Rapid Review of Incidence, Associated Risk Factors, and Clinical Course of Myocarditis and Pericarditis following COVID-19 vaccination

Myocarditis and pericarditis following COVID-19 vaccination: Rapid review

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Prepared By:
Lisa Hartling, PhD, Jennifer Pillay, MSc, Liza Bialy, MSc, Lindsay Gaudet, MSc, Aireen Wingert, MSc, Andrew S. Mackie, MD, SM, FRCPC, D. Ian Paterson, MD, FRCPC, Linda Wilhelm, Natasha Trehan, Becky Skidmore, PhD

For and in close collaboration with:
Susanna Ogunnaike-Cooke and Natalia Abraham, Public Health Agency of Canada

Contact:
Lisa Hartling, PhD
Professor, Department of Pediatrics
Director, Alberta Research Centre for Health Evidence
University of Alberta, 4-472 Edmonton Clinic Health Academy
11405-87 Avenue, Edmonton, AB, T6G 1C9

Email: hartling@ualberta.ca

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Land Acknowledgement(s)

SPOR Evidence Alliance operates from the St. Michael's Hospital, Unity Health Toronto which is located on the traditional land of the Huron-Wendat, the Seneca, and the Mississaugas of the Credit. Today, this meeting place is still the home to many Indigenous people from across Turtle Island.

COVID-END is housed within McMaster University which is located on the traditional territories of the Mississauga and Haudenosaunee nations, and within the lands protected by the "Dish With One Spoon" wampum, an agreement to peaceably share and care for the resources around the Great Lakes.

The University of Alberta acknowledges that we are located on Treaty 6 territory, and respects the histories, languages, and cultures of First Nations, Métis, Inuit, and all First Peoples of Canada, whose presence continues to enrich our vibrant community.

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Project Contributors

Lisa Hartling, PhD & Jennifer Pillay, MSc (Project Leads)
Liza Bialy, MSc, Lindsay Gaudet, MSc, Aireen Wingert, MSc (Review team)
Alberta Research Centre for Health Evidence, University of Alberta

Andrew Mackie, MD, SM, FRCPC (Clinical expert)
Department of Pediatrics, Division of Pediatric Cardiology, University of Alberta

Ian Paterson, MD (Clinical expert)
Department of Medicine, Division of Cardiology, University of Alberta

Linda Wilhelm & Natasha Trehan (Patient partners)

Becky Skidmore, PhD (Information specialist) (Developed and ran searches); Kaitryn Campbell, MLIS, MSc (St. Joseph's Healthcare Hamilton/McMaster University) (Peer reviewed search).

Susanna Ogunnaike-Cooke & Natalia Abraham (Knowledge Users)
Public Health Agency of Canada

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Abbreviations and Descriptions of Data Sources used for Adverse Events

CAEFISS: Canadian Adverse Events Following Immunization Surveillance System
CVP: Canada Vigilance Program
CDC: Centers for Disease Control and Prevention
EEA: European Economic Area
ICU: Intensive care unit
IRR: Incidence rate ratio
KPSC: Kaiser Permanente Southern California
MOH: Ministry of Health
PHAC: Public Health Agency of Canada
RCT: randomized controlled trial
VSD: Vaccine Safety Datalink
VAERS: Vaccine Adverse Events Reporting System.

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

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

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

VAERS: 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.

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

Risk interval: The period after each person's vaccine receipt when adverse event report data were collected.

EXECUTIVE SUMMARY

Context

Since December 2020, regulators have authorized several vaccines for COVID-19 and large-scale immunization programs are ongoing worldwide with the focus now moving towards children and booster vaccinations. Although proven highly efficacious for preventing symptomatic COVID-19 infection and hospitalizations, the safety of these vaccines as they relate to serious, rare events, particularly in subsets of the population, has been uncertain due to lack of power in clinical trials. Case reports and surveillance signals of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the two-layered sac surrounding the heart; myopericarditis when both conditions are present) after COVID-19 vaccination appeared as early as April 2021. This led to their becoming adverse events of special interest occurring after vaccination with messenger RNA (mRNA) vaccines manufactured by Pfizer/BioNTech and Moderna. Background rates of myocarditis and pericarditis following COVID-19 vaccination, adjusted for a 7-day risk period where most cases appear, may be as low as 0.2 and 1.4 per 1 million people, respectively. Historically, myocarditis has been more prevalent in males than females, from childhood through young adulthood. This rapid review aims to provide estimates of the incidence rates for these harms, including whether these vary by patient and/or vaccine characteristics. A further aim is to describe the clinical course of myocarditis and pericarditis after COVID-19 vaccination.

This rapid review includes evidence available from a search conducted on Oct 6 but with grey literature as late as Oct 21, 2021. The research questions were as follows:

1. What is the incidence of myocarditis and pericarditis following COVID-19 vaccination, and does the incidence vary by patient (e.g., age, sex, race/ethnicity, pre-existing conditions [e.g. cardiac diseases] or infections [e.g., COVID-19]) and vaccine factors (e.g. vaccine type/molecule, dose, interval)?

2. What are the characteristics and short-term clinical course in patients with myocarditis and pericarditis after COVID-19 vaccination?

Key Messages

- Incidence of myocarditis and pericarditis following mRNA CODIV-19 vaccination: The incidence of myocarditis following mRNA vaccination is low but probably highest in males 12-29 years old, with lower incidences in older ages. In females, the incidence may be very low (12-29 y) or not exist (≥30 y). The incidence of either myocarditis or pericarditis may be highest in adolescent males; among adults under 40 years there may be few cases but the broad age range may not have detected any variation by age. Among adult males under 40, Moderna compared with Pfizer may be associated with a small increase (<20 cases per million) in risk for myocarditis or (one of) myocarditis or pericarditis following vaccination (Low certainty); the evidence for youth under 18 years was very uncertain. This evidence does not strongly support that one mRNA vaccine should be preferred over the other, even in young males.

- Case characteristics and short-term clinical course: The majority of myocarditis cases involved males (often >90%) in their 20s, with a short symptom onset of 2 to 4 days after a second dose (71-100%). The large majority of cases presented with chest pain or pressure and troponin elevation, and a minority (<30%) also had left ventricular dysfunction. Most were hospitalized (≥84%), without ICU stays, for a short duration (2-4 d) and treated with anti-inflammatory and/or other standard supportive therapies. Among the confirmed cases (N=220) from series that reported on fatalities, one fatality was reported in Israel in a 22-year old with fulminant myocarditis. Within the EudraVigilance dataset (n=5,611, unconfirmed cases), 84 (1.5%) fatalities were reported, though cause of death is not confirmed. Importantly, the vast majority of affected individuals appear to make a complete recovery based on short-term follow-up. Most cases of pericarditis were unconfirmed; for this outcome there appears to be more variation in age, sex, onset timing and rate of hospitalization across cases.
- Policy and decision making about vaccination for adolescent and young adult males will need to weigh various factors such as the: i) societal benefits from preventing COVID-19 transmission, ii) individual benefits from prevention or mitigating severe COVID-19 related illness (e.g., 1000 to >2000 fewer hospitalizations per million vaccinated vs. not vaccinated at least over the short-term), and iii) the availability and efficacy of the non-mRNA vaccines.
- Although the mechanism(s) through which the mRNA vaccines may cause myocarditis or pericarditis are not known, several findings in the studies in this review support a causal association, including an excess risk compared with controls, highly significant clustering effects showing onset soon after vaccine receipt, and higher risk for younger males compared with other causative agents of myocarditis or pericarditis. Further, an immune-mediated mechanism is suspected, given the much higher incidence of myocarditis after the second dose.
- Although the short-term course of myocarditis after an mRNA vaccine is mild and self-limiting in the majority of cases, the incidence and course after booster doses and the potential for long-term sequelae such as recurrent disease and/or heart failure are not known. Further, individual risk factors other than age and sex have not been examined and warrant further attention.
- Continued active surveillance of myocarditis/myopericarditis incidence out to 30 days from dosing is recommended with respect to i) new populations (i.e., vaccinated children <12y), ii) the impact of third and subsequent doses, and iii) affected individuals receiving subsequent mRNA vaccine doses.
- Patient Partner Interpretation:
  - A risk for myocarditis after COVID-19 vaccination seems to exist for young males (<29y) although is likely very small and occurrences appear to be quite mild with full recovery.
  - Clear and effective communication of the risks (rates of myocarditis and likely clinical course), benefits from vaccination, and the availability of good alternatives will be critical for individuals, and for young males and their parents. This will help increase their confidence and ability to make decisions about vaccination.
  - Getting vaccinated is very important for young males (for their contacts and themselves) and recommendations against vaccines, even if cautionary or against a single vaccine, may lead to unnecessary harm from increasing hesitancy; recommendations could focus on positive guidance about awareness and identification of symptoms for these rare and relatively mild risks.
  - More research on what personal risk factors may put someone at higher risk for these complications (e.g., co-existing heart conditions) would be very useful.
  - Individuals should discuss their concerns about the potential for adverse events and personal risk factors of vaccination with their primary care provider.

Summary of Evidence

Incidence of myocarditis and pericarditis

- We included 7 randomized controlled trials and 22 large observational studies/data sources, with identification of cases based on passive surveillance systems (n=10) or active surveillance/registry data (n=12). Observational data came from the US, Canada, the UK, Israel, and the EEA. Several data sources were used in multiple studies (e.g., 7 relied on data from VAERS in the US), with variations in their methods (e.g., risk interval used, number of cases verified). Nine of the 12 studies using active surveillance included a comparator group. Eleven studies examined age and/or sex subgroups and 7 provided data by specific vaccine.
- RCTs provided very low certainty of evidence for these very rare outcomes.
- Most cases occur soon (0-7d) after the second dose of the vaccine.
- When looking across all ages, we are very uncertain about the incidence of myocarditis/myopericarditis, pericarditis, or (one of) myocarditis or pericarditis after receipt of mRNA vaccines. Although rates across all analyses (or subanalyses) are low, the same rate cannot be applied to the entire population based on study findings for sex and age differences.
- Incidence of presenting with ***myocarditis in males*** after two doses of mRNA vaccines:
    - Among 12-17 year old males: between 55 (7 d risk) and 134 (30 d risk) cases per million (Moderate certainty; specific to Pfizer).
    - Among 18-29 year old males: between 40 (7 d risk) and 99 (21-30 d risk) cases per million (Moderate certainty).
    - Among males 30 and older: between six (7 d risk) and 21 (30 d risk) (30-39 y) and fewer than 20 cases (≥40 y) per million (Low certainty).
- Incidence of presenting with ***myocarditis in females*** after two doses of mRNA vaccines:
    - Among 12-29 year old females: fewer than 10 cases per million (Low certainty; specific to Pfizer for 12-17 y).
    - Among females 30 and older: no excess risk (Low certainty).
- Incidence of presenting with ***pericarditis in males or females*** after two doses of mRNA vaccines:
    - No data on incidence based on age was reported in the included studies.
- Incidence of presenting with ***myocarditis or pericarditis*** after two doses of mRNA vaccines:
    - Among youth 12-17 years: approximately 50 cases (mostly males) per million (Low certainty).
    - Among adults under 40: fewer than 20 cases (mostly males) per million (Low certainty).
- Comparing vaccines (i.e., Moderna versus Pfizer):
    - Across all ages, we are uncertain about whether there is an association between mRNA vaccine type and incidence of myocarditis or pericarditis.
    - Among adult males under 40, Moderna compared with Pfizer may be associated with a small increase (<20 cases per million) in risk for myocarditis or (one of) myocarditis or pericarditis following vaccination (Low certainty).
    - This small difference in adult males along with the low incidences of myocarditis seen in young males receiving mRNA vaccines do not suggest that one vaccine should be preferred over the other.

Characteristics and Short-term Clinical Course

- We included 11 case series published as articles and 3 case series based on publicly available websites in Canada, the UK, and Europe. 12,636 cases were included across reports, with some possible overlap among the smaller series. The cases based on publicly available websites (n=11,854, 94%) were unconfirmed and may be inaccurate.
- Most case series focused on myocarditis (10 reports, n=5,955). The majority of cases (often >90%) involved males with reported median age most often between 20 and 29 years; confirmed cases ranged from 12 to 56 years. Time between last vaccine and symptom onset was on average 2 to 4 days, and the majority (71-100%) presented after a second dose. Most cases presented with chest pain or pressure, and troponin elevation; a minority (<30%) showed left ventricular dysfunction (i.e., LVEF<50%).
- The majority of myocarditis cases were hospitalized (≥84%) with few admitted to ICU; average length of hospital stay was 2-4 days. NSAIDs were most often used as treatment; other interventions included bisoprolol, ramipril, colchicine, famotidine, steroids (for myocarditis) and intravenous immune globulin (for myopericarditis).
- Among the series of confirmed cases of myocarditis that reported on fatalities (N=220), one fatality was reported in Israel in a 22-year-old with fulminant myocarditis. The unconfirmed series from the EEA reported 84 fatalities among 5,611 cases (1.5%), though cause of death was not confirmed.
- Three reports provided data for pericarditis (n=4,309; almost 99% unconfirmed). The majority involved males; however, there was variation across reports (54 to 91%). Median age (59 years) was only reported in one small series (n=37). The same series reported a median interval of 20 days between last vaccine and symptom onset, with 60% presenting after the second vaccination. Hospitalization varied (35% and 73%) in two case series (n=59); one small series (n=37) reported 3% admitted to ICU and reported median length of stay (1 day). One small series (n=37) reported 0 fatalities, and a larger series of unconfirmed cases (n=4,250) reported 15 deaths (0.4%).
- Four reports included a mix of diagnoses (myocarditis, pericarditis and/or myopericarditis). The majority of patients were males. Median age was 27 years in the report that included all ages. Time between last vaccine and symptom onset was median 2 days on one report of 323 cases. The majority presented after second vaccination. The majority (96% and 71%) in two case series (n=379) were hospitalized. One series (n=56) reported that a minority of cases were admitted to the ICU (13%), length of stay was ≤2 days in 75% of patients hospitalized, and symptoms resolved in 100% of patients. No fatalities were reported in two series (n=379); a third report identified 5 fatalities among 1,037 unconfirmed cases (0.5%).

Introduction

Vaccines for COVID-19 have been developed at unprecedented speed, with phase III clinical trials reporting results for some vaccines less than a year after the World Health Organization declared the pandemic. Since December 2020, regulators have authorized several vaccines and large-scale immunization programs are ongoing worldwide with the focus now moving towards children and booster vaccinations. Although proven highly efficacious for preventing symptomatic COVID-19 infection and hospitalizations, the safety of these vaccines as they relate to serious, rare events, particularly in subsets of the population, has been uncertain due to lack of power in clinical trials.

Myocarditis (inflammation of the heart muscle) can be caused by infectious agents (including viruses, bacteria such as Chlamydia or rickettsia, fungi, and protozoa) or noninfectious triggers (such as toxins, systemic inflammatory diseases, or hypersensitive reactions) (1, 2). Historically, post vaccination myocarditis has been reported, with attribution strongest for the live vaccine against smallpox (3). Case reports and surveillance signals (4-7) of myocarditis and pericarditis (inflammation of the two-layered sac surrounding the heart; myopericarditis when both conditions are present) after COVID-19 vaccination appeared as early as April 2021. This led to the surveillance of adverse events of special interest following vaccination with messenger RNA (mRNA) vaccines manufactured by Pfizer/BioNTech and Moderna.

Symptoms indicative of myocarditis or pericarditis typically include new onset and persisting chest pain, shortness of breath, and/or palpitations (8). Diagnosis of a probable case of myocarditis usually requires elevated troponin levels and/or findings from imaging (e.g., echocardiography, magnetic resonance imaging) or other testing (e.g., ECG); histopathology to provide definitive diagnosis is not usually performed (2). Differential diagnoses, including COVID-19 infection and community-acquired myocarditis, should be considered and ruled out (2, 9). Traditionally, the conditions can be asymptomatic and actual patient cases of myocarditis may be significantly underestimated (2). Most people experiencing these conditions will fully recover, however, in rare cases, myocarditis can lead to heart failure or asymptomatic left ventricular dysfunction. Long-term consequences associated with pericarditis include one or more recurrences and, rarely, thickening of the pericardium and constrictive heart filling (1).

Background rates of adverse events have historically served as an important baseline comparator for estimating incident rates among those vaccinated. A population-based retrospective cohort study, using electronic health records and administrative claims data spanning 2017 through 2019 from eight countries (Australia, France, Germany, Japan, the Netherlands, Spain, the United Kingdom [UK], and the United States [US]) found variable rates for myocarditis and pericarditis (combined) ranging from 6-36 (females) and 7-54 (males) per 100,000 person years (10). Rates specific to myocarditis are lower, with estimates in the UK of 11 cases (11) and in the US of 1.3 cases per 100,000 person-years (12), regardless of age. The US Centers for Disease Control and Prevention (CDC) COVID-19 Response Team has estimated that background/expected rates of myocarditis and pericarditis following COVID-19 vaccination in the US, adjusted for a 7-day risk period where most cases appear, are 0.2 and 1.4 per 1 million people, respectively (12). Historically, myocarditis has been more prevalent in males than females, from childhood through young adulthood (13), and this trend has been evident in early case series of post-COVID-19 vaccinations (14, 15).

The impact of myocarditis and pericarditis on COVID-19 vaccination decision-making will rely heavily on a risk-benefit assessment specific to the relevant populations (e.g., by age and sex). The risk for these harms could, for example, be balanced against the beneficial effects from vaccination on reduced COVID-19 infections (e.g., 56,700 and 75,200 prevented per million aged 16-17 or 18-24 year old, respectively, males vaccinated [assuming 120-day time horizon]), hospitalizations (e.g., 500 or 1,000), ICU admissions (e.g., 170 or 230), and deaths (e.g. 4 or 2) (16). Initial reports of myocarditis and pericarditis after COVID-19 vaccination suggest a mild severity illness, usually treated with anti-inflammatory drugs and requiring short-term (e.g., 1-3 day) hospital stay (14). Further, initial reports document few if any deaths, although larger studies will help inform this assessment. This review aims to provide estimates of the incidence rates for these harms, including whether these vary by patient and/or vaccine characteristics. A further aim is to describe the clinical course of myocarditis and pericarditis after COVID-19 vaccination.

Research Questions

1. What is the incidence of myocarditis and pericarditis following COVID-19 vaccination, and does the incidence vary by patient (e.g., age, sex, race/ethnicity, pre-existing conditions [e.g. cardiac diseases] or infections [e.g., COVID-19]) and vaccine factors (e.g. vaccine type/molecule, dose, interval)?

2. What are the characteristics and short-term clinical course in patients with myocarditis and pericarditis after COVID-19 vaccination?

Methods

We performed a rapid review following the WHO Rapid Review Guide (17) and report our findings according to the 2020 PRISMA statement (18).

Literature Search

We worked with an experienced medical information specialist (Skidmore) to develop the search strategy, which was peer-reviewed (19) (Appendix 1). Searches combined concepts for COVID-19, vaccines, and myocarditis/pericarditis/cardiovascular manifestations/adverse events/surveillance. We limited our search to articles published since October 2020. We did not add limits for language, country, or study design, but had limits for human (not animal only) studies and commentaries. Using the multifile option as well as the deduping tool in Ovid, we searched Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to October 05, 2021> and Embase <1974 to 2021 October 05>. We also searched the Cochrane Library and medRxiv (last 2 months). These searches were run on Oct 6, 2021. We completed a rapid grey literature search by scanning 20 key national websites (e.g., Public Health Agency of Canada, UK's Medicines & Healthcare Products Regulatory Agency, CDC) to identify unpublished data. Reference lists of included studies were scanned. We used Endnote for citation management.

Eligibility Criteria

Our inclusion criteria are outlined in **Table 1**.

Table 1. Eligibility Criteria for Each Research Question

Population	1. People of any age 2. People of any age experiencing myocarditis, pericarditis, or myopericarditis after receiving a COVID-19 vaccine
Intervention/ Exposure	1. Health Canada approved COVID-19 vaccine: BNT162b2 mRNA/PfizerBioNTech/Comirnaty, mRNA-1273/Moderna Spikevax, AZD1222 (ChAdOx1 nCoV-19)/AstraZeneca Vaxzevria, Ad26.COV2.S/Janssen (alternative manufacturers of same vaccine are eligible) 2. Same as 1.
Control/ Comparator	1. Comparators of previously vaccinated people (no longer at risk for outcome) or unvaccinated people; or no comparator. Risk factors include; age, sex, race/ethnicity, preexisting chronic conditions [e.g. cardiac diseases, immunocompromise] or infections (e.g., recent/past COVID-19), vaccine type (e.g., mRNA vs vector)/dose/interval 2. No comparator
Outcomes	1. Incidence rate/cummulative risk of myocarditis, pericarditis, and/or myopericarditis after receipt of vaccine (any dose). 2. Characteristics of the patients (e.g., age, sex, pre-existing conditions [e.g. cardiac diseases] and infections [e.g. recent/past COVID-19], race/ethnicity) and case presentation (e.g., timing/dose/type of vaccine, diagnostics, illness severity, treatments provided, short-term outcomes, disposition)
Setting	Any setting and country
Study designs	1. Phase 3/4 RCTs; large (>1000 vaccinated people) population/multisite/health system-based observational studies and surveillance data 2. Systematic/rapid reviews and data on cases from studies included in question 1.
Publication Language	1. English full texts 2. English full texts We will cite those excluded based only on language.
Publication Date	1. Oct 2020-onwards (vaccines were authorized mid-Sept 2020) 2. Oct 2020-onwards

Study Selection

One lead (Pillay) and all three review team members conducted a pilot round in Excel using 300 records. We then conducted screening and selection in DistillerSR (Evidence Partners) using structured forms. For title and abstract review, we applied the machine learning program Daisy AI which continually reprioritizes records during screening (20). A single reviewer screened all titles/abstracts and another reviewer verified exclusions for the first 50% of records. For full text selection, a single reviewer reviewed all records, with all exclusions verified by another reviewer. Studies were further verified for inclusion during data extraction.

For research question 1, when reports collected data from similar/overlapping populations (e.g., US VAERS data, Israel Ministry of Health [national] and an individual health system), we first included the

study with the most recent data and then included additional studies if they differed in their methods (e.g., of verifying cases, differing risk intervals, differing age and/or sex stratification, use of unvaccinated or similar control). For randomized controlled trials (RCTs), we used the report of the largest population as the primary (included) publication and cited associated papers used for data extraction; sub-studies within RCTs, for example of different ages, were considered different studies.

For research question 2, we mapped the case series and case reports contained within the relevant reviews. This served as a baseline for identifying the most recent and comprehensive data source for each geographic region (i.e., USA, Canada, UK, Europe, and Israel). When more recent data were identified in studies included in research question 1, these were included in place of studies identified through the reviews. For regions with multiple reports, we prioritized data that was most recent, most comprehensive (largest numbers), and that verified cases. Our goal was to avoid overlap in data, i.e., the same cases reported in different sources. However, we did include sources that reported on specific sub-groups (e.g., 12 to 17 year-olds) to present more details on these groups of interest. We have noted in the evidence tables where there may be overlap in cases between reports.

Data Extraction

We extracted all data into structured Word forms and conducted a pilot exercise with two studies. Thereafter, one reviewer extracted all data and another verified eligibility and all data. Discrepancies were resolved by discussion or by a review lead. Specific equity-related populations of interest for study demographics and results are sex, age, and race/ethnicity.

For research question 1, extracted data related to all elements of the eligibility criteria (Table 1) and data used for risk of bias assessment, focusing on methods for identifying cases (i.e., passive surveillance versus active surveillance/registry data), outcome ascertainment and confirmation/adjudication (including criteria for case definitions and classification), as well as the risk interval for which the events were captured. We distinguished between estimates of incidence compared with an unexposed group (excess incidence/risk differences) versus without a control, and extracted data on incident rates per person-years and per doses of vaccine/people vaccinated (after either dose, dose 1, or dose 2). We extracted data on any stratified or subgroup analyses based on age, sex, different vaccine types or doses (events captured after any dose, dose 1, or dose 2), and different risk intervals (0-7d vs. 8-28d vs. longer). 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.

For research question 2, we planned to rely on data from the relevant systematic reviews identified through our search. We used the evidence table presented in an existing review (14) as the foundation for data extraction and presentation of findings as it covered most of the items specified under our outcomes in Table 1. We added the following items: criteria for confirmation of cases, breakdown of cases by diagnosis (myocarditis, pericarditis, myopericarditis), case source, age included, percent admitted to ICU, percent hospitalized, number of fatalities. Most of the studies included in Bozkurt et al.(14) (and the other relevant SRs) were superseded by more recent publications/data; therefore, we extracted data directly from the relevant case series/data sources.

Risk of Bias Assessment

For research question 1, one review lead and all other reviewers piloted each risk of bias tool with two papers. We used the Cochrane Collaboration ROB 2.0 tool (21) for RCTs, and the JBI (formally Joanna Briggs Institute) checklist for cohort studies (22) for observational studies/surveillance data. We focused on valid and reliable case finding and outcome ascertainment methods and, in observational studies, accounting for key confounders including age, sex, existing cardiac diseases/conditions, and prior COVID-19 exposure. 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 (23, 24). Assessments were completed by one reviewer and verified by another. Discrepancies were resolved by discussion or by a review lead.

For research question 2, we did not assess the risk of bias of the included systematic reviews because we did not rely on their reporting or synthesis in any way. We also did not rate the case series data, either published or derived from grey literature or publicly available data sources (e.g., Yellow Card, UK). The intent of question 2 was to characterize these patients and their clinical course without providing quantitative estimates, e.g., of incidence or effectiveness. The main differentiating feature between case series was whether they only reported on cases verified by clinicians; we extracted this information and considered this factor when summarizing the results.

Data Synthesis

For research question 1, we did not pool results from the included studies due to heterogeneity in case finding (passive vs. active surveillance), dosing and risk intervals, case ascertainment, populations (age and sex), and the large amount of overlap in some study populations. 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/upper limit based on different risk intervals or other variables), relying mostly on studies that verified cases and used active surveillance, when possible. Based on clinical input we developed primary age categories (12-17y, 18-29y, 30-39y, ≥40y) to rely on when possible. If a study contributed more than one result within these (e.g., 20-24y and 25-29y, results for each mRNA vaccine) we took the 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]). We assessed the certainty for each of our conclusion statements using GRADE (23, 24), with RCTs starting at high certainty (i.e., indicating we are very confident that the true effect lies close to that of the estimate of the effect) and observational studies starting at low certainty (i.e., our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect). We rated down based on serious concerns about risk of bias, inconsistency, indirectness, imprecision, and/or reporting biases. We did not apply a threshold for an important effect, but in general considered 10-20 or fewer cases per million doses to be less meaningful for decision-making. We rated down for risk of bias when only studies using passive surveillance (assuming some under ascertainment) and unverified cases contributed to a synthesis, and for indirectness for comparisons across all ages and 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.

For research question 2, we present the details for each case series in an evidence table and provide a descriptive summary.

Results

Study Selection

After deduplication, our database searches retrieved 3439 citations and other sources identified 18 citations (Appendix 2). After title/abstract screening, we retrieved and screened at full text 159 citations. For question 1 we included 29 studies reported in 32 publications, and for question 2 we included data for 14 case series (9 were reported in studies included in question 1). Tables of study characteristics and risk of bias ratings for question 1 are in Appendix 3.

Findings

Research Question 1: Incidence of Myocarditis and Pericarditis

We included seven RCTs (n=3732 to 44,325) (25-31) reported in 10 papers (32-34), and 22 large observational studies/data sources (reported in publications, presentations, online reports, accessible data; all are considered here as "studies" for simplicity), with identification of cases based on passive surveillance systems (n=10) (15, 35-43) or on active surveillance/registry data (n=12) (44-55). Observational data came from the US, Canada, the UK, Israel, and the EEA. Several data sources were used in multiple studies (e.g., 5 relied on data from the US VAERS) with different methods (e.g., risk interval used, whether cases were confirmed/verified). We refer to studies by their source of adverse event data and the date of data collection.

Nine of the 12 studies using active surveillance included a comparator group to estimate excess incidence. Eleven studies examined age and/or sex subgroups and seven provided data by specific vaccine. None assessed differences in incidence based on pre-existing condition(s), or race/ethnicity. Overall, risk of bias for adverse events from the RCTs was low to "some concerns". Risk of bias was low to "some concerns" for data from active surveillance systems and high for passive surveillance data.

Tables 2 and **3** include the Summary of Findings tables for evidence from the observational data, including the GRADE certainty assessments. **Appendix 4** includes the Summary of Findings table for evidence from the RCTs, from which there was low certainty mainly due to imprecision from inadequate sample sizes for these outcomes. Two observational studies using one cohort of nursing home residents (n~21,000) reported no events (45, 46).

Although the mechanism(s) through which the mRNA vaccines may cause myocarditis or pericarditis are not known, several findings in the studies in this review support a causal association, including an excess risk compared with controls, highly significant clustering effects showing onset soon after vaccine receipt (43, 50), and higher risk for younger males as seen with other causative agents of myocarditis or pericarditis. Further, an immune-mediated mechanism is suspected, given the much higher incidence of myocarditis after the second compared with first dose of mRNA vaccine (43, 48, 50, 52-54).

Research Question 2. Case Characteristics and Short-term Clinical Course

We included 11 case series reported in articles (either published, pre-proofs, or pre-prints) (15, 37, 47, 50-53, 56-59) and 3 case series compiled from publicly available websites (Public Health Agency of Canada, PHAC; UK's Medicines & Healthcare Products Regulatory Agency [Yellow Card database], UK; EudraVigilance, European Economic Area (EEA)) (35, 40, 41). For one of the research articles (Klein, 2021) (50), more recent data on some variables were available in a publicly available presentation (49).

The 14 reports included a total of 12,636 cases (median 57, IQR 9-279), although it is important to note that there may be some overlap. All reported on clinician-confirmed cases except PHAC, Yellow Card, and EudraVigilance. **Table 4** (myocarditis and myopericarditis) and **Table 5** (pericarditis and mixed diagnosis) include the data extracted from the 14 case series. In summary:

Myocarditis or myopericarditis

Nine reports provided data for patients with myocarditis and one report included children aged 12-17 years with myopericarditis, with 5,955 cases overall (median 16.5). Most cases involved males with 7 reports describing samples with ≥90% males. Among five reports that provided average age (and did not restrict inclusion/search by age), the median ranged from 20 to 36 years (median in 4 reports was between 20-29y). In addition, two reports from the US focused specifically on children aged 12 to 17 years.

Eight reports provided an average time between last vaccine and symptom onset, reporting median days from 2 to 4. Eight reports also indicated number of patients presenting after second vaccination which ranged from 71 to 100%. Seven reports described whether patients presented with chest pain or pressure, with 100% in five reports, and 95% and 86% in single reports.

Eight reports provided information on troponin elevation with 100% in seven reports, and 95% in one report. Seven reports provided numbers of patients with LVEF<50%, which ranged from 14 to 83% (six of the seven reported between 14 and 29%).

Seven reports provided information on hospitalization with 84 to 100% hospitalized. Only three reports provided information on ICU admission reporting 0 to 38% (0/13, 2/20, and 3/8). Four reports (n=47) provided median length of hospital stay, ranging from 2 to 4 days.

Six reports described medications used: all reported use of NSAIDs (though not in all patients); other interventions included colchicine, famotidine, steroids, bisoprolol, ramipril, and ibuprofen. In the series of children (12-17 y) with myopericarditis, 100% received NSAIDs, 23% were treated with intravenous immune globulin, and 15% received corticosteroids.

All but one report indicated whether symptoms had resolved: six (n=61) reported resolution of symptoms in 100% of patients; one (n=136) reported 95% (at time of publication); one (n=23) reported 70%; and one (n=5,611) reported 46% resolved/resolving, 28% not resolved, 22% unknown, 2% resolved/resolving with sequelae. Among the confirmed cases (N=220) from series that reported on fatalities, one fatality was reported in Israel in a 22-year old with fulminant myocarditis. Within the

EudraVigilance dataset (n=5,611 unconfirmed cases), 84 (1.5%) fatalities were reported, though cause of death is not confirmed.

Pericarditis

Three reports provided data for patients with pericarditis, with 4,309 cases overall (median 37). The majority of cases involved males, though the percentage varied across reports (54%, 73%, 91%). Median age was provided in only one study (59 years); another study only included children 12 to 17 years.

Only one study provided an average time between last vaccine and symptom onset (20 days). This same study reported that 60% of patients presented after the second vaccination.

Two reports (n=59) provided information on hospitalization with 35 and 73% hospitalized. One study (n=37) indicated that 3% were admitted to ICU. Only one study (n=37) provided median length of hospital stay (1 day). The same study described medications that patients received: 54% colchicine, 49% NSAIDs, 11% steroids.

Two reports indicated whether symptoms had resolved. One study (n=37) reported that 81% had resolved/improved, 5% had persistent symptoms, and information was unknown for 14%; this study reported 0 fatalities. The other report (n=4,250) found 49% resolved/resolving, 31% not resolved, 19% unknown, 1% resolved/resolving with sequelae, and 0.4% died (n=15).

Mixed diagnoses

Four reports included patients meeting criteria for myocarditis, pericarditis and/or myopericarditis. A break-down of diagnoses was provided in two reports: one reported 30% myocarditis, 56% pericarditis and 14% myopericarditis; one reported 52% myocarditis and 48% pericarditis. The majority of patients were males in three reports providing data. Median age in years was 19 (inclusion limited to those under 30 years), 24 (search limited to 12-39 year olds), and 27 (all ages included).

Only one report provided information on time between last vaccine and symptoms onset, with median 2 days. One reported median days by age group: 2 (12-17 years), 1 (18-29 years), and 5 (30-39 years). Two reported on patients presenting after second vaccination: one reported 71%; the other reported by vaccine (45% Pfizer, 68% Moderna).

Two reports (n=379) described hospitalizations with 96% and 71% patients hospitalized. Only one reported on ICU admissions: 13% of 56 patients. Only one report (n=56) provided length of stay with 75% of hospitalized for ≤2 days. None of the reports described medications.

One (n=56) reported that symptoms resolved in 100%, and another (n=323) reported 95% (at time of publication) with no fatalities. A third report identified 5 fatalities among 1,037 cases (0.5%).

Table 2: Summary of Findings for Incident Rates after Receipt of Either mRNA Vaccine

Note: Shading represents the data used to create lower and upper limits of incidence rates, when used in conclusions. See Appendix 2 for references.

Sex	Age	Studies (data source and date)	Risk interval; Confirmed cases (Y/N)	Incidence rates per million doses after dose 2 of either mRNA vaccine unless otherwise stated Ranges represent each vaccine and square brackets indicate either an average across vaccines/ages or our calculation of excess incidence*	Conclusions	Certainty about conclusions using GRADE
Myocarditis						
Both sexes	All ages (≥12y unless otherwise stated)	VAERS Aug 6	None; N	3.65-6.47 [5.1]	Across all ages, we are very uncertain about the incidence of myocarditis after vaccination with mRNA vaccines	Very low [a]
		Yellow Card Oct 13	NR; N	8-32 [20]		
		Israel MOH May 30	30 d; N	24 (Pfizer) (≥16y)		
		EudraVigilance Oct 19	NR; N	8.5-25.8 (either dose) [7.2]		
		Israel MOH May 31	30 d; N	22.8 (Pfizer) (≥16y)		
		Clalit Health May 24a	42 d after dose 1; Y	21.3 (Pfizer) (≥16y)		
		Clalit Health May 24b	42 d after dose 1; N	27 (Pfizer) (≥16y)		
		KPSC July 20	10 d; Y	5.8 (>18y)		
		Providence Health May 25	30d; Y	10		
Both sexes	<18 y	EudraVigilance Oct 19	NR; N	41.6-60.3 (either dose) [50.9]	Among youth of both sexes, we are very uncertain about the incidence of myocarditis after vaccination with the Pfizer vaccine	Very low [b]
M	All ages	Israel MOH May 31	30 d; N	38.3 (Pfizer) (≥16y)	Across all ages of males, we are very uncertain about the incidence of myocarditis after vaccination with the Pfizer vaccine	Very low [a]
		Clalit Health May 24a	42 d after dose 1; Y	41.2 (Pfizer; either dose) (≥16y)		
F	All ages	Israel MOH May 31	30 d; N	4.6 (Pfizer) (≥16y)	Across all ages of females, there may be no excess risk of myocarditis after vaccination with the Pfizer vaccine	Low
		Clalit Health May 24a	42 d after dose 1; Y	2.3 (Pfizer; either dose) (≥16y)		
M	12-17y	VAERS Jun 18a	Any; Y	162.2 (Pfizer) (12-15y) 94.02 (Pfizer) (16-17y)	Among 12-17 year old males, the incidence of presenting with myocarditis after vaccination with the Pfizer vaccine is probably	Moderate [c]
		VAERS Oct 6	7 d; Y	39.9 (Pfizer) (12-15y) 69.1 (Pfizer) (16-17y) [55]		

Sex	Age	Studies (data source and date)	Risk interval; Confirmed cases (Y/N)	Incidence rates per million doses after dose 2 of either mRNA vaccine unless otherwise stated Ranges represent each vaccine and square brackets indicate either an average across vaccines/ages or our calculation of excess incidence*	Conclusions	Certainty about conclusions using GRADE
		Israel MOH May 31	30 d; Y	150.7 (Pfizer) (16-19y) [134]	between 55 (7 d risk) and 134 (30 d risk) cases per million	
	18-29y	VAERS Jun 30	NR; N	22-27	Among 18-29 year old males, the incidence of presenting with myocarditis after vaccination with the mRNA vaccines is probably between 40 (≤7 d risk) and 99 (21-30 d risk) cases per million	Moderate[c]
		VAERS Oct 6	7 d; Y	36.8-38.5 (18-24y) [37.6] 10.8-17.2 (25-29y) [14] [25.8 across ages]		
		Israel Defense Forces Mar 7	7d; Y	50.7 (Pfizer; all cases males; 18-24 y)		
		US Military Apr 30	4 d (all cases); Y	44 (median 25 y [20-51])		
		Israel MOH May 31	30 d; Y	150.7 (Pfizer) (16-19y) [134] 108.6 (Pfizer) (20-24y) [90.9] 69.9 (Pfizer) (25-29y) [50.4] [average 91.8]		
		Clalit Health May 24a	42 d after dose 1; Y	106.9 (Pfizer; either dose; 94% had 2 doses) (16-29y)		
	30-39y	VAERS Oct 6	7 d; Y	5.2-6.7 [6.0]	Among 30-39 year old males, the incidence of presenting with myocarditis after vaccination with the mRNA vaccines may be between 6 (7 d risk) and 21 (30 d risk) cases per million	Low
		Israel MOH May 31	30 d; N	36.9 (Pfizer) [20.9]		
	≥40y	VAERS Oct 6	7 d; Y	0.1-2.9 [1.5]	Among males 40 and older, the incidence of presenting with myocarditis after vaccination with the mRNA vaccines may be fewer than 20 cases per million	Low
		VAERS Jun 11	7 d; N	2.4 (≥30y)		
		Israel MOH May 31	30 d; N	6.8 (Pfizer) (average among 40-49y and ≥50y)		
		Clalit Health May 24a	42 d after dose 1; Y	21.1 (Pfizer; either dose; 94% had 2 doses) (≥30y)		
F	12-17y	VAERS Jun 18a	Any; Y	13.0 (Pfizer) (12-15y) 13.4 (Pfizer) (16-17y) [13.2]	Among 12-17 year old females, the incidence of presenting with	Low

Sex	Age	Studies (data source and date)	Risk interval; Confirmed cases (Y/N)	Incidence rates per million doses after dose 2 of either mRNA vaccine unless otherwise stated Ranges represent each vaccine and square brackets indicate either an average across vaccines/ages or our calculation of excess incidence*	Conclusions	Certainty about conclusions using GRADE
		VAERS Oct 6	7 d; Y	3.9 (Pfizer) (12-15y) 7.9 (Pfizer) (16-17y) [11.8]	myocarditis after vaccination with the Pfizer vaccine may be fewer than 10 cases per million	
	18-29y	VAERS Jun 30	NR; N	3-4	Among 18-29 year old females, the incidence of presenting with myocarditis after vaccination with the mRNA vaccines may be fewer than 10 cases per million	Low
		VAERS Oct 6	7 d; Y	1.2-5.7 (25-29y) [3.5] 2.5-5.3 (18-24y) [4.0]		
		Israel MOH May 31	30 d; Y	10.0 (Pfizer) (16-19y) [6.7] 21.6 (Pfizer) (20-24y) [18.7] 0 (Pfizer) (25-29y) [average 8.5]		
		Clalit Health May 24a	42 d after dose 1; Y	3.4 (Pfizer; either dose) (16-29y)		
	30-39y	VAERS Oct 6	7 d; Y	0.4-0.7 [0.55]	Among 30-39 year old females, there may be no excess risk of myocarditis after vaccination with the mRNA vaccines	Low
		Israel MOH May 31	30 d; N	2.2 (Pfizer) [2.2]		
	≥40	VAERS Oct 6	7 d; Y	0.3-1.4 [0.85]	Among females 40 and older, there may be no excess risk of myocarditis after vaccination with the mRNA vaccines	Low
		VAERS Jun 11	7 d; Y	1.0 (≥30 y)		
		Israel MOH May 31	30 d; N	1.9-4.5 (Pfizer) [3.2]		
		Clalit Health May 24a	42 d after dose 1; Y	2.0 (Pfizer; either dose) (≥30y)		
Pericarditis						
Both sexes	All ages	EudraVigilance Oct 19	NR; N	6.8-13.9 (either dose) [10.4]	Across all ages, we are very uncertain about the incidence of pericarditis after vaccination with mRNA vaccines	Very low [a]
		Yellow Card Oct 13	NR; N	6-19 (either dose) [12.5]		
		Clalit Health May 24b	42 d after dose 1; N	10 (Pfizer; either dose) (≥16y)		
		Providence Health May 25	30d; Y	18 (either dose)		
Myocarditis/pericarditis						
Both sexes	All ages	CAEFISS & CVP	None; Y (not all probable though)	13.7-25.1 (either dose) [19.4]	Across all ages, we are very uncertain about the incidence of	Very low [a]
		VSD Oct 9	21 d; N	9.7 (either dose)		

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Sex	Age	Studies (data source and date)	Risk interval; Confirmed cases (Y/N)	Incidence rates per million doses after dose 2 of either mRNA vaccine unless otherwise stated Ranges represent each vaccine and square brackets indicate either an average across vaccines/ages or our calculation of excess incidence*	Conclusions	Certainty about conclusions using GRADE
					myocarditis or pericarditis after vaccination with mRNA vaccines	
Both sexes	12-17y	VSD Oct 9	7 d; Y	54 (Pfizer)	Among youth 12-17 years, the incidence of presenting with myocarditis or pericarditis after vaccination with the Pfizer vaccine may be approximately 50 cases (mostly males)** per million	Low
		VSD Oct 9	21 d; Y	56.7 (Pfizer)		
		Yellow Card Oct 13	NR; N	0-10 (either dose)		
Both sexes	18-39y	VSD Oct 9	7 d; Y	21.5 (Pfizer) (12-39y) 13.1 (18-39y)	Among adults under 40, fewer than 20 cases (mostly males)** per million may present with myocarditis or pericarditis after vaccination with mRNA vaccines	Low
		VSD Aug 21	21 d; Y	13.6 (Pfizer) (12-39y)		
		Yellow Card Oct 13	NR; N	18-44 (either dose) (18-49y) [31]		

*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)

** Case series data from the VSD Aug 21 found 56% pericarditis and 84% males (see Table 4)

Explanations for GRADE:

[a] 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.

[b] Rated down for risk of bias (lack of case confirmation and passive surveillance) and indirectness for expectation of differences between sexes.

[c] Rated up for large magnitude, highly unlikely to be seen by chance and credible to be higher than for other age categories.

Table 3. Summary of Findings for Comparison of Data in Studies Reporting on Moderna and Pfizer

Note: Shading represents the data used to create lower and upper limits for incidence rates, when used in conclusions. See Appendix 2 for references.

Sex	Age	Study (by data source & date)	Risk interval; confirmed cases (Y/N)	Incidence/reporting rates per million doses by vaccine after dose 2, unless otherwise stated	Conclusions	Certainty about conclusions using GRADE
Myocarditis						
Both	All ages (≥12 unless stated)	VAERS Aug 6	None applied; N	Moderna: 3.65 vs. Pfizer: 6.47	Across all ages, we are very uncertain about whether there is an association between mRNA vaccine type and incidence of myocarditis	Very low[a,b]
		Yellow Card Oct 13	NR; N	Moderna: 32 (either dose) vs. Pfizer: 8 (either dose)		
		EudraVigilance Oct 19	NR; N	Moderna: 25.8 (either dose) vs. Pfizer: 8.5 (either dose)		
Both	<18 y	EudraVigilance Oct 19	NR; N	Moderna: 60.3 (either dose) events per million vs. Pfizer: 41.6 (either dose) events per million	Among youth under 18 years, we are very uncertain about whether there is an association between mRNA vaccine type and incidence of myocarditis.	Very low[b]
Both	18-29y	VSD Oct 9	7d; Y	Moderna vs. Pfizer (risk difference) 13.3 (adjusted RR [aRR]: 2.28 [95% CI, 1.25 to 6.05]) (18-39y)	Among 18-29 year old adults, we are very uncertain about whether there is an association between mRNA vaccine type and incidence of myocarditis.	Very low[a]
		VSD Oct 9	21d; Y	Moderna vs. Pfizer (risk difference) 9.4 (aRR: 2.19 [95% CI, 0.98 to 4.97]) (18-39y)		
M	18-29y	VAERS Oct 6	7d; Y	Moderna: 38.5 vs. Pfizer: 36.8 (18-24y) Moderna: 17.2 vs. Pfizer: 10.8 (25-29y)	Among 18-29 year old males, Moderna compared with Pfizer may be associated with a small increase (4-20 cases per million) in risk for myocarditis following vaccination	Low
		VSD Oct 9	7d; Y	Moderna vs. Pfizer (risk difference) 19.1 (aRR: 2.14 [95% CI, 0.93 to 4.98]) (18-39y)		
	30-39y	VAERS Oct 6	7d; Y	Moderna: 6.7 vs. Pfizer: 5.2	Among 30-39 year old males, there may be little-to-no difference in risk of myocarditis	Low

Sex	Age	Study (by data source & date)	Risk interval; confirmed cases (Y/N)	Incidence/reporting rates per million doses by vaccine after dose 2, unless otherwise stated	Conclusions	Certainty about conclusions using GRADE
					after vaccination with Moderna compared with Pfizer	
	≥40y	VAERS Oct 6	7d; Y	Moderna: 2.9 vs. Pfizer: 2.0 (40-49 y)	Among 30-39 year old males, there may be little-to-no difference in risk of myocarditis after vaccination with Moderna compared with Pfizer	Low
F	18-29y	VAERS Oct 6	7d; Y	Moderna: 5.3 vs. Pfizer: 2.5 (18-24y) Moderna: 5.7 vs. Pfizer: 1.2 (25-29y)	Among 18-29 year old females, there may be little-to-no difference in risk of myocarditis after vaccination with Moderna compared with Pfizer	Low
	30-39y	VAERS Oct 6	7d; Y	Moderna: 0.4 vs. Pfizer: 0.7	Among 30-39 year old females, there may be little-to-no difference in risk of myocarditis after vaccination with Moderna compared with Pfizer	Low
	40-49y	VAERS Oct 6	7d; Y	Moderna: 1.4 vs. Pfizer: 1.1	Among 40-49 year old females, there may be little-to-no difference in risk of myocarditis after vaccination with Moderna compared with Pfizer	Low
Pericarditis						
Both sexes	All ages	EEA Oct 19	NR; N	Moderna: 13.9 vs. Pfizer: 6.8	Across all ages, we are very uncertain about whether there is an association between mRNA vaccine type and incidence of myocarditis	Very low[b]
		Yellow Card Oct 13	NR; N	Moderna: 19 vs. Pfizer: 6		
Myocarditis/pericarditis						

Sex	Age	Study (by data source & date)	Risk interval; confirmed cases (Y/N)	Incidence/reporting rates per million doses by vaccine after dose 2, unless otherwise stated	Conclusions	Certainty about conclusions using GRADE
Both sexes	All ages	CAEFISS &CVP	None; Y (suspicious cases included)	Moderna: 25.1 vs. Pfizer: 13.7	Across all ages, we are very uncertain about whether there is an association between mRNA vaccine type and incidence of myocarditis or pericarditis	Very low[a,b]
Both sexes	12-17y	Yellow Card Oct 13	NR; N	Moderna: 0 vs. Pfizer: 10	Among youth 12-17 years old, we are very uncertain about whether there is an association between mRNA vaccine type and incidence of myocarditis or pericarditis	Very low[a,b]
Both sexes	18-39y	VSD Oct 9	7d; Y	Moderna: 21.0 vs. Pfizer: 8.5; risk difference 13.3 (aRR: 2.72 [955 CI, 1.25 to 6.05]) (18-39y)	Among 18-39 year old adults, Moderna compared with Pfizer may be associated with a small increase (about 10 cases per million) in risk (mostly in males)* for myocarditis or pericarditis following vaccination	Low
		VSD Oct 9	21d; Y	Moderna vs. Pfizer risk difference 11.5 (aRR: 2.19 [95% CI, 1.05 to 4.65]) (18-39y)		
		Yellow Card Oct 13	NR; N	Moderna: 44 vs. Pfizer: 18 (18-49y)		

* Case series data from the VSD studies (Aug) found 56% pericarditis and 84% males (see Table 4).

Explanations for GRADE

[a] 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.

[b] Rated down for risk of bias from use of passive surveillance and lack of case verification.

Table 4. Results from Case Series of Myocarditis and Myopericarditis after COVID-19 Vaccination

Case series (Country)	Dickey 2021 (US)	Diaz 2021 (US)	Hoeg 2021* (US)	Montgomery 2021 (US)	Rosner 2021 (US)	Larson 2021 (Italy & US)	Mevorach 2021 (Israel)	Levin 2021 (Israel)	EudraVigilance (European Economic Area)	Schauer 2021 (US)
Date of cases last updated	Sep 2021	25 May 2021	18 Jun 2021	30 Apr 2021	10 Aug 2021 (publication date)	10 Aug 2021 (date published)	31 May 2021	1 Mar 2021	25 Oct 2021	21 Jun 2021
Cases of myocarditis, n	6	20	124	23	7	8	136	7	5611	13
Confirmed cases	All CMR-proven myocarditis	Clinically confirmed with troponin values or cardiac MRI	Inclusion criteria aligned with CDC working case definition for probable myocarditis, pericarditis, or myopericarditis	Diagnoses reviewed and met the CDC case definition criteria for probable myocarditis	Confirmed via diagnostic testing	Diagnosed with myocarditis by laboratory and cardiac MRI	Brighton Collaboration case definition	Based on clinical records	Reported by healthcare or non-healthcare professionals	All CMR-proven **myopericarditis**
Case source	University of Massachusetts Memorial Health	40 hospitals that were part of Providence health care system and using same electronic medical record (Washington, Oregon, Montana, Los Angeles County, California)	VAERS	US Military Health System	Two US medical centers in Falls Church, Virginia, and Dallas, Texas	Hospitalized patients in Italy and USA	Israeli MOH	Hospitalized patients in Israeli Defense Forces Medical Corps	EudraVigilance	Seattle Children's Hospital
Male, %	100%	75%	91%	100%	100%	100%	87%	100%	72%	92%
Median age (range), y Ages included	NR (17-37) All ages included	36 (26.3-48.3) All ages included	NR (12-17) Search limited to 12-17 years	25 (20–51) All ages included	24 (19–30) All ages included	29 (21–56) All ages included	NR (76% under the age of 30) All ages included	20 (18-24) All ages included	NR All ages included	15 (12-17) Search limited to 12-17 years
% Patients with pre-existing conditions (excluding prior COVID-19 infection, see below)	All patients were previously healthy	Alcohol or drug dependence = 20%; coronary artery disease = 5%; cancer = 10%; heart failure = 0;	NR	Patients had no history of cardiac disease, significant cardiac risk factors, or exposure to	No patients had evidence of an autoimmune disease	All patients were otherwise healthy	NR	ADHD = 14%; celiac disease = 14%; allergic asthma = 14%; myocarditis 5 years earlier =	NR	Two cases (15%) had history of myocarditis in first degree relative

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Case series (Country)	Dickey 2021 (US)	Diaz 2021 (US)	Hoeg 2021* (US)	Montgomery 2021 (US)	Rosner 2021 (US)	Larson 2021 (Italy & US)	Mevorach 2021 (Israel)	Levin 2021 (Israel)	EudraVigilance (European Economic Area)	Schauer 2021 (US)
		cirrhosis = 0; chronic kidney disease = 5%; COPD = 0; diabetes = 10%; hypertension = 25%; autoimmune disease = 0		cardiotoxic agents				14%; none = 43%		
% Patients with prior COVID-19 history	0%	NR	NR	13%	14%	25%	0%	0%	NR	NR
Vaccine type, n	5 (83%) = BNT162b2 (Pfizer) 1 (17%) = mRNA-1273 (Moderna)	Myocarditis: 11 (55%) = mRNA-1273 (Moderna) 9 (45%) = BNT162b2 (Pfizer)	146 (100%) = BNT162b2 (Pfizer) (only type of vaccine offered)	7 (30%) = BNT 162b2 (Pfizer) 16 (70%) = mRNA1273 (Moderna)	5 (71%) = BNT162b2 (Pfizer) 1 (14%) = mRNA-1273 (Moderna) 1 (14%) = J&J	5 (63%) = BNT 162b2 (Pfizer) 3 (37%) = mRNA1273 (Moderna)	136 (100%) = BNT 162b2 (Pfizer) (only type of vaccine offered)	7 (100%) = BNT 162b2 (Pfizer) (only type of vaccine offered)	3610 (64%) = BNT162b2 (Pfizer) 1578 (28%) = mRNA-1273 (Moderna) 320 (6%) = AZD1222 (AstraZeneca) 103 (2%) = Ad26.CoV.S (Janssen)	13 (100%) = BNT162b2 (Pfizer) (only type of vaccine offered)
% Patients in ICU	NR	10%	NR	NR	NR	38%	NR	NR	NR	0%
% Hospitalized	NR	95%	89%	NR	100%	100%	84%	100%	NR	100%
% Patients presenting after second vaccination	100%	80%	NR	87%	71%	88%	86%	100%	NR	100%
% Patients COVID-19 polymerase chain reaction positive	0% (6/6 tested)	NR	NR	0% (19/23 tested)	0% (6/7 tested, all negative)	0% (all tested)	NR	0% (all tested)	NR	NR
% Patients with COVID nucleocapsid antibody present (% of tested)	NR	NR	NR	NR	0% (4/7 tested, all negative)	NR	90% (35/39 tested)	100% (2/7 tested)	NR	0% (9/13 tested, all negative)

Case series (Country)	Dickey 2021 (US)	Diaz 2021 (US)	Hoeg 2021* (US)	Montgomery 2021 (US)	Rosner 2021 (US)	Larson 2021 (Italy & US)	Mevorach 2021 (Israel)	Levin 2021 (Israel)	EudraVigilance (European Economic Area)	Schauer 2021 (US)
% Patients with SARS-CoV-2 spike antibody	NR	NR	NR	NR	67 (4/6 tested 2 presented after first vaccination)	NR	100% (62/62 tested)	100% (2/7 tested)	NR	NR
Presentation										
Time between last vaccine and symptom onset, median days, (range)	3.5 (2-4)	3.5 (IQR 3-10.8)	NR	2 (1–4)	3 (2-7)	3 (2–4)	4 (1-30)	NR (1-5)	NR	3 (2-4)
% Patients with chest pain on presentation	83% = had chest pain; 17% = non-positional chest pressure	NR	NR	100%	100%	100%	95%	86%	NR	100%
% Patients with other symptoms (e.g., myalgia, fatigue, fever)	83%	NR	NR	NR	42%	63%	47%	86%	NR	62%
Diagnostic evaluation										
% Patients with troponin elevation (of tested)	100% (6/6 tested)	95%	NR	100% (all tested)	100% (6/7 tested)	100%	100% (all tested)	100%	NR	100% (median 9.18 ng/mL, range 0.65-18.5)
Median time to troponin peak after vaccination, days	Range 2-4	NR	NR	NR	NR	3	NR	NR	NR	NR
% Patients with BNP or NT pro BNP elevation (among tested)	NR	NR	NR	NR	50% (6 tested)	NR	If examined, modest NT Pro-BNP elevation	NR	NR	38% (all tested)
% Patients with CRP elevation (among tested)	NR	NR	NR	NR	71% (all tested)	88%	87% (all tested)	100% (all tested)	NR	100% (10/13 tested)
% Patients with eosinophilia (among tested)	NR	NR	NR	NR	NR	0%	NR	NR	NR	NR
% Patients with abnormal ECG (among tested)	83% = ST elevations; 17% = sinus rhythm with non-specific	45% = ST elevation	NR	83% (19/23 ST-segment elevations, T-wave	71% (4 ST elevations, 1 patient with nonspecific ST/T	88% (6 patients with ST elevation, 1 patient peaked T	69% ECG changes (all tested)	86% (all tested; 5 ST elevation, 1 sinus tachycardia	NR	69% abnormal with the most common finding being ST segment

Rapid Review of Incidence, Associated Risk Factors, and Clinical Course of Myocarditis and Pericarditis following COVID-19 vaccination

Case series (Country)	Dickey 2021 (US)	Diaz 2021 (US)	Hoeg 2021* (US)	Montgomery 2021 (US)	Rosner 2021 (US)	Larson 2021 (Italy & US)	Mevorach 2021 (Israel)	Levin 2021 (Israel)	EudraVigilance (European Economic Area)	Schauer 2021 (US)
	T wave abnormalities			inversions, nonspecific ST changes)	changes)	waves, 1 patient normal)		and consistent with MV and hypertrophy, 1 normal)		elevation (all tested)
% Patients with abnormal cardiac MRI (among tested)	83% = abnormal left ventricular systolic function; 100% = patchy midmyocardial increased T2 signal with corresponding late gadolinium enhancement	NR	NR	100% (all tested; with subepicardial late gadolinium enhancement or focal myocardial edema	100% (all LGE, 1 with wall motion abnormality, 3 with myocardial edema in T2)	100% (all with LGE, 6 with edema)	100% (performed in 48; mild-to-moderate subepicardial and mid-myocardial late gadolinium enhancement (LGE) more significantly affecting the lateral and inferior LV segments)	100% (3/7 tested)	NR	100% abnormal showing late gadolinium enhancement in a patchy subepicardial to transmural pattern with predilection for the inferior left ventricle free wall
% Patients with abnormal echocardiogram (among tested)	83% = LVEF <50%; 17% = LVEF >=50%	NR	NR	17% = LVEF <50%; 83% = no structural abnormality	57% = (mild hypokinesis in 3, 1 low LVEF, 1 mild LV enlargement); normal in 43%	Wall motion abnormality with regional or generalized hypokinesis in all (100%)	NR	29% (all tested)	NR	15% left ventricular wall notion abnormalities; 15% LVEF < 55%
% Patients with LVEF<50% (among tested)	83%	25%	NR	17% (4/23 tested)	14% (1 patient with LVEF 35%–40%)	25% (1 patient with LVEF 34%, another 47%)	3% severely reduced (total tested NR)	29% (all tested)	NR	23% (all tested)
Outcome										
% Patients with symptoms resolved	100%	100% resolved/ improved	NR	70% (16/23 patients)	100%	100%	95%	100%	46% resolved/ resolving 28% not resolved 22% unknown 2% resolved/ resolving with sequelae	100%
Fatalities, n	0	0	NR	0	0	0	1 (0.7%) (22-year-old with fulminant myocarditis)	0	84 (1.5%)	0

Case series (Country)	Dickey 2021 (US)	Diaz 2021 (US)	Hoeg 2021* (US)	Montgomery 2021 (US)	Rosner 2021 (US)	Larson 2021 (Italy & US)	Mevorach 2021 (Israel)	Levin 2021 (Israel)	EudraVigilance (European Economic Area)	Schauer 2021 (US)
Median hospitalization length of stay, days (range)	NR	2 (IQR 2-3) (myocarditis) 1 (IQR 1-2) (pericarditis)	NR	NR	3 (2-4)	NR (all reported as stable)	NR (3-4)	4 (1-5)	NR	2 (1-4)
% Patients treated with medications for myocarditis	NR	45% colchicine 75% NSAIDS 0% steroids	NR	NR	43% = NSAIDS 43% = colchicine 43% = famotidine 14% = steroids	38% = NSAID 25% = colchicine 25% = steroids	Most treated with NSAIDS, with or without colchicine	100%; 43% = bisoprolol and ramipril 29% = colchicine and ibuprofen 14% = colchicine and bisoprolol 14% = colchicine	NR	23% = Intravenous immune globulin 15% =corticosteroid 100% = NSAID

Abbreviations: **CMR** = cardiovascular magnetic resonance imaging; **ICU** = intensive care unit; **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; **yr** = years

*Data from this source may overlap with other US case series

Table 5. Results from Case Series of Pericarditis or Mixed Diagnoses after COVID-19 Vaccination

Case series	Diaz 2021 (US)	Hoeg 2021* (US)	EudraVigilance (European Economic Area)	Gargano 2021* (US)	Klein 2021 (US)	Yellow Card (UK)	PHAC 2021 (Canada)
Date of cases last updated	25 May 2021	18 Jun 2021	25 Oct 2021	6 Jul 2021	21 Aug 2021	13 Oct 2021	15 Oct 2021
Cases, n	37	22	4250	323	56	1037	956
Confirmed cases	Clinically confirmed with troponin values or cardiac MRI	Inclusion criteria aligned with CDC working case definition for probable myocarditis, pericarditis, or myopericarditis	Reported by healthcare or non-healthcare professionals	All met CDC criteria for myocarditis, pericarditis, or myopericarditis	ICD-10 used then diagnoses confirmed by medical record review	NR	Brighton Collaboration case definition for myocarditis/ pericarditis (inflammation of the heart muscle and lining around heart)
Myocarditis, %	0%	0%	0%	NR	30%	52%	NR
Pericarditis, %	100%	100%	100%	NR	56%	48%	NR
Myopericarditis, %	0%	0%	0%	NR	14%	0%	0%

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Case series	Diaz 2021 (US)	Hoeg 2021* (US)	EudraVigilance (European Economic Area)	Gargano 2021* (US)	Klein 2021 (US)	Yellow Card (UK)	PHAC 2021 (Canada)
Case source	40 hospitals that were part of Providence health care system and use same electronic medical record (Washington, Oregon, Montana, Los Angeles County, California)	VAERS	EudraVigilance	VAERS	Kaiser Permanente: Colorado, Northern and Northwest, Southern California, Washington; Marshfield Clinic; Health Partners; and Denver Health (from Vaccine Safety Datalink)*	Yellow Card Scheme	Canadian Adverse Events Following Immunization Surveillance System and Health Canada's Canada Vigilance System
Male, %	73%	91%	54%	90%	84%	NR	62% Pfizer, 73% Moderna
Median age (range), y Ages included	59 (46-69) All ages included	NR (12-17) Search limited to 12-17 years	NR All ages included	19 (12–29) Limited to those under 30 years	24 (13-39) Medical record search limited to 12-39 years	NR All ages included	27 (12-87 Pfizer), (17-95 Moderna) All ages included
% Patients with pre-existing conditions (excluding prior COVID-19 infection, see below)	Alcohol or drug dependence = 14%; coronary artery disease = 11%; cancer = 14%; heart failure = 5%; cirrhosis = 3%; chronic kidney disease = 11%; COPD = 11; diabetes = 11%; hypertension = 49%; autoimmune disease = 8%	NR	NR	NR	History of myo/pericarditis = 7%	NR	NR
% Patients with prior COVID-19 history	NR	NR	NR	NR	5%	NR	NR
Vaccine type, n	12 (32%) = mRNA-1273 23 (62%) = BNT162b2 (Pfizer) 2 (5%) = Ad26.CoV.S (Janssen)	146 (100%) = BNT162b2 (Pfizer)	2883 (68%) = BNT162b2 (Pfizer) 850 (20%) = mRNA-1273 (Moderna) 416 (10%) = AZD1222 (AstraZeneca) 101 (2%) = Ad26.CoV.S (Janssen)	NR	14 (41%) = BNT 162b2 (Pfizer) 20 (59%) = mRNA1273 (Moderna) *	Myocarditis: 337 (56%) = BNT162b2 (Pfizer) 86 (62%) = mRNA-1273 (Moderna) 120 (40%) = AZD1222 (AstraZeneca) Pericarditis: 265 (44%) = BNT162b2 (Pfizer) 52 (38%) = mRNA-1273 (Moderna)	573 (60%) = BNT162b2 (Pfizer) 357 (37%) = mRNA-1273 (Moderna) 21 (2%) = AZD1222 (AstraZeneca) 5 (5%) = unspecified vaccine

Rapid Review of Incidence, Associated Risk Factors, and Clinical Course of Myocarditis and Pericarditis following COVID-19 vaccination

Case series	Diaz 2021 (US)	Hoeg 2021* (US)	EudraVigilance (European Economic Area)	Gargano 2021* (US)	Klein 2021 (US)	Yellow Card (UK)	PHAC 2021 (Canada)
						177 (60%) = AZD1222 (AstraZeneca)	
% Patients in ICU	2.7%	NR	NR	NR	13%	NR	NR
% Hospitalized	35%	89% (myocarditis) 73% (pericarditis)	NR	96%	71%	NR	NR
% Patients presenting after second vaccination	60%	NR	NR	NR	71%*	NR	45% Pfizer, 68% Moderna
% Patients COVID-19 polymerase chain reaction positive	NR	NR	NR	NR	NR	NR	NR
% Patients with COVID nucleocapsid antibody present (% of tested)	NR	NR	NR	NR	NR	NR	NR
% Patients with SARS-CoV-2 spike antibody	NR	NR	NR	NR	NR	NR	NR
Presentation							
Time between last vaccine and symptom onset, median days, (range)	20 (IQR 6-41)	NR	NR	2 (0-40)	12-17 yr = 2 (1-20) 18-29 yr = 1 (0-11) 30-39 yr = 5 (1-20)	NR	NR (5 min-92 d Pfizer), (17 min-69 d Moderna)
% Patients with chest pain on presentation	NR	NR	NR	NR	100%	NR	NR
% Patients with other symptoms (e.g., myalgia, fatigue, fever)	NR	NR	NR	NR	59%	NR	NR
Diagnostic evaluation							
% Patients with troponin elevation (of tested)	0%	NR	NR	NR	84% abnormal troponin level (all tested)	NR	100%
Median time to troponin peak after vaccination, days	NR	NR	NR	NR	NR	NR	NR
% Patients with BNP or NT pro BNP elevation (among tested)	NR	NR	NR	NR	NR	NR	NR
% Patients with CRP elevation (among tested)	NR	NR	NR	NR	NR	NR	NR
% Patients with eosinophilia (among tested)	NR	NR	NR	NR	NR	NR	NR

Rapid Review of Incidence, Associated Risk Factors, and Clinical Course of Myocarditis and Pericarditis following COVID-19 vaccination

Case series	Diaz 2021 (US)	Hoeg 2021* (US)	EudraVigilance (European Economic Area)	Gargano 2021* (US)	Klein 2021 (US)	Yellow Card (UK)	PHAC 2021 (Canada)
% Patients with abnormal ECG (among tested)	38% = ST elevation	NR	NR	NR	84% (all tested)	NR	NR
% Patients with abnormal cardiac MRI (among tested)	NR	NR	NR	NR	92% (12/56 tested)	NR	NR
% Patients with abnormal echocardiogram (among tested)	NR	NR	NR	NR	46% (52/56 tested)	NR	NR
% Patients with LVEF<50% (among tested)	8%	NR	NR	NR	NR	NR	NR
Outcome							
% Patients with symptoms resolved	81% resolved/ improved; 5% persistent; 14% unknown	NR	49% resolved/ resolving 31% not resolved 19% unknown 1% resolved/ resolving with sequelae	95% (at time of publication)	100%	NR	NR
Fatalities, n	0	NR	15 (0.4%)	0	NR	5 total (0.5%) 3 = BNT162b2 (Pfizer) 0 = mRNA-1273 (Moderna) 2 = AZD1222 (AstraZeneca)	NR
Median hospitalization length of stay, days (range)	1 (IQR 1-2)	NR	NR	NR	0 days = 14% 1 day = 38% 2 days = 23% 3 days = 13% 4 days = 5% 5 days = 4% ≥6 days = 4%	NR	NR
% Patients treated with medications for myocarditis	54% colchicine 49% NSAIDs 11% steroids	NR	NR	NR	NR	NR	NR

Abbreviations: **CMR** = cardiovascular magnetic resonance imaging; **ICU** = intensive care unit; **LVEF** = left ventricular ejection fraction; **NR** = not reported; **NSAID** = non-steroidal anti-inflammatory drugs.

*Data from this source may overlap with other US case series.

Discussion

Summary of Findings

The incidence of myocarditis following mRNA vaccines is low but probably highest in males 12-29 years old, with lower incidences in older ages. In females, the incidence may be very low (12-29 y) or not exist (≥30 y). The incidence of either myocarditis or pericarditis may be highest in adolescent males; among adults under 40 years there may be few cases but the broad age range may not have detected any variation by age. Among adult males under 40, Moderna compared with Pfizer may be associated with a small increase (<20 cases per million) in risk for myocarditis or (one of) myocarditis or pericarditis following vaccination; the evidence for youth under 18 years was very uncertain. This evidence does not strongly support that one mRNA vaccine should be preferred over the other, even in young males.

The majority of myocarditis cases involved males (often >90%) in their 20s, with a short symptom onset of 2 to 4 days after a second dose (71-100%). The large majority of cases presented with chest pain or pressure and troponin elevation, and a minority (<30%) also had left ventricular dysfunction. Most were hospitalized (≥84%), without ICU stays, for a short duration (2-4 d) and treated with anti-inflammatory and/or other standard supportive therapies. Among the series of confirmed cases that reported on fatalities (N=220), one fatality was reported in a 22-year old with fulminant myocarditis. Within the EudraVigilance dataset (n=5,611 unconfirmed cases), 84 (1.5%) fatalities were reported, though cause of death is not confirmed. Importantly, the vast majority of affected individuals appear to make a complete recovery based on short-term follow-up. Most cases of pericarditis were unconfirmed; for this outcome there appears to be more variation in age, sex, onset timing and rate of hospitalization across cases.

Although the mechanism(s) through which the mRNA vaccines may cause myocarditis or pericarditis are not known, several findings in the studies in this review support a causal association, including an excess risk compared with controls, highly significant clustering effects showing onset soon after vaccine receipt, and higher risk for younger males compared with other causative agents of myocarditis or pericarditis. Further, an immune-mediated mechanism is suspected, given the much higher incidence of myocarditis after the second dose of mRNA vaccine.

Strengths and Limitations of the Review

There are several strengths of this rapid review. A comprehensive, peer-reviewed search strategy was used and inclusion of gray literature captured in several cases very recent data. A second reviewer screened the most relevant (based on machine learning) citations and verified all data and risk of bias assessments. GRADE assessments were based on team consensus including clinical experts. Patient partners reviewed the evidence and developed interpretations from the patient perspective. The main limitation is that in the era of COVID-19, the literature base is evolving with incredible rapidity and new evidence will emerge; nevertheless, there was some moderate certainty evidence found in this review. Because many reports used overlapping populations and reported findings based on different methods of case ascertainment (e.g., risk interval, whether cases were verified) a quantitative synthesis was not undertaken and some of the descriptive summary statements may not fully account for this. We also avoided making any conclusions about any one possible estimate of average incidence and instead rely on ranges.

Conclusions

Policy and decision making about vaccination for adolescent and young adult males will need to weigh various factors such as the: i) societal benefits from preventing COVID-19 transmission, ii) individual benefits from prevention or mitigating severe COVID-19 related illness (e.g., 1000 to >2000 fewer hospitalizations per million vaccinated vs. not vaccinated at least over the short-term), and iii) availability and efficacy of the non-mRNA vaccines.

Although the short-term course of myocarditis after an mRNA vaccine is mild and self-limiting in the majority of cases, the incidence and course after booster doses and the potential for long-term sequelae such as recurrent disease and/or heart failure are not known. Further, individual risk factors other than age and sex have not been examined and warrant further attention.

Continued active surveillance of myocarditis/myopericarditis incidence out to 30 days from dosing is recommended with respect to i) new populations (i.e., vaccinated children <12y), ii) the impact of 3rd and subsequent doses, and iii) affected individuals receiving subsequent mRNA vaccine doses.

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Appendices

Appendix 1. Search strategies
Ovid Multifile

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to October 05, 2021>, Embase <1974 to 2021 October 05>
Search Strategy:
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1 COVID-19 Vaccines/ [COVID VACCINES PT 1] (11038)
2 COVID-19/ (152175)
3 SARS-CoV-2/ (101136)
4 Coronavirus/ (13257)
5 Betacoronavirus/ (40795)
6 Coronavirus Infections/ (56640)
7 (COVID-19 or COVID19).tw,kf. (324030)
8 ((coronavirus* or corona virus*) and (hubei or wuhan or beijing or shanghai)).tw,kf. (10884)
9 (wuhan adj5 virus*).tw,kf. (569)
10 (2019-nCoV or 19nCoV or 2019nCoV).tw,kf. (3694)
11 (nCoV or n-CoV or "CoV 2" or CoV2).tw,kf. (124619)
12 (SARS-CoV-2 or SARS-CoV2 or SARSCoV-2 or SARSCoV2 or SARS2 or SARS-2 or severe acute respiratory syndrome coronavirus 2).tw,kf. (126706)
13 (2019-novel CoV or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or Pandemi*2)) or (coronavirus* and pneumonia)).tw,kf. (41877)
14 (novel coronavirus* or novel corona virus* or novel CoV).tw,kf. (20703)
15 ((coronavirus* or corona virus*) adj2 "2019").tw,kf. (71612)
16 ((coronavirus* or corona virus*) adj2 "19").tw,kf. (11500)
17 ("coronavirus 2" or "corona virus 2").tw,kf. (38199)
18 (OC43 or NL63 or 229E or HKU1 or HCoV* or Sars-coronavirus*).tw,kf. (8144)
19 COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os. (9120)
20 (coronavirus* or corona virus*).ti. (48015)
21 COVID.ti. (254131)
22 ("B.1.1.7" or "B.1.351" or "B.1.617" or "B.1.427" or "B.1.429").tw,kf,rx,px,ox. (1406)
23 ("P.1" and (Brazil* or variant?)).tw,kf,rx,px,ox. (3731)
24 (((alpha or beta or delta or eta or gamma or iota or kappa or lambda) adj3 variant?) and (coronavirus* or corona virus* or covid*)).tw,kf. (459)
25 or/2-24 [COVID-19] (397323)
26 exp Vaccination/ (278048)
27 ((COVID or COVID-19 or COVID19) adj5 (immunis* or immuniz* or inoculat* or vaccin*)).tw,kf. (15689)
28 ((coronavirus* or corona virus*) adj5 (immunis* or immuniz* or inoculat* or vaccin*)).tw,kf. (3065)
29 ((2019-nCoV or nCoV or n-CoV or SARS-CoV-2 or SARS-CoV2 or SARSCoV-2 or SARSCoV2 or SARS2 or SARS-2 or OC43 or NL63 or 229E or HKU1 or HCoV*) adj5 (immunis* or immuniz* or inoculat* or vaccin*)).tw,kf. (8201)
30 (BNT162 or BNT162-01 or BNT162a1 or BNT162b1 or BNT162b2 or BNT162c2 or N38TVC63NU).tw,kf. (1584)
31 (AZD1222 or ChAdOx1 or Covishield$2 or B5S3K2V0G8).tw,kf. (967)

Rapid Review of Incidence, Associated Risk Factors, and Clinical Course of Myocarditis and Pericarditis following COVID-19 vaccination

32 (mRNA-1273 or EPK39PL4R4).tw,kf. (596)
33 (mRNA adj5 (immunis* or immuniz* or inoculat* or vaccin*)).tw,kf. (4901)
34 (messenger RNA adj5 (immunis* or immuniz* or inoculat* or vaccin*)).tw,kf. (462)
35 LV-SMENP-DC.tw,kf. (6)
36 (Ad5-nCoV or hAdOx1 nCoV-19).tw,kf. (39)
37 ("Ad26.COV2.S" or Ad26COVS1 or JNJ 78436735 or JNJ-78436735 or JT2NS6183B).tw,kf. (195)
38 (Janssen adj5 (immunis* or immuniz* or inoculat* or vaccin*)).tw,kf. (142)
39 CX-024414.tw,kf. (2)
40 (Moderna adj5 (immunis* or immuniz* or inoculat* or vaccin*)).tw,kf. (470)
41 Spikevax$2.tw,kf. (11)
42 ((Pfizer or Pfizer-BioNTech) adj5 (immunis* or immuniz* or inoculat* or vaccin*)).tw,kf. (1249)
43 (Comirnaty$2 or Tozinameran$2).tw,kf. (202)
44 ((AstraZeneca or AZ or Oxford) adj5 (immunis* or immuniz* or inoculat* or vaccin*)).tw,kf. (731)
45 Vaxzevria$2.tw,kf. (119)
46 or/26-45 [VACCINES] (295717)
47 25 and 46 [COVID-VACCINES PT 2] (26788)
48 1 or 47 [COVID-VACCINES PTS 1-2] (28932)
49 COVID-19 Vaccines/ae [adverse events] (933)
50 Viral Vaccines/ae [adverse events] (2911)
51 Adverse Drug Reaction Reporting Systems/ (10804)
52 ((immunis* or immuniz* or inoculat* or vaccin*) adj10 (adverse* or ADE or ADEs or ADR or ADRs or complication* or harm* or safe or safety or side effect? or undesirable effect? or undesirable consequence? or undesirable outcome? or unintended effect? or unintended consequence? or unintended outcome?)).tw,kf. (76675)
53 ((post-vaccin* or post-immuni#ation* or post-innoculat* or after vaccin* or after immuni#ation* or after innoculat* or (following adj3 vaccin*) or (following adj3 immuni#ation*) or (following adj3 innoculat*)) adj10 (adverse* or ADE or ADEs or ADR or ADRs or complication* or harm* or safe or safety or side effect? or undesirable effect? or undesirable consequence? or undesirable outcome? or unintended effect? or unintended consequence? or unintended outcome?)).tw,kf. (6413)
54 ((post-vaccin* or post-immuni#ation* or post-innoculat* or after vaccin* or after immuni#ation* or after innoculat* or (following adj3 vaccin*) or (following adj3 immuni#ation*) or (following adj3 innoculat*)) adj10 (complication? or consequenc* or effect? or event? or harm* or outcome?)).tw,kf. (7716)
55 (vaccine-associated or vaccine-induced or vaccine-related).tw,kf. (20509)
56 (immuni#ation-associated or immuni#ation-induced or immuni#ation-related).tw,kf. (1855)
57 ((data or vaccin*) adj3 (monitor* or surveillance*)).tw,kf. (73396)
58 Pharmacovigilance/ (5248)
59 (pharmacovigilan* or pharmaco-vigilan*).tw,kf. (18894)
60 (Canada Vigilance or Eudravigilance* or FAERS or VAERS).tw,kf. (2780)
61 Product Surveillance, Postmarketing/ (19287)
62 ((postmarket* or post-market*) adj3 surveillance*).tw,kf. (9589)
63 "Clinical Trial, Phase IV".pt. (2193)
64 ((Phase 4 or Phase IV) adj3 (evaluation? or study or studies or trial?)).tw,kf. (4910)
65 Cardiomyopathies/ (54974)
66 (cardiomyopath* or cardio-myopath* or myocardiopath* or myo-cardiopath*).tw,kf. (209222)
67 Myocarditis/ (42633)
68 myocarditis.tw,kf. (41845)
69 ((myocard* or myo-card) adj3 inflam*).tw,kf. (10214)
70 carditis.tw,kf. (4148)

71 exp Pericarditis/ (31618)
72 pericarditis.tw,kf. (27519)
73 ((pericard* or peri-card*) adj3 inflam*).tw,kf. (1118)
74 epicarditis.tw,kf. (249)
75 ((epicard* or epi-card*) adj3 inflam*).tw,kf. (260)
76 (myopericarditis or myo-pericarditis).tw,kf. (1763)
77 ((myopericard* or myo-pericard*) adj inflam*).tw,kf. (13)
78 (pleuropericarditis or pleuro-pericarditis).tw,kf. (412)
79 ((pleuropericard* or pleuropericard*) adj3 inflam*).tw,kf. (12)
80 or/49-79 [AEs, MYOCARDITIS, PERICARDITIS] (535683)
81 48 and 80 [COVID-VACCINES - AEs, MYOCARDITIS, PERICARDITIS] (6406)
82 exp Animals/ not Humans/ (16924647)
83 81 not 82 [ANIMAL-ONLY REMOVED] (4653)
84 (comment or editorial or news or newspaper article or (letter not (letter and randomized controlled trial))).pt. (4104337)
85 83 not 84 [OPINION PIECES REMOVED] (4141)
86 limit 85 to yr="2020-current" (4046)
87 (202010* or 202011* or 202012* or 2021*).dt. (1600708)
88 86 and 87 [RECORDS SINCE 1 OCT 2020] (2589)
89 88 use ppez [MEDLINE RECORDS] (2589)
90 SARS-CoV-2 vaccine/ [COVID VACCINES - PT 1] (11038)
91 coronavirus disease 2019/ (261337)
92 severe acute respiratory syndrome coronavirus 2/ (130655)
93 Coronavirinae/ (5218)
94 Betacoronavirus/ (40795)
95 coronavirus infection/ (57662)
96 (COVID-19 or COVID19).tw,kw,kf. (324030)
97 ((coronavirus* or corona virus*) and (hubei or wuhan or beijing or shanghai)).tw,kw,kf. (10884)
98 (wuhan adj5 virus*).tw,kw,kf. (584)
99 (2019-nCoV or 19nCoV or 2019nCoV).tw,kw,kf. (3694)
100 (nCoV or n-CoV or "CoV 2" or CoV2).tw,kw,kf. (124619)
101 (SARS-CoV-2 or SARS-CoV2 or SARSCoV-2 or SARSCoV2 or SARS2 or SARS-2 or severe acute respiratory syndrome coronavirus 2).tw,kw,kf. (126706)
102 (2019-novel CoV or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or Pandemi*2)) or (coronavirus* and pneumonia)).tw,kw,kf. (41884)
103 (novel coronavirus* or novel corona virus* or novel CoV).tw,kw,kf. (20703)
104 ((coronavirus* or corona virus*) adj2 "2019").tw,kw,kf. (71614)
105 ((coronavirus* or corona virus*) adj2 "19").tw,kw,kf. (11502)
106 ("coronavirus 2" or "corona virus 2").tw,kw,kf. (38199)
107 (OC43 or NL63 or 229E or HKU1 or HCoV* or Sars-coronavirus*).tw,kw,kf. (8144)
108 (coronavirus* or corona virus*).ti. (48015)
109 COVID.ti. (254131)
110 ("B.1.1.7" or "B.1.351" or "B.1.617" or "B.1.427" or "B.1.429").tw,kw,kf. (1406)
111 ("P.1" and (Brazil* or variant?)).tw,kw,kf. (3704)
112 (((alpha or beta or delta or eta or gamma or iota or kappa or lambda) adj3 variant?) and (coronavirus* or corona virus* or covid*)).tw,kw,kf. (461)
113 or/91-112 [COVID-19] (404957)
114 vaccination/ (246289)

115 ((COVID or COVID-19 or COVID19) adj5 (immunis* or immuniz* or inoculat* or vaccin*)).tw,kw,kf. (17544)
116 ((coronavirus* or corona virus*) adj5 (immunis* or immuniz* or inoculat* or vaccin*)).tw,kw,kf. (3913)
117 ((2019-nCoV or nCoV or n-CoV or SARS-CoV-2 or SARS-CoV2 or SARSCoV-2 or SARSCoV2 or SARS2 or SARS-2 or OC43 or NL63 or 229E or HKU1 or HCoV*) adj5 (immunis* or immuniz* or inoculat* or vaccin*)).tw,kw,kf. (9069)
118 (BNT162 or BNT162-01 or BNT162a1 or BNT162b1 or BNT162b2 or BNT162c2 or N38TVC63NU).tw,kw,kf. (1584)
119 (AZD1222 or ChAdOx1 or Covishield$2 or B5S3K2V0G8).tw,kw,kf. (967)
120 (mRNA-1273 or EPK39PL4R4).tw,kw,kf. (596)
121 (mRNA adj5 (immunis* or immuniz* or inoculat* or vaccin*)).tw,kw,kf. (4944)
122 (messenger RNA adj5 (immunis* or immuniz* or inoculat* or vaccin*)).tw,kw,kf. (475)
123 LV-SMENP-DC.tw,kw,kf. (6)
124 (Ad5-nCoV or hAdOx1 nCoV-19).tw,kw,kf. (39)
125 ("Ad26.COV2.S" or Ad26COVS1 or JNJ 78436735 or JNJ-78436735 or JT2NS6183B).tw,kw,kf. (195)
126 (Janssen adj5 (immunis* or immuniz* or inoculat* or vaccin*)).tw,kf. (142)
127 CX-024414.tw,kw,kf. (2)
128 (Moderna adj5 (immunis* or immuniz* or inoculat* or vaccin*)).tw,kw,kf. (483)
129 Spikevax$2.tw,kw,kf. (11)
130 ((Pfizer or Pfizer-BioNTech) adj5 (immunis* or immuniz* or inoculat* or vaccin*)).tw,kf,kw. (1264)
131 (Comirnaty$2 or Tozinameran$2).tw,kw,kf. (202)
132 ((AstraZeneca or AZ or Oxford) adj5 (immunis* or immuniz* or inoculat* or vaccin*)).tw,kw,kf. (733)
133 Vaxzevria$2.tw,kw,kf. (119)
134 or/114-133 [VACCINES] (265426)
135 113 and 134 [COVID VACCINES - PT 2] (27369)
136 90 or 135 [COVID VACCINES - PTS 1 & 2] (29374)
137 virus vaccine/ae [adverse drug event] (999)
138 exp severe acute respiratory syndrome vaccine/ae [adverse drug event] (470)
139 ((immunis* or immuniz* or inoculat* or vaccin*) adj10 (adverse* or ADE or ADEs or ADR or ADRs or complication* or harm* or safe or safety or side effect? or undesirable effect? or undesirable consequence? or undesirable outcome? or unintended effect? or unintended consequence? or unintended outcome?)).tw,kw,kf. (76966)
140 ((post-vaccin* or post-immuni#ation* or post-innoculat* or after vaccin* or after immuni#ation* or after innoculat* or (following adj3 vaccin*) or (following adj3 immuni#ation*) or (following adj3 innoculat*)) adj10 (adverse* or ADE or ADEs or ADR or ADRs or complication* or harm* or safe or safety or side effect? or undesirable effect? or undesirable consequence? or undesirable outcome? or unintended effect? or unintended consequence? or unintended outcome?)).tw,kw,kf. (6417)
141 ((post-vaccin* or post-immuni#ation* or post-innoculat* or after vaccin* or after immuni#ation* or after innoculat* or (following adj3 vaccin*) or (following adj3 immuni#ation*) or (following adj3 innoculat*)) adj10 (complication? or consequenc* or effect? or event? or harm* or outcome?)).tw,kw,kf. (7718)
142 (vaccine-associated or vaccine-induced or vaccine-related).tw,kw,kf. (20509)
143 (immuni#ation-associated or immuni#ation-induced or immuni#ation-related).tw,kw,kf. (1855)
144 exp pharmacovigilance/ (5254)
145 (pharmacovigilan* or pharmaco-vigilan*).tw,kw,kf. (18894)
146 (Canada Vigilance or Eudravigilance* or FAERS or VAERS).tw,kw,kf. (2780)

147 exp postmarketing surveillance/ (37209)
148 ((postmarket* or post-market*) adj3 surveillance*).tw,kw,kf. (9603)
149 phase 4 clinical trial/ (4491)
150 ((Phase 4 or Phase IV) adj3 (evaluation? or study or studies or trial?)).tw,kw,kf. (4910)
151 cardiomyopathy/ (90014)
152 (cardiomyopath* or cardio-myopath* or myocardiopath* or myo-cardiopath*).tw,kw,kf. (209222)
153 exp myocarditis/ (45666)
154 myocarditis.tw,kw,kf. (41845)
155 ((myocard* or myo-card) adj3 inflam*).tw,kw,kf. (12899)
156 carditis.tw,kw,kf. (4148)
157 exp pericarditis/ (31618)
158 pericarditis.tw,kw,kf. (27519)
159 ((pericard* or peri-card*) adj3 inflam*).tw,kw,kf. (1222)
160 epicarditis.tw,kw,kf. (249)
161 ((epicard* or epi-card*) adj3 inflam*).tw,kw,kf. (391)
162 (myopericarditis or myo-pericarditis).tw,kw,kf. (1763)
163 ((myopericard* or myo-pericard*) adj inflam*).tw,kw,kf. (25)
164 (pleuropericarditis or pleuro-pericarditis).tw,kw,kf. (412)
165 ((pleuropericard* or pleuropericard*) adj3 inflam*).tw,kw,kf. (13)
166 or/137-165 [MYOCARDITIS, PERICARDITIS] (483566)
167 136 and 166 [COVID-VACCINES - MYOCARDITIS, PERICARDITIS] (6014)
168 exp animal/ or exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (54214081)
169 exp human/ or exp human experimentation/ or exp human experiment/ (42550990)
170 168 not 169 (11664830)
171 167 not 170 [ANIMAL-ONLY REMOVED] (5784)
172 editorial.pt. (1287357)
173 letter.pt. not (letter.pt. and randomized controlled trial/) (2336030)
174 171 not (172 or 173) [OPINION PIECES REMOVED] (5259)
175 limit 174 to yr="2020-current" (5170)
176 (202010* or 202011* or 202012* or 2021*).dc. (2457999)
177 175 and 176 [RECORDS PUBLISHED/ADDED SINCE OCT 2020] (2500)
178 177 use oemezd [EMBASE RECORDS] (2500)
179 89 or 178 [BOTH DATABASES] (5089)
180 remove duplicates from 179 (3235) [TOTAL UNIQUE RECORDS]
181 180 use ppez [MEDLINE UNIQUE RECORDS] (2530)
182 180 use oemezd [EMBASE UNIQUE RECORDS] (705)

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Cochrane Library

#1	[mh "COVID-19 Vaccines"]	Limits	55
#2	[mh "COVID-19"]	Limits	657
#3	[mh "SARS-CoV-2"]	Limits	479
#4	[mh ^Coronavirus]	Limits	4
#5	[mh ^Betacoronavirus]	Limits	127
#6	[mh ^"Coronavirus Infections"]	Limits	657
#7	("COVID-19" or COVID19):ti,ab,kw	Limits	7299
#8	((coronavirus* or corona virus*) and (hubei or wuhan or beijing or shanghai)):ti,ab,kw	Limits	219
#9	(wuhan NEAR/5 virus*):ti,ab,kw	Limits	9
#10	("2019-nCoV" or 19nCoV or 2019nCoV):ti,ab,kw	Limits	10
#11	(nCoV or "n-CoV" or "CoV 2" or CoV2):ti,ab,kw	Limits	690
#12	("SARS-CoV-2" or "SARS-CoV2" or "SARSCoV-2" or SARSCoV2 or SARS2 or "SARS-2" or "severe acute respiratory syndrome coronavirus 2"):ti,ab,kw	Limits	3039
#13	("2019-novel CoV" or "Sars-coronavirus2" or "Sars-coronavirus-2" or "SARS-like coronavirus" or "SARS-like coronaviruses" or ((novel or new or nouveau) NEAR/2 (CoV or nCoV or covid or coronavirus* or "corona virus" or Pandemi*2)) or (coronavirus* and pneumonia)):ti,ab,kw	Limits	1367
#14	("novel coronavirus" or "novel coronaviruses" or "novel corona virus" or "novel corona viruses" or "novel CoV"):ti,ab,kw	Limits	478
#15	((coronavirus* or "corona virus" or "corona viruses") NEAR/2 "2019"):ti,ab,kw	Limits	2503
#16	((coronavirus* or "corona virus" or "corona viruses") NEAR/2 "19"):ti,ab,kw	Limits	299
#17	("coronavirus 2" or "corona virus 2"):ti,ab,kw	Limits	765
#18	(OC43 or NL63 or 229E or HKU1 or HCoV* or (Sars NEXT coronavirus*)):ti,ab,kw	Limits	84
#19	(coronavirus* or "corona virus" or "corona viruses"):ti	Limits	736
#20	COVID:ti	Limits	5641

#21	("B.1.1.7" or "B.1.351" or "B.1.617" or "B.1.427" or "B.1.429"):ti,ab,kw	Limits	16
#22	("P.1" and (Brazil* or variant*)):ti,ab,kw	Limits	175
#23	(((alpha or beta or delta or eta or gamma or iota or kappa or lambda) NEAR/3 variant*) and (coronavirus* or corona virus* or covid*)):ti,ab,kw	Limits	7
#24	{or #2-#23}	Limits	7898
#25	[mh Vaccination]	Limits	2680
#26	((COVID or "COVID-19" or COVID19) NEAR/5 (immunis* or immuniz* or inoculat* or vaccin*)):ti,ab,kw	Limits	493
#27	((coronavirus* or "corona virus" or "corona viruses") NEAR/5 (immunis* or immuniz* or inoculat* or vaccin*)):ti,ab,kw	Limits	100
#28	(("2019-nCoV" or nCoV or "n-CoV" or "SARS-CoV-2" or "SARS-CoV2" or "SARSCoV-2" or SARSCoV2 or SARS2 or "SARS-2" or OC43 or NL63 or 229E or HKU1 or HCoV*) NEAR/5 (immunis* or immuniz* or inoculat* or vaccin*)):ti,ab,kw	Limits	221
#29	(BNT162 or "BNT162-01" or BNT162a1 or BNT162b1 or BNT162b2 or BNT162c2 or N38TVC63NU):ti,ab,kw	Limits	38
#30	(AZD1222 or ChAdOx1 or Covishield* or B5S3K2V0G8):ti,ab,kw	Limits	63
#31	("mRNA-1273" or EPK39PL4R4):ti,ab,kw	Limits	24
#32	(mRNA NEAR/5 (immunis* or immuniz* or inoculat* or vaccin*)):ti,ab,kw	Limits	100
#33	("messenger RNA" NEAR/5 (immunis* or immuniz* or inoculat* or vaccin*)):ti,ab,kw	Limits	24
#34	"LV-SMENP-DC":ti,ab,kw	Limits	0
#35	("Ad5-nCoV" or "hAdOx1 nCoV-19"):ti,ab,kw	Limits	0
#36	("Ad26.COV2.S" or Ad26COVS1 or "JNJ 78436735" or "JNJ-78436735" or JT2NS6183B):ti,ab,kw	Limits	22
#37	(Janssen NEAR/5 (immunis* or immuniz* or inoculat* or vaccin*)):ti,ab,kw	Limits	18
#38	"CX-024414":ti,ab,kw	Limits	2
#39	(Moderna NEAR/5 (immunis* or immuniz* or inoculat* or vaccin*)):ti,ab,kw	Limits	20
#40	Spikevax*:ti,ab,kw	Limits	0

−	+	#41	((Pfizer or "Pfizer-BioNTech") NEAR/5 (immunis* or immuniz* or inoculat* or vaccin*)):ti,ab,kw	Limits	47
−	+	#42	(Comirnaty* or Tozinameran*):ti,ab,kw	Limits	10
−	+	#43	((AstraZeneca or AZ or Oxford) NEAR/5 (immunis* or immuniz* or inoculat* or vaccin*)):ti,ab,kw	Limits	34
−	+	#44	Vaxzevria*:ti,ab,kw	Limits	6
−	+	#45	{or #25-#44}	Limits	3419
−	+	#46	#24 AND #45	Limits	638
−	+	#47	#1 OR #46	Limits	638
−	+	#48	[mh "COVID-19 Vaccines"/AE]	Limits	30
−	+	#49	[mh ^"Viral Vaccines"/AE]	Limits	221
−	+	#50	[mh "Adverse Drug Reaction Reporting Systems"]	Limits	90
−	+	#51	((immunis* or immuniz* or inoculat* or vaccin*) NEAR/10 (adverse* or ADE or ADEs or ADR or ADRs or complication* or harm* or safe or safety or "side effect" or "side effects" or "undesirable effect" or "undesirable effects" or "undesirable consequence" or "undesirable consequences" or "undesirable outcome" or "undesirable outcomes" or "unintended effect" or "unintended effects" or "unintended consequence" or "unintended consequences" or "unintended outcome" or "unintended outcome"s)):ti,ab,kw	Limits	12385
−	+	#52	(((post NEXT vaccin*) or (post NEXT immunisation*) or (post NEXT immunization*) or (post NEXT innoculat*) or (after NEXT vaccin*) or (after NEXT immunisation*) or (after NEXT immunization*) or (after NEXT innoculat*) or (following NEAR/3 vaccin*) or (following NEAR/3 immunisation*) or (following NEAR/3 immunization*) or (following NEAR/3 innoculat*)) NEAR/10 (adverse* or ADE or ADEs or ADR or ADRs or complication* or harm* or safe or safety or "side effect" or "side effects" or "undesirable effect" or "undesirable effects" or "undesirable consequence" or "undesirable consequences" or "undesirable outcome" or "undesirable outcomes" or "unintended effect" or "unintended effects" or "unintended consequence" or "unintended consequences" or "unintended outcome" or "unintended outcome"s)):ti,ab,kw	Limits	1493
−	+	#53	(((post NEXT vaccin*) or (post NEXT immunisation*) or (post NEXT immunization*) or (post NEXT innoculat*) or (after NEXT vaccin*) or (after NEXT immunisation*) or (after NEXT immunization*) or (after NEXT innoculat*) or (following NEAR/3 vaccin*) or (following NEAR/3 immunisation*) or (following NEAR/3 immunization*) or (following NEAR/3 innoculat*)) NEAR/10 (complication* or consequenc* or effect or effects or event or events or harm* or outcome*)):ti,ab,kw	Limits	1214
−	+	#54	("vaccine-associated" or "vaccine-induced" or "vaccine-related"):ti,ab,kw	Limits	1451
−	+	#55	("immunisation-associated" or "immunisation-induced" or "immunisation-related" or "immunization-associated" or "immunization-induced" or "immunization-related"):ti,ab,kw	Limits	38
−	+	#56	((data or vaccin*) NEAR/3 (monitor* or surveillance*)):ti,ab,kw	Limits	4798
−	+	#57	[mh Pharmacovigilance]	Limits	18

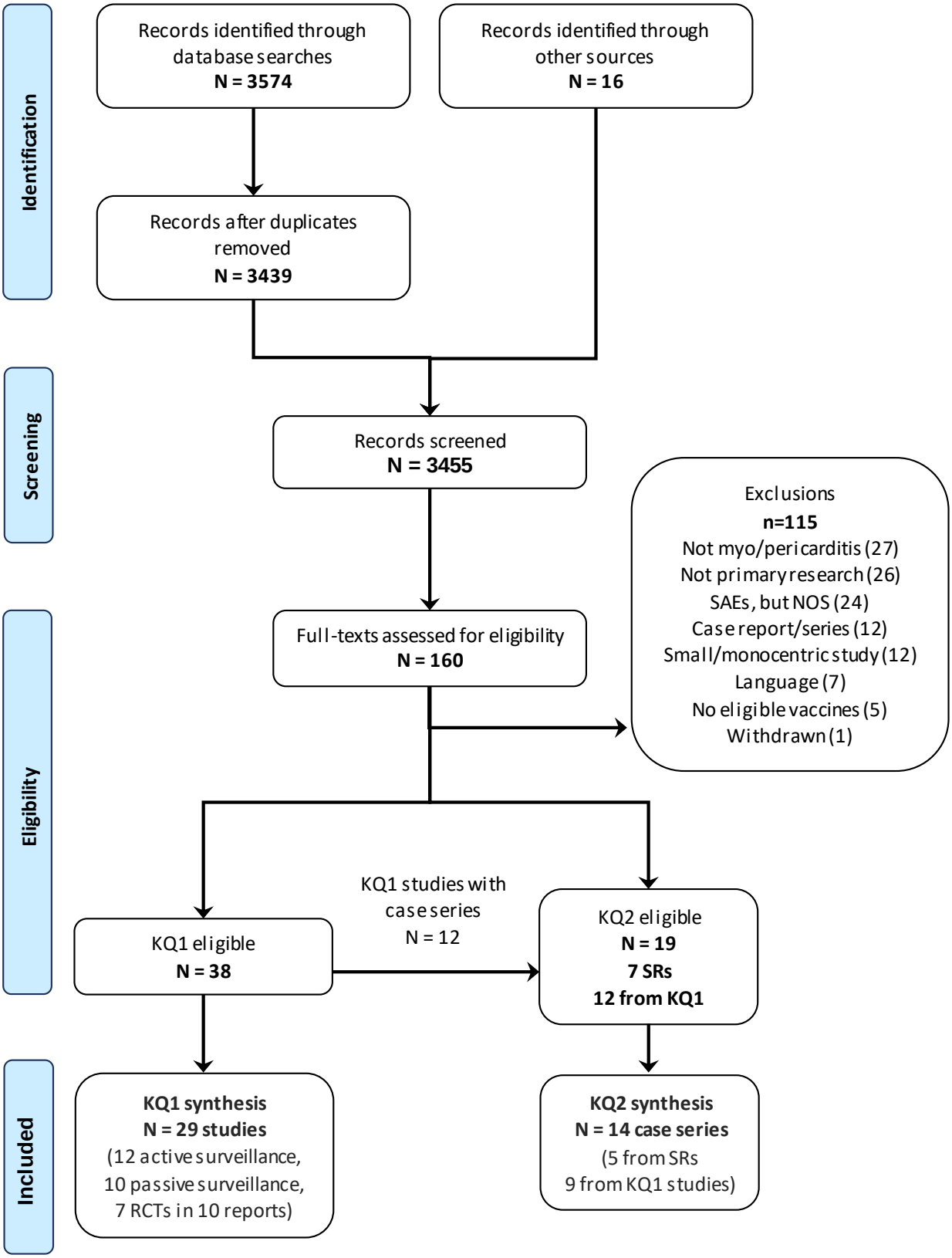
#58	(pharmacovigilan* or (pharmaco NEXT vigilan*)):ti,ab,kw	Limits	318
#59	("Canada Vigilance" or Eudravigilance* or FAERS or VAERS):ti,ab,kw	Limits	19
#60	[mh ^"Product Surveillance, Postmarketing"]	Limits	100
#61	((postmarket* or (post NEXT market*)) NEAR/3 surveillance*):ti,ab,kw	Limits	732
#62	"Clinical Trial, Phase IV":pt	Limits	1201
#63	(("Phase 4" or "Phase IV") NEAR/3 (evaluation* or study or studies or trial or trials)):ti,ab,kw	Limits	2770
#64	[mh ^Cardiomyopathies]	Limits	677
#65	(cardiomyopath* or (cardio NEXT myopath*) or myocardiopath* or (myo NEXT cardiopath*)):ti,ab,kw	Limits	4440
#66	[mh Myocarditis]	Limits	93
#67	myocarditis:ti,ab,kw	Limits	1208
#68	((myocard* or (myo NEXT card*)) NEAR/3 inflam*):ti,ab,kw	Limits	268
#69	carditis:ti,ab,kw	Limits	36
#70	[mh Pericarditis]	Limits	63
#71	pericarditis:ti,ab,kw	Limits	349
#72	((pericard* or (peri NEXT card*)) NEAR/3 inflam*):ti,ab,kw	Limits	22
#73	epicarditis:ti,ab,kw	Limits	2
#74	((epicard* or (epi NEXT card*)) NEAR/3 inflam*):ti,ab,kw	Limits	5
#75	(myopericarditis or "myo-pericarditis"):ti,ab,kw	Limits	12
#76	((myopericard* or (myo NEXT pericard*)) NEAR/3 inflam*):ti,ab,kw	Limits	1
#77	(pleuropericarditis or "pleuro-pericarditis"):ti,ab,kw	Limits	3
#78	((pleuropericard* or (pleuro NEXT pericard*)) NEAR/3 inflam*):ti,ab,kw	Limits	0
#79	{or #48-#78}	Limits	27721
#80	#47 AND #79	Limits	339

with Cochrane Library publication date from Oct 2020 to Oct 2021

6-Oct-21

	Original	Deduped
MEDLINE	2530	2511
Embase	705	675
CDSR	2	0
CENTRAL	337	253
TOTAL	3574	3439

Appendix 2. Literature flow & Table of References to Included Studies



References for included studies in question 1 labeled based on data sources

Study	Reference(s)
Active Surveillance	
Clalit Health May 24a	Witberg G, Barda N, Hoss S, et al. Myocarditis after Covid-19 Vaccination in a Large Health Care Organization. N Engl J Med. 2021. doi:https://dx.doi.org/10.1056/NEJMoa2110737.
Clalit Health May 24b	Barda N, Dagan N, Ben-Shlomo Y, et al. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. N Engl J Med. 2021;385(12):1078-1090. doi:https://dx.doi.org/10.1056/NEJMoa2110475.
Genesis Healthcare Jan 3	Bardenheier BH, Gravenstein S, Blackman C, et al. Adverse events following mRNA SARS-CoV-2 vaccination among U.S. nursing home residents. Vaccine. 2021;39(29):3844-3851. doi:https://dx.doi.org/10.1016/j.vaccine.2021.05.088.
Genesis HealthcareFeb 14	Bardenheier BH, Gravenstein S, Blackman C, et al. Adverse Events Following One Dose of mRNA COVID-19 Vaccination Among US Nursing Home Residents With and Without a Previous SARS-CoV-2 Infection. J Am Med Dir Assoc. 2021;28:28. doi:https://dx.doi.org/10.1016/j.jamda.2021.08.024.
Israel MOH May 31	Mevorach D, Anis E, Cedar N, et al. Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel. N Engl J Med. 2021. doi:https://dx.doi.org/10.1056/NEJMoa2109730.
Israeli Defense Forces May 7	Levin D, Shimon G, Fadlon-Derai M, et al. Myocarditis following COVID-19 vaccination - A case series. Vaccine. 2021;39(42):6195-6200. doi:https://dx.doi.org/10.1016/j.vaccine.2021.09.004.
KPSC Jul 20	Simone A, Herald J, Chen A, et al. Acute Myocarditis Following COVID-19 mRNA Vaccination in Adults Aged 18 Years or Older. JAMA Intern Med. 2021;04:04. doi:https://dx.doi.org/10.1001/jamainternmed.2021.5511.
Providence Health May 25	Diaz GA, Parsons GT, Gering SK, Meier AR, Hutchinson IV, Robicsek A. Myocarditis and Pericarditis After Vaccination for COVID-19. Jama. 2021;326(12):1210-1212. doi:https://dx.doi.org/10.1001/jama.2021.13443.
US Military Apr 30	Montgomery J, Ryan M, Engler R, et al. Myocarditis Following Immunization With mRNA COVID-19 Vaccines in Members of the US Military. JAMA Cardiol. 2021;29:29. doi:https://dx.doi.org/10.1001/jamacardio.2021.2833.
VSD Jun 26	Klein NP, Lewis N, Goddard K, et al. Surveillance for Adverse Events After COVID-19 mRNA Vaccination. Jama. 2021;03:03. doi:https://dx.doi.org/10.1001/jama.2021.15072.
VSD Aug 21	Klein NP. Rapid Cycle Analysis to Monitor the Safety of COVID-19 Vaccines in Near Real-Time within the Vaccine Safety Datalink: Myocarditis and Anaphylaxis. Aug 30 Advisory Committee on Immunization Practices (ACIP) https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/04-COVID-Klein-508.pdf

Study	Reference(s)
VSD Oct 6	Klein NP. Myocarditis Analysis in the Vaccine Safety Datalink: Rapid Cycle Analyses and "Head-to-Head" Product Comparisons. 21 October 2021 2021. Advisory Committee on Immunization Practices (ACIP). Available from: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/08-COVID-Klein-508.pdf.
Passive Surveillance	
CAEFISS & CVP	Public Health Agency of Canada. Canadian COVID-19 vaccination safety report. Ottawa: Public Health Agency of Canada; October 18, 2021 2021. Available from: https://health-infobase.canada.ca/covid-19/vaccine-safety/#a4.
EudraVigilance Oct 19	European Medicines Agency. EudraVigilance - European database of suspected adverse drug reaction reports. European Medicines Agency. Available from: https://www.adrreports.eu/en/eudravigilance.html. Published 2021. Accessed October 26, 2021, 2021.
Israel MOH May 30	Israel Ministry of Health. Surveillance of Mycocarditis (Inflammation of the Heart Muscle) Cases Between December 2020 and May 2021 (Including). Available from: https://www.gov.il/en/departments/news/01062021-03. Published 2021. Updated June 2, 2021. Accessed.
VAERS Jun 11	Gargano JW, Wallace M, Hadler SC, et al. Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices - United States, June 2021. MMWR Morb Mortal Wkly Rep. 2021;70(27):977-982. doi:https://dx.doi.org/10.15585/mmwr.mm7027e2.
VAERS Jun 18a	Høeg TB, Krug A, Stevenson J, Mandrola J. SARS-CoV-2 mRNA Vaccination-Associated Myocarditis in Children Ages 12-17: A Stratified National Database Analysis. 2021. doi:https://dx.doi.org/10.1101/2021.08.30.21262866.
VAERS Jun 18b	Lazaros G, Anastassopoulou C, Hatziantoniou S, et al. A case series of acute pericarditis following COVID-19 vaccination in the context of recent reports from Europe and the United States. Vaccine. 2021. doi:https://dx.doi.org/10.1016/j.vaccine.2021.09.078.
VAERS Jun 30	Rosenblum HG, Hadler SC, Moulia D, et al. Use of COVID-19 Vaccines After Reports of Adverse Events Among Adult Recipients of Janssen (Johnson & Johnson) and mRNA COVID-19 Vaccines (Pfizer-BioNTech and Moderna): Update from the Advisory Committee on Immunization Practices - United States, July 2021. MMWR Morb Mortal Wkly Rep. 2021;70(32):1094-1099. doi:https://dx.doi.org/10.15585/mmwr.mm7032e4.
VAERS Aug 6	Lane S, Shakir S. Reports of myocarditis and pericarditis following mRNA COVID-19 vaccines: A review of spontaneously reported data from the UK, Europe, and the U. 2021. doi:https://dx.doi.org/10.1101/2021.09.09.21263342.
VAERS Oct 6	Su JR. Myopericarditis following COVID-19 vaccination: Updates from the Vaccine Adverse Event Reporting System (VAERS). CDC October 21, 2021 2021. Available from: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/07-COVID-Su-508.pdf.

Study	Reference(s)
Yellow Card Oct 13	Medicine & Healthcare products Regulatory Agency. Coronavirus vaccine - weekly summary of Yellow Card reporting. Government of the United Kingdom. Available from: https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting. Published 2021. Updated October 21, 2021. Accessed October 21, 2021, 2021.
Randomized Controlled Trials	
AZD1222 Trial, Phase 3 (AstraZeneca)	Falsey AR, Sobieszczyk ME, Hirsch I, et al. Phase 3 Safety and Efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 Vaccine. N Engl J Med. 2021;29:29. doi:https://dx.doi.org/10.1056/NEJMoa2105290.
AZD1222 Trial, Pooled Analysis (AstraZeneca)	Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2021;397(10269):99-111. doi:https://dx.doi.org/10.1016/S0140-6736(20)32661-1.
	Voysey M, Costa Clemens SA, Madhi SA, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. Lancet. 2021;397(10277):881-891. doi:https://dx.doi.org/10.1016/S0140-6736(21)00432-3.
C4591001 Trial, Adolescent cohort (Pfizer)	Frenck RW, Jr., Klein NP, Kitchin N, et al. Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. N Engl J Med. 2021;385(3):239-250. doi:https://dx.doi.org/10.1056/NEJMoa2107456.
C4591001 Trial, Adult cohort (Pfizer)	Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020;383(27):2603-2615. doi:https://dx.doi.org/10.1056/NEJMoa2034577.
	Thomas SJ, Moreira ED, Jr., Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months. N Engl J Med. 2021;15:15. doi:https://dx.doi.org/10.1056/NEJMoa2110345.
COVE trial (Moderna)	Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021;384(5):403-416. doi:https://dx.doi.org/10.1056/NEJMoa2035389.
	El Sahly HM, Baden LR, Essink B, et al. Efficacy of the mRNA-1273 SARS-CoV-2 Vaccine at Completion of Blinded Phase. N Engl J Med. 2021. doi:https://dx.doi.org/10.1056/NEJMoa2113017.
Teen COVE trial (Moderna)	Ali K, Berman G, Zhou H, et al. Evaluation of mRNA-1273 SARS-CoV-2 Vaccine in Adolescents. N Engl J Med. 2021;11:11. doi:https://dx.doi.org/10.1056/NEJMoa2109522.
ENSEMBLE Trial (Janssen)	Sadoff J, Gray G, Vandebosch A, et al. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. N Engl J Med. 2021;384(23):2187-2201. doi:https://dx.doi.org/10.1056/NEJMoa2101544.

Appendix 3: Study Characteristics Tables and Risk of Bias Tables

Table A1. Study characteristics of observational studies using data from active surveillance systems (question 1)

Dataset Dates Country	Vaccines Studied	Sample Size; Demographics; Previous Covid-19 diagnoses	Study Group(s)	Outcome(s); Risk Interval; Case Ascertainment	Analysis	Results
VSD† Oct 9 Dec 14 2020 to Oct 9 USA (Klein, 2021a)	Pfizer-BioNTech (60% of dose 2) or Moderna	Total doses 14,214,955 (71.5% eligible people fully vaccinated) to 7.5 million people NR Excluded from analysis if COVID-19 diagnosis ≤30 d before vaccination	1. Vaccinated in previous 0-21 d 2. Concurrent previous vaccinees (22 to 42 d previously for similar individuals after vaccine dose 1 or 2 [most dose 2]) Interval between doses: majority 21 d (Pfizer) and 28 d Moderna)	Myocarditis/pericarditis/ myopericarditis (combined & separate for head-to-head comparison) ICD-10 using inclusion and exclusionary codes via clinical expert consultation; cases among 12-39 y confirmed by medical record review ED and in-patient records used Blinding to vaccine status NR Risk interval: 0-21 d & 0-7 d	Weekly, rapid cycle analysis Adjusted incident rate ratio (aIRR) estimated by Poisson regression adjusted for age, sex, race and ethnicity, health plan, and calendar day; 1-sided P < .0048 for statistical signal Excess risk/incidence per million doses (IR – [IR/IRR]) Exploratory analyses (no prespecified level of significance): by dose and vaccine type; for 12-39 y by dose, vaccine type and with shorter risk intervals; head-to-head Moderna vs Pfizer in 18-39 y (also excluded pericarditis)	Events: 138 (not confirmed) after either dose Incidence: 138/14,214,955 = 9.7 per million doses aIRR: 1.72 p <.001 (statistical signal) Exploratory analyses: 12-39 y (all confirmed cases) Group 1: 74 cases in 0-21 d interval (59 [80%] after dose 2; 39 [53% in 0-7 d)); 44 (59%) in 18-39 y and 30 (40.5% in 12-17 y Clustering at 0-5 d after vaccine (p<.0001) **0-7 d risk interval** aIRR (95% CI) Excess risk per million doses Both doses 21.73 (9.53 to 57.34) 11.8 Dose 2 31.28 (12.83 to 91.40) 21.1 Pfizer (12-39y) 19.31 (7.66 to 57.79) 11.5 Dose 2 30.27 (11.01 to -104.4) 21.5 Moderna (18-39y) 37.51 (6.69 to 803.00) 12.8 Dose 2 NE (11.75 to NE) 21.0 (For dose 1: aIRR range 8.7-10.5, all significant; excess cases 2.3-5.2) **0-7 d risk interval (*18-39 y only*)** aIRR (95% CI) Excess risk per million doses Both doses 12.61 (5.27 to 34.47) 8.4 Dose 2 14.33 (5.50 to 43.88) 13.1 Pfizer 7.98 (2.72 to 26.50) 5.7

Dataset Dates Country	Vaccines Studied	Sample Size; Demographics; Previous Covid-19 diagnoses	Study Group(s)	Outcome(s); Risk Interval; Case Ascertainment	Analysis	Results
						Dose 2 8.77 (2.56 to 35.34) 8.5 Moderna 37.42 (6.68 to 801.33) 12.8 Dose 2 NE (11.70 – NE) 21.0 (For dose 1: aIRR range 8.05 to 10.47; all significant; excess cases 3.3 to 5.2) **0-7 d risk interval (*12-17 y only*)** aIRR (95% CI) Excess risk per million doses Pfizer NE (16.88 to NE) 29.6 Dose 2 NE (28.83 to NE) 54.0 **0-21 d risk interval (*12-17 y only*)** aIRR (95% CI) Excess risk per million doses Pfizer NE (5.68 to NE) 29.6 Dose 2 NE (9.09 to NE) 56.7 **Head-to-head Moderna vs Pfizer in 18-39 y** (0-7 d) aIRR Excess risk per million doses Both doses 2.56 (1.32 to 5.03) 8.0 Dose 2 2.72 (1.25 to 6.05) 13.3 Dose 2 (males) 2.26 (1.00 to 5.19) 21.5 (0-21 d) aIRR Excess risk per million doses Both doses 2.05 (1.11 to 3.83) 7.1 Dose 2 2.19 (1.05 to 4.65) 11.5 Dose 1 all nonsignificant **Head-to-head Moderna vs Pfizer in 18-39 y (without pericarditis)** aIRR Excess cases per million doses (0-7 d) Both doses 2.24 (1.09 to 4.63) 5.6 Dose 2 2.28 (1.25 to 6.05) 13.3 Dose 2 (males) 2.14 (0.93 to 4.98) 19.1 (0-21 d)

Dataset Dates Country	Vaccines Studied	Sample Size; Demographics; Previous Covid-19 diagnoses	Study Group(s)	Outcome(s); Risk Interval; Case Ascertainment	Analysis	Results
						Both doses 1.96 (**0.99** to 3.91) 5.3 Dose 2 2.19 (**0.98** to 4.97) 9.4 Dose 1 all nonsignificant
VSD† Aug 21 Dec 14 2020 to Aug 21 2021 USA (Klein 2021b)	Pfizer-BioNTech (57% overall) or Moderna	Total doses 13,334,831 (66.5% fully vaccinated) to 7.1 million people	1. Vaccinated in previous 0-21 d 2. Concurrent previous vaccinees (22 to 42 d previously for similar individuals after vaccine dose 1 or 2 [most dose 2])	Myocarditis/pericarditis/ myopericarditis (combined) Risk interval: 0-21 d		Events: 115 aIRR: 1.57 p=0.010 (not meeting p<0.0048 signal) <u>Subgroups</u>: *12-39 y* 56 cases in 0-21 d risk interval aIRR — Excess risk per million doses Both doses 5.63 (2.31 to 16.44) 8.9 Dose 2 8.31 (3.07 to 28.28) 15.5 Pfizer 3.62 (1.39 to 11.11) 7.2 Dose 2 5.74 (1.98 to 20.52) 13.6 Moderna NE (3.32 to NE) 12.7 Dose 2 NE (3.79 to NE) 19.8 Dose 1 aIRR 2.3 to 3.8 and imprecise for separate vaccines **For 0-7 risk interval – see more recent data in Klein Oct 21, 2021**
VSD† Jun 26 Dec 14 2020 to Jun 26 2021 USA Klein 2021c	Pfizer-BioNTech (57% overall) or Moderna	10,162,227 doses to 6.2 million vaccine-eligible members (≥12 y) (60.7% received at least 1 dose) Females 52.4% Mean age 49 y; 5.5% 12-15 y; 2.8%16-17 y; 50.4% 18-49 y White non-Hispanic 40.6% Excluded from analysis if COVID-19 diagnosis ≤30 d before vaccination	1. Vaccinated in previous 0-21 d 2. Concurrent previous vaccinees (22 to 42 d previously for similar individuals after vaccine dose 1 or 2 [most dose 2]) 3. Unvaccinated concurrent comparators (same day) Interval between doses NR	Myocarditis/pericarditis/ myopericarditis (combined) Risk interval: 0-21 d and 0-7 d ICD-10 using inclusion and exclusionary codes via clinical expert consultation; cases among 12-39 y confirmed by medical record review ED and in-patient records used	Weekly, rapid cycle analysis Incidence after any dose, after dose 1 and after dose 2 Incident rate ratio (IRR) estimated by Poisson regression adjusted for age, sex, race and ethnicity, health plan, and calendar day; 1-sided P < .0048 for statistical signal	**Group 1 vs. 2** Events: 87 vs 39 events Incidence: 131.1 vs. 106.9 per million person-years aIRR: 1.18 (95% CI, 0.79 to 1.79) Excess risk/cases per million doses: 1.2 (95% CI, –2.1 to 3.3) <u>Exploratory analyses</u>: *By dose and vaccine type:* p > 0.0048 for all *12-39y:* 34 cases (53% 12-24y; 85% male; 82% hospitalized; 71% after dose 2; 7 myocarditis; 6 pericarditis; 21 myopericarditis) Clustering at 0-5 d after vaccine (p<.001) During 0-21 d after vaccination (either dose):

Dataset Dates Country	Vaccines Studied	Sample Size; Demographics; Previous Covid-19 diagnoses	Study Group(s)	Outcome(s); Risk Interval; Case Ascertainment	Analysis	Results
				Blinding to vaccine status NR	Excess risk/incidence per million doses (IR – [IR/IRR]) Exploratory analyses (no prespecified level of significance): by dose and vaccine type; for 12-39 y by dose, vaccine type and with shorter risk intervals	Incidence: 141.2 vs. 35.0 cases per million person-years aIRR: 3.74 (95% CI, 1.38 to 12.84) Similar results for each dose but most precise for dose 2 having more data During 0-7 d after vaccination (either dose): Incidences: 321 vs 35 cases per million person-years aIRR: 9.83 (95% CI, 3.35 to 35.77) Excess risk per million doses: 6.3 (95% CI, 4.9 to 6.8) Similar results for each dose but most precise for dose 2 having more data Similar findings in analyses by vaccine type **Group 1 vs 3:** Events: 87 vs. 293 Incidence 132 vs. 83 cases per million person-years aIRR: 1.39 (95% CI, 1.05 to 1.82)
US Military Apr 30 Jan 1 to Apr 30 2021 USA Montgomery 2021	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
Providence Health May 25 Up to May 25 2021 USA Diaz 2021	Pfizer, Moderna, Janssen At least one dose (23.5% more than 1)	N=2,000,287 Female 58.9% Median age 57 y (IQR 40-70)	1. Individuals vaccinated with at least 1 dose 2. Unvaccinated individuals Jan 19 – Jan21	Myocarditis, Pericarditis w/o myocarditis Emergency department or inpatient encounters with diagnoses of myocarditis/ myopericarditis, or pericarditis	Change/excess in incidence between periods	Excess incidence of myocarditis/myopericarditis: 1.0 (0.61-1.54) per 100,000 vaccinees Excess incidence of pericarditis: 1.8 (1.30-2.55) per 100,000 vaccinees

Dataset Dates Country	Vaccines Studied	Sample Size; Demographics; Previous Covid-19 diagnoses	Study Group(s)	Outcome(s); Risk Interval; Case Ascertainment	Analysis	Results
				Patients with previous diagnoses (cardiac, immunological, infectious) excluded Risk interval: 30d		
KPSC Jul 20 Dec 14 2021 to Jul 20 2021 USA Simone 2021	BNT162b2 (Pfizer) or mRNA-1273 (Moderna) (93.5% fully vaccinated)	KPSC members ≥18y Vaccinated group n=2,392,924 Median age 49y (IQR: 34-64y) Age <40 y: 35.7% Females 54.0% Black 6.7%; Hispanic 37.8%; Asian 14.3% Unvaccinated group: n=1 577 741, median (IQR) age was 39 (28-53) years Age <40y: 53.7% Females: 49.1% Black 8.8%; Hispanic 39.2%; Asian 6.6%	1. Vaccinated 2. Concurrent unvaccinated 3. Vaccinated individuals during a 10-day period 1 year prior to vaccination	Myocarditis Reports from clinicians to the KPSC Regional Immunization Practice Committee and by identifying hospitalization within 10 days of vaccine administration with a discharge diagnosis of myocarditis All cases were independently adjudicated by at least 2 cardiologists. Risk interval: 10d	Incidence rates and 95% confidence intervals (CIs) IRR 1 vs 2, 1 vs 3	Observed incidence: Dose 1: 0.8 (0.2-3.3) cases per 1 million first doses Dose 2: 5.8 (3.4-10) cases per 1 million second doses Unvaccinated: 2.2 (1.7-2.7) cases per million people 100% cases men IRR (95% CI): 1 v 2 Dose 1: 0.38 (0.05-1.40) Dose 2: 2.7 (1.4-4.8) IRR 1 v 3 Dose 1: 1.0 (0.1-13.8) Dose 2: 3.3 (1.0-13.7)
Israel MOH* May 31 Dec 20 2020 to May 31 2021 Israel Mevorach, 2021	Pfizer-BioNTech 2 doses to 5.12 million people	Surveillance population 9,289,765 Israeli residents ≥16 y 29 of 98 cases in unvaccinated population had confirmed Covid-19 (timing NR); NR for vaccinated Age, sex, race/ethnicity NR	1. Received dose 1 (n=5,442,696) 2. Received dose 2 (n=5,125,635) 3. Concurrent unvaccinated persons matched by date 4. Historical controls from 2017-2019 Interval between doses 21 d	Myocarditis/myopericarditis ICD-9 codes 422.0-9x and 429.0x; cases 12-29 yrs old confirmed by medical record review using Brighton Criteria via consensus Assessors not blinded to vaccine status	Incidence in groups 1 and 2 (cumulative risks) Risk difference (incidence) between 1 vs 2 Standardized incidence ratio of observed-to-expected (historical controls) Attributable risk to dose 2	Total events in groups 1 and 2: 142 (136 definitive or probable [117 after dose 2], used for analysis except for standardized IR); group 3: 101 Incidence: dose 1: 0.35 per 100,000 persons; dose 2: 2.28 per 100,000 persons Risk difference dose 2 – dose 1: 1.76 per 100,000 persons (95% CI, 1.33 to 2.19) Standardized incidence ratio: group 1 vs 4 1.42 (95% CI, 0.92 to 2.10); group 2 vs 4: 5.34 (95% CI, 4.48 to 6.40)

Dataset Dates Country	Vaccines Studied	Sample Size; Demographics; Previous Covid-19 diagnoses	Study Group(s)	Outcome(s); Risk Interval; Case Ascertainment	Analysis	Results
		None of the post-vaccination cases had concurrent Covid-19 via symptoms or PCR; 35/39 had negative serology tests		Cases of pericarditis without myocarditis were excluded Risk interval: 21 d for dose 1 and 30d for dose 2	IRR group 2 vs 3 (weighted by age and sex) Subgroups: sex, 5-yr age categories <30; 10 yr after 30; shorter risk interval 0-7 d	aIRR group 2 vs 3: 2.35 (95% CI, 1.10 to 5.02) <u>Subgroup analyses</u> Males vs females: Incidence: dose 1: 0.64 vs 0.07 per 100,000 persons dose 2: 3.83 vs. 0.46 per 100,000 persons Risk difference dose 2 – dose 1: 3.19 (95% CI, 2.37 to 4.02) vs. 0.39 (95% CI, 0.10 to 0.68) IRR: NR By age categories: Males Dose 1 incidence per 100,000 persons 16-19 y 1.34 20-24 y 1.91 25-29y 1.22 30-39 y 0.41 40-49y 0.65 ≥50y 0.10 Dose 2 incidence 16-19 y 15.07 20-24 y 10.86 25-29 y 6.99 30-39 y 3.69 40-49 y 1.15 ≥50 y 0.21 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) Females Dose 1 incidence 16-39 y 0 40-49 y 0.21 ≥50 y 0.09 Dose 2 incidence 16-19 y 1.00 20-24 y 2.16

Dataset Dates Country	Vaccines Studied	Sample Size; Demographics; Previous Covid-19 diagnoses	Study Group(s)	Outcome(s); Risk Interval; Case Ascertainment	Analysis	Results
						25-29 y 0 30-39 y 0.22 40-49 y 0.45 ≥50 y 0.19 IRR 20-24 y 7.56 (95 CI, 1.47 to 8.96); others imprecise Shorter risk interval (7 d after dose 2): Males 16-19 y: Risk difference: 13.62 per 100,000 persons (95% CI, 8.31 to 19.03) IRR: 31.90 (95% CI, 15.88 to 64.08)
Clalit Health** May 24a Dec 20 2020 to May 24 2021 Israel Witberg, 2021	Pfizer-BioNTech 94% received 2 doses	2,558,421 ≥16 y receiving at least 1 dose (94% 2 doses) 2 cases had Covid-19 (125 and 186 d) prior to vaccine but NR if any others and NR if active testing of cases	1. Received 1 dose (n=2,558,421) Interval between doses 21 d	Myocarditis Risk interval: 42 d after dose 1 ICD-9 (codes 422, 429.0, 398.0, and 391.2 and their respective subcodes), with adjudication by cardiologists using medical and CDC case definition, with consensus Unblinded to vaccine status (all vaccinated and author adjudicating)	Incidence after dose 1 or 2 using Kaplan–Meier analysis Subgroups: Sex; Ages 16-29 y; ≥30 y	Events: 54 (of 159 potential cases; 37 after dose 2; with 17/37 >7 days post dose 2) Incidence: 2.13 cases per 100,000 persons (95% CI: 1.56 to 2.70) <u>Subgroup analysis</u> Males vs females: Incidence: 4.12 (95% CI: 2.99 to 5.26) vs. 0.23 (95% CI: 0 to 0.49) <u>By age categories</u>: Overall 16-29 y: 5.49 per 100,000 persons (95% CI: 3.59 to 7.39) Overall ≥30 y: 1.13 per 100,000 persons (95% CI: 0.66 to 1.60) Males 16-29 y: 10.69 per 100,000 persons (95% CI: 6.93 to 14.46) Males ≥30 y: 2.11 per 100,000 persons (95% CI, 1.19 to 3.04) Females 16-29 y: 0.34 per 100,000 persons (95% CI, 0 to 1) Females ≥30 y: 0.20 per 100,000 persons (95% CI, 0 to 0.48)
Clalit Health** May 24b Dec 20 2020 to May 24 2021 Israel Barda, 2021	Pfizer-BioNTech NR how may had 1 vs 2 doses	Surveillance population 1,877,624 ≥16 y Excluded people with previous events, residing in nursing homes, healthcare workers, no BMI or residential area data Mean age 38 y Females 48%	1. Received 1 dose (n=884,828) 2. Concurrent unvaccinated, matched 1:1 by age, sex, place of residence, socioeconomic status, population sector (general Jewish, Arab, or ultra-Orthodox Jewish), number of preexisting conditions at risk for	Myocarditis & pericarditis after at least 1 dose Risk interval: 42 d after dose 1 ICD-9 codes (422, 429.0, 398.0, 391.2, 420) after the index date Blinding NR	Incidence using Kaplan–Meier estimator Risk difference Risk Ratio	Events in group 1 vs 2: myocarditis 21 (91% male; median age 25y [IQR 20-34]) vs 6; pericarditis: 27 vs 18 Risk difference (all ages): myocarditis: 2.7 events per 100,000 persons (95% CI, 1.0 to 4.6); pericarditis: 1.0 events per 100,000 persons (95% CI, −1.6 to 3.4) RR: myocarditis: 3.24 (95% CI, 1.55 to 12.44); pericarditis: 1.27 (95% CI, 0.68 to 2.31)

Dataset Dates Country	Vaccines Studied	Sample Size; Demographics; Previous Covid-19 diagnoses	Study Group(s)	Outcome(s); Risk Interval; Case Ascertainment	Analysis	Results
		Previous Covid-19 cases excluded	severe Covid-19. (n=884,828) Interval between doses 21 d			
Israeli Defense Forces May 7 Dec 28 2020 to Mar 7 2021 Israel Levin, 2021	Pfizer-BioNTech 138,000 military personnel receiving 2 doses	138,000 NR NR	1. 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
Genesis Healthcare*** Feb 14 Dec 18 2020 to Feb 14 2021 USA Bardenheier, 2021a	Moderna or Pfizer-BioNTech All had 1 dose	20,918 nursing home residents Females 61.9% <65 y 18.5% African American or Latinx 16.9% Excluded if Covid-19 +ve within 20 d of vaccination, or treated with SARS-CoV-2 monoclonal antibodies within 90 days before vaccination	1. No prior infection at vaccination (n=13.163) 2. Symptomatic infection >20 days before vaccination (n=5,617) 3. Asymptomatic infection >20 days before vaccination (n=2,138) 4. Unvaccinated (from Bardenheier, 2021b) Interval between doses NA	Myocarditis/pericarditis Risk interval: 15 days after dose 1 Active, prospective surveillance; medical record review for ICD-10-CM codes, confirmed by physician chart review, using Brighton Collaboration Criteria Blinding NR	Incidence (if events) Comparisons between groups by multilevel logistic regression that adjusted for clustering and applied propensity scoring for age, sex, pre-existing conditions	Events: group 1 vs 2 vs 3: 0 vs. 0 vs. 0
Genesis Healthcare*** Jan 3 Dec 18 2020 to Jan 3 2021 USA	Moderna or Pfizer-BioNTech (70.6%) 1st dose or 2nd dose	21,222 nursing home residents Females 61.9% <65 y 18.8 African American or Latinx 18%	1. After dose 1 (n=8553) 2. After dose 2 (n=8371) 3. Unvaccinated (n=11072) Interval between doses 3 to 6 weeks	Myocarditis Active, prospective surveillance; medical record review for ICD-10 codes, confirmed by physician chart review,	Incidence IRR, adjusted for age, sex, pre-existing conditions	Events: 0 vs. 0 vs. 0

Dataset Dates Country	Vaccines Studied	Sample Size; Demographics; Previous Covid-19 diagnoses	Study Group(s)	Outcome(s); Risk Interval; Case Ascertainment	Analysis	Results
Bardenheier, 2021b		Excluded if Covid-19 +ve within 20 d of vaccination, or treated with SARS-CoV-2 monoclonal antibodies within 90 days before vaccination		using Brighton Collaboration Criteria Blinding NR		

Table A2. Study characteristics of observational studies using data from passive surveillance systems (question 1)

Dataset Dates of data Country of Data	Vaccines Studied	Outcome(s); Case Ascertainment & Risk Interval	Analysis	Results
VAERS* Oct 6 Up to Oct 6, 2021 USA Su, 2021	Pfizer-BioNTech, Moderna and Janssen	Myopericarditis (myocarditis +/- pericardtis); pericarditis Screening via 30 MedDRA terms and ICD-10; all analyzed reports verified to meet CDC case definition by provider interview or medical record review Risk interval: 7 d	Crude reporting rates of confirmed cases of myopericarditis after each dose	Total events: 2,459 myopericarditis (1,181 have been verified and 935 occurred in 0-6 d after vaccination; 877 pericarditis (366,062,239 doses of mRNA vaccines) For myopericarditis: 67% Pfizer; 29% Moderna; 76% after dose 2 (50 preliminary reports after Janssen not in analysis) <u>Reporting rates of myopericarditis per 1 million doses administered (N=935 verified cases):</u> **Pfizer** **Moderna** Ages Dose 1 Dose 2 Dose 1 Dose 2 12-15 **2.3*** **21.5** 0.0 not calculated 16-17 **2.8** **37.4** 0.0 not calculated 18-24 1.2 **18.1** **3.1** **20.7** 25-29 0.7 **5.7** 1.8 **11.2** 30-39 0.6 **2.8** 1.4 **3.6** 40-49 0.2 1.5 0.2 **2.1** 50-64 0.3 0.4 0.5 0.5 65+ 0.1 0.2 0.0 0.3 <u>Males (N=797):</u> Ages Dose 1 Dose 2 Dose 1 Dose 2 12-15 **4.2** **39.9** 0.0 not calculated 16-17 **5.7** **69.1** 0.0 not calculated 18-24 **2.3** **36.8** **6.1** **38.5** 25-29 1.3 **10.8** **3.4** **17.2** 30-39 0.5 **5.2** **2.3** **6.7** 40-49 0.3 2.0 0.2 **2.9** 50-64 0.2 0.3 0.5 0.6 65+ 0.2 0.1 0.1 0.3 <u>Females (N=138):</u> Ages Dose 1 Dose 2 Dose 1 Dose 2 12-15 0.4 **3.9** 0.0 0.0 16-17 0.0 **7.9** 0.0 0.0 18-24 0.2 **2.5** 0.6 **5.3** 25-29 0.2 1.2 0.4 **5.7** 30-39 0.6 0.7 0.5 0.4 40-49 0.1 1.1 0.2 1.4 50-64 0.3 0.5 0.5 0.4 65+ 0.1 0.3 0.0 0.3 *Reporting rates exceed background incidence (bolded data above))

Dataset Dates of data Country of Data	Vaccines Studied	Outcome(s); Case Ascertainment & Risk Interval	Analysis	Results
				An estimated 1–10 cases of myocarditis per 100,000 person years occurs among people in the United States, regardless of vaccination status; adjusted for the 7-day risk period, this estimated background is 0.2 to 1.9 per 1 million person 7-day risk period
VAERS* Jun 30 Up to Jun 30 2021 USA Rosenblum, 2021	Pfizer-BioNTech or Moderna After dose 2, timing NR	Myocarditis Cases in persons aged 18–29 yrs were individually reviewed and confirmed to meet CDC case definitions Risk interval: 42 d	Crude reporting rates after dose 2 Subgroups by age and sex	Overall ≥18 yrs: 3.5 cases per million second doses <u>Subgroups (all after dose 2):</u> Females 18-29 yrs: 3-4 cases per million second doses 30-49 yrs: 1-2 cases per million second doses 50-64 yrs: 1 case per million second doses ≥65 yrs: <1 case per million second doses Males 18-29 yrs: 22-27 cases per million second doses 30-49 yrs: 5-6 cases per million second doses 50-64 yrs: 1 case per million second doses ≥65 yrs: 1 case per million second doses
VAERS* Jun 11 Up to Jun 11 2021 USA Gargano 2021	Pfizer-BioNTech or Moderna After dose 2, timing NR	Myocarditis Note: Subset of confirmed cases described and included in KQ2 Risk interval: 7 d	Crude reporting rates (i.e., using confirmed and unconfirmed cases), after dose 2	Males 12-29 yrs: 40.6 cases per million second doses Males 12-17 yrs: 62.8 cases per million second doses Males 18-24 yrs: 50.5 cases per million second doses Males ≥30 yrs: 2.4 cases per million second doses Females 12-29 yrs: 4.2 cases per million second doses Females ≥30 yrs: 1.0 cases per million second doses
VAERS* Aug 6 Up to Aug 6 2021 US Lane 2021	Pfizer-BioNTech, Moderna At least one dose (UK, EEA) or 2 doses (US); schedule NR.	Myocarditis and pericarditis Events labelled "Myocarditis" or "Pericarditis" Risk interval: None applied (date of vaccine launch to datalock point)	Crude reporting rates per million people receiving at least one dose (UK, EEA) or receiving both doses (US)	<u>UK</u> Pfizer/BioNTech: 7.93 cases of myocarditis and 6.73 cases pericarditis per million vaccinees Moderna: 2.07 cases of myocarditis and 1.79 cases of pericarditis per million vaccinees <u>EEA</u> Pfizer/BioNTech: 4.23 cases of myocarditis and 2.87 cases of pericarditis per million vaccinees Moderna: 6.15 cases of myocarditis and 3.84 cases of pericarditis per million vaccinees <u>US (after dose 2)</u> Pfizer/BioNTech: 6.47 cases of myocarditis and 3.53 cases of pericarditis per million vaccinees Moderna: 3.65 cases of myocarditis and 2.69 cases of pericarditis per million vaccinees
VAERS* Jun 18a Jan 1 to Jun 18 2021 USA Høeg 2021	Pfizer-BioNTech or Moderna (but only 1 of 257 cases since not approved for <18y at that time) Schedule NR	Myocarditis "Myocarditis," "pericarditis," "myopericarditis" or "chest pain" in the symptom notes; "troponin" required element in the laboratory data.	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	Events: 257 (92% within 5 d; 90% males) <u>At least Dose 1</u> Males 12-15 yrs: 12.0 per million vaccinees Males 16-17 yrs: 8.2 per million vaccinees Females 12-15 yrs: 0 per million vaccinees Females 16-17 yrs: 2.0 per million vaccinees <u>Dose 2</u> Males 12-15 yrs: 162.2 per million vaccinees

Dataset Dates of data Country of Data	Vaccines Studied	Outcome(s); Case Ascertainment & Risk Interval	Analysis	Results
		CDC working case definition of probable myocarditis Risk interval: Any timing	following dose 1 and 85% occurred following dose 2	Males 16-17 yrs: 94.0 per million vaccinees Females 12-15 yrs: 13.0 per million vaccinees Females 16-17 yrs: 13.4 per million vaccinees
VAERS* Jun 18b USA Lazaros 2021	AstraZeneca Janssen Moderna Pfizer-BioNTech Dose and schedule not specified.	Pericarditis Ascertainment NR	Crude rate per million vaccine doses Raw data available to calculate crude age and sex subgroup rates if needed.	<u>EEA</u> AstraZeneca: 2.604 per million doses Janssen: 2.530 per million doses Total vectored: 2.596 per million doses Moderna: 4.023 per million doses Pfizer-BioNTech: 1.613 per million doses Total mRNA: 1.882 per million doses
CAEFISS & CVP Up to Oct 8 2021 Canada PHAC 2021	AstraZeneca, Moderna (≥12 y), Pfizer-BioNTech (≥12 y) Dose and schedule not specified.	Myocarditis or pericarditis Cases meeting Level 1-4 to Brighton Criteria of Diagnostic Certainty (not all probable or definitive) Risk interval: Any timing	Reported rates per 100,000 doses administered	Events: 913 Moderna: 2.51 cases per 100,000 doses Pfizer-BioNTech: 1.37 cases per 100,000 doses AstraZeneca: 0.72 cases per 100,000 doses
Yellow Card Oct 13 Dec 9 2020 to Oct 13 2021 UK Medicines & Healthcare Products Regulatory Agency 2021	AstraZeneca, Moderna, Pfizer-BioNTech After dose 1 or 2; schedule NR	Myocarditis and pericarditis (including those from viral/other infective causes) Ascertainment NR Risk interval: NR	Reporting rates per million doses	<u>Overall</u> Pfizer-BioNTech: myocarditis 8 cases per million doses; pericarditis 6 cases per million doses Moderna: myocarditis 32 case per million doses; pericarditis 19 cases per million doses AstraZeneca: myocarditis 3 case per million doses; pericarditis 4 cases per million doses <u>Subgroups:</u> Myocarditis/pericarditis <18 yrs Pfizer-BioNTech: 10 cases per million doses Moderna: 0 cases AstraZeneca: 0 cases 18-49 yrs Pfizer-BioNTech: 18 cases per million doses Moderna: 44 cases per million doses AstraZeneca: 8 cases per million doses ≥50 yrs Pfizer-BioNTech: 5 cases per million doses Moderna: 29 cases per million doses AstraZeneca: 4 cases per million doses
Israel MOH* May 30 Dec 2020 to May 30 2021	Pfizer-BioNTech (≥16 y)	Myocarditis Ascertainment NR	Crude number of cases and doses	Dose 1: 27 cases of 5,401,150 vaccinated individuals (5 per million) (11 had pre-existing conditions)

Dataset Dates of data Country of Data	Vaccines Studied	Outcome(s); Case Ascertainment & Risk Interval	Analysis	Results
Israel	Dose 1 and 2; schedule NR	Risk interval: 30 d after dose 2		Within 30 d after dose 2: 121 cases of 5,049,424 vaccinated individuals (24 per million) (60 had pre-existing conditions)
EudraVigilance Oct 19** Up to Oct 19 2021 EEA European Medicines Agency 2021	AstraZeneca Janssen Moderna Pfizer-BioNTech Dose and schedule NR	Myocarditis, pericarditis Ascertainment NR Risk interval: NR	Crude number of case and doses	<u>Overall</u>: Moderna: 1578 cases of myocarditis and 850 cases of pericarditis across 61,172,753 doses administered† (25.8 per million & 13.9 per million) Pfizer: 3610 cases of myocarditis and 2883 cases of pericarditis across 424,162,518 doses administered† (8.5 per million & 6.8 per million) AstraZeneca: 320 cases of myocarditis and 416 cases of pericarditis across 68,799,957 doses administered† (4.7 per million & 6.0 per million) Janssen: 103 cases of myocarditis and 101 cases of pericarditis across 15,782,596 doses administered† (6.5 per million & 6.4 per million) <u>Age<18y</u> Moderna: 32 reports of myocarditis across 531,050 people receiving at least one dose † (60.3 events per million) Pfizer: 369 reports of myocarditis across 8,874,141 people receiving at least one dose † (41.6 events per million)

*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)

Table A3. Summary of risk of bias assessments for observational studies/surveillance data (question 1)

Dataset	Were the two groups similar and recruited from the same population?	Was vaccination status measured in a reliable or valid way?	Were confounding factors identified and appropriately addressed in design or analysis?	Were the outcomes measured in a valid and reliable way?	Was the follow up time long enough for outcomes to occur?	Were the large majority of cases likely to have been identified?	Overall assessment of risk of bias
Active Surveillance Studies							
VSD Jun 26 Klein 2021 Ref ID 22	Y	Y	U	Y	Y	Y	Some concerns
Israel MOH May 31 Mevorach 2021 Ref ID 3440	Y	U	N	Y	Y	Y	Some concerns
Clalit Health May 24a Witberg Ref ID 3441	NA	Y	Y	Y	Y	Y	Low
Clalit Health May 24b Barda 2021 Ref ID 1282	Y	Y	Y	Y	Y	Y	Low
Israeli Defense Forces May 7 Levin 2021 Ref ID 512	NA	Y	N	Y	N	Y	Some concerns
Genesis Healthcare Feb 14 Bardenheier 2021a Ref ID 144	Y	Y	Y	Y	U	Y	Some concerns
Genesis Healthcare Jan 3 Bardenheier, 2021b ref ID 1972	Y	Y	Y	Y	U	Y	Some concerns
KPSC Jul 2 Simone 2021 Ref ID 22	Y	Y	U	Y	U	Y	Some concerns
Providence Health May 25 Diaz 2021 Ref ID 525	Y	Y	N	U	N	Y	High
VSD Oct 9	Y	Y	U	Y	Y	Y	Some concerns

(Klein 2021 Oct ACIP)							
VSD Aug 21 Klein 2021 Aug ACIP)	Y	Y	U	Y	Y	Y	Some concerns
Passive Surveillance Studies							
VAERS Oct 6 Su, 2021 (ACIP Oct 20-21 2021 meeting)	NA	N	N	Y	Y	N	High
VAERS Jun 30 Rosenblum, 2021	NA	N	N	U	U	N	High
VAERS Jun 11 Gargano 2021	NA	N	N	U	Y	N	High
VAERS Aug 6 Lane 2021	NA	N	N	N	U	N	High
VAERS Jun 18a Høeg 2021	NA	N	N	U	U	N	High
VAERS Jun 18b Lazaros 2021	NA	U	N	U	U	N	High
CAEFISS & CVP PHAC 2021	NA	U	N	N	N	U	High
Yellow Card Oct 13 Medicines & Healthcare Products Regulatory Agency 2021	NA	U	N	U	U	N	High
Israel MOH May 30 Israel Ministry of Health 2021	NA	U	N	U	Y	U	High
EudraVigilance Oct 19 European Medicines Agency 2021	NA	Y	N	U	U	N	High

Table A4. Study characteristics of randomized controlled trials (question 1)

Trial name; Author (year); Country (number of sites); Dates of enrolment Funding	Eligibility, Randomization & Blinding	Study Arms		Baseline Demographics	Outcome(s); Safety Assessment	Analysis	Results
		Vaccine arm	Placebo arm				
Teen COVE trial, **Phase 2/3,** Ali (2021) USA (26) Dec 9, 2020 – Feb 28, 2021 USA (26) Industry-funded	Included adolescents 12-17 y Exclusions: travel outside of USA 28 d prior to screening; acute illness or fever 24 h prior to or at screening; previous administration of an investigational SARS-CoV-2 vaccine; pregnant or breastfeeding. Randomized 2:1; centralized interactive response technology system Study personnel and participants were blinded; pharmacists and vaccine administrators unblinded.	mRNA-1273 (Moderna), 2 doses 28 d apart 100 mcg per 0.5 ml dose Randomized: 2,489 Dose 1: 2,486 Dose 2: 2,480 Safety population: 2,486 Withdrawals: After dose 1: 18 After dose 2: 188	Saline placebo 2 doses 28 d apart 0.5 ml per dose Randomized: 1,243 Dose 1: 1,240 Dose 2: 1,222 Safety population: 1,240 Withdrawals: After dose 1: 6 After dose 2: 57	Total randomized: 3,732 Total safety population: 3,726 Male 51% Mean age 14.3 y 12-15 y: 74% 16-17 y: 26% White 84% Baseline SARS-CoV-2 status: Positive: 216 (6%), similar between arms; Missing: 268 (7%), similar between arms	Myocarditis & pericarditis Solicited local and systemic adverse reactions during 7 d after each injection; **Unsolicited adverse events (AEs)**, defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure, observed or reported during 28 d after each injection; AEs leading to discontinuation from a dose and/or study withdrawal, medically attended (MAAEs) and serious AE (SAEs), throughout study period Unblinded safety data reviewed by independent data and safety monitoring board	Safety analysis included all participants who received at least one injection, according to treatment group	**Myocarditis:** 0 **Pericarditis:** 0
COVE trial, **Phase 3** Baden (2021; primary publication) & El-Sahly (2021) Jul 27, 2020 – Oct 23, 2020 USA (99)	Included adults ≥18 y at appreciable risk of acquiring infection or high risk of severe COVID-19, or both; Exclusions: immunosuppression or received systemic immunosuppressant/	mRNA-1273 (Moderna) 2 doses 28 d apart 100 mcg per 0.5 ml dose Randomized: 15,210 Dose 1: 15,181 Dose 2: 14,711	Saline placebo 2 doses 28 d apart 0.5 ml dose Randomized: 15,210 Dose 1: 15,170 Dose 2: 14,617	Total randomized: 30,420 Total safety population: 30,351 Male 52.6% Mean age 51.4 y White 79.2% 18 to <65 y at risk: 16.7% 18 to <65 y not at risk: 58.6%	Solicited local and systemic adverse reactions during 7 d following each injection; **Unsolicited adverse events (AEs)** for 28 d following each injection, including treatment-emergent AE	Safety analysis included all participants who received at least one injection, according to product received.	From associated publication: **Myocarditis:** 0 **Pericarditis:** 2 (68 d & 73 d after dose 2) vaccine vs. 2 placebo

Trial name; Author (year); Country (number of sites); Dates of enrolment Funding	Eligibility, Randomization & Blinding	Study Arms		Baseline Demographics	Outcome(s); Safety Assessment	Analysis	Results
		Vaccine arm	Placebo arm				
Industry-funded	immune-modifying drugs for >14 d total in prior 6 mos; known history of SARS-CoV-2 infection; pregnant or breastfeeding, Randomized 1:1, stratified by age (≥18 to <65 y vs. ≥65 y) and being at risk for severe Covid-19 based on pre-existing risk factors as per CDC; centralized interactive response technology system Study personnel and participants were blinded, but pharmacists and vaccine administrators were unblinded; participants informed of group assignment at end of blinded phase and offered vaccine.	Safety population (unsolicited AEs): 15,185 Withdrawals: 233 (45 discontinued study due to SARS-CoV-2 diagnosis)	Safety population (unsolicited AEs): 15,166 Withdrawals: 290 (69 discontinued study due to SARS-CoV-2 diagnosis)	≥65 y: 24.8% Significant cardiac disease 4.9% HIV infection 0.6% Baseline SARS-CoV-2 status: Positive: 680 (2.2%), similar between arms; Missing: 523 (1.7%), similar between arms	(any event during study not present before exposure to injection or any event already present that worsens after exposure to study vaccine; AEs leading to discontinuation from a dose and/or study withdrawal, MAAEs and SAEs, throughout study period (1-759 d) MedDRA classification for all solicited adverse reactions and unsolicited AEs Unblinded safety data reviewed by independent data and safety monitoring board		
C4591001 Trial, Phase 3 - adolescent cohort Frenck (2021) Oct 15, 2020 – Jan 12, 2021 Argentina (NR), Brazil (NR), Germany (NR), South Africa (NR), Turkey (NR), USA (29) Industry-funded	Included adolescents 12-15 y and adults 16-25 y who were healthy or with stable pre-existing conditions Exclusions: medical history of SARS-CoV-2 infection or Covid-19 diagnosis; treatment with immunosuppressive	BNT162b2 (Pfizer-BioNTech) 2 doses 21 d apart 30 mcg per 0.3 ml dose Randomized: 12-15 y: 1,134 Dose 1: 1,131 Dose 2: 1,124 16-25 y: 1,875 Dose 1: 1,869	Saline placebo 2 doses 21 d apart 0.3 ml per dose Randomized: 12-15 y: 1,130 Dose 1: 1,129 Dose 2:1,117	Total randomized: 12-15 y: 2,264 16-25 y: 3,788 Total safety population: 12-15 y: 2,260 16-25 y: 1,098 (subset with e-diary data) Male 51% White 86% Baseline SARS-CoV-2:	Solicited local and systemic AEs during 7 d following each injection; **Unsolicited AEs** for 1 mo after dose 1 and SAEs for 6 mos after dose 2. MedDRA v23.1 classification.	12-15 y: Safety analysis included all participants who received at least one injection. 16-25 y: subset of participants who received an e-diary to record reactogenicity events	Myocarditis/pericarditis: 0

Trial name; Author (year); Country (number of sites); Dates of enrolment Funding	Eligibility, Randomization & Blinding	Study Arms		Baseline Demographics	Outcome(s); Safety Assessment	Analysis	Results
		Vaccine arm	Placebo arm				
	therapy; diagnosed with immunocompromising condition Randomized 1:1; web-based system Study personnel evaluating safety were blinded to group assignments	Dose 2: 1,826 Withdrawals: 12-15 y After dose 1: 7 After dose 2: 0 16-25 y After dose 1: 43 After dose 2: 20	16-25 y: 1,913 Dose 1: 1,906 Dose 2: 1,836 Withdrawals: 12-15 y After dose 1: 12 After dose 2: 1 16-25 y After dose 1: 70 After dose 2: 22	Positive: 12-15 y: 93 (4.1%), similar between arms 16-25 y: 64 (5.8%), similar between arms	Unblinded safety data reviewed by independent data and safety monitoring board; ongoing for 2 y after dose 2.		
C4591001 Trial, Phase 2/3 Polack (2021, primary publication) & Thomas (2021) Jul 27, 2020 – October 29, 2020 Argentina (1), Brazil (2), Germany (6), South Africa (4), Turkey (9), USA (130) Industry-funded	Included participants ≥16 y, healthy or with stable pre-existing conditions Exclusions: medical history of SARS-CoV-2 infection or Covid-19 diagnosis; treatment with immunosuppressive therapy; diagnosed with immunocompromising condition Randomized 1:1; web-based system Study personnel evaluating safety were blinded to group assignments; unblinded follow-up started Dec 2020	BNT162b2 (Pfizer-BioNTech) 2 doses 21 d apart 30 mcg per 0.3 ml dose Randomized: 22,085 Dose 1: 22,030 Dose 2: 21,759 Safety population: 21,926 Withdrawals: After dose 1: 271 After dose 2: 167	Saline placebo 2 doses 21 d apart 0.3 ml dose Randomized: 22,080 Dose 1: 22,030 Dose 2: 21,650 Safety population: 21,921 Withdrawals: After dose 1: 380 After dose 2: 273	Total randomized: 44,165 Total safety population: 43,847 Male 50.9% Median age 51.0 y 16-55 y 59.4% >55 y 40.6% White 82.0% Congestive heart failure 0.5% Myocardial infarction 1.0% Any malignancy 3.6% Rheumatic disease 0.3% AIDS/HIV 0.5% Baseline SARS-CoV-2 status: Positive: 1,405 (3.2%), similar between arms Missing: 277 (0.6%), similar between arms	Solicited local and systemic AEs during 7 d after each injection; **Unsolicited AEs** and SAEs for 1 mo and 6 mos after dose 2, respectively. MedDRA v23.1 classification; Unblinded safety data reviewed by independent data and safety monitoring board; ongoing for 2 y after second dose.	Safety analysis included all participants who received at least one injection irrespective of follow-up time.	**Myocarditis:** 0
ENSEMBLE Trial, Phase 3 Sadoff (2021) Sep 21, 2020 – Jan 22, 2021	Adults ≥18 y, healthy or with stable pre-existing conditions; excluded those who received chronic/recurrent	Ad26.COV2.S (Janssen) 1 dose 5×10^{10} vp per 0.5 ml dose Randomized: 21,895	Saline placebo 1 dose x 0.5ml Randomized: 21,888	Total randomized: 44,325 Total safety population: 43,783 Male 54.9%	Solicited local and systemic AEs 7 d after injection (for subset of 6,000 participants); **Unsolicited SAEs** up to 28 d after injection,	Safety analysis included all participants who received injection	**Pericarditis:** 1 (<0.1%) vaccine vs. 0 placebo

Trial name; Author (year); Country (number of sites); Dates of enrolment Funding	Eligibility, Randomization & Blinding	Study Arms		Baseline Demographics	Outcome(s); Safety Assessment	Analysis	Results
		Vaccine arm	Placebo arm				
Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, USA Industry-funded	systemic corticosteroids, or antineoplastic and immunomodulating agents or radiotherapy in prior 6 mo before study vaccine and during study, or are pregnant Randomized 1:1, stratified by site, age, and being at risk for severe Covid-19 based on pre-existing risk factors; interactive web response system Participants and study personnel (including HCW administering vaccine) blinded until either discontinuation or an event	Safety population: 21,895 Withdrawals: 49	Safety population: 21,888 Withdrawals: 96	Median age 52 y White 58.7% Serious heart condition 2.3% Immunocompromised from blood transplant, immune deficiencies, use of corticosteroids or other immunosuppressing medicines 0.2% Immunocompromised from organ transplant <0.1% Baseline SARS-CoV-2 status: Positive: 4,217 (9.6%), similar between arms Missing: 1,271 (2.9%), similar between arms	MAAEs until 6 mos after vaccination, and MAAEs leading to study withdrawal Independent data and safety monitoring board reviewed unblinded safety data.		
AZD1222 Trial, Phase 3 Falsey (2021) Aug 28, 2020 – Jan 15, 2021 Chile, Peru, USA (88 total) Industry-funded	Included adults ≥18 y, with stable pre-existing conditions, at high risk for exposure to SARS-CoV-2 and at increased risk for severe Covid-19 Exclusions: history of SARS-CoV-2 infection; confirmed or suspected immunodeficiency, or with significant disease; pregnant or breastfeeding	AZD1222 (AstraZeneca) 2 doses 4 wks apart 5 x 10^{10} vp per dose Randomized: 21,635 Dose 1: 21,583 Dose 2: 20,769 Safety population: 21,587 Withdrawals: After dose 1: 283 After dose 2: 228	Saline placebo 2 doses 4 wks apart Randomized: 10,816 Dose 1: 10,769 Dose 2: 9951 Safety population: 10,792 Withdrawals: After dose 1: 240 After dose 2: 258	Total randomized: 32,451 Total safety population: 32,379 Male 55.6% Mean age: 50.2 y ≥18-64 y 77.6% ≥65 y 22.4% White 79.0% Serious heart condition 3.3% Cancer 6.5% Immunocompromised due to solid organ transplantation <0.1% HIV infection 1.6%	Solicited local and systemic AEs 7 d after each injection; **Unsolicited AEs** up to 28 d after injection, SAEs, MAAEs, and MEs of special interest up to 730 d after informed consent	Safety analysis included all participants who received at least one injection.	Myocarditis/pericarditis: 0

Trial name; Author (year); Country (number of sites); Dates of enrolment Funding	Eligibility, Randomization & Blinding	Study Arms		Baseline Demographics	Outcome(s); Safety Assessment	Analysis	Results
		Vaccine arm	Placebo arm				
	Randomized 2:1, stratified by age; method NR Group assignment unblinded for 7,635 (35.3%) AstraZeneca and 4,157 (38.4%) placebo participants, after the second dose.			Baseline SARS-CoV-2 status: Positive: 915 (2.8%), similar between arms Missing/not performed: 575 (1.8%), similar between arms			
AZD1222 **Phase 1/2/3, pooled analysis** Voysey (2021a; primary publication) & Voysey (2021b) Apr 23, 2020 – Dec 6, 2020 Brazil (6), South Africa (8), UK (5+19) Industry-funded	Adults ≥18 y, healthy or with stable pre-existing conditions, or at risk of exposure (health and social care setting workers, 58.5%) Exclusions: confirmed or suspected immunosuppressive or immunodeficiency state; current diagnosis of cancer; pregnant or breastfeeding Randomized 1:1, stratified by study site and study group; secure web platform Single blind (Brazil, UK); double blind (South Africa) - study personnel and participants blinded, but pharmacist preparing vaccines unblinded	AZD1222 (AstraZeneca) 2 doses 4-12 wks apart $2.2\text{-}6.5 \times 10^{10}$ vp per 0.5ml dose, 2 Randomized: 12,408 Safety population: 12,282 (after exclusion of 52 participants in HIV cohort) Withdrawals NR	Meningococcal ACWY vaccine (UK) OR Meningococcal ACWY vaccine (dose 1) + saline placebo (dose 2; Brazil) OR Saline placebo (South Africa) For all: 2 doses 4-12 wks apart 0.5 ml dose Randomized: 12014 Safety population: 11,962 (after exclusion of 52 participants in HIV cohort) Withdrawals NR	Total randomized: 24,422 Total safety population: 24,244 Male 44% Median age NR 18-55 y 82.5% 56-69 y 11.3% 70+ y 6.1% White 75.2% Cardiovascular disorder (includes cardiac diseases) 12.3% Baseline SARS-CoV-2 status: Positive: 731 (3.0%), similar between arms Missing: 200 (0.8%), similar between arms Sensitivity analyses for participants positive for SARS-CoV-2 at baseline and using ITT were similar to main results	Solicited local and systemic AEs for 7 d after each injection observed by investigator or reported by participant; **Unsolicited AEs** through to 28 d after each injection, and SAEs and AEs of special interest throughout study period from last dose to 364 d. MedDRA v23.1 classification, severity classified according to FDA toxicity rating scales. Independent data monitoring safety board reviewed safety data on an ongoing basis	Safety analysis included all participants who received at least one injection.	**Pericarditis:** 1 vaccine (0 grade 3 severity) vs. 2 (1 grade 3 severity) controls

AE: adverse event(s); LTFU: lost to follow-up; MAAE: medically-attended adverse event(s); mcg: microgram(s); mo: month(s); no.: number; NR: not reported; SAE: serious adverse event(s); vp: viral particle(s); wks: weeks; y: year(s)

Table A5. Risk of bias assessments for randomized controlled trials (question 1)

Vaccine (Trial name)	Randomization	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall assessment of risk of bias
Moderna (Teen COVE Trial) Ali 2021	Low	Low	Some concerns	Low	Low	Some concerns
Moderna (COVE Trial) Baden 2021 & El-Sahly 2021	Low	Low	Low	Low	Low	Low
Pfizer-BioNTech (Teen C4591001 Trial) Frenck 2021	Low	Low	Low	Some concerns	Low	Some concerns
Pfizer-BioNTech (C4591001 Trial) Polack 2021 & Thomas 2021	Low	Low	Low	Some concerns	Low	Some concerns
AstraZeneca (AZD1222 Trial) Falsey 2021	Low	Some concerns	Some concerns	Low	Low	Some concerns
AstraZeneca (Oxford Vaccine Trial) Voysey 2021a & 2021b	Low	Some concerns	Some concerns	Low	Low	Some concerns
Janssen (ENSEMBLE Trial) Sadoff 2021	Low	Low	Low	Low	Low	Low

Appendix 4. Summary of Findings from the Randomized Controlled Trials (question 1)

Age category	Age, risk status	Country (number of sites)	Vaccine (risk interval)	Number of participants in safety analysis	Number of participants with outcome	Conclusion	GRADE
	Myocarditis						
12-17 y	12-17 y	USA (26) Ali	Moderna (28 d)	3,726	0	RCTs provided very uncertain evidence about the incidence of myocarditis after receipt of Moderna in youth 12-17 years of age.	Very low [a]
Adolescents and young adults	12-25 y	USA (29) Frenck	Pfizer (21 d)	3,357	0 (assumed, NR)	RCTs provided very uncertain evidence about the incidence of myocarditis after receipt of Pfizer in adolescents and young adults.	Very low [a]
Adolescents and adults	≥16 y	Argentina (1), Brazil (2), Germany (6), South Africa (4), Turkey (9), USA (130) Polack/Thomas	Pfizer (21 d)	43,847	0	RCTs provided very uncertain evidence about the incidence of myocarditis after receipt of Pfizer in adolescents and adults.	Very low [b]
Adults	≥18 y, at risk of exposure to SARS-CoV-2 and/or increased risk for severe Covid-19	USA (99) Baden/El-Sahly	Moderna (28 d)	30,351	0	RCTs provided very uncertain evidence about the incidence of myocarditis after receipt of currently available vaccine by adults	Very low [b]
	≥18 y, at high-risk of exposure to SARS-CoV-2 and increased risk for severe Covid-19	Chile, Peru, USA (88 altogether) Falsey	AstraZeneca (28 d)	32,379	0 (assumed, NR)		
	≥18 y, 59% at risk of exposure to SARS-CoV-2	Brazil (6), South Africa (8), UK (24) Voysey	AstraZeneca (4-12 w k)	24,244	0 (assumed, NR)		
	≥18 y	Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, USA (number of sites NR)	Janssen (single dose)	43,783	0 (assumed, NR)		

Age category	Age, risk status	Country (number of sites)	Vaccine (risk interval)	Number of participants in safety analysis	Number of participants with outcome	Conclusion	GRADE
		Sadoff					
	Pericarditis						
12-17 y	12-17 y	USA (26) Ali	Moderna (28 d)	3,726	0	RCTs provided very uncertain evidence about the incidence of pericarditis after receipt of Moderna in youth 12-17 years f age.	Very low [a]
Adolescents and young adults	12-25 y	USA (29) Frenck	Pfizer (21 d)	3,357	0 (assumed, NR)	RCTs provided very uncertain evidence about the incidence of pericarditis after receipt of Pfizer in adolescents and young adults.	Very low [a]
Adolescents and adults	≥16 y	Argentina (1), Brazil (2), Germany (6), South Africa (4), Turkey (9), USA (130) Polack/Thomas	Pfizer (21 d)	43,847	0 (assumed, NR)	RCTs provided very uncertain evidence about the incidence of pericarditis after receipt of Pfizer in adolescents and adults.	Very low [b]
Adults	≥18 y, at risk of exposure to SARS-CoV-2 and/or increased risk for severe Covid-19	USA (99) Baden/El-Sahly	Moderna (28 d)	30,351	2 (68 d & 73 d post-second dose) vs. 2 placebo	RCTs provided very uncertain evidence about the incidence of pericarditis after receipt of currently available vaccine by adults	Very low [b]
	≥18 y, at high-risk of exposure to SARS-CoV-2 and increased risk for severe Covid-19	Chile, Peru, USA (88 altogether) Falsey	AstraZeneca (28 d)	32,379	0 (assumed, NR)		
	≥18 y, 59% at risk of exposure to SARS-CoV-2	Brazil (6), South Africa (8), UK (24) Voysey	AstraZeneca (4-12 w k)	24,244	1 vs. 2 controls		
	≥18 y	Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa,	Janssen (single dose)	43,783	1 (<0.1%) vs. 0 placebo		

Age category	Age, risk status	Country (number of sites)	Vaccine (risk interval)	Number of participants in safety analysis	Number of participants with outcome	Conclusion	GRADE
		USA (number of sites NR) Sadoff					

GRADE Explanations:

[a] Rated down for indirectness since results by sex are expected to differ; rated down twice for high imprecision for these very rare events.

[b] Rated down twice for indirectness and for imprecision for these very rare events.