2 December 2021
EMA/PRAC/759618/2021
Pharmacovigilance Risk Assessment Committee (PRAC)

Signal assessment report on myocarditis and pericarditis with Spikevax - COVID-19 mRNA vaccine (nucleoside-modified)

EPITT no: 19713
Procedure no: SDA 033.2

Confirmation assessment report	12/10/2021
Adoption of first PRAC recommendation	14/10/2021
Adoption of second PRAC recommendation	28/10/2021
Submission of data/responses from MAHs	17/11/2021
Preliminary assessment report on additional data	25/11/2021
Deadline for comments	26/11/2021 (Noon)
Updated rapporteur assessment report	29/11/2021
Adoption of third PRAC recommendation	02/12/2021

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Administrative information

Active substance(s) (invented name)	COVID-19 mRNA vaccine (nucleoside-modified) (Spikevax)
Strength(s)	100 microgram per dose (0.5 mL) in course of 2 doses in the primary vaccination series
Pharmaceutical form(s)	Dispersion for injection
Route(s) of administration	Intramuscularly
Indication(s)	Indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 in individuals 12 years of age and older.
Marketing authorisation holder(s)	Moderna
Authorisation procedure	
☒	Centralised
☐	Mutual recognition or decentralised
☐	National

Adverse event/reaction:	Myocarditis, pericarditis

Signal validated by:	SE
Date of circulation of signal validation report:	7 October 2021
Signal confirmed by:	DK
Date of confirmation:	12 October 2021
PRAC Rapporteur appointed for the assessment of the signal:	Anette Kirstine Stark

Table of contents

1. Background

This signal was triggered by the Swedish Medical Products Agency following the circulation of preliminary results dated 5th October 2021 of a study entitled" SARS-CoV-2 vaccination and risk of pericarditis and myocarditis: Nordic nationwide cohort study of 20 million individuals".

These analyses are undertaken within a request from the Swedish government to the Medical Products Agency of in depth safety evaluation of covid-19 vaccines.

The attached report is based on a meta-analysis of data from Denmark, Finland, Norway and Sweden.

Myocarditis and pericarditis have been followed specifically due to the previous signal of these events.

2. Initial evidence

2.1. Signal validation

The preliminary analyses show that the occurrence of myocarditis is more frequent after the second vaccine dose, than after the first, and in younger men. Analyses are ongoing to further characterize these risks, which include similar analyses of pericarditis.

The previous PRAC recommendation was mainly based on data from spontaneous reporting. The new data, based on national population registers, linked to vaccination and health care registries in the respective countries, contribute with new information regarding the magnitude of risk for the two respective vaccines, including in different age strata.

Prompt evaluation on the need for updates on e.g. the product information for these respective vaccines is proposed.

It should also be noted that these data can be important for ongoing vaccination campaigns.

2.2. Signal confirmation

A signal on Spikevax and myocarditis/pericarditis was evaluated and concluded earlier this year. At that time, the signal evaluation was based upon spontaneous reports. In addition to a DHPC and also a request to update the RMP, the procedure resulted in an update of the product information to add a warning on the risk of development of myocarditis and pericarditis following vaccination:

Current SmPC 4.4: *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.*

Current SmPC 4.8: *Myocarditis, Pericarditis with a frequency "Not known"*

Meanwhile, a Nordic collaboration has performed a study on SARS-CoV-2 vaccination and the risk of pericarditis and myocarditis in Denmark, Finland, Norway and Sweden, based on interlinked national

registers with information on SARS-CoV-2 vaccinations, hospital diagnoses of myocarditis or pericarditis, and SARS-CoV-2 PCR positive infections.

Preliminary results from this study, dated 5th October 2021, has been shared and the preliminary main conclusions regarding Moderna (Spikevax) in a 28 day risk window is:

- 2nd dose of Spikevax (both homologous and heterologous schedules) is strongly associated with myocarditis in the general population and in men 18-39 (14 and 28 excess cases 28d/100k for homologous and heterologous schedules in men 18-39 years, respectively).
- Estimates in men 18-39 yrs are far from precise but are consistent over countries
- 2nd dose of Spikevax (both homologous and heterologous schedules) is associated with pericarditis in the general population and in men 18-39 (6 and 17 excess cases 28d/100k for homologous and heterologous schedules in men 18-39 years, respectively).
- SARS-CoV-2 infection is associated with myocarditis, more strongly in those 40 years and older (3 excess cases 28d/100k for 18 to 39 and 8 excess cases 28d/100k for 40+)
- Further evaluation of biases are ongoing, and sensitivity analyses of primary outcomes are planned.

Heterologous vaccination (BNT 1st+MOD 2nd) is associated with the highest IRR/er28d100k. It is noted that all data regarding heterologous vaccination originate from one country (NO), and only includes the combination BNT 1st+MOD 2nd.

In the preliminary results, it is noted that among the homologous scheduled vaccines, Moderna has the highest IRR, compared to the other vaccines in the study.

The preliminary results confirm the known risk of an association of Spikevax and development of myocarditis and pericarditis, with an increased risk found after the 2nd vaccination and primarily in younger men.

At present, it has not been able to estimate a frequency of myocarditis and pericarditis following vaccination, and the frequency is "not known" in section 4.8 of the SmPC. The new data presented provide new information on the magnitude of the risk, and on the risk estimation in different age groups and gender.

Further assessment of the risk, including risk characterisation and frequency estimates of myocarditis and pericarditis following vaccination with Spikevax is considered warranted. The signal is confirmed.

2.3. Proposed recommendation

The MAH is requested to discuss these new findings, dated 5th October 2021, including the need to amend the current labelling.

The MAH should discuss possible explanations for the disproportionate incidence rates of myocarditis and pericarditis for Moderna compared to the other vaccines in the study.

In addition, the MAH is requested to present any support for estimation of frequency of myocarditis and/or pericarditis from clinical trial data or post-authorization data, preferably stratified by age and sex, if possible.

Also, the MAH is requested to present any new information from all available sources, including MAH safety database and literature, related to the risk characterization of myocarditis/pericarditis, including severity of the events and long term outcome.

The PRAC Rapporteur will perform a separate evaluation of the preliminary report which describes a meta-analysis of data from Denmark, Finland, Norway and Sweden.

2.4. Adopted PRAC recommendation

Having considered that new data on the known risk of myocarditis, pericarditis has become available from a preliminary report which describes a meta-analysis of data from Denmark, Finland, Norway and Sweden, the PRAC has recommended the following:

1. The PRAC Rapporteur for the COVID-19 mRNA Vaccine Spikevax should perform an in-depth evaluation of the preliminary report and compile a List of Questions for the researchers and the MAH for the COVID-19 mRNA Vaccine Spikevax (Moderna Biotech Spain, S.L.), as appropriate. Considering that the results of the study are expected to become available starting 25 October 2021 at the earliest, these Lists of Questions will be further discussed in the PRAC plenary 25-28 October.

2. The MAH for the COVID-19 mRNA Vaccine Spikevax (Moderna Biotech Spain, S.L.) should continuously monitor the emerging evidence on the association between COVID-19 mRNA vaccine Spikevax and myocarditis and pericarditis arising from all available of sources (e.g. clinical studies, observational studies considering in various jurisdictions, company data bases).

3. The Agency will provide an updated observed to expected analysis considering the most recent EudraVigilance data and the EEA exposure to COVID-19 mRNA vaccines including the in under 18 years old.

2.5. Adopted (second) PRAC recommendation

Considering the current EU product labelling for COVID-19 mRNA vaccines and the new data on the risk of myocarditis and pericarditis that have become available after the PRAC recommendation in July 2021, the PRAC has agreed that the MAH of COVID-19 mRNA vaccine Spikevax (Moderna Biotech Spain, S.L.) should provide by 15 November 2021 a review of the respective data from clinical studies, from the scientific literature and other data available in public domain (e.g. published data from Canada, Israel, US and other jurisdictions). The MAH should respond to the below List of Questions separately for myocarditis and pericarditis.

List of Questions:

1. The MAH should provide a risk estimation of myocarditis and pericarditis overall and per age groups (e.g. 5-11, 12-15, 16-17, 18-24, 25-29, 30-39, 40+ also depending on age groups used in studies), gender, vaccine dose(s) (i.e. first, second or booster).

2. The MAH should perform further characterisation of myocarditis and pericarditis, with focus on the following:

- Provide an estimation of the incidence of myocarditis and pericarditis, with the view to better characterize the current 'unknown' frequency in the product labelling.
- Discuss any plausible pathophysiological mechanism(s) of myocarditis and pericarditis observed after COVID-19 mRNA vaccine Spikevax.
- Data on the characteristics, severity, duration and outcome of myocarditis and pericarditis after vaccination with Covid-19 mRNA vaccine Spikevax.

3. Considering that the risks of myocarditis and pericarditis are outcomes of interest in the two ongoing PASSs in the EU/EEA (IT, ES, NL, UK, NO, DK) and in the US, the MAH should investigate if the planned analyses, including O/E and SCCS/SCRI, of myocarditis/pericarditis could be expedited and indicate when these can be submitted. In adolescents, narrow age strata should be applied, as feasible (currently EU PASS only).

3. Additional evidence

The MAH have submitted a response to the LoQ as requested by PRAC and evaluated the data from the Nordic Cohort study and the French case-control study.

3.1. Assessment of additional data

3.1.1. ITEM 1- Risk estimation

The MAH should provide a risk estimation of myocarditis and pericarditis overall and per age groups (e.g. 5-11, 16-17, 18-24, 25-29, 30-39, 40+ also depending on age groups used in studies), gender, vaccine dose(s) (i.e. first, second or booster).

Sponsor Response

Multiple studies have recently estimated the risk of myocarditis following receipt of mRNA vaccines targeting SARS CoV-2. Both literature and surveillance sources consistently describe an increase in the incidence of myocarditis, predominantly within the days following receipt of a second dose of vaccine, that appears largely isolated to younger men (from 12 years to <30 years of age). Some variation has been observed in the magnitude of the association, which may be partially attributable to factors such as random variation (given the very low incidence of the outcomes) and differential ascertainment (based upon differences in data sources, search strategies, and stimulated reporting given increased awareness and monitoring following identification of the risk and appropriate public health measures to ensure appropriate treatment of potential cases).

Moderna US PASS (mRNA-1273-P903)

In the third interim report of the US PASS study (31 October 2021), a retrospective observational cohort study used secondary, de-identified individual-level medical and pharmacy claims data provided by HealthVerityTM to assess risk of AESI including myocarditis and pericarditis. This data source includes more than 140 million patients insured under commercial, Medicare or Medicaid plans, and/or served by providers participating in several large US medical and pharmacy insurance claims submission systems.

Myocarditis was observed in 2,186 patients in a historical comparison cohort (IR 9.98 cases per 100,000 person-years 95% CI 9.47 - 10.30) and in 253 patients following vaccination (IR 9.94 cases per 100,000 person-years, 95% CI 8.72 - 11.17), producing a non-significant incidence rate ratio of

that was effectively null 1.01 (95% CI 0.88 - 1.14). An increased risk was observed in young men, where the incidence following vaccination was 34.71 cases per 100,000 personyears (IRR 3.30, 95% CI 2.29 - 4.65). Although there were small numerical increases in men ages 30-39 and young women, these estimates are based on small numbers and lack precision. Observed vs expected analyses considering a 7-day risk window following vaccination produced findings with similar interpretation with an increase was observed in all individuals 18 to 29 years of age, where 9 events were observed and 2 expected (O/E ratio 4.93, 95% CI 2.25 - 9.36). A smaller, numerical increase for men ages 18 to 29 was also observed for pericarditis. This outcome was observed in 5,418 patients in the historical cohort (IR 24.51, cases per 100,000 person-years 95% CI 23.86-25.16) and in 533 patients following vaccination (age and sex standardized IR 20.95 cases per 100,000 person-years, 95% CI 19.17 - 22.73), producing an incidence rate ratio of 0.85 (95% CI 0.78 - 0.93). In young males, 32 cases after vaccination produced an IR of 30.85 per 100,000 person-years (95% CI 20.16 - 41.54), corresponding to an IRR of 1.41 (95% CI 0.97 - 1.99). Overall observed to expected analyses and most age and sex specific analyses did not show an increase for the 7-day risk window, however an increase was observed in the 18 to 29-year age group (4 cases expected, 14 observed, OE ratio 3.31, 95% CI 1.81 - 5.56). This was again driven by young males, where 2 cases were expected and 10 observed (OE ratio 4.19, 95% CI 2.01 - 7.71).

PRAC Rapporteurs assessment comment:

Additional details on study design

In the US PASS study, myo- and pericarditis are included in the list of AESI. The study operates in a stepwise design: (1) estimation of IRR, (2) observed-expected (O/E) analysis and (3) self-controlled risk interval (SCRI) analysis. As stated by the MAH, IRR and O/E analyses of myo- and pericarditis were included in the third interim report.

The IRR estimation is based on comparison of the vaccinated with a historical control cohort prior to the COVID-19 pandemic (01 Dec 2018-30 Nov 2019). A comparison with an "active" COVID cohort (01 Dec 2019 – 10 Dec 2020) is planned but not part of the interim analysis.

Persons with myocarditis/pericarditis prior to follow-up were excluded from the analysis. Exposure was defined as vaccination with at least one dose of Spikevax.

Myocarditis

Myocarditis was observed in 2,186 patients in the historical cohort (IR 9.98, cases per 100,000 person-years 95% CI 9.47 – 10.30) and in 253 patients following vaccination (IR 9.94 cases per 100,000 person-years, 95% CI 8.72 – 11.17). The IRR of myocarditis for the general adult population was 1.01 (95% CI 0.88 - 1.14). However, for males 18-29 years the IR was significantly increased compared to historical IR: IRR 3.3 (95% CI 2.29 - 4.65). This was based on an IR of 34.71/ 100,000 person-years. Of note, these were crude estimates and adjustment for age and sex did increase the IRR for male adults (all ages) from 1.12 (crude) to 1.41 (adjusted). For females 18-29 years, there was only a slight numerical increase (IRR 1.57, 95% CI 0.8-2.85).

O/E analyses were performed considering a 7-day risk window following vaccination. For males 18-29 years, 8 observed events versus 1 expected (based on the IR in the background population standardized to the vaccinated population) produced an O/E ratio of 6.97 (95% CI 3.01 - 13.74). No significantly increased O/E was observed for any other age group in males or any age group in females.

Pericarditis

Regarding pericarditis, in males 18-29 years, the IRR was 1.41 (95% CI 0.97 - 1.99). In this group, 10 events were observed versus 2 expected leading to an O/E of 4.19 (95% CI 2.01 – 7.71). No significant increase was observed in females in any age group.

Moderna Global Safety Database (Data Through 31 October 2021)

As recently described in the 10th Monthly Summary Safety Report, myocarditis (with or without pericarditis) was reported in 1,807 cases cumulatively (reporting rate 9.89 per 100,000 personyears) and in 353 cases during this review period (reporting rate 14.47 per 100,000 personyears).

Considering the rate of myocarditis occurrence as a proportion of vaccine recipients rather than as a function of estimated person-years, the cumulative reported cases corresponds to an overall reporting rate of 1.02 cases of myocarditis per 100,000 vaccine recipients. Data from the US military suggest an expected incidence of 2.12 cases per 100,000 vaccine recipients (Gubernot 2021). Compared to this background rate an increase in the reporting rate is apparent for males ages 18-24 years, with a reporting rate of 7.79 cases per 100,000 person-years (O/E rate ratio 3.68, 95% CI 3.09 - 4.38). Sensitivity analyses assuming that the reported cases correspond to 50% or 25% of total exposed cases suggest that the increased risk could plausibly extend to men under 50 years of age and potentially include young women.

Table 1. Observed/Expected Analyses Stratified by Age, Myocarditis, Expected Rate Based on US Military Data, Cases per 100,000 Vaccine Recipients – Cumulative to 31 Oct 2021

	Vaccine recipients*	Observed		Expected		As observed: RR (95% CI)	Assuming 50% of cases were reported: RR (95% CI)	Assuming 25% of cases were reported: RR (95% CI)
		Cases	Rate	Cases	Rate			
All	177,096,375	1,807	1.02	3754	2.12	0.48 (0.46, 0.51)	*0.96 (0.92, 1.01)*	*1.93 (1.85, 2)*
By age								
<18	5,312,891	51	0.96	89	1.67	0.57 (0.41, 0.81)	*1.15 (0.86, 1.53)*	*2.3 (1.79, 2.94)*
18-24	15,938,674	664	4.17	267	1.67	2.49 (2.16, 2.87)	*4.98 (4.37, 5.68)*	*9.96 (8.78, 11.3)*
25-39	38,961,202	628	1.61	652	1.67	0.96 (0.86, 1.08)	*1.93 (1.75, 2.12)*	*3.85 (3.54, 4.2)*
40-49	26,564,456	179	0.67	563	2.12	0.32 (0.27, 0.38)	*0.64 (0.56, 0.73)*	*1.27 (1.14, 1.42)*
50-64	46,045,057	136	0.30	976	2.12	0.14 (0.12, 0.17)	*0.28 (0.24, 0.32)*	*0.56 (0.5, 0.62)*
65-74	26,564,456	64	0.24	563	2.12	0.11 (0.09, 0.15)	*0.23 (0.19, 0.28)*	*0.45 (0.39, 0.53)*
75+	17,709,637	31	0.18	375	2.12	0.08 (0.06, 0.12)	*0.17 (0.13, 0.22)*	*0.33 (0.27, 0.4)*
By gender								
Male	84,120,778	1,424	1.69	1783	2.12	0.8 (0.74, 0.86)	*1.6 (1.51, 1.69)*	*3.19 (3.03, 3.37)*
Female	92,975,597	355	0.38	1615	1.74	0.22 (0.2, 0.25)	*0.44 (0.4, 0.48)*	*0.88 (0.82, 0.94)*
By age and gender								
Male								
<18	2,523,623	48	1.90	54	2.12	0.9 (0.61, 1.32)	*1.79 (1.28, 2.51)*	*3.59 (2.65, 4.86)*
18-24	7,570,870	590	7.79	161	2.12	3.68 (3.09, 4.38)	*7.35 (6.23, 8.67)*	*14.7 (12.53, 17.25)*
25-39	18,506,571	517	2.79	392	2.12	1.32 (1.16, 1.5)	*2.64 (2.35, 2.96)*	*5.27 (4.73, 5.87)*
40-49	12,618,117	118	0.94	268	2.12	0.44 (0.36, 0.55)	*0.88 (0.74, 1.05)*	*1.76 (1.52, 2.05)*
50-64	21,871,402	75	0.34	464	2.12	0.16 (0.13, 0.21)	*0.32 (0.27, 0.39)*	*0.65 (0.56, 0.75)*
65-74	12,618,117	34	0.27	268	2.12	0.13 (0.09, 0.18)	*0.25 (0.19, 0.33)*	*0.51 (0.41, 0.62)*
75+	8,412,078	14	0.17	178	2.12	0.08 (0.05, 0.14)	*0.16 (0.11, 0.23)*	*0.31 (0.23, 0.42)*
Female								
<18	2,789,268	3	0.11	34	1.23	0.09 (0.03, 0.29)	*0.18 (0.07, 0.42)*	*0.35 (0.18, 0.68)*
18-24	8,367,804	74	0.88	103	1.23	0.72 (0.54, 0.97)	*1.44 (1.12, 1.86)*	*2.89 (2.31, 3.61)*
25-39	20,454,631	107	0.52	251	1.23	0.43 (0.34, 0.54)	*0.85 (0.71, 1.02)*	*1.71 (1.46, 2)*
40-49	13,946,340	60	0.43	296	2.12	0.2 (0.15, 0.27)	*0.41 (0.33, 0.5)*	*0.81 (0.68, 0.96)*
50-64	24,173,655	59	0.24	512	2.12	0.12 (0.09, 0.15)	*0.23 (0.19, 0.28)*	*0.46 (0.39, 0.54)*
65-74	13,946,340	30	0.22	296	2.12	0.1 (0.07, 0.15)	*0.2 (0.15, 0.27)*	*0.41 (0.33, 0.5)*
75+	9,297,560	17	0.18	197	2.12	0.09 (0.05, 0.14)	*0.17 (0.12, 0.25)*	*0.34 (0.26, 0.45)*

*Rates presented per 100,000 person-years; vaccine recipients extrapolated based on the proportion of vaccine administrations given as first vs. second doses in the US. Gubernot 2021. Expected rate of 2.12 cases per 100,000 vaccine recipients has been adjusted for lower prevalence among females 12 to 39 years of age relative to males by factor of 1.73 as presented by the Centers for Disease Control and Prevention.

The reporting rate was comparable to population-based estimates from the US not limited to the armed forces (Kang 2021: 10 per 100,000 person-years, 1,807 cases expected, rate ratio 0.99, 95% CI 0.93 – 1.06) when considering a 21-day risk window following vaccination. It should be noted that background estimates of the incidence of myocarditis vary widely, with some sources citing a range of 1-10 cases per 100,000 person-years (Gubernot 2021) and others citing a range of 10-20 per 100,000 person-years (Kang 2021). A recent publication from the OHDSI project saw higher estimates, noting that algorithms used have not yet been validated (e.g., Li 2021: average incidence of 29.79 per 100,000 person-years with an estimate of 37 cases per 100,000 person-years in young males (Li 2021)).

Further stratification suggests that the rate is higher after the second dose, however not all reports could be classified by dose based on limitations of spontaneous adverse event reporting (e.g., missing data). Considering cases with known onset and dose number that occur within the 7 days following vaccination, the same pattern of increased reporting in younger men is present. The MAH has not been able to conduct a similar age stratified analysis for myocarditis following a booster dose – due current product distribution. No similar increase has yet been observed following a third dose, however, use of third doses had been more common in older and immunocompromised individuals as of the end of the relevant data availability period (Table 2).

Table 2. Reporting Rate of Myocarditis within 7 Days of Vaccination by Age and Dose per 100,000 Doses Administered of SPIKEVAX, Cumulative Through 31 Oct 2021

	All			Males			Females		
	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3
Age (years)									
<18	0.5	0.7	0.0	1.1	1.3	0.0	0.0	0.0	0.0
18-24	2.3	3.1	0.0	4.4	5.9	0.0	0.3	0.6	0.0
25-39	0.7	1.0	0.1	1.3	1.9	0.2	0.2	0.3	0.0
40-49	0.3	0.5	0.1	0.4	0.6	0.3	0.1	0.3	0.0
50-64	0.1	0.2	0.1	0.1	0.2	0.0	0.0	0.1	0.1
65-74	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.0
75+	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.0

Includes cases with known dose and time to onset. Number of SPIKEVAX recipients by dose recipients extrapolated based on the proportion of vaccine administrations given as first vs. second doses in the US.

Comparison to data from ACCESS sites shows a similar pattern, with the magnitude of the increase in young men variable based on the participating data center and year for which the estimate was produced. ACCESS rates span a broad range, and not all settings included within the project provide suitable reference rates. For example, conditions captured primarily in hospital settings will be poorly identified in general practice databases and vice versa. Further, differences in underlying disease incidence may be present comparing different countries, and studies drawn from smaller populations may be poorly precise for stratified analysis of rare outcomes. For these reasons as well as the observation that the majority of doses administered to data have occurred in the US, we consider the US estimates a preferable comparator group. Sensitivity analyses were, however, performed within ACCESS settings likely to capture both inpatient and outpatient care. The cumulative reporting rate (9.09 per 100,000 person-years) was between ACCESS estimates from Spain (FISABIO 2019, 3.36 per 100,000 person-years, 614 expected, rate ratio 2.94, 95% CI 2.69 - 3.23) and the Netherlands (PHARMO 2019: 23.68 per 100,000 person-years, rate ratio 0.42, 95% CI 0.40 - 0.44).

PRAC Rapporteurs assessment comment:

The MAH performed an O/E analysis and calculated reporting rates of myocarditis within 7 days of vaccination stratified by dose, age and gender. The risk of myocarditis has previously been considered causally related to the Spikevax mRNA vaccine. The current SmPC states that myocarditis occurs more often in men and after the 2nd dose.

The O/E analysis shows that for both genders, 18 – 24 yo have an imbalance in observed / expected with a rate ratio of 2.49 (2.16, 2.87); however these data are mainly driven by males where the RR in the same age group is higher 3.68 (3.09,4.38). The RR for males is also higher than 1 in the age group 25 – 39 (1.32 (1.16,1.5)). No imbalance of O/E is observed for females in the same age groups.

When considering the sensitivity analysis, there have been observed more cases of myocarditis than expected in 18 – 39 yo when assuming 50% of all cases were reported, and up to 49 yo when assuming 25 % of all cases were reported for both genders. Again, this is mainly driven by males. For females the only increase is observed in 18-24 yo when assuming 50% of all cases were reported, and 18 – 39 when assuming 25 % of all cases were reported.

In conclusion, the O/E analysis confirms what is already known and stated in the SmPC regarding the risk of myocarditis. The reporting rate of myocarditis pr. 100.000 doses show the same tendency.

Since the last evaluation of myocarditis, Spikevax has been approved for use in children 12 – 17 yo. Exposure in this group is still limited and Moderna reports an exposure of 5.312.891 vaccine recipients < 18 yo and is almost equally distributed between males and females. O/E is still below 1, however taking the sensitivity analysis into consideration the RR exceeds 1 significantly and more specifically for males. The rates in the age group <18 should be interpreted with caution, as the exposure estimation is imprecise. Only 3 cases have been observed in females while 48 cases have been observed in males <18yo. The reporting rate remains low and is highest for males.

Observed vs Expected, Pericarditis

Pericarditis (with or without myocarditis) was reported in 974 cases cumulatively (reporting rate 5.33 per 100,000 person-years) and in 172 cases during this reporting period (reporting rate 7.05 per 100,000 person-years). Pericarditis without myocarditis was reported in 823 cases cumulatively (reporting rate 4.51 per 100,000 person-years) and in 147 cases during this reporting period (reporting rate 6.03 per 100,000 person-years).

The cumulative rate for pericarditis was below the US-based incidence estimates, including an estimate of 5.7 hospitalizations per 100,000 person-years has been identified in data from the Nationwide Inpatient Sample (1,041 cases expected, rate ratio 0.94, 95% CI 0.86 - 1.02) and an estimate of 7.4 cases per 100,000 that has been observed in US armed service members deployed in the Middle East (1,352 cases expected, rate ratio 0.72, 95% CI 0.66 - 0.78).

Considering European background estimates, the cumulative reporting rate (5.33 per 100,000 person-years) was above published estimates from Finland (Kyto 2014: 3.30 per 100,000 personyears, 603 cases expected, rate ratio 1.62, 95% CI 1.46 - 1.79) and below estimates from Italy (27.70 per 100,000 person-years, 5,059 cases expected, rate ratio 0.19, 95% CI 0.18 - 0.21). Findings were similar when considering pericarditis without myocarditis reported within the case and consistent with the last monthly report.

Stratification of observed to expected analyses based on data from the US Nationwide Inpatient sample suggest an increased reporting rate for pericarditis in those ages 18-50 years of age, with larger increases occurring in men ages 18-24. Interpretation is similar in sensitivity analyses where it is assumed that 50% or 25% of cases are captured with no false positive errors, noting that risk becomes larger, and potential increases in young women more plausible (Table 3).

Table 3. Observed/Expected Analyses Stratified by Age, Pericarditis (Without Myocarditis) Expected Rates from the United States Nationwide Inpatient Sample Cases per 100,000 person years - Cumulative to 31 Oct 2021

	Person-years	Observed		Expected		As observed: RR (95% CI)	Assuming 50% of cases were reported: RR (95% CI)	Assuming 25% of cases were reported: RR (95% CI)
		Cases	Rate	Cases	Rate			
All	18,264,867	974	5.33	986	5.40	0.99 (0.9, 1.08)	1.98 (1.83, 2.13)	3.95 (3.68, 4.24)
By age								
<18 years	547,946	7	1.28	20	3.70	0.35 (0.15, 0.82)	0.69 (0.35, 1.37)	1.38 (0.78, 2.45)
18-24 years	1,643,838	199	12.11	61	3.70	3.27 (2.46, 4.36)	6.54 (5, 8.57)	13.09 (10.09, 16.98)
25-39 years	4,018,271	277	6.89	149	3.70	1.86 (1.53, 2.27)	3.73 (3.11, 4.47)	7.45 (6.28, 8.84)
40-49 years	2,739,730	135	4.93	101	3.70	1.33 (1.03, 1.72)	2.66 (2.12, 3.35)	5.33 (4.31, 6.59)
50-64 years	4,748,865	187	3.94	323	6.80	0.58 (0.48, 0.69)	1.16 (1, 1.34)	2.32 (2.03, 2.64)
65-74 years	2,739,730	99	3.61	233	8.50	0.43 (0.34, 0.54)	0.85 (0.7, 1.03)	1.7 (1.45, 2)
75+ years	1,826,487	42	2.30	159	8.70	0.26 (0.19, 0.37)	0.53 (0.41, 0.69)	1.06 (0.85, 1.31)
By gender								
Male	8,675,812	587	6.77	581	6.70	1.01 (0.9, 1.13)	2.02 (1.83, 2.23)	4.04 (3.69, 4.42)
Female	9,589,055	369	3.85	393	4.10	0.94 (0.81, 1.08)	1.88 (1.66, 2.12)	3.75 (3.36, 4.2)
By age and gender								
Male								
<18 years	260,274	6	2.31	12	4.59	0.5 (0.19, 1.34)	1 (0.45, 2.24)	2.01 (1, 4.02)
18-24 years	780,823	154	19.72	36	4.59	4.3 (2.99, 6.18)	8.59 (6.08, 12.14)	17.18 (12.28, 24.05)
25-39 years	1,908,679	172	9.01	88	4.59	1.96 (1.52, 2.54)	3.93 (3.11, 4.96)	7.85 (6.29, 9.8)
40-49 years	1,301,372	74	5.69	60	4.59	1.24 (0.88, 1.74)	2.48 (1.84, 3.34)	4.95 (3.75, 6.54)
50-64 years	2,255,711	99	4.39	190	8.44	0.52 (0.41, 0.66)	1.04 (0.85, 1.27)	2.08 (1.75, 2.47)
65-74 years	1,301,372	51	3.92	137	10.55	0.37 (0.27, 0.51)	0.74 (0.58, 0.96)	1.49 (1.2, 1.85)
75+ years	867,581	20	2.31	94	10.79	0.21 (0.13, 0.35)	0.43 (0.3, 0.62)	0.85 (0.63, 1.15)
Female								
<18 years	287,672	1	0.35	8	2.81	0.12 (0.02, 0.99)	0.25 (0.05, 1.17)	0.49 (0.15, 1.64)
18-24 years	863,015	44	5.10	24	2.81	1.81 (1.1, 2.98)	3.63 (2.31, 5.7)	7.26 (4.74, 11.12)
25-39 years	2,109,592	102	4.84	59	2.81	1.72 (1.25, 2.37)	3.44 (2.58, 4.6)	6.88 (5.24, 9.05)
40-49 years	1,438,358	61	4.24	40	2.81	1.51 (1.01, 2.25)	3.02 (2.11, 4.32)	6.04 (4.32, 8.44)
50-64 years	2,493,154	85	3.41	129	5.16	0.66 (0.5, 0.87)	1.32 (1.05, 1.66)	2.64 (2.16, 3.23)
65-74 years	1,438,358	47	3.27	93	6.45	0.51 (0.36, 0.72)	1.01 (0.76, 1.35)	2.03 (1.58, 2.6)
75+ years	958,905	22	2.29	63	6.61	0.35 (0.21, 0.56)	0.69 (0.47, 1.02)	1.39 (1.01, 1.92)

Abbreviations: CI = confidence interval; NA = not applicable; RR = rate ratio.

*Rates presented per 100,000 person-years; Kumar 2016. Age by sex stratified estimates were estimated by multiplying the overall age stratified estimates by the ratio of the applicable gender-specific estimate to the overall estimate. Data from the 2012 calendar year were used.

It should be noted that these analyses are performed based on all reported cases without adjudication and may include both confirmed and not confirmed myocarditis cases as well as miss other cases that could had not being reported to the MAH. Given the high level of international attention that myocarditis has received, and regulatory actions taken to enhance awareness of this important identified risk, we expect that sensitivity is likely high, but the challenge with specificity remains.

In summary, observed vs. expected analyses show an increase in the reporting rate of myocarditis (with or without pericarditis) and pericarditis that is strongest for young men within a few days after the second dose. Although there is a possibility that the risk extends to young women, similar increases are not observed in older vaccine recipients. This is consistent with observations from the literature and observed vs. expected analyses performed in recent monthly reports.

PRAC Rapporteurs assessment comment:

The MAH performed an O/E analysis of pericarditis (without myocarditis) stratified by age and gender. The risk of pericarditis has previously been considered causally related to the Spikevax mRNA vaccine. Current SmPC states that myocarditis and pericarditis occur more often in men and after the 2nd dose.

The O/E analysis shows that the RR exceeds 1 in the age groups 18-24, 25-39 and 40 – 49. This is seen for all, males and females. The highest RR is seen for males 18 – 24 yo (4.3 (2.99, 6.18)). In the pediatric population (<18yo) there is not observed any significantly increased RR. However, as mentioned previously the exposure estimation in this population is imprecise.

In conclusion, the O/E analysis confirms what is already known and stated in the SmPC regarding the risk of pericarditis.

Other Sources of Surveillance Data

Surveillance data from the Paul Ehrlich Institute in Germany suggested qualitatively similar but somewhat higher reporting rates for myocarditis, especially for men 18 - 29 years of age (11.71 cases per 100,000 vaccine recipients in German data, 7.79 in the Moderna Global Safety Database). Observed vs. expected analyses were similar, however, with German data showing an SMR of 4.44 (95% CI 3.57 - 5.46) for this group. In Canada, published surveillance data from Ontario have followed the same demographic trend, with clustering of cases in young men after the second dose of vaccine. Observed reporting rates in the province were higher at 17.1 doses per 100,000 vaccine recipients among men ages 18-24 overall and 28.3 per 100,000 vaccine recipients following dose 2.

Literature Assessing the Risk of Myocarditis and Pericarditis

SARS-CoV-2 Vaccination and Myocarditis in a Nordic Cohort Study of 23 Million Residents[1]

In a Nordic cohort study including a meta-analysis of the 23 million residents of Denmark, Finland, Norway and Sweden made available to the MAH prior to publication (Karlstad, 2021), during the 28-day risk-periods following vaccination and during unvaccinated periods experienced by the study participants (6.7 million person-years in total), they observed 1092 incident myocarditis cases and 1154 incident pericarditis cases. Incidence rates of myocarditis during unvaccinated time was 9.7 per 100,000 person-years for men, and 4.2 for women. Among 16- to 24-year-old, incidence rates were 18.7 for men and 4.4 for women. Incidence rates of pericarditis increased with increasing age. During the 28-day risk period, they observed 106 and 123 myocarditis cases following first- and second-dose vaccinations with BNT162b2, respectively, and 15 and 67 following mRNA-1273, respectively.

The results of the study showed:

- Adjusted RRs comparing the 28-day risk periods following first- and second-dose vaccinations to unvaccinated periods were 1.2 (95%CI, 0.7 to 1.9) and 7.2 (95%CI, 5.3 to 9.8)
- In males, following the first and second dose, adjusted RRs were 1.5 (95%CI, 0.8 to 2.5) and 9.1 (95%CI, 6.9 to 12).
- In males, 16-24 years of age, the adjusted RR was 14.2 (95%CI, 8.4—23.8) for a second dose of mRNA-1273. For females, the comparative adjusted IRRs were lower
- Among all males, the excess number of events per 100,000 vaccinated in the 28-day risk periods were 0.3 (95%CI, -0.1 to 0.8) and 5.4 (95%CI, 4.0 to 6.8) following first and second doses for mRNA-1273. The excess number of events for females were low.

- Among males 16–24 years, the excess number of events per 100,000 vaccinated in the 28-day risk periods following first and second doses were 1.7 (95%CI, -0.2 to 3.7) and 18.8 (95%CI, 9.6 to 28.0) for mRNA-1273.The corresponding excess number of events for males 25 to 39 years of age were somewhat lower.
- In a mixed schedule (BNT162b2—mRNA-1273), close to 40 cases (34 males) occurred following the second dose. In males 16-24 years, 17 cases occurred, with an excess number of events of 26.5 (95%CI, 13.9 to 39.1).
- IRRs of myocarditis or pericarditis combined in males 16–24 years were close to those of myocarditis.
- In males 25–39 years the RRs were generally lower. In females 16–24 years the IRRs were similar to those of males of the same age, however, with wider confidence intervals.
- A 7-day risk period was also evaluated for the 228 myocarditis cases in the 28-day risk-window after a second dose of mRNA
    - 145 vaccination, events occurred within the first week, yielding higher IRRs. The excess events, per 100,000 vaccinated, during 7-day risk-window represented the majority of excess events during the 28-day risk-window.
    - In males 12–39 years, at least 75% of the cases were admitted to hospital within 10 days of vaccination
    - Comorbid conditions did not differ markedly between vaccinated and unvaccinated cases
    - Length of stay did not markedly differ between vaccinated and unvaccinated cases

The authors concluded that the information collected in this study of 23.1 million individuals shows higher rates of myocarditis and pericarditis within 28 days following vaccination with SARS-CoV-2 mRNA vaccines when compared to unvaccinated. These associations were strongest within the first 7 days, were increased for all combinations of mRNA vaccines and were more pronounced after the second dose. A second dose of mRNA-1273, either after mRNA-1273 or BNT162b2 as a first dose, had the highest risk. Young males aged 16-24 years had the highest increased risk. They also concluded that there was a higher risk after a second dose and a higher risk in young men, information that has already been documented and communicated to health care provided through appropriate risk communication measures.

The authors also presented excess events within 28 days in young males of 5.7 per 100,000 after a second-dose vaccination with BNT162b2 and 18.8 after a second-dose vaccination with mRNA- 1273 which are higher than previously reported.

PRAC Rapporteurs assessment comment:

Additional details on study design

The registry cohort study followed individuals from the start of the vaccination campaign in Nordic countries (Denmark, Finland, Norway and Sweden) until first outcome event, a positive SARS-CoV-2 test, a third vaccination, emigration, death, or end of follow-up. All Nordic national registries allow analyses on the entire population and individual level through linkage to other registries such as health care utilization. In the main analysis, the IRRs and risk differences of myo- and pericarditis were estimated based on comparison of vaccinated with unvaccinated follow-up time (considering a 28-day risk window following vaccination). The estimates were adjusted for sex, age, vaccine priority groups, comorbidities and prior SARS-CoV-2 infection (before start of follow up, 27

December 2020; infection after this date was a censoring event). Country-specific estimates were pooled via meta-analysis, considering heterogeneity between the databases.

Results

As summarized by the MAH above. Additional results and important details:

- The main estimates discussed here were based on 2,004,059 patients (male and female combined) who received two doses of Spikevax.
- The estimates were based on a risk period of 28 days following vaccination. In sensitivity analyses, a 7-day risk period was applied, which resulted in higher estimates. For males 16-24 years the IRR after the second dose was 37.7 (95% CI 21.6 - 65.8).
- In males 12-15 years, the IRR of myocarditis following the second dose was very high (89.05). However, this was based on very few events and the precision was therefore very low.
- The risk estimates were generally higher (across all age groups) for Spikevax compared with Comirnaty. In males, 16-24 years of age, the adjusted RR was 5.4 (95%CI, 3.8 to 7.6) for a second dose of Comirnaty and 14.2 (95%CI, 8.4—23.8) for Spikevax. Among males 16–24 years, the excess number of events per 100,000 vaccinated in the 28-day risk periods following the second dose was 5.7 (95%CI, 3.9 to 7.5) for Comirnaty 18.8 (95%CI, 9.6 to 28.0) for Spikevax.
- Data on time to admission was included in supplementary analyses. The median time to admission was 5 days (p25% 3 days; p75% 7 days) in Denmark, 11 days in Finland (p25% 4 days; p75% 15 days), 5 days in Norway (p25% 3 days; p75% 19 days) and 7 days in Sweden (p25% 3 days; p75% 18 days).
- Data on time to discharge and death after myocarditis was included in supplementary analyses. For male and females combined (all ages), 49.5% (95% CI 26.0 – 73.3) were discharged on day 4 or later following the second dose of Spikevax, while 53.7% (95% CI 39.4 – 67.4) were discharged on day 4 or later in the unvaccinated. Following the second dose of Spikevax, 4.5% of patients died within 28 days (95% CI 0.0 – 13.2) versus 1.2% (95% CI 0.5 – 2.7) among unvaccinated.

Strengths and limitations

Inherent to the Nordic registries, this study captures the entire national population in the 4 countries with a total study population of over 23 million with a complete follow-up and independent ascertainment of vaccinations and diagnoses from nationwide registers to which reporting is mandatory. In the meta-analysis, the between-database heterogeneity was not statistically significant, despite some country-specific differences. Prior to follow-up myo- and pericarditis were exclusion criteria while individuals with COVID-19 during follow-up were censored. Likely confounders were appropriately adjusted for and the robustness of the results was assessed in sensitivity analyses (e.g. 7-day risk window, additional adjustment for calendar time).

Myo- and pericarditis were defined as inpatient hospital admission with main or secondary discharge diagnosis. In the Danish registry, diagnostic codes have been shown to have an 85% positive predictive value in male patients below the age of 60 years[7]. Without access to data on clinical measures like troponin levels, diagnostic imaging results, or endomyocardial biopsy, it could not be assessed how many patients fulfill all criteria for a myocarditis diagnosis. However, median length-of-stay was 4-5 days for both unvaccinated and vaccinated cases indicative of sufficient time for adequate diagnostic procedures. Assuming this source of misclassification would be non-differential,

this would bias risk estimates towards the null. However, the authors also highlight that aascertainment bias whereby increased focus on myocarditis as an adverse event after mRNA vaccination has resulted in more subclinical cases being diagnosed, cannot be ruled out. However, the authors highlight that this is unlikely to fully explain the differences between the two mRNA vaccines or between age groups. Considering such differential awareness between vaccines exists, this would bias the risk estimates away from the null.

Time-dependent unmeasured confounding could have impacted the estimates, as the background incidence of myocarditis fluctuates with infectious-disease burden (higher during winter) and vaccines were utilized according to their availability (i.e. for younger age groups primarily during summer). Considering a skewed comparison of IRs based on the vaccinated primarily during summer with IRs from including the winter months, this would bias the estimates towards the null. However, adjustment for calendar time in sensitivity analysis did not change the results substantially.

In a mass vaccination campaign, estimates based on a contemporary unvaccinated comparator group may be biased since unvaccinated persons are not likely to be representative of the appropriate background rates due to e.g. healthy vaccinee/ sick vaccinee effects. Considering a scenario in which the unvaccinated were sicker than the vaccinated and if these comorbidities were associated with the outcome, this would bias the estimates towards the null. However, comorbid conditions did not differ markedly between vaccinated and unvaccinated cases. Moreover, the authors highlight that potentially future sensitivity analysis (planned according to the preliminary report) may inform about the robustness of the estimates using the unvaccinated as a comparator, i.e. changing the comparator to the follow-up time day 29 or later following any vaccination.

Association between COVID-19 messenger RNA vaccines and the occurrence of myocarditis and pericarditis in people aged 12 to 50 in France - Study based on data from the National Health Data System (SNDS)[2]

Similarly, a population-based case-control analysis using French national health data has shown a large increase in the odds of myocarditis within 7 days after vaccination, noting that confidence intervals were wide. The association with the risk of myocarditis appears particularly pronounced in young men under 30 years of age, particularly after the second dose of Moderna vaccine (adjusted odds ratio (OR) 79.8; 95% confidence interval [29.8-213.4]), leading to an excess of cases reaching 132 per million doses in this population. Although the occurrence of myocarditis is less frequent than in men, this risk is also increased in young women under 30 years old after the second dose (OR 40.6 [9.9-166.4] and 37 cases in excess per million doses for Moderna). The risk of pericarditis also appears to be more marked after the Moderna vaccine in people under 30 years of age, in particular after second dose in men (OR 15.0 [3.3-68.4] and 18 excess cases per million doses) and after the first dose in women (OR 27.9 [2.4-328, 0] and 6 excess cases per million doses). The conclusion of this study is that the number of cases attributable to vaccines appears to be infrequent in relation to the number of doses administered.

This study also confirms the favorable clinical course of cases of myocarditis and pericarditis following vaccination.

PRAC Rapporteurs assessment comment:

Additional details on study design

This matched case-control study based on French national health data utilized all cases of hospitalization for myocarditis and pericarditis recorded between 15 May and 31 August 2021 involving patients between the ages of 12 and 50.

Each case was matched with 10 controls (randomly selected from among the whole population, not diagnosed with myocarditis or pericarditis during the study period) of the same age, gender and *département* of residence. Additional adjustment considered history of myocarditis or pericarditis in the last 5 years, infection with SARS-CoV-2 in the previous month, and the deprivation index. In sensitivity analyses, prior myocarditis/ pericarditis or prior SARS-CoV-2 are exclusion criteria. The relative risk was estimated using odds ratio of the association within the risk windows 1-7 days and 8-21 days.

Results

As summarized by the MAH above. Additional results and important details:

- The risk was also increased in males 30-50 years with an OR of 18.0 (95% CI 8.0 – 40.6) and 26.5 excess cases per million doses.
- Estimates were similar upon exclusion of cases with prior myocarditis or pericarditis in sensitivity analysis
- Estimates were similar upon exclusion of cases with prior SARS-CoV-2 infection in the month preceding the index date in sensitivity analysis
- The risk estimates were generally higher (across all age groups) for Spikevax compared with Comirnaty. In males, 12-29 years, the adjusted OR was 10.9 (95% CI 7.6 – 15.8) for a second dose of Comirnaty and 79.8 (95% CI 29.8 – 213.4) for Spikevax. Among males 12-29 years, the excess number of events per 100,000 vaccinated was 2.67 (95% CI 2.55 – 2.75) for Comirnaty and 13.16 (95% CI 12.99 – 13.33) for Spikevax.
- Among the exposed subjects, the median time to admission for myocarditis was 9.5 and 4 days following the first and second dose of Spikevax, respectively. For pericarditis, the median time to admission was 9.5 and 10 days following the first and second dose, respectively.
- Data were presented for length of hospital stay for myocarditis (based on 919 cases) and pericarditis (based on 917 cases) following vaccination with any mRNA vaccine (no stratification) compared with the unexposed. For myocarditis, the median length of stay was 4 days (IQR 2; 5) for unexposed, 4 days (IQR 2; 5) for vaccinated with onset of myocarditis within the risk window 0-7 days and 3 days (IQR 2; 5) for vaccinated with onset of myocarditis within the risk window 8-21 days. The time to discharge was longer than 5 days in 22.6% of patients amongst the unvaccinated, and 12.3% and 16.8% amongst the vaccinated 1-7 days and 8-21 days post-vaccination, respectively. Overall only 1 death was observed (among the unexposed). For pericarditis, length of stay was considerably shorter, but a similar pattern between vaccinated and unvaccinated was observed.

Strengths and limitations

During the study period 919 cases of hospitalization for myocarditis and 917 for pericarditis were identified. Given the low number of cases overall some estimates have low precision, and a narrower

stratification was likely not feasible. However, the link with the risk of myocarditis appears to be particularly strong among young men below the age of 30, which is in line with other studies.

The definition of cases was solely based on diagnosis codes associated with hospital admissions. However, the incidence rates of myocarditis and pericarditis in France prior to the pandemic are consistent with those reported by other countries.

Ascertainment bias whereby increased focus on myocarditis as an adverse event after mRNA vaccination has resulted in more subclinical cases being diagnosed, cannot be ruled out. Moreover, calendar time was not considered as a matching variable so that cases from the period of increased focus on myocarditis may be compared with controls prior to this period. However, it is unlikely that the differences between the two mRNAs and between age groups can be fully explained by such bias. Considering a scenario in which differential awareness between the vaccines exists, this would bias the risk estimates away from the null.

Myocarditis Following COVID-19 mRNA Vaccine: A Case Series and Incidence Rate Determination [3]

A retrospective case-series was performed utilizing the Mayo Clinic COVID-19 Vaccine Registry. The authors measured the incidence rate ratio for myocarditis temporally related to COVID-19 mRNA vaccination compared to myocarditis in a comparable population from 2016 through 2020. Clinical characteristics and outcomes of the affected patients was collected. A total of 21 individuals were identified, but ultimately 7 patients met the inclusion criteria for vaccineassociated myocarditis. An incidence rate ratio for myocarditis following COVID-19 mRNA vaccination was found to be increased for males at a rate ratio of 6.69 (95% CI 2.35 - 15.52) with poor precision for females (IRR 1.41, 95% CI 0.03 - 8.45). Limited sample size precluded stratified analyses (Perez 2021).

In a US a population-based cohort study of approximately 2.4 million patients aged ≥18 years observed 15 cases of confirmed myocarditis after any dose of a mRNA COVID-19 vaccine (2 cases after dose 1; 13 cases after dose 2), for an incidence of 0.08 per 100,000 first doses and 0.58 per 100,000 second doses; acute myocarditis was described as a rare event. All reported occurred in younger males (median age, 25 years) who were hospitalized and had symptoms resolve with conservative management. The US FDA recently presented an assessment of myocarditis/pericarditis rates using the FDA Biologics and Effectiveness Safety (BEST) active surveillance system, which consists of 4 health claims data sources with a total 76.5-89.5 million annual enrollees. Within the first 7 days after administration of any mRNA COVID-19 vaccine dose (eg, mRNA-1273 or BNT162b2), the incidence rate of myocarditis/pericarditis per 1 million person-days was generally low for all age groups; rates were highest for males aged 18-25 years after dose 2. At the October 21, 2021 CDC ACIP meeting, the COVID-19 Vaccine Safety Technical (VaST) Work Group summarized the available data to date on myocarditis rates after mRNA COVID-19 vaccination from multiple worldwide safety monitoring systems, which indicated myocarditis was associated with both mRNA-1273 and BNT162b2 among adolescents and young adults, more frequently among males. The COVID-19 subcommitee of the WHO Global Advisory Committee on Vaccine Safety (GACVS) also recently reviewed available evidence from multiple countries and noted that while some data suggest increased myocarditis incidence in young males after dose 2 of mRNA-1273 versus BNT162b2, other data do not support this finding, and the overall risk is low.

Several large US surveillance systems have shown comparable risk of myocarditis between mRNA-1273 and BNT162b2 (eg, Vaccine Adverse Event Reporting System [VAERS], FDA BEST System, and Department of Veterans Affairs active surveillance Rapid Cycle Analysis for COVID-19 vaccines). For example, the CDC COVID-19 Vaccine Task Force provided the reporting rate of myocarditis among

males aged 18-24 years after mRNA-1273 and BNT162b2 as 3.68 and 3.85 per 100,000 second doses administered, respectively, based on data from the VAERS safety passive monitoring system. However, a recent analysis from the Vaccine Safety Datalink (VSD) estimated that there was an excess 9.7 myocarditis/myopericarditis cases per million doses of mRNA-1273 versus BNT162b2 among 18-39-year-olds (adjusted rate ratio [95% CI]: 2.28 [1.00-5.22]; 2-sided p-value: 0.049). Of note, the VSD analysis was based on small case numbers within 7 days after dose 2 (mRNA-1273: 14 cases [810,839 total second doses]; BNT162b2: 12 cases [1,256,525 total second doses]).

PRAC Rapporteurs assessment comment:

Perez et al. performed a retrospective case-series using the Mayo Clinic COVID-19 vaccine registry and estimated the IRR for myocarditis temporally related to COVID-19 mRNA vaccination compared to myocarditis in a comparable population from 2016 through 2020. The estimated IRR is 4.18 (1.63, 8.89) for any mRNA vaccine. For females the IRR was 1.41 (0.03, 8.45) and for males it was 6.69 (2.35, 15.52). However, the IRR is based on few cases as only 7 cases of myocarditis after mRNA vaccination were included in the study. The authors mention a few limitations to the study including selection bias due to regional population demographics (Midwest states, US), potential bias for more severe cases due to the use of hospital codes which could lead to underestimation of the risk and that the cohort does not include adolescents <16 yo. In conclusion, the study confirms that males are at higher risk of myocarditis following mRNA vaccination, which the current PI already adequately describes.

The MAH refers to an unidentified US population-based study of 2.4 million patients age 18 or older, that found an incidence of 0.08 per 100,000 first doses and 0.58 per 100,000 second doses of any mRNA vaccine.

In addition, the MAH refers to incidence rates of myocarditis from the CDC and the WHO subcommittee GACVS which confirmed previous observations that the risk of myocarditis was higher in young men after the second dose. Furthermore, the GACVS noted that the risk of myocarditis in this age group seem to be higher for Spikevax compared to Comirnaty. An analysis from the Vaccine Safety Datalink (VSD) estimated an excess 9.7 myocarditis/myopericarditis cases per million doses of Spikevax versus Comirnaty among 18-39-year-olds.

There were not presented any data from the CDC on the incidence rate of myocarditis in adolescents receiving Spikevax.

Conclusion

Considering evidence across these sources, it is suggested that the risk of myocarditis following SPIKEVAX is meaningfully increased, especially in younger men and after the second dose of vaccine. Although some estimates have limited precision given the low expected incidence of myocarditis. Associations with pericarditis have been comparatively attenuated, however the same pattern of an increased risk in younger men has been observed in several assessments.

PRAC Rapporteurs assessment comment:

Based on the evidence across different sources, the MAH concludes that the risk of myocarditis following Spikevax is meaningfully increased. This is acknowledged.

Vaccine Safety Datalink study

In addition, the PRAC Rapporteur wants to highlight the interim analysis of the Vaccine Safety Datalink in the US (Klein et al, 2021)[1]. The MAH mentioned this study with regards to the further characterization of myocarditis (ITEM 2), but the data are considered relevant for the risk estimation as well.

In this safety surveillance study, the incidence of serious outcomes (including myocarditis/ pericarditis) among vaccine recipients within the risk period (i.e. 1-21 days post-vaccination for myocarditis) were compared to those of concurrent comparators outside of the risk period (i.e. 22-42 days post-vaccination for myocarditis).

For 18-39-year-olds, considering a 0-7-day risk interval, the adjusted IRR after the second dose was "very high" (95% CI 11.70 - ∞). No definite estimate could be made here, since no event was observed in the comparison interval (versus 17 events in the risk interval). The excess number of events per 100,000 doses was 2.1. In the interim results available to the assessor, no stratification by gender was performed (except in the comparative analysis commented on further below).

For Spikevax, no data on >18-year-olds are available (for data for Comirnaty see further below – Data on >18-year-olds).

Klein et al also performed a comparative analysis between the two mRNA vaccines. For males 18-39 years, the adjusted rate ratio (Spikevax rate versus Comirnaty rate) for myocarditis after the second dose in the 0-7-day risk window was 2.14 (95% CI 0.93 – 4.98), with 1.91 excess cases per 100,000 doses.

Summary and comparison of the major risk estimates from different sources

The MAH commented on risk estimates from the following sources: the US PASS, the Moderna safety database O/E analysis, the Nordic cohort study (Karlstad et al, 2021), the French National Health Data System study and the Mayo Clinic case-series study (Perez et al, 2021).

Across different populations and study designs, with different strengths and limitations, a robust increased risk for myocarditis following Spikevax has been observed in males <30 years.

Myocarditis

US PASS

- For **males 18-29 years the IRR was 3.3** (95% CI 2.29 - 4.65). The **O/E was 6.97** (95% CI 3.01 - 13.74) in this population.
- No significantly increased IRR or O/E was observed for any other age group in males or any age group in females.

MAH safety database

- The O/E analysis was 3.68 (95 % CI 3.09 - 4.38) for males 18-24 and 1.32 (95 % CI 1.16 - 1.5) for males 25 – 39. No imbalance of O/E is observed for females in the same age groups.
- Reporting rates were higher after the 2nd dose. The highest reporting rate was 5.9 / 100.000 doses and was observed for males 18 – 24 yo.

[1] Klein N. Myocarditis Analyses in the Vaccine Safety Datalink: Rapid Cycle Analyses and "Head-to-Head" Product Comparisons [Internet]. Advisory Committee on Immunization Practices (ACIP); 2021 oct 21. Accessible from: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-10-20-21/08- COVID-Klein-508.pdf

Nordic cohort study

- The risk was estimated highest after the second dose for **males 16-24 years with an IRR of 14.2** (95% CI 8.4 - 23.8). The excess number of events per 100,000 vaccinated in the 28-day risk period was 18.8 (95% CI, 9.6 to 28.0).
- For males 25-39 years, the IRR was 13.53 (95% CI 8.85 – 20.68) and the excess number of events 8.49 (5.33-11.65).
- For females above 12 years, the IRR was 3.61 (95% CI 1.83 – 7.10) and the excess number of events 0.68 (95% CI 0.20 – 1.16)

French case-control study

- The estimate was highest after the second dose for **males 12-29 years with an OR of 79.8** (95% CI 29.8 - 213.4). The excess number of events per 100,000 vaccinated in the 7-day risk period was 13.2 (95% CI 12.9 – 13.3).
- In males 30-50 years, the OR was 18.0 (95% CI 8.0 – 40.6) with 2.65 (95% CI 2.44 – 2.76) excess cases per 100,000 doses.
- In females 12-29 years, the OR was 40.6 (95% CI 9.9 - 166.4) with 3.73 (95% CI 3.47 – 3.77) excess cases per 100,000 doses.

<u>Pericarditis</u>

US PASS

- In **males 18-29 years, the IRR was 1.41** (95% CI 0.97 - 1.99). In this group, 10 events were observed versus 2 expected leading to an O/E of 4.19 (95% CI 2.01 – 7.71).
- No significant increase was observed in females in any age group.

MAH safety database

- O/E analysis for pericardiutis showed the highest RR for males 18 – 24 yo which was 4.3 (95% CI 2.99 - 6.18).
- The O/E analysis showed that the RR exceeded 1 in the age groups 18-24, 25-39 and 40 – 49. This is seen for all, males and females.

Nordic cohort study

- The risk was estimated highest in males 16-24 years, with 7.04 (1.39-12.7) excess number of events per 100,000 doses.
- No significantly increased risk was observed for females in general or in any particular age group.

French case-control study

- For males 12-29 years, the **OR following the second dose was 15.0** (95% CI 3.3-68.4) and the number of excess cases per 100,000 doses was 178.
- No increased risk was observed for males 30-50 years.
- For females 12-29 years, the **OR following the second dose was 27.9** (95% CI 2.4 – 328) and the number of excess cases per 100,000 doses was 58.

- For females 30-50 years, the **OR following the second dose was 18.7** (95% CI 4.7 – 74.9) and the number of excess cases per 100,000 doses was 105.

In summary, an increased risk of myo- and pericarditis following Spikevax was observed across different studies. It is important to highlight that these studies, based on large populations and different study designs with unique strengths and limitations, led to similar results: an increased risk particularly in males <30 years, which confirms the information already reflected in the SmPC While some variation in the magnitude of the association was observed, the association is also strengthened by the fact that 3 independent large studies (Vaccine Safety Datalink study, Nordic cohort study and French case-control study) observed higher estimates for Spikevax compared with Comirnaty.

Data on <18-year-olds

Very limited data on myocarditis/pericarditis following vaccination with Spikevax are available for 12-17-year-olds. In the Nordic cohort study, stratification for 12-15-year-olds was presented. For males in this age group, after the second dose of Spikevax, the IRR was 89.05 (95% CI 21.23-373.49) with 36.51 (-4.81 – 77.82) excess cases per 100,000 doses. However, given the very low exposure (35,524 [males and females combined] in this age group received two doses) and the rarity of the events (<5 cases), the precision was very low. For females in this age group, no estimates were available, as there was no event in the unvaccinated to compare with.

As no details were available regarding the proportion of <18-year-olds in the stratum 16-24 years, no definite conclusions can be drawn with regards to the risk estimation in <18-year-olds. This summer, the indication of Spikevax was extended to include the 12-17-year-olds. The exposure of Spikevax in 16-17-year-olds is still limited. It should be noted that for the other mRNA vaccine, the vaccine was indicated from 16 years and older from first authorization.

The French case-control study did include persons vaccinated down to 12 years; however, data was too limited to allow for a detailed estimation in 12-17-year-olds at the time of data lock (August 31). As a result, stratification narrower than 12-29 years was not performed. 9.2% of all myocarditis and 5.8% of all pericarditis cases were observed in 12-17-year-olds. Given the lack of comparative data in this age group, no definite conclusions can be drawn with regards to the risk estimation in <18-year-olds at this point in time.

3.1.2. ITEM 2 - further characterization of myocarditis and pericarditis

Sponsor Response

- **Provide an estimation of the incidence of myocarditis and pericarditis, with the view to better characterize the current 'unknown' frequency in the product labeling.**

Data on the incidence of myocarditis and pericarditis following vaccination from VAERS that were presented to the US ACIP in October 2021 (Su, 2021) appear consistent with other sources reporting rates including the MAH Global Safety Database.

For men, incidence peaks in adolescents (noting that these data are available for Pfizer only in the United States), with the highest observed rate falling at 38.5 cases per 1,000,000 doses administered (Figure 1).

Reporting rates (per 1 million doses administered) of myocarditis among males after mRNA COVID-19 vaccines, 7-day risk period (N=797)*

- **169,740,953** doses of mRNA vaccine administered to males (dose 1 and dose 2) *
- Reporting rates exceed background incidence**
  - After dose 1 of Pfizer (12–24 years) and Moderna (18–39 years)
  - After dose 2 of Pfizer (12–39 years) and Moderna (18–49 years)

	Pfizer (Males)		Moderna (Males)	
Ages	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**
12-15	**4.2**	**39.9**	0.0	not calculated
16-17	**5.7**	**69.1**	0.0	not calculated
18-24	**2.3**	**36.8**	**6.1**	**38.5**
25-29	1.3	**10.8**	**3.4**	**17.2**
30-39	0.5	**5.2**	**2.3**	**6.7**
40-49	0.3	2.0	0.2	**2.9**
50-64	0.2	0.3	0.5	0.6
65+	0.2	0.1	0.1	0.3

* As of Oct 6, 2021; 797 of 935 reports after doses 1 and 2 of mRNA vaccines occurred during Days 0–6 after vaccination among males; reports verified to meet case definition by provider interview or medical record review
** An estimated 1–10 cases of myocarditis per 100,000 person years occurs among people in the United States, regardless of vaccination status; adjusted for the 7-day risk period, this estimated background is **0.2 to 1.9 per 1 million person 7-day risk period**

8

In women, a similar age distribution in the reporting rate is observed, however the overall magnitude is substantially lower.

Reporting rates (per 1 million doses administered) of myocarditis among females after mRNA COVID-19 vaccines, 7-day risk period (N=138)*

- **193,215,313** doses of mRNA vaccine administered to females (dose 1 and dose 2)*
- Reporting rates exceed background incidence**
  - After dose 2 of Pfizer (12–24 years) and dose 2 Moderna (18–29 years)

	Pfizer (Females)		Moderna (Females)	
Ages	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**
12-15	0.4	**3.9**	0.0	0.0
16-17	0.0	**7.9**	0.0	0.0
18-24	0.2	**2.5**	0.6	**5.3**
25-29	0.2	1.2	0.4	**5.7**
30-39	0.6	0.7	0.5	0.4
40-49	0.1	1.1	0.2	1.4
50-64	0.3	0.5	0.5	0.4
65+	0.1	0.3	0.0	0.3

* As of Oct 6, 2021; 138 of 935 reports after doses 1 and 2 of mRNA vaccines occurred during Days 0–6 after vaccination among females; reports verified to meet case definition by provider interview or medical record review
** An estimated 1–10 cases of myocarditis per 100,000 person years occurs among people in the United States, regardless of vaccination status; adjusted for the 7-day risk period, this estimated background is **0.2 to 1.9 per 1 million person 7-day risk period**

9

Based on the above-mentioned estimations from VAERS, myocarditis can then be considered a **very rare event** (Very rare (<1/10,000)) = ~ 0.385 cases per 10,000 in the subgroup at highest risk).

PRAC Rapporteurs assessment comment:

The MAH provided a frequency based on reporting rates provided by the CDC based on data from the VAERS database. Frequencies were based on the reporting rate for the subgroups at highest risk and were estimated to "very rare".

It should be noted that the estimated frequency from VAERS provided by the MAH is based only on US data. In the 10th MSSR, it was reported that 50 % of all administered doses were in the US and approximately 20 % of the doses were administered in the EEA. 60.6% of the cumulative cases originated from the US. Nevertheless, the VAERS reporting rates and estimated frequency match the observations from the MAHs safety database regarding myocarditis. Below are the reporting rates and estimated frequencies of myocarditis using the MAHs' approach for the age group 18-24 yo from the MAHs Safety database:

Sex	Dose	Reporting rate (cases/ doses)	Estimation of frequency	Potential PI frequency
Al	1st dose	2.3 /100.000	~ 0,23 cases/ 10.000	Very rare
	2nd dose	3.1 /100.000	~ 0,31 cases/ 10.000	Very rare
Males	1st dose	4.4 /100.000	~ 0,44 cases/ 10.000	Very rare
	2nd dose	5.9 /100.000	~ 0,59 cases/ 10.000	Very rare

In addition, the MAH provided a reporting rate from based on surveillance data from the Paul Ehrlich Institute in Germany. For 18 – 29 yo, 11.71 cases per 100,000 vaccine recipients in results in ~ 1.17 cases/ 10.000(frequency estimation "rare"). For the same age group in the MAHs' database 7.79 cases per 100.000 doses were reported (~ 0.78 cases/ 10.000, frequency estimation "very rare").

Both the Nordic cohort study and the French case control study contribute with data about the risk of myocarditis from the EU. Below is an overview of excess cases reported from the epidemiological studies for myocarditis after 2 doses of Spikevax.

Study	Sex	Age	Excess cases / doses	Estimation of frequency	Potential PI frequency
Nordic Cohort Study*	Men	16 - 24	18.8 /100.000	~ 1.88 cases/ 10.000	Rare
		12+	5,38 / 100.000	~ 0.538 cases/ 10.000	Very rare
		25 - 39	8.49 / 100.000	~ 0.849 cases/ 10.000	Very rare
	Women	16 - 24	N/A		
		12+	0.68 / 100.000	~ 0.068 cases/ 10.000	Very rare
		25 - 39	10.8 /100.000	~ 0.108 cases/ 10.000	Very rare
French case-control study**	Male	12- 29	131.6/1.000.000	~ 1.32 cases/ 10.000	Rare
		30-50	26.5/1.000.000	~ 0.265 cases/ 10.000	Very rare
	Women	12- 29	37.3/1.000.000	~ 0.375 cases/ 10.001	Very rare
		30-50	N/a	N/a	

** Excess cases per 28 days*
*** Excess cases per 7 days*

As previously noted by the MAH, the Nordic Cohort study and the French case-control study show a more frequent occurrence of myocarditis for young males expressed as excess cases per 100.000 or 1.000.000 doses respectively. If the no. of excess cases provided in the studies is used as a measure to estimate frequency, the frequency for males 16-24 from the Nordic study and males 12-29 from the French study would be "Rare" and for the remaining stratified groups it would be "Very rare" (please see above table).

Considering risk of pericarditis, the Nordic study and the French case control study present an excess no. of cases of 7.04/ 100.000 doses and 17.8/ 1.000.000 doses, respectively, younger males at highest risk. The estimated frequency for myocarditis then will be "very rare", and there is therefore not observed a difference in frequency category as observed for myocarditis.

An alternative non-comparative approach to the estimation of frequency would have been to simply use IRs per doses whereas the Nordic study express IRs per 1000 PY (common approach in epidemiological studies). However, in the Nordic cohort study, the number of persons vaccinated in the various age strata was only presented for females and males combined, whereas the number of events was only presented stratified by age. As an example, approximately 200,000 16-24-year-olds (male and female) received 2 doses; 16 events occurred in males 16-24 years, 0 events in females 16-24 years. Speculating that half of the 200,000 doses were received by males, this would amount to 1.6 cases per 10,000 doses (frequency "rare") in males 16-24 years. However, the precise exposure in terms of doses is unknown and this is roughly in line with the frequency estimation based on the excess-cases approach described above. Estimating frequency from excess cases therefore seems to be the best approach considering the presented data. No exposure data were presented in the French case-control study.

It should be noted, that estimating frequency from excess case from epidemiological studies or from spontaneous reporting poses some challenges. Among others the following limitations: First, spontaneous reporting is potentially underreported. One could argue that increased awareness of the risk for myocarditis and pericarditis as a part of national vaccination campaigns, have decreased the risk of underreporting. This is likely true; however, it does not eliminate the risk entirely and underreporting will still be present. Second, the possibility that not all cases are "true" cases, i.e. causally related to the vaccine. This is a limitation for both spontaneous reporting and the two epidemiological studies. However, the nature of the epidemiological studies with comparison to background rates of myocarditis/pericarditis or controls from the respective countries for estimation of risk does in some way correct for this. The no. of excess cases derived from the observed risk estimates in the studies should therefore be a measure of cases that is above background rates and would result from vaccination. Third, the epidemiological studies use hospital codes to retrieve data on myocarditis and pericarditis. The Nordic study has an inclusion criteria of at least 24 hours hospitalisation. Less severe cases of myocarditis or pericarditis not requiring hospitalisation for this long would therefore not be included. Furthermore, most of the mentioned biases in the two studies (as previously mentioned in this AR) would affect the estimated risks towards null. Hence, estimated risks in the Nordic and French studies are potentially not overestimated.

Considering available data on a potential frequency, especially data from the EU, the frequencies of myocarditis and pericarditis would be estimated to be "very rare" overall and the frequency of myocarditis would be "rare" for younger males.

- **Discuss any plausible pathophysiological mechanisms of myocarditis and pericarditis observed after COVID-19 vaccine Spikevax.**

Several hypotheses have been proposed in the literature to explain the pathophysiology of the mechanisms involved in the occurrence of myocarditis and pericarditis observed after vaccination with any of the two mRNA COVID-19 vaccines. Some of those articles are included below, but still the mechanisms for development of myocarditis or pericarditis are not understood.

Literature Assessing the Pathophysiology Mechanisms

Myocarditis With COVID-19 mRNA Vaccines. Bozkurt et al[4]

SARS-CoV-2 mRNA vaccines contain nucleoside-modified mRNA, encoding the viral spike glycoprotein of SARS-CoV-2, but not live virus or DNA. They are encapsulated in lipid nanoparticles that act as delivery vehicles to transport mRNA into the cells and may include inactive ingredients such as buffer and salts. Once inside the host cells, the vaccine' s mRNA causes the cells to build the spike protein which then stimulates an adaptive immune response to identify and destroy a virus expressing spike protein. Vaccine-induced spike protein IgG antibodies prevent attachment of SARS-COV-2 to its host cell via spike protein binding to the angiotensin-converting enzyme 2 receptor, and thereby neutralizes the virus.

Selected RNA molecules can be immunogenic and stimulate the mammalian innate immune system, destroying the mRNA before it reaches target cells, preventing the spike protein and neutralizing antibody production. Nucleoside modifications of mRNA have been groundbreaking, shown to reduce innate immunogenicity, and result in less activation of cytokines, paving the path for mRNA vaccine development.

Although nucleoside modifications of mRNA have been shown to reduce their innate immunogenicity, in certain individuals with genetic predisposition, the immune response to mRNA may not be turned down and may drive the activation of an aberrant innate and acquired immune response. The dendritic cells or Toll-like receptor expressing cells exposed to RNA may still have the capacity to express cytokines and activation markers in certain individuals, although this may be markedly less when exposed to mRNA with nucleoside modifications than when treated with unmodified RNA. The immune system may therefore detect the mRNA in the vaccine as an antigen, resulting in activation of proinflammatory cascades and immunologic pathways that may play a role in the development of myocarditis as part of a systemic reaction in certain individuals.

Another important potential mechanism for myocarditis is molecular mimicry between the spike protein of SARS-CoV-2 and self-antigens. Antibodies against SARS-CoV-2 spike glycoproteins have been experimentally shown to cross-react with structurally similar human peptide protein sequences, including α-myosin. However, severe adverse events or autoimmune reactions have been very rare. Although COVID-19 vaccination does not appear to provoke de novo immune-mediated adverse events, it is possible that it may trigger preexisting dysregulated pathways in certain individuals with predisposition, resulting in a polyclonal B-cell expansion, immune complex formation, and inflammation.

In-Depth Evaluation of a Case of Presumed Myocarditis After the Second Dose of COVID-19 mRNA Vaccine. Muthukumar et al[5]

To explore potential mechanisms of myocardial injury in temporal association with vaccination in the studied case, written informed consent was obtained for additional in-depth analysis of viral, cytokine, and autoimmune panels and subsequent research publication of the case. Samples from the patient of interest were compared with excess, remnant blood specimens that were available in the laboratory after routine clinical testing. Samples from the case of interest (CI) were collected on days 1 to 4 after symptom onset (CIS1‐S4) and were compared with 4 groups: naive unvaccinated (NUV; n=8), unvaccinated patients hospitalized with COVID-19 (n=10), naive vaccinated (NV; n=10), and age-matched controls receiving Moderna vaccine (NM, n=2). NV and NM groups were tested ≈?2 weeks after receiving their second vaccine dose. The studies were performed as part of a biorepository protocol approved by the University of Texas Southwestern Institutional Review Board, and waiver of

Institutional Review Board consent was obtained to use the remnant blood specimens. Detailed methods are provided in the Methods in the Data Supplement.

Results of Exploratory Studies

Antibody response to viral antigens and SARS-CoV-2 nucleocapsid and spike proteins serum immunoglobulin (Ig) G antibodies against 18 different viral antigens and SARS-CoV-2 serology testing were measured using a custom developed proteome array and US Food and Drug Administration-approved standard assays, respectively, using the methods described in the Methods in the Data Supplement. These studies confirmed the absence of previous COVID-19 infection (negative reactivity for SARS-CoV-2 nucleocapsid IgG). As expected, a clear immune response to the vaccine (SARS-CoV-2 spike as a component) was observed in the case of interest 5 and 6 days after the second dose of Moderna vaccine, which corresponds with the third and fourth day after symptom onset in the case of interest (CIS3 and CIS4). Comparison of the strength of vaccine-induced immune responses in the case of interest at the measured sampling period CIS2 and CIS4 with either NV or NM did not reveal abnormally elevated SARS-CoV-2 spike IgG or SARS-CoV-2 spike IgM levels. Low IgG serology reactivity was noted in the case patient samples (CIS1-S4) for the other viral antigens, including cytomegalovirus, Epstein-Barr virus, influenza A, and respiratory syncytial virus compared with vaccinated control samples. It is interesting that, although anti-spike antibody levels were higher than the manufacturerrecommended positive threshold, the SARS spike protein antibody levels were either lower or just comparable in the case compared with NV. This may be partly explained by a difference in the timing of blood sampling after immunization among the vaccinated controls (2 weeks) versus case patient for assessing antibody response. Concurrent clinical evaluation for known infectious causes of acute myocarditis, including multiple SARS-CoV-2 nasopharyngeal polymerase chain reaction tests and Food and Drug Administration-approved multiplex respiratory viral polymerase chain reaction panels and serologies, were all negative with 2 exceptions. An IgG antibody for Mycoplasma pneumoniae was positive but IgM antibody was negative, consistent with previous exposure and not acute infection. In addition, an IgG titer of 1:320 was reported for coxsackie B virus 4, but IgM antibody titers were negative. However, convalescent serum antibody testing 3 weeks later revealed a titer of 1:160, consistent with remote and not acute or recent infection.

Genetic Testing

Given that inherited cardiomyopathy may present clinically as myocarditis, a panel test for variants in 121 genes potentially linked to cardiomyopathy was performed (Invitae, San Francisco, CA). No pathogenic variants and 1 intronic variant of unknown significance (heterozygous, ACTN2, c2367+5G>A) were identified, suggesting that the known gene variants are not the cause of myocarditis in the case patient.

Screening of Cytokine Response

Although the vaccine-induced immune response is chiefly linked to protective immunity, an exaggerated and unwarranted immune reaction could potentially heighten inflammation and augment the risk of immunopathology. The authors measured a panel of 48 cytokines and chemokines in the case patient using fluorescent bead-based Bio-Plex Pro Human Cytokine Screening Panel, per the manufacturer's instructions (Bio-Rad, CA). Cytokine levels in the case patient were NV or NM. This analysis revealed in the case patient elevated levels of 4 cytokines (IL-1ra, IL-5, IL-16, and MIG), diminished levels of 1 cytokine LIF (leukemia inhibitory factor), and 3 other cytokines (IL-10, MIF, and VEGF) with bidirectional pattern (increase or decrease) relative to the comparators, NM or NUV (Table 3). Although statistical inference is not possible because of the single case patient, and the clinical relevance of the magnitude of difference seen is not clear, some of the following changes are of potential interest. The level of IL-1ra (IL-1 receptor antagonist) in the first sample from the case

patient after symptom onset (CIS1; 1174 pg/mL) was comparable with levels in patients with active COVID-19 infection (unvaccinated patients hospitalized with COVID-19; 1183 pg/mL). Generation of IL-1ra could be a compensatory counterattacking mechanism to limit excessive inflammation. In support of this notion, it has been documented that treatment with IL-1ra rescues myocarditis-associated endstage heart failure. Around the time of symptom onset, the case patient also displayed elevated levels of other cytokines, IL-5, IL-16, and MIG (CXCL9), which play inflammatory roles in either myocarditis or related cardiac complications in humans or in experimental animal models. In contrast, relative to NM or NUV, the first sample of the case patient (CIS1) showed a decrease in the levels of cytokine LIF, which provides cellular stability and ensures survival of cardiomyocytes during stress. The other 3 cytokines, VEGF, IL-10, and MIF did not reveal a unidirectional regulatory pattern with comparators (NM and NUV); however, each spiked above the NUV reference group and has been individually implicated in immune vasculitis. Additional clinical laboratory assessment of IL-1β, IL-2, and IL-6 cytokines revealed normal levels of these cytokines.

Autoantibodies

Immunizations with adverse effects typically induce disproportionate autoantibody generation. Thus, the authors investigated whether the COVID-19 mRNA vaccine and the associated nonviral acute myocarditis seen in the patient of interest may be a consequence of an autoimmune response, using a proteome array printed with HuProtTM version 3.1 arrays (CDI Laboratories, Mayaguez, PR) comprised of ≈19,500 unique full-length human proteins. Analyses for potentially informative autoantibodies were clustered into 3 separate subpanels representing common, COVID-specific, and CIS-specific groups for both IgM and IgG classes of circulating autoantibodies. In the common subpanel, the case patient was characterized by higher levels of 2 IgM autoantibodies (CRK and UNC45B) and 6 IgG autoantibodies (IL-10, KCNK5, PARP1, VCL, AKAP5, and IFNγ) compared with the patient with active COVID-19 and NUV controls, suggesting potential specific associations with myocarditis. Autoantibodies against IL-10 and IFNγ have been detected in patients with life-threatening COVID-19, and previous reports indicate a cardioprotective effect for these cytokines in humans and rodents.15–17 IgM autoantibodies against several common antigens, including TNNC1 (troponin C1) and IL-1RN, were elevated in both the case patient and the patient with COVID-19, which is expected given the presence of cardiac injury and inflammation present in both disease scenarios.

In the CIS-specific cluster, the case patient (CIS) had a pronounced excess of 3 IgM (CCDC97, CDK6, and EPHX2) and 21 IgG (AK1, CIRBP, CKM, CTGF, CXCL16, DGKZ, DNAI1, DNAI2, GDI1, HIP1R, HSPA9, IFT122, JUNB, KIF6, PQBP1, SF3A2, SH3GL2, STAMBP, THBD, TSEN34, and XXYLT1) specific autoantibodies compared with NUV or unvaccinated patients hospitalized with COVID-19. Out of this list, CXCL16 protein has been shown to increase in acute versus chronic myocarditis and suggested to be a novel biomarker for inflammatory cardiomyopathy. Likewise, elevated levels of connective tissue growth factor (CTGF/CCN2) have been elevated in fibrotic and tissue injury in heart failure. In addition, CIRBP/CIRP (cold-inducible RNA binding protein), a known cardiac electrophysiological regulator, has been shown to govern ventricular and atrial repolarization on cellular stress. The absence of antibody levels exceeding the prespecified criteria that cross-react with cardiac myosin and first and second extracellular loops of the β-adrenergic receptor is notable given previous reports of these autoantibodies in viral myocarditis. Whether the specific autoantibodies identified in the case patient play a role in disease progression or resolution needs to be determined by assessing their dynamics over longer-term follow-up in studies with larger sample sizes.

This exploratory autoantibody analysis encompasses changes in autoantibodies against both intracellular and extracellular proteins/targets. However, it should be noted that autoantibodies against extracellular proteins/targets are more plausibly linked to disease pathology, in part because of their easy accessibility for binding. Also, autoantibodies to extracellular proteins are frequently reported to

mimic genetic diseases for the same target protein or pathway with corresponding gain or loss of function. When autoantibodies against intracellular proteins are linked to a pathogenesis, it is often indirect, because the clonal expansion and the related process of recognition of antigens through the B-cell receptor occur in extracellular space with the support of extracellular proteins. Nevertheless, the autoimmune reactivity seen in the patient with respect to these self-antigens need not necessarily be pathogenic and could also be a part of the normal healing process of the inflamed myocardium. According to the authors future studies that specifically characterize the function and origin of these autoantibodies will be essential to understand their potential role in vaccine-associated myocarditis. It is ideal for such future studies to include a baseline sample from the same patient and also age-, sex-, and vaccine type– matched controls.

Immune Cell Subsets

Last, the authors assessed alterations in immune cell subsets in the patient of interest by enumerating T, B, and natural killer (NK) lymphocytes and investigating immunophenotypic aberrancy. This was performed using Becton Dickinson's Multitest 6-color lymphocyte subsetting reagent with Becton Dickinson Trucount and additional immunophenotyping (CD3, CD4, CD5, CD7, CD8, CD10, CD11b, CD13, CD14, CD16, CD19, CD20, CD22, CD25, CD31, CD34, CD38, CD45, CD45RA, CD62L, CD64, CD123, CD127, CD197, HLA-DR, TCRαβ, TCRγδ) by flow cytometry on a Becton Dickinson FACSCanto. A naive vaccinated subject had a frequency of CD3negCD16posCD56pos NK cells within the normal reference range. In contrast, the case patient had a nearly 2-fold increase in the frequency of CD3negCD16posCD56pos NK cells from the upper limit of the reference interval. This may indicate activation of a distinct subset of NK cells (CD3negCD16posCD56pos) that have been documented to be the most abundant (10% peripheral blood lymphocytes) and efficient cytotoxic effectors that kill their target cells by secreting cytoplasmic proteins. Although the changes in the absolute NK cell number are intriguing at present, the surge may have either contributed to the pathology or the disease resolution process. Low absolute CD3negCD16posCD56pos NK cell counts have been shown to correlate with orbital myositis, and the levels of these cells normalized with improvement in the disease activity. In addition, the patient showed a marginal increase in percentage and absolute count of NK lymphocytes by about 17% relative to the NM sample. This finding of high NK cell fraction in the case patient with resolved myocarditis contrasts with the recent multicenter IPAC study (Investigation of Pregnancy-Associated Cardiomyopathy), which showed reduced levels of NK cells in peripartum cardiomyopathy, which normalized over time postpartum. Although the significance of this finding in the current patient with nonviral myocarditis is unclear, NK cells are known to play a cardioprotective role in viral myocarditis and autoimmune myocarditis by limiting viral replication and through modulation and inhibition of cardiodestructive activity by eosinophils, respectively. No other disease-driving immunophenotypic aberrancies were noted in the patient.

In conclusion the authors noted that although multiple cytokines and autoantibodies with plausible links to myocarditis or cardiac pathogenesis appeared to differ in the case patient compared with controls, a specific signature was not identified. There was an increase in numbers of a specific subset of NK cells and increased expression of several autoantibodies compared with controls. T helper 17 cells–related IL-17–enriched immune signature has been implicated in the development of myocarditis and its associated transition of fibrosis to heart failure. It is interesting that such upregulation of IL-17 levels was not observed in their patient. The lack of evidence for upregulation of this cytokine, combined with the increased NK cell numbers observed in the case patient, could suggest a distinct vaccine-associated immunophenotype with a high likelihood for rapid recovery. However, it is not clear whether the observed differences reflect a potential (causal) pathological immune response or rather appropriate healing responses to myocardial inflammation. These differences may also be chance findings, given the exploratory nature of our investigations and large numbers of tests performed in few patients.

Shedding the Light on Post-Vaccine Myocarditis and Pericarditis in COVID-19 and Non-COVID-19 Vaccine Recipients. Hajjo et al[6]

In an effort to understand post-vaccine myocarditis and pericarditis side effects that have been linked to mRNA vaccines lately, according to a statement from the CDC, the authors applied an informatics workflow to mine the VAERS database for post-vaccine myocarditis, followed by a systems biology analysis that relied on mining specialized chemogenomics databases for genes, proteins and chemicals that are linked to myocarditis. There were three COVID-19 vaccines included in VAERS database (i.e., vaccines approved by the U.S. FDA) including Pfizer/BioNTech, Moderna and Janssen. The different vaccine preparations enter dendritic cells (DCs) at site of injection or within lymph nodes, resulting in production of S protein.

The authors results indicated that post-COVID-19 vaccine myocarditis and pericarditis adverse events were more prevalent in young males 18-29 years old. Their data also showed that the number of myocarditis and pericarditis adverse events was higher for Pfizer/BioNTech vaccine followed by Moderna's and then Janssen's. They also found evidence in the biomedical literature documenting cardiac side effects after receiving smallpox and anthrax vaccines.

The author's systems biology results highlighted central signaling roles for IFN-gamma and TNF-alpha in both myocarditis and viral disease maps. Finally, combing the knowledge from searching both VAERS and MetaCoreTM enabled the exploration of age and sex differences of post-vaccine myocarditis. They suggest that they found evidence in the biomedical literature indicating gender and age differences in many immunological factors. The sex differences in the levels of proinflammatory cytokines, including TNF-alpha and IFN-gamma, increase at puberty and then wane later in life suggesting hormonal effects. This goes in concert with our findings about the prevalence of post-vaccine myocarditis in the age group in adolescents and young adults. Furthermore, Aomatsu et al. reported on the gender differences in in TNF-alpha production in human neutrophils stimulated by lipopolysaccharide (LPS) or IFN-gamma plus LPS. It was suggested that the lower sensitivity of female neutrophils to LPS and IFN-gamma, was due to the anti-inflammatory effects of estradiol on vascular endothelial cells and monocytes/macrophages. However, for immune response factors the sex difference remains constant from birth to old age (for example higher numbers of CD4+ T cells and higher rations of CD4/CD8 T have been reported in females at all age groups).

To fathom post-vaccine myocarditis, it is important to understand that post-vaccine side effects (e.g., injection site pain, fever, chills, swelling fatigue, headache, muscle pain, joints pain, and others) are caused by the secondary enhancement of the inflammatory response which often results from short-term changes to innate cells such as macrophages through 'trained immunity', and/or from the activation of memory T cells and B cells generated from the initial injection. There is also evidence that systemic vaccine side effects can be augmented with the second vaccine doses due to an amplified release of type 1 interferon which plays a central role in amplifying T-cell memory and B-cell differentiation and survival. This implies that post-vaccine inflammation after receiving booster doses, can further promote the generation and perpetuation of long-term immunological memory.

The authors mentioned that they found evidence that IFN-gamma is also key component of the host defense to viral infection that is also elicited in response to viral vaccines. MRNA and viral vector vaccines trigger spike protein synthesis inside human cells which can then be presented on cell surfaces to cytotoxic T cells by the major histocompatibility complex (MHC) MHC class I and MHC class II molecules, leading to virus-specific recognition and killing of infected or vaccinated cells. Interferons alpha, beta and gamma are required to induce MHC class I expression, while MHC class II transactivator factor (CIITA) is the master regulator of MHC class II expression and it is efficiently induced by IFN-gamma. However, most cell types do not express basal CIITA, and its expression is induced by IFN-gamma. In myocarditis, T lymphocytes (T cells), have been reported to home the

myocardium and to acutely reduce left ventricular (LV) function and this has been associated with increased levels of circulating cytokines, such as TNF-α which led to the prioritization of proinflammatory cytokines as markers of myocarditis and heart failure. It is also known that antigen presentation by endothelial cells may initiate rapid and localized 'memory' immune responses in peripheral tissues. Antigens displayed on major histocompatibility complex (MHC) molecules on the surface of endothelial cells can then be recognized by T-cell receptors on circulating effector memory T cells triggering both trans-endothelial migration and activation.

Type I interferons are key drivers for the antiviral state in non-immune cells and they orchestrate antiviral immune responses through: (i) the inhibition of viral replication in infected cells during the innate stage of the immune response; (ii) the activation and enhancement of antigen presentation in the "early induced" immune response, and (iii) the generation of the adaptive immune response through direct and indirect actions on T and B cells that constitute the memory response. TH1 response, which triggers IFN-gamma expression that in turn activates CTLs and NK cells. From a homeostatic point of view, prolonged effector function of these cells may lead to excessive cytotoxicity and other detrimental effects resulting in host tissue damage. Additional support for the identified role of IFN-gamma in myocarditis came from a recent Nature publication by Arunachalam et al. confirming that Pfizer/BioNTech mRNA vaccine induced a heightened innate immune response after secondary immunization relative to primary immunization implicating the overexpression of IFN-gamma in driving innate and antiviral responses after the booster.

It should be noted that this study has a few limitations. First, while VAERS is a valuable source for monitoring vaccine adverse effects, reports from VAERS alone may not be conclusive to establish a causal relationship between an adverse event and a vaccine use. Due to the voluntary nature of VAERS reports, the information provided about an adverse effect can be imperfect, imprecise, coincidental, or unconfirmed, limiting the scientific use of such reports.

PRAC Rapporteurs assessment comment:

The MAH has presented literature where several potential pathophysiological mechanisms have been suggested.

Bozkurt et al. proposes three potential mechanisms for mRNA vaccines to cause myocarditis or pericarditis.

The first is that some individuals have a genetic predisposition that makes them react differently to mRNA component in the mRNA vaccine. Nucleoside modifications of mRNA have been shown to reduce their innate immunogenicity, in these individuals, the immune response to mRNA may not be turned down and may drive the activation of an aberrant innate and acquired immune response. The authors proposed that the immune system may detect the mRNA in the vaccine as an antigen, resulting in activation of proinflammatory cascades and immunologic pathways that may play a role in the development of myocarditis as part of a systemic reaction.

The second possible mechanism for myocarditis is molecular mimicry of SARS-CoV-2 and self-antigens (e.g. alpha myosin).

The third hypothesis is that vaccination may trigger preexisting dysregulated pathways in predisposed individuals resulting in e.g. inflammation.

Muthukumar et al. presents a case of a 52-year-old male, who develops myocarditis 3 days after his second dose of Spikevax. In addition, the authors perform a wide range of exploratory tests to explore potential mechanisms of myocardial injury in temporal association with vaccination. The Authors compare the patient with excess, remnant blood specimens that were available in the laboratory after routine clinical testing. The comparators include "naive unvaccinated" (n=8),

"unvaccinated patients hospitalized with COVID-19" (n=10), "naive vaccinated" (NV; n=10), and "age-matched controls receiving Moderna vaccine" (n=2). The exploratory tests included genetic testing, cytokine response, autoantibodies and immune cells subsets. No genetic predisposition of myocarditis was identified. Tests for cytokine response and autoantibodies showed a difference in multiple cytokines and autoantibodies with plausible links to myocarditis or cardiac pathogenesis compared to controls. The results of the test for immune cells subsets showed that CD3negCD16posCD56pos posed a 2-fold increase compared to a native vaccinated subject. The authors conclude that no specific signature was identified for the case of myocarditis post vaccination. It is also highlighted that the it is not clear whether the observed differences reflect a potential tendency of myocarditis after vaccination or could be a part of the normal healing process in response to myocardial inflammation. Although interesting, the study is based on a single case and a range of tests from the same person. The PRAC rapporteur agrees with the observation that, the observed differences may be chance findings.

Hajjo et al. performed and study using an informatics approach to study post-vaccine adverse events on the systems biology level. They performed and analysis of VAERS using systems biology methods and used MetaCore to identify a potential pathway for post-vaccine induced myocarditis. The systems biology results suggested a central role of interferon-gamma (INF-gamma) in the biological processes leading to cardiac adverse events. The authors found evidence that IFN-gamma is also key component of the host defense to viral infection that is also elicited in response to viral vaccines.

In conclusion, the mechanism explaining how Spikevax causes myocarditis or pericarditis is still to be elucidated. However, several mechanisms have been suggested in the literature.

- **Data on the characteristics, severity, duration and outcome of myocarditis and pericarditis after vaccination with COVID-19 mRNA vaccine Spikevax.**

Although most cases of vaccine-associated myocarditis have been described as mild and selflimiting, additional data are needed to characterize the natural history and long-term outcomes of these events. In a study by Klein et al (2021) using the VSD, 34 confirmed cases of myocarditis/pericarditis had elevated troponin levels, and many had electrocardiographic changes, cardiac MRI changes, or both. However, 2 individuals (6%) required intensive care unit care, and consistent with previously described cases, all patients survived to hospital discharge.

In a hospital-based study describing 20 cases of myocarditis and 37 cases of pericarditis without myocarditis (Diaz 2021), all were discharged after a median of two days, and no readmission or death events occurred. For two patients who received a second vaccination after onset of myocarditis, symptoms did not worsen.

In the most recent MSSR, cases of myocarditis and pericarditis continue to primarily occur in young adult males, between 18 to 29 years of age, shortly after the second dose of the vaccine and within the first 6 days after vaccination. Most events were considered mild to moderate in severity and were reported as either resolved or resolving.

PRAC Rapporteurs assessment comment:

The MAH references the Vaccine Safety Datalink study (Klein et al, 2021)[2] in which the medical record was reviewed for 34 confirmed myocarditis/ pericarditis cases following vaccination among

[2] Klein NP, Lewis N, Goddard K, et al. Surveillance for Adverse Events After COVID-19 mRNA Vaccination. *JAMA.* 2021;326(14):1390–1399. doi:10.1001/jama.2021.15072

individuals aged 12-39 years. 2 individuals (6%) required intensive care unit care, and all patients survived to hospital discharge. The MAH concludes that most events were considered mild to moderate in severity and were reported as either resolved or resolving. However, The PRAC rapporteur wants to highlight that serious cases are also reported. In the 10th MSSR a fatal case in a 24-y/o male was reported:

This case, is highlighted here: The case concerns a 24-year old male, with no reported medical history or concomitant medication, who developed acute myocarditis (biopsy confirmed) and were found dead 3 days after the 2nd vaccination. Acute myocarditis was considered cause of death, and although there is no information on concurrent medical comorbidities, a causal association with the vaccine cannot be excluded. The case is Level 1 according to the Brighton and "confirmed" according to the CDC case definition, and causality assessed as WHO Possible by the MAH

The MAH also references a hospital-based study in the US by Diaz et al (2021)[3] investigating time to onset and time to discharge for myocarditis/ pericarditis following vaccination. Based on 20 cases of myocarditis (11 cases following Spikevax), the median time-to-onset was 3.5 days (IQR 3.0-10.9). The median time to discharge was 2 days (IQR 2-3). For pericarditis, the median time-to-onset was 20 days (IQR 6.0 – 41.0) and the median time to discharge was 1 day (IQR 1-2). No deaths were reported for myocarditis and pericarditis.

In addition, studies mentioned in ITEM 1 presented relevant comparative data to further characterize myocarditis following vaccination.

In the Nordic cohort study, data on time to admission and time to discharge for myocarditis were included in supplementary analyses.

The median time to admission following vaccine-associated myocarditis was 5 days (p25% 3 days; p75% 7 days) in Denmark, 11 days in Finland (p25% 4 days; p75% 15 days), 5 days in Norway (p25% 3 days; p75% 19 days) and 7 days in Sweden (p25% 3 days; p75% 18 days).

Data on time to discharge and death after myocarditis was included in supplementary analyses. For male and females combined (all ages), 49.5% (95% CI 26.0 – 73.3) were discharged on day 4 or later following the second dose of Spikevax, while 53.7% (95% CI 39.4 – 67.4) were discharged on day 4 or later in the unvaccinated. For Comirnaty, a similar pattern was observed. Following the second dose of Spikevax, 4.5% of patients died within 28 days (95% CI 0.0 – 13.2) versus 1.2% (95% CI 0.5 – 2.7) among unvaccinated.

In the French case-control study, data on time to admission was presented. Among the exposed subjects, the median time to admission for myocarditis was 9.5 and 4 days following the first and second dose of Spikevax, respectively. For pericarditis, the median time to admission was 9.5 and 10 days following the first and second dose, respectively.

Moreover, data was presented for length of hospital stay for myocarditis (based on 919 cases) and pericarditis (based on 917 cases) following vaccination with any mRNA vaccine (no stratification) compared with the unexposed. For myocarditis, the median length of stay was 4 days (IQR 2; 5) for unexposed, 4 days (IQR 2; 5) for vaccinated with onset of myocarditis within the risk window 0-7 days and 3 days (IQR 2; 5) for vaccinated with onset of myocarditis within the risk window 8-21 days. The time to discharge was longer than 5 days in 22.6% of patients amongst the unvaccinated, and 12.3% and 16.8% amongst the vaccinated 1-7 days and 8-21 days post-vaccination, respectively. Overall only 1 death was observed (among the unexposed). For pericarditis, length of

[3] Diaz GA, Parsons GT, Gering SK, Meier AR, Hutchinson IV, Robicsek A. Myocarditis and Pericarditis After Vaccination for COVID-19. *JAMA.* 2021;326(12):1210–1212. doi:10.1001/jama.2021.13443

stay was considerably shorter, but a similar pattern between vaccinated and unvaccinated was observed.

Overall, considering time to discharge as a measure of severity, these data indicate that the clinical picture of myo- and pericarditis following vaccination is similar to that of these events in the unvaccinated. However, as pointed out by the MAH, although most cases of vaccine-associated myocarditis have been described as mild and self-limiting, additional data are needed to characterize the natural history and long-term outcomes of these events. Of note, in the ongoing procedure EMEA/H/C/005791/II/0028, the MAH proposes an additional PASS to address this specific issue. The proposed submission of the study protocol is 28 February 2022. Similarly, time to admission seem can be seen as a measure of time to onset, and confirms previous observations that cases primarily occur within 14 days following vaccination as stated in the SmPC of Spikevax

In conclusion, the current PI wording regarding severity or characteristics of the events and time to onset of myocarditis or pericarditis seem to be consistent with observations made in the above mentioned epidemiological studies.

3.1.3. ITEM 3 - US PASS

Considering that the risks of myocarditis and pericarditis are outcomes of interest in the two ongoing PASSs in the EU/EEA (IT, ES, NL, UK, NO, DK) and in the US, the MAH should investigate if the planned analyses, including O/E and SCCS/SCRI, of myocarditis/pericarditis could be expedited and indicate when these can be submitted. In adolescents, narrow age strata should be applied, as feasible (currently EU PASS only).

Sponsor Response

Preliminary analyses of myocarditis and pericarditis were included within the most recent interim report for the US PASS (mRNA-1273-P903) submitted on 31 October 2021. Additional descriptive analyses are ongoing and will be submitted along with SCRI analyses upon approval of the applicable protocol appendix by the US FDA (also submitted 31 October 2021) detailing the risk windows and additional considerations to be applied in execution. The MAH has asked that analyses of these outcomes are expedited for the European PASS (mRNA-1273-P904), and participating data partners from the VAC4EU network are working to confirm the feasibility of this request. At present, it is anticipated that the timeline for data extraction (31 December 2021) cannot be modified, however analyses for myocarditis and pericarditis will be prioritized as the first to be executed. Results will be shared upon their availability, and the study team will work to prepare these in advance of the next interim report (31 March 2022).

PRAC Rapporteurs assessment comment:

The MAH's effort to expedite the myocarditis/ pericarditis analyses in the ongoing PASSs (US and EU) are acknowledged.

PRAC Rapporteurs overall assessment comment:

<u>Risk estimation</u>

An increased risk of myo- and pericarditis following Spikevax was observed across different studies. While other sources such as an O/E analysis from the company safety database confirm the association, the assessment focused particularly on the following large comparative studies: interim

report of the Moderna US PASS (2,438 myocarditis and 5951 pericarditis events), the Nordic cohort study (1092 myocarditis and 1154 pericarditis events) and the French National Health Data System study (919 myocarditis and 917 pericarditis events).

It is important to highlight that these studies, based on large populations and different study designs with unique strengths and limitations, led to similar results: an increased risk of myocarditis particularly in men <30 years. For pericarditis, a similar pattern but a less strong association was observed. While some variation in the magnitude of the association was observed, the association is also strengthened by the fact that 3 independent large studies (Vaccine Safety Datalink study (Klein et al, 2021), Nordic cohort study and French case-control study) observed higher estimates for Spikevax compared with Comirnaty. Overall, the current PI wording of myocarditis and pericarditis is considered to sufficiently cover the observations made in the beforementioned studies.

Very limited data on myocarditis/pericarditis following vaccination with Spikevax are available for 12-17-year-olds. In the Nordic cohort study, estimates for males 12-15 years were very imprecise and based on <5 cases. 35,524 (males and females combined) in this age group received two doses. For females in this age group, no estimates were available. As no details were available regarding the proportion of <18-year-olds in the stratum 16-24 years, no definite conclusions can be drawn with regards to the risk estimation in <18-year-olds. Based on the recent extension of indication of Spikevax to include the 12-17-year-olds approved late July 2021, exposure in 16-17-year-olds is still limited. In comparison Comirnaty has been approved in the 16-17 year old from first authorization. The French case-control study did include persons vaccinated down to 12 years; however, data was too limited to allow for a detailed estimation in 12-17-year-olds at the time of data lock (August 31). As a result, stratification narrower than 12-29 years was not performed. In conclusion, the data currently available for the paediatric population are too limited to provide a comprehensive estimation of the risk for myo- and pericarditis following vaccination with Spikevax.

Further characterization

The MAH provided an estimation of frequency based on reporting rates from VAERS and estimated the frequency to the category "Very rare". Additional data from epidemiological studies was not taking into consideration by the MAH for the purpose of estimating frequency. Best estimates of frequency from the Nordic cohort study and French case-control study were provided by the PRAC rapporteur. Data from these studies on myocarditis suggest that the frequency for males 16-24 from the Nordic study and males 12-29 from the French study would fall into the frequency category "Rare" and for the remaining stratified groups it would be "Very rare". For pericarditis, the frequency would be "very rare" for all stratum. As mentioned above, information about the risk in the population < 18 is limited and as a consequence hereof, the PRAC rapporteurs considers the data too sparse to conclude on the risk in this population which includes a frequency estimation. In conclusion, data have been presented that can be used to estimate a frequency of myocarditis or pericarditis with Spikevax. Therefore, the PRAC rapporteur considers that the current frequency "not known" should be updated.

The Nordic cohort study assessed time to admission for vaccine-associated myocarditis. The median time to admission was between 5 and 11 days in the different countries, which is in line with the information reflected in the current SmPC section 4.4. *("[…] primarily occurred within 14 days following vaccination […]"*). A similar pattern was observed in the French case-control study. Among the exposed subjects, the median time to admission for myocarditis was 9.5 and 4 days following the first and second dose of Spikevax, respectively.

Data on time to discharge and death from the Nordic cohort and the French case-control studies showed a similar picture for vaccine-associated myocarditis compared with myocarditis occurring in

the unvaccinated. These data confirmed what is reflected in the SmPC ("*Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general*"). However, as pointed out by the MAH, although most cases of vaccine-associated myocarditis have been described as mild and self-limiting, additional data are needed to characterize the natural history and long-term outcomes of these events. Of note, in the ongoing procedure EMEA/H/C/005791/II/0028, the MAH proposes an additional PASS to address this specific issue. The proposed submission of the study protocol is 28 February 2022.

In conclusion, the presented data confirms previous observations about the risk of myocarditis and pericarditis. The current SmPC wording is there for largely in line with the observed characteristic of the ADRs and only few updates is considered warranted. The PRAC rapporteur considers that the frequency should be updated to reflect the new information.

3.2. Rapporteur's proposed recommendation

Overall, the new data confirmed previous observations of an increased risk of myocarditis following vaccination with Spikevax. The risk was generally higher after the second dose and particulary in younger males. The risk of pericarditis showed the same trends. However, the new data made an estimation of frequency feasible.

Therefore the PRAC rapporteur proposes to update the product information of Spikevax regarding the risk of myocarditis and pericarditis with the following:

Summary of product information:

Section 4.4:

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 **(see section 4.8)**. 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.

The risk of myocarditis after a third dose (0.5 mL, 100 micrograms) or booster dose (0.25 mL, 50 micrograms) of Spikevax has not yet been characterised.

Based on very limited data in the paediatric population, the risks of myocarditis and pericarditis have not yet been characterised.

Section 4.8:

SOC cardiac disorders:

Frequency: ~~not known~~ **Very rare**: Myocarditis*****

Frequency: ~~not known~~ **Very rare**: Pericarditis

*** The frequency is estimated from a Nordic cohort study of 23.1 million individuals from DK, FI, NO and SE. After 2 doses Spikevax there were estimated 8.49 (95% CI 6.76 – 10.22) and 2.13 (95% CI 1.23 – 3.04) excess cases of myocarditis per 100.000 vaccinated in 28 days in men and women over the age of 12, respectively. The increased risk of myocarditis and pericardits after vaccination with Spikvax is highest in younger men (see section 4.4). For Pericarditis there were estimated 7.04 (95% CI 1.39-12.7) excess cases per 100.000 vaccinated in 28 days in younger males after 2 doses of Spikevax. For myocarditis, after 2 doses of Spikevax there were estimated to 18.8 (95% CI 9.56 – 28.04) excess cases per 100.000 vaccinated in 28 days. The frequency of myocarditis in younger men is considered to be within the freqeuncy category "Rare".**

Package leaflet:

Section 4 - Possible side effects

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

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

Comments were received from Member State (MS)1, MS2, MS3, MS4, MS5 and MS6. Full endorsement was received from MS7.

3.3.1. MS2

We generally support the rapporteur's assessment report. However, we have an additional comment regarding the harmonization of the data between Comirnaty and Spikevax, particularly on the denominator of the incidence which differs for the two vaccines.

PRAC Rapporteurs assessment comment:
The comment is highly appreciated. The PRAC rapporteur agrees that harmonization of the data between the two mRNA vaccines would be ideal. This would also enable to highlight the difference in the magnitude of the risk between Spikevax and Comirnaty. However, in the studies the proposed update for Comirnaty is based on, no data for Spikevax was available. In the updated recommendation, we propose to reflect the increased risk in younger men based on two large European studies (EPI-PHARE and Nordic cohort study), which include data for both Comirnaty and Spikevax. For younger men, considering the estimates of "excess number of cases per 100,000 doses" from these studies, this would result in the frequency "Rare" for Spikevax and "Very Rare" for Comirnaty.

3.3.2. MS5

The PRAC Rapporteur's AR is generally endorsed. However, we have some additional comments.

- With regards to the wording in 4.8: As multiple studies show an increased risk of myocarditis/pericarditis, the reference to the Nordic cohort study may be questioned, a more general reference could be considered.

- The information about risk should be uniformly presented in the product information for both mRNA vaccines for easy interpretation and risk comparison.

- The last sentence included in section 4.4 is in particular endorsed, and should also be included for Comirnaty:

Based on very limited data in the paediatric population, the risks of myocarditis and pericarditis have not yet been characterised.

PRAC Rapporteurs assessment comment:

The comment is highly appreciated. The PRAC rapporteur agrees that a more general reference is favorable. We would like highlight that all the evidence was considered for the proposed recommendation. Across multiple sources, the frequency of myocarditis in the general population is very rare and a higher frequency is seen in younger men. In the updated recommendation we propose to contextualize the frequency "very rare" with data from two studies (EPI-PHARE and Nordic cohort study, without referencing these specifically) highlighting an increased risk particularly in younger men (frequency "Rare). The primary reasons for focusing on data from these studies are:

1. The estimates on number of excess cases in the vaccinated population is helpful from a public health perspective
2. Data are available for both Spikevax and Comirnaty, which would facilitate harmonization/ comparison between the two (as highlighted in MS5's comment and MS2 further above)

Regarding the last sentence in 4.4, the particular endorsement is appreciated. It should be emphasized that this is to highlight that for Spikevax there is currently not enough data available to inform about the risk. However, we do not agree with MS5 in that this should be included for Comirnaty, as there is considerably more evidence available in <18-year-olds.

3.3.3. MS6

In large, we agree with the assessment by the PRAC rapporteur and the need to update the PI. However, we have some additional comments, including a proposal for a more detailed update of the PI, given that there currently is a substantially larger data set available than at the time of deciding the current wording (See below).

CLINICAL SAFETY

Evaluation of myocarditis and pericarditis cases:

- When presenting some of the data, and particularly in summaries, myocarditis and pericarditis are lumped together. This is unfortunate, as these are not the same diseases, and e.g. the clear sex difference in both natural and vaccine induced occurrence of myocarditis, is not at all obvious for pericarditis. Thus, we find it important to analyse these entities separately.
- We note that for myocarditis only BC level 1 cases are primarily reviewed. However, for future reviews, we find it important that also BC level 2 cases are closely considered in the analysis, as cases assessed as BC level 2 add valuable information regarding myocarditis risk after vaccination.

PRAC Rapporteurs assessment comment:

It is agreed that myocarditis and pericarditis preferably should be analyzed separately. Regarding the comment on case definitions; since this signal assessment for Spikevax has focused on new data regarding the frequency of myocarditis and pericarditis, case reviews have not played a part in this signal assessment. It is however agreed that both cases of myocarditis with BC level 1 and 2 provide valuable information, and should be considered in qualitative analyses.

Regarding subsequent outcomes for those developing vaccine induced myocarditis /pericarditis:

We acknowledge that there is a continued lack of knowledge regarding potential underlying mechanisms as well as of long-term outcomes of both vaccine induced diseases. Continued work is important.

We note in the conclusion from e.g. the French study, stating: *the study confirms the positive clinical prognosis for cases of myocarditis and pericarditis arising after vaccination*.

We find it too early to draw such conclusions, particularly considering the so far short follow up time analysed. The sentence in the current SmPC : *'Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.* is not optimal, given the substantial uncertainties regarding long-term consequences, as well as the fact that there are some serious cases also observed in the short term. This is a very important issue for further follow up.

PRAC Rapporteurs assessment comment:

It is agreed that there are still uncertainties regarding the long-term consequences of vaccine induced myocarditis, and this is a topic with a continuous focus of attention in the post marketing surveillance. In particular, in the ongoing procedure EMEA/H/C/005791/II/0028, a category 3 PASS is proposed as an additional pharmacovigilance activity to further characterize vaccine-associated myocarditis.Considering the time-to-discharge as an indicator of severity, based on the data from the Nordic cohort study and the EPI-PHARE study, there does not seem to be a difference in severity between vaccine-induced and naturally occurring myocarditis. Therefore, at present, and to our knowledge, there are no data indicating that the course of myocarditis/pericarditis following vaccination should be more detrimental/ have worse long-term outcome than e.g. viral induced myocarditis/pericarditis. However, if new information arises, this section in 4.4 should be updated accordingly.

SUMMARY OF PRODUCT CHARACTERISTICS, PACKAGE LEAFLET AND LABELLING

Section 4.4:

We note that only minor changes are proposed for the current wording, which is based on the review of a limited number of spontaneously reported cases, which were available by the end of June 2021. However, at present, the available data have increased substantially since then. For instance, it can clearly be concluded that there is an increased risk of myocarditis and pericarditis following vaccination with Comirnaty. The present text is very vague by stating 'cases have been observed', which we do not find adequate anymore. A revision should be made (see below).

Further, we suggest revising the wording related to time to onset with some more detail. The reason is that, although the current wording 'within 14 days' is not incorrect, there is a notable number of cases (both among the spontaneously reported, as well as in e.g. the Nordic data), occurring within just a few days. Further, we have been informed by HCPs, that they misunderstand the current statement; interpreting it as there is little risk after the first 14 days. We therefore propose to revise the wording on TTO. See below (proposed addition underlined; wording to be removed – strikethrough):

Section 4.4 Warnings and Precautions

Myocarditis and pericarditis

There is an increased risk for ~~Very rare cases of~~ myocarditis and pericarditis ~~have been observed~~ following vaccination with Comirnaty. ~~These~~ These conditions ~~cases~~ can develop within just a few days after vaccination and have primarily occurred within 14 days ~~following vaccination~~. They have more often been observed after the second vaccination, and more often in younger ~~men~~ **males**. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

Regarding the proposed addition to section 4.8

We agree with the detailed description of the Nordic data, including presenting excess risk. It is noted that the frequencies are based on excess risk. This is not the general way of estimating frequency, which rather is based on the absolute numbers observed / number of exposed. Using excess risk will lead to an underestimation of the frequency. If clearly stated, the proposal may be accepted.

Some small clarifications of the wording are suggested (addition in red, removal in strikethrough):

The frequency is estimated from a Nordic cohort study of 23.1 million individuals from DK, FI, NO and SE. After 2 doses of Spikevax ~~there were estimated~~ 8.49 (95% CI 6.76 – 10.22) and 2.13 (95% CI 1.23 – 3.04) excess cases of myocarditis per 100.000 vaccinated ~~in 28 days in~~men and women over the age of 12, respectively, and with a 28 days follow up time, were estimated. The increased risk of myocarditis and pericardits after vaccination with Spikevax is highest in younger men (see section 4.4). For p~~P~~ericarditis, in younger males given 2 doses ~~there were estimated~~ 7.04 (95% CI 1.39-12.7) excess cases per 100.000 vaccinated are estimated within a 28 days follow up period ~~in younger males after 2 doses of Spikevax~~. For myocarditis in younger males~~, after~~given 2 doses of Spikevax ~~there were estimated to~~ 18.8 (95% CI 9.56 – 28.04) excess cases per 100.000 vaccinated were estiamted within 28 days follow up period. The frequency of myocarditis in younger men is considered to be within the fregeuncy category "Rare".

PRAC Rapporteurs assessment comment: The arguments regarding section 4.4 are acknowledged, and it is agreed that the wording can be updated and more precisely formulated, as there is now more knowledge regarding the disease course. The comments have been taken into consideration in the updated proposal. The support to include the Nordic data in the frequency calculation is noted and appreciated. The suggested adjustments of the wording in 4.8 are appreciated, however a different approach has been taken, to shorten the wording and also to include the data from the French study, in the updated proposal, see section 3.4

3.3.4. MS4

The PRAC Rapporteur's AR is generally endorsed. However, we have some additional comments.

- We do not agree to include numbers from the unpublished Nordic study, as this gives an incomplete picture and is prone to updates. Should the PRAC decide to include incidences this should be based on all available data (i.e. EU and non-EU studies)
- The last sentence included in section 4.4 ("*Based on very limited data … not yet been characterized*") is not endorsed, and should be omitted. If included this could create a precedence for many products for which risks have not yet been characterized.

PRAC Rapporteurs assessment comment:

The endorsement by the PRAC rap, including the two additional comments, is noted. There are considerably less studies on the incidence of myocarditis or pericarditis from Spikevax compared to the other mRNA vaccine, Comirnaty. The Nordic and the French studies contribute with a large amount of data, also when taking all presented data into consideration. Please see also comment below.

Regarding the last sentence in 4.4., while we agree that this may not be applicable for Comirnaty, given the higher exposure, for Spikevax, only very few cases were observed which precludes a characterization of the risk at this point in time. The PRAC rapporteur acknowledges the concern that the proposed last sentence in section 4.4 could create a precedence for this kind of updates. The rapporteur also acknowledges that data on myocarditis/pericarditis in the pediatric population will probably change and that this update would need amendments in the future. However, the rapporteur considers this information to be important from a public health perspective, especially considering the assessment of the extension of indication to children 5-11 years starting soon and that countries have started vaccinating <12yo with the other mRNA vaccine.

3.3.5. MS1

Please find below some comments for both Signal pARs regarding mRNA COVID-19 vaccines and myo/pericarditis signal:

- We concur with MS4 regarding not to include data from Nordic registry. An overall estimate or an interval estimated with all available data would be fine for us.
- Regarding wording for 4.4, we would support Rapporteur's proposal. There are many uncertainties regarding children administration and we consider it is important this should be reflected in the SmPC to be known for other stakeholders.

PRAC Rapporteurs assessment comment:

The comment on the Nordic data is noted – please see MS4 comment or comment below for further comments. The support for the wording in 4.4 regarding available data in the paediatric population is appreciated.

PRAC Rapporteurs assessment comment:

A general comment raised by some member states is that the frequency should not be based solely on the Nordic cohort study or that the data should not be explicitly mentioned in the PI. All available data presented by the MAH was considered by the PRAC rapporteur when estimating the frequency. The PRAC rapporteur chose to reference to the Nordic study as this study is easily comparable to Comirnaty and clearly showed the increased risk in younger men when estimating frequency. The same is true for the FR case-control study. When considering all the available data in studies presented by the MAH on myocarditis, the Nordic study, the French study, Klein et al. and the US PASS study were the epidemiological studies presented. See overview of data below:

Study	Sex	Age	Excess cases / doses	Estimation of frequency	Potential PI frequency
Nordic Cohort Study*	Men	16 - 24	18.8 /100.000	~ 1.88 cases/ 10.000	Rare
		12+	5,38 / 100.000	~ 0.538 cases/ 10.000	Very rare
		25 - 39	8.49 / 100.000	~ 0.849 cases/ 10.000	Very rare
	Women	16 - 24	N/A		
		12+	0.68 / 100.000	~ 0.068 cases/ 10.000	Very rare
		25 - 39	10.8 /100.000	~ 0.108 cases/ 10.000	Very rare
French case-control study**	Male	12-29	131.6/1.000.000	~ 1.32 cases/ 10.000	Rare
		30-50	26.5/1.000.000	~ 0.265 cases/ 10.000	Very rare
	Women	12-29	37.3/1.000.000	~ 0.375 cases/ 10.000	Very rare
		30-50	N/a	N/a	
US PASS study***	Men	18-29	N/A	~ 0.632 cases/ 10.000	Very rare
	Women	18-29	N/A	~ 0.13 cases/ 10.000	Very rare
Klein et al.****	All	18 - 39	2.1/100.000	~ 0.21 cases/ 10.000	Very rare

** Excess cases per 28 days*
*** Excess cases per 7 days*
**** preliminary data*
***** in 7 days, no gender stratification available*

The MAH also provided the reporting rates from their safety database and from VAERS. An overview of those is shown below. It should be noted that reporting rates is a snapshot of reporting and is prone to changes over time.

Study	Sex	Age	Reporting rate (cases/ doses)	Estimation of frequency	Potential PI frequency
MAH database	All (1st dose	18 - 24	2,3/100.000	~ 0,23 cases/ 10.000	Very rare
	All (2nd dose)	18 - 24	3.1 /100.000	~ 0,31 cases/ 10.000	Very rare
	Men (1st dose)	18 - 24	4.4 /100.000	~ 0,44 cases/ 10.000	Very rare
	Men (2nd dose)	18 - 24	5.9 /100.000	~ 0,59 cases/ 10.000	Very rare

VAERS	Men	18-24	3.85/100.000	~ 0,385 cases/ 10.000	Very rare
	Women	18-24	0.53/100.000	~ 0.053 cases/ 10.000	Very rare

Nevertheless, the PRAC rapporteur has proposed a new wording to the asterix including data from the FR study and the Nordic study with less exact data from the studies than the previous wording. These two studies are considered to appropriately reflect the current knowledge of data.

3.4. Updated rapporteur's proposed recommendation

Overall, the new data confirmed previous observations of an increased risk of myocarditis following vaccination with Spikevax. The risk was generally higher after the second dose and particulary in younger males. The risk of pericarditis showed the same trends. However, the new data made an estimation of frequency feasible.

Therefore the PRAC rapporteur proposes to update the product information of Spikevax regarding the risk of myocarditis and pericarditis with the following:

Summary of product information:

Section 4.4:

Myocarditis and pericarditis

There is an increased risk for~~Very rare cases of~~ myocarditis and pericarditis ~~have been observed~~ following vaccination with Spikevax. These **conditions can develop within just a few days after vaccination, and** ~~cases~~ have primarily occurred within 14 days~~following vaccination~~. **They have** more often **been observed** after the second vaccination, and more often in younger **males**~~en~~ **(see section 4.8)**. 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.

The risk of myocarditis after a third dose (0.5 mL, 100 micrograms) or booster dose (0.25 mL, 50 micrograms) of Spikevax has not yet been characterised.

Based on very limited data in the paediatric population, the risks of myocarditis and pericarditis in this population have not yet been characterised.

Section 4.8:

SOC cardiac disorders:

Frequency: ~~not known~~ **Very rare**: Myocarditis*****

Frequency: ~~not known~~ **Very rare**: Pericarditis

*** The increased risk of myocarditis after vaccination with Spikevax is highest in younger men (see section 4.4). Two large European pharmacoepidemiological studies have estimated the risk of myocarditis following vaccination after 2 doses of Spikevax in younger males: in one study, there were between 9-28 excess cases of myocarditis within 28 days per 100,000 vaccinations; in another study, there were between 129-134 excess cases of myocarditis within 7 days per 1,000,000 vaccinations. Based on this, the frequency in younger men is considered to be within the frequency category "Rare" (estimated from excess cases: ~ 1.9 cases/10,000 and 1.3/10,000, respectively).**

Package leaflet:

Section 2 – Warning and precautions

There is an increased risk for ~~Very rare cases of~~ myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) ~~have been reported after~~ **following** vaccination with Spikevax. **These conditions can develop within just a few days after vaccination, and have primarily occurred within 14 days. They have more often been observed after the second vaccination, and more often in younger males (see section 4).** ~~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~~" **Very rare**: Inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain. **The risk has been shown to be increased in younger males, corresponding to a frequency "Rare".**

3.5. Adopted PRAC recommendation

Having considered the available evidence from large observational studies in and outside the EEA, as well as the data provided by the Marketing Authorisation Holder (MAH), the PRAC has agreed that the MAH for COVID-19 mRNA vaccine (nucleoside-modified) Spikevax (Moderna Biotech Spain, S.L.) should submit by Monday 6 December (by 9am CET time) 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

There is an increased risk for ~~Very rare cases of~~ myocarditis and pericarditis ~~have been observed~~ following vaccination with Spikevax.

These ~~cases~~ conditions can develop within just a few days after vaccination, and ~~cases~~ have primarily occurred within 14 days ~~following vaccination~~. They have been observed more often after the second vaccination, and more often in younger ~~men~~ males (see section 4.8).

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.

The risk of myocarditis after a third dose (0.5 mL, 100 micrograms) or booster dose (0.25 mL, 50 micrograms) of Spikevax has not yet been characterised.

Section 4.8 Undesirable effects

SOC cardiac disorders:

[Frequency] ~~not known~~ Very rare: Myocarditis

[Frequency] ~~not known~~ Very rare: Pericarditis

Description of selected adverse reactions

Myocarditis

The increased risk of myocarditis after vaccination with Spikevax is highest in younger males (see section 4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males following the second dose of Spikevax. One study showed that in a period of 7 days after the second dose there were about 1.316 (95% CI 1.299 – 1.333) extra cases of myocarditis in 12-29 year old males per 10,000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there were 1.88 (95% CI 0.956 – 2.804) extra cases of myocarditis in 16-24 year old males per 10,000 compared to unexposed persons.

Package leaflet:

Section 2 – What you need to know before you receive Spikevax

Warning and precautions

There is an increased risk ~~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 (see section 4).

These conditions can develop within just a few days after vaccination and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males.

~~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"~~ Very rare (may affect up to 1 in 10,000 people): Inflammation of the heart muscle (myocarditis) or inflammation of the lining outside the heart (pericarditis) which can result in breathlessness, palpitations or chest pain.

4. References

From MAH's response in section 3.1 of this AR:

1. SARS-CoV-2 Vaccination and Myocarditis in a Nordic Cohort Study of 23 Million Residents. Karlstad, Øystein, et al.
2. Association between COVID-19 messenger RNA vaccines and the occurrence of myocarditis and pericarditis in people aged 12 to 50 in France - Study based on data from the National Health Data System (SNDS)
3. Yalile Perez, MD, MS, Emily R Levy, MD, Avni Y Joshi, MD, MS, Abinash Virk, MD, Martin Rodriguez-Porcel, MD, Matthew Johnson, MPH, Daniel Roellinger, Greg Vanichkachorn, MD, MPH, W Charles Huskins, MD, MS, Melanie D Swift, MD, MPH, Myocarditis Following COVID-19 mRNA Vaccine: A Case Series and Incidence Rate Determination, Clinical Infectious Diseases, 2021;, ciab926, https://doi.org/10.1093/cid/ciab926
4. Bozkurt B, Kamat I, Hotez PJ. Myocarditis With COVID-19 mRNA Vaccines. Circulation. 2021 Aug 10;144(6):471-484. doi: 10.1161/CIRCULATIONAHA.121.056135. Epub 2021 Jul 20. PMID: 34281357; PMCID: PMC8340726.
5. Muthukumar A, Narasimhan M, Li QZ, Mahimainathan L, Hitto I, Fuda F, Batra K, Jiang X, Zhu C, Schoggins J, Cutrell JB, Croft CL, Khera A, Drazner MH, Grodin JL, Greenberg BM, Mammen PPA, Morrison SJ, de Lemos JA. In- Depth Evaluation of a Case of Presumed Myocarditis After the Second Dose of COVID-19 mRNA Vaccine. Circulation. 2021 Aug 10;144(6):487-498. doi: 10.1161/CIRCULATIONAHA.121.056038. Epub 2021 Jun 16. PMID: 34133883; PMCID: PMC8340727.
6. Hajjo R, Sabbah DA, Bardaweel SK, Tropsha A. Shedding the Light on Post-Vaccine Myocarditis and Pericarditis in COVID-19 and Non-COVID-19 Vaccine Recipients. Vaccines (Basel). 2021;9(10):1186. Published 2021 Oct 15. doi:10.3390/vaccines9101186

PRAC Rapporteurs references from section 3.1 of this AR:

7. Sundbøll J, Adelborg K, Munch T, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open*. 2016;6(11):e012832. Published 2016 Nov 18. doi:10.1136/bmjopen-2016-012832