02 September 2021
EMA/PRAC/326194/2021
Pharmacovigilance Risk Assessment Committee (PRAC)

Signal assessment report on myocarditis and pericarditis with Spikevax (previously COVID-19 Vaccine Moderna)

EPITT no: 19713

Procedure no: SDA 033.1

Confirmation assessment report	09 June 2021
Adoption of first PRAC recommendation	10 June 2021
Preliminary assessment report on additional data	29 June 2021
Deadline for comments	01 July 2021
Updated rapporteur assessment report	05 July 2021
Adoption of second PRAC recommendation	08 July 2021
Preliminary assessment report on additional data	18 August 2021
Deadline for comments	23 August 2021
Updated rapporteur assessment report	26 August 2021
Adoption of third PRAC recommendation	02 September 2021

Note

Assessment report as adopted by the PRAC with all information of a (commercially) confidential nature deleted and personal data anonymised.

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Administrative information

Active substance(s) (invented name)	Covid-19 mRNA Vaccine Moderna (Cx-024414)
Strength(s)	<Text> *[Only if relevant to the signal]*
Pharmaceutical form(s)	<Text> *[Only if relevant to the signal]*
Route(s) of administration	<Text> *[Only if relevant to the signal]*
Indication(s)	<Text> *[Only if relevant to the signal]*
Marketing authorisation holder(s)	<Name(s)>

Authorisation procedure *[Tick the appropriate box(es) below.]*	
☒	Centralised
☐	Mutual recognition or decentralised
☐	National

Adverse event/reaction:[1]	Myocarditis and pericarditis

Signal validated by:	EMA
Date of circulation of signal validation report:	08 June 2021
Signal confirmed by:	DK
Date of confirmation:	09 June 2021
PRAC Rapporteur appointed for the assessment of the signal:	Hans Christian Siersted Anette Kirstine Stark

[1] Please use MedDRA terminology whenever possible

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1. Background

COVID-19 Vaccine Moderna received a conditional marketing authorisation in the EU on 6 January 2021 for active immunisation against COVID-19 in individuals 18 years of age and older. It contains mRNA encapsulated in lipid nanoparticles. The mRNA encodes for the full-length SARS-CoV-2 spike protein modified with 2 proline substitutions within the heptad repeat 1 domain (S-2P) to stabilise the spike protein into a prefusion conformation.

Myocarditis, also known as inflammatory cardiomyopathy, is inflammation of the heart muscle. Symptoms can include shortness of breath, chest pain, decreased ability to exercise, and an irregular heartbeat. The duration of problems can vary from hours to months. Complications may include heart failure due to dilated cardiomyopathy or cardiac arrest. On 30 May, Brighton Collaboration issued an interim case definition for myocarditis, available from the link: https://brightoncollaboration.us/myocarditis-case-definition-update/.

Pericarditis is inflammation of the pericardium (the fibrous sac surrounding the heart). Symptoms typically include sudden onset of sharp chest pain, which may also be felt in the shoulders, neck, or back. The pain is typically less severe when sitting up and more severe when lying down or breathing deeply.

2. Initial evidence

2.1. Signal validation

As of 26 May 2021, in Eudravigilance were received 16 cases in the combined search for HLT Infectious myocarditis and HLT Non-infectious myocarditis in the EEA. Out of these cases, 69% were in males. There were no fatal cases. The median age of the vaccinees was 26 years.

There were 9 EEA case reports of myocarditis with COVID-19 Vaccine Moderna in people under 30 years old. Six patients were males, 3 were females. 3 cases were from Germany, 1 from France, 1 from Italy, 1 from Lithuania, 1 from The Netherlands, 1 from Spain and 1 from Sweden. The 9 cases were matched to the latest Brighton Collaboration criteria for myocarditis [1, 2]. 6 cases were assessed as level 1-3 and 3 as level 4-5. In 4 cases event occurred after the first dose, in 3 – after the 2nd dose. There was 1 case mentioning biopsy in case narrative ("Diagnosis by laboratory, ECG, echocardiography, cardio-MRI, and myocardial biopsy" – but no more details provided). In 2 cases patients had medical history of Covid-19 infection which could be considerate as a potential confounder.

An Observed/Expected analysis was performed on different risk periods: 14d and 42d. Cases where TTO > 42 days were excluded from OE analysis. Cases where TTO was missing were assigned to the shortest risk period.

The Incidence rates for myocarditis only were obtained from IMRD UK (primary care healthcare records), noting the following. The myocarditis diagnosis is likely to be made in secondary care, so there is a risk of underreporting in primary care records. Rates from ACCESS databases that include both primary and secondary care are for myocarditis and pericarditis combined, hence they couldn't be used. Sensitivity analysis with rates from IMS France, which provides a higher estimate of the risk in the younger population (in males ~10/100,000 vs ~5/100,000 of IMRD UK).

Exposure data: age stratification from ECDC (up to 16 May), gender distribution from MSs end of April 2021. Observed cases from EV: HLT Infectious myocarditis and HLT Noninfectious myocarditis (incl. myopericarditis).

The results showed an elevated OE ratio (> 5) in the male 18-24 age group, statistically significant. The OE ratio was > 1 in the male 25-49 age group. In the female 18-24 age group, OE ratio was > 1.

Similar conclusions were drawn from the sensitivity analysis (using higher incidence rates IMS-FR -> higher expected number of cases; OE ratio > 2.5 in male 18-24).

Caveats of the analysis: The OE analysis should be treated as a tool for signal detection rather than signal validation; the comparison of EV event rates with those observed in healthcare records should be interpreted cautiously, for contextualisation only; the extent of underreporting in EV is not known; As 18 -24 is a smaller age group, with a more limited number of doses received, it is more susceptible to extreme results.

Taking into consideration the above initial evidence of myocarditis, with cases revealing a plausible temporal association to COVID-19 Vaccine Moderna, it is considered that the signal deserves further assessment. It is suggested that the MAH for COVID-19 Vaccine Moderna (Moderna Biotech Spain, S.L.) should provide answers to a LoQ on myocarditis and pericarditis. The MAH should discuss the need to update the product information and risk management plan and submit proposals as appropriate.

References:

1. Myocarditis CD_v.1.4.2_28.May.2021.xlsx (brightoncollaboration.us)

2. Myocarditis-decision-tree_brief-format_-5-28-2021_Final_forPosting-1.pdf (brightoncollaboration.us)

2.2. Signal confirmation

The search in EVDAS performed on the 26 May 2021, identified 16 cases related to myocarditis. 6 of these cases were assessed as level 1-3 (definitive/probable/possible case of diagnostic certainty) according to the latest Brighton Collaboration criteria for myocarditis. The O/E analysis showed an elevated O/E ratio (>5) in the male 18-24 age group that were statistically significant.

In the 4th monthly safety report for the Moderna vaccine, there were identified 4 WHO possible cases and 1 WHO probable case for myocarditis and 9 WHO possible cases for pericarditis. However, the myocarditis cases were not assessed by the Brighton case definition for myocarditis. Furthermore, in the age- and gender stratified O/E analyses for the myocarditis events, the observed rates were close to equal or slightly above the expected rates for in males aged 18-29 and males aged 30-39 (rate ratio 0.73 when comparing to the low background IRs. This could indicate a potential increased risk in these populations, as some degree of underreporting is likely (Please refer to Annex 1 for the assessment of myocarditis and pericarditis in the 4th MSSR for Moderna).

Considering the above signal description and the available evidence from the 4th monthly safety report for Moderna, the signal needs further evaluation. The signal is confirmed.

2.3. Proposed recommendation

The MAH (Moderna) is requested to provide separate analysis of myocarditis and pericarditis as described in the LoQs below.

Myocarditis LoQ

The MAH should provide a cumulative review of all cases of myocarditis and cases reporting both myocarditis and pericarditis (from all sources). The review should include case ascertainment (as per Brighton collaboration case definition), diagnostic work-up, causality assessment and outcome of the events (e.g. hospitalization, life-threatening, or death) for each case report. The MAH should ensure that all relevant cases are processed (not in backlog) and included in the review. The MAH should use a DLP as recent as possible, but at least up to 31st May 2021.

The review should include the following:

- A tabulated overview of all cases; stratified by
    - Age, by 10-year strata (10-19, 20-29, …)
    - Gender
    - Time to onset (TTO)
    - Dose (1st or 2nd)
    - WHO-UMC causality
    - Brighton collaboration case definition (https://brightoncollaboration.us/myocarditis-case-definition-update/): Definitive/Probable/Possible
- For the causality assessment of the cumulative cases, the MAH is requested to present the following:
    - A summary overview of the cases for which the causality (as per WHO-UMC causality assessment system) is considered at least WHO Possible or WHO Probable. The summary overview should include the following details for each case:
        - Case ID (Eudravigilance no. if possible)
        - Age/gender
        - TTO, and whether following 1st dose/2nd dose
        - Associated clinical signs/co-reported PTs.
        - Brighton collaboration case definition: Definitive/Probable/Possible
        - Any underlying condition(s) (including COVID-19), other medical confounders or risk factors present (including latency/TTO as applicable)
        - Confounding medications (including latency/TTO as applicable)
        - Outcome
        - WHO-UMC causality assessment
    - The cases with an "Unlikely" WHO-UMC causal association in a tabulated format. The table should include, but not restricted to, the following information for each case:
        - Case ID (Eudravigilance no. if possible)
        - Age/gender
        - TTO, and whether following 1st dose/2nd dose

- Brighton collaboration case definition: Definitive/Probable/Possible (myocarditis cases only)
- Any underlying condition(s) (including COVID-19), other medical confounders or risk factors present (including latency/TTO as applicable)
- Confounding medications (including latency/TTO as applicable)
- Outcome

- The review should explore possible risk factors, taking into account the gender, age, and dose distribution of reported cases. Specifically, the MAH is requested to comment on the number of cases occurring after the 2nd dose as compared to the 1st dose, also considering the differences in exposure for these two groups. The MAH should discuss whether any patterns or trends can be identified concerning risk factors.
- Specific O/E analyses should be performed for the 1st dose and 2nd dose receivers respectively. Thus, for the cumulative review, O/E analyses should be stratified by age, gender and dose (1st or 2nd). For the analyses, the MAH should clearly state and justify the background rates used. The MAH should retrieve the most relevant background rates and take the source of the cases into consideration. Several risk windows should be considered (eg. 7, 14 and 21 days). In the O/E analysis, the MAH is requested to perform adjustment for underreporting, backlog of case handling and sensitivity analysis.
- The MAH should further evaluate and discuss potential mechanisms:
  - The MAH should consider multisystem inflammatory syndrome (MIS) as an alternative etiology upon evaluation of the myocarditis cases. The MAH should discuss the immunologic mechanism of multisystem inflammatory syndromes (MIS)-induced myocarditis following COVID-19, and if any parallels can be drawn to the immunologic reactions following vaccination.
  - The MAH should review the published literature, and present and discuss relevant publications concerning plausible mechanisms of myocarditis following the vaccination, concerning both COVID-19 vaccine Moderna and vaccines in general.
  - The MAH is requested to comment and discuss the potential mechanism of vaccine triggered autoimmune reaction as hypothesized by Garcia et al. in a literature case report concerning a case of myocarditis after 2nd dose in a 39-year-old male physician with a past medical history of auto-immune conditions. (Bautista García J,et al.Acute myocarditis after administration of theBNT162b2 vaccine against COVID-19. Rev Esp Cardiol. 2021. https://doi.org/10.1016/j.rec.2021.04.005)
- In conclusion, the MAH should discuss the need to update the product information and risk management plan, including relevant risk minimisation measures.

Pericarditis LoQ

The MAH should provide a cumulative review of all cases of pericarditis (from all sources). The review should include case ascertainment, diagnostic work-up, causality assessment and outcome of the events (e.g. hospitalization, life-threatening, or death) for each case report. The MAH should ensure that all relevant cases are processed (not in backlog) and included in the review. The MAH should use a DLP as recent as possible, but at least up to 31st May 2021.

The review should include the following:

- A tabulated overview of all cases; stratified by
    - Age, by 10-year strata (10-19, 20-29, …)
    - Gender
    - Time to onset (TTO)
    - Dose (1st or 2nd)
    - WHO-UMC causality
- For the causality assessment of the cumulative cases, the MAH is requested to present the following:
    - A summary overview of the cases: 1) for which the causality (as per WHO-UMC causality assessment system) is considered at least WHO Possible or WHO Probable. The summary overview should include the following details for each case:
        - Case ID (Eudravigilance no. if possible)
        - Age/gender
        - TTO, and whether following 1st dose/2nd dose
        - Associated clinical signs/co-reported PTs.
        - Any underlying condition(s) (including COVID-19), other medical confounders or risk factors present (including latency/TTO as applicable)
        - Confounding medications (including latency/TTO as applicable)
        - Outcome
        - WHO-UMC causality assessment
    - The cases with an "Unlikely" WHO-UMC causal association in a tabulated format. The table should include, but not restricted to, the following information for each case:
        - Case ID (Eudravigilance no. if possible)
        - Age/gender
        - TTO, and whether following 1st dose/2nd dose
        - Any underlying condition(s) (including COVID-19), other medical confounders or risk factors present (including latency/TTO as applicable)
        - Confounding medications (including latency/TTO as applicable)
        - Outcome
- The review should explore possible risk factors, taking into account the gender, age, and dose distribution of reported cases. Specifically, the MAH is requested to comment on the number of cases occurring after the 2nd dose as compared to the 1st dose, also considering the differences in exposure for these two groups. The MAH should discuss whether any patterns or trends can be identified concerning risk factors.
- Specific O/E analyses should be performed for the 1st dose and 2nd dose receivers respectively. Thus, for the cumulative review, O/E analyses should be stratified by age, gender and dose (1st or 2nd). For the analyses, the MAH should clearly state and justify the background rates used. The MAH should retrieve the most relevant background rates and take the source of the cases into consideration. Several risk windows should be considered (eg. 7, 14 and 21 days). In the O/E

analysis, the MAH is requested to perform adjustment for underreporting, backlog of case handling and sensitivity analysis.

- The MAH should further evaluate and discuss potential mechanisms:
    - The MAH should consider multisystem inflammatory syndrome (MIS) as an alternative etiology upon evaluation of the pericarditis cases. The MAH should discuss the immunologic mechanism of multisystem inflammatory syndromes (MIS)-induced pericarditis following COVID-19, and if any parallels can be drawn to the immunologic reactions following vaccination.
    - The MAH should review the published literature, and present and discuss relevant publications concerning plausible mechanisms of pericarditis following the vaccination, concerning both COVID-19 vaccine Moderna and vaccines in general.
- In conclusion, the MAH should discuss the need to update the product information and risk management plan, including relevant risk minimisation measures.

2.4. Adopted PRAC recommendation

Having considered all available evidence, the PRAC has agreed that MAH for Covid-19 mRNA Vaccine Moderna (Cx-024414) (Moderna Biotech Spain, S.L.) should provide by 21 June 2021 responses to the list of questions described below (as two separate analyses for myocarditis and pericarditis):

List of questions for myocarditis

The MAH should provide a cumulative review of all cases of myocarditis and cases reporting both myocarditis and pericarditis (from all sources). The review should include case ascertainment (as per Brighton collaboration case definition), diagnostic work-up, causality assessment and outcome of the events (e.g. hospitalization, life-threatening, or death) for each case report. The MAH should ensure that all relevant cases are processed (not in backlog) and included in the review. The MAH should use a DLP as recent as possible, but at least up to 31st May 2021.

The review should include the following:

1. A tabulated overview of all cases; stratified by
    - Age, by strata of 12–15, 16–19, 20-24, 25-29, 30-39, and thereafter 10 years intervals
    - Gender
    - Time to onset (TTO)
    - Dose (1st or 2nd)
    - WHO-UMC causality
    - Brighton collaboration case definition (https://brightoncollaboration.us/myocarditis-case-definition-update/): Definitive/Probable/Possible

2. For the causality assessment of the cumulative cases, the MAH is requested to present the following:

- A summary overview of the cases for which the causality (as per WHO-UMC causality assessment system) is considered at least WHO Possible or WHO Probable. The summary overview should include the following details for each case:

- Case ID (Eudravigilance no. if possible)
- Age/gender
- TTO, and whether following 1st dose/2nd dose
- Associated clinical signs/co-reported PTs.
- Brighton collaboration case definition: Definitive/Probable/Possible
- Any underlying condition(s) (e.g. specific medical history such as autoimmune diseases, previous COVID-19 disease), other medical confounders or risk factors present (including latency/TTO as applicable)
- Confounding medications (including latency/TTO as applicable)
- Outcome
- WHO-UMC causality assessment

- The cases with an "Unlikely" WHO-UMC causal association in a tabulated format. The table should include, but not restricted to, the following information for each case:
  - Case ID (Eudravigilance no. if possible)
  - Age/gender
  - TTO, and whether following 1st dose/2nd dose
  - Brighton collaboration case definition: Definitive/Probable/Possible (myocarditis cases only)
  - Any underlying condition(s) (including COVID-19), other medical confounders or risk factors present (including latency/TTO as applicable)
  - Confounding medications (including latency/TTO as applicable)
  - Outcome

3. The review should explore possible risk factors, taking into account the gender, age, and dose distribution of reported cases. Specifically, the MAH is requested to comment on the number of cases occurring after the 2nd dose as compared to the 1st dose, also considering the differences in exposure for these two groups. The MAH should discuss whether any patterns or trends can be identified concerning risk factors.

4. Specific observed/expected (O/E) analyses should be performed for the 1st dose and 2nd dose receivers respectively. Thus, for the cumulative review, O/E analyses should be stratified by age, gender and dose (1st or 2nd). For the analyses, the MAH should clearly state and justify the background rates used. The MAH should retrieve the most relevant background rates and take the source of the cases into consideration. Several risk windows should be considered (14 and 21 days). In the O/E analysis, the MAH is requested to perform adjustment for underreporting, backlog of case handling and sensitivity analysis.

5. The MAH should further evaluate and discuss potential mechanisms:

- The MAH should consider multisystem inflammatory syndrome (MIS) as an alternative etiology upon evaluation of the myocarditis cases. The MAH should discuss the immunologic mechanism of multisystem inflammatory syndromes (MIS)-induced myocarditis following COVID-19, and if any parallels can be drawn to the immunologic reactions following vaccination.

- The MAH should review the published literature, and present and discuss relevant publications concerning plausible mechanisms of myocarditis following the vaccination, concerning both COVID-19 vaccine Moderna and vaccines in general.
- The MAH is requested to comment and discuss the potential mechanism of vaccine triggered autoimmune reaction as hypothesized by Garcia et al. in a literature case report concerning a case of myocarditis after 2nd dose in a 39-year-old male physician with a past medical history of auto-immune conditions. (Bautista García J,et al. Acute myocarditis after administration of theBNT162b2 vaccine against COVID-19. Rev Esp Cardiol. 2021. https://doi.org/10.1016/j.rec.2021.04.005)

6. In conclusion, the MAH should discuss the need to update the product information and risk management plan, including relevant risk minimisation measures.

List of questions for pericarditis

The MAH should provide a cumulative review of all cases of pericarditis (from all sources). The review should include case ascertainment, diagnostic work-up, causality assessment and outcome of the events (e.g. hospitalization, life-threatening, or death) for each case report. The MAH should ensure that all relevant cases are processed (not in backlog) and included in the review. The MAH should use a DLP as recent as possible, but at least up to 31st May 2021.

The review should include the following:

1. A tabulated overview of all cases; stratified by

    - Age, by strata of 12–15, 16–19, 20-24, 25-29, 30-39, and thereafter 10 years intervals
    - Gender
    - Time to onset (TTO)
    - Dose (1st or 2nd)
    - WHO-UMC causality

2. For the causality assessment of the cumulative cases, the MAH is requested to present the following:

- A summary overview of the cases: 1) for which the causality (as per WHO-UMC causality assessment system) is considered at least WHO Possible or WHO Probable. The summary overview should include the following details for each case:
    - Case ID (Eudravigilance no. if possible)
    - Age/gender
    - TTO, and whether following 1st dose/2nd dose
    - Associated clinical signs/co-reported PTs.
    - Any underlying condition(s) (e.g. specific medical history such as autoimmune diseases, previous COVID-19 disease, etc.), other medical confounders or risk factors present (including latency/TTO as applicable)
    - Confounding medications (including latency/TTO as applicable)
    - Outcome

    - WHO-UMC causality assessment
- The cases with an "Unlikely" WHO-UMC causal association in a tabulated format. The table should include, but not restricted to, the following information for each case:
    - Case ID (Eudravigilance no. if possible)
    - Age/gender
    - TTO, and whether following 1st dose/2nd dose
    - Any underlying condition(s) (including COVID-19), other medical confounders or risk factors present (including latency/TTO as applicable)
    - Confounding medications (including latency/TTO as applicable)
    - Outcome

3. The review should explore possible risk factors, taking into account the gender, age, and dose distribution of reported cases. Specifically, the MAH is requested to comment on the number of cases occurring after the 2nd dose as compared to the 1st dose, also considering the differences in exposure for these two groups. The MAH should discuss whether any patterns or trends can be identified concerning risk factors.

4. Specific O/E analyses should be performed for the 1st dose and 2nd dose receivers respectively. Thus, for the cumulative review, O/E analyses should be stratified by age, gender and dose (1st or 2nd). For the analyses, the MAH should clearly state and justify the background rates used. The MAH should retrieve the most relevant background rates and take the source of the cases into consideration. Several risk windows should be considered (14 and 21 days). In the O/E analysis, the MAH is requested to perform adjustment for underreporting, backlog of case handling and sensitivity analysis.

5. The MAH should further evaluate and discuss potential mechanisms:

- The MAH should consider multisystem inflammatory syndrome (MIS) as an alternative etiology upon evaluation of the pericarditis cases. The MAH should discuss the immunologic mechanism of multisystem inflammatory syndromes (MIS)-induced pericarditis following COVID-19, and if any parallels can be drawn to the immunologic reactions following vaccination.
- The MAH should review the published literature, and present and discuss relevant publications concerning plausible mechanisms of pericarditis following the vaccination, concerning both COVID-19 vaccine Moderna and vaccines in general.

6. In conclusion, the MAH should discuss the need to update the product information and risk management plan, including relevant risk minimisation measures.

The PRAC will assess the MAH's answers to this List of questions within an accelerated timetable, which would allow for the following PRAC discussion to take place in July 2021 PRAC.

3. Additional evidence

Additional evidence was received in response to the adopted PRAC recommendation and request for information.

Below, a summary of the responses from the MAH is presented.

The terminology in this part of the assessment report will follow the terminology used in the submitted material, and the name: COVID-19 Vaccine Moderna (and not Spikevax) will be used.

3.1. Assessment of additional data

3.1.1. ITEM 1 - MYOCARDITIS

The MAH should provide a cumulative review of all cases of myocarditis and cases reporting both myocarditis and pericarditis (from all sources). The review should include case ascertainment (as per Brighton collaboration case definition), diagnostic work-up, causality assessment and outcome of the events (e.g. hospitalization, life-threatening, or death) for each case report. The MAH should ensure that all relevant cases are processed (not in backlog) and included in the review. The MAH should use an OLP as recent as possible, but at least up to 31st May 2021.

The review should include the following:

A tabulated overview of all cases; stratified by

- *Age, by strata of 12-15, 16-19, 20-24, 25-29, 30-39, and thereafter 10 years intervals*
- *Gender*
- *Time to onset (TTO)*
- *WHO-UMC causality*
- *Dose 1st or 2nd*
- *Brighton collaboration case definition*

(https ://brightoncollaboration. us/myocarditis-case-definition-update/): Definitive/Probable/Possible

Sponsor Response:

As of the end of the reporting period (31 May 2021), a total of 250,275,820 doses of the Moderna COVID-19 mRNA Vaccine had been distributed to 39 countries, with a majority (201,078,720) distributed in the US. As of the end of the reporting period, a total of 155,522,108 doses of the vaccine had been administered, based on information retrieved through the US Centers for Disease Control and Prevention (https://covid.cdc.gov/covid-data- tracker/#vaccinations), the European Centres for Disease Control (https://qap.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#distribution-tab), Health Canada (https://health-infobase.canada.ca/covid-19/vaccination-coverage/), the Swiss Federal Office of Public Health (https://www.covid19.admin.ch/en/epidemiologic/vacc-doses), and Our World in Data (https://ourworldindata.org/covid-vaccinations) (data retrieved on 01 June 2021.

The company clinical database and the global safety database were queried for valid, clinical and spontaneous case reports received from HCP, HA, consumers and literature, cumulative from 18 December 2020 to 31 May 2021, worldwide, reported for the mRNA-1273 vaccine (Moderna COVID-19 vaccine Moderna) using the following Preferred Terms (PTs): "***Viral pericarditis; Pericarditis; Pericarditis infective; Myocarditis; Myocarditis septic; Myocarditis infectious; Viral myocarditis; and Myocarditis post-infection***". The clinical trial data is from the Phase 3 clinical trial mRNA- 1273 P301. As of 31 May 2021, there have been 250,275,820 doses of the mRNA vaccine distributed worldwide.

a. Clinical Trials information

During the Phase 3 pivotal clinical trial of the mRNA-1273 P301, in the safety set, up to 28 days after any vaccination, there were 15,184 participants exposed to the mRNA-1273 vaccine, and 15,166 participants in the placebo arm. There were 6,823 (22.5%) unsolicited treatment- emergent adverse event (TEAEs) reported, 3,234 (21.3%) in the placebo arm, and 3,589 (23.6%) in the mRNA vaccine arm. There were no reported TEAEs of "Myocarditis" in P301. There were three (3) unsolicited TEAE of "Pericarditis" reported in P301; two TEAEs in the Placebo arm, and one in the Vaccine arm of the

safety set in the overall stage after any injection. The 2 events in the placebo arm were reported in the ≥18 to ≤65 years of age, and the event in the vaccination arm was reported in the ≥65 years of age group (Table 1 of the MAH response).

PRAC Rapporteur assessment comment:

In the phase 3 clinical trial, P301, there were no reported TEAEs of myocarditis, and 3 reports of pericarditis; two TEAEs in the Placebo arm, and one in the Vaccine arm.

b. Global Safety Database information: Myocarditis and Myocarditis/Pericarditis (Myo/Pericarditis) Cases

The company global safety database was queried for spontaneous, valid, case reports received from HCP, HA, literature, and consumers, cumulatively (18 December 2020 to 31 May 2021), worldwide, using the PTs of "***Viral pericarditis; Pericarditis; Pericarditis infective; Myocarditis; Myocarditis septic; Myocarditis infectious; Viral myocarditis; and Myocarditis post-infection***".

A review of the spontaneous reports from the company's global safety identified **77** case reports with the PTs of Myocarditis or both Myocarditis and Pericarditis. All of the aforementioned reports were considered serious reports. Most of the reports (68.8%) involved persons under age 40 years, 27.3% were patients >40 years of age, and 3.9% the information was missing (See Table 2).

Table 2. Number and Percentage of Spontaneous Cases of Myocarditis and Myo/Pericarditis Reported by Age for the mRNA-1273 vaccine. Cumulative to 31 May 2021

Age in Years	Number of Reports	%
12-15	0	0
16-19*	6	8
20-24	21	27
25-29	12	16
30-39	14	18
40-49	9	12
50-59	5	6
60-69	5	6
70-79	2	3
80-89	0	0
Not reported	3	4
Total	77	100

* No cases age 16 or 17 years

Most of the reports of Myocarditis or Myo/Pericarditis concerned males (75%).

Table 3. Number and Percentage of Spontaneous Cases of Myocarditis and Myo/Pericarditis Reported by Gender for the mRNA-1273 vaccine. Cumulative to 31 May 2021

Gender	Number	%
Male	58	75
Female	17	22
Missing	2	3
Total	77	100

The majority of the reports (63.6%) had onset of the myocarditis or myo/pericarditis within three days following last vaccination (See Table 4). Occurrence following dose 1 was noted in 35% of reports, following dose 2 in 53%, and dose number was not reported in 9% of the cases (See Table 5).

Table 4. Number and Percentage of Spontaneous Cases of Myocarditis and Myo/Pericarditis Reported by Time-To-Onset (TTO) for the mRNA-1273 vaccine. Cumulative to 31 May 2021

TTO	Number of Cases	%
≤1 day	21	27
2-3 days	28	36
4-7 days	11	14
8-29 days	8	10
≥30 days	1	1
Unknown	8	10
Total	77	100

Table 5. Number and Percentage of Spontaneous Cases of Myocarditis and Myo/Pericarditis Reported by Dose Number for the mRNA-1273 vaccine.

Cumulative to 31 May 2021

Dose Number	Number	%
1st dose	27	35
2nd dose	41	53
Not reported	9	12
Total	77	100

PRAC Rapporteur assessment comment:

The MAH has used a DLP up to 31 May 2021. The search strategy is similar to the prior search presented in MSSR 4 "Viral pericarditis; Pericarditis; Pericarditis infective; Myocarditis; Myocarditis septic; Myocarditis infectious; Viral myocarditis; and Myocarditis post-infection"

A search on all myocarditis and pericarditis related PT's was made in Eudravigilance confirmed that the search strategy was sufficient in terms of retrieving all relevant myocarditis cases, since all cases up to DLP 31 May 2021 were coded with the PT 'myocarditis'. In regard to the pericarditis cases, a small number of cases were coded with different PT's than included in the above-mentioned search strategy, for the PT's 'Pericarditis constrictive' and 'Pleuropericarditis' 2 and 3 cases were identified, respectively.

Furthermore, a search was made in Eudravigilance to identify the number of cases of myocarditis and pericarditis reported after DLP (31/5-21). This revealed an increase in reported cases from 73 to 152 cases of pericarditis in the interval from DLP up to 24 June 2021 and from 74 to 197 cases of myocarditis in the same interval, possibly due to enhanced reporting due to media attention.

The MAH has identified 77 case reports with the PTs Myocarditis or both Myocarditis and Pericarditis. Most of the reports (68.8%) involved persons under age 40 years, and **35% of cases were patients under the age of 25**. This should be held up against the administration of the vaccine in this age group, which in the last MSSR was, estimated to be 11.6% in the age group <25 in the US, and only 2.8% of the same age group in EU/EEA. It is acknowledged that the incidence of myocarditis in the background differ between age groups, which is further taken into consideration in the age stratified O/E analyses (section 3.1.4)

The majority of cases were in men (75%). Myocarditis is more commonly reported in men, which is further discussed by the MAH in section 3.1.3, however this risk factor is also taken into account in the O/E analyses stratified into age and sex.

The cases are further characterized by a short TTO; 63% of the cases had a reported event onset within 3 days post vaccination.

Importantly, the majority of cases were reported after the 2nd dose; 53% compared to 35% of 1st dose (12% unknown). This is further discussed in section 3.1.3 and 3.1.4.

3.1.2. ITEM 2 – causality assessment

For the causality assessment of the cumulative cases, the MAH is requested to present the following:

A summary overview of the cases for which the causality (as per WHO-UMC causality assessment system) is considered at least WHO Possible or WHO Probable. The summary overview should include the following details for each case:

- *Case ID (Eudravigilance no. if possible)*
- *Age/gender*
- *TTO, and whether following pt dose/2nd dose*
- *Associated clinical signs/co-reported PTs.*
- *Brighton collaboration case definition: Definitive/Probable/Possible*
- *Any underlying condition(s) (e.g. specific medical history such as autoimmune diseases, previous COVID-19 disease), other medical confounders or risk factors present (including latency/TTO as applicable)*
- *Confounding medications (including latency/TIO as applicable)*
- *Outcome*
- *WHO-UMC causality assessment*

Sponsor Response:

The sponsor conducted and evaluation of all the cases identified as cases of Myocarditis and/or Myo/Pericarditis according to the PRAC's recommendation (See Table 6 (Annex II of this report)), utilizing the WHO-UMC causality assessment (which allow to perform a combined assessment of the reported cases taking into account the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation)[1] and the newly developed DRAFT Myocarditis Brighton Collaboration case definition (30 May 2021) which allows classification of the cases on whether or not they are true cases of Myocarditis. It is important to define that the WHO-UMC causality assessment and the Brighton Collaboration case definitions provide different classification of cases reported to the MAH, the first by assessing causality, and the second one by identifying clinically if this is a true case of myocarditis or not (which is separate from causality assessment).

Based on the assessment conducted on the 77 cases reporting both Myocarditis or Myo/Pericarditis PTs, there were 20 reports that were classified as "Possible" according to the WHO-UMC causality assessment (*Event or laboratory test abnormality, with reasonable time relationship to drug intake; could also be explained by disease or other drugs; information on drug withdrawal may be lacking or unclear*). Out of those 20 reports, according to the Myocarditis Brighton case definition, there were 2 classified as Level 1 (*Definitive case*); 12 classified as Level 2 (*Probable case*); and 6 were classified as Level 4 (*a reported event of myocarditis with insufficient evidence to meet level 1,2 or 3 of the case definition*).

The MAH considers that because 1) there are no pathognomonic findings that are indicative of certain vaccine causality of myocarditis or pericarditis; 2) there exists a background incidence of these illnesses that pre-dated mRNA-1273 and would be expected to occur independent of vaccine exposure, and 3) it has not been proven that immunization with mRNA-1273 or any mRNA vaccine can cause myocarditis or pericarditis, no cases were classified as certain or probable according to the WHO-UMC causality assessment.

PRAC Rapporteur assessment comment:
As requested, the MAH has evaluated all cases identified as myocarditis and/or myo/pericarditis, utilizing the WHO- UMC causality assessment and the newly developed DRAFT Myocarditis Brighton Collaboration case definition (BC) (30 May 2021).
20 cases were considered WHO Possible causality by the MAH. Of these, 2 classified as BC Level 1 (Definitive case) and 12 classified as BC Level 2 (Probable case). No case narratives were provided.
A causality assessment was performed of the cases that were classified by the MAH as WHO Possible and myocarditis Brighton definition 1-2. The assessment included 14 cases where a full case narrative could be retrieved from Eudravigilance.
The cases comprised 13 males and 1 female aged 18-50 years of age (stratified by decades there was one aged 10-19 years, 7 were 20-29 ys, 2 aged 30-39 ys, 3 aged 40-49 ys, and 1 aged 50-59 ys).
Most were diagnostically well-supported with 5 cases Brighton level 1, 7 cases Brighton level 2, one case level 4 and one level 5.
Regarding causality to the vaccination, 7 cases are considered WHO Probable, 3 cases WHO Possible, 2 are found WHO Unlikely, and 2 cases are unclassifiable due to other health conditions. The 10 WHO Probable/Possible cases are all on males aged 18-50 years of age.
In 12 of the 14 cases, myocarditis was diagnosed 1-4 days after receiving the 2nd dose of the COVID-19-vaccine Moderna; two cases were reported after the 1st dose. It should be noted that the cases reported after the 1st dose are evaluated as Brighton 4-5 and WHO-UMC unlikely. Therefore, the assessment of these 14 cases in conclusion indicate an association between COVID-19-vaccine Moderna and myocarditis, with perceived symptoms and clinical findings within the first week after receiving the 2nd dose.

Looking at the outcome of the myocarditis events, none of them were fatal, 4 were recovered or recovering at the time of reporting the suspected adverse event, 6 were not yet recovered, and for 4 the outcome of the event was reported as unknown. Comparing to the nature of myocarditis there is no indication so far that myocarditis as a possible side effect to the vaccine should have a more severe course than otherwise seen.
Although the positive cases all represent males this is not sufficient to indicate a gender difference in myocarditis after immunization.
In two cases considered WHO Possible, the patients had co-reported pericarditis and pericardial effusion.
The cases considered WHO Probable or Possible are presented shortly below:

7 cases considered WHO Probable:

Case 1
Myocarditis
A 50-59 year old healthy male who the day after receiving the 2nd dose of covid-19-vaccine experienced fever and rigoring compatible with known general side effects to the vaccine; the close temporal association to the immunization and no other symptoms indicating infection taken into account.
On the second day after receiving the 2nd dose he experienced chest pain and increased biomarker level (TnT) was demonstrated. ECG, ECHO and angiography were performed, these were non-pathological.
There was no known risk-factors, and the fever and rigoring were attributable to general side effects.
-Therefore, based on the cardiac symptoms and increased biomarker concentration this is a myocarditis Brighton level 2 (probable).
-Based on laboratory test abnormality, a short and reasonable time relationship to the 2nd immunization, unlikely to be attributed to disease or other drugs as the man is otherwise healthy, this case is WHO-UMC Probable.

Case 2
Myocarditis
A 40-49 year old male who on the third day after receiving the 2nd dose of covid-19-vaccine experienced chest discomfort, increased biomarker level (Tn, unspecified if TnT or TnI) was demonstrated, and ECG showed diffuse ST-elevations. Furthermore, ECHO and angiography were performed, these were non-pathological.
No medical history was reported.
-Based on the cardiac symptoms, increased biomarker concentration and ST-elevations in ECG and no indication of other etiology, this is a myocarditis Brighton level 2 (probable).
-Based on laboratory test abnormality, a short and reasonable time relationship to the 2nd immunization, unlikely to be attributed to other etiology, this case is WHO-UMC: Probable.

Case 3
Myocarditis
A 18-29 year old male who the day after receiving the 2nd dose of covid-19-vaccine experienced chest pain and dyspnoea; increased biomarker level (TnI) was demonstrated, and ECG showed ST depressions in some leads and elevations in others.
There is no information on ECHO nor angiography, and no medical history was reported.
-Based on the cardiac symptoms, increased biomarker concentration and ST-abnormalities ECG and no indication of other etiology, this is a myocarditis Brighton level 2 (probable).
-Based on laboratory test abnormality, the short and reasonable time relationship to the 2nd immunization, and considered unlikely to be attributed to other disease in this young man despite no medical history reported. WHO-UMC: Probable.

Case 4
Myocarditis
A 18-29 year old male who on the second day after receiving the 2nd dose experienced chest pain and increased biomarker levels (Tn, unspecified if TnT or TnI) were demonstrated. Cardiac magnetic resonance scan was performed and gave rise to the diagnosis perimyocarditis. Furthermore, ECG and CT scan were performed but results are not provided. There was no known risk-factors.
The patient has Penicillin allergy.
-As the specific results of the cardiac magnetic resonance scan are not reported, the causality association is primarily based on the cardiac symptoms and increased biomarker concentrations and the temporal relationship leading to this a myocarditis Brighton level 2 (probable).
-Based on laboratory test abnormality, a short and reasonable time relationship to the 2nd immunization, unlikely to be attributed to other etiology, this case is WHO-UMC: Probable.

Case 5
Myocarditis
A 30-39 year old male who on the third day after receiving the 2nd dose of covid-19-vaccine experienced chest pain and increased biomarker level (Tn, unspecified if TnT or TnI) was demonstrated. Acute coronary syndrome was excluded. There is no available information on ECG, ECHO nor angiography.
The patient has food allergies
-Based on the cardiac symptoms and increased biomarker concentration and no indication of other etiology, this is a myocarditis Brighton level 2 (probable).
-Based on laboratory test abnormality, a short and reasonable time relationship to the 2nd immunization, and based on the available information unlikely to be attributed to other etiology, this case is WHO-UMC: Probable.

Case 6
Myocarditis
A 18-29 year old healthy male who the day after receiving the 2nd dose of covid-19-vaccine experienced fever, chills and myalgia compatible with known general side effects to the vaccine; the close temporal association to the immunization and no other symptoms indicating infection taken into account.
Also, on the day after receiving the 2nd dose he experienced chest pain and increased biomarker level (Tn, unspecified if TnT or TnI) was demonstrated. ECG showed ST-abnormalities, ST-elevations included, and myocardial inflammation was confirmed by both ECHO and by thoracic CT scan.
There was no known risk-factors, and the fever, chills and myalgia were attributable to general side effects.
-Based on the abnormal ECHO and increased biomarker concentration this is a myocarditis Brighton level 1 (definite).
-Based on laboratory test abnormality, a short and reasonable time relationship to the 2nd immunization, unlikely to be attributed to other etiology, this case is WHO-UMC: Probable.

Case 7
Myocarditis
A 18-29 year old male who four days after receiving the 2nd dose of covid-19-vaccine experienced chest pain. Cardiac magnetic resonance scan is described in detail and compatible with myocarditis.
He was broadly tested microbiologically for infections; all tests were negative including SARS-CoV-2.
There is no information on biomarkers, ECG, ECHO or angiography.
The patient has food allergies (eggs, peanuts, nuts).
-Based on the cardiac symptoms and the abnormal cardiac MRI this is considered equivalent to a myocarditis Brighton level 2 (probable).
-Based on the event with cardiac symptoms and MRI supported diagnosis, the short and reasonable time relationship to the 2nd immunization, and unlikely to be attributed to other etiology, this case is WHO-UMC: Probable.

3 cases considered WHO Possible:

Case 1
Myocarditis
A 18-29 year old male who four days after receiving the 2nd dose of covid-19-vaccine experienced chest pain, increased biomarker level (TnI) was demonstrated, and ECG showed non-specific ST abnormalities. Chest X-ray was normal. ECHO and angiography were not reported.
Medical history included teratoma.
-Based on the cardiac symptoms and increased biomarker concentration this is a myocarditis Brighton level 2 (probable).
-Based on the laboratory test abnormality, the reasonable time relationship to immunization, but that the condition could have other causes this is WHO-UMC: Possible.

Case 2
Myocarditis
A 18-29 year old male who on the second day after receiving the 2nd dose of covid-19-vaccine experienced headache, musculoskeletal stiffness and pain in extremities compatible with known general side effects to the vaccine; the close temporal association to the immunization taken into account.
On the same day he also experienced chest pain, and increased biomarker level (Troponin) was demonstrated. ECHO was performed and proved decreased ejection fraction; and ECG was reported as abnormal although unspecified how.
No medical history was reported.
-Based on the increased biomarker concentration and the ECHO demonstrated decreased injection fraction this is a myocarditis Brighton level 1 (definit).
-Based on the laboratory test abnormality, the reasonable time relationship to immunization, but that the condition could have other causes as no medical history is reported, this is WHO-UMC: Possible.

Case 3
Myocarditis
An 18-29 year old male who on the second day after receiving the 2nd dose of covid-19-vaccine experienced chest pain and increased biomarker level (TnI) was demonstrated. ECG showed ST-abnormalities with diffuse ST-elevations, ECHO showed decreased ejection fraction and slight pericardial effusion, while cardiac magnetic resonance scan with findings consistent with myocarditis and not ischemia.
No medical history was reported.
-Based on the abnormal ECHO and increased biomarker concentration this is a myocarditis Brighton level 1 (definite).
-Based on the laboratory test abnormality, the reasonable time relationship to immunization, but that the condition could have other causes as no medical history is reported, this is WHO-UMC: Possible.

Request ITEM 2, part 2:

The cases with an "Unlikely" WHO-UMC causal association in a tabulated format. The table should include, but not restricted to, the following information for each case:

- *Case ID (Eudravigilance no. if possible)*
- *Age/gender*
- *TTO, and whether following pt dose/2nd dose*
- *Brighton collaboration case definition: Definitive/Probable/Possible (myocarditis cases only)*

- *Any underlying condition(s) (including COVID-19), other medical confounders or risk factors present (including latency/TIO as applicable)*
- *Confounding medications (including latency/TIO as applicable)*
- *Outcome*

Sponsor Response:

Out of the 77 cases reporting both Myocarditis or Myo/Pericarditis PTs, there were 17 reports that were classified as "Unlikely" according to the WHO-UMC causality assessment (*Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible); Disease or other drugs provide plausible explanations*). Out of those 17 reports, according to the Myocarditis Brighton case definition, there were 3 classified as Level 1 (*Definitive case*); 5 classified as Level 2 (*Probable case*); 1 was classified as Level 3 (*Possible case*); and 8 were classified as Level 4 (*a reported event of myocarditis with insufficient evidence to meet level 1,2 or 3 of the case definition*). (See Table 7 Annex III of this report)

PRAC Rapporteurs assessment comment:

The MAH has listed the cases that were considered WHO Unlikely in a tabulated format. It is not clear from the presentation on which basis the cases were considered unlikely. For case 2 a causality "unlikely" is questioned based on the information presented, considering that nothing is reported under medical history and medications. Similar applies for case 15 and 9 in which nothing is reported in medical history and comedication includes drugs for which cardiac disease (myocardial ischemia) is listed but not myocarditis.

3.1.3. ITEM 3 – risk factors / Myocarditis

The review should explore possible risk factors, taking into account the gender, age, and dose distribution of reported cases. Specifically, the MAH is requested to comment on the number of cases occurring after the 2nd dose as compared to the 1st dose, also considering the differences in exposure for these two groups. The MAH should discuss whether any patterns or trends can be identified concerning risk factors.

Sponsor Response:

Myocarditis is an under-diagnosed cardiac disease resulting from any one of a broad range of infectious, immune, and toxic causes. In many cases, the etiology is not conclusively determined. Most cases of myocarditis are caused by infectious agents, toxic substances, drugs or autoimmune disorders. Hence, it is increasingly recognized that myocarditis is an inflammatory condition of the myocardium triggered by various factors rather than a distinct cardiovascular disease. Infectious causes include viruses, bacteria, Chlamydia, rickettsia, fungi, and protozoa.

Noninfectious triggers have been identified such as toxins, autoimmune disease and hypersensitive reactions. Numerous medications like antipsychotics (e.g., clozapine), antibiotics (penicillin, ampicillin, sulfonamides, tetracyclines), and antiphlogistic (e.g., mesalamine) can induce hypersensitivity eosinophilic myocarditis. Myocarditis has been reported following many different vaccines including flu vaccine, however the smallpox vaccine has the strongest association. During the influenza epidemic of the winter 1998-1999 there were several reports of patients who had preceding flu-like symptoms and fever and developed cardiac involvement between 4 and 7 days after the onset of influenza symptoms.

Viral myocarditis is thought to be the most frequent type, mostly affecting children and young adults[2]. A recent study using International Classification of Diseases codes estimated the global prevalence of myocarditis to be ≈22 of 100 000 patients annually. Approximately 1% to 5% of patients that test positive for acute viral infection(s) may exhibit a form of myocarditis.

Nowadays, the prevalence of myocarditis has been reported from 10.2 to 105.6 per 100,000 worldwide, and its annual occurrence is estimated at about 1.8 million cases. The incidence of confirmed myocarditis secondary to smallpox vaccination was estimated to be 16.1 per 100 000 service members, with a recent Department of Defense study estimating 12 per 100 000 in a review of 730 000 service members. Most studies of acute myocarditis report a greater prevalence and severity in male patients, speculated to be caused by a protective effect of natural hormonal influences on immune responses in women when compared with men. Patients are usually between the ages of 20 and 50. Acute myocarditis and hyperthyroidism are also common diseases that often present in young, otherwise healthy patients. Autoimmunity is central to the pathogenesis of both[3].

When assessing whether a vaccine is potentially associated with myocarditis, it is useful to consider whether myocarditis is caused by the infection that the vaccine is intended to prevent. Various viruses have been associated with myocarditis and are believed to have different pathophysiological mechanisms, probably related to their different tropisms. Some viruses have primary cardiotropism, such as Coxsackie A and B viruses or echoviruses. Other viruses are vasculotropic, such as parvovirus B19. Yet others are lymphotropic, such as HHV6, EBV and CMV. Some viruses are believed to induce cardiac inflammation through activation of the immune system, such as HIV, HCV and influenza A and B. By far the highest documented incidence of myocarditis following immunization is with smallpox vaccine (https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0118283); however, it is important to note that smallpox vaccine is fundamentally different than mRNA-1273, not only with respect to the target, but also because smallpox vaccine is a live viral vaccine. Moreover, despite large prospective clinical safety investigations of smallpox and myocarditis within the last 20 years, the pathophysiological mechanism remain remains obscure.

As coronavirus disease 2019 (COVID-19) rapidly expanded as a global pandemic caused by severe acute respiratory syndrome coronavirus 2, some COVID-19 patients that were hospitalized developed an acute COVID-19 cardiovascular syndrome, which can manifest with a variety of clinical presentations but often presents as an acute cardiac injury with cardiomyopathy, ventricular arrhythmias, and hemodynamic instability in the absence of obstructive coronary artery disease. The cause of this injury is uncertain but is suspected to be related to myocarditis, microvascular injury, systemic cytokine-mediated injury, or stress-related cardiomyopathy. Although histologically unproven, severe acute respiratory syndrome coronavirus 2 has the potential to directly replicate within cardiomyocytes and pericytes, leading to viral myocarditis.

SARS-COV-2 has angiotensin converting enzyme 2 (ACE2) tropism. ACE2 is an enzyme located on the cell membranes of various types of cells in the body, including cardiomyocytes. It has been suggested, on this basis, that SARS-COV-2 could potentially mediate direct cardiac injury. To document such injury, the strongest evidence would come from laboratory investigations conducted on endomyocardial biopsy material obtain from significant numbers of patients with active SARS-COV-2 infections and myocarditis. Such endomyocardial biopsy procedures pose non-trivial risks not only to patients but also to medical staff. We noted only one such biopsy in our spontaneous reports, and it was not etiologically informative. A published review of 9 reported cases of endomyocardial biopsy in the setting of suspected cardiac illness and SARS-COV-2 virus infection concluded that direct proof is lacking that the virus infects myocytes leading to cell death and troponin release

(Kawakami et al. 2020 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7816957/). Thus, potential mechanisms underlying myocarditis (and heart disease in general) in SARS-CoV-2 infections that involve direct cardiomyocyte infection or other direct viral attack have not been demonstrated and would require intense investigation of endomyocardial biopsy and autopsy samples. Eight of the reported cases of Myocarditis had previous COVID-19 infection.

There are more cases of myocarditis reported after the 2nd dose (53.2%) than after the 1st dose (35%). Exposure to two doses is a bit less for the second dose than the first because of time truncation at the end of the reporting period (data lock point), when some vaccinees have not yet had their second dose. Also, a small proportion of vaccinees will not, for a variety of reasons, receive a second dose. These exposure differences are unlikely to have a substantial effect on our observed findings. The main risk factors we observed for myocarditis are an overrepresentation of cases in young men, but this male predominance is consistent with the situation in the general population prior to the vaccination with mRNA-1273. Most studies of acute myocarditis report a greater prevalence and severity in male patients, speculated to be caused by a protective effect of natural hormonal influences on immune responses in women when compared with men. Patients are usually between the ages of 20 and 50.

No other important trending was observed with the reported cases of Myocarditis.

PRAC Rapporteurs assessment comment:

The MAH has provided a discussion on risk factors, including infectious and non-infectious triggers, and highlights that myocarditis has been reported after other vaccines such as flu vaccine and smallpox. Viral myocarditis is considered the most frequent type, mostly affecting children and young adults.

Most studies of acute myocarditis report a greater prevalence and severity in male patients, speculated to be caused by a protective hormonal effect on the immune system in women. Patients are usually between the ages of 20 and 50. Autoimmunity is central to the pathogenesis of acute myocarditis and hyperthyroidism that often present in young, otherwise healthy patients.

The potential cardiotrophism of SARS-CoV-2 is discussed, including the potential of the virus to mediate direct cardiac injury through angiotensin converting enzyme 2 (ACE2) tropism, located on the cardiomyocytes. It is however difficult to prove such a direct relationship, as it requires antigen demonstration in endomyocardial biopsies. No discussion has been provided regarding the fact that it is the Spike protein that attach to the ACE2 receptor, and whether this could impact the possibility of initiating a local reaction in the cardiac tissue post vaccination. Eight of the reported cases of Myocarditis had previous COVID-19.

There were more cases after 2nd dose compared to 1st dose, although the exposure is greater after the 1st dose compared to the 2nd. This fact is only commented by the MAH as: "These exposure differences are unlikely to have a substantial effect on our observed findings" – the MAH has not provided a discussion of the unexpected finding of increased reporting after 2nd dose.

3.1.4. ITEM 4 – O/E analyses

Specific observed/expected (O/E) analyses should be performed for the 1st dose and 2nd dose receivers respectively. Thus, for the cumulative review, O/E analyses should be stratified by age, gender and dose (1st or 2nd). For the analyses, the MAH should clearly state and justify the background rates used. The MAH should retrieve the most relevant background rates and take the source of the cases into consideration. Several risk windows

should be considered (14 and 21 days). In the O/E analysis, the MAH is requested to perform adjustment for underreporting, backlog of case handling and sensitivity analysis.

Sponsor Response:

In the US, myopericarditis has been observed at a rate of 0.95 - 2.16 per 100,000 population in the military[4]. Military service members are screened at entry to exclude those with significant medical conditions; consequently, military populations are healthier than the general population and may have lower disease rates. The cumulative reporting rate for myocarditis was 0.87 per 100,000 person- years, which was below the ACCESS incidence estimate from Spain (FISABIO; 2017: 1.58 per 100,000 person-years, 141.3 cases expected, rate ratio 0.55, 95% CI 0.42 – 0.73) and the United States (Kang 2021: 10.0 per 100,000 person-years, 894.2 cases expected, rate ratio 0.09, 95% CI 0.07 -0.1). (See Table 8)

Table 8. Observed to expected analyses: Myocarditis

	Cases	Person-time	Rate	Rate ratio (95% CI)
As observed				
Myocarditis, all				
Observed: Post authorization	78.0	8,941,723	0.87	
Expected: ACCESS, Spain (FISABIO) 2017	141.3	8,941,723	1.58	0.55 (0.42, 0.73)
Expected: ACCESS, Spain (BIFAP) 2017				
Expected: US, Kang 2021	1,051.5	8,941,723	11.76	0.07 (0.06,
Myocarditis, dose 1				
Observed: Post authorization	27.0	4,989,481	0.54	
Expected: ACCESS, Spain (FISABIO) 2017	78.8	4,989,481	1.58	0.34 (0.22, 0.53)
Expected: ACCESS, Spain (BIFAP) 2017				
Expected: US, Kang 2021	586.8	4,989,481	11.76	0.05 (0.03,
Myocarditis, dose 2				
Observed: Post authorization	41.0	3,952,242	1.04	
Expected: ACCESS, Spain (FISABIO) 2017	62.4	3,952,242	1.58	0.66 (0.44, 0.97)
Expected: ACCESS, Spain (BIFAP) 2017				
Expected: US, Kang 2021	464.8	3,952,242	11.76	0.09 (0.06,
Assuming sensitivity of 50%				
Myocarditis, all				
Observed: Post authorization	156.0	8,941,723	1.74	
Expected: ACCESS, Spain (FISABIO) 2017	141.3	8,941,723	1.58	1.1 (0.88, 1.39)
Expected: ACCESS, Spain (BIFAP) 2017				
Expected: US, Kang 2021	1,051.5	8,941,723	11.76	0.15 (0.13,
Myocarditis, dose 1				
Observed: Post authorization	54.0	4,989,481	1.08	
Expected: ACCESS, Spain (FISABIO) 2017	78.8	4,989,481	1.58	0.68 (0.48, 0.97)
Expected: ACCESS, Spain (BIFAP) 2017				
Expected: US, Kang 2021	586.8	4,989,481	11.76	0.09 (0.07,
Myocarditis, dose 2				
Observed: Post authorization	82.0	3,952,242	2.07	

Expected: ACCESS, Spain (FISABIO) 2017	62.4	3,952,242	1.58	1.31 (0.94,
Expected: ACCESS, Spain (BIFAP) 2017			1.83)	
Expected: US, Kang 2021	464.8	3,952,242	11.76	0.18 (0.14,
Assuming sensitivity of 25%				
Myocarditis, all				
Observed: Post authorization	312.0	8,941,723	3.49	
Expected: ACCESS, Spain (FISABIO) 2017	141.3	8,941,723	1.58	2.21 (1.81,
Expected: ACCESS, Spain (BIFAP) 2017			2.69)	
Expected: US, Kang 2021	1,051.5	8,941,723	11.76	0.3 (0.26,
Myocarditis, dose 1				
Observed: Post authorization	108.0	4,989,481	2.16	
Expected: ACCESS, Spain (FISABIO) 2017	78.8	4,989,481	1.58	1.37 (1.02,
Expected: ACCESS, Spain (BIFAP) 2017	586.8	4,989,481	11.76	0.18 (0.15,
Expected: US, Kang 2021	498.9	4,989,481	10.00	0.22 (0.18,
Myocarditis, dose 2				
Observed: Post authorization	164.0	3,952,242	4.15	
Expected: ACCESS, Spain (FISABIO) 2017	62.4	3,952,242	1.58	2.63 (1.96,
Expected: ACCESS, Spain (BIFAP) 2017	464.8	3,952,242	11.76	0.35 (0.3,
Expected: US, Kang 2021	395.2	3,952,242	10.00	0.41 (0.35,

PRAC Rapporteur assessment comment:

The unadjusted overall reporting rate was below the ACCESS estimate from FISABIO, BIFAP and the US estimate from Kang 2021. The MAH has not justified the background rates used. FISABIO is a Spanish database of primary care, outpatient specialists and hospitalisation discharge diagnosis, BIFAP is a Spanish primary care and hospital discharge diagnoses. FISABIO is in the lower end of the ACCESS databases, and the BIFAP have the highest incidence rates of myocarditis in ACCESS, especially in the 20-49 year age group. The US incidence rates are referred to be retrieved from a publication by Kang 2021. It is of notice that the rate provided in the publication by Kang are not based on specific studies. Only a statement that "incidence is usually estimated between 10 to 20 cases per 100,000 persons" is included in this paper without any further reference to a source of this incidence. Therefore, a use of this US background rate is not considered scientifically justified. According to the 2019 Update from the GBD 2019 Study (Roth GA et al., 2020), a global 2019-annual rate of myocarditis was estimated 6.1 per 100,000 (95% UI: 4.2 to 8.7 per 100,000) in men and 4.4 per 100,000 (95% UI: 3.0 to 6.3 per 100,000) in women, in the age between 35 and 39 years. These rates lie between the above selected rates from the ACCESS study.

The MAH has stratified the overall O/E into 1st and 2nd dose, and presented different calculations for assuming sensitivity of 25% and 50%, which adjusts for underreporting. This approach is endorsed.

Considering 2nd dose, the observed exceeds the expected in FISABIO, both when assuming a sensitivity of 25% and 50%. When assuming a sensitivity of 25%, the observed exceeds the expected in the FISABIO database, for both the 1st, 2nd dose and overall. Of note, these calculations are not stratified by age or gender.

1 Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, Bonny A, Brauer M, Brodmann M, Cahill TJ, Carapetis J, Catapano AL, Chugh SS, Cooper LT, Coresh J, Criqui M, DeCleene N, Eagle KA, Emmons-Bell S, Feigin VL, Fernández-Solà J, Fowkes G, Gakidou E, Grundy SM, He FJ, Howard G, Hu F, Inker L, Karthikeyan G, Kassebaum N, Koroshetz W, Lavie C, Lloyd-Jones D, Lu HS, Mirijello A, Temesgen AM, Mokdad A, Moran AE, Muntner P, Narula J, Neal B, Ntsekhe M, Moraes de Oliveira G, Otto C, Owolabi M, Pratt M, Rajagopalan S, Reitsma M, Ribeiro ALP, Rigotti N, Rodgers A, Sable C, Shakil S, Sliwa-Hahnle K, Stark B, Sundström J, Timpel P, Tleyjeh IM, Valgimigli M, Vos T, Whelton

PK, Yacoub M, Zuhlke L, Murray C, Fuster V; **GBD-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study.** J Am Coll Cardiol. 2020 Dec 22;76(25):2982-3021. doi: 10.1016/j.jacc.2020.11.010. Erratum in: J Am Coll Cardiol. 2021 Apr 20;77(15):1958-1959. PMID: 33309175; PMCID: PMC7755038.

Stratification by age, gender and dose number was conducted applying two different risk windows, a 14-day risk window and a 21-day risk window. The stratification with a 14-day risk window shows an increase in the observed to expected for both males and females ages 18-29 when comparing reporting rates to the FISABIO 2017 ACCESS estimates (e.g., for males: 33 cases observed, 10.2 expected, rate ratio 3.23 (95% CI 1.6, 6.52). The observed cases remain at less than half of the expected for comparisons against the BIFAF database. (See Table 9)

When adding stratification by dose and by the 14-day risk window, shows the same pattern for males after the first dose, but a larger increase after dose 2. Comparison to the FISABIO 2017 estimates shows a small increase in the reporting rate for males 18-29 years of age following dose 1 (11 events observed, 8.9 expected, rate ratio 1.31, 95% CI 0.53-3.20) and a larger increase in the reporting rate following dose 2 (22 observed, 4.4 expected (rate ratio 4.88, 95% CI 1.77-13.43). The same increase is noted using the 21-day risk windows (See Table 10). Interesting to note is that an increase for women in the same age group is also observed (rate ratio 2.35, 95% CI 0.29- 17.95) in the overall analysis, but when stratifying by age and dose and the two risk windows, the increase is also observed in the 30-39 years old group (See Tables 9 and 10). Comparisons to the BIFAP 2017 ACCESS estimates do not show an excess in observed to expected cases (i.e., rate ratio above 1) for any of the age, sex, dose, or risk window strata.

Table 9. Stratification with a 14-day risk window by Age, Sex, and Dose Number

		Observed		Expected (FISABIO 2017)			Expected (BIFAP 2017)		
	Person-time	Cases	Rate	Cases	Rate	Rate Ratio (95% CI)	Cases	Rate	Rate Ratio (95% CI)
Myocarditis: All									
All	5,961,149	78	1.31	94.2	1.58	0.83 (0.61, 1.12)	701.0	11.76	0.11 (0.09, 0.14)
Male									
<18 years	29,000	0	0.00	0.1	0.18	#NUM	2.8	9.59	#NUM!
18-29 years	224,839	33	14.68	10.2	4.54	3.23 (1.6, 6.52)	72.6	32.31	0.45 (0.3, 0.69)
30-39 years	572,348	12	2.10	17.0	2.97	0.71 (0.34, 1.48)	154.3	26.96	0.08 (0.04, 0.14)
40-49 years	408,630	7	1.71	11.1	2.71	0.63 (0.25, 1.63)	80.3	19.66	0.09 (0.04, 0.19)
50-64 years	765,100	3	0.39	8.3	1.09	0.36 (0.1, 1.35)	116.2	15.19	0.03 (0.01, 0.08)
65-74 years	484,131	3	0.62	13.7	2.83	0.22 (0.06, 0.76)	76.3	15.77	0.04 (0.01, 0.12)
75+ years	335,573	1	0.30	5.6	1.68	0.18 (0.02, 1.49)	42.1	12.54	0.02 (0, 0.17)
Female									
<18 years	32,973	0	0.00	0.0	0.00	#DIV/0	0.4	1.16	#NUM!
18-29 years	255,642	6	2.35	2.0	0.77	3.05 (0.61, 15.25)	11.1	4.34	0.54 (0.2, 1.46)
30-39 years	650,759	2	0.31	3.6	0.55	0.56 (0.1, 3.15)	36.3	5.58	0.06 (0.01, 0.23)
40-49 years	464,611	2	0.43	2.2	0.47	0.92 (0.13, 6.24)	29.2	6.29	0.07 (0.02, 0.29)
50-64 years	869,917	4	0.46	13.9	1.60	0.29 (0.09, 0.87)	72.0	8.28	0.06 (0.02, 0.15)
65-74 years	550,456	1	0.18	10.4	1.89	0.1 (0.01, 0.75)	48.3	8.77	0.02 (0, 0.15)
75+ years	381,546	1	0.26	6.0	1.56	0.17 (0.02, 1.4)	18.1	4.75	0.06 (0.01, 0.41)
Myocarditis: Dose 1									

All	3,278,632	27	0.82	51.8	1.58	0.52 (0.33, 0.83)	385.6	11.76	0.07 (0.05, 0.1)
Male									
<18 years	15,950	0	0.00	0.0	0.18	#NUM	1.5	9.59	#NUM!
18-29 years	123,662	11	8.90	5.6	4.54	1.96 (0.71, 5.42)	40.0	32.31	0.28 (0.14, 0.54)
30-39 years	314,792	3	0.95	9.3	2.97	0.32 (0.09, 1.18)	84.9	26.96	0.04 (0.01, 0.11)
40-49 years	224,746	4	1.78	6.1	2.71	0.66 (0.19, 2.32)	44.2	19.66	0.09 (0.03, 0.25)
50-64 years	420,805	0	0.00	4.6	1.09	#NUM	63.9	15.19	#NUM!
65-74 years	266,272	2	0.75	7.5	2.83	0.27 (0.06, 1.26)	42.0	15.77	0.05 (0.01, 0.2)
75+ years	184,565	0	0.00	3.1	1.68	#NUM	23.1	12.54	#NUM!
Female									
<18 years	18,135	0	0.00	0.0	0.00	#DIV/0	0.2	1.16	#NUM!
18-29 years	140,603	0	0.00	1.1	0.77	#NUM	6.1	4.34	#NUM!
30-39 years	357,917	5	1.40	2.0	0.55	2.54 (0.49, 13.21)	20.0	5.58	0.25 (0.09, 0.67)
40-49 years	255,536	0	0.00	1.2	0.47	#NUM	16.1	6.29	#NUM!
50-64 years	478,455	0	0.00	7.7	1.60	#NUM	39.6	8.28	#NUM!
65-74 years	302,751	0	0.00	5.7	1.89	#NUM	26.6	8.77	#NUM!
75+ years	209,850	0		3.3	1.56	#NU	10.0	4.75	#NUM!
Myocarditis: Dose 2									
All	2,634,828	27		41.6	1.58	0.65 (0.4, 1.05)	309.9	11.76	0.09 (0.06, 0.13)
Male									
<18 years	12,818	0		0.0	0.18	#NU	1.2	9.59	#NUM!
18-29 years	99,379	22	2	4.5	4.54	4.88 (1.77,	32.1	32.31	0.69 (0.4, 1.18)
30-39 years	252,978	7		7.5	2.97	0.93 (0.33,	68.2	26.96	0.1 (0.05, 0.22)
40-49 years	180,614	3		4.9	2.71	0.61 (0.15,	35.5	19.66	0.08 (0.03, 0.27)
50-64 years	338,174	2		3.7	1.09	0.54 (0.1,	51.4	15.19	0.04 (0.01, 0.16)
65-74 years	213,986	0		6.1	2.83	#NU	33.7	15.77	#NUM!
75+ years	148,323	0		2.5	1.68	#NU	18.6	12.54	#NUM!
Female									
<18 years	14,574	0		0.0	0.00	#DIV/	0.2	1.16	#NUM!
18-29 years	112,994	3		0.9	0.77	3.45 (0.32,	4.9	4.34	0.61 (0.15, 2.57)
30-39 years	287,635	2		1.6	0.55	1.26 (0.16,	16.1	5.58	0.12 (0.03, 0.54)
40-49 years	205,358	1		1.0	0.47	1.04 (0.06,	12.9	6.29	0.08 (0.01, 0.59)
50-64 years	384,504	1		6.2	1.60	0.16 (0.02,	31.8	8.28	0.03 (0, 0.23)
65-74 years	243,302	0		4.6	1.89	#NU	21.3	8.77	#NUM!
75+ years	168,643	0		2.6	1.56	#NU	8.0	4.75	#NUM!

Table 10. Stratification with a 21-day window by Age, Sex, and Dose Number

	Person-time	Observed		Expected (FISABIO 2017)			Expected (BIFAP 2017)		
		Cases	Rate	Cases	Rate	Rate Ratio (95% CI)	Cases	Rate	Rate Ratio (95% CI)
Myocarditis: All									
All	8,941,723	78	0.87	141.3	1.58	0.55 (0.42, 0.73)	1051.5	11.76	0.07 (0.06, 0.09)
Male									
<18 years	43,500	0	0.00	0.1	0.18	#NUM!	4.2	9.59	#NUM!
18-29 years	337,259	33	9.78	15.3	4.54	2.16 (1.18, 3.95)	109.0	32.31	0.3 (0.21, 0.45)
30-39 years	858,523	12	1.40	25.5	2.97	0.47 (0.24, 0.93)	231.5	26.96	0.05 (0.03, 0.09)

40-49 years	612,945	7	1.14	16.6	2.71	0.42 (0.17, 1.02)	120.5	19.66	0.06 (0.03, 0.12)
50-64 years	1,147,650	3	0.26	12.5	1.09	0.24 (0.07, 0.85)	174.3	15.19	0.02 (0.01, 0.05)
65-74 years	726,197	3	0.41	20.6	2.83	0.15 (0.04, 0.49)	114.5	15.77	0.03 (0.01, 0.08)
75+ years	503,360	1	0.20	8.5	1.68	0.12 (0.01, 0.94)	63.1	12.54	0.02 (0, 0.11)
Female									
<18 years	49,460	0	0.00	0.0	0.00	#DIV/0!	0.6	1.16	#NUM!
18-29 years	383,463	6	1.56	3.0	0.77	2.03 (0.5, 8.19)	16.6	4.34	0.36 (0.14, 0.92)
30-39 years	976,139	2	0.20	5.4	0.55	0.37 (0.07, 1.89)	54.5	5.58	0.04 (0.01, 0.15)
40-49 years	696,917	2	0.29	3.3	0.47	0.61 (0.11, 3.55)	43.8	6.29	0.05 (0.01, 0.19)
50-64 years	1,304,876	4	0.31	20.9	1.60	0.19 (0.07, 0.56)	108.0	8.28	0.04 (0.01, 0.1)
65-74 years	825,685	1	0.12	15.6	1.89	0.06 (0.01, 0.48)	72.4	8.77	0.01 (0, 0.1)
75+ years	572,320	1	0.17	8.9	1.56	0.11 (0.01, 0.88)	27.2	4.75	0.04 (0, 0.27)
Myocarditis: Dose 1									
All	4,917,948	27	0.55	77.7	1.58	0.35 (0.22, 0.54)	578.4	11.76	0.05 (0.03, 0.07)
Male									
<18 years	23,925	0	0.00	0.0	0.18	#NUM!	2.3	9.59	#NUM!
18-29 years	185,492	11	5.93	8.4	4.54	1.31 (0.53, 3.2)	59.9	32.31	0.18 (0.1, 0.35)
30-39 years	472,188	3	0.64	14.0	2.97	0.21 (0.06, 0.74)	127.3	26.96	0.02 (0.01, 0.07)
40-49 years	337,120	4	1.19	9.1	2.71	0.44 (0.14, 1.42)	66.3	19.66	0.06 (0.02, 0.17)
50-64 years	631,208	0	0.00	6.9	1.09	#NUM!	95.9	15.19	#NUM!
65-74 years	399,408	2	0.50	11.3	2.83	0.18 (0.04, 0.8)	63.0	15.77	0.03 (0.01, 0.13)
75+ years	276,848	0	0.00	4.7	1.68	#NUM!	34.7	12.54	#NUM!
Female									
<18 years	27,203	0	0.00	0.0	0.00	#DIV/0!	0.3	1.16	#NUM!
18-29 years	210,904	0	0.00	1.6	0.77	#NUM!	9.2	4.34	#NUM!
30-39 years	536,876	5	0.93	3.0	0.55	1.69 (0.4, 7.14)	30.0	5.58	0.17 (0.06, 0.43)
40-49 years	383,304	0	0.00	1.8	0.47	#NUM!	24.1	6.29	#NUM!
50-64 years	717,682	0	0.00	11.5	1.60	#NUM!	59.4	8.28	#NUM!
65-74 years	454,127	0	0.00	8.6	1.89	#NUM!	39.8	8.77	#NUM!
75+ years	314,776	0	0.00	4.9	1.56	#NUM!	15.0	4.75	#NUM!
Myocarditis: Dose 2									
All	3,952,242	27	0.68	62.4	1.58	0.43 (0.28, 0.68)	464.8	11.76	0.06 (0.04, 0.09)
Male									
<18 years	19,227	0	0.00	0.0	0.18	#NUM!	1.8	9.59	#NUM!
18-29 years	149,068	22	14.76	6.8	4.54	3.25 (1.37, 7.69)	48.2	32.31	0.46 (0.28, 0.76)
30-39 years	379,467	7	1.84	11.3	2.97	0.62 (0.24, 1.6)	102.3	26.96	0.07 (0.03, 0.15)
40-49 years	270,922	3	1.11	7.3	2.71	0.41 (0.11, 1.57)	53.3	19.66	0.06 (0.02, 0.18)
50-64 years	507,261	2	0.39	5.5	1.09	0.36 (0.07, 1.82)	77.1	15.19	0.03 (0.01, 0.11)
65-74 years	320,979	0	0.00	9.1	2.83	#NUM!	50.6	15.77	#NUM!
75+ years	222,485	0	0.00	3.7	1.68	#NUM!	27.9	12.54	#NUM!
Female									
<18 years	21,861	0	0.00	0.0	0.00	#DIV/0!	0.3	1.16	#NUM!
18-29 years	169,490	3	1.77	1.3	0.77	2.3 (0.29, 17.95)	7.4	4.34	0.41 (0.11, 1.56)
30-39 years	431,453	2	0.46	2.4	0.55	0.84 (0.13, 5.53)	24.1	5.58	0.08 (0.02, 0.35)
40-49 years	308,037	1	0.32	1.4	0.47	0.69 (0.05, 8.83)	19.4	6.29	0.05 (0.01, 0.39)
50-64 years	576,755	1	0.17	9.2	1.60	0.11 (0.01, 0.85)	47.8	8.28	0.02 (0, 0.15)
65-74 years	364,953	0	0.00	6.9	1.89	#NUM!	32.0	8.77	#NUM!

75+ years	252,965	0	0.00	3.9	1.56	#NUM!	12.0	4.75	#NUM!

PRAC Rapporteur assessment comment:

The MAH has performed O/E analyses by applying a 14 day and 21 day risk window, as requested, and further stratified into age and sex, 1st dose and 2nd dose. Of note, no adjustment for underreporting has been applied in these calculations, hence, the true rate is likely higher than estimated in table 9.

It is noted that in the 14-day risk window, an increase in the observed to expected for both males and females ages 18-29 were noted, when comparing reporting rates to the FISABIO 2017. If a sensitivity of 25-50% would be considered, the observed would also exceed the BIFAP rate in this age group, which would not be the case in the older age groups. It should be kept in mind that global myocarditis 2019 rates were lower than rates BIFAB (11.76 per 100,000 PYs). Thus, rates from BIFAB may at the high end of what to expect.

When stratifying further into dose 1 and 2, and still using a 14-day risk window, an increased reporting rate following dose 2 is noted in males aged 18-29. The rate ratio (using FISABIO) was **1.96** (0.71-5.42) after dose 1 and **4.88** (1.77-13.43) after dose 2 – indicating a clear signal of increased risk in this population. For the BIFAP database, the corresponding rate ratios were 0.28 (0.14-0.54) for dose 1 and 0.69 (0.4-1.18) for dose 2 - and importantly, this is without adjusting for underreporting, hence the true rate is greater than what has been calculated.

For females, the absolute numbers are small, giving greater uncertainties and precludes conclusion.

It is of importance to note that when several stratifications are applied, the absolute numbers get lower, which increases the uncertainties of the calculations (this specifically applies to the calculation regarding females)

In the 21-day risk window, the same pattern is seen, although with slighter lower rate ratios compared to the 14 days risk window.

The MAH concludes that the comparisons to the BIFAP 2017 ACCESS estimates do not show an excess in observed to expected cases (i.e., rate ratio above 1) for any of the age, sex, dose, or risk window strata. This cannot be endorsed, as the MAH has not applied any sensitivity adjustment for underreporting. If a 25-50% underreporting was considered, the observed number of cases in males aged 18-19 would have exceeded the expected also in the BIFAP 2017.

An imbalance in observed versus expected cases of myocarditis is seen, especially in males aged 18-29, following the 2nd dose.

As a consequence, the MAH argument (in section 3.1.3) that the higher incidence of post-vaccination myocarditis in young males is confounded by a higher background rate of myocarditis in this population, cannot be acknowledged when considering excessive observed rates in the age, sex and dose-stratified O/E-analyses.

3.1.5. ITEM 5 – discussion of mechanisms

The MAH should further evaluate and discuss potential mechanisms:

- The MAH should consider multisystem inflammatory syndrome (MIS) as an alternative etiology upon evaluation of the myocarditis cases. The MAH should discuss the immunologic mechanism of multisystem inflammatory syndromes (MIS)-induced myocarditis following

COVID-19, and if any parallels can be drawn to the immunologic reactions following vaccination.

- The MAH should review the published literature, and present and discuss relevant publications concerning plausible mechanisms of myocarditis following the vaccination, concerning both COVID-19 vaccine Moderna and vaccines in general.
- The MAH is requested to comment and discuss the potential mechanism of vaccine triggered autoimmune reaction as hypothesized by Garcia et al. in a literature case report concerning a case of myocarditis after 2nd dose in a 39-year-old male physician with a past medical history of auto-immune conditions. (Bautista Garcia J,et al. Acute myocarditis after administration of theBNT162b2 vaccine against COVID-19. Rev Esp Cardiol. 2021. https ://doi .org/10.1016/j. rec. 2021.04.005).

Sponsor Response:

The US CDC, in an internet posting last reviewed May 11, 2021 (https://www.cdc.gov/mis- c/mis-a/hcp.html), provides a case definition of Multisystem Inflammatory Syndrome in Adults (MIS-A) as follows:

D. *Primary clinical criteria*
   - *Severe cardiac illness*
     Includes myocarditis, pericarditis, coronary artery dilatation/aneurysm, or new-onset right or left ventricular dysfunction (LVEF<50%), 2nd/3rd degree A-V block, or ventricular tachycardia. (Note: cardiac arrest alone does not meet this criterion)
   - *Rash AND non-purulent conjunctivitis*

E. *Secondary clinical criteria*
   - *New-onset neurologic signs and symptoms*
     Includes encephalopathy in a patient without prior cognitive impairment, seizures, meningeal signs, or peripheral neuropathy (including Guillain- Barré syndrome)
   - *Shock or hypotension not attributable to medical therapy (e.g., sedation, renal replacement therapy)*
   - *Abdominal pain, vomiting, or diarrhea*
   - *Thrombocytopenia (platelet count <150,000/ microliter*

Except for possibly the primary clinical criterion of severe cardiac illness (primarily myocarditis and pericarditis), the other primary and secondary clinical criteria noted above for MIS-A are not common co-occurring findings in the case reports of myocarditis and pericarditis following mRNA-1273 immunization that we have received. Moreover, the draft Brighton Collaboration Definition of myocarditis does not specifically address severity, and at least some of the cases of reported Brighton levels 1,2 or 3 myocarditis after vaccination would not be classified as severe.

Similarly, a recent publication from Israel reported six cases of myocarditis post-vaccination with BNT162b2 (https://www.sciencedirect.com/science/article/pii/S0264410X21006824?via%3Dihub); in describing the findings in these patients, there was no mention of the above MIS-A non-cardiac signs and symptoms. It was also noted that the disease course was mild in all patients. A recent case series, collected from various medical centers in the USA, of myopericarditis in seven male adolescent BNT162b2 vaccinees specifically noted that none of them met criteria for MIS-C.

(https://pediatrics.aappublications.org/content/pediatrics/early/2021/06/04/peds.2021-052478.full.pdf). In addition, the authors highlighted that "all cardiac MRIs were diagnostic for myocarditis based on the modified Lake Louise criteria rather than MIS-C characteristics described by Blondiaux et al." Further, none of these patients was critically ill, and each was discharged home.

Regarding the immunologic mechanisms of MIS-A-related myocarditis, Tenforde from CDC has written "further research is needed to understand the pathophysiology of cardiac injury, including cellular and molecular mechanisms"…"further studies on the immunopathogenesis of this syndrome are needed" (https://journal.chestnet.org/action/showPdf?pii=S0012-3692%2820%2934519-0). The lack of endomyocardial biopsy studies of MIS-A related myocarditis highlights this challenge.

PRAC Rapporteur assessment comment:

The MAH states that except for myocarditis and pericarditis, the other primary and secondary clinical criteria for MIS-A are "not common co-occurring findings" in the case reports of myocarditis and pericarditis. Although this is acknowledged, it would have been preferred if the MAH had shown the actual numbers of cases with these co-occurring criteria, and discussed whether there were any cases susceptive of MIS among those.

The MAH also highlights that in a literature case series of myopericarditis, it was specifically noted that none of them met the criteria for MIS-C.

Immunologic mechanistic parallels between SARS-CoV-2 infection that sometimes leads to MIS-A and vaccination with mRNA that codes for spike protein to prevent this infection can be addressed. Antibodies generated vs SARS-CoV-2 are greatly more heterogenous than those generated by mRNA-1273 that codes only for spike protein. Shrock et al (Science. 2020 Nov 27; 370(6520): eabd4250) noted that "Deep serological profiling of 232 coronavirus disease 2019 (COVID-19) patients and 190 pre–COVID-19 era controls using VirScan revealed more than 800 [823] epitopes in the SARS-CoV-2 proteome, including 10 epitopes likely recognized by neutralizing antibodies" and "Examination of the humoral response to SARS-CoV-2 at the epitope level using the triple-alanine scanning mutagenesis library revealed 145 (17.6%) epitopes in S, 116 in N, and 562 across the remainder of the SARS-CoV-2 proteome." Thus, 145 epitopes of the spike protein "S" represented only 17.6% of the 823 epitopes of SARS-CoV-2 identified in this study. The other 678 (82.4%) epitopes identified in this study are not spike protein epitopes and therefore not contained in the mRNA-1273 vaccine.

Regarding cellular immunity, in Cell Grifoni et al noted CD4+ T cell responses against M, spike and N proteins, nsp3, nsp4, ORF3s, ORF7a, nsp12, and ORF8. Similar to the serological study noted above, this study focusing on cellular immunity suggests that the immunologic response to SAR-CoV-2 is far broader than simply to spike protein. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7237901/

The case reported by Bautista Garcia involved BNT162b2 and not mRNA1273. This report involves an unusual patient with an extremely rare combination of diverse and significant clinical illnesses that predated his vaccination. These illnesses include asthma, autoimmune hypothyroidism, chronic atrophic gastritis, multiple episodes of spontaneous pneumothorax, and an episode of atrial fibrillation. The time from vaccination to fever above 38 degrees was 6 hours. The time from vaccination to onset of cardiac symptoms post vaccination was not reported. This patient clearly had dysregulation of his immune system prior to vaccination as is evidenced by previously diagnosed autoimmune hypothyroidism (mechanism unspecified), asthma and possibly also his atrophic gastritis. To speculate on a mechanism for his myocarditis, it would be important to begin with his host factors and environment. The autoimmune dysregulation that has resulted in his hypothyroidism, asthma and possibly chronic atrophic gastritis was not described but would be an

excellent place to start to understand a potential mechanism. The challenge of developing such a mechanism is highlighted by the fact that even though there have been very large numbers of clinical cases of myocarditis in patients with SARS-Cov-2 infection, the mechanism of myocarditis has not yet been elucidated (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7816957/). Thus, for this case, mechanistic determination is immensely challenging, especially in the absence of endomyocardial biopsy. If we knew the exact host factor immune defects in this case, we could assess better a potential mechanism for the vaccine's possibly triggering the myocarditis. In this regard, we fully agree with the author of the case report, who best knows the patient, and wrote: "In the case reported here, as often occurs in acute myocarditis, the definitive etiological diagnosis was difficult to determine."

PRAC Rapporteur assessment comment:

The MAH has addressed the immunologic mechanistic parallels between SARS-CoV-2 infection (that sometimes leads to MIS-A) and vaccination by comparing the number of epitopes on SARS-CoV-2 and the spike protein encoded by the vaccine mRNA. It is concluded that the natural infection initiates a broader humoral and cellular immune response compared to the vaccination, due to the more extensive amount of epitopes present on the virus.

No discussion has been provided regarding similarities and differences between infection-driven and vaccine-initiated pro-inflammatory cascades, CD4/CD8 T-cell responses, Th1/Th2/Th17 differentiation, which could impact the development of dysregulated inflammatory reactions.

The MAH has satisfactorily discussed the paper by Baustia Garcia.

3.1.6. ITEM 6 – discussion on need to update product information

In conclusion, the MAH should discuss the need to update the product information and risk management plan, including relevant risk minimisation measures.

Sponsor Response:

In the scientific literature to date we have not noted reports of Myocarditis or Pericarditis following vaccination with mRNA-1273. There have been news reports of the US Department of Defense noting 11 cases of myocarditis after vaccination with mRNA-1273 (https://www.military.com/daily-news/2021/04/26/pentagon-tracking-14-cases-of-heart-inflammation-troops-after-covid-19-shots.html). As noted in our O:E analysis, there is a background rate of myocarditis in the general population. Thus, at least some of the cases of myocarditis following vaccination would definitely have occurred in the absence of vaccination.

The MAH also recognize that there have been reports of myocarditis and pericarditis following vaccination with BNT162b2 (a different mRNA-based vaccine). In addition to the Bautista Garcia article and the US Department of Defense noting three cases, reports have included a published case series from Israel of six male patients (https://www.sciencedirect.com/science/article/pii/S0264410X21006824?via%3Dihub), a multi-center case series of seven adolescent males in the USA (https://pediatrics.aappublications.org/content/pediatrics/early/2021/06/04/peds.2021-052478.full.pdf) in which the authors concluded that "currently no causal association has been established between this vaccine and myopericarditis", and news reports of a nationwide study in Israel (https://pediatrics.aappublications.org/content/pediatrics/early/2021/06/04/peds.2021-052478.full.pdf)–all involving BNT162b2.

Spontaneous adverse event reports involving mRNA-1273 reviewed above show a greater number of reports involving young men after the second dose. The background rates from our O:E analyses show that young men have higher background rates than young women, a potential contributing factor.

The CDC's Advisory Committee on Immunization Practices (ACIP) COVID-19 Vaccine Safety Technical (VaST) Work Group reported on May 24 that data from VAERS show that in the 30- day window following dose 2 mRNA COVID-19 vaccination, there was a higher number of observed than expected myocarditis/pericarditis cases in 16–24-year-olds. (https://www.cdc.gov/vaccines/acip/work-groups-vast/report-2021-05-24.html). To date there have not been to the MAH knowledge any medical/scientific reports of population-based studies that found increased incidence of myocarditis or pericarditis following immunization with mRNA-based vaccines. Indeed, CDC's Vaccine Safety Technical Work Group reported that data from their Vaccine Safety Datalink, which is population-based, "do not show that rates of myocarditis/pericarditis reports in the window following COVID-19 vaccination differ from expected at this time."

At this time, available data are not conclusive. Findings now available may relate to the wide spectrum of severity of myocarditis and pericarditis. There is variation in the reporting of the events, as likely evidenced by the widely varying incidence rates among the European ACCESS sites that could be due to variations in diagnostic procedures, case detection sensitivity and reporting. Moreover, in the USA, such age-based rates are not even readily available. In addition, because there is a background rate of myocarditis that preceded the SARS-CoV-2 pandemic, there is also the possibility that vaccine reactogenicity or simply knowledge of vaccination led to cases coming to clinical attention and reporting that might not have otherwise.

The current situation as outlined above is materially little different from what CDC's VaST Work Group appreciated at the time it made its May 24 report cited above, with the vast majority of the evidence related to BNT162b2 rather than mRNA-1273. Consequently CDC has addressed the issue by posting on its website: "Clinical Considerations: Myocarditis and Pericarditis after Receipt of mRNA COVID-19 Vaccines Among Adolescents and Young Adults" (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html\); this is directed to clinicians and deals with diagnostic evaluation and follow-up, among other issues.

Another, related CDC web posting is "Myocarditis and Pericarditis Following mRNA COVID-19 Vaccination" (https://www.cdc.gov/coronavirus/2019-cov/vaccines/safety/myocarditis.html).

Key points that CDC makes in the latter publication are as follows:

D. "Most patients who received care responded well to medicine and rest and quickly felt better.

E. Cases reported to VAERS have occurred:
   - Mostly in male adolescents and young adults age 16 years or older
   - More often after getting the second dose of one of these two COVID-19 vaccines than after the first dose
   - Typically within several days after COVID-19 vaccination"

The above steps by CDC in the USA, where most doses of mRNA-1273 have been administered, have served to minimize risk without involving change of the product information. At the same time, adverse event surveillance continues, including the performance of population-based pharmacoepidemiological studies aimed at quantifying any potential increase in risk of myocarditis or

pericarditis as well as identifying any possible risk factors. At this time, this approach seems prudent and appropriate.

Based on the analysis of all the safety data available as of 31 May 2021, the MAH considers that Myocarditis and/or Pericarditis are not presently a safety issue of concern that would justify inclusion of "Myocarditis and/or Pericarditis" in the ADR table in section 4.8 of the SmPC nor in section 4 of the PL. The MAH will continue to closely evaluate events of "Myocarditis and/or Pericarditis" using routine surveillance as well as already planned pharmacoepidemiological studies.

PRAC Rapporteur assessment comment:

The MAH considers that Myocarditis and/or Pericarditis are not presently a safety issue of concern that would justify inclusion of "Myocarditis and/or Pericarditis" in the ADR table in section 4.8 of the SmPC nor in section 4 of the PL.

The MAH has not noted any scientific publications regarding reports of Myocarditis or Pericarditis following vaccination with mRNA-1273. However, three recent publications (case reports) have been identified, which are commented upon in section 3.3.

The MAH acknowledge that there were greater number of reports involving young men after the second dose, and argues that background rates from the O:E analyses show that young men have higher background rates than young women. Although it is acknowledged that there is a higher background rate among young men, it does not explain the greater increase in rate ratio following the 2nd dose compared to 1st dose, in men aged 18-29 years.

According to the CDC's ACIP COVID-19 Vaccine Safety Technical (VaST) Work Group, data from VAERS (May 24) show that in the 30- day window following dose 2 mRNA COVID-19 vaccination, there was a higher number of observed than expected myocarditis/pericarditis cases in 16–24-year-olds; a finding in line with the O/E analyses of myocarditis presented in this report. The MAH has no knowledge of any medical/scientific reports of population-based studies that found increased incidence of myocarditis or pericarditis following immunization with mRNA-based vaccines. To the knowledge of the Rapporteur, such studies are ongoing in the European/Nordic setting, and results are expected to be available shortly.

For PRAC Rapporteur discussion and conclusion, see section 3.3

3.1.7. ITEM 1 - PERICARDITIS

Sponsor Response:

The company clinical database and the global safety database were queried for valid, clinical and spontaneous case reports received from HCP, HA, consumers and literature, cumulative from 18 December 2020 to 31 May 2021, worldwide, reported for the mRNA-1273 vaccine (Moderna COVID-19 vaccine Moderna) using the following Preferred Terms (PTs): "***Viral pericarditis; Pericarditis; Pericarditis infective; Myocarditis; Myocarditis septic; Myocarditis infectious; Viral myocarditis; and Myocarditis post-infection***". As of 31 May 2021, there have been 250,275,820 doses of the mRNA vaccine distributed worldwide.

A review of the spontaneous reports from the company's global safety identified 68 case reports with the PTs of Pericarditis. All of the aforementioned reports were considered serious reports. As a difference with the Myocarditis reports, most of the Pericarditis reports (64.7%) involved persons >50 years of age (See Table 11).

Table 11. Number and Percentage of Spontaneous Cases of Pericarditis Reported by Age for the mRNA-1273 vaccine. Cumulative to 31 May 2021

Age in Years	Number of Reports	Percent
12-15	0	0
16-19	1	1
20-24	2	3
25-29	3	4
30-39	13	19
40-49	5	7
50-59	8	12
60-69	15	22
70-79	13	19
80-89	4	6
Not reported	4	6
Total	68	100

There was not an important difference between the reported genders, with 51% Males, and 47% females (See Table 12).

Table 12. Number and Percentage of Spontaneous Cases of Pericarditis Reported by Gender for the mRNA-1273 vaccine. Cumulative to 31 May 2021

Gender	Number of Cases	%
Male	35	51
Female	32	47
Missing	1	1
Total	68	100.00

There was not an important difference in the TTO for the pericarditis cases with 16% reporting a TTO less than 1 day, 18 % for each 2 to 3 days and 4 to 7 days. The majority of the reports reported a TTO of more than 8 days following last vaccination (See Table 13). Occurrence following dose 1 was very similar (37% of reports) to the one seeing following dose 2 (41%). Dose number was not reported in 22% of the cases (See Table 14).

Table 13. Number and Percentage of Spontaneous Cases of Pericarditis Reported by Time-To-Onset (TTO) for the mRNA-1273 vaccine. Cumulative to 31 May 2021

Time to Onset	Number of Reports	%
<=1 day	11	16
2-3 days	12	18

4-7 days	12	18
8-29 days	20	29
>=30 days	4	6
Unknown	9	13
Total	68	100

Table 14. Number and Percentage of Spontaneous Cases of Pericarditis Reported by Dose Number for the mRNA-1273 vaccine. Cumulative to 31 May 2021

Dose	Number of Reports	%
#1	25	37
#2	28	41
Not reported	15	22
Total	68	100

PRAC Rapporteur assessment comment:

The MAH has identified 68 case reports with PTs of Pericarditis, without concurrent myocarditis. In contrast to myocarditis, the cases were not primarily in the younger age group. Only 4% of the reports were patients under the age of 25, and 65% of the reports were in patients >50 years (in myocarditis, only 19% of reports were in age group >50). Of note, 19% were reported in the age group 30-39, which is different from the age groups immediately younger and older. However, as the numbers are relatively low, interpretation should be made with caution.

There reports are equally distributed among sex, and compared to myocarditis, the TTO are more equally distributed up to 30 days. 34 % of the cases are reported within 3 days of vaccination, compared with Myocarditis, where 63% of the cases had a reported event onset within 3 days.

Also regarding 1st and 2nd dose, the reports are equally distributed (37% after dose 1 and 41% after dose 2), as opposed to myocarditis, where a disproportion was noted for 2nd dose.

3.1.8. ITEM 2 – causality assessment

Sponsor Response:

The sponsor conducted and evaluation of all the cases identified as cases of Pericarditis according to the PRAC's recommendation (See Table 15, Annex IV of this report), utilizing the WHO-UMC causality assessment (which allow to perform a combined assessment of the reported cases taking into account the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation)[1].

Based on the assessment conducted on the 68 cases reporting Pericarditis PTs, there were 18 reports that were classified as "Possible" according to the WHO-UMC causality assessment (*Event or laboratory test abnormality, with reasonable time relationship to drug intake; could also be explained by disease or other drugs; information on drug withdrawal may be lacking or unclear*).

The MAH considers that because 1) there are no pathognomonic findings that are indicative of certain vaccine causality of pericarditis; 2) there exists a background incidence of these illnesses that pre-dated mRNA-1273 and 3) it has not been proven that immunization with mRNA-1273 or any mRNA vaccine can cause pericarditis, no cases were classified as certain or probable according to the WHO-UMC causality assessment.

Out of the 68 cases reporting Pericarditis PTs, there were 18 reports that were classified as "Unlikely" according to the WHO-UMC causality assessment (*Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible); Disease or other drugs provide plausible explanations*). (See Table 16, Annex V of this report)

PRAC Rapporteurs assessment comment:

As requested, the MAH has evaluated all cases identified as pericarditis, utilizing the WHO- UMC causality assessment.
A causality assessment was performed on cases that were classified by the MAH as WHO Possible. The assessment included 18 cases where a full case narrative could be retrieved from EudraVigilance.
The cases comprised 9 males and 9 females aged 20-89 years of age (stratified by decades there was one aged 20-29 ys, five aged 30-39 ys, three aged 40-49 ys, one aged 50-59 ys, four aged 60-69, three aged 70-79, and one 80-89 ys.).
Generally, the diagnostic basis for the reported events of pericarditis is rather poor; in several cases pericarditis is reported as an adverse event but the available information is rather incomplete regarding clinical findings and/or tests results and/or symptoms. This has led to 3 cases being concluded as unassessable.
Three cases are considered possible, these are all in younger adults, age range 20-39 ys., of these 2 females after the 1st dose of covid-19 vaccine and 1 male after the 2nd dose. There are 12 cases that are assessed as unlikely.
Summing up on the assessment of causality to the immunization 3 cases are found possible, 12 are found unlikely, while 3 are unassessable. For short summaries of the cases, see below.
3 cases considered WHO Possible:

Case 1
Pericarditis
A 30-39 year old female who 12 days after receiving the 1st dose of covid-19-vaccine experienced chest pain. Ultrasonography showed trace pericardial effusion, ECG abnormalities consistent with pericarditis; the ECG was normalized a week later.
Medical history included pericarditis, Covid-19 in September and November 2020.
The patient is reported allergic to ciprofloxacin and milk.
Symptoms and findings are consistent with pericarditis, and there is a reasonable time relationship to the immunization although it could be temporally coincidental and other causes for pericarditis are not excluded. Therefore, this is **WHO-UMC: Possible**.

Case 2
Pericarditis
A 20-29 year old male who two days after receiving the 2nd dose of covid-19-vaccine experienced chest pain. ECG showed unspecified abnormalities; blood test results included increased biomarker (elevated troponin levels). Furthermore, X-ray, ECHO, MRI scan, and heart catherization were performed, but results are not reported.
Medical history included nasal congestion and cough, sleep apnoea and neurodevelopmental disorder.

- Symptoms and abnormal ECG findings, and a reasonable time relationship to the immunization although it could be temporally coincidental, however other causes for pericarditis not being excluded. Therefore, this is **WHO-UMC: Possible.**

Case 3
Pericarditis
A 30-39 year old female who 5 days after receiving the 1st dose of covid-19-vaccine experienced chest pain, shortness of breath, and fatigue.
ECG demonstrated first degree AV block with right bundle branch block. Additionally, a cardiologist diagnosed her with pericarditis 13 days later.
Medical history was not reported, but medicine included a sedative/hypnotica and contraceptive.

- Pericarditis was diagnosed by a cardiologist. There is a temporal relationship to the immunization. The pericarditis could be due to other causes, however, when considering association to the vaccine a possible relation that she within a few days from receiving the 1st dose had myocarditis leading to the right bundle branch block, pericarditis developed subsequently. Other causes for pericarditis are not excluded. Therefore, this is **WHO-UMC: Possible.**

12 cases considered WHO Unlikely:

Case 1
Pericarditis
A 30-39 year old male who 18 days after receiving the 1st dose of covid-19-vaccine experienced chest pain and ECHO showed pericardial effusion.
Medical history included chronic renal insufficiency secondary to glomerulonephritis membranosa proliferative with hypertension and hyperuricemia and need for dialysis.
Symptoms and findings are consistent with pericarditis. There is a reasonable time relationship to the immunization although it could be temporally coincidental. The patient suffers from chronic renal failure which is a plausible cause of pericarditis. Therefore, this is WHO-UMC: Unlikely.

Case 2
Pericarditis
A 60-69 year old male who four days after receiving the 2nd dose of covid-19-vaccine experienced onset of fever and symptoms with malaise, fatigue, fever, chest discomfort and dyspnoea.
ECHO showed effusion.
Medical history included type 2 diabetes, depression, hyperlipidemia.
Symptoms and findings are consistent with pericarditis. However, onset of fever with other symptoms not until four days after vaccination is more likely to be infection-related, temporally coincidental to the immunization, and other causes for pericarditis are more likely. Therefore, this is WHO-UMC: Unlikely.

Case 3
Pericarditis
A 40-49 year old female who the day after receiving the 2nd dose of covid-19-vaccine experienced a variety of symptoms including chest pain, painful respiration, cold sweat, hyperhidrosis, vomiting, presyncope and more widespread pain.
The only paraclinical results reported are ECG with ST-elevations. ECHO performed but not described.
Concomitant disease was Covid-19.
Symptoms and findings may be due to other conditions including other cardial conditions e.g. infarction. Furthermore, in case of pericarditis, there could be a causal relationship to the concomitant Covid-19

disease. The time relationship to immunization may therefore be coincidental. This is WHO-UMC: Unlikely.

Case 4
Pericarditis
A 40-49 year old male who 7 days after receiving a dose of covid-19-vaccine, unknown if it was the 1st or 2nd, experienced thoracal back pain and later painful respiration.
CT scan demonstrated pericardial and pleural fluid. Blood test results reported comprise increased CRP and increased sedimentation rate, both being unspecific inflammation markers.
Medical history included colitis ulcerosa, and the patient was treated with anti-TNF-alpha-antibodies. (immunosuppressive).
Symptoms and findings are consistent with pericarditis, however, also pleuritis was demonstrated, other health issues in this patient provide plausible explanations, and the time relationship to immunization may therefore be coincidental. This is WHO-UMC: Unlikely.

Case 5
Pericarditis
A 70-79 year old male who the day after receiving the 2nd dose of covid-19-vaccine experienced chest pain, more widespread pain, loss of appetite, somnolence and chills.
He had high fever, ECG with normal sinus rhythm, chest X-ray showed cardiomegaly, CT scan demonstrated pulmonary embolism, Fibrin D-dimer was highly increased.
Medical history included bigeminy, scleroderma, essential tremor and bowel obstruction.
Allergies included drug allergy and unspecified food allergy.
The patient had cardiomegaly and lung embolism, hence other health issues in this patient provide plausible explanations, and the time relationship to immunization may therefore be coincidental. This is WHO-UMC: Unlikely.

Case 6
Pericarditis
A 70-79 year old female who the day after receiving the 2nd dose of covid-19-vaccine experienced myalgia, fatigue, pyrexia, consistent with known side effects to the vaccine, furthermore mental impairment.
As late as 46 days after the 2nd dose of covid-19-vaccine she got pericarditis; no test results or findings from physical examination are reported.
Medical history includes hypertension, rheumatoid arthritis, allergy to seafood.

Report suggesting pericarditis and atrial fibrillation as an adverse reaction. However, there is no test results or findings from physical examination to support or contradict the suggested diagnosis. This case cannot be judged due to the available information being insufficient. WHO-UMC Unassessable.
In case of test results being reported later the temporal relationship is improbable and other explanations could be plausible making it WHO-UMC: Unlikely.

Case 7
Pericarditis
A 40-49 year old female who 3 days after receiving the 2nd dose of covid-19-vaccine experienced an extremely wide variety of symptoms of which some as myalgia, fatigue, pyrexia are consistent with known side effects to the vaccine, anxiety which be an immunization-related anxiety reaction, to

symptoms as cardiac pain and short of breath and gastrointestinal symptoms which could be either anxiety-related or on somatic basis.
She was thoroughly tested, high blood pressure was demonstrated on the day of hospitalization. Endoscopy of upper gastrointestinal tract showed hiatus hernia and gastritis.
All other tests were found normal, these tests were: ECG, ECHO, chest X-ray, CT scan, ultrasonography, biopsy, colonoscopy, stress test and blood test.
Concurrent medical conditions included thyreoiditis.

- This patient experienced an extremely wide variety of symptoms, pericarditis was reported as suggested adverse reaction. This patient has been thoroughly examined corresponding to the many symptoms, and there is no test result or finding to support or contradict the suggested diagnoses; in fact, the test results show no pericarditis. Therefore WHO-UMC: Unlikely.

Case 8
Pericarditis
A 30-39 year old female who 23 days after receiving the 1st dose of covid-19-vaccine was hospitalized for pericarditis. No symptoms are reported. No physical examination or test results are reported.
Medical history included hypothyreoidism, cerebral infarction, thalassemia, allergy.

- According to the literature there is an association between pericardial effusion or pericarditis and hypothyreoidism. Therefore, in this case other health issues provide plausible explanations, furthermore the temporal relationship to immunization may be coincidental. This is therefore assessed as WHO-UMC: Unlikely.

Case 9
Pericarditis
A 70-79 year old female who 21 days after receiving the 1st dose of covid-19-vaccine was medically examined having several blood tests, respiratory viral PCR, ECG, ECHO. Pericardial effusion was reported, but no other test results, and no symptoms were reported.
Medical history included hypertension and primary biliary cirrhosis.
Furthermore, a list of concomitant medicines was reported including for hypertension, gall stones, allergy, asthma, anxiety.

- The pericarditis is according to the available information diagnostically only supported by pericardial effusion; other plausible explanations are not excluded, and the 21 days long time relationship to immunization may be coincidental. This is WHO-UMC: Unlikely.

Case 10
Pericarditis
A 50-59 year old female who 18 days after receiving the 1st dose of covid-19-vaccine experienced thoracal pain and dyspnoea. Medical examinations included increased CRP, increased fibrin D-dimer, increased leucocytes, abnormal full blood count, increased platelet concentration, abnormal liver parameters. A covid-19 virus test was positive. ECHO demonstrated pericardial effusion, pleural effusion, pneumonitis. Hepatitis was also diagnosed.

- Symptoms and test results are compatible with pericarditis as one of more diagnoses also comprising pneumonitis with pleural effusion and hepatitis, the temporal relationship is a little long and may be coincidental taking all other concurrent diagnoses into account. Furthermore, other conditions could provide plausible explanations. WHO-UMC: Unlikely.

Case 11
Pericarditis

A 60-69 year old male who approximately 9 days after receiving the 1st dose of covid-19-vaccine experienced fever and chills, lymphadenopathy, chest pain and painful respiration.
Clinical findings included blood tests, test for SARS-CoV-2, urinanalysis, ECG, chest X-ray, ECHO, pericardiocentesis, pericardial fluid analysis. No test results provided.
Medical history included hypertension, recurrent syncopal episodes, atrial fibrillation, reflux disease and anxiety with concomitant medication corresponding to more of these diagnoses.

- Despite the temporal association to immunization, onset of fever and chills as late as nine days after immunization talk against these symptoms being general side effects and together with the lymphadenopathy, they suggest an underlying disease as e.g. infection. Underlying disease as suspected due to fever and lymphadenopathy could provide plausible explanations for the reported pericarditis. This case is WHO-UMC: Unlikely.

Case 12
Pericarditis
A 60-69 year old male who approximately 9 days after receiving the 1st dose of covid-19-vaccine experienced severe chest pain and dyspnoea. According to the provided information, he himself suspected having pericarditis but did not seek medical attention, instead he self-medicated himself using an over-the-counter painkiller; nevertheless, the chest pain and dyspnoea continued for 8 days whereupon he called for emergency help, ST-elevation myocardial infarction was found. He died. Clinical findings were ST-elevation myocardial infarction.
Medical history included hypertension, hyperlipidemia, pericarditis.

- This patient had symptoms consistent with cardiac symptoms for 8 days whereupon test results demonstrated acute myocardial infarction with ST-elevations. Among risk factors were hypertension, hyperlipidemia and being of male gender; hence underlying health issues provide plausible explanations for the event, including that the delay in seeking medical attention may well have worsened the situation. Pericarditis was suspected by the patient, but not diagnosed. There is a temporal association to the vaccination, however considering the course this is likely to be coincidental. WHO-UMC. Unlikely.

3 cases considered WHO Unassessable:

Case 1
Pericarditis
A 30-39 year old male who 3 days after receiving the 2nd dose of covid-19-vaccine experienced chest pain, dyspnoea and paraesthesia. CT scan, MRI scan and ultrasonography were performed, but results are not provided.
No medical history was reported, however, concomitant medication included 5-alpha-reductase inhibitor.
Due to lack of reported results including from the three performed scans, the information is insufficient both regarding the diagnosis (only perceived symptoms) and regarding possible etiology. Therefore, this case is WHO-UMC: Unassessable.

Case 2
Pericarditis
A 60-69 year old female who the first and second day after receiving the 2nd dose of covid-19-vaccine experienced symptoms compatible with known side effects to the vaccine, e.g. body aches, headache, fever, chills, muscle stiffness.
Three to four days after the vaccination she reported painful respiration, tremor and had atrial fibrillation treated with medication. Furthermore, heart murmur and pericarditis are reported. However, no findings from medical examination or test results are provided.

Report suggesting pericarditis as an adverse reaction. However, there is no test results or findings from physical examination to support or contradict the suggested diagnosis. This case cannot be judged due to the available information being insufficient. WHO-UMC Unassessable.

Case 3
Pericarditis
An 80-89 year old male who the day after receiving the 2nd dose of covid-19-vaccine experienced malaise, chest pain, dyspnoea, asthenia.
Chest X-ray, chest CT scan, and ECG were performed, but all are reported as being inconclusive.
Report suggesting pericarditis and atrial fibrillation as an adverse reaction. However, there is no test results or findings from physical examination to support or contradict the suggested diagnosis. This case cannot be judged due to the available information being insufficient. WHO-UMC Unassessable.

3.1.9. ITEM 3 – risk factors / Pericarditis

The review should explore possible risk factors, taking into account the gender, age, and dose distribution of reported cases. Specifically, the MAH is requested to comment on the number of cases occurring after the 2nd dose as compared to the 1st dose, also considering the differences in exposure for these two groups. The MAH should discuss whether any patterns or trends can be identified concerning risk factors.

Sponsor Response:

Acute pericarditis is an inflammatory process involving the pericardium that results in a clinical syndrome characterized by chest pain, pericardial friction rub, changes in the electrocardiogram (ECG) and occasionally, a pericardial effusion. Generally, the diagnosis requires 2 of these 4 features.

Epidemiologic data on the incidence of acute pericarditis are lacking, likely because this condition is frequently inapparent clinically, despite its presence in numerous disorders. However, it appears to be the most common form of pericardial disease and a relatively common cause of chest pain. Acute pericarditis is the most common affliction of the pericardium. It is diagnosed in approximately 0.1% of patients hospitalized for chest pain and in 5% of patients admitted to the emergency department for chest pain unrelated to acute myocardial infarction (MI). Although acute pericarditis occurs in all age groups and in men and women, it presents most often in men 20 to 50 years of age. The most common form of acute pericarditis is idiopathic, which accounts for about 90% of cases. Other common causes include infection, renal failure, myocardial infarction (MI), post-cardiac injury syndrome, malignancy, radiation, and trauma. Acute pericarditis is more common in men than in women. However, although this condition is more common in adults than in children, adolescents are more commonly affected than young adults.

There were no important differences observed in the cases reported with Pericarditis, as explained above, regarding age, gender, or TTO after the 1st or the 2nd dose of the mRNA-1273 vaccine.

No other important trending was observed with the reported cases of Pericarditis.

PRAC Rapporteur assessment comment:

The MAH has shortly presented risk factors, and states that pericarditis can occur in all age groups, in both men and women, however presents most often in men 20-50 years of age. 90% of cases are

idiopathic; other causes include infection, renal failure, myocardial infarction (MI), post-cardiac injury syndrome, malignancy, radiation, and trauma. The MAH concludes that no important differences were observed in the cases reported with Pericarditis, regarding age, gender, or TTO after the 1st or the 2nd dose of the mRNA-1273 vaccine, and no other important trending was observed with the reported cases of Pericarditis.

3.1.10. ITEM 4 – O/E analyses

Specific O/E analyses should be performed for the 1st dose and 2nd dose receivers respectively. Thus, for the cumulative review, 0/E analyses should be stratified by age, gender and dose (l5t or 2nd). For the analyses, the MAH should clearly state and justify the background rates used. The MAH should retrieve the most relevant background rates and take the source of the cases into consideration. Several risk windows should be considered (14 and 21 days). In the 0/E analysis, the MAH is requested to perform adjustment for underreporting, backlog of case handling and sensitivity analysis.

Sponsor Response:

In the US, acute pericarditis has been observed at a rate of 5.73 - 26 per 100,000 person-years, and at a rate of 0.25 - 55 per 100,000 individuals' post-vaccination(6). The MAH was able to find few estimates of the incidence of pericarditis. Sources describing the incidence of pericarditis specifically in the US were not identified, and the individual condition is not described by the ACCESS study. However, some data in Europe have been published. A prospective clinical cohort study in Italy identified an incidence of 27.7 cases per 100,000 person-years. Another study, a retrospective analysis of Finnish registry data capturing admissions to 29 hospitals over a span of 9.5 years identified an age standardized incidence of 3.32 per 100,000 person-years, with higher rates in men ages 16-65.15 Hospitalization is not necessary for all cases of pericarditis; thus, hospitalization rates for pericarditis are underestimates of the overall incidence of the disease. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2878263/)

Stratification by age, gender and dose number was conducted applying two different risk windows, a 14-day risk window and a 21-day risk window. The stratification with a 14-day risk window shows an increase in the observed to expected for both males and females ages 18-29 when comparing reporting rates to the **Finland (Kyto 2014)** estimates (See Table 18).

When adding stratification by dose and by the 14-day risk window, the data show the same pattern for males after the first dose, but a larger increase after dose 2. Comparison to the **Finland (Kyto 2014)** estimates shows a small increase in the reporting rate for males 18-29 years of age following dose 1 and a larger increase in the reporting rate following dose 2 (See Table 18). The same increase is noted using the 21-day risk windows (See Table 19). Interesting to note is that an increase for women in the same age group (18-29 years old) is also observed in the overall analysis, but when stratifying by age and dose and the two risk windows, the increase is also observed in the 30-39 years old group (See Tables 18 and 19).

PRAC Rapporteur assessment comment:

Since the ACCESS project does not include pericarditis in the background rate calculations, the MAH has looked into background incidences from different sources. Background incidence estimates included data from the US (5.73 – 26 cases per 100,000 PY), Italy (27.7 cases per 100,000 PY) and Finland (3.32 per 100,000 PY – hospital records). In the data from Finland, there were higher rates in

men ages 16-65 years. The MAH points out that since hospitalisation is not necessary for all cases of pericarditis, rates deriving from hospital records might underestimate the true incidence rate, which could explain the lower incidence in the Finnish data.

It was unclear to the assessor which "observed" data that was used for calculations of Observed/Expected. On 28 Jun 2021, the MAH provided clarification and also updated Observed/Expected calculations, both for "pericarditis with myocarditis", and for "pericarditis without myocarditis". See Annex VI for the MAH response. In the analyses, no conclusions can be drawn regarding the "pericarditis without myocarditis", based on low numbers in each category. For the analyses regarding "pericarditis with or without myocarditis", it is evident that more cases are observed in the younger age groups (males 18-29 years), after the 2nd dose; a finding of borderline significance (lower bound of 95% CI>1), however with no adjustment for underreporting.

3.1.11. ITEM 5 – discussion of mechanisms

The MAH should further evaluate and discuss potential mechanisms:

F. **The MAH should consider multisystem inflammatory syndrome (MIS) as an alternative etiology upon evaluation of the pericarditis cases. The MAH should discuss the immunologic mechanism of multisystem inflammatory syndromes (MIS)-induced pericarditis following COVID-19, and if any parallels can be drawn to the immunologic reactions following vaccination.**

G. **The MAH should review the published literature, and present and discuss relevant publications concerning plausible mechanisms of pericarditis following the vaccination, concerning both COVID-19 vaccine Moderna and vaccines in general.**

Sponsor Response:

With regard to pericarditis, multisystem inflammatory syndrome (MIS) and potential mechanisms, the MAH's discussion of this issue related to Myocarditis in this report remains relevant and applicable for cases of Pericarditis. Moreover, similar to the situation with the cases who had myocarditis, the cases who had pericarditis did not commonly exhibit other clinical criteria of the adult form of MIS that was described in detail above. (See *section 3.1.5 ITEM 5* for reports of Myocarditis)

PRAC Rapporteur assessment comment: please refer to comment in section 3.1.5.

3.1.12. ITEM 6 – discussion on the need to update product information

In conclusion, the MAH should discuss the need to update the product information and risk management plan, including relevant risk minimisation measures.

The PRAC will assess the MAH's answers to this List of questions within an accelerated timetable, which would allow for the following PRAC discussion to take place in July 2021 PRAC.

Sponsor Response:

As discussed above under *section 3.1.6 ITEM 6* of the Myocarditis evaluation, at this time, available data is not conclusive. The CDC communications described in *section 3.1.6 ITEM 6* above address both myocarditis and pericarditis. Findings now available may relate to the wide spectrum of severity

of myocarditis and pericarditis. There is variation in the reporting of the events, as likely evidenced by the widely varying incidence rates among the European ACCESS sites that could be due to variations in diagnostic procedures, case detection sensitivity and reporting. Moreover, in the USA, such age-based rates are not even readily available. In addition, because there is a background rate of myocarditis and pericarditis that preceded the SARS-CoV-2 pandemic, there is also the possibility that vaccine reactogenicity or simply knowledge of vaccination led to cases coming to clinical attention and reporting that might not have otherwise.

Based on the analysis of all the safety data available as of 31 May 2021, the MAH considers that Myocarditis and/or Pericarditis are not presently a safety issue of concern that would justify inclusion of "Myocarditis and/or Pericarditis" in the ADR table in section 4.8 of the SmPC nor in section 4 of the PL. The MAH will continue to closely evaluate events of "Myocarditis and/or Pericarditis" using routine surveillance as well as already planned pharmacoepidemiological studies.

PRAC Rapporteur assessment comment:

The MAH concludes that available data is not conclusive. The MAH further highlights the variation among reporting of events, diagnostic procedures, case detection sensitivity, and that vaccine reactogenicity or simply knowledge of vaccination led to cases coming to clinical attention and reporting that might not have otherwise. It is acknowledged that the COVID-19 vaccines with the concurrent media attention and national local initiatives to enhance reporting of adverse events, have increased the reporting, hence, compared to other medicinal products, the under-reporting of events might not be as high as for other products.

3.2. Latest OE analysis by gender – DLP 13 June

An updated OE analyses with a DLP 13 June 2021 was provided by the EMA. For full presentation, please refer to Annex VII

Myocarditis

EUROPEAN

ARS Males

Legend
OE point est. > 1 **OE point est. > 1 and lower bound of 95% CI > 1**

Comirnaty

TTO missing (17)
TTO > 42d (7)

Myocarditis	IR per 100,000 Py	Doses	Expected 14d	Observed 14d	OE 14d with 95% c.i.	Expected 42d	Observed 42d	OE 42d with 95% c.i.
18-24	20.20	2,045,490	13.01	30	2.31 (1.56 - 3.29)	24.20	31	1.28 (0.87 - 1.82)
25-29	20.20	1,964,917	12.91	11	0.85 (0.42 - 1.52)	24.87	13	0.52 (0.28 - 0.89)
30-39	13.86	5,161,976	23.26	18	0.77 (0.46 - 1.22)	44.82	19	0.42 (0.26 - 0.66)
40-49	10.85	9,219,525	32.55	8	0.25 (0.11 - 0.48)	62.70	10	0.16 (0.08 - 0.29)
50-59	8.48	16,834,588	45.78	18	0.39 (0.23 - 0.62)	82.87	20	0.24 (0.15 - 0.37)
60-69	4.81	16,356,118	27.15	9	0.33 (0.15 - 0.63)	52.92	10	0.19 (0.09 - 0.35)
70-79	3.82	20,740,645	29.25	5	0.17 (0.06 - 0.40)	60.94	6	0.10 (0.04 - 0.21)
80+	4.80	14,370,423	26.18	3	0.11 (0.02 - 0.33)	63.10	5	0.08 (0.03 - 0.18)
Missing	-		-	1		-	1	
Total		86,693,682	**210.1**	**103**	**0.49 (0.40 - 0.59)**	**416.4**	**115**	**0.28 (0.23 - 0.33)**

Moderna

TTO missing (1)
TTO > 42d (0)

18-24	20.20	278,725	1.87	7	3.75 (1.50 - 7.73)	3.27	7	2.14 (0.86 - 4.42)
25-29	20.20	261,300	1.72	2	1.16 (0.13 - 4.20)	3.07	3	0.98 (0.20 - 2.86)
30-39	13.86	726,805	3.28	3	0.91 (0.18 - 2.67)	5.85	3	0.51 (0.10 - 1.50)
40-49	10.85	1,358,230	4.81	2	0.42 (0.05 - 1.50)	8.57	2	0.23 (0.03 - 0.84)
50-59	8.48	2,520,454	6.99	0	0.00 (0.00 - 0.52)	11.72	1	0.09 (0.00 - 0.47)
60-69	4.81	2,202,752	3.63	1	0.28 (0.00 - 1.53)	6.82	2	0.29 (0.03 - 1.06)
70-79	3.82	2,252,130	3.15	1	0.32 (0.00 - 1.77)	6.67	1	0.15 (0.00 - 0.83)
80+	4.80	1,348,664	2.43	0	0.00 (0.00 - 1.51)	5.75	0	0.00 (0.00 - 0.64)
Missing	-		-			-		
Total		10,949,060	**27.9**	**16**	**0.57 (0.33 - 0.93)**	**51.7**	**19**	**0.37 (0.22 - 0.57)**

Vaxzevria

TTO missing (1)
TTO > 42d (1)

18-24	20.20	456,253	3.17	7	2.21 (0.89 - 4.55)	5.95	8	1.34 (0.58 - 2.65)
25-29	20.20	593,330	4.19	2	0.48 (0.05 - 1.72)	7.99	2	0.25 (0.03 - 0.90)
30-39	13.86	1,850,953	8.97	1	0.11 (0.00 - 0.62)	17.10	4	0.23 (0.06 - 0.60)
40-49	10.85	2,658,314	10.09	2	0.20 (0.02 - 0.72)	19.24	2	0.10 (0.01 - 0.38)
50-59	8.48	3,185,013	9.58	2	0.21 (0.02 - 0.75)	18.12	2	0.11 (0.01 - 0.40)
60-69	4.81	8,263,449	14.74	1	0.07 (0.00 - 0.38)	29.51	2	0.07 (0.01 - 0.24)
70-79	3.82	3,340,432	4.70	3	0.64 (0.13 - 1.86)	9.74	3	0.31 (0.06 - 0.90)
80+	4.80	457,639	0.79	0	0.00 (0.00 - 4.63)	1.60	1	0.63 (0.01 - 3.48)
Missing	-		-			-		
Total		20,805,383	**56.2**	**18**	**0.32 (0.19 - 0.51)**	**109.2**	**24**	**0.22 (0.14 - 0.33)**

Myocarditis

ARS Females

Legend
OE point est. > 1 **OE point est. > 1 and lower bound of 95% CI > 1**

Comirnaty

TTO missing (8)
TTO > 42d (3)

Myocarditis	IR per 100,000 Py	Doses	Expected 14d	Observed 14d	OE 14d with 95% c.i.	Expected 42d	Observed 42d	OE 42d with 95% c.i.
18-24	4.55	2,863,016	4.10	7	1.71 (0.68 - 3.52)	7.62	7	0.92 (0.37 - 1.89)
25-29	4.55	2,968,820	4.39	2	0.46 (0.05 - 1.64)	8.46	2	0.24 (0.03 - 0.85)
30-39	3.07	7,272,446	7.25	7	0.97 (0.39 - 1.99)	13.97	10	0.72 (0.34 - 1.32)
40-49	4.30	12,245,193	17.11	6	0.35 (0.13 - 0.76)	32.97	6	0.18 (0.07 - 0.40)
50-59	3.46	19,348,272	21.47	12	0.56 (0.29 - 0.98)	38.86	13	0.33 (0.18 - 0.57)
60-69	4.20	18,057,033	26.17	7	0.27 (0.11 - 0.55)	51.01	12	0.24 (0.12 - 0.41)
70-79	4.83	23,403,089	41.74	7	0.17 (0.07 - 0.35)	86.96	8	0.09 (0.04 - 0.18)
80+	2.86	22,209,884	24.10	4	0.17 (0.04 - 0.42)	58.08	5	0.09 (0.03 - 0.20)
Missing	-		-	3		-	3	
Total		108,367,753	**146.3**	**55**	**0.38 (0.28 - 0.49)**	**297.9**	**66**	**0.22 (0.17 - 0.28)**

Moderna

TTO missing (1)
TTO > 42d (0)

18-24	4.55	400,041	0.60	2	3.32 (0.37 - 11.97)	1.06	2	1.90 (0.21 - 6.84)
25-29	4.55	381,049	0.56	2	3.54 (0.40 - 12.78)	1.01	2	1.99 (0.22 - 7.17)
30-39	3.07	1,016,262	1.02	1	0.98 (0.01 - 5.48)	1.81	1	0.55 (0.01 - 3.07)
40-49	4.30	1,695,995	2.38	1	0.42 (0.01 - 2.34)	4.24	1	0.24 (0.00 - 1.31)
50-59	3.46	2,712,069	3.07	1	0.33 (0.00 - 1.81)	5.14	1	0.19 (0.00 - 1.08)
60-69	4.20	2,432,681	3.50	0	0.00 (0.00 - 1.05)	6.57	0	0.00 (0.00 - 0.56)
70-79	4.83	2,634,740	4.65	2	0.43 (0.05 - 1.55)	9.87	2	0.20 (0.02 - 0.73)
80+	2.86	2,256,959	2.42	0	0.00 (0.00 - 1.51)	5.73	0	0.00 (0.00 - 0.64)
Missing	-		-			-		
Total		13,529,796	**18.2**	**9**	**0.49 (0.23 - 0.94)**	**35.4**	**9**	**0.25 (0.12 - 0.48)**

Vaxzevria

TTO missing (4)
TTO > 42d (0)

18-24	4.55	761,885	1.19	0	0.00 (0.00 - 3.08)	2.24	0	0.00 (0.00 - 1.64)
25-29	4.55	965,171	1.53	3	1.95 (0.39 - 5.71)	2.93	4	1.37 (0.37 - 3.50)
30-39	3.07	2,448,750	2.63	3	1.14 (0.23 - 3.34)	5.01	3	0.60 (0.12 - 1.75)
40-49	4.30	3,651,636	5.49	3	0.55 (0.11 - 1.60)	10.46	3	0.29 (0.06 - 0.84)
50-59	3.46	4,145,930	5.09	4	0.79 (0.21 - 2.01)	9.62	6	0.62 (0.23 - 1.36)
60-69	4.20	8,490,655	13.23	8	0.60 (0.26 - 1.19)	26.48	8	0.30 (0.13 - 0.60)
70-79	4.83	3,766,059	6.70	3	0.45 (0.09 - 1.31)	13.88	3	0.22 (0.04 - 0.63)
80+	2.86	667,347	0.69	0	0.00 (0.00 - 5.33)	1.39	0	0.00 (0.00 - 2.64)
Missing	-		-			-		
Total		24,897,433	**36.5**	**24**	**0.66 (0.42 - 0.98)**	**72.0**	**27**	**0.37 (0.25 - 0.55)**

Considerations on the OE results – Myocarditis

Looking at the 14-day risk period (where the vast majority of cases were received), the results show:

- **OE ratio > 2 in the male 18-24 group for all three vaccines** (stat. significant for COM & MOD)
- OE ratio ~ 1 in the male 25-29 group for COM and MOD, lower for AZ
- More fragmented picture in the female group: OE ratio > 1 for COM 18-24; OE ratio > 1 for AZ 25-29; OE ratio > 3 for MOD 18-24 and 25-29
- **Sensitivity analysis** uses much lower rates (THIN UK), therefore OE ratio > 9 in male 18-24 and OE ratio > 2 in male 25-29 for all three vaccines
- **Caveats** of the analysis:
  - The OE analysis should be treated as a tool for signal detection rather than signal validation. The comparison of EV event rates with those observed in healthcare records should be interpreted cautiously, for contextualisation only
  - The extent of underreporting in EV is not known (presumably low for serious events such as myocarditis)
  - The analysis did not include the age group 15-17 because of the lack of exposure data from ECDC/MSs; 6 cases of myocarditis were reported to EV, 5 for Comirnaty (of which 4 from DE) and 1 for Moderna (all males)

PRAC Rapporteur assessment comment:

The EMA has performed an updated O/E analysis of cases of myocarditis in the EU/EEA with a DLP 13 June 2021. The analysis was made using the background incidence from the ACCESS database ARS, which includes outcomes from primary and secondary care. The observed cases included cases from Eudravigilance retrieved from HLT infectious myocarditis and HLT Noninfectious myocarditis.

The number of observed cases of myocarditis with Moderna are low, which could be explained by the fact the US cases are not included in the analysis.

Statistically significant OE ratios were observed in the male group aged 18-24 for Comirnaty and Moderna, when using a 14 day risk window. The analyses have not been stratified into 1st dose and 2nd dose. For the other age groups and females, the numbers are considered too low in order to draw any conclusions.

Nevertheless, these results are in line with the findings from the more robust overall O/E analyses performed by the MAH, for which both EEA and US cases were included, indicating a higher risk in young males.

Myocarditis and Pericarditis

EUROPEAN

ARS Males

Legend
OE point est. > 1 **OE point est. > 1 and lower bound of 95% CI > 1**

Comirnaty

TTO missing (23)
TTO > 42d (12)

Myo/Peri	IR per 100,000 Py	Doses	Expected 14d	Observed 14d	OE 14d with 95% c.i.	Expected 42d	Observed 42d	OE 42d with 95% c.i.
18-24	36.69	2,045,490	23.64	32	1.35 (0.93 - 1.91)	43.96	33	0.75 (0.52 - 1.05)
25-29	36.69	1,964,917	23.45	15	0.64 (0.36 - 1.06)	45.17	17	0.38 (0.22 - 0.60)
30-39	33.40	5,161,976	56.08	25	0.45 (0.29 - 0.66)	108.04	27	0.25 (0.16 - 0.36)
40-49	35.66	9,219,525	106.93	14	0.13 (0.07 - 0.22)	206.00	19	0.09 (0.06 - 0.14)
50-59	36.95	16,834,588	199.47	30	0.15 (0.10 - 0.21)	361.10	32	0.09 (0.06 - 0.13)
60-69	43.91	16,356,118	247.86	23	0.09 (0.06 - 0.14)	483.11	29	0.06 (0.04 - 0.09)
70-79	63.87	20,740,645	489.51	15	0.03 (0.02 - 0.05)	1,019.82	19	0.02 (0.01 - 0.03)
80+	77.47	14,370,423	422.82	12	0.03 (0.01 - 0.05)	1,019.07	19	0.02 (0.01 - 0.03)
Missing	-		-	1		-	2	
Total		86,693,682	**1,569.8**	**167**	**0.11 (0.09 - 0.12)**	**3,286.3**	**197**	**0.06 (0.05 - 0.07)**

Moderna

TTO missing (3)
TTO > 42d (1)

18-24	36.69	278,725	3.39	8	2.36 (1.02 - 4.65)	5.93	8	1.35 (0.58 - 2.66)
25-29	36.69	261,300	3.13	5	1.60 (0.52 - 3.73)	5.57	6	1.08 (0.39 - 2.34)
30-39	33.40	726,805	7.92	4	0.51 (0.14 - 1.29)	14.11	5	0.35 (0.11 - 0.83)
40-49	35.66	1,358,230	15.79	3	0.19 (0.04 - 0.56)	28.15	3	0.11 (0.02 - 0.31)
50-59	36.95	2,520,454	30.46	2	0.07 (0.01 - 0.24)	51.06	3	0.06 (0.01 - 0.17)
60-69	43.91	2,202,752	33.12	3	0.09 (0.02 - 0.26)	62.22	4	0.06 (0.02 - 0.16)
70-79	63.87	2,252,130	52.64	3	0.06 (0.01 - 0.17)	111.65	4	0.04 (0.01 - 0.09)
80+	77.47	1,348,664	39.27	0	0.00 (0.00 - 0.09)	92.86	0	0.00 (0.00 - 0.04)
Missing	-		-			-		
Total		10,949,060	**185.7**	**28**	**0.15 (0.10 - 0.22)**	**371.6**	**33**	**0.09 (0.06 - 0.12)**

Vaxzevria

TTO missing (1)
TTO > 42d (2)

18-24	36.69	456,253	5.75	7	1.22 (0.49 - 2.51)	10.81	8	0.74 (0.32 - 1.46)
25-29	36.69	593,330	7.61	3	0.39 (0.08 - 1.15)	14.51	3	0.21 (0.04 - 0.60)
30-39	33.40	1,850,953	21.62	3	0.14 (0.03 - 0.41)	41.22	6	0.15 (0.05 - 0.32)
40-49	35.66	2,658,314	33.15	3	0.09 (0.02 - 0.26)	63.20	3	0.05 (0.01 - 0.14)
50-59	36.95	3,185,013	41.73	4	0.10 (0.03 - 0.25)	78.96	6	0.08 (0.03 - 0.17)
60-69	43.91	8,263,449	134.57	5	0.04 (0.01 - 0.09)	269.43	6	0.02 (0.01 - 0.05)
70-79	63.87	3,340,432	78.66	6	0.08 (0.03 - 0.17)	162.93	6	0.04 (0.01 - 0.08)
80+	77.47	457,639	12.79	0	0.00 (0.00 - 0.29)	25.79	1	0.04 (0.00 - 0.22)
Missing	-		-			-		
Total		20,805,383	**335.9**	**31**	**0.09 (0.06 - 0.13)**	**666.9**	**39**	**0.06 (0.04 - 0.08)**

Myocarditis and Pericarditis

EUROPEAN

ARS Females

Legend
OE point est. > 1 **OE point est. > 1 and lower bound of 95% CI > 1**

Comirnaty

TTO missing (20)
TTO > 42d (8)

Myo/Peri	IR per 100,000 Py	Doses	Expected 14d	Observed 14d	OE 14d with 95% c.i.	Expected 42d	Observed 42d	OE 42d with 95% c.i.
18-24	15.43	2,863,016	13.92	12	0.86 (0.44 - 1.51)	25.88	14	0.54 (0.30 - 0.91)
25-29	15.43	2,968,820	14.90	5	0.34 (0.11 - 0.78)	28.71	5	0.17 (0.06 - 0.41)
30-39	15.03	7,272,446	35.54	22	0.62 (0.39 - 0.94)	68.47	25	0.37 (0.24 - 0.54)
40-49	22.11	12,245,193	88.06	18	0.20 (0.12 - 0.32)	169.65	21	0.12 (0.08 - 0.19)
50-59	26.25	19,348,272	162.88	27	0.17 (0.11 - 0.24)	294.87	32	0.11 (0.07 - 0.15)
60-69	36.82	18,057,033	229.45	16	0.07 (0.04 - 0.11)	447.23	24	0.05 (0.03 - 0.08)
70-79	42.48	23,403,089	367.32	19	0.05 (0.03 - 0.08)	765.25	24	0.03 (0.02 - 0.05)
80+	57.54	22,209,884	485.36	11	0.02 (0.01 - 0.04)	1,169.82	14	0.01 (0.01 - 0.02)
Missing	-		-	5		-	5	
Total		108,367,753	**1,397.4**	**135**	**0.10 (0.08 - 0.11)**	**2,969.9**	**164**	**0.06 (0.05 - 0.06)**

Moderna

TTO missing (1)
TTO > 42d (0)

18-24	15.43	400,041	2.05	2	0.98 (0.11 - 3.53)	3.58	2	0.56 (0.06 - 2.02)
25-29	15.43	381,049	1.92	2	1.04 (0.12 - 3.77)	3.42	2	0.59 (0.07 - 2.11)
30-39	15.03	1,016,262	4.98	1	0.20 (0.00 - 1.12)	8.88	2	0.23 (0.03 - 0.81)
40-49	22.11	1,695,995	12.23	3	0.25 (0.05 - 0.72)	21.80	4	0.18 (0.05 - 0.47)
50-59	26.25	2,712,069	23.29	3	0.13 (0.03 - 0.38)	39.04	3	0.08 (0.02 - 0.22)
60-69	36.82	2,432,681	30.67	3	0.10 (0.02 - 0.29)	57.62	3	0.05 (0.01 - 0.15)
70-79	42.48	2,634,740	40.95	6	0.15 (0.05 - 0.32)	86.86	6	0.07 (0.03 - 0.15)
80+	57.54	2,256,959	48.81	1	0.02 (0.00 - 0.11)	115.42	2	0.02 (0.00 - 0.06)
Missing	-		-			-		
Total		13,529,796	**164.9**	**21**	**0.13 (0.08 - 0.19)**	**336.6**	**24**	**0.07 (0.05 - 0.11)**

Vaxzevria

TTO missing (9)
TTO > 42d (1)

18-24	15.43	761,885	4.04	4	0.99 (0.27 - 2.53)	7.59	4	0.53 (0.14 - 1.35)
25-29	15.43	965,171	5.21	4	0.77 (0.21 - 1.97)	9.93	7	0.70 (0.28 - 1.45)
30-39	15.03	2,448,750	12.87	8	0.62 (0.27 - 1.22)	24.53	9	0.37 (0.17 - 0.70)
40-49	22.11	3,651,636	28.24	7	0.25 (0.10 - 0.51)	53.83	7	0.13 (0.05 - 0.27)
50-59	26.25	4,145,930	38.59	15	0.39 (0.22 - 0.64)	73.02	18	0.25 (0.15 - 0.39)
60-69	36.82	8,490,655	115.94	12	0.10 (0.05 - 0.18)	232.14	14	0.06 (0.03 - 0.10)
70-79	42.48	3,766,059	58.97	5	0.08 (0.03 - 0.20)	122.16	6	0.05 (0.02 - 0.11)
80+	57.54	667,347	13.86	0	0.00 (0.00 - 0.26)	27.93	0	0.00 (0.00 - 0.13)
Missing	-		-	2		-	2	
Total		24,897,433	**277.7**	**57**	**0.21 (0.16 - 0.27)**	**551.1**	**67**	**0.12 (0.09 - 0.15)**

Considerations on the OE results – Myocarditis and Pericarditis

Looking at the 14-day risk period (where the vast majority of cases were received), the results show:

- **OE ratio > 2 in the male 18-24 group for MOD, > 1 for COM** and ~ 1 for AZ
- OE ratio > 1 in the male 25-29 group for MOD, < 1 for COM and AZ
- OE ratio ~ 1 in the female 18-24 group for all three vaccines
- **Sensitivity analysis** uses lower rates, therefore OE ratio > 2 in male 18-24 for all three vaccines and OE ratio > 1 in female 18-24 for all three vaccines
- **Caveats** of the analysis:
  - The OE analysis should be treated as a tool for signal detection rather than signal validation. The comparison of EV event rates with those observed in healthcare records should be interpreted cautiously, for contextualisation only
  - The extent of underreporting in EV is not known (presumably low for serious events such as myo/pericarditis)
  - The analysis did not include the age group 15-17 because of the lack of exposure data from ECDC/MSs; 6 cases of myocarditis (0 for pericarditis) were reported to EV, 5 for Comirnaty and 1 for Moderna (all males)
  - The analysis did not include the Janssen vaccine because only 3 cases were received in EV (of which 1 in the < 30 age group)

Final considerations on both OE analyses

- Clarity on the incidence rates is crucial considering the extreme variability observed across databases. The decision to select the new rates from ARS, which includes secondary care data, seemed the best approach given the circumstances
- Despite rather high incidence rates, OE ratio remains > 1 in the male 18-24 group for both analyses
- Incidence rates for myo+peri in the < 30 age group are ~ twice those for myocarditis, while the majority (~ 75 %) of EV cases is for myocarditis, therefore the OE results for myo+peri are more diluted in the younger age groups
- The OE patterns are fairly comparable across vaccines (i.e. higher OE ratio in the < 30 age group), yet the OE results for AZ are lower than COM and MOD
- OE results in the female group are generally lower than in the male group
- < 18 age groups to be considered once more exposure data becomes available

PRAC Rapporteur assessment comment:

EMA has also performed an updated O/E-analysis on cases of myocarditis and pericarditis, with DLP 13 June 2021.

The same background incidence database as for myocarditis was used (ARS). In addition to the observed cases from Eudravigilance regarding myocarditis (HLT infectious myocarditis and HLT Noninfectious myocarditis), also cases within HLT Infectious pericarditis and HLT Noninfectious pericarditis were included.

Also in this analysis, a statistically significant OE ratio was observed in the male group aged 18-24, although, as pointed out by EMA, the incidence rates for myocarditis+pericarditis in the < 30 age group are ~ twice those for myocarditis, while the majority (~ 75 %) of EV cases is for myocarditis, therefore the OE results for myocarditis+pericarditis are more diluted in the younger age groups.

Again, the number of cases in other age groups and in females are considered too low in order to base conclusions on.

3.3. Discussion and conclusion

The MAH has presented data, for the occurrence of myocarditis / pericarditis and Spikevax (previous COVID-19 vaccine Moderna).

The MAH has based their analysis on 77 cases of myocarditis and 68 reports of pericarditis retrieved in the period from IBD to 31 May 2021. A search was made in Eudravigilance to identify the number of cases of myocarditis and pericarditis reported after DLP (31/5-21). This revealed a significant increase in reported cases from 73 to 152 cases of pericarditis in the interval from DLP up to 24 June 2021 and from 74 to 197 cases of myocarditis in the same interval. The remarkable increased amount of case reports can possibly be due to enhanced reporting due to media attention.

Pericarditis

In the O/E analyses, no conclusions can be drawn on the analyses of "pericarditis without myocarditis", based on low case numbers. In the analyses of "pericarditis with or without myocarditis", higher observed than expected were observed in the age group of males 18-29 years following the 2nd dose, a finding of borderline significance (lower bound of 95% CI>1), however with no adjustment for underreporting.

A causality assessment was performed on all cases that were classified by the MAH as WHO Possible. The assessment included 18 cases, and case narratives were retrieved from EudraVigilance. The cases comprised 9 males and 9 females aged 20-89 years of age. Generally, the diagnostic basis for the reported events of pericarditis was poor; in many cases pericarditis is reported as an adverse event but the available information is rather incomplete regarding clinical findings and/or tests results and/or symptoms. Out of the 18 cases, three cases are considered WHO Possible, these are all in younger adults, age range 28-37 ys., of these 2 females after the 1st dose, and 1 male after the 2nd dose. There are 12 cases that were assessed as WHO Unlikely and 3 were WHO Unassessable.

Based on assessment of the presented evidence, including cases of pericarditis, a causal association cannot be established.

Myocarditis

In the O/E analyses, an increased rate ratio of myocarditis was seen following the 2nd dose, primarily in men in the age group 18-29. For females, the absolute numbers were smaller, leading to higher uncertainties. An increased risk for females in the similar age group cannot be excluded.

In addition to the analysis performed by the MAH, EMA has conducted an updated O/E analyses of EU/EEA data of myocarditis and myocarditis+pericarditis, with a DLP 13 June 2021. Both analyses showed a significantly increased OE ration in males aged 18-24, compared to background incidences of a European database including outcomes from primary and secondary care.

Case narratives, considered by the MAH being of WHO Possible causality, and considered myocarditis Brighton definition 1-2 (n=14), were retrieved from Eudravigilance, and assessed for causality. Of the 14 myocarditis cases, 7 cases were considered WHO Probable and 3 cases WHO Possible, 2 were found WHO Unlikely, and 2 cases were unclassifiable due to other health conditions.

The 10 WHO Probable/Possible cases were all males aged 18-50 years of age and myocarditis was diagnosed 1-4 days after receiving the 2nd dose of the COVID-19-vaccine Moderna. None of the cases were fatal. The assessment of these cases indicates an association between Spikevax (previous COVID-19-vaccine Moderna) and myocarditis, with perceived symptoms and clinical findings within the first week after receiving the 2nd vaccination. Comparing to the nature of myocarditis there is no indication so far that myocarditis as a possible side effect to the vaccine should have a more severe course than otherwise seen.

In addition, 3 literature articles including 6 case reports of Spikevax (previous COVID-19-vaccine Moderna) -myocarditis have been identified, supporting the causality. In all 6 cases the patients were hospitalized with chest pain and diagnosed with myocarditis by laboratory and cardiac magnetic resonance imaging (MRI) within 2-3 days of receiving mRNA-1273. Besides one patient aged 52 years, all cases involved younger patients of 21-31 years and otherwise healthy. Five cases were in males, and all cases were in relation to 2nd dose.

Myocarditis after BNT162b2 and mRNA-1273 Vaccination; K. F. Larson et al; Originally published 16 Jun 2021, Circulation, https://doi.org/10.1161/CIRCULATIONAHA.121.055913.

Acute myocarditis after a second dose of the mRNA COVID-19 vaccine: a report of two cases; J. Mansour et al; Clinical Imaging, Volume 78, October 2021, Pages 247-249; https://doi.org/10.1016/j.clinimag.2021.06.019

In Depth Evaluation of a Case of Presumed Myocarditis Following the Second Dose of COVID-19 mRNA Vaccine; A. Muthukumar; Originally published 16 Jun 2021, Circulation, https://doi.org/10.1161/CIRCULATIONAHA.121.056038

FDA and MHRA label updates

On 23 June 2021, the CDC issued a press release regarding myocarditis and pericarditis following mRNA COVID-19 Vaccination (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myocarditis.html) and FDA has informed that myocarditis and pericarditis will be added to the label of Spikevax (25 June 2021: https://www.fda.gov/media/150387/download).

On 25 June, 2021, the MHRA updated the label to include myocarditis and pericarditis: https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-moderna/information-for-healthcare-professionals-on-covid-19-vaccine-moderna

Conclusion

In conclusion, based on the evidence provided, including OE analyses, pattern analysis, case series assessment and literature reports, a causal association between Spikevax (previous COVID-19 vaccine Moderna) and myocarditis is considered at least a reasonable possibility. Myocarditis is considered an important identified risk and should be further characterized in the ongoing and planned studies in the PhV plan of the RMP.

An update of the SmPC section 4.4 and 4.8 is considered warranted, as well as the PIL section 2 and 4. In addition, distribution of a DHPC is considered warranted.

Based on the data available during this assessment, the data regarding pericarditis is currently not sufficient to establish causality.

3.4. New information obtained after circulation of the preliminary assessment report

Two new relevant publications in JAMA on 29 June 2021:

Myocarditis Following Immunization With mRNA COVID-19 Vaccines in Members of the US Military. Montgomery J, Ryan M, Engler R, et al. JAMA Cardiol. Published online June 29, 2021. doi:10.1001/jamacardio.2021.2833

A total of 23 male patients (median [range] age, 25 [20-51] years) presented with acute onset of marked chest pain within 4 days after receipt of an mRNA COVID-19 vaccine. All military members were previously healthy with a high level of fitness. Seven received the BNT162b2-mRNA vaccine and 16 received the mRNA-1273 vaccine. A total of 20 patients had symptom onset following the second dose. Among the 3 patients presenting after an initial vaccine dose, all had confirmed COVID-19 infection more than 2 months prior to vaccination. Overall, 2 810 000 doses were administered; 1 065 000 second doses were administered. Cardiac symptoms resolved within 1 week of onset for 16 patients. Seven patients continued to have chest discomfort at the time of this report; follow-up is ongoing. This early report is also unable to describe longer-term outcomes among these patients.

Patients With Acute Myocarditis Following mRNA COVID-19 Vaccination. Kim HW, Jenista ER, Wendell DC, et al. JAMA Cardiol. Published online June 29, 2021. doi:10.1001/jamacardio.2021.2828

In the 3-month period between February 1 and April 30, 2021, (at Duke University Medical Center), 4 patients with acute myocarditis were identified, which occurred within 5 days of COVID-19 vaccination. Three were younger male individuals (age, 23-36 years) and 1 was a 70-year-old female individual. All 4 had received the second dose of an mRNA vaccine (2 received mRNA-1273 [Moderna], and 2 received BNT162b2 [Pfizer]). All presented with severe chest pain, had biomarker evidence of myocardial injury, and were hospitalized. Coincident testing for COVID-19 and respiratory viruses provided no alternative explanation. Cardiac magnetic resonance imaging findings were typical for myocarditis, including regional dysfunction, late gadolinium enhancement, and elevated native T1 and T2. The hospital courses for all 4 were uneventful without evidence of arrhythmias or heart failure, and treatment was conservative with nonsteroidal anti-inflammatory drug and colchicine, with 1 receiving corticosteroids. All were discharged within 2 to 4 days of hospitalization.

Health Canada label update

On 30 June 2021, Health Canada updated the Moderna COVID-19 vaccine labels to include information on myocarditis and pericarditis. https://covid-vaccine.canada.ca/info/pdf/covid-19-vaccine-moderna-pm-en.pdf

3.5. Rapporteur's proposed recommendation

In conclusion, based on the evidence provided, a causal association between Spikevax (previous COVID-19 vaccine Moderna) and myocarditis is considered at least a reasonable possibility.

An update of the SmPC section 4.4 and 4.8 is considered warranted, as well as the PIL section 2 and 4.

Also, Myocarditis is considered as an important identified risk and should be further characterized in the ongoing and planned studies in the PhV plan, as appropriate. The RMP should be updated accordingly.

In addition, based on the identification of this important risk, distribution of a DHPC is considered warranted.

Proposed update of the product information:

SmPC 4.4

Cases of myocarditis have been reported following vaccination with Spikevax. The majority of these cases occurred within one week following the 2nd dose of vaccination, and mainly in men aged 30 years or younger. Currently, there is no indication that the cases have had a more severe course than otherwise seen for myocarditis. Healthcare professionals should be alert to the signs and symptoms of myocarditis. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain or palpitations following vaccination.

SmPC 4.8

"Myocarditis" in SOC: "Cardiac disorder" with frequency "unknown"

PIL 2:

Cases of myocarditis (inflammation of the heart) have been reported after vaccination with Spikevax. The cases have primarily occurred within one week following the 2nd dose of vaccination, and mainly in men aged 30 years or younger. The patient should be alert to signs of myocarditis and seek medical attention if symptoms such as breathlessness, palpitations or chest pain occur.

PIL 4:

Frequency unknown: Inflammation of the heart muscle (myocarditis) which can result in breathlessness, palpitations or chest pain

3.6. Comments from other PRAC members and MAH(s)

Fully endorsements were received from **MS1** and additional comments were received from **eight other MSs** and **MAH**:

3.6.1. Comments from other PRAC members

3.6.1.1. MS2

We generally endorse the Rapporteur's assessment however we have further comments to add:

Based on the available evidences we consider that both myocarditis and pericarditis should be included in section 4.4 and 4.8. This is also supported by the recent label updates from Health Canada, FDA and MHRA.

The dissemination of a DHPC is also supported.

We also consider that the wording should be aligned for both mRNA vaccines and have the following suggestion:

Section 4.4 Warnings and Precautions

Very rare cases of myocarditis and pericarditis have been observed following vaccination with Spikevax.

These cases have occurred predominantly in men aged 30 years or younger, and within one week after the second dose of the vaccine. These are typically mild cases and patients tend to recover within a short time following standard treatment and rest.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, palpitations or arrhythmias, sometimes with accompanying fever and shortness of breath.

Section 4.8

"Myocarditis" "Pericarditis" in SOC: "Cardiac disorder" with frequency "unknown"

PRAC Rapporteur assessment comment:

The MS endorsement is appreciated and noted.

The MS consider that the update also should include pericarditis, both in section 4.4 and 4.8. At present, the Rapporteur consider that the evidence is not sufficient to include pericarditis in 4.8, however, since cases of pericarditis have been reported after vaccination, and that myocarditis and pericarditis share clinical features, an update of section 4.4. is considered adequate.

See section 3.7 for updated proposed wording for the SmPC.

3.6.1.2. MS3

The PRAC Rapporteurs assessment is in general endorsed. However, we have the following additional comment;

Pericarditis

With regards to pericarditis, the PRAC Rapporteur conclude that 'Based on the data available during this assessment, the data regarding pericarditis is currently not sufficient to establish causality'. Clearly separating pericarditis from myocarditis is challenging as the term pericarditis can refer to inflammation of the pericardium and myocarditis. In addition, myocarditis and pericarditis share clinical features and pathomechanisms. Therefore, inclusion of both terms in section 4.4 and 4.8 is considered warranted, in line with the label updates from MHRA, CDC and Health Canada.

PRAC Rapporteur assessment comment:

The MS endorsement is noted and appreciated. The MS proposes also to include pericarditis in 4.4 and 4.8. The Rapporteur consider that the evidence is not sufficient to include pericarditis in 4.8, however, since cases of pericarditis have been reported after vaccination, and that myocarditis and pericarditis share clinical features, an update of section 4.4. is considered adequate.

See section 3.7 for updated proposed wording for the SmPC.

3.6.1.3. MS4

We fully support Rapp assessment and conclusions for this signal, but we would like to add the following considerations:

The MAH should discuss if there are RMMs that could be identified in this younger population at higher risk of myocarditis, or the possibility to perform specific studies (ie. testing a lower vaccination dose?).

The additional EMA analysis is very useful and informative. However, for future O/E analysis, estimations according to dose (1st and 2nd) will be valuable.

PRAC Rapporteur assessment comment:

The MS support is noted and appreciated. The MS suggest that the MAH should be requested to discuss if there are RMMs that could be identified in the younger population at higher risk of myocarditis, or the possibility to perform specific studies. The suggestion is agreed, see List of outstanding issues, section 3.8

It is also agreed that O/E analyses should preferably be stratified into 1st dose/2nd dose, when possible.

3.6.1.4. MS5

In consistence with our previous position, a PI/RMP update is considered warranted. Also, a DHPC should be disseminated.

In accordance with MS3 comments, and based on updated available information, besides an update of the SmPC section 4.4, an update of Section 4.8 is warranted for both myocarditis and pericarditis, in line with MHRA, CDC and Health Canada label updates.

We also agree with the proposal from MS4 for the MAH to discuss if there are appropriate RMMs that could be identified in younger population at higher risk or studies to identify them.

Based on available evidence, we consider that mRNA vaccines should be aligned.

PRAC Rapporteur assessment comment:

The MS support is noted and appreciated. The MS proposes also to include pericarditis in 4.4 and 4.8. The Rapporteur consider that the evidence is not sufficient to include pericarditis in 4.8, however, since cases of pericarditis have been reported after vaccination, and that myocarditis and pericarditis share clinical features, an update of section 4.4. is considered adequate.

The MS suggest that the MAH should be requested to discuss if there are RMMs that could be identified in the younger population at higher risk of myocarditis. This is agreed to, please see section 3.8 for List of outstanding issues.

3.6.1.5. MS6

We generally endorse Prac Rapp AR. We agree for the update of section 4.4 of the SmPC, the distribution of a DHPC and that risk of Myocarditis should be further characterized in the ongoing and planned studies in the PhV plan. However, we find the labelling in section 4.8 of Myocarditis with a frequency of "unknown" premature and would favour waiting for more investigations.

In addition, we would suggest that an ad-hoc expert group of cardiologists would be very helpful for the next steps of this signal. Indeed, the causality is especially complex to analyse and none of the mechanisms put forward by the MAH to explain the occurrence of myocarditis after mRNA vaccine immunization have been validated. This AHEG might also be helpful to reflect on risk minimisation measures.

PRAC Rapporteur assessment comment:

The MS endorsement is noted and appreciated.

It is considered that, based on the evidence provided, which includes a case series with a probable causality, several literature case reports and a supportive O/E analyses, that the evidence is sufficient to include "myocarditis" in section 4.8 of the SmPC, and accordingly in the PIL.

The MS suggest to consult an expert group, which is agreed by the PRAC Rapporteur especially in the light of the expected increased exposure in the younger age groups.

3.6.1.6. MS7

We generally endorse the PRAC Rapporteurs assessment and have some additional comments.

Pericarditis: based on available evidences, a possible causative role of the Spikevax vaccine cannot be excluded. Moreover, it's difficult to clearly separating pericarditis from myocarditis, since both conditions share some pathophysiological mechanisms and some cases of myopericarditis and perimyocarditis have also been reported. Thus, we support the proposal to also include the term pericarditis in section 4.4 and 4.8.

PRAC Rapporteur assessment comment:
The endorsement is noted and appreciated. The MS suggest also to include pericarditis in 4.4 and 4.8. An inclusion of pericarditis in 4.4 is proposed in the updated recommendation, however the evidence is not considered sufficient to include pericarditis in 4.8 at this stage.

3.6.1.7. MS8

We thank the PRAC Rapporteur for their careful assessment of the data.

We support the proposals to update section 4.4 with a warning on myocarditis and to include myocarditis as an adverse reaction in section 4.8. Given the challenges in separating pericarditis from myocarditis and noting that cases considered possibly related to Spikevax have been identified, we consider that the warning in section 4.4 of the SmPC should include reference to pericarditis in addition to myocarditis, and that pericarditis should also be included as an adverse reaction in section 4.8.

The data assessed do not seem to support inclusion of the statement "Currently, there is no indication that the cases have had a more severe course than otherwise seen for myocarditis." We consider that the clinical course of cases particularly in terms of severity and time to resolution, in addition to information on treatments administered requires further characterisation in order to inform the appropriate PI wording.

The dissemination of a DHPC to inform HCPs of the risk of myocarditis and pericarditis in association with Spikevax is supported.

Please find below our suggested amendments to the proposals for the SmPC and PL.

SmPC section 4.4:
Myocarditis and pericarditis

Very rare c Cases of myocarditis **and pericarditis** have been reported following vaccination with Spikevax. The majority of ~~these~~ cases **of myocarditis** occurred within one week following the 2nd dose of vaccination, and mainly in men aged 30 years or younger. ~~Currently, there is no indication that the cases have had a more severe course than otherwise seen for myocarditis.~~ **Available data suggest resolution of symptoms within a short timeframe, however, information on potential long-term sequelae is not yet available.**
Healthcare professionals should be alert to the signs and symptoms of myocarditis. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain or palpitations following vaccination.

PIL Section 2:

Very rare c Cases of myocarditis (inflammation of the heart **muscle**) **and pericarditis (inflammation of the lining outside the heart)** have been reported after vaccination with Spikevax. The cases of **myocarditis** have primarily occurred within one week following the 2nd dose of vaccination, and mainly in men aged 30 years or younger. **You should urgently seek medical attention if you experience new onset of symptoms such as chest pain, breathlessness, or feelings of having a fast-beating, fluttering, or pounding heart.** ~~The patient should be alert to signs of myocarditis and seek medical attention if symptoms such as breathlessness, palpitations or chest pain occur.~~

PRAC Rapporteur assessment comment:

The support is noted and appreciated. The MS suggest also to include pericarditis in 4.4 and 4.8. An inclusion of pericarditis in 4.4 is proposed in the updated recommendation, however the evidence is not considered sufficient to include pericarditis in 4.8 at this stage.

It is agreed that information on treatments administered requires further characterisation in order to inform the appropriate PI wording. For updated wording, please refer to section 3.7

3.6.1.8. MS9

The PRAC Rapporteur is thanked for a comprehensive report. The overall conclusions are endorsed. It is agreed that there is sufficient evidence for a causal relationship between myocarditis and vaccination with Comirnaty, and thus we support the inclusion of myocarditis in section 4.8.

We would like to propose that the warning in section 4.4 of the SmPC and section 2 of the PL should be in line with that proposed for Comirnaty as provided below. If serious cases of myocarditis have been reported, it is suggested to add such information (see text marked in yellow below).

SmPC Section 4.4

~~Cases of myocarditis have been reported following vaccination with Spikevax. The majority of these cases occurred within one week following the 2nd dose of vaccination, and mainly in men aged 30 years or younger. Currently, there is no indication that the cases have had a more severe course than otherwise seen for myocarditis. Healthcare professionals should be alert to the signs and symptoms of myocarditis. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain or palpitations following vaccination.~~

Very rare cases of myocarditis have been observed following vaccination of Spikevax.

These cases occurred predominantly in adolescents and young adults, more often in males than females, more often after the second dose of the vaccine, and typically within 14 days after vaccination (after the 2nd dose mostly within 6 days). *Although*, these are typically mild cases and individuals tend to recover within a short time following standard treatment and rest, *occasional serious cases have been reported.*

Healthcare professionals should be alert to the signs and symptoms of myocarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis such as (acute and persisting) chest pain, sometimes with accompanying fever and shortness of breath.

Healthcare professionals should consult applicable guidance and/or consult specialists (e.g. cardiologist) to diagnose and treat this condition.

Package leaflet, section 2:

~~Cases of myocarditis (inflammation of the heart) have been reported after vaccination with Spikevax. The cases have primarily occurred within one week following the 2nd dose of vaccination, and mainly in men aged 30 years or younger. The patient should be alert to signs of myocarditis and seek medical attention if symptoms such as breathlessness, palpitations or chest pain occur.~~

Very rare cases of myocarditis (inflammation of the heart) have been reported after vaccination with Spikevax. The cases have primarily occurred within two weeks following vaccination and occurred more often after the 2nd vaccination. Following vaccination, you should be alert to signs of myocarditis, such as breathlessness, palpitations and chest pain, and seek medical attention should these occur.

PRAC Rapporteur assessment comment:

The MS endorsement is noted and appreciated. It is agreed that the wording should be aligned with Comirnaty, an updated proposal has been made.

3.6.2. Comment from the MAH

Moderna disputes the characterisation of myocarditis as an important *identified* risk. Moderna proposes characterising myocarditis as an important *potential* risk. This conclusion is based on available data from ongoing clinical trials and post-authorisation safety information (including reports from public health and regulatory authorities) and is consistent with existing guidance.

According to CoreRMP19 guidance v2.0[i], "the list of important potential risks should include risks with potential impact on the risk/benefit balance, for which there is clinical and/or pre-clinical evidence suggesting a causal relationship with the vaccine, but for which the strength of the evidence does not (yet) allow to infer causality."

WHO (report received 10 June 2021) reviewed myocarditis in association with COVID-19 vaccines, and considers myocarditis "a potential serious adverse event following vaccination with the COVID-19 vaccines." According to the WHO report, the association between the event of myocarditis and the COVID-19 vaccines was "better defined with the two mRNA vaccines of Pfizer-BioNTech and Moderna, with disproportionate reporting and a possible dose-response relationship. This case series did not establish causality of myocarditis by the mRNA vaccines."

In its review of the post-authorisation safety data, WHO noted that myocarditis has been observed following vaccination with the COVID-19 vaccines, with an apparent increased risk in adolescents and young adults based on temporal relationship, particularly after dose 2 of both the Pfizer-BioNTech and Moderna vaccine. The cases of myocarditis tend to be mild and to resolve without sequelae.

There seemed to be also a shorter time-to-onset (TTO) for cases following the second vaccine dose (median = 3 days, range = 0-22 days) compared to the first dose (median = 4 days, range = 0-34 days).

The ACIP/Centers for Disease Control and Prevention (CDC) reviewed currently available data on mRNA vaccines Benefit-Risk assessment on 23 June 2021. The ACIP stated:

> "The facts are clear: this is an extremely rare side effect, and only an exceedingly small number of people will experience it after vaccination. Importantly, for the young people who do, most cases are mild, and individuals recover often on their own or with minimal

treatment. In addition, we know that myocarditis and pericarditis are much more common *if you get COVID-19*, and the risks to the heart from COVID-19 infection can be more severe."

The ACIP provided epidemiological analyses indicating cases of myocarditis observed with mRNA vaccines were more common in younger males, typically observed shortly after receipt of the second dose, and tended to be mild and self-limited. There was no biological explanation provided to account for the epidemiological findings.

The PRAC Preliminary Assessment Report (received 30 June 2021) which is based upon Moderna's safety evaluation of myocarditis/pericarditis (submitted 21 June 2021), concluded that "based on the evidence provided, a causal association between Spikevax (previous COVID-19 vaccine Moderna) and myocarditis is considered at least a reasonable possibility."

At this time, in none of these reviews has causality been demonstrated.

Characterization of the safety data from the Moderna clinical studies did not show an imbalance between the placebo group and the vaccination group. Indeed, no reports of myocarditis were observed in the Ph 3 trial of more than 15,000 subjects exposed to mRNA-1273.

Moderna does not believe that the currently available data support inclusion of this finding as an important identified risk due to:

D. No cases of myocarditis were observed in the Ph 3 clinical trial in which more than 15,000 subjects exposed to mRNA-1273.

E. Post-marketing data and low event rate (see below).

F. Current evidence relies overwhelmingly upon epidemiological evaluations.

G. Causality has not been demonstrated.

Moderna is aware of the epidemiological findings that observe myocarditis disproportionately in younger males and most commonly shortly after receipt of the second dose of the vaccine. Moderna is also aware that these cases tend to be mild and self-limited.

For these reasons, Moderna believes that the available evidence supports inclusion of myocarditis as an important potential risk.

SmPC section 4.4 and 4.8

Moderna accepts to include myocarditis in Section 4.4 with the following edits: Myocarditis

Cases of myocarditis have been reported very rarely following vaccination with Spikevax, often in younger men and shortly after the second dose of the vaccine. These are typically mild cases and individuals tend to recover within a short time following standard treatment and rest. ~~The majority of these cases occurred within one week following the second dose of vaccination, and mainly in men aged 30 years or younger. Currently, there is no indication that the cases have had a more severe course than otherwise seen for myocarditis.~~

Healthcare professionals should be alert to the signs and symptoms of myocarditis. ~~Those~~ ~~v~~Vaccinated individuals should ~~be instructed to~~ also seek immediate medical attention ~~if they develop symptoms such as shortness of breath,~~ should they experience new onset of chest pain, shortness of breath, ~~or~~ palpitations ~~following vaccination~~ or arrhythmias.

Moderna does not accept the inclusion of myocarditis in section 4.8 (Undesirable effects) nor section 4 of the PIL.

The rationale for the edits to section 4.4 is as follows:

D. Evidence suggests cases are rare, mild and resolve without sequelae. There were no cases in the Ph 3 trial in which more than 15,000 subjects received mRNA-1273. The rate is therefore unknown and corresponds to the category of "very rare." Our post-authorisation data indicate that as of 31 May 2021, 77 reports of myocarditis have been reported with more than 155 million doses administered (0.5 cases per 1 million doses administered). Of the 77 reports, only 20 were evaluated as possible according to WHO causality assessment. The remainder were considered as less than possible or unassessable.

E. Shorter time to onset usually following second dose of vaccine.

F. Symptoms of myocarditis are very common and are non-specific. Routine referral for medical attention would be expected to unnecessarily raise patient anxiety and burden the healthcare system. For example, an individual with asthma who receives the vaccine would be expected to receive medical care for an event such as an asthma attack that would typically be self-managed.

[i] Consideration on core requirements for RMPs of COVID19 vaccines coreRMP19 guidance v2.0. EMA/PRAC/234052/2021. 10 June 2021.

https://www.ema.europa.eu/en/documents/other/consideration-core-requirements-rmps-covid-19-vaccines_en.pdf

PRAC Rapporteurs assessment comment:

The MAH considers myocarditis as an important potential risk, and not an identified risk. This conclusion is based on available data from ongoing clinical trials and post-authorisation safety information (including reports from public health and regulatory authorities) and is consistent with existing guidance. The MAH refers to a WHO report dated 10 June 2021, stating that "this case series did not establish causality of myocarditis by the mRNA vaccines", which is in contrast to the case series assessment presented in this report, where causality was concluded by the PRAC Rapporteur to be "at least of reasonable possibility". Additionally, the MAH states that, according to the WHO, the cases of myocarditis tend to be mild and to resolve without sequelae. This could not be confirmed in the assessment of the case series in this report. The cases of myocarditis did not seem to be more severe than otherwise known, but as the outcome is unknown for most cases, it is not possible to make conclusions on severity until follow up measures are available in these cases.

Further on, the MAH highlights that, according to the ACIP, "myocarditis and pericarditis are much more common if you get COVID-19, and the risks to the heart from COVID-19 infection can be more severe". This is an important point that should be highlighted in the communication of the outcome of this signal, to ensure adequate and risk proportionate measures to be taken. Nevertheless, this fact does not diminish the importance of this rare side effect to be reflected in the product information.

The MAH considers that causality has not been demonstrated. This is not agreed on. In this report, a case series with a WHO Probable causality is presented, these are cases with a strikingly consistent

pattern; short TTO (<5 days), 2nd dose, primarily young men, lack of confounders – features which are further supported by the O/E analyses and also by several published case series reports, further described in section 3.3 and 3.4 of this report.

Finally, the MAH considers that myocarditis should not be considered an important identified risk, since no cases of myocarditis were observed in the phase 3 clinical trial in which more than 15,000 subjects were exposed to mRNA-1273. To our knowledge, the phase 3 clinical trial included 11,415 participants in the age group 18-64 years. It is unknown how many of these participants were in the age group <30 years, but if the participants were equally distributed among age, there would not be more than 3000 participants below the age of 30. A rare adverse event would therefore not necessarily be expected to occur in this setup.

The PRAC Rapporteur maintains the position that the causality of Spikevax and myocarditis is considered to be "at least of reasonable possibility", and an update of 4.4 and 4.8, and correspondingly in the PIL, is warranted.

3.7. Updated rapporteur's proposed recommendation

In conclusion, based on the evidence provided, a causal association between Spikevax (previous COVID-19 vaccine Moderna) and myocarditis and pericarditis is considered at least a reasonable possibility.

An update of the SmPC to include myocarditis in section 4.4 and 4.8 is considered warranted, as well as the PIL section 2 and 4. Also, an update of the SmPC to include pericarditis in section 4.4, and correspondingly in PIL section 2, is considered warranted. For proposed wording, see below.

Also, Myocarditis is considered as an important identified risk, and pericarditis an important potential risk, and should be further characterized in the ongoing and planned studies in the PhV plan, as appropriate. The RMP should be updated accordingly.

In addition, based on the identification of these new important risks, distribution of a DHPC is considered warranted.

The MAH is also requested to respond to the issues listed in section 3.8.

It is also proposed that an expert group should be consulted to reflect upon the mechanism of myocarditis/pericarditis, as well as risk minimisation measures, especially in the light of the expected increased exposure in the younger age groups.

Proposed update of the product information:

SmPC 4.4

Myocarditis and pericarditis

Cases of myocarditis have been reported following vaccination with Spikevax. The majority of these cases occurred within one week following the 2nd dose of vaccination, and mainly in men aged 30 years or younger. Currently, there is no indication that the cases have had a more severe course than otherwise seen for myocarditis. However, information on potential long-term sequalae is not yet available.

Also, cases of pericarditis have been reported following vaccination with Spikevax. These cases have shown no specific tendencies regarding dose, time to onset, gender and age.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Those vaccinated should be instructed to seek immediate medical attention if they develop symptoms such as shortness of breath, chest pain or palpitations following vaccination.

SmPC 4.8

"Myocarditis" in SOC: "Cardiac disorder" with frequency "unknown"

PIL 2:

Cases of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) have been reported after vaccination with Spikevax. The cases of myocarditis have primarily occurred within one week following the 2nd dose of vaccination, and mainly in men aged 30 years or younger. You should urgently seek medical attention if you experience new onset of symptoms such as chest pain, breathlessness, or feelings of having a fast-beating, fluttering, or pounding heart.

PIL 4:

Frequency unknown: Inflammation of the heart muscle (myocarditis) which can result in breathlessness, palpitations or chest pain

3.8. List of outstanding issues

Having considered the available evidence, the PRAC Rapporteur considers that more information is needed to fully characterize the risk of myocarditis and pericarditis with Spikevax (previous COVID-19 Vaccine Moderna) and to further evaluate the potential risk minimization measures. Therefore, the MAH is requested to:

- Make an evaluation upon the diagnostic criteria used for determining pericarditis, since it is not entirely clear on which basis the diagnosis was made from the information available in the cases. For comparison the myocarditis definition relies on the Brighton criterions.

- propose how to further characterise the new important risks, including evaluation of the outcome (mild/severe/sequelae), in ongoing and future studies.

Proposal of further routine risk minimization measures:

- The MAH should consider specific clinical guidance, regarding the age group 30 years and younger (considering e.g. spacing between 1st and 2nd dose, dosage, revaccination/booster for this individual group).

- The MAH should propose a recommendation (in SmPC 4.4) regarding clinical follow up of myocarditis/pericarditis cases, e.g. 3 months / 6 months clinical evaluation post event, including specific clinical measurements.

3.9. Adopted PRAC recommendation

Having considered the available evidence from the data provided by the Marketing Authorisation Holder (MAH) and from the EudraVigilance database, including data from clinical trials, post-marketing

experience, the literature and from observed to expected analyses, the PRAC has agreed that based on the evidence assessed, a causal association between COVID-19 mRNA Vaccine (nucleoside-modified) Spikevax (previously COVID-19 vaccine Moderna) and myocarditis/pericarditis is considered of at least a reasonable possibility. The PRAC has agreed that the MAH for Spikevax (Moderna Biotech Spain, S.L.) should address the below recommendation:

1. Product information update

The MAH should submit by 12 July 2021, 9 a.m. CEST a variation to amend the product information as described below (new text underlined):

Summary of Product Characteristics

Section 4.4 – Special warnings and precautions for use:

Myocarditis and pericarditis

Very rare cases of myocarditis and pericarditis have been observed following vaccination with Spikevax These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger men. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

Section 4.8 – Undesirable effects:

"Myocarditis" and "Pericarditis" in SOC: "Cardiac disorders" with frequency "unknown"

Package Leaflet:

Section 2 - What you need to know before you are given Spikevax

Warnings and precautions

Very rare cases of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) have been reported after vaccination with Spikevax. The cases have primarily occurred within two weeks following vaccination, more often after the second vaccination, and more often occurred in younger men. Following vaccination, you should be alert to signs of myocarditis and pericarditis, such as breathlessness, palpitations and chest pain, and seek immediate medical attention should these occur.

Section 4 - Possible side effects

Frequency "unknown": Inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain.

2. Direct healthcare professional communication (DHPC)

The MAH should distribute a DHPC according to the text and communication plan agreed with the CHMP.

3. Request for supplementary information

The MAH should provide recommendations for administration of the second dose, in case of the occurrence of myocarditis/pericarditis following the first dose, taking into account the totality of the available data, including relevant publications, by 02/08/2021.

The PRAC will assess the answer within a 30-days timetable.

4. Risk management plan (RMP) update

The PRAC considered that myocarditis/pericarditis should be considered as an important identified risk in the RMP. The necessary RMP update should be submitted at the next regulatory opportunity. The risk should be further characterized in the ongoing and planned studies in the pharmacovigilance plan. The MAH should:

a) Propose how to further characterise the new important risk, including evaluation of the outcomes (e.g. mild/severe/sequelae);

b) Discuss any risk factors that could be identified, as well as the need and possibility to perform specific studies to investigate risk factors for myocarditis and pericarditis after Spikevax administration with the aim to implement measures to mitigate the risk. If appropriate, PI updates should be proposed.

c) Assure long term follow up of myocarditis and pericarditis cases in order to better characterize long term consequences.

d) Number of young patients included in the studies should assure timely characterisation of the risk in this population of special interest.

4. Additional evidence

4.1. Assessment of additional data

ITEM 1:

The MAH should provide recommendations for administration of the second dose, in case of the occurrence of myocarditis/pericarditis following the first dose, taking into account the totality of the available data, including relevant publications, by 02/08/2021. The PRAC will assess the answer within a 30-days timetable.

Sponsor Response:

The MAH has no clinical data to inform this issue. It has not been evaluated in the clinical program.

The MAH has conducted a cumulative review of the clinical studies and post-authorization safety data for Spikevax, as well as literature looking for safety data and relevant publications related to the administration of the 2nd dose of Spikevax after the occurrence of myocarditis or pericarditis following

the 1st dose of the vaccine. For the ongoing clinical studies for Spikevax, having myocarditis or pericarditis after the 1st dose would had been a reason for study discontinuation. There were 2 reports of pericarditis in P301 in participants after they had received the 2nd dose of Spikevax. There have been no reports of myocarditis in any of the ongoing clinical trials for Spikevax.

There were 15 different publications that were reviewed based on a search strategy that included "mRNA vaccines"; "mRNA vaccine and myocarditis/ pericarditis"; "Moderna mRNA vaccine myocarditis/ pericarditis", etc. There was only one publication[1] (an editorial) that was identified as discussing the occurrence of myocarditis after the administration of the 1st dose of mRNA-based vaccines. The authors cited the Centers for Disease Control and Prevention guidance[2] issued on 23 June 2021, which does not advise against vaccination and recommend that individuals who have experienced myocarditis — either from non-COVID-19 causes, from COVID-19 itself, or even from vaccination — discuss vaccination with their health care providers.

Considering that the MAH has no clinical data and very limited post-authorization to characterize use of mRNA-1273 in this clinical setting, the MAH is not currently in a position to make a recommendation for receipt of a second dose among persons who have experienced myocarditis or pericarditis after the 1st dose of Spikevax. Such decisions should be individualized and made between patients and their providers, incorporating potential benefit/risk at the individual level.

[1] Venkatesh L. Murthy, Vinay Prasad, and Brahmajee K. Nallamothu. If Covid-19 vaccines can cause heart inflammation, caution should be warranted in those at risk. June 2021. https://www.statnews.com/2021/06/29/myocarditis-covid-19-vaccine-connection-caution-needed-for-those-atrisk/

[2] Clinical Considerations: Myocarditis and Pericarditis after Receipt of mRNA COVID-19 Vaccines Among Adolescents and Young Adults. Centers for Disease Control and Prevention. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html

PRAC Rapporteur assessment comment:

The MAH has conducted a cumulative review of the clinical studies and post-authorization safety data for Spikevax, as well as literature, looking for safety data and relevant publications related to the administration of the 2nd dose of Spikevax after the occurrence of myocarditis or pericarditis following the 1st dose of the vaccine.
In the clinical trials, no cases of myocarditis were detected, and the two cases of pericarditis both occurred after the 2nd dose.
The MAH detected one relevant publication in their literature search, an opinion article by Murthy et al, dated 29 June 2021, published in the online news magazine "Stat". The paper cites the CDC ACIP presentation of 23 June 2021, https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-06/05-COVID-Wallace-508.pdf , where clinical considerations in people with a history of myocarditis or pericarditis is presented (slide 39 and below). Here, it is recommended that the 2nd dose of mRNA vaccine should be deferred if myocarditis occurred after the 1st dose, "until more information is known", but also that the 2nd dose could be considered under certain circumstances, however it should be discussed with the patient, guardian and clinical team.

Vaccine considerations in people with a history of myocarditis or pericarditis

Scenario	Recommendation
Pericarditis prior to COVID-19 vaccination	Receive any FDA-authorized COVID-19 vaccine
Pericarditis after 1st dose of an mRNA COVID-19 vaccine but prior to 2nd dose	Proceed with a 2nd dose of mRNA COVID-19 vaccine after resolution of symptoms. Discuss with patient, guardian, and clinical team
Myocarditis prior to COVID-19 vaccination	Receive any FDA-authorized COVID-19 vaccine if heart has recovered
Myocarditis after 1st dose of an mRNA COVID-19 vaccine but prior to 2nd dose	Defer 2nd dose of mRNA COVID-19 vaccine until more information is known However, if heart has recovered, could consider proceeding with 2nd dose under certain circumstances. Discuss with patient, guardian, and clinical team

The authors of the opinion paper, Murthy et al., argue that caution should be employed for administering mRNA vaccines to individuals who experienced myocarditis after receiving a first dose. The authors further speculate that a single dose could be adequate, unless the individual is at high risk of complications from COVID-19. Also, the authors mention the possibility of smaller doses of vaccine as well as more widely spaced doses, although highlighting that the safety benefits of such measures are unclear.

The Warning section of the FDA fact sheet of the Moderna COVID-19 Vaccine, revised 24 Jun 2021, states that "*the decision to administer the Moderna COVID-19 Vaccine to an individual with a history of myocarditis or pericarditis should take into account the individual's clinical circumstances*".

In conclusion, no new data or information have been presented which could provide basis for an updated recommendation regarding the 2nd vaccination in persons experiencing myocarditis or pericarditis after the 1st dose.

Until such evidence is provided, it is agreed that no further update of the product information is considered warranted at present. Clinical recommendations are currently made on national level. The MAH should keep this issue under close monitoring, and should suggest an update of the product information accordingly when new relevant information regarding administration of the 2nd dose in patients experiencing myocarditis or pericarditis after the 1st dose becomes available.

4.2. Rapporteur's proposed recommendation

In conclusion, no new data or information have been presented which could provide basis for an updated recommendation regarding the 2nd vaccination in persons experiencing myocarditis or pericarditis after the 1st dose.

Until such evidence is provided, it is agreed that no further update of the product information is considered warranted at present. The MAH should keep this issue under close monitoring during routine pharmacovigilance activities. Once new relevant information become available regarding administration of the 2nd dose in patients experiencing myocarditis or pericarditis after the 1st dose, the MAH should suggest an update of the product information accordingly and without delay.

4.3. Comments from other PRAC members

Fully endorsements were received from **four MSs** and additional comments were received from MS5**:**

4.3.1. MS5

The PRAC Rapporteurs assessment is in general endorsed. However, we have the following additional comments;

The PRAC Rapporteur conclude that no new data or information have been presented which could provide basis for an updated recommendation regarding the 2nd vaccination in persons experiencing myocarditis or pericarditis after the 1st dose.

Although several national authorities currently advise to defer the 2nd dose in case of myocarditis/pericarditis, a more detailed wording regarding dose 2 in section 4.4 of the SmPC and section 2 of the PIL is considered warranted, in line with the recommendation from Health Canada and CDC:

'As a precaution, individuals who experienced myocarditis and/or pericarditis after a first dose of an mRNA vaccine should wait to get their second dose until more information is available. The decision to administer dose 2 to an individual with a history of myocarditis or pericarditis should take into account the individual's clinical circumstances'.

PRAC Rapporteur assessment comment:

The MS consider that a more detailed wording regarding dose 2 in section 4.4 of the SmPC and section 2 of the PIL is warranted, in line with the recommendation from Health Canada and CDC.

The position of the MS is acknowledged, however, the PRAC Rapporteur maintain the position that no update of the product information is warranted at present. The national authorities have guidelines based on their specific situation, both regarding vaccination coverage and present rate of infection. The MAH is keeping this issue under close monitoring, and continuously reports new information of myocarditis/pericarditis in the MSSRs. Also, further characterization of myocarditis and pericarditis will be addressed in the ongoing and planned additional pharmacovigilance studies as per EU RMP (assessment ongoing EMEA/H/C/005791/II/0028).

Once new information arises, an updated warning could be considered.

4.4. Updated rapporteur's proposed recommendation

In conclusion, no new data or information have been presented which could provide basis for an updated recommendation regarding the 2nd vaccination in persons experiencing myocarditis or pericarditis after the 1st dose.

Until such evidence is provided, it is agreed that no further update of the product information is considered warranted at present. The MAH should keep this issue under close monitoring during routine pharmacovigilance activities. Once new relevant information become available regarding administration of the 2nd dose in patients experiencing myocarditis or pericarditis after the 1st dose, the MAH should suggest an update of the product information accordingly and without delay.

4.5. Adopted PRAC recommendation

Having considered the available evidence from the data provided by the Marketing Authorisation Holder (MAH), the PRAC has agreed that no further changes to the previous recommendation by PRAC (i.e. updates to the product information and risk management plan) are warranted at this stage.

The PRAC has agreed that the signal can therefore be closed, and that the MAH for Spikevax (Moderna Biotech Spain, S.L.) should continuously monitor this topic within the MSSR-submissions. As soon as new relevant information becomes available, the MAH should further characterise this risk and suggest updates of the product information accordingly and without delay.

5. Annexes

5.1. Annex I – Assessment of myocarditis and pericarditis in the 4th MSSR of Moderna

Request:
On 5 May 2021, the company received the following request from the PRAC:
"The MAH is requested to evaluate the safety topic of myocarditis and pericarditis, including comment on the reports of myocarditis cases in Israel and among US military personnel following vaccination with COVID-19 mRNA vaccines reported in various media (https://www.timesofisrael.com/israel-said-probing-link-between-pfizer-shot-and-heart-problem-in-men-under-30/ and https://www.military.com/daily-news/2021/04/26/pentagon-tracking-14-cases-of-heart-inflammation-troops-after-covid-19-shots.html).
The MAH is requested to provide a ***cumulative review of myocarditis and pericarditis, from all available sources****. In the cumulative review, the MAH should provide at least but not limited to the following:*

- *A tabulated overview of all cases stratified by 1) Age; 2) Gender; 3) Time-to onset.*
- *A summary overview of the serious cases 1) for which the causality (as per WHO-UMC causality assessment system) is considered at least possible or probable; and 2) for which the role of the vaccine cannot be excluded.*
- *The summary overview should include the following details for each case:*
  - *Patient's age and gender.*
  - *EVDAS/Eudravigilance case ID.*
  - *Associated clinical signs/co-reported PTs.*
  - *Any underlying condition(s) (including COVID-19) or other confounders.*
  - *Time to onset, and whether following the 1st or 2nd dose.*
  - *Outcome.*
  - *Assessment of the causal relationship with the vaccine.*
- *Based on their review of the cases, the MAH should discuss any plausible mechanisms and whether any risk factors could be identified.*

In conclusion, the MAH should discuss the need to update the product information, including relevant risk minimisation measures. Also, in the next MSSR, the MAH is requested to present more in-depth O/E analyses of AESIs Myocarditis and Pericarditis, including O/E analyses stratified by age and gender. The MAH should ensure that the most relevant background incidence rates are selected and used for comparison, e.g. based on the origin of the cases. A justification for the selected IR should be provided."

Company response:

1. Background

Myocarditis is identified as an inflammatory disease of the heart muscle cells and is pathologically identified by conventional histology and immunohistochemical techniques as an infiltration of mononuclear cells to the myocardium. Myocarditis can be acute, subacute, or chronic and may either involve focal or diffuse areas of the myocardium. Endomyocardial biopsy remains the gold standard for in vivo diagnosis of myocarditis. A recent update to the definition of myocarditis has been discussed by Caforio et al in defining myocarditis, using immunohistochemical data, as individuals who exhibit ≥14 lymphocytes/mm^2 including ≤4 monocytes/mm^2 with the presence of CD3-positive T lymphocytes ≥7 cells/mm.[2] It is imperative to rule out other possible causes, specifically acute ischemia[1].

Myocarditis is an under-diagnosed cardiac disease resulting from any one of a broad range of infectious, immune, and toxic causes. Most cases of myocarditis are caused by infectious agents, toxic substances, drugs or autoimmune disorders. Hence, it is increasingly recognized that myocarditis is an inflammatory condition of the myocardium triggered by various factors rather than a distinct cardiovascular disease. Infectious causes include viruses, bacteria, Chlamydia, rickettsia, fungi, and protozoa. Noninfectious triggers have been identified such as toxins, auto immunes disease and hypersensitive reactions. Numerous medications like antipsychotics (e.g., clozapine), antibiotics (penicillin, ampicillin, sulfonamides, tetracyclines), and antiphlogistic (e.g., mesalamine) can induce

hypersensitivity eosinophilic myocarditis. Myocarditis has been reported following many different vaccines including flu vaccine, however the smallpox vaccine has the strongest association. During the influenza epidemic of the winter 1998-1999 there were several reports of patients who had preceding flu-like symptoms and fever and developed cardiac involvement between 4 and 7 days after the onset of influenza symptoms[2].[2].

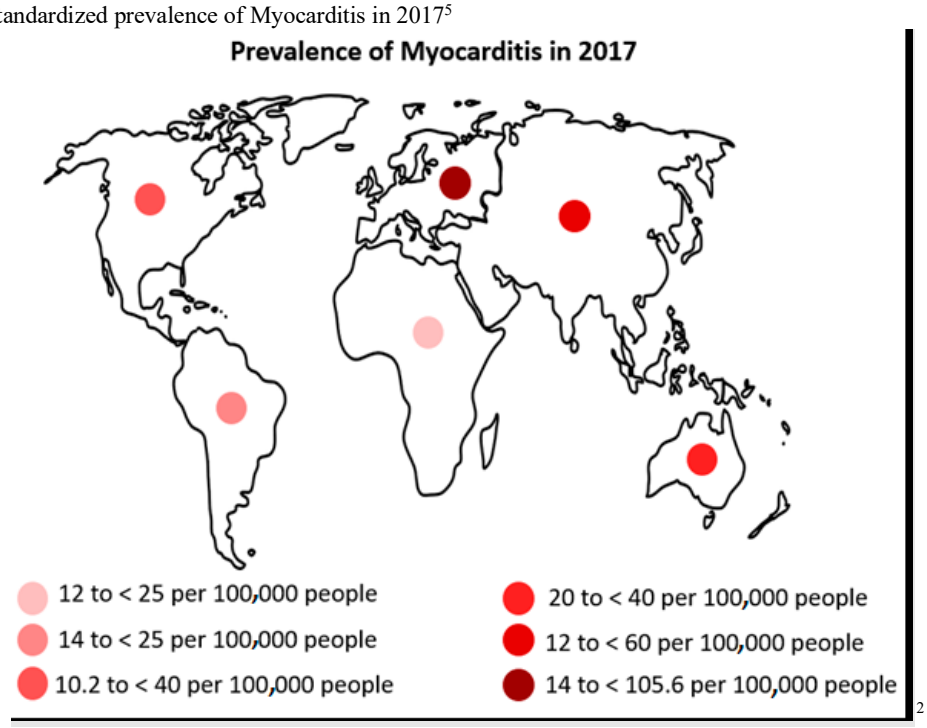
Viral myocarditis is thought to be the most frequent type, mostly affecting children and young adults[3]. A recent study using International Classification of Diseases codes estimated the global prevalence of myocarditis to be ≈22 of 100 000 patients annually. Approximately 1% to 5% of patients that test positive for acute viral infection(s) may exhibit a form of myocarditis. Nowadays, the prevalence of myocarditis has been reported from 10.2 to 105.6 per 100,000 worldwide, and its annual occurrence is estimated at about 1.8 million cases. The incidence of confirmed myocarditis secondary to smallpox vaccination was estimated to be 16.1 per 100 000 service members, with a recent Department of Defense study estimating 12 per 100 000 in a review of 730 000 service members. Most studies of acute myocarditis report a greater prevalence and severity in male patients, speculated to be caused by a protective effect of natural hormonal influences on immune responses in women when compared with men. Patients are usually between the ages of 20 and 50. Acute myocarditis and hyperthyroidism are also common diseases that often present in young, otherwise healthy patients. Autoimmunity is central to the pathogenesis of both[4].

As coronavirus disease 2019 (COVID-19) rapidly expanded as a global pandemic caused by severe acute respiratory syndrome coronavirus 2, some COVID-19 patients that were hospitalized developed an acute COVID-19 cardiovascular syndrome, which can manifest with a variety of clinical presentations but often presents as an acute cardiac injury with cardiomyopathy, ventricular arrhythmias, and hemodynamic instability in the absence of obstructive coronary artery disease. The cause of this injury is uncertain but is suspected to be related to myocarditis, microvascular injury, systemic cytokine-mediated injury, or stress-related cardiomyopathy. Although histologically unproven, severe acute respiratory syndrome coronavirus 2 has the potential to directly replicate within cardiomyocytes and pericytes, leading to viral myocarditis.

PRAC Rapporteurs assessment comments:

Myocarditis is an inflammatory condition of the myocardium which can be triggered by various factors besides a distinct cardiovascular disease. Most common cause of myocarditis are infectious agents, toxic substances, drugs or autoimmune disorders. Viral myocarditis is thought to be the most frequent type. The global prevalence of myocarditis is estimated to be approximately 22 per 100 000 patients annually. Higher prevalence and severity of acute myocarditis have been observed in male patients between the ages of 20 and 50.

Figure 1. Age-standardized prevalence of Myocarditis in 2017[5]



Acute pericarditis is an inflammatory process involving the pericardium that results in a clinical syndrome characterized by chest pain, pericardial friction rub, changes in the electrocardiogram (ECG) and occasionally, a pericardial effusion. Generally, the diagnosis requires 2 of these 3 features.

Epidemiologic data on the incidence of acute pericarditis are lacking, likely because this condition is frequently inapparent clinically, despite its presence in numerous disorders[6]. However, it appears to be the most common form of pericardial disease and a relatively common cause of chest pain. Acute pericarditis is the most common affliction of the pericardium. It is diagnosed in approximately 0.1% of patients hospitalized for chest pain and in 5% of patients admitted to the emergency department for chest pain unrelated to acute myocardial infarction (MI). Although acute pericarditis occurs in all age groups and in men and women, it presents most often in men 20 to 50 years of age. The most common form of acute pericarditis is idiopathic, which accounts for about 90% of cases. Other common causes include infection, renal failure, myocardial infarction (MI), post-cardiac injury syndrome, malignancy, radiation, and trauma. Acute pericarditis is more common in men than in women. However, although this condition is more common in adults than in children, adolescents are more commonly affected than young adults.

PRAC Rapporteurs assessment comments:

Acute pericarditis is an inflammatory process involving the pericardium that results in a clinical syndrome characterized by chest pain, pericardial friction rub, changes in the electrocardiogram (ECG) and occasionally, a pericardial effusion.

Epidemiologic data on the incidence of acute pericarditis are lacking, likely because this condition is frequently inapparent clinically. Acute pericarditis is more common in men than in women, and presents most often in men 20 to 50 years of age.

The most common form of acute pericarditis is idiopathic. Other common causes include infection, renal failure, myocardial infarction (MI), post-cardiac injury syndrome, malignancy, radiation, and trauma.

2. Methods:

The company clinical database and the global safety database were queried for valid, clinical and spontaneous case reports received from HCP, HA, consumers and literature, cumulative from 18 December 2020 to 30 April 2021, worldwide, reported for the mRNA-1273 vaccine (Moderna COVID-19 vaccine Moderna) using the following Preferred Terms (PTs): "***Viral pericarditis; Pericarditis; Pericarditis infective; Myocarditis; Myocarditis septic; Myocarditis infectious; Viral myocarditis; and Myocarditis post-infection***". The clinical trial data is from the Phase 3 clinical trial mRNA- 1273 P301.

PRAC Rapporteurs assessment comments:

The MAH's search strategy and used preferred terms are considered acceptable.

As of 30 April 2021, 182,568,555 doses of the mRNA-1273 vaccine had been distributed worldwide, an a total of 119,066,486 doses of the vaccine had been administered based on information retrieved through the US Centers for Disease Control and Prevention (https://covid.cdc.gov/covid-data-tracker/#vaccinations), the European Centres for Disease Control (https://covid19-vaccine-report.ecdc.europa.eu/#6_Reported_data), Health Canada (https://health-infobase.canada.ca/covid-19/vaccination-coverage/), and Swiss Federal Office of Public Health (https://www.covid19.admin.ch/en/epidemiologic/vacc-doses) on 01 May 2021. Distribution of vaccine administered by region is shown in Table 1.

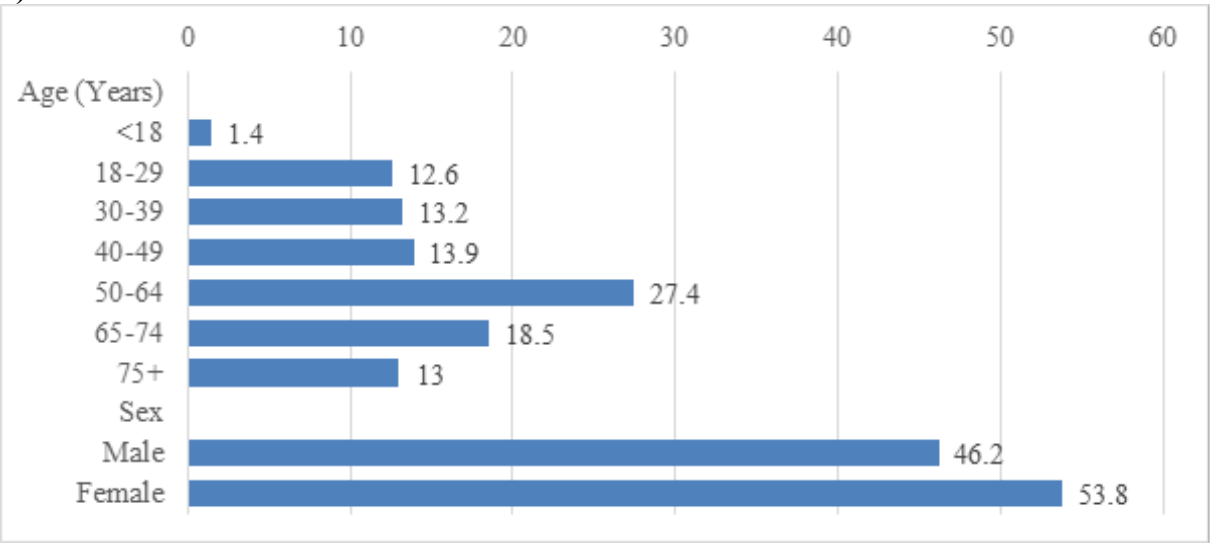
Table 1. Number of doses of the Moderna COVID-19 vaccine distributed and administered by Region Cumulative from 20DEC2020 to 30APRIL2021

	Doses Distributed		Doses administered	
	N	%	N	%
Total	182,568,555	100.0	119,066,486	100.0
United States	156,849,355	85.9	104,613,893	87.9
European Economic Area	19,362,100	10.6	11,429,281	9.6
Canada	3,507,100	1.9	2,030,792	1.7
Rest of World[1]	2,850,000	1.6	992,520	0.8

1: Includes Israel, Japan, Qatar, and Singapore

Within the US, where approximately 87.9% of doses have been administered to date, 104,613,893 individuals had received at least one dose, and 42,065,146 had received 2 doses as of the end of this reporting period. The age and sex distribution of vaccine recipients is shown in **Figure 2**.

Figure 2. COVID-19 Vaccines Administered by Age and Sex, United States (as of 30 April 2021)



In order to calculate observed reporting rates, a risk window of 21 days was assigned after each administered vaccine dose. This window was selected for consistency with analyses conducted by the US Vaccine Safety Datalink. The sum of all person-time was then used as a denominator to calculate the reporting rate. ACCESS or literature based expected rates were then multiplied by the same person-time estimate to identify the count of expected cases.

Because a large majority of both doses administered and reported events were identified in the US, we applied the US age distribution shown above to the total doses of vaccine administered and corresponding person-time accrued. Age-specific incidence rates identified from ACCESS or other published literature were then used to ascertain expected cases within each category. Where age groups used in sources of background incidence did not align with the available grouping for population-based vaccine administration, we conservatively chose the lower rate of adjacent categories to produce more conservative expected case counts.

PRAC Rapporteurs assessment comments:

The MAH's approach to use the US vaccination age and gender distribution for the O/E analyses is considered acceptable. Even though this data is not vaccine specific, this is considered the closest estimate available for the exposure in the different age groups.

3. Observed/ Expected:

Myopericarditis

Population-based data characterizing the incidence of myocarditis in the US are limited, however studies have been conducted considering myocarditis as an adverse event following immunization. In the Vaccine Safety Datalink (VSD), for example, a retrospective study based on administrative data was conducted to assess the occurrence of myopericarditis following live viral vaccination. The study investigators calculated incidence (after excluding about half the potential cases originally identified

from the automated data - due largely to miscoded or unverifiable diagnoses). In this assessment, the self-controlled risk interval analysis found that, based on one case identified during the risk interval and 10 cases during the control interval, there is no increased risk of myopericarditis in the 42 days following vaccination (IRR, 0.57; 95% CI, 0.07, 4.51). The study suggests that the occurrence of myopericarditis following live viral vaccination is rare with an estimated incidence of 0.24 per 100,000 vaccinated, which is not higher than the background rate and is much lower than the incidence rates reported following smallpox vaccination. The risk interval was defined as the 42-day window following measles-mumps-rubella, varicella, oral polio, or yellow fever vaccination; the control interval was defined as the time period 85 to 365 days following vaccination. The study investigators censored a 'wash out' period of 43 to 84 days after vaccination. The selected 42-day exposure window was based on prior smallpox vaccination investigations that suggested these cardiac events developed soon after vaccination at a mean onset time of 10 days..[7] In that control period, 10 cases were observed between days 85-365 after vaccination in 416,629 patients, an incidence of 3.13 per 100,000 person-years. Compared to this rate, the observed number of myocarditis/pericarditis cases after administration of the Moderna COVID-19 vaccine were within the expected range (84 cases observed vs 214 expected), with a rate ratio suggesting that sensitivity of the reporting rate would need to be below 23% for a possible increase in risk to be masked by low reporting. [7] In that control period, 10 cases were observed between days 85-365 after vaccination in 416,629 patients, an incidence of 3.13 per 100,000 person-years. Compared to this rate, the observed number of myocarditis/pericarditis cases after administration of the Moderna COVID-19 vaccine were within the expected range (84 cases observed vs 214 expected), with a rate ratio suggesting that sensitivity of the reporting rate would need to be below 23% for a possible increase in risk to be masked by low reporting.

Myopericarditis	Cases	Person-years	Rate	Rate Ratio
Observed: Post authorization	84.0	6,845,712	0.73	
Expected: US Vaccine Safety Datalink	214.3	6,845,712	3.13	0.23 (0.18, 0.30)

PRAC Rapporteurs assessment comments:

In the combined O/E analysis for the cases of myocarditis and pericarditis, the expected incidence rate of 3.13 per 100,000 person-years was used, based on the retrospective study by VSD in 416,629 patients. Data used for this study was validated prior to the calculation of the incidences, thus approximately a half of the potential cases had been excluded, mainly due to miscoding or unverifiable diagnoses.

In this combined O/E analysis, the observed rate was below the expected. Also, when taking into consideration the possible underreporting, as it is considered less likely that underreporting of the myocarditis and pericarditis events is as high as 60%-70% which would be needed to reach the expected number of cases.

Myocarditis

[7]The estimated incidence of Myocarditis is between 10 to 20 cases per 100,000 persons, however underdiagnosis is recognized as common[8,9]. Most studies report a higher incidence in men than women[10,11], with mean age lower for men (34.3 vs. 49 years)[12]. In the Global Burden of Disease study in 2013, the age standardized incidence was identified as 22.0 (95% CI 20.5-23.6).[13]

The ACCESS project has recently characterized the incidence of myocarditis in European populations, and estimates vary by country, ranging from 0.33/100,000 person-years in Spain to 21.34/100,000 person-years in Italy. Unlike identified US-based estimates, ACCESS includes stratification by age and gender. Given alignment with the estimated incidence from population-based studies,[6,7] and the US

VSD estimate, incidence rates from Spain (FISABIO), the United Kingdom (CPRD) and Italy (ARS) were used to generate the expected number of myocarditis cases in our analysis. Overall, observed rates did not exceed expectation.

Myocarditis	Cases	Person-years	Rate	Rate Ratio
Observed: Post authorization	50.0	6,845,712	0.73	
Expected: ACCESS, Spain (FISABIO) 2017	108.2	6,845,712	1.58	0.46 (0.33, 0.65)
Expected: ACCESS, UK (CPRD) 2018	592.2	6,845,712	8.65	0.08 (0.06, 0.11)
Expected: ACCESS, Italy (ARS) 2017	1,467.0	6,845,712	21.43	0.03 (0.03, 0.05)

PRAC Rapporteurs assessment comments:

According to the MAH, the population-based data characterizing the incidence of myocarditis in the US are limited. As US data did not include stratification by age and gender, the MAH has chosen ACCESS incidence rates comparable with the above mentioned VSD incidence rate (3.13 per 100,000 PYs) and global prevalence (22 per 100,000 PYs). The MAH's approach is considered acceptable.

It is not quite clear where (which version of ACCESS draft report) the referred ACCESS incidence rates are obtained from. For future submission, the MAH should note that updated (v1.2) draft ACCESS report is now available through EnCEPP: https://vac4eu.org/wp-content/uploads/2021/05/D3_ACCESS_Report_BGR_20210430_v.1.2_submitted.pdf

Also, all ACCESS AESI background rates are now available from VAC4EU Dashboard: https://vac4eu.org/covid-19-tool/

The MAH should clearly state from which source the used IRs were retrieved.

Stratifying by age, observed rates were below expected rates for subgroups except for males ages 18-29, where the observed reporting rate of 4.77 cases per 100,000 person-years was nearly identical to the expected rate from Spain (4.54) and the UK (4.68/100,000 person-years), and substantially lower than the rate from Italy (28.24/100,000 person-years). Young women (18-29) had a higher reporting rate than the expected in Spain only. Given that perfect sensitivity of the reporting rate is unlikely, this may reflect an increase in risk for this group if the true background rate is better aligned with the UK population than the Italian population-based estimate. Alternatively, it is possible that not all reported cases are true myocarditis, as was seen in the VSD study referenced above.

Myocarditis, Male	Cases	Person-years	Rate	Rate Ratio
Age 18-29				
Observed: Post authorization	19.0	398,503	4.77	
Expected: ACCESS, Spain (FISABIO) 2017	18.1	398,503	4.54	1.05 (0.55, 2.00)
Expected: ACCESS, UK (CPRD) 2018	18.6	398,503	4.68	1.02 (0.54, 1.93)
Expected: ACCESS, Italy (ARS) 2017	112.5	398,503	28.24	0.17 (0.10, 0.27)
Age 30-39				
Observed: Post authorization	9.0	417,479	2.16	
Expected: ACCESS, Spain (FISABIO) 2017	12.4	417,479	2.97	0.73 (0.31, 1.71)
Expected: ACCESS, UK (CPRD) 2018	20.7	417,479	4.95	0.44 (0.20, 0.95)
Expected: ACCESS, Italy (ARS) 2017	92.4	417,479	22.14	0.10 (0.05, 0.19)
Age 40-49				
Observed: Post authorization	5.0	439,618	1.14	
Expected: ACCESS, Spain (FISABIO) 2017	11.9	439,618	2.71	0.42 (0.15, 1.19)
Expected: ACCESS, UK (CPRD) 2018	45.4	439,618	10.32	0.11 (0.04, 0.28)

Myocarditis, Male	Cases	Person-years	Rate	Rate Ratio
Expected: ACCESS, Italy (ARS) 2017	78.8	439,618	17.92	0.06 (0.03, 0.16)
Age 50-64				
Observed: Post authorization	1.0	866,585	0.12	
Expected: ACCESS, Spain (FISABIO) 2017	9.4	866,585	1.09	0.11 (0.01, 0.83)
Expected: ACCESS, UK (CPRD) 2018	81.7	866,585	9.43	0.01 (<0.01, 0.09)
Expected: ACCESS, Italy (ARS) 2017	194.9	866,585	22.49	0.01 (<0.01, 0.04)
Age 65-74				
Observed: Post authorization	1.0	585,103	0.17	
Expected: ACCESS, Spain (FISABIO) 2017	13.6	585,103	2.33	0.07 (0.01, 0.56)
Expected: ACCESS, UK (CPRD) 2018	82.1	585,103	14.03	0.01 (<0.01, 0.09)
Expected: ACCESS, Italy (ARS) 2017	190.7	585,103	32.59	0.01 (<0.01, 0.04)
Age 75+				
Observed: Post authorization	0.0	411,153	0.00	
Expected: ACCESS, Spain (FISABIO) 2017	6.9	411,153	1.68	NA
Expected: ACCESS, UK (CPRD) 2018	81.1	411,153	19.73	NA
Expected: ACCESS, Italy (ARS) 2017	159.2	411,153	38.72	NA

PRAC Rapporteurs assessment comments:

Age and gender stratified O/E analyses showed observed rates close to expected rates in males aged 18-29 (rate ratios 1.05 (0.55, 2.00); FISABIO 2017; and 1.02 (0.54, 1.93); CPRD 2018) and males aged 30-39 (rate ratio 0.73 (0.31, 1.71); FISABIO 2017) when compared with the low background IRs. This could indicate a potential increased risk in these populations, as some degree of underreporting is likely.

Myocarditis, Female	Cases	Person-years	Rate	Rate Ratio
Age 18-29				
Observed: Post authorization	4.0	464,057	0.86	
Expected: ACCESS, Spain (FISABIO) 2017	3.6	464,057	0.77	1.12 (0.27, 4.66)
Expected: ACCESS, UK (CPRD) 2018	15.2	464,057	3.27	0.26 (0.09, 0.79)
Expected: ACCESS, Italy (ARS) 2017	42.8	464,057	9.23	0.09 (0.03, 0.26)
Age 30-39				
Observed: Post authorization	2.0	486,155	0.41	
Expected: ACCESS, Spain (FISABIO) 2017	2.6	468,155	0.55	0.75 (0.12, 4.74)
Expected: ACCESS, UK (CPRD) 2018	16.9	468,155	3.60	0.11 (0.03, 0.49)
Expected: ACCESS, Italy (ARS) 2017	56.2	468,155	12.00	0.03 (0.01, 0.14)
Age 40-49				
Observed: Post authorization	2.0	511,936	0.39	
Expected: ACCESS, Spain (FISABIO) 2017	2.4	511,936	0.47	0.83 (0.13, 5.42)
Expected: ACCESS, UK (CPRD) 2018	31.7	511,936	6.19	0.06 (0.02, 0.26)
Expected: ACCESS, Italy (ARS) 2017	49.6	511,936	9.68	0.04 (0.01, 0.17)
Age 50-64				
Observed: Post authorization	3.0	1,009,140	0.30	
Expected: ACCESS, Spain (FISABIO) 2017	16.1	1,009,140	1.60	0.19 (0.05, 0.64)
Expected: ACCESS, UK (CPRD) 2018	118.1	1,009,140	11.70	0.03 (0.01, 0.08)

Expected: ACCESS, Italy (ARS) 2017	171.7	1,009,140	17.01	0.02 (0.01, 0.05)
Age 65-74				
Observed: Post authorization	1.0	681,354	0.15	
Expected: ACCESS, Spain (FISABIO) 2017	10.6	681,354	1.56	0.09 (0.01, 0.73)
Expected: ACCESS, UK (CPRD) 2018	97.0	681,354	14.23	0.01 (<0.01, 0.07)
Expected: ACCESS, Italy (ARS) 2017	183.8	681,354	26.97	0.01 (<0.01, 0.04)
Age 75+				
Observed: Post authorization	0.0	478,781	0.00	
Expected: ACCESS, Spain (FISABIO) 2017	7.5	478,781	1.56	NA
Expected: ACCESS, UK (CPRD) 2018	88.8	478,781	18.55	NA
Expected: ACCESS, Italy (ARS) 2017	144.2	478,781	30.11	NA

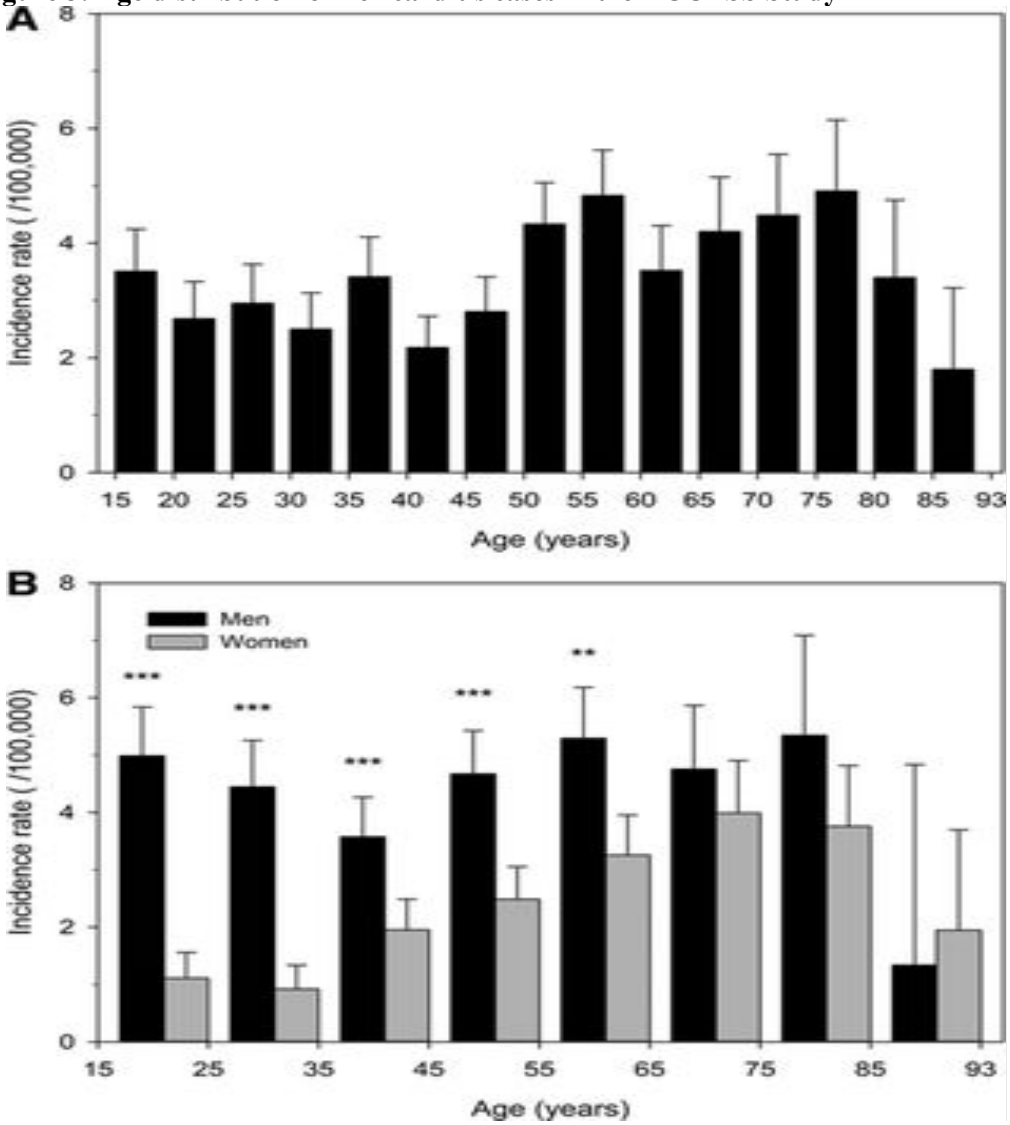
PRAC Rapporteurs assessment comments:

Similar findings as in males were seen in females aged 18-29, 30-39 and 40-49, however, these observed rates were based on a low number of cases and thus should be interpreted with caution.

Pericarditis

The MAH was able to fine few estimates of the incidence of pericarditis. Sources describing the incidence of pericarditis specifically in the US were not identified, and the individual condition is not described by the ACCESS study. However, some data in Europe have been published. A prospective clinical cohort study in Italy identified an incidence of 27.7 cases per 100,000 person-years.[14] Another study, a retrospective analysis of Finnish registry data capturing admissions to 29 hospitals over a span of 9.5 years identified an age standardized incidence of 3.32 per 100,000 person-years, with higher rates in men ages 16-65.[15] Figures showing the age distribution of pericarditis cases in this study are shown in **Figure 3**.[14] Another study, a retrospective analysis of Finnish registry data capturing admissions to 29 hospitals over a span of 9.5 years identified an age standardized incidence of 3.32 per 100,000 person-years, with higher rates in men ages 16-65.[15] Figures showing the age distribution of pericarditis cases in this study are shown in **Figure 3**.

Figure 3. Age distribution of Pericarditis cases in the ACCESS Study



Ville Kytö. Circulation. Clinical Profile and Influences on Outcomes in Patients Hospitalized for Acute Pericarditis, Volume: 130, Issue: 18, Pages: 1601-1606, DOI: (10.1161/CIRCULATIONAHA.114.010376)

Overall, there were 41 pericarditis cases observed in the MAH global safety database through 30 April 2021. Based on incidence rates from the two studies noted above, 225-1896 cases would be expected.

Pericarditis	Cases	Person-years	Rate	Rate Ratio
Observed: Post authorization	41.0	6,845,712	0.60	
Expected: Publication, Kyto, 2014 (Finland)	225.9	6,845,712	3.30	0.18 (0.13, 0.25)
Expected: Publication, Imazio, 2008 (Italy)	1,896.3	6,845,712	27.70	0.02 (0.02, 0.03)

PRAC Rapporteurs assessment comments:

As no pericarditis specific data from the ACCESS IRs is available, the MAH based their O/E analyses on published data from a prospective clinical cohort study in Italy reporting an incidence of 27.7 cases per 100,000 person-years, and a retrospective analysis of Finnish registry data reporting an

age standardized incidence of 3.32 per 100,000 person-years. The MAH's approach is considered acceptable.

O/E analyses based on these IRs and without age- or gender stratification showed lower observed than expected rates.

In the absence of publications offering more precise incidence estimates by age and sex group, approximations of the expected rate were derived based on Figure 2 produced by Kytö et al shown above.

For males, all observed rates were below the expected:

Pericarditis, Male	Cases	Person-years	Rate	Rate Ratio
Age 18-29				
Observed: Post authorization	8.0	398,503	2.01	
Expected: Publication, Kyto, 2014 (Finland)	17.9	398,502	4.50	0.45 (0.19, 1.03)
Age 30-39				
Observed: Post authorization	2.0	417,479	0.48	
Expected: Publication, Kyto, 2014 (Finland)	14.6	417,479	3.50	0.14 (0.03, 0.6)
Age 40-49				
Observed: Post authorization	0.0	439,618	0.00	
Expected: Publication, Kyto, 2014 (Finland)	15.4	439,618	3.50	NA
Age 50-64				
Observed: Post authorization	3.0	866,585	0.35	
Expected: Publication, Kyto, 2014 (Finland)	47.7	866,585	5.50	0.06 (0.02, 0.2)
Age 65-74				
Observed: Post authorization	6.0	585,103	1.03	
Expected: Publication, Kyto, 2014 (Finland)	29.3	585,103	5.00	0.21 (0.09, 0.49)
Age 75+				
Observed: Post authorization	2.0	411,153	0.49	
Expected: Publication, Kyto, 2014 (Finland)	22.6	411,153	5.50	0.09 (0.02, 0.38)

For females, rates were below the expected with the exception of the 30-39 age group, where the reporting rate was approximately equal to the expected:

Pericarditis, Female	Cases	Person-years	Rate	Rate Ratio
Age 18-29				
Observed: Post authorization	1.0	464,057	0.22	
Expected: Publication, Kyto, 2014 (Finland)	4.6	464,057	1.00	0.22 (0.02, 1.87)
Age 30-39				
Observed: Post authorization	5.0	486,155	1.03	
Expected: Publication, Kyto, 2014 (Finland)	4.7	468,155	1.00	1.03 (0.29, 3.63)
Age 40-49				
Observed: Post authorization	1.0	511,936	0.20	
Expected: Publication, Kyto, 2014 (Finland)	10.2	511,936	2.00	0.10 (0.01, 0.76)
Age 50-64				
Observed: Post authorization	2.0	1,009,140	0.20	
Expected: Publication, Kyto, 2014 (Finland)	30.3	1,009,140	3.00	0.07 (0.02, 0.28)
Age 65-74				
Observed: Post authorization	3.0	681,354	0.44	
Expected: Publication, Kyto, 2014 (Finland)	27.3	681,354	4.00	0.11 (0.03, 0.36)

Pericarditis, Female	Cases	Person-years	Rate	Rate Ratio
Age 75+				
Observed: Post authorization	4.0	478,781	0.84	
Expected: Publication, Kyto, 2014 (Finland)	19.2	478,781	4.00	0.21 (0.07, 0.61)

It is expected that these background rates are highly conservative as the Finnish study from which they were drawn captured primarily hospitalization data, which is, by definition, unlikely to detect (presumably) less severe cases not resulting in hospitalization. Given that the Italian data suggested a much higher rate, the sensitivity of the rates used in age stratification is likely to be poor.

Assuming that the distribution of incidence by age and sex identified in the data from Finland are applicable to the Italian population, the rate for females ages 30-39 would have been approximately 8.39, which would have created an expectation of 39.3 cases compared to the 5 observed (rate ratio 0.12, 95% CI 0.05-0.31).

PRAC Rapporteurs assessment comments:

Age- and gender-stratified O/E analyses in males showed lower observed than expected rates and indicated apparently no increased risk.

In females aged 30-39 showed observed rates close to expected rates. However, the Italian data suggested a much higher overall rate, and as IRs from the Finnish study were primarily based on hospital data, this finding should be interpreted with caution.

4. Results:

a. Clinical Trials information

During the Phase 3 pivotal clinical trial of the mRNA-1273 P301, in the safety set, up to 28 days after any vaccination, there were 15,184 participants exposed to the mRNA-1273 vaccine, and 15,166 participants in the placebo arm. There were 6,823 (22.5%) unsolicited treatment-emergent adverse event (TEAEs) reported, 3,234 (21.3%) in the placebo arm, and 3,589 (23.6%) in the mRNA vaccine arm. There were no reported TEAEs of "Myocarditis" in P301. There were three (3) unsolicited TEAE of "Pericarditis" reported in P301; two TEAEs in the Placebo arm, and one in the Vaccine arm of the safety set in the overall stage after any injection. The 2 events in the placebo arm were reported in the $\geq$18 to $\leq$65 years of age, and the event in the vaccination arm was reported in the $\geq$65 years of age group (**Table 2**).

PRAC Rapporteurs assessment comments:

No imbalance was seen in the clinical trial (P301). No cases of myocarditis were reported in P301. Concerning pericarditis, 2 cases were reported in the placebo arm; and 1 case in the vaccine arm.

Table 2.

Subject Incidence of Unsolicited TEAE by System Organ Class and Preferred Term in Overall Stage Safety Set

System Organ Class Preferred Term	Placebo (N=15166) n (%)	mRNA-1273 (N=15185) n (%)	Total (N=30351) n (%)
Cardiac disorders (Cont.)			
Mitral valve incompetence	0	1 (<0.1)	1 (<0.1)
Pericarditis	2 (<0.1)	1 (<0.1)	3 (<0.1)
Supraventricular extrasystoles	0	1 (<0.1)	1 (<0.1)
Ventricular extrasystoles	1 (<0.1)	1 (<0.1)	2 (<0.1)
Ventricular tachycardia	0	1 (<0.1)	1 (<0.1)
Atrial flutter	1 (<0.1)	0	1 (<0.1)
Atrial tachycardia	2 (<0.1)	0	2 (<0.1)
Cardiac failure acute	1 (<0.1)	0	1 (<0.1)
Cardiac flutter	1 (<0.1)	0	1 (<0.1)
Extrasystoles	1 (<0.1)	0	1 (<0.1)
Sinus arrest	1 (<0.1)	0	1 (<0.1)
Sinus bradycardia	1 (<0.1)	0	1 (<0.1)
Ventricular fibrillation	1 (<0.1)	0	1 (<0.1)
Vascular disorders	196 (1.3)	201 (1.3)	397 (1.3)
Hypertension	153 (1.0)	150 (1.0)	303 (1.0)
Hot flush	6 (<0.1)	12 (<0.1)	18 (<0.1)
Flushing	3 (<0.1)	7 (<0.1)	10 (<0.1)
Deep vein thrombosis	2 (<0.1)	4 (<0.1)	6 (<0.1)
Haematoma	4 (<0.1)	4 (<0.1)	8 (<0.1)
Hypertensive urgency	2 (<0.1)	4 (<0.1)	6 (<0.1)
Hypotension	6 (<0.1)	4 (<0.1)	10 (<0.1)
Orthostatic hypotension	0	4 (<0.1)	4 (<0.1)
Systolic hypertension	4 (<0.1)	4 (<0.1)	8 (<0.1)

A treatment-emergent adverse event (TEAE) is defined as any event not present before exposure to study vaccination or any event already present that worsens in intensity or frequency after exposure.
Percentages are based on the number of safety subjects.
MedDRA version 23.0.

b. Global Safety Database information:

The company global safety database was queried for spontaneous, valid, case reports received from HCP, HA, literature, and consumers, cumulatively (18 December 2020 to 30 April 2021), worldwide, using the PTs of "***Viral pericarditis; Pericarditis; Pericarditis infective; Myocarditis; Myocarditis septic; Myocarditis infectious; Viral myocarditis; and Myocarditis post-infection***"". As of 30 April 2021, there have been 182,568,555 doses of the mRNA vaccine distributed worldwide.

A review of the spontaneous reports from the company's global safety identified 84 case reports (0.1% of all cases reported to the MAH) with the PTs of Myocarditis and/or Pericarditis. There were 49 cases (0.1% of all cases) reported with Myocarditis-related PTs, and 41 cases (0.04% of all cases) with Pericarditis-related PTs. There were 6 cases (0.01% of all cases) that reported both events of Myocarditis and Pericarditis-related PTs. All 84 reports were considered serious reports.

Most of the reports concerned males (65.9%), and in individuals between the ages of 18 to 39 years of age (45; 52.9%).

Table 3. Number and Percentage of Spontaneous Cases of Myocarditis/ Pericarditis Reported per Age and Sex for the mRNA-1273 vaccine.
Cumulative to 31 March 2021

	All		Myocarditis and/or pericarditis		Myocarditis		Pericarditis		Myocarditis and Pericarditis	
	N	%	N	%	N	%	N	%	N	%
All	96,695	100.0	84	0.1	49	0.1	41	0.04	6	0.01
Age (years)										
<18	938	1.0	0	0	0	0	0	0	0	0
18-29	6,729	7.0	27	32.1	22	44.9	9	22.0	4	66.7
30-39	11,897	12.3	17	20.2	11	22.4	7	17.1	1	16.7
40-49	11,682	12.1	7	8.3	7	14.3	1	2.4	1	16.7
50-64	19,737	20.4	9	10.7	4	8.2	5	12.2	0	0
65-74	17,107	17.7	11	13.1	2	4.1	9	22.0	0	0

75+	15,591	16.1	6	7.1	0	0	6	14.6	0	0
Missing	13,014	13.5	7	8.3	3	6.1	4	9.8	0	0
Sex										
Male	22,005	22.8	55	65.5	35	71.4	24	58.5	4	66.7
Female	69,831	72.2	27	32.1	13	26.5	16	39.0	2	33.3
Missing	4,859	5.0	2	2.4	1	2.0	1	2.4	0	0

The majority of the reports were from the USA (77; 90.6%).

Table 4. Number and Percentage of Spontaneous Cases of Myocarditis/ Pericarditis Reported per Region for the mRNA-1273 vaccine.
Cumulative to 31 March 2021

	All		Myocarditis and/or pericarditis		Myocarditis		Pericarditis		Myocarditis and Pericarditis	
	N	%	N	%	N	%	N	%	N	%
Region										
Canada	324	0.3	0	0	0	0	0	0	0	0
European Economic Area	10,991	11.4	8	9.4	5	10.00	3	7.32	0	0
Rest of World	8	0.0	0	0	0	0	0	0	0	0
United States	85,372	88.3	76	90.6	44	90.00	38	92.68	6	100.00

The reported time-to-onset (TTO) is presented in **Table 5**. Most of the reports with a reported TTO happened during the first 24 hours after receiving the Moderna mRNA vaccine (31, 36.5%) with 7 females (4 after the 1st dose and 3 after the 2nd dose), 23 males (6 after the 1st dose, and 17 after the 2nd dose) and 1 unknown gender report after the 1st dose. Most of those reports were in the 18 to 39 years old group (14, 16.5%), with 3 were females (all 3 had the event after their 2nd dose of the Moderna COVID-19 vaccine) and 11 males with 4 reporting the event after the 1st dose and 7 after their 2nd dose.

Table 5. Number and Percentage of Spontaneous Cases of Myocarditis/ Pericarditis Reported per Age and Time-To-Onset for the mRNA-1273 vaccine.
Cumulative to 31 March 2021

	Myocarditis and/or pericarditis by age (years)															
	18-29		30-39		40-49		50-64		65-74		75+		Unknown		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Duration																
≤1 day	14	16.5	2	2.4	3	3.5	3	3.5	5	5.9	2	2.4	2	2.4	31	36.5
2-3 days	10	11.8	4	4.7	2	2.4	1	1.2	1	1.2	1	1.2	1	1.2	20	23.5
4-7 days	3	4.7	4	4.7	2	2.4	2	2.4	0	0.0	1	1.2	1	1.2	13	16.5
8-29 days	2	2.4	6	7.1	0	0.0	2	2.4	5	5.9	1	1.2	1	1.2	17	20.0
≥30 days	0	0.0	0	0.0	0	0.0	1	1.2	0	0.0	1	1.2	0	0.0	2	2.4
Unknown	0	0.0	1	1.2	1	1.2	0	0.0	0	0.0	0	0.0	2	2.4	4	4.7

PRAC Rapporteurs assessment comments:

The MAH identified 84 case reports with the PTs of Myocarditis and/or Pericarditis from their safety database, of which 49 cases with Myocarditis-related PTs, and 41 cases with Pericarditis-related PTs. There were 6 cases that reported both events of Myocarditis and Pericarditis-related PTs. All 84 reports were considered serious reports.

The majority of the myocarditis and/or pericarditis cases were in males (55/84; 65.9%), and in individuals between the ages of 18 to 39 years of age (45/84; 52.3%). When looking at myocarditis separately, there were 35/49 (71.4%) cases in males, and 33/49 (67.3%) in individuals with age 18-39 years. The majority of the reports were from the USA (76; 90.6%). A total of 8 myocarditis and/or pericarditis cases were reported in the EEA; of these 5 concerns myocarditis and 3 pericarditis.

When looking at TTO, the most of the reports are with TTO within the first 24 hours (31/84; 36.5%). Of these cases, 7/31 were in females with almost equal distribution between doses (4 after the 1st dose and 3 after the 2nd dose), and 23/31 in males with most cases following the 2nd dose (6 after the 1st dose, and 17 after the 2nd dose). There was 1 case following the 1st which did not report gender.

In total, 14 of the cases (TTO<24h) were in the 18 to 39 years old group (14/31), with 3 females (all after 2nd dose) and with 11 males (4 after the 1st dose; 7 after 2nd dose).

A total of 20 cases were reported with TTO 2-3 days, of these 10 cases were in age group 18-29. However, the MAH did not provide additional information on these cases regarding gender or dose.

A higher number of cases in males, and in age below < 40 may be expected as prevalence in the general population exhibits a similar pattern with a highest prevalence in young males between 20-50 years of age. The total number of events following the 2nd dose is not clear from the provided data, however when looking into the events occurring within 24 hours, 10 events are reported after 1st dose, and 20 after the 2nd dose. Considering the lower exposure in 2nd dose receivers, compared to 1st dose, it indicates that the event is occurring more frequent following 2nd dose. The MAH did not further discuss this finding. Importantly, there can be a difference between events of myocarditis and pericarditis as discussed later in this section.

Most of the events for which the event outcome was reported showed not recovered/ not resolved (34.1%) followed by recovered/ resolved (23.5%). The majority of the events of Myocarditis were recovered/ resolved (30%) and for Pericarditis most of the events were reported as not recovered/ resolved (46.3%). (See **Table 6**). The same reporting trend was observed according to age (see **Table 7**) with the ≥65 years of age reporting the majority of the not recovered/ recovered event outcome, and the 40 to 49 years of age reporting most of the recovered/ resolved event outcome. Most of the spontaneous reports included in the MAH global safety database are obtained from regulatory authorities. This preclude the MAH to obtain follow-up information for the cases reported. It is also important to note that the reports are usually provided to the regulatory authorities usually when the patient was admitted to the hospital or recently discharged hence the fact that most of the events have a "not resolved" reported outcome.

Table 6. Number and Percentage of Spontaneous Cases of Myocarditis/ Pericarditis Reported per Event Outcome for the mRNA-1273 vaccine.
Cumulative to 31 March 2021

Event Outcome	Myocarditis and/or pericarditis		Myocarditis		Pericarditis		Myocarditis and Pericarditis	
	N	%	N	%	N	%	N	%
Fatal	1	1.2	0	0.0	1	2.4	0	0.0
Not Recovered/Not Resolved	28	33.3	12	24.5	19	46.3	3	50.0
Recovered/Resolved	20	23.8	15	30.6	7	17.1	2	33.3
Recovered/Resolved with Sequelae	0	0.0	0	0.0	0	0.0	0	0.0
Recovering/Resolving	4	4.8	3	6.1	1	2.4	0	0.0
Unknown	31	36.9	19	38.8	13	31.7	1	16.7
Worsened	0	0.0	0	0.0	0	0.0	0	0.0

Table 7. Number and Percentage of Spontaneous Cases of Myocarditis/ Pericarditis Reported per Event Outcome for the mRNA-1273 vaccine.
Cumulative to 31 March 2021

	Myocarditis and/or pericarditis by age (years)													
	18-29		30-39		40-49		50-64		65-74		75+		Unknown	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
All (84)	27	32.1	17	20.0	7	8.2	9	10.6	11	12.9	6	7.1	7	8.2
Event Outcome														
Fatal	0	0	0	0	0	0	0	0	1	9.1	0	0	0	0
Not Recovered/Not Resolved	10	37.0	5	29.4	0	0	3	33.3	4	36.4	4	66.7	2	28.6
Recovered/Resolved	7	25.9	5	29.4	4	57.1	0	0.0	4	36.4	0	0.0	0	0.0
Recovered/Resolved with Sequelae	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Recovering/Resolving	2	7.4	1	5.9	0	0.0	0	0.0	0	0.0	1	16.7	0	0.0
Unknown	8	29.6	6	35.3	3	42.9	6	66.7	2	18.2	1	16.7	5	71.4
Worsened	0	0	0	0	0	0	0	0	0	0	0	0	0	0

PRAC Rapporteurs assessment comments:

It is acknowledged that 'Not Recovered/Not Resolved' likely reflects the lack of follow-up at present, rather than that events have an outcome not resolved/recovered.

There was one fatal case reported (3). This report (See Table 9) described a 60-69 year old male who developed acute myocardial infarction, chest pain, dyspnea, pericarditis and died. The patient's medical history included hypertension, hyperlipidemia, and previous event of pericarditis. Concomitant medications were not provided. The patient reported the events of severe chest pain and dyspnea approximately 9 days following the first dose of the Moderna COVID-19 vaccine. The next day, according to the family the symptoms were most severe, and he was going to seek medical attention, but he did not. He purchased OTC acetaminophen for relief of symptoms. Symptoms of dyspnea and chest pain continued for 8 additional days, when he called the emergency service complaining of chest pain and was found to have a STEMI (ST-elevation myocardial infarction). The patient subsequently died the next day. It was unknown if an autopsy was performed. The company assessment for this

case is that it is heavily confounded by the patient's previous (pericarditis, hypertension, hyperlipidemia) and concurrent medical history (acute MI). According to the WHO-UMC causality assessment the case is considered possible given that there is a temporal relationship to the occurrence of the event after vaccination but the previous and concurrent medical history are a more plausible explanation for the occurrence of the event of pericarditis.

PRAC Rapporteurs assessment comments:

The MAH's conclusion is acknowledged. The presented fatal case is confounded by the prior and concurrent medical history.

Regarding documented previous medical history, there were 4 cases that reported previous COVID-19 infection (5.9%) with these reports in the 18 to 39 years of age group. There were 5 reports of previous Myocarditis/ Pericarditis medical history (5.9%), 14 reports of cardiovascular conditions (16.5%), 5 with Thyroid conditions (5.9%), and 12 (14.1%) had previous medical histories of allergy-type conditions including history of anaphylaxis. (See **Table 8**)

Table 8. Number and Percentage of Spontaneous Cases of Myocarditis/ Pericarditis Reported per Medical History for the mRNA-1273 vaccine.
Cumulative to 31 March 2021

	Myocarditis and/or pericarditis by age (years)															
	18-29		30-39		40-49		50-64		65-74		75+		Unknown		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Documented Medical History																
COVID-19	3	10.7	1	5.9	1	14.3	0	0	0	0	0	0	0	0	**5**	**5.9**
Hypertension	0	0	1	5.9	0	0	0	0	4	36.4	2	33.3	0	0	**7**	**8.2**
Allergy/hypersensitivity	4	14.3	5	29.4	0	0	1	11.1	1	9.1	1	16.7	0	0	**12**	**14.1**
Myocarditis or pericarditis	1	3.6	0	0	1	14.3	0	0	3	27.3	0	0	0	0	**5**	**5.9**
Cardiac conditions or procedures	2	7.1	1	5.9	3	42.9	1	11.1	5	45.5	2	33.3	0	0	**14**	**16.5**
Asthma	3	11.1	0	0	0	0	0	0	1	9.1	0	0	0	0	**4**	**4.8**
Thyroid conditions	0	0	3	17.7	0	0	0	0	0	0	2	33.3	0	0	**5**	**5.9**

Coronavirus disease (SARS-CoV-2) have been associated with viral pneumonia with additional extrapulmonary manifestations and complications as well as high inflammatory burden that can induce vascular inflammation, myocarditis, and cardiac arrhythmias[16]. A significant proportion of patients that have been infected with SARS-CoV-2 have underlying cardiovascular disease and/or cardiac risk factors. Factors associated with mortality include male sex, advanced age, and presence of comorbidities including hypertension, diabetes mellitus, cardiovascular diseases, and cerebrovascular diseases. Acute cardiac injury determined by elevated high-sensitivity troponin levels is commonly observed in severe cases and is strongly associated with mortality. Acute respiratory distress syndrome is also strongly associated with mortality.

PRAC Rapporteurs assessment comments:

No clear risk factors, or patterns or trends could be identified from the provided overview of medical history.

A recent publication, Garcia et al. (2021)[1] concerned a case of myocarditis in a 30-39-year-old male, with a past medical history of auto-immune conditions who developed suspected acute myopericarditis 6 hours post vaccination with the second dose of mRNA vaccine. In this case, of a patient with a past medical history of asthma, autoimmune hypothyroidism, and chronic atrophic gastritis, the authors hypothesized that the vaccine may have been the trigger of an autoimmune reaction manifesting as acute myocarditis.

For the next MSSR, the MAH is requested to comment the literature case report by Garcia et al. and discuss the proposed mechanism (Bautista García J,et al.Acute myocarditis after administration of theBNT162b2 vaccine against COVID-19. *Rev Esp Cardiol. 2021.* https://doi.org/10.1016/j.rec.2021.04.005)

The MAH emphasized that SARS-CoV-2 have been associated with viral pneumonia with additional extrapulmonary manifestations including myocarditis. It is acknowledged that a high proportion of the vaccinated persons may have previous history of COVID-19 infection, in addition to few cases which reported COVID-19 infection as medical history. However, only a recent or concurrent infection should be considered as a confounder or a risk factor for the development of myocarditis/pericarditis.

Unless a further characterization of the latency from infection to onset of event is presented for each case, it cannot be a general conclusion that the events of myocarditis/pericarditis can be explained by previous possible COVID-19 infection.

References:

[1]Bautista García J,et al.Acute myocarditis after administration of theBNT162b2 vaccine against COVID-19. *Rev Esp Cardiol. 2021.* https://doi.org/10.1016/j.rec.2021.04.005)

i. Myocarditis cases:

Analysis of the 49 cases that reported events of Myocarditis using the WHO-UMP standardized case causality assessment[17] revealed that there were 4 reports (8% of the Myocarditis cases) classified as "Possible" events. There were 3 males and 1 female. Their ages were between 19 and 59 years of age. The reported TTO was between 0 days and 4 days (Mean 3 days). A summary of these events is provided below (**See Table 9**).

The rest of the 49 cases that reported Myocarditis, twelve cases (24%) were classified as "Conditional"; 17 cases (34%) were classified as "Unassessable/ Unclassifiable"; and 15 (30%) were classified as "Unlikely".

The "Conditional" cases were reported in 7 males, 4 females, and 1 unknown. Their ages were between 18 to 59 years of age; 5 cases were reported after the 1st dose of the Moderna COVID-19 vaccine, and 7 after the 2nd dose of the vaccine. TTO was between same day to 11 days after the vaccine (Mean 3.8 days). These events had reports of myocarditis occurring after receiving the vaccine but important information necessary to conduct an appropriate causality assessment were missing, including previous and concurrent medical history, previous and concurrent medications, course of the current disease, and in one case age and sex as well as TTO was missing.

The 17 cases that were classified as "Unassessable/ Unclassifiable" were reported in 15 males, 2 females and 1 unknown between 18 and 49 years of age; 9 cases were reported after the 1st dose, and 7 after the second dose of the Moderna COVID-19 vaccine. TTO was between same day to 23 days

(Mean 4.1 days). These events had reports of myocarditis occurring after receiving the vaccine but important information necessary to conduct an appropriate causality assessment were missing, including previous and concurrent medical history, previous and concurrent medications, course of the current disease, and in several cases age, sex, dose number, as well as TTO was missing.

The 15 cases that were classified as "Unlikely" were reported in 9 males, and 6 females between 18 and 69 years of age; 9 cases were reported after the 1st dose, and 6 after the second dose of the Moderna COVID-19 vaccine. TTO was between same day to 2 months and 17 days (Mean 6.9 days). These events had reports of myocarditis occurring after receiving the vaccine but the reports are heavily confounded by concurrent medical history (COVID-19 infection, Influenza, cardiovascular disorders, asthma, hyperthyroidism) as well as concurrent medications that are currently labeled for serious cardiovascular events including myocarditis (amphetamines, statins, etc.).

PRAC Rapporteurs assessment comments:

The MAH has performed causality assessment of the 49 cases of Myocarditis. Of these, 29 cases were classified as either "Conditional" or "Unassessable", due to limited information. Of these, 14 were reported after the 1st dose, and 14 after the 2nd dose (one case with no dose information).

15 cases were classified as "Unlikely". Nine cases were reported after the 1st dose, and 6 after the 2nd dose. According to the MAH, these cases were confounded by concurrent medical history (COVID-19 infection, Influenza, cardiovascular disorders, asthma, hyperthyroidism) as well as concurrent medications that are currently labelled for serious cardiovascular events including myocarditis (amphetamines, statins). To consider a concurrent medication a confounder, it is required that the medication has the adverse event listed in the product information. Also, the TTO and outcome following dechallenge/rechallenge for the potential confounding medicinal product must be taken into consideration when assessing causality. If a medication has been used for a long time (chronic treatment), it is less likely to have caused the acute onset of myocarditis occurring shortly after vaccination. The MAH further states that the reports were confounded by concurrent medical history, such as COVID-19 or Influenza. Here, it is important to look at the latency from the infections in order to assess the credibility of these confounding factors.
No information is given regarding the specific concomitant medications, nor the specific concurrent medical conditions, in these 15 cases which the MAH considers WHO "Unlikely".

The MAH has classified four cases as WHO Possible, further presented in table 9 and commented below. **All four cases had a TTO of 3-4 days and occurred after the 2nd vaccination**.

For case 1, concerning a 18-29-year old man, the MAH considers the causality based on its confounding by concurrent medical history (asthma) as well as concurrent medications. The reference used by the MAH refers to a publication where a case of viral myocarditis was masked by the patient's asthma; the asthma was not concluded to be causally related to development of myocarditis in this literature case. The concurrent asthma in the current case is not considered an important confounder in this case. Also, considering the concurrent medications, none have myocarditis listed in the product information, and in addition, treatment had been ongoing for two years prior to event onset for Dupilumab, Montelukast, Budesonid/Formoterol and Cetirizine (unknown for Epinephrine and Salbutamol), which make them less likely to be associated to the onset of myocarditis. This case is considered **WHO Probable**.

The second case, concerns a 50-59-year old male. The MAH states that concurrent medication had the event labelled, this could however not be confirmed. The case lacks medical history, however

the concomitant medications indicate hypertension/cardiovascular risk. Consequently, a **WHO Possible** causality is agreed.

The third case, concerns a 20-29-year old male. In this case, the MAH focus on the patient's concurrent medical history (COVID-19 infection). It is acknowledged that COVID-19 has been linked to cardiovascular pathologies, including myocarditis. This case does however lack information on when the disease course occurred concurrent, or shortly prior to the vaccination, which is important in order to determine causality. **WHO Possible** causality is agreed.

The fourth case, concerns a 4049-year-old, female patient with mild Sjögren syndrome who developed myocarditis and pericarditis following vaccination. It is acknowledged that the autoimmune disorder Sjögren syndrome has been associated with myocarditis, however cardiac involvement is not considered a typical manifestation of the syndrome. It is notable that also in this case, the TTO of myocarditis is 4 days after 2nd dose. Concurrent medications were not reported. **WHO Possible** causality is agreed.

In addition, one case, case no 1, presented under Pericarditis case review, had concurrent myocarditis and pericarditis, occurring 11 days after 1st dose. This case is also considered WHO Possible. The case is further discussed under Pericarditis case review.

In conclusion, one case is considered WHO Probable and four cases WHO Possible. It is remarkable that three of four cases have a consistent feature regarding occurrence after 2nd dose and a short TTO of 3-4 days.

The MAH has not commented on the disproportionate reporting of cases after the 2nd dose, compared to 1st dose (considering the difference in exposure). Considering the pathophysiology of myocarditis, which includes infiltration of lymphocytes in the myocardium, an onset of event occurring a few days after the booster immunization is considered biologically plausible. The MAH is requested to comment specifically on the number of cases occurring after the 2nd dose as compared to the 1st dose, also considering the differences in exposure for these two groups. A specific O/E analyses should be performed for the 1st dose and 2nd dose receivers respectively.

Also, the MAH is requested to present the cases with an "Unlikely" causal association in a tabulated format. The table should include, but not restricted to, the following information: Case ID (Eudravigilance no if possible) – age/gender - TTO - 1st dose/2nd dose – underlying condition(s) (including COVID-19), other medical confounders or risk factors present (including latency/TTO as applicable) - Confounding medications (including latency/TTO as applicable) – outcome

Table 9. Summary Narratives of Spontaneous Cases of Myocarditis Reported per WHO/UMC "Possible" Causality Assessment for the mRNA-1273 vaccine.
Cumulative to 31 March 2021

Case No.	TTO	Narrative
1	4 days	A spontaneous report was received concerning a 18-29-year-old, male patient, who received Moderna's COVID-19 vaccine (mRNA-1273) and experienced soreness of the arm, acute onset of chest pain with a diagnosis of myocarditis. The patient's medical history, as provided by the reporter, included asthma, and allergy to egg, peanut and tree nuts. Concomitant medications reported included dupilumab, montelukast, budesonide / formoterol, cetirizine, albuterol and epinephrine. . Prior to the onset of events, the patient received their second of two planned doses of mRNA-1273 intramuscularly in the left deltoid for prophylaxis of COVID-19 infection.

Case No.	TTO	Narrative
		On the same day, after receiving the second dose of the vaccine, the patient reported soreness of the arm for 3 to 4 days. Four days later, the patient presented to the hospital with acute onset of left sided chest pain. The physician reported that the patient developed myocarditis. His cardiac MRI on day 7 showed sub epicardial and mid myocardial late gadolinium enhancement in the basal inferior and inferolateral segments of the LV with additional patchy LGE in all 4 apical segments along with the LV edema. He had two different PVC morphologies. Infectious workup was negative, including a negative biofire, two covid-19 PCR, SARs Covid 2 antibodies, Lyme antibodies, coxsackie antibodies, CMV, EBV, PCR and HIV studies and negative T spot. His ANA was abnormal, but his dsDNA , anti la antibodies and anti smith antibodies were negative. No treatment information was provided. The patient was discharged from the hospital on day 8 with instructions to restrict physical activity and follow up with cardiologist. The event, soreness of the arm, was resolved. The event myocarditis was not resolved. **Company assessment**: This report of myocarditis occurring after receiving the Moderna-COVID-19 vaccine is confounded by concurrent medical history (asthma[18]) as well as concurrent medications that are currently labeled for serious cardiovascular events including myocarditis (dupilumab, budesonide / formoterol, albuterol). These confounders provide a more plausible explanation for the occurrence of the event of myocarditis.
2	3 days	A regulatory authority report was received from an healthcare professional concerning a 50-59-years-old male patient who experienced myalgia, headache, fever/pyrexia, fatigue, severe substernal chest pain, myocarditis, left ventricular dysfunction, and malaise. The patient's medical history was not provided. Concomitant medications reported included, lisinopril, atorvastatin, and ezetimibe. On day 0, prior to the onset of the events, the patient received their second of two planned doses of mRNA-1273 intramuscularly for prophylaxis of COVID-19 infection. On day 3, the patient experienced the events, myalgia, headache, fever, fatigue,. This subsided and then on day 6 he developed severe substernal chest pain and came to the ER where he had labs revealed myocarditis with left ventricular dysfunction. The patient was hospitalized. Laboratory details included, HS-CTnI was greater than 2000 ng/L and peaked at 6700 ng/L, ECG, echo and cardiac were normal but MRI showed evidence of myocarditis with mild left ventricular dysfunction. No treatment details information was provided. At the time of this report, the outcome of the events, myalgia, headache, fever, fatigue, severe substernal chest pain, myocarditis, left ventricular dysfunction, and malaise were unknown. **Company assessment**: This report of myocarditis occurring after receiving the Moderna-COVID-19 vaccine is confounded by concurrent medications that are currently labeled for serious cardiovascular events (atorvastin). Also given that the patient is taking medications usually prescribed for cardiovascular

Case No.	TTO	Narrative
		conditions, including hypertension, coronary artery disease, etc., it provides additional confounding factors that may explain better the occurrence of myocarditis. These confounders provide a more plausible explanation for the occurrence of the event of myocarditis.
3	4 days	A regulatory report was received from a consumer for a 18-29-year-old male patient who received Moderna's COVID-19 vaccine (mRNA-1273) and experienced myocarditis, fever, chest pain, myalgia, headache, chills and nausea. The patient's medical history included COVID-19, Hereditary hemorrhagic telangiectasia and Nasal bleeding. No concomitant medication use was reported. On day 0, the patient received his second of two planned doses of mRNA-1273 intramuscularly for prophylaxis of COVID-19 infection. On the same day of vaccination, the patient experienced nausea, fever and headache. On day 1, the patient experienced chills and myalgia and on day 3, the patient experienced myocarditis and chest pain. The patient was hospitalized due to the events on an unspecified date. Treatment information was not provided. The outcome of the events, myocarditis was not recovered, outcome for events chest pain, headache and fever was recovering/ resolving and outcome for events myalgia, chills, nausea was unknown. **Company assessment**: This report of myocarditis occurring after receiving the Moderna-COVID-19 vaccine is confounded by concurrent medical history (COVID-19 infection). Previous COVID-19 infection provides a more plausible explanation for the occurrence of the event of myocarditis[5].
4	4 days	A regulatory authority report was received from a healthcare facility staff member concerning a 40-49-year-old, female patient who developed myocarditis and pericarditis. The patient's medical history included Sjogren's Syndrome - mild, mostly with just dry eyes. Products known to have been used by the patient, within two weeks prior to the event, included ethinyl estradiol. The patient received the first of two planned doses of mRNA-1273 (Batch number not provided) on unknown. On day 0, prior to the onset of the symptoms, the patient received the second of two planned doses of mRNA-1273 (Batch number not provided) intramuscularly in the arm for prophylaxis of COVID-19 infection. On day 4 the patient was diagnosed with myocarditis and pericarditis; lab examinations were performed which included troponin (elevated), CK (elevated), ESR (increased). ECG with 1 mm ST elevations, cardiac catheterization and echocardiogram normal. Treatment information was not provided. The outcome of the events myocarditis and pericarditis was unknown. **Company assessment**: This report of myocarditis occurring after receiving the Moderna-COVID-19 vaccine is confounded by concurrent medical history (Sjögren's syndrome). Primary Sjögren's syndrome is rarely associated with a heart condition, but several cases of myocarditis have been described in this syndrome either alone or in the context of multisystem

Case No.	TTO	Narrative
		involvement. The etiologic mechanism of this myocarditis has been related to a possible leukocytoclastic vasculitis[19]. This confounder provides a more plausible explanation for the occurrence of the event of myocarditis.

ii. Pericarditis:

Analysis of the 41 cases that reported events of Pericarditis using the WHO-UMP standardized case causality assessment revealed that there were 9 reports (21.9% of the Pericarditis cases) classified as "Possible" events. There were 4 males and 5 females. Their ages were between 18 and 79 years of age. 7 reports were after the 1st dose, and 2 after the 2nd dose of the Moderna COVID-19 vaccine. The reported TTO was between 2 days and 24 days (Mean 11.3 days). A summary of these events is provided below (See **Table 10**).

The rest of the 41 cases that reported Pericarditis, 12 cases (29.3%) were classified as "Conditional"; 4 cases (9.7%) were classified as "Unassessable/ Unclassifiable"; and 16 (39%) were classified as "Unlikely".

The "Conditional" cases were reported in 9 males, and 2 females. Their ages were between 18 to 89 years of age; 6 cases were reported after the 1st dose of the Moderna COVID-19 vaccine, and 6 after the 2nd dose of the vaccine. TTO was between same day to 13 days after the vaccine (Mean 8,5 days). These events had reports of myocarditis occurring after receiving the vaccine but important information necessary to conduct an appropriate causality assessment were missing, including previous and concurrent medical history, previous and concurrent medications, course of the current disease, and in one case age was missing.

The 5 cases that were classified as "Unassessable/ Unclassifiable" were reported in 2 males, 2 females, and 1 unknown, between 21 and 89 years of age; 3 cases were reported after the 1st dose, and 2 after the second dose of the Moderna COVID-19 vaccine. TTO was between hours after the first dose to 1 days (Mean 0.6 days). These events had reports of pericarditis occurring after receiving the vaccine but important information necessary to conduct an appropriate causality assessment were missing, including previous and concurrent medical history, previous and concurrent medications, course of the current disease.

The 15 cases that were classified as "Unlikely" were reported in 8 males, 7 females and 1 unknown between 18 and 89 years of age; 7 cases were reported after the 1st dose, and 9 after the second dose of the Moderna COVID-19 vaccine. TTO was between one hour to 32 days (Mean 6.5 days). These events had reports of pericarditis occurring after receiving the vaccine but the reports are heavily confounded by concurrent medical history (Influenza, cardiovascular disorders, asthma, hyperthyroidism, sepsis) as well as concurrent medications that are currently labeled for serious cardiovascular events including myocarditis.

PRAC Rapporteurs assessment comments:

The MAH assessed 9 cases with pericarditis as possible (as per WHO-UMP causality assessment categories).

Remaining 32/41 cases were either considered by the MAH as "Conditional" (12 cases), as "Unassessable/ Unclassifiable" (4 cases) and as "Unlikely" (16 cases).

For the cases assessed as Possible, the TTO ranged from 2 days to 24 days, and 7 of 9 reports occurred after the 1st dose and the remaining 2 cases after the 2nd dose. Two cases reported both

myocarditis and pericarditis. One of these cases (case no. 1) has not been presented as a myocarditis case with a possible causality. It is unclear why, as the case have a possible causality for both myocarditis and pericarditis.

In general, the same limitations of the MAHs causality assessment as described for the myocarditis case are present for the pericarditis cases. In general, the rapporteur agrees with the overall assessment of causality but does not agree with the MAHs assessment of confounders in most cases. The MAH is quick to consider any cardiac or thrombotic event related to a concomitant medication enough to consider that medication is a more plausible explanation for the event of pericarditis. An example hereof is case no 2 where the MAH considers the contraceptive implant containing etonogestrel, a more plausible explanation for the event of pericarditis as the medication currently labels "serious cardiovascular events" according to the MAH. When assessing the case, the assessor found no cardiac or relevant vascular ADRs are listed in the ADR table in the SmPC of this drug, however, in section 4.4 the well-known risk of VTE or ATE of oral contraceptives is mentioned. The duration of treatment with the contraceptive is unknown, though it should be noted that the implant is inserted and effective for 3 years. Hence, this drug alone does not provide a more plausible explanation for the event than the mRNA-1273 Moderna vaccine. Rapporteurs assessment of potential confounders in the 9 pericarditis cases is presented below:

Case no	PRAC rapporteurs assessment:
1	18-29-year old male patient was hospitalized and diagnosed with pericarditis and myocarditis 11 days after 1st dose. The case has a possible temporal relationship. Concomitant medication were phenylpropanolamine, diclofenac sodium, and colchicine. No medical history was reported. The MAH mentions diclofenac as a more plausible explanation. Diclofenac has several cardiac ADRS listed, but not pericarditis. The risk of cardiac events related to Diclofenac is mainly related to patients with preexisting heart disease. **WHO Possible** for both the event of myocarditis and pericarditis
2	30-39-year old female experienced symptoms of pericarditis 5 days after the 1st dose. The case has a plausible TTO. Concomitant medication were etonogestrel containing contraceptive implant , prenatal vitamin, and eszopiclone. No medical history was reported. The MAH mentions the implant as a more plausible explanation, which is not agreed to, as no cardiac or relevant vascular ADRs are listed in the ADR table in the SmPC of this drug, however, in section 4.4 the well-known risk of VTE or ATE of oral contraceptives is mentioned. **WHO Possible.**
3	60-69-year old male with a medical history of pericarditis experienced pericarditis 9 days after 1st dose of the vaccine. The case was fatal. The cases have a possible TTO. Concomitant medications were not provided. patient's medical history included hypertension, hyperlipidemia, pericarditis (start date 2014). **WHO Possible**
4	60-69-year-old male experienced symptoms of pericarditis 9 days after the 1st dose. The case has a possible time to onset. Concomitant medication included Paracetamol, Aspirin, Clonazepam, Colchicine, Famotidine, Metoprolol, Omeprazole. Medical history included

	hypertension, gastroesophageal reflux disease, anxiety, recurrent syncopal episodes in the past, new onset atrial fibrillation at time of adverse event (Not specified). Pericarditis is not listed for any of the concomitant medications. However, some other cardiac ADRs were listed for some the concomitant drugs, most of them more severe (e.g. cardiac failure, AV-block, cardiac arrest). The patient's current cardiac disease is a risk factor for pericarditis **WHO Possible**
5	18-29-year-old male experienced pericarditis 2 days after the 2nd dose. The case has a possible time to onset. Concomitant medication included methylphenidate hydrochloride, aripiprazole, and clonidine. Medical history included attention deficit hyperactivity disorder, mood swings, sleep apnea, and current conditions of nasal congestion and cough. The MAH states that the concomitant medication has several cardiovascular events labelled and therefore is a more plausible explanation for the event. methylphenidate hydrochloride and aripiprazole both have a warning of use in patients with a medical history of cardiac disease due to risk of severe arrhythmias. However, pericarditis is not listed. **WHO possible**
6	50-59-year old female patients experienced onset of pericarditis symptoms 18 days after the 1st dose. It is acknowledged that COVID-19 has been linked to cardiovascular pathologies. This case do however lack information on when the patient experienced COVID-19 disease in relation to the vaccination, which is important in order to determine causality. **WHO Possible**
7	Discussed under the myocarditis cases. **WHO Possible** for the event of pericarditis.
8	70-79-year old female patient experienced onset of symptoms 21 days after 1st dose. The case has a positive temporal relationship. Concomitant medication included valsartan, ursodiol, citalopram, montelukast, ASA, lorazepam, tamsulosin, fluticasone. Patients medical history included hypertension and primary biliary cirrhosis. It is acknowledged that hypertension is a risk factor for several cardiac events. However, the same cannot be said for biliary cirrhosis. The MAH should not consider a clinical entity a confounder unless clinical evidence can support it. However, the reported concomitant drugs suggest the reported current medical conditions is not complete. **WHO Possible.**
9	30-39-year-old patient experienced pericarditis 24 days after the 1st dose. The case has a positive temporal relationship. The case has limited information about the event ad diagnosis of pericarditis. No concomitant medications are reported. The patient's past medical history included CVA. Concurrent medical conditions included Thalassaemia, Hypothyroidism and Allergy. **WHO Possible.**

Approximately, half of the cases had a well described diagnosis of pericarditis which included various testing. In contrast to myocarditis, where most cases occur after the second dose, most of the pericarditis cases assessed as possible occurs after the first dose. The TTO varies significantly (from

2 days to 24 days) in these cases compared to the myocarditis cases. Only 1 case had a medical history of pericarditis.
The MAH is requested to present all cases with an "unlikely" casual association for myocarditis cases also applies to pericarditis cases.

Table 10. Summary Narratives of Spontaneous Cases of Pericarditis Reported per WHO/UMC "Possible" Causality Assessment for the mRNA-1273 vaccine.
Cumulative to 31 March 2021

Case No.	TTO	Narrative
1	11 days	A spontaneous report was received from a 18-29-year- old male patient who experienced chest pain, myocarditis, pericarditis, inflammation of pericardium. The patient's medical history was not provided. Concomitant medications included phenylpropanolamine, diclofenac sodium, and colchicine. The patient received their first of two planned doses of mRNA-1273 (Batch number: unknown) on day 0 intramuscularly for the prophylaxis of COVID-19 infection. On day 10, the patient experienced chest pain, rapid heartbeat and went to emergency room (ER). He was hospitalized and was diagnosed with myocarditis, pericarditis, inflammation of pericardium. The patient was discharged on day 11. Treatment information was not provided. The outcome of the events, chest pain, myocarditis, pericarditis, inflammation of pericardium, was considered not resolved. **Company assessment:** This report of both pericarditis and myocarditis occurring after receiving the Moderna-COVID-19 vaccine is confounded by concurrent medications that are currently labeled for serious cardiovascular events (diclofenac sodium). This confounder provides a more plausible explanation for the occurrence of the event of pericarditis and myocarditis.
2	5 days	A regulatory authority report was received from another healthcare professional (HCP) concerning a 30-39-year-old, female patient who experienced chest pain, shortness of breath/dyspnea, pericarditis, and fatigue. The patient's medical history was not provided. Products known to have been used by the patient, within two weeks prior to the event, included etonogestrel containing contraceptive implant , prenatal vitamin, and eszopiclone. The patient received their first of two planned doses of mRNA-1273 on day 0 , approximately five days prior to the onset of the symptoms intramuscularly in the right arm for prophylaxis of COVID-19 infection. On day 5, during exercise the patient experienced shortness of breath, and chest pain. This lasted for one to two hours post her cardio exercise. These symptoms continued for two to three days along with fatigue. The patient had an EKG performed which showed first degree AV block with RBBB. She was then referred to a cardiologist and on day 18 she was diagnosed with pericarditis. Treatment of these events included NSAIDs. The outcome of the events, dyspnea, chest pain, fatigue and pericarditis were unknown. **Company assessment:** This report of pericarditis occurring after receiving the Moderna-COVID-19 vaccine is confounded by concurrent medications that are currently labeled for serious cardiovascular events (etonogestrel containing contraceptive implant). This confounder provides a more plausible explanation for the occurrence of the event of pericarditis.
3	9 days	A regulatory authority report was received from a healthcare professional concerning a 60-69 years old male patient who developed acute myocardial infraction, chest pain, dyspnea, pericarditis and died. The patient's medical history included hypertension, hyperlipidemia, pericarditis (start date 2014). Concomitant medications were not provided. On day 0, the patient received their first of two planned doses of mRNA-1273 intramuscularly in the left arm for prophylaxis of COVID-19 infection. The patient experienced severe chest pain and dyspnea approximately 9 days following the first series of the vaccine. He reported to family members that he was having a severe reaction to the vaccine and believed it was acute pericarditis, due to the same symptoms he experienced prior. On day 9 around 0300 hours, the symptoms were the most severe and he was going to seek medical attention, but he did not. He purchased OTC paracetamol for relief of symptoms. Symptoms of dyspnea and chest pain continued until day 17, when he called the emergency service complaining of chest pain and was found to have a STEMI (ST-elevation myocardial infarction). He subsequently died on day 17. It was unknown if an autopsy was performed. **Company assessment:** This case is heavily confounded by the patient's previous (pericarditis, hypertension, hyperlipidemia) and concurrent medical history (acute MI). According to the WHO-UMC causality assessment the case is considered possible given that there is a temporal relationship to the occurrence of the event after vaccination but the previous and concurrent medical history are a more plausible explanation for the occurrence of the event of pericarditis. This confounder provides a more plausible explanation for the occurrence of the event of pericarditis.

Case No.	TTO	Narrative
4	9 days	A regulatory authority report was received concerning an 60-69-year-old, male patient who received Moderna's COVID-19 Vaccine (mRNA-1273) and who experienced Pericarditis with pericardial effusion/ Pericarditis; pericardial effusion, retrosternal chest heaviness and aching worse with inspiration/ Chest discomfort; Chest pain; Painful respiration, fever/ pyrexia, chills, lymphadenopathy and pain. The patient's medical history included hypertension gastroesophageal reflux disease, anxiety, recurrent syncopal episodes in the past, new onset atrial fibrillation at time of adverse event (Not specified). Products known to have been used by the patient, within two weeks prior to the event, included paracetamol 650 milligram q 6 hours as needed, Aspirin 81 milligram daily, Clonazepam 1 milligram as needed, Colchicine 0.6 milligram daily, Famotidine 20 milligram daily as needed, Metoprolol tartrate 100 milligram every twelve hours Omeprazole 20 milligram daily as needed (Not specified). On day 0, approximately nine days prior to the onset of the symptoms, the patient received their first of two planned doses of mRNA-1273 intramuscularly in the arm for prophylaxis of COVID-19 infection. The patient had pericarditis with pericardial effusion. Other symptoms began with syncopal episode, retrosternal chest heaviness and aching worse with inspiration, fever, chills, lymphadenopathy for a for nine days following vaccination and was hospitalized for three days. Relevant laboratory tests and procedures included complete blood count with differential, complete metabolic panel, troponin x 2, B-Type natriuretic peptide, Covid swab, urinalysis, C reactive protein, electrocardiogram and chest X ray on day 9 and cardiac echocardiogram, pericardiocentesis, pericardial fluid analysis and thyroid stimulating hormone on day 9 (results not specified). Treatment for the event included Pericardiocentesis, Colchicine, Aspirin, Ibuprofen, Omeprazole for pericarditis with pericardial effusion. Treatments for other events was not provided. The events, Pericarditis with pericardial effusion, retrosternal chest heaviness and aching worse with inspiration, fever, chills, lymphadenopathy and pain were considered recovered/resolved on after third day of hospitalization and was feeling better after one week of follow up. **Company assessment:** This report of pericarditis occurring after receiving the Moderna-COVID-19 vaccine is confounded by concurrent medical history (hypertension gastroesophageal reflux disease, anxiety, recurrent syncopal episodes) as well as concurrent medications that are currently labeled for cardiovascular events. These confounders provide a more plausible explanation for the occurrence of the event of pericarditis.
5	2 days	A regulatory authority report was received from a healthcare professional concerning a 18-29-year old, male patient who received Moderna's COVID-19 vaccine (mRNA-1273) and experienced chest pain and pericarditis. The patient's medical history included attention deficit hyperactivity disorder, mood swings, sleep apnea, and current conditions of nasal congestion and cough. Products known to have been used by the patient, within two weeks prior to the event, included methylphenidate hydrochloride, aripiprazole, and clonidine. On day 0, the patient received their second of two planned doses of mRNA-1273 intramuscularly in the left arm for prophylaxis of COVID-19 infection. Two days after receiving the vaccine, the patient was hospitalized due to chest pain and pericarditis. On the same day, the patient underwent X-ray, electrocardiogram, echocardiogram, laboratory tests, magnetic resonance imaging. The findings of electrocardiogram were abnormal and laboratory findings revealed increased troponin levels. Subsequently, heart catheterization was performed the very same day. Treatment information was not provided. The outcome of the events, chest pain and pericarditis, was considered not recovered. **Company assessment:** This report of pericarditis occurring after receiving the Moderna-COVID-19 vaccine is confounded by concurrent medications that are currently labeled for cardiovascular events. These confounders provide a more plausible explanation for the occurrence of the event of pericarditis.
6	18 days	A regulatory report was received from a other healthcare professional concerning a 50-59 years old, female patient who experienced back pain/back pain, chest pain/chest pain, dyspnea/dyspnea, hepatitis/hepatitis, pericardial effusion/pericardial effusion, pericarditis/pericarditis, pleural effusion/pleural effusion, pneumonitis/pneumonitis. The patient's medical history indicated exposure to COVID-19 just prior to getting the vaccination. Products known to have been used by the patient, within two weeks prior to the event, included Zinc, vitamin D3 and vitamin c. The patient received their first of two planned doses of mRNA-1273 intramuscularly in the left arm for prophylaxis of COVID-19 infection. Approximately after 2.5 weeks after vaccination, she developed severe increasing back

Case No.	TTO	Narrative
		pain, chest pain, shortness of breath Dx, acute moderately severe pericarditis with pericardial effusion, pneumonitis with bilateral small pleural effusions, hepatitis with elevated alk phos and LFT, bone marrow reaction with elevated WBC, new anemia and elevated platelets, markedly elevated d dimer and CRP with normal troponin and negative imaging for PE. Treatment information was not provided. The events, back pain, chest pain, dyspnea, hepatitis, pericardial effusion, pericarditis, pleural effusion, pneumonitis was not resolved. **Company assessment**: This report of pericarditis occurring after receiving the Moderna-COVID-19 vaccine is confounded by concurrent medical history (COVID-19 infection). Previous COVID-19 infection provides a more plausible explanation for the occurrence of the event of myocarditis[5].
7	4 days	A regulatory authority report was received from a healthcare facility staff member concerning a 40-49-year-old, female patient who developed myocarditis and pericarditis. The patient's medical history included Sjogren's Syndrome - mild, mostly with just dry eyes. Products known to have been used by the patient, within two weeks prior to the event, included ethinylestradiol. The patient received the first of two planned doses of mRNA-1273 (Batch number not provided) on unknown. On day 0, prior to the onset of the symptoms, the patient received the second of two planned doses of mRNA-1273 (Batch number not provided) intramuscularly in the arm for prophylaxis of COVID-19 infection. On day 4 the patient was diagnosed with myocarditis and pericarditis; lab examinations were performed which included troponin (elevated), CK (elevated), ESR (increased). ECG with 1 mm ST elevations, cardiac catheterization and echocardiogram normal. Treatment information was not provided. The outcome of the events myocarditis and pericarditis was unknown. **Company assessment**: This report of pericarditis and myocarditis occurring after receiving the Moderna-COVID-19 vaccine is confounded by concurrent medical history (Sjögren's syndrome). Primary Sjögren's syndrome is rarely associated with a heart condition, but several cases of myocarditis and pericarditis have been described in this syndrome either alone or in the context of multisystem involvement. The etiologic mechanism of this myocarditis has been related to a possible leukocytoclastic vasculitis. This confounder provides a more plausible explanation for the occurrence of the event of pericarditis and myocarditis.
8	21 days	A regulatory authority report was received from a health care professional concerning a 70-79 year-old, female patient who received Moderna's COVID-19 vaccine (mRNA-1273) and experienced pericarditis and pericardial effusion. The patient's medical history included HTN (hypertension), primary biliary cirrhosis. Concomitant medicines included valsartan, ursodiol, citalopram, montelukast, ASA, lorazepam, tamsulosin, fluticasone. On day 0, prior to the onset of the events, the patient received their one of two planned doses of mRNA-1273 intramuscular in left arm for prophylaxis of COVID-19 infection. On day 21, the patient experienced pericarditis and pericardial effusion. Laboratory exams included CRP, echocardiogram, respiratory viral PCR, CBC, CMP, ASO titer, ANA, EKG, antinuclear antibody, c-reactive protein, echocardiogram, electrocardiogram, full blood count, metabolic function test, polymerase chain reaction, respiratory viral panel and streptococcus test (results not reported). No treatment information was provided. The outcomes of the events, pericarditis and pericardial effusion, were resolved. **Company assessment**: This report of pericarditis occurring after receiving the Moderna-COVID-19 vaccine is confounded by concurrent medical history (hypertension, biliary cirrhosis) as well as concurrent medications that are currently labeled for cardiovascular events. These confounders provide a more plausible explanation for the occurrence of the event of pericarditis.
9	24 days	This case was received via an unknown source (no reference has been entered for a health authority or license partner) and was forwarded to Moderna . This regulatory authority case was reported by a physician (subsequently medically confirmed) and describes the occurrence of pericarditis in a 30-39-year-old female patient who received mRNA-1273 (COVID 19 Vaccine Moderna) for COVID-19 vaccination. The patient's past medical history included CVA. Concurrent medical conditions included Thalassaemia, Hypothyroidism and Allergy. On day 0, the patient received first dose of mRNA-1273 (COVID 19 Vaccine Moderna) (Intramuscular) 1 dosage form. On day 23, the patient experienced Pericarditis. At the time of the report, pericarditis had resolved. Treatment information was not reported. **Company assessment**: This report of pericarditis occurring after receiving the Moderna-COVID-19 vaccine is confounded by concurrent medical history (Thalassaemia, Hypothyroidism and Allergy). These confounders provide a more plausible explanation for the occurrence of the event of pericarditis.

5. Associated Preferred Terms (PTs) with the Events of Myocarditis and/or Pericarditis:

As per request from the PRAC, an analysis of the most common associated PT that were reported in conjunction with the 84 reports of Myocarditis and/or Pericarditis, showed that "Chest Pain" (11.7%), "Pyrexia" (5.3%), "Dyspnoea" (4.1%), and "Chills" (3.5%) were the PT most commonly reported with the Myocarditis and Pericarditis events. There was no trending associated with any other PTs. The events of chest pain and dyspnoea are expected events associated with the diagnosis of Myocarditis and Pericarditis. Pyrexia and chills, are already events labelled for the Moderna COVID 19 vaccine, but are also associated with some of the concomitant medical histories reported for the cases of Myocarditis and/or Pericarditis, like Influenza, Influenza-like symptoms, COVID-19 infection, sepsis and other bacterial infections.

Table 11. PTs reported within cases of Myocarditis and/or Pericarditis Reported for the mRNA-1273 vaccine.
Cumulative to 31 March 2021

SOC	PT	N	%
Blood and lymphatic system disorders	Anaemia	1	0.3
	Lymphadenopathy	4	1.0
Cardiac disorders	Conduction disorder	1	0.3
	Cardiac disorder	1	0.3
	Palpitations	2	0.5
	Cardiac failure congestive	1	0.3
	Acute coronary syndrome	1	0.3
	Acute myocardial infarction	3	0.8
	Angina pectoris	2	0.5
	Myocardial infarction	2	0.5
	Left ventricular dysfunction	1	0.3
	Left ventricular hypertrophy	1	0.3
	Right ventricular hypertrophy	1	0.3
	Ventricular enlargement	1	0.3
	Ventricular hypokinesia	1	0.3
	Myocarditis	49	12.4
	Pericarditis	40	10.1
	Cardiac tamponade	2	0.5
	Pericardial effusion	9	2.3
	Pericardial fibrosis	1	0.3
	Arrhythmia	1	0.3
	Tachycardia	1	0.3
	Atrial fibrillation	2	0.5
	Atrial flutter	3	0.8

SOC	PT	N	%
	Cardiac arrest	1	0.3
Eye disorders	Vision blurred	1	0.3
	Visual field defect	1	0.3
Gastrointestinal disorders	Dyspepsia	1	0.3
	Abdominal discomfort	1	0.3
	Nausea	5	1.3
	Vomiting	1	0.3
General disorders and administration site conditions	Asthenia	2	0.5
	Fatigue	13	3.3
	Malaise	6	1.5
	Death	1	0.3
	Pyrexia	21	5.3
	Chills	14	3.5
	Feeling abnormal	1	0.3
	Condition aggravated	3	0.8
	Influenza like illness	3	0.8
	Injection site erythema	1	0.3
	Injection site inflammation	1	0.3
	Injection site pain	1	0.3
	Oedema peripheral	1	0.3
	Chest discomfort	9	2.3
	Chest pain	45	11.4
	Pain	8	2.0
	Vaccination site pain	1	0.3
	Vaccination site warmth	1	0.3
Hepatobiliary disorders	Hepatitis	1	0.3
Infections and infestations	Influenza	1	0.3
	Viral cardiomyopathy	2	0.5
	Viral pericarditis	1	0.3
Injury, poisoning and procedural complications	Fall	1	0.3
	Inappropriate schedule of product administration	1	0.3
	Incorrect route of product administration	1	0.3
	Vaccination complication	1	0.3
Investigations	Ejection fraction decreased	2	0.5
	Electrocardiogram abnormal	1	0.3
	Computerised tomogram abdomen normal	1	0.3
	Red blood cell sedimentation rate increased	2	0.5
	Heart rate increased	1	0.3

SOC	PT	N	%
	Heart rate irregular	1	0.3
	Computerised tomogram normal	1	0.3
	Liver function test	1	0.3
	Brain natriuretic peptide increased	1	0.3
	Blood culture negative	1	0.3
	Blood iron decreased	1	0.3
	Body temperature increased	1	0.3
	C-reactive protein increased	1	0.3
	Blood urea increased	1	0.3
	Computerised tomogram pelvis	1	0.3
	Computerised tomogram thorax normal	1	0.3
	Blood creatine phosphokinase increased	1	0.3
	Troponin increased	3	0.8
	SARS-CoV-2 antibody test	1	0.3
	SARS-CoV-2 antibody test negative	1	0.3
	SARS-CoV-2 test negative	1	0.3
Metabolism and nutrition disorders	Decreased appetite	1	0.3
	Hyperglycaemia	1	0.3
Musculoskeletal and connective tissue disorders	Pain in jaw	2	0.5
	Myalgia	8	2.0
	Musculoskeletal stiffness	1	0.3
	Back pain	4	1.0
	Neck pain	2	0.5
	Pain in extremity	5	1.3
Nervous system disorders	Cerebral artery stenosis	1	0.3
	Balance disorder	1	0.3
	Hypokinesia	1	0.3
	Headache	12	3.0
	Dizziness	1	0.3
	Unresponsive to stimuli	1	0.3
	Hypoaesthesia	1	0.3
	Tremor	1	0.3
Psychiatric disorders	Abnormal dreams	1	0.3
	Sleep disorder	1	0.3
Renal and urinary disorders	Renal pain	1	0.3
Respiratory, thoracic and mediastinal disorders	Dyspnoea	16	4.1
	Hypoxia	1	0.3
	Cough	1	0.3
	Pneumonitis	1	0.3

SOC	PT	N	%
	Pleuritic pain	2	0.5
	Pleural effusion	4	1.0
	Painful respiration	1	0.3
Skin and subcutaneous tissue disorders	Hyperhidrosis	1	0.3
	Night sweats	4	1.0
	Dry skin	1	0.3
	Pruritus	2	0.5
Social circumstances	Bedridden	1	0.3
	Impaired work ability	1	0.3

PRAC Rapporteurs assessment comments:

No trends or patterns could be identified from the provided overview of co-reported events, besides the usual symptoms related to myocarditis/pericarditis and reactogenicity.

6. Discussion and Conclusions:

The company clinical database and the global safety database were queried for valid, clinical and spontaneous case reports received from HCP, HA, consumers and literature, cumulative from 18 December 2020 to 30 April 2021, worldwide, reported for the mRNA-1273 vaccine (COVID-19 vaccine Moderna) using the following Preferred Terms (PTs): "***Viral pericarditis; Pericarditis; Pericarditis infective; Myocarditis; Myocarditis septic; Myocarditis infectious; Viral myocarditis; and Myocarditis post-infection***". The clinical trial data is from the Phase 3 pivotal clinical trial mRNA-1273 P301.

As of 30 April 2021, there have been 182,568,555 doses of the mRNA-1273 vaccine distributed worldwide. Out of those 119,066,486 doses have been administered, with 87.9% of doses administered in the US, 9.6% in the European Economic Area, 1.7% in Canada, and 0.8% in other countries.

The data from the mRNA-1273 P301 clinical trials showed that there were no reported TEAEs of "Myocarditis" in P301. There were three (3) unsolicited TEAE of "Pericarditis" reported in P301; two TEAEs in the Placebo arm, and one in the Vaccine arm of the safety set in the overall stage after any injection. The 2 events in the placebo arm were reported in the $\geq$18 to $\leq$65 years of age, and the event in the vaccination arm was reported in the $\geq$65 years of age group. Data from this pivotal clinical trial does not suggest a relationship between administration of the mRNA-1273 vaccine and the events of Myocarditis and/or Pericarditis.

The company global safety database was also queried for spontaneous, valid, case reports received from HCP, HA, literature, and consumers, cumulatively (18 December 2020 to 30 April 2021), worldwide, using the PTs of "***Viral pericarditis; Pericarditis; Pericarditis infective; Myocarditis; Myocarditis septic; Myocarditis infectious; Viral myocarditis; and Myocarditis post-infection"***. There were 84 case reports (0.1% of all cases reported to the MAH) with the PTs of Myocarditis and/or Pericarditis. There were 49 cases (0.1% of all cases) reported with Myocarditis-related PTs, and 41 cases (0.04% of all cases) with Pericarditis-related PTs. There were 6 cases (0.01% of all cases) that reported both events of Myocarditis and Pericarditis-related PTs. All 84 reports were considered serious reports. Most of the reports were in individuals between the ages of 18 to 39 years of age, and in

males (75.4%). The majority of the reports had a TTO of <14 days (Mean 6 days). Most of the events for which the event outcome was reported showed not recovered/ not resolved (34.1%) followed by recovered/ resolved (23.5%). It is important to note that most of the spontaneous reports included in the MAH global safety database are obtained from regulatory authorities. This preclude the MAH to obtain follow-up information for the cases reported. It is also important to note that the reports are usually provided to the regulatory authorities usually when the patient was admitted to the hospital or recently discharged hence the fact that most of the events have a "not resolved" reported outcome.

Given that the majority of the cases (90.6%) with the PTs of Myocarditis were reported in the USA, the MAH used data from the Vaccine Safety Datalink (VSD), given that population-based data characterizing the incidence of myocarditis in general are limited. The study from the VSD considered myocarditis as an adverse event following immunization (AEFI). In this assessment, an incidence of 0.24 per 100,000 individuals within 42 days after receiving measles-mumps-rubella, varicella, oral polio, or yellow fever vaccines did not exceed the rate in a control period. Even though the Moderna COVID-19 vaccine is not a live-virus vaccine the information from this study do allow to provide information related to AEFIs in vaccines that have been widely used in the world. Compared to this rate, the observed number of Myocarditis cases within the MAH global safety database, were within the expected range (49 cases observed vs 108 expected), with a rate ratio suggesting that sensitivity of the reporting rate would need to be below 29% for a possible increase in risk to be masked by low reporting.

Regarding Pericarditis, there were 41 pericarditis cases observed in the MAH global safety database through 30 April 2021. Based on incidence rates from the prospective clinical cohort study in Italy that identified an incidence of 27.7 cases per 100,000 person-years, and the retrospective analysis of the Finnish registry data capturing admissions to 29 hospitals over a span of 9.5 years identified an age standardized incidence of 3.32 per 100,000 person-years, with higher rates in men ages 16-65, around 225-1896 cases would be expected. The analysis of the MAH post-marketing data shows that for males, all observed rates were below the expected, and for females, rates were below the expected with the exception of the 30-39 age group, where the reporting rate was approximately equal to the expected (1.03 vs. 1.00).

Review of the 84 serious case reports associated with the chosen PTs for Myocarditis and Pericarditis, and using the WHO-UMP standardized case causality assessment of 2018, showed that there were 24 cases classified as "Conditional", 16 classified as "Unlikely", 20 classified as "Unassessable", and 13 as "Possible". Most of the reports were heavily confounded by previous or concomitant medical history, including concomitant medications. Review of these cases do not show that Myocarditis and/or Pericarditis are related to the Moderna COVID-19 vaccine. Most of the cases are in general heavily confounded and are missing important medical information in order to make an informed causality assessment. There is a wide spectrum of severity among the Myocarditis and/or Pericarditis reported cases.

During the Advisory Committee on Immunization Practices (ACIP) COVID-19 Vaccine Safety Technical (VaST) Work Group conducted on May 12 several presentations on myocarditis following mRNA vaccines, from the Department of Defense (DoD), the Vaccine Adverse Event Reporting System (VAERS), and Vaccine Safety Datalink (VSD) were discussed. There were also brief updates from the Veteran's Administration (VA) and the Clinical Immunization Safety Assessment (CISA) groups about their plans for future investigation of myocarditis. VaST concluded that there are relatively few reports of myocarditis to date and that these cases seem to occur predominantly in adolescents and young adults, more often in males than females, more often following dose 2 than dose 1, and typically within 4 days after vaccination. Most cases appear to be mild, and follow-up of cases is ongoing. Within CDC

safety monitoring systems, rates of myocarditis reports in the window following COVID-19 vaccination have not differed from expected baseline rates[20].

Review of the information provided by the Department of Defense (DoD) on 14 reports of Myocarditis on military members[21], shows that of the 14 cases, one patient, who tested positive for COVID-19 three months ago, developed myocarditis after their first dose of vaccine. The remaining 13 patients developed myocarditis after their second vaccine doses. No other information on these reports is available regarding previous and current medical history, previous and concomitant medications, as well as medical course of the current disease. According to the report, 11 cases received the Moderna COVID-19 vaccine, and 3 received another mRNA vaccine. The DoD has administered 2,713,640 COVID-19 vaccines, with diagnoses of myocarditis occurring in 0.000516% of that group.

Regarding the information provided by the Israeli Health Ministry, more than 5 million people have been vaccinated in Israel (https://www.timesofisrael.com/israel-said-probing-link-between-pfizer-shot-and-heart-problem-in-men-under-30/). There were 62 recorded cases of myocarditis following vaccination with another mRNA vaccine in the days after receiving the vaccine. According to the report 56 of those cases came after the second dose and most of the affected were men under the age of 30 years old. Sixty of the 62 patients were treated and released from hospital in good condition. Two of the patients, who were reportedly healthy until receiving the vaccination, including a 18-29-year-old woman and a 30-39-year's old man, died. The report found that of those who received the second dose, 1-in-100,000 had possible side effects of myocarditis; however, this number rose to 1-in-20,000 among those aged 16-30.

Information provided in these two reports do not provide enough information regarding the cases previous and current medical history, previous and concomitant medications, as well as medical course of the current disease. The reports also show a very similar occurrence of these conditions when compared with the general population. Very limited studies of the background rates of Myocarditis and Pericarditis, and likely large differences in detection and reporting that contribute to the extremely wide variation in background rates by geographic area. Viral myocarditis is thought to be the most frequent type, mostly affecting children and young adults. A recent study using International Classification of Diseases codes estimated the global prevalence of myocarditis to be ≈22 of 100 000 patients annually. Approximately 1% to 5% of patients that test positive for acute viral infection(s) may exhibit a form of myocarditis. The prevalence of myocarditis has been reported from 10.2 to 105.6 per 100,000 worldwide, and its annual occurrence is estimated at about 1.8 million cases. Most studies of acute myocarditis report a greater prevalence and severity in male patients, speculated to be caused by a protective effect of natural hormonal influences on immune responses in women when compared with men. Patients are usually between the ages of 20 and 50.

It is important to note that under the current enhanced safety monitoring activities that are being conducted throughout the world for those recipients of the COVID-19 vaccines, including the Moderna COVID-19 vaccine, and more specifically in the US with the use of the v-safe mobile application, there is an increase in the number of spontaneous reports received by the MAH, especially during the first 7 days after the administration of the vaccine. Reported incidence of the event of Myocarditis and/or Pericarditis follows a similar latency distribution pattern of the overall number of all of the reported events suggesting that the fact that those two events are reported with higher frequency within 7 days of the vaccine is a consequence of the enhanced surveillance activities mentioned above, and there is a potential for increased detection of illnesses post-vaccination due to well-described vaccine reactogenicity after exposure to the COVID-19 vaccines in general or simply knowledge of vaccination.

Based on the analysis of all the safety data available as of 30 April 2021, the MAH considers that Myocarditis and/or Pericarditis are not presently a safety issue of concern that would justify o inclusion

of "Myocarditis and/or Pericarditis" in the ADR table in section 4.8 of the SmPC nor in section 4 of the PL. The MAH will continue to closely evaluate events of "Myocarditis and/or Pericarditis" using routine surveillance.

PRAC Rapporteurs assessment comments:

In the previous MSSR AR, the MAH was requested to perform a cumulative review of the cases myocarditis and pericarditis. The MAH provided their evaluation during the current procedure as a separate submission.

Background

Myocarditis is an inflammatory condition of the myocardium. Pericarditis is an inflammatory process involving the pericardium. Both can be triggered by various factors, including viral infections and autoimmune conditions. The global prevalence of myocarditis is estimated to be approximately 22 per 100 000 PYs, with a greater prevalence and severity in male patients between the ages of 20 and 50. Global epidemiologic data on the incidence of acute pericarditis is not available.

Methodology

Search strategy

The MAH searched their company clinical database and the global safety database for cumulative (from 18 December 2020 to 30 April 2021) reports with PTs: Viral pericarditis; Pericarditis; Pericarditis infective; Myocarditis; Myocarditis septic; Myocarditis infectious; Viral myocarditis; and Myocarditis post-infection. The MAH's search strategy and used preferred terms are considered acceptable.

O/E analyses

The MAH performed both overall combined O/E analyses, and age- and gender stratified specific O/E analyses concerning the events of myocarditis and/or pericarditis. The MAH calculated exposure for the O/E analyses based on the US age and gender vaccination distribution data. For the age stratified myocarditis O/E analyses, ACCESS incidence rates comparable with available US and global incidence rates were used, due to a lack of US specific age or gender stratified background rates. In the age- and gender stratified O/E analyses for the pericarditis events, as no pericarditis specific data from the ACCESS IRs is available, the MAH based their O/E analyses on published incidence rates. The MAH's methodological approach is in general considered acceptable.

Results

Clinical database

No imbalance was seen in the clinical trial (P301), and data from P301 does not suggest a relationship between administration of the mRNA-1273 vaccine and the events of Myocarditis and/or Pericarditis.

Company global safety database

The MAH identified 84 case reports with the PTs of Myocarditis and/or Pericarditis from their safety database, of which 49 cases with Myocarditis-related PTs, and 41 cases with Pericarditis-related PTs. There were 6 cases that reported both events of Myocarditis and Pericarditis-related PTs.

O/E analyses

In the age- and gender stratified O/E analyses for the myocarditis events, the observed rates were close to equal or slightly above the expected rates for in males aged 18-29 and males aged 30-39

(rate ratio 0.73 when comparing to the low background IRs. This could indicate a potential increased risk in these populations, as some degree of underreporting is likely. Similarly, the observed rates were close to the expected rates for in females aged 18-29, 30-39 and 40-49, however, these findings rates were based on a low number of cases and thus should be interpreted with caution. In the age- and gender stratified O/E analyses for the pericarditis events, no significant findings were observed. The MAH is reminded to perform adjustment for underreporting, backlog of case handling and sensitivity analysis.

Case characteristics overview

The majority of the myocarditis and/or pericarditis cases were in males (55/84; 65.9%), and in individuals between the ages of 18 to 39 years of age (45/84; 52.3%). Most of the reports were with TTO within 1 day (31/84; 36.5%). Of these cases, 23/31 in males with most cases following the 2nd dose (6 after the 1st dose, and 17 after the 2nd dose), and 14/31 in the 18 to 39 years old group. A total of 20/84 cases were reported with TTO 2-3 days, of these 10 cases in age group 18-29.

A higher number of cases in males, and in age below < 40 may be expected as prevalence in the general population exhibits a similar pattern with a highest prevalence in young males between 20-50 years of age. Nevertheless, the number of cases reported after 1st or 2nd dose seem to differ substantially and may indicate a potential higher risk after 2nd dose.

No risk factors, or patterns or trends could be identified from the medical history or co-reported events.

Case causality assessment

Myocarditis cases

The MAH performed causality assessment of the 49 cases of Myocarditis. Of these, 29 cases were classified as either "Conditional" or "Unassessable", due to limited information. Of these, 14 were reported after the 1st dose, and 14 after the 2nd dose. 15 cases were classified as "Unlikely". Nine cases were reported after the 1st dose, and 6 after the 2nd dose. No information is given regarding the specific concomitant medication, nor the specific concurrent medical conditions, in these 15 cases which the MAH considers WHO "Unlikely".

Four (4) cases, classified as WHO Possible by the MAH, were further classified by the PRAC Rapporteur as one case being WHO Probable, and three cases WHO Possible. It is considered remarkable that all four cases have a consistent feature regarding occurrence after 2nd dose and a short TTO of 3-4 days.

Pericardititis cases

In total, 41 cases of Pericarditis were assessed by the MAH according the WHO-UMC causality categories. The MAH assessed 9 cases as *Possible*, 12 cases as *Conditional*, 4 cases as *Unassessable* and 16 cases were assessed as *Unlikely.*

The PRAC Rapporteur agrees with the causality classified by the MAH for the nine (9) cases classified as possible, however, the MAHs assessment of confounders is not fully agreed in all cases. Of the 9 cases with a possible causality, two cases reported both myocarditis and pericarditis. In contrast to the overall cases presentation, where most cases occur after the second dose, most of the pericarditis cases occurs after the first dose (7 of 9 cases). The TTO varies significantly (from 2 days to 24 days) in these cases compared to the myocarditis cases. Only 1 case had a medical history of pericarditis.

Other relevant safety information

In their signal evaluation, the MAH also refers to other safety information on this topic.

Vaccine Safety Technical (VaST) Work Group

VaST reviews COVID-19 vaccine safety data on weekly basis in the US. During the VaST meeting on May 17, 2021, myocarditis following mRNA vaccines was discussed. VaST concluded that there are relatively few reports of myocarditis to date and that these cases seem to occur:

- predominantly in adolescents and young adults,
- more often in males than females,
- more often following dose 2 than dose 1, and
- typically within 4 days after vaccination.

Most cases appeared to be mild, and follow-up of cases is ongoing. Within CDC safety monitoring systems, rates of myocarditis reports in the window following COVID-19 vaccination have not differed from expected baseline rates. https://www.cdc.gov/vaccines/acip/work-groups-vast/technical-report-2021-05-17.html

Department of Defense (DoD)

Of the 14 reports of Myocarditis on military members, based on the MAH's review of the information provided by the Department of Defense (DoD), one patient, who tested positive for COVID-19 three months ago, developed myocarditis after their first dose of vaccine. The remaining 13 patients developed myocarditis after their second vaccine doses. Eleven received the COVID-19 vaccine Moderna; three got another mRNA vaccine. No other information on these reports was available. https://www.military.com/daily-news/2021/04/26/pentagon-tracking-14-cases-of-heart-inflammation-troops-after-covid-19-shots.html

Israeli Health Ministry

Regarding the information provided by the Israeli Health Ministry, there were 62 cases of myocarditis following vaccination with another mRNA vaccine. Of those, 56 cases came after the 2nd dose and most of the affected were men under the age of 30 years old. There were two fatal cases, in a 18-29-year-old woman and a 30-39-year's old man, who were reportedly healthy prior to the vaccination. https://www.timesofisrael.com/israel-said-probing-link-between-pfizer-shot-and-heart-problem-in-men-under-30/

The MAH's overall conclusion

Based on the analysis of all the safety data available as of 30 April 2021, the MAH considered that Myocarditis and/or Pericarditis is not a safety issue of concern that would at present warrant an update of the product information.

PRAC Rapporteur's overall conclusion

Based on the presented information, it is agreed upon that the current evidence is not sufficient to establish causal association between COVID-10 vaccine Moderna and the risk of myocarditis and/or pericarditis. However, a need for further evaluation of this topic is considered warranted.

The MAH did not comment on the disproportionate reporting of cases after the 2nd dose, compared to 1st dose. Considering the pathophysiology of myocarditis, which includes infiltration of lymphocytes in the myocardium, an onset of event occurring a few days after the booster immunization is considered biologically plausible.

Also, the PRAC Rapporteur did not fully agree on the MAH's classification of the confounders. For the future causality assessment, the MAH is reminded that to consider a concurrent medication a confounder, it is required that the medication has the adverse event listed in the product information. Also, the TTO and outcome following dechallenge/rechallenge for the potential confounding medicinal product must be taken into consideration when assessing causality. If a medication has been used for a long time (chronic treatment), it is less likely to have caused the acute onset of myocarditis occurring shortly after vaccination. When the reports are considered confounded by concurrent medical history, such as COVID-19 or Influenza, it is important to look at the latency from the infections in order to assess the credibility of these confounding factors.

In the O/E-analysis, the MAH is reminded to perform adjustment for underreporting, backlog of case handling and sensitivity analysis.

Of note, the Brighton Collaboration working group has recently published a draft case definition of myocarditis, available at https://brightoncollaboration.us/myocarditis-case-definition-update/

The case definition should be implemented in the assessment of cases of myocarditis.

Finally, the MAH is reminded to actively follow-up on cases concerning myocarditis and pericarditis as the outcome of the events are important to fully characterize the seriousness of events and the potential risk of myocarditis/pericarditis.

5.2. Annex II – Summary Narratives of Spontaneous Cases of Myocarditis and Myo/Pericarditis Reported per WHO/UMC Causality Assessment as "Certain/ Probable/Possible"

Table 6. Summary Narratives of Spontaneous Cases of Myocarditis and Myo/Pericarditis Reported per WHO/UMC Causality Assessment as "Certain/ Probable/Possible" for the mRNA-1273 vaccine. Cumulative to 31 May 2021

Case No	Patient Age Band (Years)	Patient Gender	Time to Onset (days)	Dose Number	Medical History	Medications	Event Outcome	WHO-UMC Causality	MYO/ PERI/ MYOPERI	Brighton Definition	ALL PTs
1	18-29	Male	10	1	Not reported	Not reported	Not Recovered / Not Resolved	Possible	Myo-pericarditis	Level 4	Angina pectoris, Heart rate increased, Myocarditis, Pericarditis
2	18-29	Male	8	1	Attention deficit hyperactivity disorder(C)	amfetamine, dexamfetamine	Recovered / Resolved	Possible	Myo-pericarditis	Level 2	Chest pain, Dyspnoea, Myocarditis, Pericarditis, Pyrexia, Tachycardia
3	40-49	Male	4	1	Not reported	Not reported	Recovering/Resolving	Possible	Myocarditis	Level 2	Myocarditis
4	18-29	Male	10	1	Not reported	Not reported	Not Recovered /Not Resolved	Possible	Myo-pericarditis	Level 4	Angina pectoris, Heart rate increased, Myocarditis, Pericarditis

5	18-29	Male	2	2	Not reported	Not reported	Not Recovered /Not Resolved	Possible	Myocarditis	Level 2	Chest pain, Myocarditis, Pericardial effusion
6	18-29	Male	2	2	Not reported	Not reported	Not Recovered /Not Resolved	Possible	Myocarditis	Level 2	Chest pain, Headache, Musculoskeletal stiffness, Myocarditis, Pain, Pain in extremity
7	50-59	Male	2	2	Not reported	Not reported	Unknown	Possible	Myocarditis	Level 2	Chest pain, Chills, Myocarditis, Pyrexia
8	40-49	Male	3	2	Not reported	Not reported	Recovered /Resolved	Possible	Myocarditis	Level 2	Chest discomfort, Myocarditis
9	30-39	Male	2	2	Not reported	Not reported	Not Recovered /Not Resolved	Possible	Myocarditis	Level 1	Chest discomfort, Chills, Dyspnoea, Lymphadenopathy, Myocarditis, Nausea, Pyrexia, Vomiting
10	18-29	Male	4	2	Asthma(C); Food allergy; Food allergy; Food allergy; Eczema(C); Food allergy	montelukast, formoterol, budesonide, albuterol, dupilumab, cetirizine	Not Recovered /Not Resolved	Possible	Myocarditis	Level 1	Chest pain, Myalgia, Myocarditis, Vaccination site pain
11	18-29	Male	1	2	Tendonitis(C)	Not reported	Not Recovered /Not Resolved	Possible	Myocarditis	Level 2	Chest pain, Chills, Myalgia, Myocarditis, Pyrexia
12	18-29	Male	2	2	Drug hypersensitivity	multivitamin	Not Recovered /Not Resolved	Possible	Myo-pericarditis	Level 2	Chest pain, Myocarditis
13	18-29	Male	3	2	Congenital teratoma(H)	acetaminophen	Unknown	Possible	Myo-pericarditis	Level 2	Chest pain, Myocarditis, Pericarditis
14	30-39	Male	3	2	Food allergy(C)	multivitamin	Recovered /Resolved	Possible	Myocarditis	Level 2	Chest pain, Myocarditis

15	40-49	Female	4	2	Sjogren's syndrome(H)	ethinylestradiol	Unknown	Possible	Myo-pericarditis	Level 2	Blood creatine phosphokinase increased, Electrocardiogram abnormal, Myocarditis, Pericarditis, Red blood cell sedimentation rate increased, Troponin increased
16	18-29	Male	1	2	Not reported	Not reported	Recovered /Resolved	Possible	Myocarditis	Level 2	Chest pain, Dyspnoea, Myocarditis
17	18-29	Male	1	2	Not reported	Not reported	Recovered /Resolved	Possible	Myocarditis	Level 4	Chest pain, Condition aggravated, Dizziness, Myocarditis, Thrombocytosis
18	18-29	Male	3	2	Not reported	Not reported	Recovering/Resolving	Possible	Myocarditis	Level 4	Myocarditis
19	18-29	Male	3	2	COVID-19(H); Hereditary haemorrhagic telangiectasia(H); Epistaxis(H)	Not reported	Not Recovered /Not Resolved	Possible	Myocarditis	Level 4	Chest pain, Chills, Headache, Myalgia, Myocarditis, Nausea, Pyrexia
20	50-59	Female	6	?	Headache(H); Diverticulum intestinal(H); Thyroidectomy(H)	Not reported	Not Recovered /Not Resolved	Possible	Myocarditis	Level 4	Myocarditis

5.3. Annex III - Summary Narratives of Spontaneous Cases of Myocarditis and Myo/Pericarditis Reported per WHO/UMC "Unlikely" Causality Assessment for the mRNA-1273 vaccine. Cumulative to 31 May 2021

Table 7. Summary Narratives of Spontaneous Cases of Myocarditis and Myo/Pericarditis Reported per WHO/UMC Causality Assessment as "Unlikely" for the mRNA-1273 vaccine. Cumulative to 31 May 2021

Case No	Patient Age	Patient Gender	Days to Onset	Dose Number	Co-reported PTs	Brighton Collaboration	Medical History	Medications	Event Outcome
1	18-29	Male	1	2	Headache, Malaise, Myalgia, Myocarditis, Pyrexia, Vaccination site warmth	Level 2	Myocarditis(H); INFLUENZA VACCINE; COVID-19(H); Haematochezia(H) ; Diarrhoea(H)	Not reported	Not Recovered/Not Resolved
2	18-29	Male	2	2	Acute coronary syndrome, Chest pain, Chills, Pain, Pericarditis, Pyrexia	Level 2	Not reported	Not reported	Unknown
3	18-29	Male	3	2	Chest discomfort, Chest pain, Pericardial effusion, Pericardial fibrosis, Pericarditis	Level 1	Drug hypersensitivity(C); Allergy to animal(C); Attention deficit hyperactivity disorder(H)	emtricitabine, tenofovir, amfetamines	Unknown

4	30-39	Female	4	1	Myocarditis	Level 4	Anxiety(H); Rubber sensitivity	Not reported	Unknown
5	50-59	Male	3	2	Chills, Fatigue, Headache, Influenza like illness, Malaise, Myalgia, Myocarditis, Pyrexia	Level 1	Disease risk factor(H)	lisinopril, atorvastatin, ezetimibe	Unknown
6	60-69	Male	.	.	Cardiac arrest, Fall, Myocarditis, Unresponsive to stimuli, Viral cardiomyopathy	Level 4	Not reported	Not reported	Recovered/Resolved
7	18-29	Female	1	2	Chest pain, Dyspnoea, Myocarditis	Level 3	Gluten sensitivity	Lamictal, Trileptal, Prozac, birth control contraceptive	Not Recovered/Not Resolved
8	60-69	Female	46	2	Myocarditis, Vaccination complication	Level 4	Blood donor(C)	ASA, atorvastatin, escitalopram	Unknown
9	18-29	Male	1	2	Cerebral artery stenosis, Chest pain, Myocarditis, Vision blurred, Visual field defect	Level 2	Not reported	marijuana, lisdexamfetamine	Unknown
10	40-49	Male	29	2	Body temperature increased, Cardiac disorder, Chills, Myalgia, Myocarditis	Level 4	Deafness bilateral(H); Back pain(H); Hyperlipidaemia(H); Catheterisation cardiac	naproxen, buproprion, prazosin, vitamin D2	Recovered/Resolve d
11	18-29	Male	2	1	Myocardial infarction, Myocarditis	Level 4	Hypersensitivity; Asthma(H); Catheterisation cardiac	buspirone, sertraline, aripiprazole	Not Recovered/Not Resolved

12	60-69	Female	6	1	Cardiac disorder, Chest pain, Fatigue, Headache, Myocarditis, Pyrexia, Renal pain	Level 4	Not reported	metformin, glimepiride, simvastatin, losartan	Unknown
13	40-49	Male	2	1	Chest pain, Incorrect route of product administration, Myocarditis	Level 4	Depression(H); Anxiety(H); Cardiac murmur(H)	bupropion, venlafaxine	Recovered/Resolved
14	30-39	Female	7	1	Chest pain, Ejection fraction decreased, Myocarditis, Pericarditis	Level 2	Drug hypersensitivity; Hypertension(C); Obesity(H); Gastrooesophageal reflux disease(H); Depression(C); Hypothyroidism(C)	aripiprazole, ethinylestradiol, norethindrone, hyroxyzine, lamotrigine, levothyroxine, liothyronine, lisinopril, rosuvastatin, omeprazole, venlafaxine	Not Recovered/Not Resolved
15	60-69	Female	0	2	Dyspnoea, Myocarditis	Level 1	Asthma(C)	salbutamol, albuterol HFA	Unknown
16	40-49	Male	2	1	Acute myocardial infarction, Chest pain, Myocarditis	Level 2	COVID-19(H); COVID-19(H); Depression(C)	venlafaxine, bupropion	Unknown
17	60-69	Male	29	1	Encephalopath y, Myocarditis	Level 4	Benign prostatic hyperplasia(H); Renal cancer metastatic(H); Nephrectomy(H); Pulmonary embolism(H); Hypothyroidism(H)	nivolumab	Not Recovered/Not Resolved

5.4. Annex IV - Summary Narratives of Spontaneous Cases of Pericarditis Reported per WHO/UMC Causality Assessment as "Certain/ Probable/Possible" for the mRNA-1273 vaccine. Cumulative to 31 May 2021

Table 15. Summary Narratives of Spontaneous Cases of Pericarditis Reported per WHO/UMC Causality Assessment as "Certain/Probable/Possible" for the mRNA-1273 vaccine. Cumulative to 31 May 2021.

Case No	Age	Gender	TTO	Dose Number	Co- reported PTs	Medical History	Medications	Event Outcome	WHO- UMC Causality
1	30-39	Female	5	1	Chest pain, Dyspnoea, Fatigue, Pericarditis	No adverse event(H)	Not reported	Unknown	Possible
2	60-69	Male	9	1	Acute myocardial infarction, Chest pain, Death, Dyspnoea, Pericarditis	Hypertension (H); Hyperlipidae mia(H); Pericarditis(H)	Not reported	Fatal	Possible
3	60-69	Male	9	1	Chest discomfort, Chest pain, Chills, Lymphaden opathy, Pain, Painful respiration, Pericardial effusion, Pericarditis, Pyrexia	Hypertension (H); Gastrooesoph ageal reflux disease(H); Anxiety(H); Syncope(H); Atrial fibrillation(H); Chest X-ray; Electrocardiogram; Echocardiogr am; Pericardial drainage	aspirin, paracetamol, clonazepa m, colchicine famotidine, metoprolol, omeprazole	Recovered/Resolved	Possible

4	18-29	Male	2	2	Chest pain, Pericarditis	Attention deficit hyperactivity disorder(H); Mood swings(H); Sleep apnoea syndrome(H); Nasal congestion(C) ; Cough(C)	methylphe nidate, aripriprazol e, clonidine	Not Recovered/No t Resolved	Possible
5	70-79	Male	21	1	Pericardial effusion, Pericarditis	Hypertension (C); Primary biliary cholangitis(C)	valsartan, ursodiol, citalopram, montelukas t, ASA, lorazepan, tamsulosin, fluticasone	Recovered/Re solved	Possible
6	40-49	Femal e	3	2	Abdominal distension, Angina pectoris, Anxiety, Chest pain, Decreased appetite, Dizziness, Dyspnoea, Fatigue, Food intolerance, Gastritis, Headache, Hiatus hernia, Hypertensio n, Hypoaesthes ia, Influenza like illness, Loss of consciousne ss, Myalgia, Palpit	Electrocardio gram; Echocardiogr am; Ultrasound scan; Computerised tomogram; X-ray; Endoscopy; Colonoscopy; Biopsy; Thyroiditis(C)	levothyroxi ne	Unknown	Possible
7	30-39	Femal e	23	1	Pericarditis	Thalassaemia (C); Hypothyroidi sm(C); Cerebrovascu lar accident(H); Food allergy	Not reported	Recovered/Re solved	Possible
8	40-49	Femal e	1	2	Chest pain, Cold sweat, Hyperhidros is, Pain, Pain in extremity, Pain in jaw, Painful respiration, Pallor, Pericarditis, Presyncope, Vomiting	COVID- 19(C)	Not reported	Unknown	Possible

9	70-79	Female	1	2	Fatigue, Mental impairment, Myalgia, Pericarditis, Pyrexia	Food allergy; Food allergy; Blood pressure increased(H); Rheumatoid arthritis(H)	Not reported	Recovered/Resolved	Possible
10	80+	Female	1	2	Asthenia, Atrial fibrillation, Chest pain, Dyspnoea, Malaise, Pericarditis	Hypersensitiv ity	calcium, vitamin D	Not Recovered/No t Resolved	Possible
11	60-69	Female	5	2	Atrial fibrillation, Cardiac murmur, Chills, Dyspnoea, Headache, Immune system disorder, Musculoskeletal stiffness, Pain, Painful respiration, Pericarditis, Pulmonary pain, Pyrexia, Tremor		Not reported	Recovered/Resolved	Possible
12	40-49	Male	7	1	Pericarditis, Pleural effusion	Colitis ulcerative(H)	infliximab	Unknown	Possible
13	70-79	Male	1	2	Asthenia, Cardiomegaly, Chest pain, Chills, Decreased appetite, Pain, Pain in extremity, Pericarditis, Pulmonary embolism, Somnolence	Drug hypersensitivi ty; Allergy to arthropod sting; Food allergy; Dyspnoea(C); Dizziness(C); Syncope(C); Essential tremor(H); Intestinal obstruction(H); Extrasystoles(H); Scleroderma(H)	omeprazole , primidone, cetirizine, metoprolol	Not Recovered/No t Resolved	Possible
14	30-39	Male	3	2	Chest pain, Dyspnoea, Paraesthesia, Pericarditis		finasteride	Not Recovered/No t Resolved	Possible

15	60-69	Male	4	2	Chest discomfort, Dyspnoea, Fatigue, Malaise, Pericardial effusion, Pericarditis, Pyrexia	Type 2 diabetes mellitus(C); Depression(C); Hyperlipidae mia(C)	ASA, metformin, atorvastatin , sertraline, ibuprofen, fish oil	Unknown	Possible
16	30-39	Male	18	1	Pericarditis	Chronic kidney disease(C); Hypertension (C)	Not reported	Recovering/Re solving	Possible
17	30-39	Femal e	12	1	Chest pain, Pericardial effusion, Pericarditis	Drug hypersensitivi ty; Milk allergy; Food allergy; Asthma exercise induced(C); Pericarditis(H); COVID-19(H); COVID-19(H)	cipro, gluten and milk allergy, exercise- induced asthma	Recovered/Re solved	Possible
18	50-59	Femal e	.	.	Back pain, Chest pain, Dyspnoea, Hepatitis, Pericardial effusion, Pericarditis, Pleural effusion, Pneumonitis	No adverse event(H)	Not reported	Not Recovered/No t Resolved	Possible

5.5. Annex V - Summary Narratives of Spontaneous Cases of Pericarditis Reported per WHO/UMC "Unlikely" Causality Assessment for the mRNA-1273 vaccine. Cumulative to 31 May 2021

Table 16. Summary Narratives of Spontaneous Cases of Pericarditis Reported per WHO/UMC Causality Assessment as "Unlikely" for the mRNA-1273 vaccine. Cumulative to 31 May 2021.

Case No	Age	Gender	TTO	Dose Number	Co- reported PTs	Medical History	Medications	Event Outcome
1	60-69	Female	8	2	Atrial fibrillation, Bedridden, Decreased appetite, Feeling abnormal, Hyperglycae mia, Hypoxia, Pericardial effusion, Pericarditis, Pleural effusion, Pyrexia	Hypertension(H); Type 2 diabetes mellitus(H); Crohn's disease(H); Hepatic cirrhosis(H); Gastrooesopha geal reflux disease(H); Type IIa hyperlipidaemi a(H)	atorvastatin, mesalazine, sertraline, iron, metformin	Recovered/Res olved
2	30-39	Female	14	1	Pericarditis, Pleural effusion, Pleuritic pain	Hypothyroidis m(H); Food allergy; Drug hypersensitivit y; Viral infection(C)	Not reported	Not Recovered/Not Resolved
3	70-79	Female	43	1	Back pain, Pericardial effusion, Pericarditis	Hypothyroidis m(C); Pericardial drainage	clopidogrel	Not Recovered/Not Resolved
4	40-49	Female	26	.	Chest pain, Headache, Myalgia, Pain, Painful respiration, Pyrexia, Viral pericarditis	Not reported	Not reported	Recovered/Res olved
5	70-79	Female	3	1	Cardiac tamponade, Pericardial effusion, Pericarditis	Diabetes mellitus(C); Hypersensitivit y	fluoxetine, metformin, gabapentin, simvastatin, cetirizine	Not Recovered/Not Resolved
6	80+	Female	.	.	Atrial fibrillation, Cardiac failure congestive, Chest pain, Condition aggravated, Influenza like illness, Pericarditis	Dyspnoea(C); Hyponatraemi a(C)	Not reported	Not Recovered/Not Resolved

7	60-69	Male	0	2	Atrial flutter, Chest pain, Dyspnoea, Pericarditis, Pleural effusion	Pericarditis(H) ; Cardiac pacemaker insertion(H); Sepsis(H); SARS-CoV-2 test positive(H); Hypertension(C)	hydrochlorothi azide, losartan, hydrochlorothi azide, ASA, atorvastatin, tamsulosin, vitC	Unknown
8	70-79	Male	0	2	Back pain, Chest pain, Influenza, Myocardial infarction, Pain, Pericarditis, Pyrexia	Drug hypersensitivit y	rosuvastatin	Not Recovered/Not Resolved
9	50-59	Male	0	2	Chest pain, Left ventricular hypertrophy, Neck pain, Pain in extremity, Right ventricular hypertrophy, Ventricular enlargement, Viral pericarditis	Seasonal allergy	Not reported	Not Recovered/Not Resolved
10	70-79	Female	22	2	Chest pain, Dehydration , Neck pain, Pain, Pericardial effusion, Pericarditis, Syncope	Tooth abscess(H); Hypertension(C); Ischaemic stroke(H)	escitalopram, atorvastatin, atenolol, ASA, ciclesonide, HCTZ, Azelastine	Not Recovered/Not Resolved
11	70-79	Female	63	2	Chest pain, Pericarditis, Pyrexia	Coronary artery disease(C); Stent placement; Hyperlipidaem ia(C)	ASA, famotidine, rosuvastatin, estradiol	Not Recovered/Not Resolved
12	40-49	Female	27	2	Acute respiratory failure, Anxiety, Asthenia, Atelectasis, Cardiac failure congestive, Cardiomegal y, Cardiomyopathy, Chest pain, Cholecystiti s, Congestive hepatopathy, Cough, Cystic lung disease, Dyspnoea, Dyspnoea exertional, Fatigue, Fluid overload, Hep	Hypertension(C); Developmental delay(C); Deep vein thrombosis(H); Gastrooesopha geal reflux disease(C); Anxiety(C); Lung assist device therapy; Acute respiratory distress syndrome(H); Viral infection(H); Biopsy lung; Mass excision; Cholecystecto my; Dyspnoe	Not reported	Recovered/Res olved
13	30-39	Male	1	2	Chest discomfort, Pericarditis	Anxiety(H); Cerebral palsy(H); Gastrooesopha geal reflux disease(C); Rhinitis allergic; Drug hypersensitivit y; COVID- 19(H)	cetirizine, escitalopram, fluticasone, omeprazole	Not Recovered/Not Resolved
14	50-59	Female	5	1	Chest pain, Pericarditis	Not reported	Not reported	Unknown

15	30-39	Male	22	2	Chest pain, Pericarditis	Not reported	Not reported	Recovered/Resolved
16	60-69	Female	20	1	Chest discomfort, Gastrointestinal disorder, Muscle spasms, Myalgia, Pericarditis	Not reported	Not reported	Recovered/Resolved
17	50-59	Male	Unknown	Unknown	Angina pectoris, Chills, Condition aggravated, Hyperhidrosis, Malaise, Pain, Pericarditis, Pyrexia	Nephrostomy; Cardiac ablation; Cardiac failure(C); Acute kidney injury(C); Renal cancer(C); Atrial flutter(C); Pericarditis(C)	Not reported	Unknown
18	50-59	Male	21	2	Chest pain, Chills, Dyspnoea, Inappropriate schedule of product administration, Pericarditis, Pyrexia	Blood cholesterol increased(C)	Not reported	Unknown

5.6. Annex VI – updated OE analyses of pericarditis, provided by the MAH on 28 June 2021

5.7. Annex VII - EMA OE analysis by gender – DLP 13 June

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