VAERS Feb 20/22 Dec 9 2021 to Feb 20 2022 United States Hause 2022e[30]	Pfizer Dose 3 Boost interval: (≥2 months after dose 1 of Janssen or ≥5 months after dose 2 of an mRNA vaccine	Myocarditis Confirmed to meet CDC working definition Risk interval NR	Crude reporting rate per million doses administered	Males, 12-17y: 11.4 per million booster doses administered
VAERS Feb 6/22 Sep 22 2021 to Feb 6 2022 United States Hause 2022f[31]	Pfizer or Moderna Dose 3 Boost interval: ≥5 months after dose 2 of an mRNA vaccine	Myocarditis Confirmed to meet CDC working definition Risk interval: 0-6d	Crude reporting rate per million doses administered	**Crude reporting rate per million booster doses** Males — Pfizer — Moderna — Average 18-24 y — 4.1 — 8.7 — 6.4 25-29 y — 1.1 — 3.2 — 2.15 30-39 y — 1.7 — 1.0 — 1.35 Females — Pfizer — Moderna — Average 18-24 y — <1.0 — 1.1 — ~1.0 25-29 y — NE — 1.2 — <1 30-39 y — <1.0 — 1.5 — ~1.0
VAERS Jan 13/22 Through Jan 13 2022 United States Shimabukuro 2022b[35]	Moderna Dose 1 or 2 Dose interval NR	Myocarditis Verified to meet CDC case definition Risk interval: 0-7d	Crude reporting rate per million doses	**Reporting rate, per million doses (95% CI)** Dose 1 — Dose 2 Males 18-24 y — 5.8* — 40.0* 25-29 y — 2.9* — 18.3* 30-39 y — 3.3* — 8.4* Females 18-24 y — 0.5 — 5.5* 25-29 y — 0.3 — 5.8* 30-39 y — 0.6 — 0.6 *Reporting rate exceeds background incidence

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Dataset Dates of data Country of Data Study (RefID)	Vaccines Studied	Outcome(s); Case Ascertainment & Risk Interval	Analysis	Results
VAERS Dec 9/21 Nov 2 to Dec 10 2021 United States Su 2021[43]	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 18/21 Jan 1 to Jun 18 2021 United States Høeg 2021[37]	Pfizer-BioNTech Moderna (only 1 of 257 cases; not approved for <18y) Dose schedule NR	Myocarditis "Myocarditis," "pericarditis," "myopericarditis" or "chest pain" in the symptom notes; "troponin" required element in the laboratory data; cases were required to meet the 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** <u>Dose 2</u> 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
Moderna global safety database Feb 15/22 Dec 18 2020 to Feb 15 2022 Worldwide Strauss 2022[25]	Moderna (568,668,391 doses administered to ~252 million people) Any dose Dose schedule NR	Myocarditis and myopericarditis Brighton Collaboration case definition for myocarditis Risk interval: 0-21d	The reporting rate was calculated as the number of reported cases per 100 000 person-years according to age group and sex. 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.	**Reported Rates of Myocarditis and Myopericarditis Within 7 Days of mRNA-1273 According to Age and Dose Number (per million Doses Administered)** Dose 1 / Dose 2 / Dose 3 Male recipients <12 y: 0 / 0 / 0 12-17y: 2.6 / 14.6 / 0 18-24y: 8.2 / 42.3 / 4.0 25-39y: 4.1 / 14.0 / 3.3 Female recipients <12 y: 0 / 0 / 0 12-17y: 0.5 / 1.3 / 0 18-24y: 1.5 / 3.8 / 0.6 25-39y: 1.2 / 1.6 / 1.4 **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)** Dose 1 / Dose 2 / Dose 3 Male recipients <12 y: NA / NA / NA 12-17y: 7.9 (3.3 to 19) / 44.1 (21.6 to 89.9) / NA

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Dataset Dates of data Country of Data Study (RefID)	Vaccines Studied	Outcome(s); Case Ascertainment & Risk Interval	Analysis	Results
				18-24y: 24.8 (16.8 to 36.5); 127.4 (87.5 to 185.4); 12.1 (6.2 to 23.7) 25-39y: 16.1 (11.9 to 21.9); 54.9 (41.2 to 73.1); 12.9 (8.0 to 20.9) Female recipients <12 y: NA; NA; NA 12-17y: 3.2 (0.7 to 15.7); 7.8 (2.1 to 28.9); NA 18-24y: 9.1 (4.8 to 17.2); 22.9 (12.8 to 41.1); 3.5 (0.9 to 13) 25-39y: 9.7 (6.1 to 15.3); 12.8 (8.0 to 20.6); 11.1 (5.7 to 21.7)

Green text = new evidence identified by February 2023 update.
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.

Dataset **Dates of data** (mmm dd yyyy) **Country of Data** **Author year** (RefID)	**Vaccines Studied** Manufacturer Dose #	**Sample Size; Demographics; Previous Covid-19 diagnoses**	**Outcome(s)** Myo-, peri- and/or myopericarditis; Case Ascertainment & Risk Interval; Risk/protective factors considered	**Outcome measures Analysis** (e.g., adjustment for confounders)	**Results** Stratified by age and sex If required, zero cell correction proportional to the reciprocal of the size of the contrasting study arm (i.e., # events = 1/n of the other
TGA Aug 21/22 Up to Aug 21 2022 Australia Therapeutic Goods Administration 2022[26]	Pfizer or Moderna Dose 1, Dose 2, or Dose 3	49,000,000 total doses (43.7 million Pfizer and 5.3 million Moderna) Demographics NR Previous Covid-19 Diagnoses NR	Myocarditis (including myopericarditis) Reports are reviewedagainst an internationally accepted criteria to classify the likelihood of myocarditis. Risk interval NR Moderna dose 2 vs. Pfizer dose 2	Crude reporting rate of likely myocarditis cases per 100,000 doses administered	**Crude incidence rate ratio for occurrence of myocarditis after vaccination with Dose 2 of Moderna compared with Dose 2 o**
BC COVID-19 Cohort Mar 10/22 Dec 15 2020 to Mar 10 2022 Canada Naveed 2022[10]	Pfizer-BioNTech 6,989,921 total doses Moderna 3,265,464 total doses Interval between doses NR	3,994,380 individuals receiving at least Pfizer dose 1 or Moderna dose 1 Previous Covid-19 NR	Emergency department visit or hospitalization for myocarditis; Emergency department visit or hospitalization for myopericarditis ICD-10 codes for myocarditis (I40.1, I40.8, I51.4), myopericarditis (I30.0, I30.8, I30.9)	Calculated rates of myocarditis per 100 000 mRNA vaccines by sex, age, vaccine type and dose number and 95% confidence intervals (CIs)	**Incidence rate of myocarditis per 100 000 doses (95% CI)**

Age (years)	**Moderna, Dose 2**	**Pfizer Dose 2**	**Incidence rate ratio**
Males	Rate* per million doses		
12-17	213	131	1.626
18-29	223	90	2.478
30-39	50	30	1.667
40-49	16	14	1.143
50-59	20	7	2.857
60-69	0	4	0.000
70+	0	0	NE
Females			
12-17	5	28	0.1786
18-29	48	26	1.846
30-39	0	10	0.000
40-49	20	17	1.176
50-59	50	3	16.667
60-69	0	4	0.000
70+	0	4	0.000

Age group Males (y)	Dose 1	Dose 2	Dose 3
Pfizer, 7 day risk interval			
18–29	0.36 (0.01–2.03)	5.06 (2.70–8.66)	2.98 (0.61–8.70)
30–39	0.43 (0.01–2.40)	0.46 (0.01–2.57)	1.63 (0.04–9.08)
40–49	0.00 (0.00–2.01)	0.59 (0.01–3.27)	1.86 (0.05–10.35)
50–59	0.00 (0.00–1.99)	1.20 (0.14–4.32)	0.00 (0.00–6.02)
60–69	0.00 (0.00–1.86)	0.58 (0.01–3.24)	0.00 (0.00–4.91)
70–79	0.00 (0.00–2.27)	0.00 (0.00–2.49)	0.00 (0.00–4.95)
≥ 80	0.00 (0.00–4.81)	2.78 (0.34–10.03)	0.00 (0.00–10.31)
Moderna, 7 day risk interval			
18–29	0.90 (0.02–5.04)	22.05 (14.13–32.81)	3.95 (0.10–22.02)
30–39	0.00 (0.00–3.82)	6.99 (2.81–14.40)	1.16 (0.03–6.48)

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Dataset **Dates of data** (mmm dd yyyy) **Country of Data** **Author year** (RefID)	**Vaccines Studied** Manufacturer Dose #	**Sample Size; Demographics; Previous Covid-19 diagnoses**	**Outcome(s)** Myo-, peri- and/or myopericarditis; Case Ascertainment & Risk Interval; Risk/protective factors considered	**Outcome measures Analysis** (e.g., adjustment for confounders)	**Results** Stratified by age and sex If required, zero cell correction proportional to the reciprocal of the size of the contrasting study arm (i.e., # events = 1/n of the other
Naveed 2022 cont			Risk interval: 0-7d, 0-21d Moderna dose 1 vs Pfizer dose 1, Moderna dose 2 vs. Pfizer dose 2; Moderna dose 3 vs. Pfizer dose 3	for rates using the exact method.	40–49 0.00 (0.00–5.21) 1.32 (0.03–7.33) 0.00 (0.00–4.63) 50–59 1.41 (0.04–7.85) 0.00 (0.00–4.50) 0.00 (0.00–3.77) 60–69 0.00 (0.00–5.51) 0.00 (0.00–4.21) 0.00 (0.00–2.91) 70–79 0.00 (0.00–9.13) 0.00 (0.00–6.93) 1.83 (0.22–6.62) ≥ 80 0.00 (0.00–18.31) 0.00 (0.00–14.87) 0.00 (0.00–6.85) Pfizer, 21 day risk interval 18–29 0.73 (0.09–2.63) 5.84 (3.27–9.63) 2.98 (0.61–8.70) 30–39 2.59 (0.95–5.63) 1.38 (0.29–4.05) 3.26 (0.39–11.77) 40–49 0.54 (0.01–3.03) 1.17 (0.14–4.23) 1.86 (0.05–10.35) 50–59 1.08 (0.13–3.90) 1.20 (0.14–4.32) 1.63 (0.04–9.09) 60–69 0.00 (0.00–1.86) 0.58 (0.01–3.24) 1.33 (0.03–7.41) 70–79 0.00 (0.00–2.27) 0.00 (0.00–2.49) 0.00 (0.00–4.95) ≥ 80 0.00 (0.00–4.81) 2.78 (0.34–10.03) 0.00 (0.00–10.31) Moderna, 21 day risk interval 18–29 0.90 (0.02–5.04) 22.97 (14.87–33.91) 3.95 (0.10–22.02) 30–39 2.07 (0.25–7.48) 6.99 (2.81–14.40) 1.16 (0.03–6.48) 40–49 0.00 (0.00–5.21) 1.32 (0.03–7.33) 0.00 (0.00–4.63) 50–59 2.82 (0.34–10.17) 0.00 (0.00–4.50) 0.00 (0.00–3.77) 60–69 0.00 (0.00–5.51) 0.00 (0.00–4.21) 0.79 (0.02–4.40) 70–79 0.00 (0.00–9.13) 0.00 (0.00–6.93) 1.83 (0.22–6.62) ≥ 80 0.00 (0.00–18.31) 0.00 (0.00–14.87) 1.86 (0.05–10.34) **Rate per 100 000 doses (95% CI)** **Females Dose 1 Dose 2 Dose 3** Pfizer, 7 day risk interval 18–29 0.00 (0.00–1.30) 1.13 (0.23–3.30) 0.00 (0.00–2.96) 30–39 0.00 (0.00–1.49) 0.00 (0.00–1.58) 0.00 (0.00–5.04) 40–49 0.00 (0.00–1.76) 0.51 (0.01–2.84) 0.00 (0.00–5.37) 50–59 0.00 (0.00–1.71) 0.51 (0.01–2.82) 0.00 (0.00–4.84) 60–69 0.00 (0.00–1.61) 0.50 (0.01–2.78) 2.23 (0.27–8.07) 70–79 0.00 (0.00–2.05) 0.00 (0.00–2.23) 0.00 (0.00–4.43) ≥ 80 0.00 (0.00–3.62) 0.00 (0.00–3.84) 0.00 (0.00–8.15) Moderna, 7 day risk interval 18–29 0.00 (0.00–3.81) 1.00 (0.03–5.58) 0.00 (0.00–9.59) 30–39 0.00 (0.00–4.31) 2.18 (0.26–7.87) 1.00 (0.03–5.54) 40–49 0.00 (0.00–5.67) 0.00 (0.00–5.07) 0.00 (0.00–3.91) 50–59 0.00 (0.00–5.34) 1.22 (0.03–6.79) 0.00 (0.00–3.19) 60–69 0.00 (0.00–5.34) 0.00 (0.00–4.02) 1.38 (0.17–4.97) 70–79 0.00 (0.00–9.06) 1.85 (0.05–10.3) 0.00 (0.00–3.15) ≥ 80 0.00 (0.00–13.47) 0.00 (0.00–11.23) 1.37 (0.03–7.64) Pfizer, 21 day risk interval 18–29 0.35 (0.01–1.97) 1.13 (0.23–3.30) 0.00 (0.00–2.96) 30–39 0.81 (0.10–2.92) 0.43 (0.01–2.39) 0.00 (0.00–5.04) 40–49 0.00 (0.00–1.76) 0.51 (0.01–2.84) 1.46 (0.04–8.12) 50–59 0.00 (0.00–1.71) 1.52 (0.31–4.44) 0.00 (0.00–4.84) 60–69 0.44 (0.01–2.44) 1.00 (0.12–3.60) 2.23 (0.27–8.07) 70–79 0.00 (0.00–2.05) 0.61 (0.02–3.37) 0.00 (0.00–4.43) ≥ 80 0.98 (0.02–5.47) 1.04 (0.03–5.80) 2.21 (0.06–12.32) Moderna, 21 day risk interval

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Dataset **Dates of data** (mmm dd yyyy) **Country of Data** **Author year** (RefID)	**Vaccines Studied** Manufacturer Dose #	**Sample Size; Demographics; Previous Covid-19 diagnoses**	**Outcome(s)** Myo-, peri- and/or myopericarditis; Case Ascertainment & Risk Interval; Risk/protective factors considered	**Outcome measures Analysis** (e.g., adjustment for confounders)	**Results** Stratified by age and sex If required, zero cell correction proportional to the reciprocal of the size of the contrasting study arm (i.e., # events = 1/n of the other
Naveed 2022 cont					18–29 0.00 (0.00–3.81) 2.00 (0.24–7.23) 0.00 (0.00–9.59) 30–39 0.00 (0.00–4.31) 3.27 (0.67–9.55) 1.00 (0.03–5.54) 40–49 0.00 (0.00–5.67) 0.00 (0.00–5.07) 0.00 (0.00–3.91) 50–59 0.00 (0.00–5.34) 1.22 (0.03–6.79) 0.00 (0.00–3.19) 60–69 0.00 (0.00–5.34) 0.00 (0.00–4.02) 2.06 (0.43–6.03) 70–79 2.45 (0.06–13.68) 1.85 (0.05–10.3) 0.00 (0.00–3.15) ≥ 80 0.00 (0.00–13.47) 0.00 (0.00–11.23) 1.37 (0.03–7.64)
COVaxON Sep 4/21 Dec 14 2020 to Sep 4 2021 Canada Buchan 2021[36]	Pfizer, Moderna One or two doses Dose interval NR	19,740,741 doses Demographics NR History of COVID-19 NR	Myocarditis (product type) Myocarditis/pericarditis Group of specialized nurses and physicians classified cases according to Brighton Collaboration definition (level 1-3; myocarditis meeting level 1-2); Risk interval: any time after vaccination (97.1% onset within 30 days). Inter-dose interval ≤30 vs. ≥56 d; Moderna dose 2 vs. Pfizer dose 2	Rate ratios, unadjusted (for inter-dose interval) and adjusted for dose 1 product and interval (for dose 2, Moderna vs. Pfizer)	All ages and sexes: **Inter-dose interval ≤30 vs. ≥56 d (ref)**, crude RR (95% CI): Moderna: 5.2 (2.6-10.0) Pfizer: 5.5 (3.1-9.6) 18-24 y, males: **Dose 2: Moderna vs. Pfizer (ref)**, adjusted RR (95% CI): 6.6 (3.3-13.2) **Rate per million doses (95% CI), BC level 1-2 Myocarditis cases on or after 1 Jun 2021** Pfizer Dose 1 Dose 2 12-17 y, male 34.2 (15.6-64.9) 88.1 (53.0-137.5) 12-17 y, female 8.1 (1.0-29.1) 9.7 (1.2-35.1) 18-24 y, male 13.1 (1.6-47.3) 35.5 (7.3-103.7) 18-24 y, female 7.9 (0.2-44.1) 0.0 (0.0-50.5) 25-39 y, male 17.9 (5.8-41.8) 12.6 (1.5-45.4) 25-39 y, female 0 events 13.1 (1.6-47.5) ≥40 y, male 0 events 0.0 (0.0-23.3) ≥40 y, female 0 events 0 events Moderna Dose 1 Dose 2 12-17 y NA NA 18-24 y, male 0 events 299.5 (171.2-486.4) 18-24 y, female 0 events 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 events 21.5 (2.6 - 77.7) ≥40 y, male 18.3 (2.2-66.2) 0 events ≥40 y, female 0 events 0 events **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 events 25-39 y 13.4 (7.5-22.1) 0 events ≥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)

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Dataset **Dates of data** (mmm dd yyyy) **Country of Data** **Author year** (RefID)	**Vaccines Studied** Manufacturer Dose #	**Sample Size; Demographics; Previous Covid-19 diagnoses**	**Outcome(s)** Myo-, peri- and/or myopericarditis; Case Ascertainment & Risk Interval; Risk/protective factors considered	**Outcome measures Analysis** (e.g., adjustment for confounders)	**Results** Stratified by age and sex If required, zero cell correction proportional to the reciprocal of the size of the contrasting study arm (i.e., # events = 1/n of the other
Buchan 2021 cont					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 Interval 31-55 d 0 5,402 0 Interval ≥56 d 0 2,393 0 Pfizer-Moderna Interval ≤30 d 6 7,720 777.2 (285.2-1691.6) Interval 31-55 d 20 62,717 318.9 (194.8-492.5) Interval ≥56 d 3 15,456 194.1 (40.0-567.2) **Rate per million doses (95% CI), dose 2 by product and interval** Pfizer ≤30 d 31-55 d ≥56 d 12-17 y 101.9 (55.7-170.9) 37.7 (21.6-61.3) 55.7 (20.4-121.2) 18-24 y 45.3 (5.5-163.7) 34.7-15.9-66) 10.1 (1.2-36.5) 25-39 y 42.5 (11.6-108.7) 8.7 (2.8-20.3) 12.3 (4.5-26.7) ≥40 y 0 events 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 events 7.4 (2.0-19.0) 7.5 (3.2-14.7)
Nordic cohort Oct 5/21 Dec 27 2020 to Oct 5 2021 Denmark, Finland, Norway, Sweden Karlstadt 2022[32]	Pfizer-BioNTech 15,064,585 Dose 1 or 2 Moderna 2,390,870 Dose 1 or 2	Surveillance population: 23,122,522 nordic residents ≥12 y 50% males Previous covid-19 infection NR but	Myocarditis inpatient stay; Myo- or pericarditis inpatient or outpatient stay ICD-10 codes: I400 I401 I408 I409 I411 I418 I514 in primary or	Crude incident rate; Incidence rate ratio, [32]adjusted Poisson regression comparing rates (vs	**Myocarditis, 0-7 d interval, Moderna vs Pfizer** **Myocarditis, 0-28 d risk interval, Moderna vs Pfizer** **Dose 1** / **Dose 2** **Male** / **Female** / **Male** / **Female** events IR **cRR** events IR **cRR** events IR **cRR** events IR **cRR** 12-15 y

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Dataset **Dates of data** (mmm dd yyyy) **Country of Data** **Author year** (RefID)	**Vaccines Studied** Manufacturer Dose #	**Sample Size; Demographics; Previous Covid-19 diagnoses**	**Outcome(s)** Myo-, peri- and/or myopericarditis; Case Ascertainment & Risk Interval; Risk/protective factors considered	**Outcome measures Analysis** (e.g., adjustment for confounders)	**Results** Stratified by age and sex If required, zero cell correction proportional to the reciprocal of the size of the contrasting study arm (i.e., # events = 1/n of the other
Karlstadt 2022 cont	Homologous or heterologous dose 2 Interval between doses NR	accounted for in analysis	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.	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)	

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

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

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

Myocarditis, 0-28 d interval, Homologous vs. Heterologous Dose 2
cIR per 1000 person-years (95% CI), by product

Males	Pfiz-Pfiz	Pfiz-Mod	cRR	Mod-Mod	Mod-Pfiz	cRR
16-24 y	0.891	3.687		2.584	NR	NE
25-39 y	0.179	1.543		1.132	NR	NE
≥40 y	0.085	NE		0.254	NR	NE
Females						
16-24 y	NE	NE	71.7/2.86	NE	NE	NE
25-39 y	NE	NE		NE	NE	NE
≥40 y	NE	NE	8.12/1.02	NE	NE	NE

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Karlstadt 2022 cont					**Myocarditis, 0-7 d interval, Homologous vs. Heterologous Dose 2** **cIR per 1000 person-years (95% CI), by product** Males: Pfiz-Pfiz 2.190; Pfiz-Mod 13.028; cRR —; Mod-Mod 7.379; Mod-Pfiz NR; cRR NE 16-24 y: Pfiz-Pfiz 0.383; Pfiz-Mod 4.767; Mod-Mod 3.898; Mod-Pfiz NR; cRR NE 25-39 y: Pfiz-Pfiz 0.072; Pfiz-Mod NE; cRR 6.95/1.50; Mod-Mod NE; Mod-Pfiz NR; cRR NE ≥40 y Females: Pfiz-Pfiz NE; Pfiz-Mod NE; cRR 210.81/7.88; Mod-Mod NE; Mod-Pfiz NR; cRR NE 16-24 y: Pfiz-Pfiz NE; Pfiz-Mod NE; cRR NE; Mod-Mod NE; Mod-Pfiz NR; cRR NE 25-39 y: Pfiz-Pfiz NE; Pfiz-Mod NE; cRR NE; Mod-Mod NE; Mod-Pfiz NR; cRR NE ≥40 y **Pericarditis, 0-28 d interval, Homologous vs. Heterologous Dose 2** **cIR per 1000 person-years (95% CI), by product** Males: Pfiz-Pfiz 0.217; Pfiz-Mod NE; cRR 6.36/2.85; Mod-Mod 1.034; Mod-Pfiz NR; cRR NE 16-24 y: Pfiz-Pfiz 0.215; Pfiz-Mod NE; cRR 4.33/2.95; Mod-Mod 0.305; Mod-Pfiz NR; cRR NE 25-39 y: Pfiz-Pfiz 0.168; Pfiz-Mod NE; cRR 1.32/1.09; Mod-Mod 0.30; Mod-Pfiz NR; cRR NE ≥40 y Females: Pfiz-Pfiz NE; Pfiz-Mod NE; cRR 3.43/2.47; Mod-Mod NE; Mod-Pfiz NR; cRR NE 16-24 y: Pfiz-Pfiz NE; Pfiz-Mod NE; cRR 23.21/3.34; Mod-Mod NE; Mod-Pfiz NR; cRR NE 25-39 y: Pfiz-Pfiz 0.098; Pfiz-Mod NE; cRR 1.61/1.39; Mod-Mod NE; Mod-Pfiz NR; cRR NE ≥40 y IR: crude incident rate per 1,000 person-years ND: not determined
Nordic Cohort Sep 1/22 Dec 27 2020 to Sep 1 2022 Denmark, Finland, Norway, Sweden Hviid 2022[8]	Pfizer-BioNTech Dose 2 or 3 Moderna Dose 2 or 3 Homologous Dose 3 Interval between doses NR	Surveillance population: 8,859,339 12-to-39-year-olds Previous Covid-19 NR	Myocarditis First occurrence of a main or secondary myocarditis diagnosis (ICD-10 codes: I40.0, I40.1, I40.8, I40.9, I41.1, I41.8, or I51.4) at discharge from inpatient hospital care. Blinding of assessors NR Risk interval: 0-28	Poisson regression estimated adjusted incidence rate ratios (IRRs) of myocarditis, with associated 95% confidence intervals (CIs) for the 28-day period after booster dose to unvaccinated follow-up,	Incidence rate per 100,000 and IRR of myocarditis within 28 days Sex, Age | Events | Person-years of follow-up | Incidence per 100,000 vaccinees | Adjusted incidence rate ratio (95% CI) *BNT1BNT2 acute 28-day risk period vs unvaccinated follow-up* Females, 16-24 y | 8 | 160806.33 | 0.36 | 3.12 (1.36 to 7.17) Females, 25-39 y | 10 | 307206.31 | 0.24 | 2.20 (1.09 to 4.46) Males, 12-15 y | 9 | 55890.23 | 1.22 | 3.59 (1.52 to 8.51) Males, 16-24 y | 60 | 170560.15 | 2.70 | 4.13 (2.90 to 5.88) Males, 25-39 y | 27 | 323930.60 | 0.64 | 1.77 (1.14 to 2.76) *BNT1BNT2BNT3 acute 28-day risk period vs unvaccinated follow-up* Females, 12-39 y | 4 | 167827.82 | 0.15 | 3.14 (0.79 to 12.57) Males, 12-39 y | 21 | 186849.06 | 0.86 | 2.21 (1.37 to 3.57) *MOD1MOD2 acute 28-day risk period vs unvaccinated follow-up*

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Hviid 2022 cont			Moderna dose 2 and 3 vs. Pfizer dose 2 and 3	adjusted for age, calendar period, and vaccination priority group (e.g., frontline personnel and high-risk individuals).	

Females, 12-39 y	5	102917.95	0.37	3.82 (1.52 to 9.60)
Females, 25-39 y	4	55866.20	0.55	4.22 (1.47 to 12.12)
Males, 12-39	71	79227.55	6.87	12.56 (9.42 to 16.73)
Males, 16-24	29	15655.35	14.20	15.04 (9.57 to 23.63)
Males, 25-39	38	54509.16	5.34	10.21 (6.78 to 15.38)
MOD1MOD2MOD3 acute 28-day risk period vs unvaccinated follow-up				
Males, 12-39	4	8214.30	1.95	6.47 (2.09 to 20.01)

EULAR COVAX Jul 27/21 Feb 5 to Jul 27 2021 Europe (30 countries) Machado 2021[49]	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
SNDS Oct 31/21 May 12 to Oct 31 2021 France Le Vu 2022a[22]	Pfizer or Moderna Dose 1 & Dose 2 Dose timing NR	1612 cases of myocarditis and 1613 cases of pericarditis, matched with 16,120 and 16,130 control subjects, respectively.	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 Moderna dose 2 vs. Pfizer dose 2	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.	**Association between myocarditis and exposure to mRNA vaccines within 7 days, according to sex and age group**

Age	mRNA-1273, Dose 2 aOR (95% CI)	BNT162b2, Dose 2 aOR (95% CI)	Ratio of aORs (Ratio of 95% CIs)
Males			
12-17y	NA	18 (9-35)	NA
18-24y	44 (22-88)	13 (9.2-19)	3.38 (2.39 to 4.63)
25-29y	19 (8.3-43)	7.1 (4.2-12)	2.67 (1.98 to 3.58)
30-39y	45 (19-110)	5.7 (3.4-9.5)	7.89 (5.59 to 11.58)
Females			
12-17y	NA	7.1 (1.5-33)	NA

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Le Vu 2022a cont				Ratio of aORs used by this review to compare Moderna to Pfizer.	18-24y 41 (12-140) 9.6 (4.3-22) 4.27 (2.79 to 6.36) 25-29y 23 (2.1-270) 10 (2.1-47) 2.3 (1 to 5.74) 30-39y 1.4 (0.11-18) 4 (1.4-11) 0.35 (0.08 to 1.64)
BNPV Sep 30/21 Up to Sep 30 2021 France Salvo 2022[23] Salvo 2022 cont	Pfizer or Moderna Dose 1 or Dose 2 Dose timing NR	~83 million total doses (73 million BNT162b2 and 10 million mRNA-1273 doses) Demographics NR	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	Reporting rates (Rr) per 100.000 injections were calculated according to age, gender and injection rank; Poisson distribution was used to compute Rrs 95%	

Incidence of pericarditis per million vaccinees, by age and sex for 7days following vaccinatio

		BNT162b2				mRNA-1273			
		Dose 2				**Dose 2**			
Sex	Age	Cases	Vacinees	IR	aOR	Cases	Vacinees	IR	aC
Female	12-17	5	1,459,109	3.4	10 (2.5-41)	0	61,359	0.0	NI
	18-24	13	1,723,910	7.5	5.9 (2.9-12)	0	204,319	0.0	NI
	25-29	6	1,118,612	5.4	6.4 (2.3-18)	0	143,668	0.0	NI
	18-29	19	2,842,522	6.7		0	347,987	0.0	NE
	30-39	9	2,437,953	3.7	2 (0.9-4.6)	5	363,903	13.7	20
	18-39y	28	5,280,475	5.3		5	711,890	7.0	NE
Male	12-17	7	1,519,395	4.6	6.8 (2.3-20)	0	67,354	0.0	NI
	18-24	21	1,733,962	12.1	6.3 (3.5-11)	8	222,008	36.0	11
	25-29	5	1,139,114	4.4	2.9 (1.1-8)	2	153,909	13.0	7.
	18-29y	26	2,873,076	9.0	4.8	10	375,917	26.6	*26*
	30-39	13	2,427,920	5.4	2.4 (1.2-4.6)	3	372,146	8.1	4.
	18-39y	39	5,300,996	7.4		13	748,063	17.4	

Reporting rate of confirmed cases of myocarditis per million doses

	Moderna, Dose 2	Pfizer, Dose 2	Reporting rate ratio, Moderna compared with Pfizer
Males			
18–24 years	139 (92 to 201)	43 (34 to 55)	3.23
25–29 years	70 (34 to 129)	19 (12 to 29)	3.68
18-29 years	110.25	33.00	3.34

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Dataset **Dates of data** (mmm dd yyyy) **Country of Data** **Author year** (RefID)	**Vaccines Studied** Manufacturer Dose #	**Sample Size; Demographics; Previous Covid-19 diagnoses**	**Outcome(s)** Myo-, peri- and/or myopericarditis; Case Ascertainment & Risk Interval; Risk/protective factors considered	**Outcome measures Analysis** (e.g., adjustment for confounders)	**Results** Stratified by age and sex If required, zero cell correction proportional to the reciprocal of the size of the contrasting study arm (i.e., # events = 1/n of the other
				Confidence Interval (95% CI). Crude reporting rate ratios calculated by review authors; crude risk differences calculated by review authors.	
SNDS Jan 31/22 Dec 27 2020 to Jan 31 2022 France Le Vu 2022b[48] Le Vu 2022b cont	Pfizer or Moderna Dose 1 or Dose 2 Dose timing NR	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.	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	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 compare Moderna to Pfizer.	**Odds of myocarditis within 7 days of dose, compared to unexposed (unvaccinated or >21days since last dose), by dose nu interval for each mRNA vaccine** **12-29y, Dose 2** **BNT162b2** / **mRNA-1273** Interval: **OR (95%CI)** / **OR (95%CI)** **<27d**: 11 (9.0-14) / 82 (34-200) 27-39d: 8.7 (5.7-13) / 25 (12-55) >39d: 5 (3.1-8.0) / 39 (17-86) **12-29y, Dose 3*** **BNT162b2** Interval: **OR (95%CI)** <170d: 6 (3.3-11) 170-193d: 3.9 (1.8-8.5) >193d: 3.3 (0.86-13) *Estimates could not be obtained for the third dose of the mRNA-1273 (Moderna) vaccine as France recommended against the use boosters in persons younger than 30 years **≥30y, Dose 2** **BNT162b2** / **mRNA-1273** Interval: **OR (95%CI)** / **OR (95%CI)** **<27d**: 4.8 (3.1-7.3) / 31 (13-73)

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Dataset **Dates of data** (mmm dd yyyy) **Country of Data** **Author year** (RefID)	**Vaccines Studied** Manufacturer Dose #	**Sample Size; Demographics; Previous Covid-19 diagnoses**	**Outcome(s)** Myo-, peri- and/or myopericarditis; Case Ascertainment & Risk Interval; Risk/protective factors considered	**Outcome measures Analysis** (e.g., adjustment for confounders)	**Results** Stratified by age and sex If required, zero cell correction proportional to the reciprocal of the size of the contrasting study arm (i.e., # events = 1/n of the other
					27-39d 0.77 (0.36-1.6) 9.9 (4.9-20) >39d 1.9 (1.1-3.2) 4.8 (2.4-9.6) **≥30y, Dose 3** Interval: **BNT162b2 OR (95%CI)** / **mRNA-1273 OR (95%CI)** <170 2.1 (0.90-4.7) 6.5 (3.3-13) 170-193 3.4 (1.8-6.6) 3 (1.2-8.0) >193 1.9 (0.91-3.9) 2.6 (1.0-6.6)
ISS/AIFA Sep 30/21 Dec 27 2020 to Sep 30 2021 Italy Massari 2022[50] Massari 2022 cont	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 mos; Corticosteroids for systemic use; NSAID use	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 SARS-CoV-2 test before and	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 facto** **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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Dataset **Dates of data** (mmm dd yyyy) **Country of Data** **Author year** (RefID)	**Vaccines Studied** Manufacturer Dose #	**Sample Size; Demographics; Previous Covid-19 diagnoses**	**Outcome(s)** Myo-, peri- and/or myopericarditis; Case Ascertainment & Risk Interval; Risk/protective factors considered	**Outcome measures Analysis** (e.g., adjustment for confounders)	**Results** Stratified by age and sex If required, zero cell correction proportional to the reciprocal of the size of the contrasting study arm (i.e., # events = 1/n of the other
				during study period (n=378); excluding people with heterologous vaccine combinations (n=440)	
NIMS Nov 15/21 Dec 1 2020 to Nov 15 2021 United Kingdom Patone 2021[42]	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 24/21 Dec 1 2020 to Aug 24 2021 United Kingdom Patone 2022[51]	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 va** 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 va** 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

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Dataset **Dates of data** (mmm dd yyyy) **Country of Data** **Author year** (RefID)	**Vaccines Studied** Manufacturer Dose #	**Sample Size; Demographics; Previous Covid-19 diagnoses**	**Outcome(s)** Myo-, peri- and/or myopericarditis; Case Ascertainment & Risk Interval; Risk/protective factors considered	**Outcome measures Analysis** (e.g., adjustment for confounders)	**Results** Stratified by age and sex If required, zero cell correction proportional to the reciprocal of the size of the contrasting study arm (i.e., # events = 1/n of the other
Singapore Military Aug 3/21 Jan 14 to Aug 3 2021 Singapore Tan 2021[44]	Pfizer (37,367 individuals with 1+ dose) Moderna (27,294 individuals with 1+ dose) Homologous dose 2 administered between 21 and 56 days after dose 1	127,081 doses administered to 64,661 military membets (96.5% with 2 doses) 92.1% male Previous or concurrent COVID-19 diagnosis NR	Myocarditis Risk interval NR Case ascertainment via military doctor or hospital diagnosis Pfizer vs Moderna	Descriptive report only; crude numbers estimated by ARCHE	3 events; all male, 18-21y, all after dose 2 of Moderna; 0 cases with history of cardiac conditions. Overall rate: 2.4 per 100,000 doses Dose 1 / Dose 2 18-20 y **Pfizer** Male 0/3,789 / 0/3,762 Female 0/326 / 0/323 **Moderna** Male 0/7,331 / 2/6,759 Female 0/629 / 0/580 20-29 y **Pfizer** Male 0/18,278 / 0/18,203 Female 0/1,568 / 0/1,562 **Moderna** Male 0/14,572 / 1/13,453 Female 0/1,251 / 0/1,155 30-39 y **Pfizer** Male 0/5,713 / 0/5,667 Female 0/491 / 0/487 **Moderna** Male 0/2,094 / 0/1,958 Female 0/180 / 0/169
VSD Jan 15/22 Dec 14 2020 to Jan 15 2022 United States Goddard 2022[46] Goddard 2022 cont	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	**Myocarditis or myopericarditis 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

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Dataset **Dates of data** (mmm dd yyyy) **Country of Data** **Author year** (RefID)	**Vaccines Studied** Manufacturer Dose #	**Sample Size; Demographics; Previous Covid-19 diagnoses**	**Outcome(s)** Myo-, peri- and/or myopericarditis; Case Ascertainment & Risk Interval; Risk/protective factors considered	**Outcome measures Analysis** (e.g., adjustment for confounders)	**Results** Stratified by age and sex If required, zero cell correction proportional to the reciprocal of the size of the contrasting study arm (i.e., # events = 1/n of the other
				Excess cases in risk period per 1M doses of mRNA-1273 vs BNT162b2	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 Jan 1/23 Oct 12 2022 to Jan 1 2023 United States Hause 2023[7]	Pfizer-BioNTech (bivalent) Booster dose (861,251 doses) Moderna (bivalent) Booster dose (92,108 doses)	953,359 children aged 5-11 y Previous Covid-19 NR	Myocarditis Confirmed to meet CDC working definition Risk interval NR **Moderna booster dose vs. Pfizer booster dose**	Crude reporting rate per million doses used to estimate rate ratio.	Pfizer-BioNTech bivalent: 0 events in 861,251 children aged 5–11 y Moderna bivalent: 0 events in 92,108 children aged 6–11 y* *Moderna only approved for ≥6 y **Estimated RR = 1**
VAERS Oct 23/22 Aug 31 to Oct 23 2022 United States Hause 2022a[5]	Pfizer-BioNTech (bivalent) Booster dose Moderna (bivalent) Booster dose	14.4 million persons aged ≥12 y receiving Pfizer bivalent 8.2 million persons aged ≥18 y receiving Moderna bivalent Previous Covid-19 NR	Myocarditis; Pericarditis Confirmed to meet CDC working definition Risk interval NR **Moderna bivalent vs. Pfizer bivalent**	Crude reporting rate per million doses used to estimate rate ratio.	**Myocarditis** Pfizer: 3 cases among 14.4 million vaccinees = 0.21 cases per million vaccinees Moderna 2 cases among 8.2 million vaccinees = 0.24 cases per million vaccinees Rate ratio: 1.14 **Pericarditis** Pfizer: 1 case among 14.4 million persons aged ≥12 y = 0.07 cases per million vaccinees Moderna: 3 cases among 8.2 million persons aged ≥18 y = 0.37 cases per million vaccinees Rate ratio: 5.29
VAERS Aug 21/22 Jun 18 to Aug 21 2022 United States Hause 2022b[6]	Pfizer-BioNTech 3 doses at 3 week intervals (599,457 vaccinnees) Moderna 2 doses 4 weeks apart (440,773 vaccinnees)	1,040,203 children aged 6 mos to 5 y who completed primary vaccination series Previous Covid-19 NR	Myocarditis Confirmed to meet CDC working definition Risk interval NR **Moderna primary series vs. Pfizer primary series**	Crude reporting rate per million doses used to estimate rate ratio.	Pfizer: 0 events in children aged 6 mos to 4 y. Moderna: 0 events in children aged 6 mos to 5 y. **Estimated RR = 1**
VAERS Feb 6/22 Sep 22 2021 to Feb 6 2022	Pfizer-BioNTech or Moderna	721,562 ≥18 y Pfizer primary series: 349,545	Myocarditis CDC case definition by clinician interview with	Crude rate	**Myocarditis, Moderna vs Pfizer** **Rate per 1M doses** **cRR** **Moderna** **Pfizer**

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Dataset **Dates of data** (mmm dd yyyy) **Country of Data** **Author year** (RefID)	**Vaccines Studied** Manufacturer Dose #	**Sample Size; Demographics; Previous Covid-19 diagnoses**	**Outcome(s)** Myo-, peri- and/or myopericarditis; Case Ascertainment & Risk Interval; Risk/protective factors considered	**Outcome measures Analysis** (e.g., adjustment for confounders)	**Results** Stratified by age and sex If required, zero cell correction proportional to the reciprocal of the size of the contrasting study arm (i.e., # events = 1/n of the other
USA Hause 2022f[31]	Dose 3	Moderna primary series: 327,464 89% with homologous mRNA vaccination Previous COVID-19 infection NR	healthcare provider, or clinician review of medical record Risk interval: 0-6 d	Stratified by sex and age group	**18-24 y** Males 8.7 4.1 2.1 Females 1.1 <1.0 1.1 **25-29 y** Males 3.2 1.1 2.9 Females 1.2 - ND **30-39 y** Males <1.0 1.7 0.58 Females 1.5 <1.0 1.5 **40-49 y** Males - - ND Females <1.0 - ND **50-64 y** Males - <1.0 ND Females <1.0 - ND **≥65 y** Males <1.0 <1.0 1.0 Females - - ND
VAERS Nov 30/21 Up to Nov 30 2021 Europe, United States Lane 2022[47] Lane 2022 cont	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	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]

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Dataset **Dates of data** (mmm dd yyyy) **Country of Data** **Author year** (RefID)	**Vaccines Studied** Manufacturer Dose #	**Sample Size; Demographics; Previous Covid-19 diagnoses**	**Outcome(s)** Myo-, peri- and/or myopericarditis; Case Ascertainment & Risk Interval; Risk/protective factors considered	**Outcome measures Analysis** (e.g., adjustment for confounders)	**Results** Stratified by age and sex If required, zero cell correction proportional to the reciprocal of the size of the contrasting study arm (i.e., # events = 1/n of the other
		Previous COVID-19 diagnosis NR			
VAERS Oct 6/21 To Oct 6 2021 US Su 2021[52]	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 Reports verified to meet case definition by provider interview or medical record review 7 day risk period Pfizer vs. Moderna	Reporting rate of myocarditis per 1 mil doses administered Compared to background risk of 0.2 to 1.9 per 1 million person 7 day risk period estimated crude Rate Ratios (for 18+ only; Moderna not authorized in <18y)	**Moderna vs. Pfizer**

		Events per 1 mil doses		crude Risk Ratio	
		Dose 1	Dose 2	Dose 1	Dose 2
18-24 y					
Female	Moderna	0.6	5.3*	3.0	2.12
	Pfizer	0.2	2.5*		
Male	Moderna	6.1*	38.5*	2.65	1.05
	Pfizer	2.3*	36.8*		
25-29 y					
Female	Moderna	0.4	5.7*	2	4.75
	Pfizer	0.2	1.2		
Male	Moderna	3.4*	17.2*	2.62	1.59
	Pfizer	1.3	10.8		
30-39 y					
Female	Moderna	0.5	0.4	0.83	0.57
	Pfizer	0.6	0.7		
Male	Moderna	2.3	6.7	4.6	1.29
	Pfizer	0.5	5.2		
40-49 y					
Female	Moderna	0.2	1.4	2	1.27
	Pfizer	0.1	1.1		
Male	Moderna	0.2	2.9	0.67	1.45
	Pfizer	0.3	2.0		
50-64 y					
Female	Moderna	0.5	0.4	1.67	0.8
	Pfizer	0.3	0.5		
Male	Moderna	0.5	0.6	2.5	2
	Pfizer	0.2	0.3		
65y+					
Female	Moderna	0.0	0.3	NE	1.0
	Pfizer	0.1	0.3		
Male	Moderna	0.1	0.3	0.5	3
	Pfizer	0.2	0.1		

Green text = evidence identified by February 2023 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 10/21	Y	Y	N	Y	Y	U	High risk
Block 2022 PCORnet Jan 31/22	Y	Y	Y	N (ICD codes only)	Y	Y	High risk
Friedensohn 2022 IDF Sep 30/21	Y	Y	Y	U	Y	Y	Some risk
Hviid 2022 Nordic Cohort Sep 1/22	Y	Y	U	N (ICD codes only)	Y	Y	High risk
Karlstadt 2022 Nordic Cohort Oct 5/21	Y	Y	Y	N (ICD codes only)	Y	U	High risk
Klein 2022 VSD Dec 30/21	Y	Y	U	Y	Y	Y	Some risk
Levin 2021 IDF Mar 7/21	NA	Y	N	Y	Y	Y	High risk
Le Vu 2022 SNDS Oct 31/21	NA	Y	Y	Y	U	N	High risk
Li 2022 eHRSS Oct 18/21	Y	Y	U	N (ICD codes only)	U	U	High risk
Mevorach 2022a Israeli MOH Nov 5/21	N – Used historical control group	Y	N (no confounders reported)	Y	Y	Y	High risk
Mevorach 2022b Israeli MOH Oct 20/21	Y	Y	N (no confounders considered)	Y	Y	U	High risk
Montgomery 2021 US Military Apr 30/21	NA	U	N (potential confounders only reported for cases; no adjustment in analysis)	U	U	U	High risk

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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
Naveed 2022 BC COVID-19 Cohort Mar 10/22	NA	Y	U	N (ICD codes only)	Y	Y	High risk
Niesen 2021 Mayo Clinic Oct 17/21	NA	Y	N (age [only < vs > 40; sex)	Y	Y	Y	High risk
Patone 2021 NIMS/NHS Nov 15/21	Y	Y	U	N (ICD codes only)	Y	U	High risk
Tan 2021 Singapore Military Aug 3/21	NA	Y	N (age and sex only)	U	U	N	High risk
Passive surveillance studies							
Buchan 2021 COVaxON Sep 4/21	Y	Y	U	Y	N	Y	High risk
Cheng 2022 SAEFVIC Feb 22/22	NA	U	N	Y	N	N	High risk
Hause 2023 VAERS Jan 1/23	NA	U	N (no confounders reported)	N/A (no suspected cases reported)	U	N	High risk
Hause 2022a VAERS Oct 23/22	NA	U	N (no confounders reported)	U	U	N	High risk
Hause 2022b VAERS Aug 21/22	NA	U	N (no confounders reported)	N/A (no suspected cases reported)	U	N	High risk
Hause 2022c VAERS Jul 31/22	NA	U	N (no confounders reported)	N/A (no suspected cases reported)	U	N	High risk
Hause 2022d VAERS Mar 28/22	NA	U	N (no confounders reported)	Y	U	N	High risk
Hause 2022e VAERS Feb 20/22	NA	U	N (age and sex only)	Y	U	N	High risk

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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**
Hause 2022f VAERS Feb 6/22	NA	U	N (age and sex only)	Y	Y	N	High risk
Høeg 2021 VAERS Jun 18/21	NA	N	N	U	U	N	High risk
Salvo 2022 BNPV Sep 30/21	NA	U	N (age and sex only)	U	N	N	High risk
Shimabukuro 2022a VAERS May 26/22	NA	U	N (age and sex only)	Y	Y	N	High risk
Shimabukuro 2022b VAERS Jan 13/22	NA	U	N (age and sex only)	Y	Y	N	High risk
Strauss 2022 Moderna Global Safety Database Feb 15/22	Y	Y	N (age and sex only)	Y	U	N	High risk
Su 2021 VAERS Dec 9/21	NA	Y	U	Y	Y	N	High risk
Australian Therapeutic Goods Agency 2022 TGA Aug 21/22	NA	U	N (age and sex only)	Y	N	N	High risk

Green text = new evidence identified by February 2023 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 2021 COVaxON Sep 4/21	U	Y	Y	N	Y	Y	N	Y	High risk
Goddard 2022 VSD Jan 15/22	Y	Y	Y	Y	Y	Y	Y	Y	Low risk
Hause 2023 VAERS Jan 1/23	Y	Y	U	N	Y	N/A (zero cases reported)	U	N	High risk
Hause 2022a VAERS Oct 23/22	Y	Y	U	N	Y	U	U	N	High risk
Hause 2022b VAERS Aug 21/22	Y	Y	U	N	Y	N/A (zero cases reported)	U	N	High risk
Hause 2022f VAERS Feb 6/22	Y	Y	U	N	U	Y	Y	N	High risk
Hviid 2022 Nordic Cohort Sep 1/22	Y	Y	Y	U	Y	N (ICD codes)	Y	Y	High risk
Karlstadt 2022 Nordic cohort Oct 5/21	Y	Y	Y	N	Y	N (ICD codes)	Y	Y	High risk
Lane 2021 VAERS Nov 30/21	Y	Y	N	N	U	N	U	N	High risk
Le Vu 2022a SNDS Oct 31/21	U	Y	Y	Y	Y	U	Y	Y	Moderate risk
Le Vu 2022b SNDS Jan 31/22	U	Y	Y	Y	Y	U	Y	Y	Moderate risk
Machado 2021 EULAR COVAX Jul 27/21	N	Y	Y	N	U	N	N	N	High risk
Massari 2022 ISS/AIFA Sep 30/21	Y	Y	Y	Y	U	N (ICD codes)	Y	Y	High risk
Naveed 2022 BC COVID-19 Cohort Mar 10/22	Y	Y	Y	U	Y	N (ICD codes)	Y	Y	High risk
Patone 2021	N	Y	Y	Y	Y	N	Y	Y	High risk

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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**
NIMS Nov 15/21									
Patone 2022 NIMS Aug 24/21	Y	Y	U	Y	U	N (ICD codes)	Y	Y	High risk
Salvo 2022 BNPV Sep 30/21	U	Y	Y	N	U	U	U	N	High Risk
Su 2021 VAERS Oct 6/21	U	Y	Y	N	Y	Y	Y	N	High risk
Tan 2021 Singapore Military Aug 3/21	Y	Y	Y	N	U	U	U	Y	High risk
Therapeutic Goods Administration 2022 TGA Aug 7/22	U	Y	Y	U	U	Y	U	N	High risk

Green text = new evidence identified by February 2023 update

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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), or when incidence rates were zero or near zero across multiple studies with large sample sizes.

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