



02 September 2021  
EMA/PRAC/325882/2021  
Pharmacovigilance Risk Assessment Committee (PRAC)

## Updated Signal assessment report on Myocarditis, pericarditis with Tozinameran (COVID-19 mRNA vaccine (nucleoside-modified) – COMIRNATY)

EPITT no: 19712

Procedure no: SDA 032.1

Confirmation assessment report	08 Jun 2021
Adoption of first PRAC recommendation	10 Jun 2021
Preliminary assessment report on additional data	29 Jun 2021
Deadline for comments	01 Jul 2021
Updated rapporteur assessment report	05 July 2021
Adoption of second PRAC recommendation	08 Jul 2021
Preliminary assessment report on additional data	18 Aug 2021
Deadline for comments	23 Aug 2021
Updated rapporteur assessment report	26 Aug 2021
Adoption of third PRAC recommendation	02 Sep 2021

### Note

This assessment report has been updated with the PRAC Rapporteur's assessment of MAH's response, received on 30 July 2021, following a Request for Supplementary Information based on PRAC recommendation received on **08 July 2021** in this Signal procedure SDA 032 for Comirnaty. Please refer to **section 4.1** and **4.2** in this report.

This assessment report has been updated with the PRAC Rapporteur's assessment following MS comments. Please refer to **section 4.3** in this report.

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



## Administrative information

<b>Active substance(s) (invented name)</b>	Tozinameran - COVID-19 mRNA vaccine (nucleoside-modified) - COMIRNATY
<b>Strength(s)</b>	<Text> [Only if relevant to the signal]
<b>Pharmaceutical form(s)</b>	<Text> [Only if relevant to the signal]
<b>Route(s) of administration</b>	<Text> [Only if relevant to the signal]
<b>Indication(s)</b>	<Text> [Only if relevant to the signal]
<b>Marketing authorisation holder(s)</b>	BioNTech Manufacturing GmbH
<b>Authorisation procedure</b> [Tick the appropriate box(es) below.]	
<input checked="" type="checkbox"/>	Centralised
<input type="checkbox"/>	Mutual recognition or decentralised
<input type="checkbox"/>	National

<b>Adverse event/reaction:</b>	Myocarditis, pericarditis
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<b>Signal validated by:</b>	EMA
<b>Date of circulation of signal validation report:</b>	08 June 2021
<b>Signal confirmed by:</b>	NL
<b>Date of confirmation:</b>	09 June 2021
<b>PRAC Rapporteur appointed for the assessment of the signal:</b>	Menno van der Elst

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# 1. Background

Myocarditis is an inflammation of the heart muscle that may present with chest pain, palpitations, arrhythmias and/or heart failure. It may occur in children and adults and is more common in young men than young women. Diagnostic work-up may include serum cardiac biomarkers such as troponins and creatine kinase, electrocardiogram, echocardiography, cardiovascular magnetic resonance imaging and endomyocardial biopsy (diagnostic gold standard). Etiologies can include infection (most commonly viral), autoimmune (e.g. sarcoid and systemic lupus erythematosus) and drugs or toxins. In 50% of cases, acute myocarditis resolves quickly within 2-4 weeks, however 25% may develop persistent cardiac dysfunction and 25% may deteriorate to end-stage dilated cardiomyopathy. Treatment is dependent on presentation and may be directed at a specific etiology, if determined, heart failure and arrhythmias, if present.<sup>1,2,3</sup>

Pericarditis is an inflammation of the pericardial sac that contains the heart and fixes it to the mediastinum. Males between 20-50 appear to be at highest risk for pericarditis. The incidence has been reported to be about 28 cases per 100,000 in an urban Italian area. Diagnosis of acute pericarditis is made if 2 of 4 clinical criteria are met: 1. Pericardial chest pain, 2. Pericardial rub on auscultation, 3. ECG changes, 4. Pericardial effusion. Etiologies can remain unknown in 40-85% of patients with pericarditis but may be microbial (most commonly viral > bacterial) or autoimmune (e.g. systemic lupus erythematosus, rheumatoid arthritis) or neoplastic. It can be self-limiting or complicated by pericardial effusion and constriction (tamponade). Treatment is directed at inflammation with colchicine or other

NSAIDs, aspirin, corticosteroids and anakinra (IL-1 receptor antagonist). Recurrences occur in about 30% of patients.<sup>4</sup>

On 30 May 2021, Brighton Collaboration issued an interim case definition for myocarditis, available from the link: <https://brightoncollaboration.us/myocarditis-case-definition-update/>.

Comirnaty is a COVID-19 mRNA vaccine which received a conditional marketing authorisation in the EU on 21 December 2020 for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 16 years of age and older. CHMP has recommended granting an extension of indication for

Comirnaty to include use in children aged 12 to 15 on 28 May 2021. Myocarditis and pericarditis are not labelled as adverse reactions in the EU SPC for Comirnaty.

Myocarditis and pericarditis were safety signals evaluated (cumulative review) and closed by the MAH of Comirnaty in the MSSR submission 15 May 2021.

The myocarditis signal was initially identified in Israel in young male vaccinees above 16 years of age mostly after 2nd dose.

In Israel, most cases were mild, as determined by short length of hospital stay (most discharged within four days). Illness severity was mild after first and second doses. All cases will be followed in the community, and overall severity can only be assessed completely if there are no long term sequelae, which at present time is unknown.

In Israel, a comparison of hospital admissions incidences rate due to myocarditis in vaccinees compared to non-vaccinees was performed in all ages groups, and the data suggested a potential signal with the vaccinees. There has not been a general comparison of hospitalizations by vaccine status.

The Israeli interim assessment was that there is a likely causal association between the second dose of mRNA vaccine (in Israel all cases were with Pfizer vaccine) and myocarditis. This association appears

stronger in young males (16-19) as opposed to females and attenuates with increasing age. The numerical estimate is still being finalized, but is approximately between 1 In 10,000 to 1 in 6,000 second doses of vaccine.

The Israeli Ministry of Health included information on myocarditis in its vaccine guidebook, and will continue to update the public with new developments or assessments. With regard to 12-15 year olds, the rate of myocarditis following vaccination is presently unknown. However because of the signal detected in 16-19 year olds, and low infection rates in Israel in general, the Israeli Ministry of Health recommended at the present to vaccinate this age group if they have risk factors for severe COVID-19, if they are household or otherwise close contacts of persons at risk, or planning travel abroad. In addition, others in this age group can receive the vaccine if they desire.

#### References:

1. Caforio ALP et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *European Heart Journal* (2013) 34, 2636-2648.
2. Ammirati E et al. Update on acute myocarditis. *Trends in Cardiovascular Medicine* 2020 Elsevier <https://doi.org/10.1016/j.tcm.2020.05.008>
3. Kindermann, I et al. Update on myocarditis. *JACC* (2012) 59, 9, 779-792
4. Adler Y 2015 ESC guidelines for the diagnosis and management of pericardial diseases. *European Heart Journal* (2015) 36, 2921-2964.

## 2. Initial evidence

### 2.1. Signal validation

As of 26 May 2021, in Eudravigilance 122 cases were received in the combined search for HLT Infectious myocarditis and HLT Non-infectious myocarditis in the EEA. Out of these cases, 64% were in males. 5 cases (4%) were fatal (in elderly people). The median age of the vaccinees was 42 years old.

Per age group, the number of cases was as follows: <20 years old (4 cases, 3%); 20-29 (34 cases, 28%); 30-39 (18 cases, 15%); 40-49 (12 cases, 10%); 50-59 (23 cases, 19%); 60-69 (9 cases, 7%); 70-79 (11 cases, 9%); >80 (9 cases, 7%); not specified (2 cases, 2%). We note the majority of cases was in the age group 20-29 years old.

Under 30 years of age, there were 38 cases received from the EEA. These cases were matched to the BC criteria of the interim definition. 25 cases were level 4-5, and 13 cases were level 1-3. The TTO was between 0-43 days following administration. 21% of cases happened after the first dose, 47% of the cases happened after the second dose, and in 31% the number of the dose was not provided.

92 cases had TTO within the first 14 days, 19 cases had TTO between 15-30 days, 2 cases had TTO between 31-42 days, 4 cases had TTO over 42 days, unknown TTO was in 5 cases.

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

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

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

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

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

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

With the same DLP of 26 May, there were 118 case reports of pericarditis, and 8 case reports of pleuropericarditis in the combined search for the HLTs Infectious pericarditis and Noninfectious pericarditis in EudraVigilance.

It is proposed to request from the MAH (BioNTech Manufacturing GmbH) answers to a LoQ on myocarditis and pericarditis. The MAH should discuss the need to update the product information and risk management plan and submit proposals as appropriate.

## **2.2. Signal confirmation**

In the context of the 5th MSSR for Comirnaty (DLP 28 April 2021), a review performed by the MAH for myocarditis and pericarditis has been assessed.

For the majority of pericarditis cases assessment of a causal role of the vaccine is hampered by confounding medical histories (e.g. pericarditis, COVID-19, influenza, neoplasms). Although a role of the vaccine cannot be excluded, a coincidental finding cannot be excluded either.

Both the cases of myocarditis and pericarditis require further in-depth evaluation, due to suggestive time-to-onset, age distribution and apparent male predominance, especially in the case reports from Israel. To allow a more thorough assessment, the MAH should provide more detailed information, including a diagnostic work-up of the cases.

The MAH is requested to present more in-depth O/E analyses of AESIs Myocarditis and Pericarditis, including more refined O/E analyses stratified by smaller age bands and gender. The MAH should ensure that the most relevant background incidence rates are selected and used for comparison, e.g. based on the origin of the cases (i.e. Israel). A justification for the selected IR should be provided.

For myocarditis, the MAH should discuss the observation that eighteen (18) of the cases occurred following dose 1 of the vaccine, 75 after dose 2 (and 15 reports did not specify the dose of vaccine)

and whether this suggests that these AEs are reported disproportionately (more frequently) after the 2nd dose.

A possible mechanism of a systemic inflammatory reaction due to an immune response to the vaccine could be postulated, but remains speculative. Upon evaluation of the cases the MAH should also consider Multisystem inflammatory syndrome in children (MIS/MIS-C) as alternative etiology.

In conclusion, the signal is hereby confirmed.

### **2.3. Proposed recommendation**

The MAH (BioNTech Manufacturing GmbH) is requested to answer to the below LoQ on myocarditis and pericarditis. The MAH should discuss the need to update the product information and risk management plan and submit proposals as appropriate.

#### *List of questions*

##### Myocarditis

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

The review should explore possible risk factors, taking into account the gender and age distribution of reported cases as well as the observation that in the cases reported in the 5<sup>th</sup> MSSR, 18 of the cases occurred following dose 1 of the vaccine, and 75 after dose 2.

The MAH should also provide a more refined O/E analysis. This O/E analysis with a DLP of 31 May 2021 or later, should be stratified by:

- age, by strata of 12–15, 16–19, 20–24, 25–29, 30–39, and thereafter 10 years intervals
- gender
- dose (1<sup>st</sup> or 2<sup>nd</sup>)

Besides the used 21-day risk window and no risk window in the O/E analysis, additional O/E analysis are requested using a 14-day risk window.

As the signal seems to be most prominent in Israel a separate O/E analysis should be performed for Israeli cases, also stratified as above.

The MAH should discuss possible mechanisms by which the vaccine may cause myocarditis. In this respect, the MAH should also consider Multisystem inflammatory syndrome in children (MIS/MIS-C) as alternative etiology. In addition, the MAH should discuss the immunologic mechanism of MIS-induced myocarditis following COVID-19, and if any parallels can be drawn to the immunologic reactions following vaccination.

Based on the above, the MAH should discuss the need to update the product information and risk management plan and submit proposals as appropriate.

## Pericarditis

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

The review should explore possible risk factors, taking into account the gender, age, and dose distribution of reported cases.

The MAH should also provide a more refined O/E analysis. This O/E analysis with a DLP of 31 May 2021 or later, should be stratified by:

- age, by strata of 12–15, 16–19, 20–24, 25–29, 30–39, and thereafter 10 years intervals
- gender
- dose (1<sup>st</sup> or 2<sup>nd</sup>)

Besides the used 21-day risk window and no risk window in the O/E analysis, additional O/E analysis are requested using a 14-day risk window.

The MAH should discuss possible mechanisms by which the vaccine may cause pericarditis. In this respect, the MAH should also consider Multisystem inflammatory syndrome in children (MIS/MIS-C) as alternative etiology. In addition, the MAH should discuss the immunologic mechanism of MIS-induced pericarditis following COVID-19, and if any parallels can be drawn to the immunologic reactions following vaccination.

Based on the above, the MAH should discuss the need to update the product information and risk management plan and submit proposals as appropriate.

## **2.4. Adopted PRAC recommendation**

Having considered the available evidence from the data in the 5th Monthly Safety Summary Report (MSSR) (submission 15 May) and from case reports in EudraVigilance, the PRAC has agreed that the MAH for COVID-19 mRNA Vaccine Comirnaty (BioNTech Manufacturing GmbH) should submit by 21 June 2021 answers to the below List of questions. This should be done separately for myocarditis and pericarditis, as follows.

List of questions

### Myocarditis

1. The MAH should provide a review of all cases of myocarditis and cases reporting both myocarditis and pericarditis with a DLP as recent as possible, but at least up to 31 May 2021. The MAH should ensure that all relevant cases are processed (not in backlog) and included in the review.

This review should include case ascertainment (as per Brighton collaboration case definition), diagnostic work-up, causality assessment and outcome of the events (e.g. hospitalization, life-threatening, or death) for each case report.

The review should explore possible risk factors (e.g specific medical history such as autoimmune diseases, previous COVID-19 disease, etc), taking into account the gender and age distribution of



reported cases, as well as the observation that in the cases reported in the 5th MSSR (submission 15 May), 18 of the cases occurred following dose 1 of the vaccine, and 75 after dose 2.

2. The MAH should also provide a more refined Observed/Expected (O/E) analysis. This O/E analysis with a DLP of 31 May 2021 or later, should be stratified by:
  - age, by strata of 12–15, 16–19, 20–24, 25–29, 30–39, and thereafter 10 years intervals
  - gender
  - dose (1st or 2nd)

Besides the used 21-day risk window and no risk window in the O/E analysis, additional O/E analysis are requested using a 14-day risk window.

3. As a substantial amount of cases occurred in Israel, a separate O/E analysis should be performed for Israeli cases, also stratified as above.
4. The MAH should discuss possible mechanisms by which the vaccine may cause myocarditis. In this respect, the MAH should also consider Multisystem inflammatory syndrome in children (MIS/MIS-C) as alternative etiology. In addition, the MAH should discuss the immunologic mechanism of MIS-induced myocarditis following COVID-19, and if any parallels can be drawn to the immunologic reactions following vaccination.
5. The MAH should also discuss the need for any potential amendment to the product information and/or the risk management plan and make accordingly a proposal for the changes to the relevant sections within this discussion.

#### Pericarditis

1. The MAH should provide a review of all cases of pericarditis with a DLP as recent as possible, but at least up to 31 May 2021. The MAH should ensure that all relevant cases are processed (not in backlog) and included in the review.

This review should include case ascertainment (as per Brighton collaboration (if available) or alternative case definition), diagnostic work-up, causality assessment and outcome of the events (e.g. hospitalization, life-threatening, or death) for each case report.

The review should explore possible risk factors (e.g. specific medical history such as autoimmune diseases, previous COVID-19 disease, etc), taking into account the gender, age and dose distribution of reported cases.

2. The MAH should also provide a more refined O/E analysis. This O/E analysis with a DLP of 31 May 2021 or later, should be stratified by:
  - age, by strata of 12–15, 16–19, 20–24, 25–29, 30–39, and thereafter 10 years intervals
  - gender
  - dose (1st or 2nd)

Besides the used 21-day risk window and no risk window in the O/E analysis, additional O/E analysis are requested using a 14-day risk window.

3. The MAH should discuss possible mechanisms by which the vaccine may cause pericarditis. In this respect, the MAH should also consider Multisystem inflammatory syndrome in children (MIS/MIS-C) as alternative etiology. In addition, the MAH should discuss the immunologic mechanism of MIS-

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

4. The MAH should also discuss the need for any potential amendment to the product information and/or the risk management plan and make accordingly a proposal for the changes to the relevant sections within this discussion.

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

### **3. Additional evidence**

The following data are reviewed here:

1. MAH response to LoQ Signal procedure EPITT ref 19712 (submitted on 22 June 2021)
2. Analysis of EEA cases in EudraVigilance by the EMA and PRAC
3. Updated O/E analyses of EEA cases in EudraVigilance by the EMA (DLP 13 June 2021)

#### **3.1. Assessment of additional data**

##### **3.1.1. MAH response to LoQ Signal procedure EPITT ref 19712 (submitted on 22 June 2021)**

###### **3.1.1.1. MYOCARDITIS**

###### **Question 1**

The MAH should provide a review of all cases of myocarditis and cases reporting both myocarditis and pericarditis with a DLP as recent as possible, but at least up to 31 May 2021. The MAH should ensure that all relevant cases are processed (not in backlog) and included in the review.

This review should include case ascertainment (as per Brighton collaboration case definition), diagnostic work-up, causality assessment and outcome of the events (e.g. hospitalization, life-threatening, or death) for each case report.

The review should explore possible risk factors (e.g. specific medical history such as autoimmune diseases, previous COVID-19 disease, etc), taking into account the gender and age distribution of reported cases, as well as the observation that in the cases reported in the 5th MSSR (submission 15 May), 18 of the cases occurred following dose 1 of the vaccine, and 75 after dose 2.

###### **MAH response**

The safety database was searched for spontaneous reports for Pfizer/BNT COVID-19 vaccine using the search criteria PT(s): Pericarditis and Myocarditis, cumulatively to 31 May 2021.

The search identified 654 potentially relevant reports out of a total of 256,340 spontaneous AE reports for Pfizer/BNT COVID-19 vaccine in the safety database as of 31 May 2021. Three hundred and fifty eight (358) reports coded Myocarditis AEs, and 296 coded Pericarditis (see **Section 3.1.1.2. Pericarditis**), including 25 reports reporting both PTs (Myocarditis and Pericarditis).

- The 24 cases meeting Brighton’s collaboration (BC) level 1 criteria were in the age group of 19-68 (median: 34, mean: 37.96) years: 11 cases were in the 19-30 years age group, 9 cases in the 31-65 year age group, 3 cases in the above 65 year age group, and in 1 case, there was no age reported. There were more reports in males (15) than in females (8); gender was not reported in 1 case. Nine (9) of these cases did not provide testing and/or evidence of a known causative etiology; 8 cases were reported in those with current or preceding COVID-19 infection (6) as well as 3 cases of other viral infection (*e.g.*, Parvoviruses, EBV, and VZV); and 7 cases had a history of cardiac and/or pulmonary disorders. Thirteen (13) cases had a Time To Onset between 0-7 days following vaccination. Thirteen (13) events occurred after dose 1, 10 events after dose 2, and dose number was not reported for one (1) case.
- 37 cases were assessed as BC level 2. The age ranged between 16-84 years; there were 27 males and 10 females.
- 42 cases were assessed as BC level 3.
- 245 cases were assessed as BC level 4.
- 10 cases were assessed as BC level 5.

Israel was the country with the most reports: 102 events of Myocarditis. The cases were reported in the age group of 16-75 years (median: 24, mean: 27.13). No cases were assessed as BC level 1. Two (2) cases were assessed as BC level 2, 10 as BC level 3, 88 as BC level 4, and 2 as BC level 5. Three (3) of these cases had a fatal outcome (see below). It is worth noting that cases of myocarditis reported by Israel lacked supporting evidence of imaging and/or laboratory values to make a definitive assessment.

Nine (9) reports describing myocarditis had a fatal outcome (Table 1); all except 1 case (BC level 3; AER#2021441169) were BC level 4, with only weak diagnostic evidence provided for the diagnosis of myocarditis. No autopsy data were provided for any of these reports. Five (5) of the cases were from Germany, 3 from Israel, and 1 from Austria. Three (3) cases were in patients greater than or equal to 80 years; the youngest was 19 years old (a consumer report from Israel with a paucity of details). In 4 of these cases, there was septic shock and/or cardiogenic shock, or acute anterior wall infarction as a predisposing cause of death. Four (4) of the deceased patients had history of diabetes, meningioma, organ damage, myocardial infarction, and/or atherosclerosis.

Brief narrative summaries of the 9 fatal cases are included below (Table 1).

None of the 358 total myocarditis events occurred in subjects below 16 years of age.

There were 6 reports of acute pericarditis co-reported with myocarditis, all from Israel. Ages ranged between 24-48 years, 5 males and 1 female. Four (4) occurred following dose 1, 2 after dose 2, and 1 following an unknown number of doses. These cases did not provide testing and/or evidence of a known causative etiology. All were assessed as serious due to being medically significant.

**Comment PRAC Rapporteur:**

Cumulatively until 31 May 2021 the MAH identified:

358 reports coded Myocarditis AEs; 296 coded Pericarditis (see Section **3.1.1.2. PERICARDITIS**), including 25 reports reporting both PTs (Myocarditis and Pericarditis)

Myocarditis Brighton’s collaboration (BC) criteria:

**BC level 1:** 24 cases. Age ranged 19-68 (median: 34, mean: 37.96) years: 11 cases 19-30 years age group, 9 cases in the 31-65 year age group, 3 cases in the above 65 year age group, and in 1 case,

there was no age reported. More reports in males (15) than in females (8); gender was not reported in 1 case

**BC level 2:** 37 cases. Age ranged between 16-84 years; there were 27 males and 10 females.

**BC level 3:** 42 cases

**BC level 4:** 245 cases.

**BC level 5:** 10 cases.

In contrast to the PRAC request the MAH **only** has presented a causality assessment of the fatal cases (see below). An evaluation of causality and outcome of the events, especially in sufficiently documented cases not reporting alternative aetiologies, confounding medical history or underlying conditions is currently lacking and no justification for this has been provided. **This is not accepted. Question 1 is not resolved.**

It is reiterated that the MAH should provide a causality assessment and outcome of the events (*e.g.* hospitalization, life-threatening, or death) for each case, in particular for those cases which are sufficiently documented and not reporting alternative etiologies, confounding medical history or underlying conditions (**Request for Supplementary Information**).

Following the PRAC Rapporteur's own assessment of a causal relation between (acute) myocarditis and the vaccination is hampered by the confounding medical history and comorbidities/conditions (*e.g.* COVID-19, diabetes, heart disease, including previous myocarditis). Nevertheless in cases that describe a suggestive short TTO and absence of confounding medical history, comorbidities or risk factors, a causal role of the vaccine cannot be excluded and is considered possible.

In addition, the MAH should provide a discussion regarding the possible mechanisms (if any) explaining the observation that O/E ratios were higher for Dose 2 compared to Dose 1 (**Request for Supplementary Information**).

Also see **Section 3.1.2 - EudraVigilance query EEA cases by EMA and assessment by PRAC Rapporteur.**

**Table 1. Summary of Myocarditis Events With Fatal Outcome**

Case No /Age Band / Gender	Medical History / Preferred Terms	BrightonLevel	Brief Narrative Summary of AER
1 18-29 years FEMALE	Dermatitis atopic Myocarditis, Cardiogenic shock, Nodal rhythm, Chest pain, Asthenia, Chills, Pyrexia, Fatigue, Dizziness, Vitamin B12 decreased, Troponin increased, Blood iron decreased	3	Medical history includes dermatitis. Received dose 2 on an unspecified date. After 11 days, she experienced myocarditis, fatigue, dizziness, fever, elevated troponins up to 270, 000. She died on an unspecified date. Cause of death myocarditis and cardiogenic shock.
2 50-59 years MALE	Arteriosclerosis / Arteriosclerosis coronary artery  Myocarditis, Acute myocardial infarction, Vaccination site inflammation, Myopathy	4	Received vaccination on day 0. On day 1, the patient experienced myocarditis and myocardial infarction of the anterior wall. Post anatomical diagnosis revealed acute anterior ventricular infarct and atherosclerotic plaques, and confirmed to be cause of death. Patient died on day 1. <sup>a</sup>
3 50-59 years MALE	Arteriosclerosis / Arteriosclerosis coronary artery  Myocardial infarction, Myocarditis	4	Received his first dose on day 0. On day 1, experienced myocarditis and myocardial infarct leading to death on day 1. Reported cause of death myocardial infarct and extensively ulcerated atherosclerotic plaques. Focal myocarditis of the left ventricular apex. Hepatic Fatty degeneration. <sup>a</sup>
4 80+ years FEMALE	Not reported  Atrial fibrillation, Hypotension, Normocytic anaemia, Haematochezia, Acute kidney injury, Hyponatraemia, Septic shock, Cardiogenic shock, Myocarditis, Transaminases increased, Pericardial effusion, Acute myocardial infarction, Ventricle rupture	4	No medical history was provided. She received the first injection on day 0. On day 4, she experienced bloody stools, tachycardia, hypotension, anaemia normocytic, hyponatremia, pericardial effusion, cardiogenic shock. No further diagnostic or etiologic evaluation was provided. She died on day 50. Autopsy data were not provided. <sup>b</sup>

5 40-49 years MALE	Diabetes mellitus / Hypercholesterolaemia / Hypertension / Hypothyroidism  Myocarditis, Pyrexia, Cough, Dyspnoea	4	Medical history includes hypertension, hypercholesterolemia, hypothyroidism, diabetes with end organ damage. The patient received his two doses of vaccine on unspecified dates. He was brought to the ED after an unspecified time post vaccination with fever for 3 days, difficulty breathing, cough, and myocarditis. He was anesthetized and resuscitated due to his rapidly deteriorating condition. The patient died due to myocarditis on an unspecified date. No cardiac imaging data was provided. No further diagnostic or etiologic evaluation was provided. No autopsy was performed. <sup>b</sup>
6 80+ years FEMALE	COVID-19 / Cerebrovascular accident / Cough / Hemiparesis / Hypertension / Intraosseous meningioma / Nasopharyngitis / Sciatica / Type 2 diabetes mellitus  Septic shock, Multiple organ dysfunction syndrome, Pericarditis, Myocarditis	4	Patient with a history of COVID-19 infection in December 2020, meningioma with symptoms of residual hemiparesis, and Type 2 diabetes mellitus. She received her first dose of the Pfizer/BioNTech vaccine on day 0. She experienced septic shock, extensive myocarditis, pericarditis, and multiple organ failure on day 3, following 2 days of a cough and cold symptoms. She died on day 5. No non-invasive or invasive cardiac imaging information was provided. An autopsy performed revealed carditis of the pericardium and myocardium. Etiologic workup of the myocarditis was not provided. <sup>b</sup>
7 18-29 years MALE	Not reported  Myocarditis, Heart rate increased, Dyspnoea, Pain in extremity	4	. No medical history reported. Received his second shot on day 0. He was hospitalized with myocarditis 5 days later, with shortness of breath, tachycardia and sharp pain on the left side. Patient died on the same day. Unknown if autopsy was performed. Cause of death: Myocarditis.
8 30-39 years FEMALE	Not reported  Death, Pericardial effusion, Myocarditis, Dyspnoea, Chest pain, Tachycardia, Neck pain, Headache	4	Medical history not reported. Received vaccination on an unspecified date. Following vaccination she experienced pericardial effusion, myocarditis, dyspnea reported as life threatening. She died and autopsy was not performed.
9 80+ years MALE	Not reported  Hypotonia, Abdominal discomfort, Vomiting, Myocarditis, Dyspnoea, Nausea	4	No medical history was provided. He received the first injection on day 0. The patient experienced gastric discomfort, vomiting, nausea, myocarditis, and dyspnea on day 5. The patient died on day 15. No other relevant information was provided. No autopsy was performed. <sup>b</sup>

- a. The similarities between the case no2 and 3 are being investigated to ascertain if the case reports have been duplicated.
- b. Included in Appendix 3.9 of SMSR #6.

**Comment PRAC Rapporteur:**

A causal role of the vaccine cannot be excluded due suggestive TTO and absence of other aetiologies in 3 fatal myocarditis cases:

Case1 (18-2F, BC 3, TTO 11 days); Case 7(18-29M, BC 4, TTO 4 days); Case8 (30-39F, BC 4, TTO unknown)

In 6 out of 9 fatal cases (all BC 4) limited information and confounding medical history/conditions precludes conclusions regarding a causal relation between the vaccine and myocarditis:

1. In case 2 (possible duplicate of Case 3) has confounding medical history of Arteriosclerosis coronary artery. However, from the case description it is not clear if the Focal myocarditis of the left ventricular apex was located within the infarction area. Moreover, this also suggests an obduction has been conducted and the diagnostic certainty should be upgraded from BC4 to BC1 ?
2. In case 4 causality assessment hampered by confounding underlying condition bloody stools, acute kidney injury, sepsis
3. In case 5 events and outcome are confounded by relevant medical history of hypertension, hypercholesterolemia, hypothyroidism, diabetes with end organ damage
4. In case 6 myocarditis and pericarditis is confounded by history of COVID-19 infection, underlying condition (meningioma and Type 2 DM) and sepsis.
5. In case 9 gastric discomfort, vomiting, nausea may also suggest an underlying gastrointestinal infection.

## Question 2

The MAH should also provide a more refined Observed/Expected (O/E) analysis. This O/E analysis with a DLP of 31 May 2021 or later, should be stratified by:

- age, by strata of 12-15, 16-19, 20-24, 25-29, 30-39, and thereafter 10 years intervals
- gender
- dose (1st or 2nd)

Besides the used 21-day risk window and no risk window in the O/E analysis, additional O/E analysis are requested using a 14-day risk window.

### MAH Response:

Observed to expected (O/E) analyses have been refined for the cumulative period through 31 May 2021 with minor modifications to the request, due to the availability of data inputs required for the calculations (*i.e.*, vaccine administration and background rate information for the requested strata).

Age-gender specific O/E analyses of myocarditis after first or second vaccine dose were determined for age categories 12-24, 25-49, 50-59, 60-69, and 70+ years for EU/US combined as well as globally. Combined EU/US are reported separately as these regions provide publicly available age-specific vaccine administration over time and thus expected counts can be estimated more accurately. Age-gender-specific vaccine administration information was not found; therefore, all age-categories for the US/EU and global analyses were assumed to be 53% female and 47% male.<sup>1</sup> Global estimates of vaccine exposure were determined by applying the age-gender distribution of exposure in the combined EU/US analysis to global counts of vaccine administration. Similarly, dose-stratified O/E analyses used EU/US reported dose-specific vaccine administration counts to determine dose-specific exposure. Global dose-specific exposure estimates assume the EU/US dose-specific exposure distribution.

Stratified O/E analyses were conducted assuming a 14-day risk window (EU/US [Table 2](#); Global [Table 3](#)) and a 21-day risk window (EU/US [Table 4](#); Global [Table 5](#)). Observed cases occurring outside of the respective risk windows were excluded from the numerator of the O/E ratio; cases with missing time to onset were included in both the 14- and 21-day risk windows. A sensitivity analysis that proportionally allocated time to onset to cases missing information based on the cases without missing data was conducted and did not meaningfully change the results.

Analysis without an assumed risk window were not conducted given the substantial challenges and assumptions required to estimate total age-, sex- or dose-specific person years of exposure for the strata and subsequent limitations in interpretation of O/E using an unrestricted risk window.

Information on the background rates is provided separately in the Myocarditis and Pericarditis (response to Question 2, [Section 2.2](#)).

### Myocarditis

Both EU/US and global O/E analyses assume age-gender specific background rates of myocarditis based on those provided by the ACCESS/VAC4EU initiative<sup>2</sup> for Italy, ARS. When age-categories differed between the vaccine administration sources and background rate source, administrations were proportionally allocated, and rates were averaged or selected based on epidemiologic considerations. Unless otherwise noted, ratios reflect events occurring after dose 1 or dose 2.



**Table 2. Myocarditis 14-day Risk Window, EU and US**

Stratification	Background rate per 100,000 PY	Observed Cases	Expected Cases	O/E Ratio	95% CI
Males 12-24 years	16.67	45	65.9	0.683	0.498, 0.914
Males 25-49 year	16.91	53	254.8	0.208	0.156, 0.272
Males 50-59 years	12.73	14	124.7	0.112	0.061, 0.188
Males 60-69 years	10.90	5	111.2	0.045	0.015, 0.105
Males 70+ years	13.60	9	252.3	0.036	0.016, 0.068
Females 12-24 years	3.60	13	16.0	0.810	0.432, 1.386
Females 25-49 year	5.36	19	91.1	0.209	0.126, 0.326
Females 50-59 years	5.34	12	59.0	0.203	0.105, 0.355
Females 60-69 years	9.58	4	110.2	0.036	0.010, 0.093
Females 70+ years	10.52	10	220.1	0.045	0.022, 0.084
Overall, dose 1	9.95	72	741.2	0.097	0.076, 0.122
Overall, dose 2	9.95	112	477.5	0.235	0.193, 0.282

Abbreviations: EU=European Union; US=United States; PY=Person years; O/E=Observed versus expected; CI=Confidence interval.

**Table 3. Myocarditis 14-day Risk Window, Globally**

Stratification	Background rate per 100,000 PY	Observed Cases	Expected Cases	O/E Ratio	95% CI
Males 12-24 years	16.67	98	76.6	1.280	1.039, 1.560
Males 25-49 year	16.91	105	335.6	0.313	0.256, 0.379
Males 50-59 years	12.73	16	168.7	0.095	0.054, 0.154
Males 60-69 years	10.90	8	151.6	0.053	0.023, 0.104
Males 70+ years	13.60	11	349.1	0.032	0.016, 0.056
Females 12-24 years	3.60	18	18.6	0.966	0.573, 1.527
Females 25-49 year	5.36	34	119.8	0.284	0.197, 0.397
Females 50-59 years	5.34	18	79.8	0.226	0.134, 0.357
Females 60-69 years	9.58	6	150.3	0.040	0.015, 0.087
Females 70+ years	10.52	10	304.5	0.033	0.016, 0.060
Overall, dose 1	9.95	106	1,009.4	0.105	0.086, 0.127
Overall, dose 2	9.95	218	642.6	0.339	0.296, 0.387

Abbreviations: PY=Person years; O/E=Observed versus expected; CI=Confidence interval.

**Table 4. Myocarditis 21-day Risk Window, EU and US**

Stratification	Background rate per 100,000 PY	Observed Cases	Expected Cases	O/E Ratio	95% CI
Males 12-24 years	16.67	48	95.5	0.503	0.371, 0.667
Males 25-49 year	16.91	55	367.0	0.150	0.113, 0.195
Males 50-59 years	12.73	15	177.5	0.084	0.047, 0.139
Males 60-69 years	10.90	5	160.1	0.031	0.010, 0.073
Males 70+ years	13.60	10	367.4	0.027	0.013, 0.050
Females 12-24 years	3.60	13	23.3	0.559	0.298, 0.956
Females 25-49 year	5.36	20	131.2	0.152	0.093, 0.235
Females 50-59 years	5.34	14	84.0	0.167	0.091, 0.280
Females 60-69 years	9.58	7	158.7	0.044	0.018, 0.091
Females 70+ years	10.52	12	320.5	0.037	0.019, 0.065
Overall, dose 1	9.95	81	1,072.5	0.076	0.060, 0.094
Overall, dose 2	9.95	118	686.2	0.172	0.142, 0.206

Abbreviations: EU=European Union; US=United States; PY=Person years; O/E=Observed versus expected; CI=Confidence interval.

**Table 5. Myocarditis 21-day Risk Window, Globally**

Stratification	Background rate per 100,000 PY	Observed Cases	Expected Cases	O/E Ratio	95% CI
Males 12-24 years	16.67	101	110.7	0.912	0.743, 1.109
Males 25-49 year	16.91	109	481.7	0.226	0.186, 0.273
Males 50-59 years	12.73	17	239.8	0.071	0.041, 0.113
Males 60-69 years	10.90	8	217.3	0.037	0.016, 0.073
Males 70+ years	13.60	12	504.5	0.024	0.012, 0.042
Females 12-24 years	3.60	18	26.9	0.668	0.396, 1.056
Females 25-49 year	5.36	36	171.9	0.209	0.147, 0.290
Females 50-59 years	5.34	21	113.4	0.185	0.115, 0.283
Females 60-69 years	9.58	10	215.4	0.046	0.022, 0.085
Females 70+ years	10.52	12	440.1	0.027	0.014, 0.048
Overall, dose 1	9.95	118	1,453.3	0.081	0.067, 0.097
Overall, dose 2	9.95	226	920.9	0.245	0.214, 0.280

Abbreviations: PY=Person years; O/E=Observed versus expected; CI=Confidence interval.

For the EU/US analysis, no O/E ratios were greater than 1. O/E ratios for both the age- gender-stratified and dose-stratified analyses were highest for the 14-day risk window, with similar patterns but numerically lower ratios using the 21-day risk window. Ratios were highest in the 12-24 age group for both males and females, with a slightly higher ratio in females. Of note the background rate for males for this age group is more than 4 times higher than the background rate for females. Although ratios did not exceed 1 for any of the age-gender strata, the upper limit of the 95% CI exceeded 1 for females in the 12-24 years stratum. Ratios were higher for Dose 2 compared to Dose 1.

The Global O/E analysis, which includes cases from Israel, demonstrated similar patterns as the EU/US analysis. The ratio was again highest in the 12-24 age group, although in contrast to the EU/US data, the ratio was higher among males in this age group. The O/E was greater than 1 for the 12-24 year old male stratum for the 14-day risk window, with the lower limit of the 95% CI exceeding 1. The upper limit of the 95% CI exceeded 1 for the 12-24 year old female stratum for the 14-day risk window. Ratios were higher for Dose 2 compared to Dose1.

**Comment PRAC Rapporteur:**

The MAH did not provide the requested age strata under 25 years of age: **12-15, 16-19, 20-24**.

This is **not acceptable** as the current signal is strongest in those age groups. Moreover, the same predominance within these age groups is consistent in several other O/E analysis conducted by Israel, USA, UK and the WHO. **Question 2 is not resolved**.

The MAH did not include an O/E analysis without an assumed risk window given the substantial challenges and assumptions required to estimate total age-, sex- or dose-specific person years of exposure for the strata and subsequent limitations in interpretation of O/E using an unrestricted risk window. This is accepted as the O/E ratio probably is lower than using a 14 or 21 d risk window.

The MAH performed a more refined O/E analysis based on the **available data** in US, EU and globally (including the cases from Israel). For a separate O/E analysis of the cases from Israel see **Question 3**.

For the EU/US analysis, no O/E ratios were greater than 1. O/E ratios for both the age- gender-stratified and dose-stratified analyses were highest for the 14-day risk window, with similar patterns but numerically lower ratios using the 21-day risk window. Ratios were highest in the 12-24 age group for both males and females, with a slightly higher ratio in females.

The MAH noted that the background rate for males for this age group is more than 4 times higher than the background rate for females. Although ratios did not exceed 1 for any of the age-gender strata, the upper limit of the 95% CI exceeded 1 for females in the 12-24 years stratum. Ratios were higher for Dose 2 compared to Dose 1.

The Global O/E analysis, which includes cases from Israel, showed similar patterns as the EU/US analysis. The ratio was again highest in the 12-24 age group, although in contrast to the EU/US data, the ratio was higher among males in this age group. The O/E was greater than 1 for the 12-24 year old male stratum for the 14-day risk window, with the lower limit of the 95% CI exceeding 1. The upper limit of the 95% CI exceeded 1 for the 12-24 year old female stratum for the 14-day risk window. Ratios were higher for Dose 2 compared to Dose 1.

Based on the total number of cases included in the O/E analyses, it is assumed that no restriction/selection was made on BC level diagnostic certainty (*i.e.* only including at least BC level 3 [possible] myocarditis cases). In principle, including all BC level cases (also BC level 4-5, *i.e.* cases not meeting BC level 1-3) in the O/E analysis is supported, as a conservative approach.

The MAH should confirm this, or otherwise justify. In addition, the MAH should clarify which and how many of the BC level cases have been included, especially in the strata that show an O/E ratio near or above 1 (**Request for Supplementary Information, also see response to Question 3**).

Regarding the Israeli cases, which appear to be the main driver of the global O/E ratio just above 1 within the 12-24 years of age group (males and females), the MAH noted that no cases were assessed as BC level 1. Two (2) cases were assessed as BC level 2, 10 as BC level 3, 88 as BC level 4, and 2 as BC level 5. Three (3) of these cases had a fatal outcome (see below). In addition cases of myocarditis reported by Israel lacked supporting evidence of imaging and/or laboratory values to make a definitive assessment.

The results of the MAH O/E analyses (EU/US and globally) are different from the results of the O/E analyses with a data cut off of 13 June 2021 performed by EMA. *I.e.* the O/E analyses with a 14d risk window showed a higher number of myocarditis cases than expected in males aged 18-24 (O/E ratio and lower 95% CI limit above 1). For females 18-24 and 25-49, the O/E ratio was above 1 but the lower limit of the 95% CI was not. See section **3.1.3 Latest O/E analysis Myocarditis by gender – DLP 13 June 2021 by EMA**.

### **PRAC Rapporteur's conclusion**

Despite the uncertainties and some differences with earlier O/E analyses (*e.g.* due to differences in chosen background rates, risk window, number of observed cases etc) the most recent MAH analyses are **not** refuting the signal, rather are in line with the previously observed trends in O/E analyses, not only by the MAH, but also those conducted independently by EMA, WHO and other authorities (Israel, US, UK). The overall pattern seems to consistently point to a higher than expected reporting rate of myocarditis within the younger age group, with a predominance in men and following the second dose.

In our view these findings must be adequately reflected in the product information (*i.e.* SmPC Section 4.4 Warnings and precautions, and PL accordingly) in order to increase HCP and vaccinee awareness, enabling early detection and adequate management as appropriate. Additionally, a DHPC should also be disseminated.

Please note the MAH did not respond to Question 5 *i.e.* 'The MAH should also discuss the need for any potential amendment to the product information and/or the risk management plan and make accordingly a proposal for the changes to the relevant sections within this discussion.'

This is **not accepted**. **Question 5 is not resolved**.

### **Limitations of O/E analyses**

There are several limitations to observed to expected analyses. The observed case counts are likely to be underestimated due to underreporting that occurs with spontaneous report surveillance. Additional reasons for underestimations include incomplete reporting and lags in reporting. Spontaneous surveillance systems are prone to reporting bias whereby events that have been previously identified as potentially related to vaccine are more likely to be reported even if they do not meet the clinical definition (stimulated reporting). Conversely, events that have not been previously associated with a vaccine are more likely to be underreported due to lack of recognition of a potential association.

With respect to the expected case counts, estimates of both exposure to vaccine and the background rate have limitations. The exposure estimate assumes that the number of reported vaccine administrations is complete and accurate when in fact globally, not all countries administering vaccine have reported to the data source. Thus, the global exposure is underestimated. Further, because age-sex-specific administration data are not provided for each country in which the vaccine is administered, exposure estimates reflect the distribution among countries for which vaccine administration data are available. A constant ratio of administration by gender was assumed globally, which may not reflect the actual distribution which could potentially over or underestimate the expected counts in any given stratum.

The expected count also assumes that the expected incidence rate in the vaccinated population is the same as that in the population used to calculate the background rate. The background rates used in the myocarditis analyses were based on one EU hospital system among several systems included in the ACCESS background rate project. It is possible that the delivery of health care, population demographics, and underlying health status of the populations used for the background rate estimates differ from those expected in the US/EU, Israeli and global vaccinated population. Similarly, for pericarditis, age-specific strata were not available and the source population from which the estimate is selected may not generalizable to the geographies analyzed here.

### **Comment PRAC Rapporteur:**

The O/E ratio above 1 in the age strata 12-24 years appears a consistent pattern in **all** (independently conducted) O/E analyses thus far. Despite the uncertainties this signal cannot be refuted and warrants further refined analyses. It is reiterated that where possible the MAH should continue their efforts to obtain more specific data regarding age and gender-specific vaccine exposure, country- specific and contemporaneous background incidence rates, outcome.

The limitations of the O/E analyses are acknowledged. Considering the current uncertainties the O/E analysis should be interpreted cautiously and should be used for signal/trend evaluation purposes only. Based on the currently available evidence, no firm conclusions can be drawn to either establish or refute causality.

However, further refinement of the analyses will - in the short term - not be expected be able to completely refute the current signal, nor will it dismiss a causal relation with the vaccine.

Despite the uncertainties and some differences with earlier O/E analyses (e.g. due to differences in chosen background rates, risk window, number of observed cases etc) the most recent MAH analyses are **not** refuting the signal, rather are in line with the previously observed trends in O/E analyses, not only by the MAH, but also those conducted independently by EMA, WHO and other authorities (Israel, US, UK). The overall pattern seems to consistently point to a higher than expected reporting rate of myocarditis within the younger age group, with a predominance in men and following the second dose.

Consequently, the importance of early detection and clear advice to HCP and vaccine recipients in our view justifies reflection of the above findings regarding the occurrence of myocarditis following vaccination in the product information as precautionary risk measure.

**See Recommendation.**

### Question 3

As a substantial amount of cases occurred in Israel, a separate O/E analysis should be performed for Israeli cases, also stratified as above.

#### MAH Response:

Observed to expected analysis stratified by age-sex and dose were also conducted specifically for Israeli reports. Generally the same methods were used as Question 2, except: 70-79 and 80+ age strata were reported and Israel- specific age, sex, and dose exposure- distribution was used. Unless otherwise noted, ratios reflect events occurring after dose 1 or dose 2.

**Table 6. Myocarditis 14-day Risk Window, Israel**

Stratification	Background rate per 100,000 PY	Observed Cases	Expected Cases	O/E Ratio	95% CI
Males 12-24 years	16.67	51	3.1	16.511	12.294, 21.709
Males 25-49 year	16.91	35	9.1	3.829	2.667, 5.325
Males 50-59 years	12.73	2	2.1	0.954	0.116, 3.446
Males 60-69 years	10.90	1	1.4	0.729	0.018, 4.061
Males 70-79 years	13.60	2	1.0	2.084	0.252, 7.529
Males 80+ years	11.82	0	0.5	0.000	-
Females 12-24 years	3.60	4	0.7	6.147	1.675, 15.739
Females 25-49 year	5.36	5	2.9	1.742	0.565, 4.064
Females 50-59 years	5.34	2	0.9	2.147	0.260, 7.755
Females 60-69 years	9.58	0	1.3	0.000	-
Females 70-79 years	10.52	0	0.9	0.000	-
Females 80+ years	9.63	0	0.6	0.000	-
Overall, dose 1	9.95	17	11.1	1.532	0.893, 2.454
Overall, dose 2	9.95	85	11.8	7.215	5.763, 8.922

Abbreviations: PY=Person years; O/E=Observed versus expected; CI=Confidence interval.

**Table 7. Myocarditis 21-day Risk Window, Israel**

Stratification	Background rate per 100,000 PY	Observed Cases	Expected Cases	O/E Ratio	95% CI
Males 12-24 years	16.67	51	4.6	11.020	8.205, 14.489
Males 25-49 year	16.91	35	13.7	2.555	1.780, 3.554
Males 50-59 years	12.73	2	3.1	0.637	0.077, 2.300
Males 60-69 years	10.90	1	2.1	0.486	0.012, 2.710
Males 70-79 years	13.60	2	1.4	1.391	0.168, 5.025
Males 80+ years	11.82	0	0.7	0.000	-
Females 12-24 years	3.60	4	1.0	4.103	1.118, 10.504
Females 25-49 year	5.36	5	4.3	1.162	0.377, 2.713
Females 50-59 years	5.34	2	1.4	1.433	0.174, 5.176
Females 60-69 years	9.58	0	2.0	0.000	-
Females 70-79 years	10.52	0	1.3	0.000	-
Females 80+ years	9.63	0	0.9	0.000	-
Overall, dose 1	9.95	17	16.6	1.023	0.596, 1.638
Overall, dose 2	9.95	85	17.7	4.815	3.846, 5.954

Abbreviations: PY=Person years; O/E=Observed versus expected; CI=Confidence interval.

In both the age-gender-stratified and dose-stratified analyses, the O/E ratios were highest for the 14-day risk window, with similar patterns but numerically lower ratios using the 21-day risk window. Ratios were highest in the 12-24 age group for both males and females, with a higher ratio in males. Using a 14-day risk window, ratios exceeded 1 for Males 12-24 years, Males 25-49 year, Males 70-79 years, Females 12-24 years, Females 25-49 years, and Females 50-59 years. Dose stratified O/E exceeded 1 for both Dose 1 and Dose 2, although the ratio was higher for dose 2.

Limitations of the Israel specific O/E include those noted in the response to Question 2, including especially the potential lack of generalizability of the background rate to other populations.

**Comment PRAC Rapporteur:**

In summary, the MAH concluded that in both the age-gender-stratified and dose-stratified analyses, the O/E ratios were highest for the 14-day risk window, with similar patterns but numerically lower ratios using the 21-day risk window.

Ratios were highest in the 12-24 age group for both males and females, with a higher ratio in males. Using a 14-day risk window, ratios exceeded 1 for Males 12-24 years, Males 25-49 year, Males 70-79 years, Females 12-24 years, Females 25-49 years, and Females 50-59 years. Dose stratified O/E exceeded 1 for both Dose 1 and Dose 2, although the ratio was higher for dose 2.

**Also see comment response to Question 2.**

Based on the total number of cases from Israel (n=102) included in the O/E analysis, it is noted that the MAH opted for a conservative approach (*i.e.* also including 88 out of 102 cases not meeting BC level 1-3), which is supported and valid approach for trend/signal identification purposes.

**See recommendation and outstanding Question 5.**

The MAH's analyses of the data from Israel are in line with the previously observed trends in O/E analyses, not only by the MAH, but also those conducted independently by EMA, WHO and other authorities (Israel, US, UK). The overall picture seems to consistently point to a higher than expected reporting rate of myocarditis within the younger age group, with a predominance in men and following the second dose.

In our view these findings must be adequately reflected in the product information (*i.e.* SmPC Section 4.4 Warnings and precautions, and PL accordingly) in order to increase HCP and vaccinee awareness, enabling early detection and adequate management as warranted. Additionally, a DHPC should be disseminated.

Please note the MAH did not respond to Question 5 *i.e.* 'The MAH should also discuss the need for any potential amendment to the product information and/or the risk management plan and make accordingly a proposal for the changes to the relevant sections within this discussion.'

#### **Question 4**

The MAH should discuss possible mechanisms by which the vaccine may cause myocarditis. In this respect, the MAH should also consider Multisystem inflammatory syndrome in children (MIS/MIS-C) as alternative etiology. In addition, the MAH should discuss the immunologic mechanism of MIS-induced myocarditis following COVID-19, and if any parallels can be drawn to the immunologic reactions following vaccination.

#### **MAH response**

A clear relationship between the vaccine and the reported myocarditis and pericarditis has not been determined. Myocarditis may be due to an assortment of causes including viral or bacterial infection, autoimmune, genetic, metabolic (*e.g.*, diabetes mellitus) and toxic factors.<sup>3</sup> Because cases of myocarditis are thought to have viral causes, the incidence could vary depending on local epidemiology.<sup>3</sup>

Nonclinical studies and protein sequence analyses have not identified any mechanism for a relationship between vaccine administration and immune-mediated myocarditis or pericarditis. In nonclinical studies in rats administered doses of up to 100 µg BNT162b2 intramuscularly (IM) once weekly for 3 times, there was no microscopic evidence of myocarditis or pericarditis at the end of either the dosing or recovery phases.

Further, there was no evidence of MIS or any other type of immune-mediated lesion. In nonhuman primates administered BNT162b2 at doses of up to 100 µg IM twice 3 weeks apart followed by SARS-CoV-2 challenge, there was no evidence of myocarditis, pericarditis, or MIS at 7-8, 14-15, or 21-23 days post challenge.

Distribution of a lipid nanoparticle (LNP) with a comparable lipid composition to BNT162b2 but with a surrogate luciferase RNA (monitoring the 3H-CHE lipid label) was investigated in blood, plasma and selected tissues (including heart) in male and female Wistar Han rats over 48 hours after a single IM injection of 50 µg mRNA/animal (Study 185350). The heart was not identified as a site of LNP distribution.

In order to identify potential epitope based molecular mimicry, the SARS-CoV-2 spike protein was computationally broken into 10 amino acid peptides with 7 amino acid overlaps with the EMBOSS splitter. These were used as BLASTP queries against the current version (May 2021) of the Swissprot human proteome, including all the isoforms at the UniProt site. Hits were evaluated for tissue distribution and cellular localization, with only membrane-expressed proteins further assessed. This review did not identify any membrane-expressed heart-specific proteins with homology to the spike protein.



The ACE2 receptor is widely expressed in human tissue. Expression is greatest in the intestine, kidney, liver, pancreas, lung, and reproductive tissues, and generally low in other tissues, including heart (The Human Protein Atlas).<sup>4</sup> Spike antigen expression by modRNA is anticipated to be primarily local, at the injection site. Systemic exposure to the expressed spike protein antigen is expected to be very low, and thus binding of the protein to ACE2 receptors leading to an off-target immune response to the antigen-receptor complex is highly unlikely, particularly in tissues with low ACE-2 expression.

Vaccine-associated myocarditis has been reported with an assortment of vaccines (e.g., influenza, smallpox, tetanus toxoid, diphtheria/poliomyelitis/tetanus, HBV, MENcn-C), although diagnostic endomyocardial biopsies are rare. An endocardial biopsy from a case of myocarditis associated with inactivated influenza vaccine demonstrated lymphocytic myocarditis, indicating a viral or delayed-type hypersensitivity mechanism.<sup>5</sup> Single reports of eosinophilic myocarditis were reported with MENcn-C, HBV, tetanus toxoid, and small pox vaccines.<sup>6,7,8</sup> Eosinophilic myocarditis is considered a hypersensitivity myocarditis and is associated with increased peripheral eosinophils in most patients. Nonclinical studies in rats administered BNT162b2 had slight increases in eosinophils along with a prominent neutrophilic response and were interpreted to be the result of generalized myeloid cell stimulation rather than a hypersensitivity reaction.

The pathophysiology of MIS-C is not well understood. It is thought to result from immune dysregulation triggered by SARS-CoV-2, stimulating an abnormal immune response having some clinical similarities to Kawasaki disease (KD), macrophage activation syndrome (MAS), and cytokine release syndrome. The exact mechanisms by which SARS-CoV-2 triggers the abnormal immune response are unknown, but a post-infectious process is suggested. Typically, elevated inflammatory markers and evidence of cytokine storm are frequently observed.<sup>9,10</sup>

The mechanisms of myocardial injury in MIS-C are not well characterized, with possible causes including injury from systemic inflammation, acute viral myocarditis, hypoxia, stress cardiomyopathy, and, rarely, ischemia caused by coronary artery (CA) involvement.<sup>9</sup> Limited data are available characterizing cardiac histopathology in MIS-C. Autopsy findings in one fatal case of MIS-C, were notable for evidence of myocarditis, pericarditis, and endocarditis characterized by inflammatory cell infiltration.<sup>11</sup> Additionally, SARS-CoV-2 virus was detected in cardiac tissue by electron microscopy and PCR, but some of the clinical features in this patient were uncharacteristic of MIS-C and possibly more reflective of severe acute COVID-19 rather than MIS-C.<sup>10,11</sup>

Preliminary studies, based on small numbers of patients, suggest children who develop MIS-C maintained highly inflammatory monocyte-activating SARS-CoV-2 IgG antibodies<sup>12</sup> and had persistent cytopenias<sup>13</sup> (particularly T cell lymphopenia). CD8+ T cells are implicated in the clinical presentation and disease course of MIS-C.<sup>14</sup> Carter et al<sup>15</sup> reported that high levels of interleukin-1 $\beta$  (IL-1 $\beta$ ), IL-6, IL-8, IL-10, IL-17, interferon- $\gamma$  and differential T and B cell subset lymphopenia are observed in the acute phase of MIS-C. High CD64 expression on neutrophils and monocytes, and high HLA-DR expression on  $\gamma\delta$  and CD4+CCR7+ T cells in the acute phase, suggested that these immune cell populations were activated.<sup>15</sup>

For BNT162b2, one non-clinical toxicity study (Study 38166) in Wistar Han rats assessed cytokine changes (IFN $\gamma$ , TNF $\alpha$ , IL-1 $\beta$ , IL-6, and IL-10) pre-dose and at 6 and 48 hours post-dose. Compared with the buffer control, there were no test-article related differences in the concentration of serum cytokines at any time point evaluated. From the Phase 1/2 clinical trial most participants had a strong IFN $\gamma$ - or IL-2-positive CD8+ and CD4+ T helper type 1 (TH1) T cell response, detectable throughout the full observation period of nine weeks following vaccine boost.<sup>16</sup>



No obvious parallels can be drawn from the limited data characterizing the immune responses in MIS-C and the known immunologic reactions following vaccination. Further, based on the age distribution of and data in the cases available in the global database drawing parallels or attributing alternate etiology to MIS-C is not supported at this time.

**Comment PRAC Rapporteur:**

The MAH provided a discussion on possible mechanisms by which the vaccine may cause myocarditis, including Multisystem inflammatory syndrome in children (MIS/MIS-C) as alternative aetiology.

In summary, at the moment a clear causal relationship between the vaccine and the reported myocarditis and pericarditis cannot be refuted.

Irrespective of vaccination, myocarditis may be due to numerous of causes including viral or bacterial infection, autoimmune, genetic, metabolic (*e.g.*, diabetes mellitus) and toxic factors. As generally cases of myocarditis are thought to have infectious causes, the incidence could vary depending on local epidemiology.

Vaccine-associated myocarditis has been reported with several vaccines (*e.g.*, influenza, smallpox, tetanus toxoid, diphtheria/poliomyelitis/tetanus, HBV, MENcn-C), although diagnostic endomyocardial biopsies are rare. An endocardial biopsy from a case of myocarditis associated with inactivated influenza vaccine demonstrated lymphocytic myocarditis, indicating a viral or delayed-type hypersensitivity mechanism.

Based on randomised clinical trial data at the moment there is no suggestion that myocarditis or pericarditis would be a risk causally related to vaccination with Comirnaty. However, the RCT was not powered to detect very rare adverse events and the younger age groups were relatively less well represented.

Nonclinical data thus far have not observed clear (mechanistic) evidence supportive of Vaccine-induced and immune-mediated myocarditis or pericarditis:

- In rats administered doses of up to 100 µg BNT162b2 intramuscularly (IM) once weekly for 3 times there was no microscopic evidence of myocarditis or pericarditis at the end of either the dosing or recovery phases
- In nonhuman primates administered BNT162b2 at doses of up to 100 µg IM twice 3 weeks apart followed by SARS-CoV-2 challenge, there was no evidence of myocarditis, pericarditis, or MIS at 7-8, 14-15, or 21-23 days post challenge
- Biodistribution studies in rats using bio-luminescent labelled LNP did not identify the heart as a site of LNP distribution

Nevertheless, eosinophilic myocarditis is considered a hypersensitivity myocarditis and is associated with increased peripheral eosinophils in most patients. Nonclinical studies in rats administered BNT162b2 had transient slight increases in eosinophils along with a prominent neutrophilic response (resolved at the end of recovery period) and were interpreted to be the result of generalized myeloid cell stimulation rather than a hypersensitivity reaction. This may suggest a possible pathogenic mechanism.

Amino-acid sequence homology search for molecular mimicry/autoimmune targets did not identify any membrane-expressed heart-specific proteins with homology to the spike protein.

Systemic exposure to the expressed spike protein antigen is expected to be very low, and thus binding of the protein to ACE2 receptors leading to an off-target immune response to the antigen-receptor complex is considered highly unlikely, particularly in tissues with low ACE-2 expression.

At the moment no obvious parallels can be drawn from the limited data characterizing the immune responses in MIS-C and the known immunologic reactions following vaccination.

The MAH's discussion is accepted.

#### **Question 5**

The MAH should also discuss the need for any potential amendment to the product information and/or the risk management plan and make accordingly a proposal for the changes to the relevant sections within this discussion.

#### **MAH response**

Not provided.

#### **Comment PRAC Rapporteur:**

**Question 5 is still outstanding. Issue not resolved.**

### **3.1.1.2. PERICARDITIS**

#### **Question 1**

The MAH should provide a review of all cases of pericarditis with a DLP as recent as possible, but at least up to 31 May 2021. The MAH should ensure that all relevant cases are processed (not in backlog) and included in the review.

This review should include case ascertainment (as per Brighton collaboration (if available) or alternative case definition), diagnostic work-up, causality assessment and outcome of the events (e.g. hospitalization, life-threatening, or death) for each case report.

The review should explore possible risk factors (e.g. specific medical history such as autoimmune diseases, previous COVID-19 disease, etc), taking into account the gender, age and dose distribution of reported cases.

#### **MAH Response:**

Two hundred and ninety-six (296) reports were coded with the PT Pericarditis, cumulatively to 31 May 2021. Of these, 162 events occurred after the dose 1, 108 events occurred after the dose 2, and the rest were of an unspecified dose sequence.

The events were evaluated based on the European Association for Cardio-Thoracic Surgery (EACTS) criteria<sup>17</sup> for evaluation of the status of pericarditis<sup>18</sup>:

Acute: At least two of the following criteria:

- Pericardiac chest pain
- Pericardial rubs
- Widespread ST elevation or PR depression in ECG
- Pericardial effusion.

Incessant: Pericarditis lasting more than 4-6 weeks but less than 3 months without remission.

Recurrent: Recurrence of pericarditis after a documented first episode of acute pericarditis and a symptom-free interval for 4-6 weeks or longer.

Chronic: Pericarditis lasting for more than 3 months.

Of the total 296 cases, 280 cases were assessed as acute, 15 cases as chronic, and 1 case as incessant.

Out of the 280 acute pericarditis cases, there were 141 females, 134 males, and 4 with unspecified gender. The age ranged between 17-89 (mean 51.75, median: 51.5). Sixteen (16) cases had a history of COVID-19, 10 had diabetes, and 16 cases had a history of pericarditis. No medical history was provided/reported for 166 cases.

Four (4) cases had a fatal outcome; these occurred in the age group of 72-92 years. Three (3) cases had a history of heart disease, and 1 case had a history of COVID-19 infection.

No cases of pericarditis were reported in subjects below 16 years of age.

France (52 cases) and Israel (47 cases) were the countries with most frequent reports of Pericarditis.

**Table 8. Summary of Pericarditis Events With Fatal Outcome**

Case No / Age Band / Gender	Medical History / Preferred Terms	EACTS Evaluation	Brief Narrative Summary of AER
1 80+ years FEMALE	COVID-19 / Cerebrovascular accident / Cough / Hemiparesis / Hypertension / Intraosseous meningioma / Nasopharyngitis / Sciatica / Type 2 diabetes mellitus  Septic shock, Multiple organ dysfunction syndrome, Pericarditis, Myocarditis	Acute	Medical history included COVID-19 infection in December 2020 as well as meningioma, hypertension and hemiparesis. She received the first injection on day 0. She had cough and cold for 2 days. She then experienced septic shock, extensive myo- and pericarditis and multiple organ failure on day 3. Lab tests reflected increase in lactate and inflammation values. The events led to a fatal outcome on day 5. An autopsy was performed revealing myopericarditis.
2 80+ years FEMALE	Chronic kidney disease / Colorectal cancer / Dementia Alzheimer's type / Dysphagia / Osteoarthritis / Pulmonary embolism / Sinoatrial block / Spinal osteoarthritis / Starvation  Acute pulmonary oedema, Dyspnoea, Cardiac failure acute, Pericarditis	Acute	. Medical history included colorectal cancer, pulmonary embolism and sinoauricular heart block. She received her first dose on day 0. On day 1, she experienced dyspnea that led to hospitalization. Imaging showed cardiomegaly. The diagnosis was acute heart failure attack with dyspnea, acute pulmonary edema on pericarditis. She received furosemid. On day 27 the patient died. Unknown if autopsy was conducted.
3 80+ years MALE	Acute myocardial infarction / Basal cell carcinoma / Bladder cancer / Cardiac failure congestive / Cataract / Cholelithiasis / Chronic kidney disease / Colitis ischaemic / Debridement / Essential hypertension / Lung neoplasm / Mitral valve incompetence / Myocardial ischaemia / Splenectomy / Stent placement / Transurethral bladder resection	Acute	Medical history included mitral regurgitation, ischemia heart disease, myocardial infarction, congestive heart failure. On day 0, he was found unresponsive and was transferred to hospital. Cardiac arrest was confirmed. The clinical event was concluded to be myocardial infarct leading to death. The patient died on day 1. The autopsy revealed pathologies in various organs. Most notably, left myocardium transmural thinning pointing to history of myocardial infarcts.
4 70-79 years FEMALE	Myocardial infarction, Cardiac arrest, Circulatory collapse, Myocardial haemorrhage, Confusional state, Hypotension, Pericarditis, Pleural effusion, Pulmonary oedema Acute myeloid leukaemia / Blood cholesterol increased / Body mass index increased / Cardiac arrest / Chest pain / Gastroesophageal reflux disease / Hypertension / Neoplasm  Pericarditis, Chest pain, Cardiac arrest, Musculoskeletal pain, Dyspnoea, Neutropenia	Acute	Patient had medical history of cardiac arrest, chest pain, high cholesterol, AML, and hypertension. She had recent chemo/radiation therapy. She received the vaccine on day 0. On day 3 she experienced chest pain and shortness of breath. The patient underwent lab tests and procedures which included COVID-19 virus test: negative on day 3, computerised tomogram (CTPA): pericardial effusion and bilateral basal atelectasis. Patient was diagnosed with pericarditis on day 3. On day 7 patient experienced cardiac arrest 2 times with return of spontaneous circulation in between, then experienced pulseless electrical activity (PEA) arrest. The patient died on day 8 reportedly due to pericarditis. Etiologic workup of the myocarditis was not provided. An autopsy was not performed. <sup>a</sup>

a. Included in Appendix 3.9 of SMSR #6

**Comment PRAC Rapporteur:**

The MAH used the European Association for Cardio-Thoracic Surgery (EACTS) criteria<sup>17</sup> for evaluation of the status of pericarditis. This is accepted.

In contrast to the PRAC request the MAH only has presented a causality assessment of the fatal cases. An evaluation of causality in all cases, especially those not reporting alternative aetiologies, confounding medical history or underlying conditions is currently lacking. This is not accepted.

It is reiterated that the MAH should provide a causality assessment and outcome of the events (e.g. hospitalization, life-threatening, or death) for each case, in particular for those cases not reporting alternative aetiologies, confounding medical history or underlying conditions (**Request for Supplementary Information**).

**Also see Section 3.1.2 for a summary of the EEA cases by the PRAC Rapporteur.**

Following the PRAC Rapporteur's own assessment of a causal relation between (acute) pericarditis and the vaccination is hampered by the confounding medical history and comorbidities/conditions (e.g. COVID-19, diabetes, heart disease, including previous pericarditis). Nevertheless in cases that describe a suggestive short TTO and absence of confounding medical history, comorbidities or risk factors, a causal role of the vaccine cannot be excluded and is considered possible.

A causal role of the vaccine in the 4 fatal cases, cannot be ruled out, but seems unlikely due to advanced age of the patients with considerable comorbidities (*i.e.* COVID, meningioma, sepsis, CVA, colorectal cancer, bladder cancer, chronic kidney disease, Acute Myeloid Leukemia, neoplasm).

**Question 2**

The MAH should also provide a more refined O/E analysis. This O/E analysis with a DLP of 31 May 2021 or later, should be stratified by:

- age, by strata of 12-15, 16-19, 20-24, 25-29, 30-39, and thereafter 10 years intervals
- gender
- dose (1st or 2nd)

Besides the used 21-day risk window and no risk window in the O/E analysis, additional O/E analysis are requested using a 14-day risk window.

**MAH Response**

Background rates of pericarditis are not provided by the ACCESS/VAC4EU initiative. Age- and gender-specific rates of pericarditis were not identified in the literature. A constant background rate of 18.0/100,000 PY<sup>19</sup> is assumed for all strata. Unless otherwise noted, ratios reflect events occurring after dose 1 or dose 2.

**Table 9. Pericarditis 14-day Risk Window, EU and US**

Stratification	Background rate per 100,000 PY	Observed Cases	Expected Cases	O/E Ratio	95% CI
Males 12-24 years	18.00	14	71.1	0.197	0.108, 0.330
Males 25-49 year	18.00	19	271.3	0.070	0.042, 0.109
Males 50-59 years	18.00	9	176.4	0.051	0.023, 0.097
Males 60-69 years	18.00	14	183.7	0.076	0.042, 0.128
Males 70+ years	18.00	14	333.9	0.042	0.023, 0.070
Females 12-24 years	18.00	5	80.2	0.062	0.020, 0.145
Females 25-49 year	18.00	35	305.9	0.114	0.080, 0.159
Females 50-59 years	18.00	15	198.9	0.075	0.042, 0.124
Females 60-69 years	18.00	9	207.1	0.043	0.020, 0.082
Females 70+ years	18.00	25	376.5	0.066	0.043, 0.098
All dose 1	18.00	89	1,340.9	0.066	0.053, 0.082
All dose 2	18.00	70	863.9	0.081	0.063, 0.102

Abbreviations: EU=European Union; US=United States; PY=Person years; O/E=Observed versus expected; CI=Confidence interval.

**Table 10. Pericarditis 14-day Risk Window, Globally**

Stratification	Background rate per 100,000 PY	Observed Cases	Expected Cases	O/E Ratio	95% CI
Males 12-24 years	18.00	22	82.7	0.266	0.167, 0.403
Males 25-49 year	18.00	40	357.2	0.112	0.080, 0.152
Males 50-59 years	18.00	14	238.5	0.059	0.032, 0.098
Males 60-69 years	18.00	22	250.4	0.088	0.055, 0.133
Males 70+ years	18.00	21	462.1	0.045	0.028, 0.069
Females 12-24 years	18.00	8	93.2	0.086	0.037, 0.169
Females 25-49 year	18.00	51	402.3	0.127	0.094, 0.167
Females 50-59 years	18.00	19	269.0	0.071	0.043, 0.110
Females 60-69 years	18.00	12	282.3	0.043	0.022, 0.074
Females 70+ years	18.00	33	521.1	0.063	0.044, 0.089
All dose 1	18.00	127	1,826.1	0.070	0.058, 0.083
All dose 2	18.00	115	1,162.4	0.099	0.082, 0.119

Abbreviations: PY=Person years; O/E=Observed versus expected; CI=Confidence interval.

**Table 11. Pericarditis 21-day Risk Window, EU and US**

Stratification	Background rate per 100,000 PY	Observed Cases	Expected Cases	O/E Ratio	95% CI
Males 12-24 years	18.00	15	103.1	0.145	0.081, 0.240
Males 25-49 year	18.00	22	390.6	0.056	0.035, 0.085
Males 50-59 years	18.00	10	251.0	0.040	0.019, 0.073
Males 60-69 years	18.00	15	264.4	0.057	0.032, 0.094
Males 70+ years	18.00	22	486.2	0.045	0.028, 0.069
Females 12-24 years	18.00	5	116.3	0.043	0.014, 0.100
Females 25-49 year	18.00	38	440.5	0.086	0.061, 0.118
Females 50-59 years	18.00	17	283.1	0.060	0.035, 0.096
Females 60-69 years	18.00	10	298.1	0.034	0.016, 0.062
Females 70+ years	18.00	26	548.3	0.047	0.031, 0.069
All dose 1	18.00	100	1,940.2	0.052	0.042, 0.063
All dose 2	18.00	80	1,241.4	0.064	0.051, 0.080

Abbreviations: EU=European Union; US=United States; PY=Person years; O/E=Observed versus expected; CI=Confidence interval.

**Table 12. Pericarditis 21-day Risk Window, Globally**

Stratification	Background rate per 100,000 PY	Observed Cases	Expected Cases	O/E Ratio	95% CI
Males 12-24 years	18.00	23	119.5	0.192	0.122, 0.289
Males 25-49 year	18.00	43	512.8	0.084	0.061, 0.113
Males 50-59 years	18.00	15	339.1	0.044	0.025, 0.073
Males 60-69 years	18.00	23	358.9	0.064	0.041, 0.096
Males 70+ years	18.00	31	667.8	0.046	0.032, 0.066
Females 12-24 years	18.00	8	134.7	0.059	0.026, 0.117
Females 25-49 year	18.00	54	577.4	0.094	0.070, 0.122
Females 50-59 years	18.00	21	382.4	0.055	0.034, 0.084
Females 60-69 years	18.00	14	404.7	0.035	0.019, 0.058
Females 70+ years	18.00	35	753.0	0.046	0.032, 0.065
All dose 1	18.00	140	2,629.0	0.053	0.045, 0.063
All dose 2	18.00	127	1,665.9	0.076	0.064, 0.091

Abbreviations: PY=Person years; O/E=Observed versus expected; CI=Confidence interval.

None of the O/E analyses had a ratio greater than 1. For the EU/US analysis, both the age- gender-stratified and dose-stratified analyses the O/E ratios were higher for the 14-day risk window ([Table 9](#)), with similar patterns but numerically lower ratios using the 21-day risk window ([Table 11](#)). Ratios were highest in the 12-24 age group for males and 25-49 age group for females. The upper level of the 95% CI did not exceed 1 for any of the age-gender strata; ratios were higher for dose 2 compared to dose 1.

The Global O/E analysis ([Table 10](#) and [Table 12](#)), which include cases from Israel, demonstrated the similar patterns as EU/US only.

**Comment PRAC Rapporteur:**

As no background rates of pericarditis are provided by the ACCESS/VAC4EU initiative and age- and gender-specific rates of pericarditis were not identified in the literature, a constant background rate of 18.0/100,000 PY is considered acceptable for signal detection purposes.

However the MAH should still present the data in the age strata (12-15, 16-19, 20-24) as requested previously. **Question 2 not resolved.**

The MAH's conclusion is accepted that none of the O/E analyses had a ratio greater than 1.

For the EU/US analysis, both the age- gender-stratified and dose-stratified analyses the O/E ratios were higher for the 14-day risk window ([Table 9](#)), with similar patterns but numerically lower ratios using the 21-day risk window ([Table 11](#)).

Ratios were highest in the 12-24 age group for males and 25-49 age group for females. The upper level of the 95% CI did not exceed 1 for any of the age-gender strata; ratios were higher for dose 2 compared to dose 1.

The MAH noted that global O/E analysis ([Table 10](#) and [Table 12](#)), which include cases from Israel, demonstrated the similar patterns as EU/US only.

Based on the currently available evidence a causal relation between Comirnaty and pericarditis is considered weak. Nevertheless, note that clearly separating pericarditis from myocarditis is challenging as the term pericarditis can refer to inflammation of the pericardium and myocarditis. Both can occur together in clinical practice, and hence the term myopericarditis is used. Sometimes myopericarditis is used interchangeably with perimyocarditis. In the EEA cases of myocarditis, cases reporting both myocarditis and pericarditis have been included (17 cases of perimyocarditis and 16 cases of myopericarditis).

Pending the MAH's response to the outstanding issues and additional analyses the signal for pericarditis should remain open.

In addition the MAH should continue to closely monitor any new cases and notify the Rapporteur in case of unexpected trends or findings.

### **Question 3**

The MAH should discuss possible mechanisms by which the vaccine may cause pericarditis. In this respect, the MAH should also consider Multisystem inflammatory syndrome in children (MIS/MIS-C) as alternative etiology. In addition, the MAH should discuss the immunologic mechanism of MIS-induced pericarditis following COVID-19, and if any parallels can be drawn to the immunologic reactions following vaccination.

#### **MAH Response:**

Please refer to the answer to Question 4 in **3.1.1.1. MYOCARDITIS**.

#### **Comment PRAC Rapporteur:**

See comment regarding Response to Question 4 in **3.1.1.1. MYOCARDITIS**, above.

### **Question 4**

The MAH should also discuss the need for any potential amendment to the product information and/or the risk management plan and make accordingly a proposal for the changes to the relevant sections within this discussion.

#### **MAH Response:**

While the MAH is committed to rapid communication of safety information that is relevant to the risk benefit assessment of the vaccine, we are aware of the importance of ensuring such information is scientifically accurate and clear. The MAH will assess emerging data on pericarditis and propose amendments to the product information and/or the risk management plan as warranted. At this time, the totality of the data does not confirm a causal relationship with the vaccine.

#### **Comment PRAC Rapporteur:**

The MAH's commitments are noted.

Based on the currently available evidence a causal relation between Comirnaty and pericarditis is considered weak. Nevertheless, it is also noted that pending the MAH's response to the outstanding issues and additional analyses the signal for pericarditis should remain open.



## MAH SUMMARY AND CONCLUSION (as included in the 6<sup>th</sup> MSSR)

In the context of over 600 million doses of the vaccine distributed, there have been 495 reports of potential myocarditis or pericarditis events. Two hundred and sixty (260) reports were coded with the PT Myocarditis and 235 coded to Pericarditis. There is a dearth of information provided with respect for the investigations into viral or other aetiologies; however, the characteristics of the reports are consistent with the usual presentation of the disease (*i.e.* age and sex). The rate at which these events are reported (even without applying the diagnostic certainty criteria) do not exceed the expected background rate. It should be noted that with the case information currently available, only 18 (6.9%) of the cases could be assessed as “confirmed cases” of myocarditis as per Brighton Collaboration criteria. It is worth noting that the incidence rate of myocarditis in COVID-19 infected patients is 2.3 out of 100 in a recovering population.<sup>5</sup> Given the totality of the data, a causal association between the vaccine and myocarditis or pericarditis cannot be established. The MAH will continue to perform robust pharmacovigilance, follow up, and monitoring of this topic.

### Comment PRAC rapporteur:

The number of cases as included in the MAH’s most recent submission (MAH response to LoQ Signal procedure EPITT ref 19712 dated 22 June 2021) is as follows:

In total **358** reports coded Myocarditis AEs; **296** coded Pericarditis, including 25 reports reporting both PTs (Myocarditis and Pericarditis)

See **Recommendation**.

### 3.1.2. EudraVigilance query EEA cases by EMA and PRAC Rapporteur

On 23 June 2021 the EMA provided (separately from the MAH submission) an EudraVigilance query of EEA cases of myocarditis and pericarditis (DLP 31 May 2021) which is summarised below.

#### 3.1.2.1. MYOCARDITIS

As of 31 May 2021, in Eudravigilance were received 145 cases reporting myocarditis with Comirnaty vaccine in the EEA. In these 145 cases, 143 cases were assessed as serious for which the seriousness criteria was ticked 172 times as follows: 5 times 'Death', 18 times 'Life-threatening', 104 times 'Hospitalization', 2 times 'Disabling' and 43 times 'Seriousness Other'.

Out of these cases, 94 patients were males (65%), 50 were females and for one case the sex was not specified. The median age of the vaccinees was 49 years old (range from <18 years to 80+ years).

58 cases were from Germany, 26 from France, 11 from Italy, 9 from Austria, 9 from Greece, 9 from Spain, 6 from Sweden, 4 from Norway, 3 from Ireland, 2 from Belgium, 2 from Finland, 2 from Portugal, 1 each from Czech Republic, Denmark, Luxembourg and Poland.

The 145 cases were matched to the latest Brighton Collaboration criteria for myocarditis: 29 cases were assessed as level 1, 36 cases as level 2, 1 case as level 3 (total of 107 cases as level 1-3), 75 cases as level 4 and 2 cases as level 5 (total of 77 cases as level 4-5). The description in one case is more like a viral pericarditis, responding to steroid therapy; therefore for this case the BC level cannot be assigned. Also, in another case, BC classification is uncertain as no information regarding symptoms (or imaging) was provided (it is likely patient has at least unspecific symptoms).

Mean TTO is 8 days (ranging from 0 to 64 days): in 82 of the 145 cases TTO was  $\leq 5$  days, in 32 cases TTO was ranging from 6 to 15 days, in 16 cases TTO was ranging from 16 to 56 days, in 3 cases TTO was 64 days and TTO could not be calculated in 12 cases. In 25 of the 145 cases the outcome was recovered, in 41 cases recovering, in 54 cases not recovered (note: including one fatal case), and in 21 cases outcome unknown. There were 5 fatal cases.

In 47 cases the event of myocarditis occurred after the first dose, in 49 cases after the 2nd dose and in 49 cases this information was not reported.

#### Myocarditis after 1<sup>st</sup> dose (n=47) compared to myocarditis after 2<sup>nd</sup> dose (n=49)

Out of the 47 cases of myocarditis after the first dose, 60% (28) were male and 19 were female. After the second dose, 73% (36) of 49 were male, 12 female and for 1 case the sex was not specified. Mean TTO of 9.3 days after first dose (range 0 to 49 days) and after second dose mean TTO is 6.0 days (range 0-64 days).

From the tables a and b below, it is shown that 55% (26/47) patients with myocarditis after first dose and 45% (22/49) patients with myocarditis after 2<sup>nd</sup> dose were recovering/recovered. Patients were not recovered from myocarditis in 36% (17/47) and 27% (13/49) of the cases after first dose and second dose, respectively. There were two cases with fatal outcome of myocarditis after the first administration of Comirnaty. After the first dose 12 patients (26%) were < 30 years old with mean TTO of 5 days (range from 1 to 13 days), of which 8 were male. After the second dose 21 patients (43%) were < 30 years with mean TTO of 2.5 days (range 0-5), of which 18 were male.

Myocarditis after second dose with mean TTO of 6,0 days is shorter than 9.3 days, compared to after first dose. 60% were male after the first dose and 73% were male after the second dose. 43% is < 30 years of age after the second dose, compared to 26% after the first dose; majority concern male patients and TTO is shorter after the second dose. However, in more cases the outcome for myocarditis was reported as recovered or recovering after the first dose. This could be explained the outcome of myocarditis was unknown for 12 cases after the second dose.

Based on this review, it seems that myocarditis occurred with a shorter TTO after second dose and concerns mostly male patients.

Tabel a – Myocarditis after 1<sup>st</sup> dose

Sex	Age Band	TTO	Outcome
Male	18-29	12	Recovering
Male	18-29	2	recovering
Male	18-29	8	recovering
Male	18-29	1	Not recovered
Male	18-29	6	recovered
Male	18-29	2	recovered
Male	18-29	1	Recovering
Female	18-29	3	not recovered
Male	18-29	4	not recovered
Female	18-29	7	recovering
Female	18-29	13	recovering
Female	18-29	2	recovering
Female	30-39	3	not recovered
Male	30-39	2	recovered
Male	30-39	5	not recovered
Male	40-49	3	Unknown
Female	40-49	17	Not recovered
Female	50-59	0	not recovered
Male	50-59	0	not recovered
Male	50-59	15	Recovered
Male	50-59	14	recovered
Male	50-59	12	Recovering
Male	50-59	4	not recovered
Female	50-59	49	recovering
Male	50-59	unknown	recovering
Female	50-59	17	recovering
Female	60-69	15	not recovered
Male	60-69	2	recovering
Female	60-69	15	Not recovered
Male	60-69	20	not recovered
Male	60-69	2	recovering
Female	60-69	17	Recovered
Female	60-69	11	not recovered
Female	60-69	9	recovering
Male	60-69	13	recovering

Female	60-69	26	recovering
Male	70-79	4	unknown
Male	70-79	10	not recovered
Female	70-79	1	recovered
Male	70-79	unknown	not recovered
Female	70-79	6	Recovered
Female	80+	21	Recovering
Male	80+	2	not recovered
Female	80+	2	fatal
Male	80+9	26	not recovered
Male	80+9	15	recovering
Male	80+	1	fatal

Tabel b – Myocarditis after 2nd dose

Sex	Age Band	TTO	Outcome
Male	18-29	5	unknown
Male	<18	5	unknown
Female	18-29	3	recovered
Male	18-29	0	recovered
Female	18-29	4	unknown
Male	18-29	4	recovered
Male	18-29	3	Unknown
Male	18-29	2	not recovered
Female	18-29	2	unknown
Male	18-29	3	not recovered
Male	18-29	4	not recovered
Male	18-29	1	recovering
Male	18-29	1	recovering
Male	18-29	2	Recovering
Male	18-29	2	unknown
Male	18-29	3	recovering
Male	18-29	4	recovering
Male	18-29	3	unknown
Male	18-29	0	Recovering
Not Specified	18-29	1	unknown
Male	18-29	1	recovering
Male	30-39	3	not recovered
Female	30-39	2	Recovering
Male	30-39	2	recovering
Male	30-39	4	not recovered
Male	30-39	3	recovered
Male	30-39	64	recovering
Male	30-39	2	not recovered
Male	30-39	2	not recovered
Male	30-39	1	not recovered
Male	30-39	2	recovered

Male	30-39	3	recovering
Female	40-49	0	recovering
Female	40-49	unknown	unknown
Male	40-49	2	recovering
Male	40-49	4	Recovering
Male	40-49	4	recovering
Female	40-49	56	not recovered
Male	40-49	2	Recovering
Female	50-59	unknown	unknown
Male	50-59	3	not recovered
Male	60-69	unknown	not recovered
Male	70-79	34	recovering
Female	70-79	3	unknown
Male	70-79	15	Unknown
Female	70-79	6	Not recovered
Female	80+	0	recovering
Female	Not Specified	unknown	Not recovered
Male	Not Specified	2	Not recovered

#### Cases with other alternative etiology or other potential confounders

In 22 of the 145 cases another alternative etiology was identified:

- 13 cases after 1<sup>st</sup> dose:
  - o 5 females:
    - viral serology + (50-59Y, TTO: 0 days, not recovered, BC L2)
    - history of pericarditis (20-29Y, TTO: 2 days, recovering, BC L1) + medical history of Covid-19 infection
    - viral serology + (60-69Y, TTO: 9 days, resolving, BC L1)
    - viral serology + (60-69Y, TTO: 11 days, not recovered, BC L1)
    - history of pericarditis (50-59Y, TTO: 49 days, recovering, could not assign BC level)
  - o 8 males:
    - insulin dependent (70-79Y, TTO: 4 days, unknown outcome, BC L2)
    - Medical history included: Chronic lymphatic leukaemia, Coronary heart disease, Aortic bypass, Cardiac insufficiency, Myocardial infarction, Heart valve insufficiency, Hypertension arterial, Hyperlipidaemia, Chronic renal insufficiency (80+Y, TTO: 1 day, fatal, BC L4)
    - viral serology + (50-59Y, TTO: 0 days, not recovered, BC L4) + medical history of Covid-19 infection
    - pre-existing tuberculosis (40-49Y, TTO: 3 days, unknown outcome, BC L1)
    - preexisting celiac disease complication (18-29Y, TTO: 1 day, recovering, BC L2)

- history of pericarditis (60-69Y, TTO: 13 days, resolving, BC L2)
- infectious (50-59Y, TTO: 14 days, recovered, BC L4)
- open heart surgery 2 months ago (60-69Y, TTO: 2 days, recovering, BC L4)
- 5 cases after 2<sup>nd</sup> dose:
  - o 3 females:
    - concurrent infection (80+Y, TTO: 0 days, resolving, BC L1)
    - Covid-19 infection (50-59Y, TTO unknown, unknown outcome, BC L4) *DE-PFIZER INC-2021390864 (see below)*
    - Concurrent acute coronary syndrome (70-79Y, TTO: 6 days, not recovered, BC L1)
  - o 2 males:
    - viral serology + (18-29Y, TTO: 4 days, recovered, BC L1)
    - pre-existing myocarditis (18-29Y, TTO: 0 days, recovering, BC L2)
- 4 cases unknown after which dose myocarditis occurred
  - o 2 females
    - myocardial infarction (80+Y, TTO: 2 days, not recovered, BC L4)
    - pre-existing myocarditis (30-39Y, TTO: 11 days, recovered, BC L4)
  - o 2 males
    - mucoviscidosis (<18Y, TTO: 3 days, recovered, BC L4)
    - history of coronary heart disease (70-79Y, TTO: NA, unknown outcome, BC L4)

In 2 cases patients had medical history of Covid-19 infection which could be considerate as a potential confounder. In one case, Covid-19 infection was identified as etiology:

Case 1 - A non-pregnant 50-59-year-old female patient received BNT162B2 (COMIRNATY), intramuscular in left upper arm, as first dose, single, and then 21 days later (day 0) as second dose, single, for COVID-19 immunization. The patient's medical history included hypertension, adipositas, and non-smoker. The patient's concomitant medications included candesartan and torasemide. No immunomodulatory or suppressive drugs were administered during COVID-19 vaccination timeframe. On day 52, the patient had a positive test result of SARS-CoV-2. It was unknown if pre-existing diseases worsened during the SARS-CoV-2 infection. It was unknown if SARS-CoV-2 antibodies present at time of diagnosis. The patient was not hospitalized, not in intensive care. The patient showed clinical signs of a severe systemic disease at rest (fever, SpO2 91%), not requiring additional oxygen (NOS). There was no multi-organ failure. Respiratory symptoms included dyspnea at load (for example when going to toilet); no tachypnea, no breathing failure, all other stated as unknown. For cardiovascular symptoms, there was no cardiac insufficiency, cardiogenic shock, or acute myocardial infarction. The patient confirmed myocarditis (confirmed via ECG and cardio MRI that showed pericardial effusion in 2021). Neurological symptoms included polyneuropathy (feel of numbness at different parts of the body). The patient also had herpes zoster that required hospitalization from 2021. The patient did not comment for gastrointestinal symptoms, vascular symptoms, renal symptoms, hematological, and dermatological

symptoms. Additional treatment against COVID-19 included dexamethasone 4 mg from day 52 to day 64. Furthermore, the patient received budesonide. The diagnostic test detecting SARS-CoV-2 for negative took 14 days (2021). The patient had not recovered from "Infected with Corona despite the vaccination". The outcome of the other events was unknown.

In 24 of the 145 cases potential confounders (e.g. co-morbidities) were identified:

- 11 cases after 1<sup>st</sup> dose:
  - o 4 females
    - History of left ventricular insufficiency, hypertension, hypercholesterolemia (60-69Y, TTO: 17 days, recovered, BC L1)
    - History of hypertension (60-69Y, TTO: 15 days, not recovered, BC L4)
    - Concurrent arrhythmia (40-49Y, TTO: 17 days, not recovered, BC L2)
    - History of arterial hypertension, dyslipidemia (80+Y, TTO: 21 days, recovering, BC L2)
  - o 7 males
    - IgM + for M. pneumoniae, but unknown if infection already present while diagnosis of myocarditis, or if hospital acquired. (18-29Y, TTO: 8 days, recovering, BC L1)
    - 2 days after diagnosis of myocarditis has acute myocardial infarction. Concurrent Lymphoma, Grade 1, Stage IIIA, reported as in remission. (60-69Y, TTO: 2 days, recovering, BC L4)
    - History of hypertension, obesity (50-59Y, TTO: 15 days, recovered, BC L1)
    - History of Covid-19 infection 192 days before event, pneumonitis (18-29Y, TTO: 1 day, not recovered, BC L4)
    - Previous history of VTE 2019 (including PE in Jan 2021). PE could be an alternative diagnosis. (60-69Y, TTO: 20 days, not recovered, BC L1)
    - Multiple comorbidities, including cardiac. Polymedicated. (80-89Y, TTO: 26 days, not recovered, BC L4)
    - Medical history of myocarditis (1,5 months ago) (50-59Y, TTO: 4 days, not recovered, BC L4) + medical history of Covid-19 infection
- 8 cases after 2<sup>nd</sup> dose:
  - o 8 males
    - 2 episodes of myopericarditis about 13 years ago (30-39Y, TTO: 3 days, recovered, BC L4)
    - History of arrhythmia. (30-39Y, TTO: 3 days, recovering, BC L1)
    - Patient in beginning of November 2020 Covid-19 infection. On 6.01.21 first dose and second dose on 27.01.2021 with clinical and echocardiographic pericarditis. (18-29Y, TTO: 5 days, unknown outcome, BC L4)

- Family history of cardiac disease (18-29Y, TTO: 4 days, recovering, BC L1)
  - History of autoimmune hepatitis and neurologic disease. (20-29Y, TTO: 2 days, recovering, BC L2)
  - History of percutaneous coronary intervention, fibromyalgia, hypothyreosis, pancreatitis, myocardial infarction, hypertension (70-79Y, TTO: 15 days, unknown outcome, BC L2)
  - Respiratory symptoms with dry cough for 2 weeks prior to vaccination (between the 2 doses) Possible perimyocarditis due to viral infection, inflammatory cannot be excluded. (40-49Y, TTO: 2 days, recovering, BC L2)
  - Medical history of myocarditis (2015) (18-29Y, TTO: 2 days, not recovered, BC L2)
- 5 cases unknown after which dose myocarditis occurred
    - o 3 females
      - Concomitantly reported with acute cardiac insufficiency. (70-79Y, TTO: 14 days, not recovered, BC L2)
      - According to the autopsy report the cause of death was shown to be related to an acute myocardial infarction with ventricular rupture and consecutive hemopericardium. (80+Y, TTO: 1 day, fatal, BC L5)
      - History of atherosclerosis, vascular encephalopathy, Type 2 diabetes mellitus (70-79Y, TTO: 7 days, not recovered, BC L4)
    - o 2 males
      - There were indications of a pulmonary embolism (18-29Y, TTO: 22 days, unknown outcome, BC L4)
      - History of coronary sclerosis (50-59Y, TTO: 1 day, fatal, BC L1)

For 46 of the 145 cases, another alternative etiology or other potential confounder could be identified. 24 cases relate to the first dose and 13 cases to the second dose. Most frequently reported were infection related: viral infection, pre-existing pericarditis/myocarditis, pre-existing infection, concurrent infection. Others concerned medical history of cardiac disorders and cardiac co-morbidities. Medical history of Covid-19 infection was also reported in 5 cases which could be considered as a potential confounder.

In the remaining 99 cases no potential confounders or other alternative etiology could be identified. Out of these 99 cases, 52 cases were not assessable, e.g. no narrative was provided by the reporter. In the other 47 cases, medical history information, concomitant medication, outcome, etc, were not reported, nevertheless a causal role of the vaccine cannot be excluded due to suggestive TTO and absence of other etiologies or potential confounders.

#### Fatal cases

Out of 145 myocarditis cases, 5 cases were reported with fatal outcome:

- Case 1 (F, 80+Y, BC L1) The patient's medical history and concurrent conditions included: COVID-19 pneumonia, Apoplexy, Hemiparesis (left) (continuing), Intraosseous meningioma, Hypertension arterial (continuing), Type 2 diabetes mellitus (continuing), Lumboischialgia, Cough (continuing), Common cold (continuing). The patient received first dose Comirnaty



vaccine on day 0. On day 2 the patient experienced carditis pericardium myocardium death, multiorgan failure, septic shock. The patient's outcome was: fatal.

- Case 2 (M, 80+Y, BC L4) A male patient, was vaccinated with the first dose of Comirnaty, for COVID-19 immunisation on day 0. Medical history included: Chronic lymphatic leukaemia, Coronary heart disease, Aortic bypass, Cardiac insufficiency, Myocardial infarction, Heart valve insufficiency, Hypertension arterial, Hyperlipidaemia, Chronic renal insufficiency. On day 1 after vaccination the patient developed weakness and pain in limb and cold symptoms and general physical condition abnormal and circulatory instability and hyperpyrexia and jaundice and myocarditis septic. The patient is dead. Death cause was reported as myocarditis septic.
- Case 3 (M, 50-59Y, BC L1) A male patient, , was treated with Comirnaty (mRNA TOZINAMERAN), unknown dosage. The patient's medical history and concurrent conditions included: Coronary sclerosis. After the vaccination the patient experienced myocarditis, acute myocardial infarction, of anterior wall. The patient's outcome was: fatal. Autopsy: Focal myocarditis of the left ventricular apex extending about 2 cm? with formation of microthrombi and small foci of associated myocardial necrosis. Myocardial necrosis with incipient granulocytic reaction in the sense of an event several hours old.
- Case 4 (F, 80+-Y, BC L5) A female patient, was treated with Comirnaty (mRNA TOZINAMERAN), unknown dosage. After the vaccination the patient experienced bloody stool, tachyarrhythmia absoluta, acute hypotension, transaminases increased, anaemia normocytic, hyponatraemia, perimyocarditis, effusion pericardial, septic shock, cardiogenic shock, acute renal failure. The patient's outcome was: fatal. According to the autopsy report the cause of death is not related to the vaccination. Rather, the cause was shown to be related to an acute myocardial infarction with ventricular rupture and consecutive hemopericardium.
- Case 5 (M, 80+, BC L4) No relevant medical history reported. The patient was treated with Comirnaty (mRNA TOZINAMERAN) on day 0, unknown dosage. No concomitant medication reported. On day 5 the patient experienced dyspnea, myocarditis. The patient experienced also nausea, vomiting, stomach discomfort, floppy. The patient's outcome was: fatal.

In 2 of the 5 cases it was reported that myocarditis occurred after the first dose; this information is lacking in the remaining 3 cases. In 4 fatal cases potential confounders were reported: co-morbidities, including cardiac, were reported in 3 cases and in one case medical history of Covid-19 infection was reported. According to the autopsy report in one case, the cause of death is not related to the vaccination. It is noted that 4 cases concern patients with advanced age (80+Y). From these cases, a causal association between Comirnaty vaccine and myocarditis cannot be confirmed.

#### Cases of people < 30 years old

There were 45 EEA case reports of myocarditis in people under 30 years old. 35 patients were males, 9 were females and for one case the sex was not specified. 18 cases were from Germany, 10 from France, 6 from Italy, 3 from Greece, 2 from Austria, 2 from Spain, 1 from Finland, 1 from Norway, 2 from Poland and 1 from Sweden.

The 45 cases were matched to the latest Brighton Collaboration criteria for myocarditis: 24 cases were assessed as level 1-3 and 21 as level 4-5. In 12 cases the event of myocarditis occurred after the first dose, in 21 cases after the 2nd dose and in 12 cases this information was not reported. Mean TTO is 5 days (ranging from 0 to 22 days): in 34 of the 45 cases TTO was  $\leq 5$  days, in 10 cases TTO was ranging from 6 to 14 days, in one case TTO was 22 days and TTO could not be calculated in one case. In 8 of the 45 cases the outcome was recovered, in 15 cases recovering, in 10 cases not recovered, and in 11 cases outcome unknown. There were no fatal cases.

In 10 of the 45 cases other alternative etiology or other potential confounders identified was identified.

In 3 of the 45 cases patients had medical history of Covid-19 infection which could be considerate as a potential confounder.

From review of the cases in this younger age group, myocarditis was reported predominantly in men and after the second dose.

#### **PRAC Rapporteur's Discussion and Conclusion**

As of 31 May 2021, there were 145 cases reporting myocarditis with Comirnaty vaccine in the EEA. 143 cases were assessed as serious. 94 patients were males (65%), 50 were females. The median age was 49 years old (range from <18 years to 80+ years). There were 5 fatal cases.

By Brighton Collaboration criteria for myocarditis, 107 cases were assessed as level 1-3 and 77 cases as level 4-5. Mean TTO is 8 days (ranging from 0 to 64 days). In 66 cases outcome of recovering/recovered was reported and myocarditis was not recovered in 54 cases. In 47 cases the event of myocarditis occurred after the first dose, in 49 cases after the 2nd dose. First or second dose could not be identified for 49 cases. When comparing the cases of myocarditis after 1<sup>st</sup> dose with myocarditis after 2<sup>nd</sup> dose, the data suggest that myocarditis occurred with a shorter TTO after the second dose than after the first dose.

In 46 of the 145 an other alternative etiology or other potential confounder could be identified. Most frequently reported were infection related: viral infection, pre-existing pericarditis/myocarditis, pre-existing infection, concurrent infection. Others concerned medical history of cardiac disorders and cardiac co-morbidities. Medical history of Covid-19 infection was also reported in 5 cases which could be considerate as a potential confounder. However, no pattern could be identified based on this small number of cases. No specific risk factors for the occurrence of myocarditis after administration of Comirnaty vaccine were identified. 24 cases relate to the first dose and 13 cases to the second dose.

Of the remaining 99 cases, 52 cases were not assessable, e.g. no narrative was provided by the reporter or date of occurrence was not reported. For the other 47 cases a causal role of the vaccine cannot be excluded due to suggestive TTO and absence of other etiologies or potential confounders.

There were 45 (31%) EEA case reports of myocarditis in people under 30 years old. 35 patients were males, 9 were females. By Brighton Collaboration criteria for myocarditis, 24 cases were assessed as level 1-3 and 21 cases as level 4-5. In 12 cases the event of myocarditis occurred after the first dose, in 21 cases after the 2nd dose. Mean TTO is 5 days (ranging from 0 to 22 days). In 23 cases outcome of recovering/recovered was reported and myocarditis was not recovered in 10 cases. Within the current query no fatal cases were identified. In 10 of the 45 an alternative etiology or other potential confounder could be identified.

Based on the PRAC Rapporteur's review of EEA case reports, myocarditis was reported almost equally after first dose (n=47) and after second dose (n=49). The sub-analysis of cases of people < 30 years old showed a predominance in males and following the second dose. Causality assessment was hampered in majority of the cases, however a causal role of the vaccine cannot be excluded due to suggestive TTO and absence of other aetiologies or potential confounders. This observation justifies inclusion of a warning in the Comirnaty PI.

### 3.1.2.2. PERICARDITIS

In total 140 pericarditis cases were identified (1 duplicate): FR (52); IT (26); ES (18); NO (17); BE (4); GR (4); NL (3); DE (2); IE (2); PT (2); RU (2); SE (2); CY(1); HU (1)

Out of 140 cases, 130 were serious and 10 nonserious. No fatal cases were identified in this query, but the MAH has identified 4 fatal cases (see **Section 3.1.1.2 Pericarditis Response to Question 1** Table 8). Of the serious cases 10 cases were designated as life-threatening, 51 were non-life-threatening, and in 79 no information was available. Of the 130 serious cases 72 cases required hospitalisation, 33 cases did not require hospitalisation (and in 30 cases no further information was available).

Pericarditis occurred after dose 1 in 69 cases with a mean TTO of 5 days (median 7 days) ranging from 0 to 26 days. In 49 cases pericarditis occurred after dose 2 with a mean TTO of 15 days (median 10 days) ranging from 1 to 90 days. In 22 cases no information on the dose was available.

#### *Symptoms and Diagnosis*

The majority of cases (82 out of 140) presented with chest pain, of which 36 cases typical chest pain [pain made worse by lying down, deep inspiration or cough, and relieved by sitting up/leaning forward], and 46 other/atypical chest pain. In 57 cases no information on chest pain was reported. One case (Case 38) did not present with chest pain but pronounced dyspnea.

In 4 cases pericardial rub was reported upon auscultation:

Case 3  
Case 39  
Case 8  
Case 25

In 24 out of 140 cases Electrocardiogram (ECG/EKG) shows new ST elevation or PR depression. In 38 out of 140 cases Echocardiogram or MRI shows new or worsening pericardial effusion. In 44 out of 140 cases Pericarditis was acute.

In 31 cases other increased inflammation markers (CRP, erythrocyte sedimentation rate, WBC) were reported. In 19 cases pericarditis was shown by other imaging techniques

#### *Age*

Age ranged from 20 to 80+ years (in 4 cases age was unknown). Number of cases per age group was as follows:

12-15	none
16-19	none
20-24	7 cases (5F, 2M)
25-29	5 cases (2F, 3M)
30-39	20 cases (13F, 7M)
40-49	23 cases (13F, 10M)
50-59	21 cases (13F, 8M)
60-69	19 cases (8F, 11M)
70-79	20 cases (12F, 8M)
80-89	21 cases (7F, 14M)
90+	none

unknown 4 cases (2F, 2M)

Overall no clear gender imbalance is observed (75 F vs 64 M), also in the different age groups, although the number of cases per group is not very high, precluding firm conclusions.

Cases **without** confounding medical history, morbidities, other aetiologies (according coding in EV)

#### **Comment PRAC Rapporteur**

PRAC Rapporteur's causality assessment is added in italic to the cases descriptions.

The following 38 cases did not report alternative aetiologies according to the coding in EudraVigilance. However upon closer look, several case narratives did report relevant medical histories (e.g. viral and idiopathic pericarditis; COVID-19; mitral valve repair for Barlow's disease) and comorbidities (i.e. Thalassaemia alpha; hypertension; T2DM,; cardiac failure; recent tooth & lung infections, chronic kidney disease, hypothyroidism and urinary and pulmonary infection, metastatic cancer, B-cell lymphoma) which hampers firm conclusions regarding a causal role of the vaccine. Six cases were insufficiently documented precluding assessment.

**Case 1** 20-29y F. In the afternoon of the vaccination, experienced an unusual pain in the chest, without any other sign. Patient, not having had COVID-19. unremarkable ECG and ETT (no pericarditis). Patient slightly hypertensive at 145 mmHg systolic (usual values 110/75). Favorable evolution thereafter. "Hypertension" and "Pericarditis" effect. History of Thalassaemia alpha and Raynaud's disease. CRP at 12 mg / L. On D6, she declares a very great asthenia and specifies that the chest pain prevents her from sleeping. She also claims to have fainted. It also has palpitations at rest which makes it difficult to sleep. She presented with hypertension for 10 days following the second injection with a SBP of between 14 and 18 for values usual between 10 and 12. At 3 weeks following vaccination ECG shows regular rhythm, sinus, normoaxed, fine QRS no disturbances of the repolarization. An ultrasound shows pericarditis. Treatment with aspirin 1g three per day for weeks then 1g twice a day for 2 weeks then 1g per day for a week associated with colchicine 0.5 mg per day for 3 months with PPI and rest. Resolving. *Causality possible, but confounded by patient's immune disorder*

**Case 2** 20-29y F. Increased shortness of breath, Pain chest (Pressuring pain in the central area of chest, suddenly occurred a week before medical consultation. Pain radiates to neck/throat but not to arms), Pain (The pain extends slightly to the neck but not to the arms), Pressure chest (Pressuring pain in the central area of chest, suddenly occurred a week before medical consultation), and Pericarditis (Pericarditis. Verified during hospitalisation). No information regarding concomitant and past medication. No information about patient's concurrent condition. Medical history included Helicobacter test: Helicobacter in 2020 (autumn): nothing abnormal. TSH, Oct2020: Nothing abnormal. The patient was vaccinated with the second dose on day 0, 28 days after the first one. On day 5 the patient developed Pericarditis, Pain chest, Pain, Pressure chest, Increased shortness of breath (onset last dose day 5). Pain did not radiate to arms and no swelling of lower extremities. The ADRs resulted in hospitalisation (day 12). No treatment or medical procedure due to the ADRs were reported. The ADR Pericarditis is recovering at the time of reporting. Echocardiogram performed bedside, normal cardiac valves and pump function. In subxephoidal section a discrete fluid barrier surrounding the heart is observed. Interpreted as pericarditis. Resolving. *Causality is possible, due to TTO and absence of other etiologies.*

**Case 3** 30-39y F. 5 days after first dose patient experiences constricting chest pain implicating a consultation with her attending physician who perceives clear signs of pericarditis. He then directs him to emergencies: Good general condition, afebrile, Pulse 85bpm, TA left arm 131/90, TA right arm 123/83, O1 saturation 99%, temperature 36.6. No signs of paleness, restlessness, drowsiness, or indrawing. On cardiological examination: chest pain worse on inspiration relieved by anteflexion, regular heart sound without audible murmur, friction frank pericardial, no edema of the lower limbs. no sign of right or left heart failure. no respiratory, digestive and neurological abnormalities. Overall: Diagnosis of acute pericarditis. Treatment with aspirin 3g / day and colchicine for 1 month. Lab - troponin negative, DDimers <270µg / L, no immunosuppression, no inflammatory syndrome. COMPLEMENTARY EXAM: Imaging: heart echo: No significant pericardial effusion. ECG: normal, regular rhythm, without rhythm disturbance or repolarization. One day later - The patient reports a clear improvement. Weekend - Patient much better. Resolving. *Causality possible due to TTO and absence of other etiologies.*

**Case 4** 40-49 y F. First dose on day 0. History of Acute lymphoblastic leukemia in remission. No transplant. One year of chemotherapy. In remission for 10 years. On the same day , 5 minutes after 1<sup>st</sup> dose: burning, intense retro sternal, tachycardia, feeling of vagal discomfort, no CP. 40 min monitoring and return at work with symptoms Chest pain G. generalized anxiety disorder posed in the emergency room. No other symptoms. PCR negative next week. Negative children and husband, had not worked the 6 days preceding the injection. OTHER CONTRIBUTIVE ADDITIONAL EXAMINATIONS: day 7: emergency room review: pericarditis, no fluid on ultrasound. Treated with colchine for debilitating pain. Day 8 Reviewed by the cardiologist. Put under aspirin 1gr 3 times a day. TROPO negative (performed because conduction disorder on ECG, compatible with pericarditis according to the cardiologist). **Not recovered.** *Causality possible due to short TTO.*

**Case 5** 40-49y F. History of hysterectomy 2011 and **pericarditis with effusion** following influenza in 2013. Comedication 80 mg of propranolol every day for 5 years as a basic treatment for migraines. Second dose on day 0. The patient describes the appearance of chest pain on inspiration and mobilization, great fatigue, lying down difficult to bear. Worse on the night of day 8 to day 9. The patient was referred on day 9 by her attending physician for chest pain reminiscent of her episode of pericarditis in 2013: Pericarditis 8 years ago treated with colchicine + aspirin for a total of 6 months (follow-up in town). No recurrence since, vaccinated every year against influenza without problem. Exam: TA: 130/80, Fc at 67bpm AP: free, AC no breath no audible friction pulse + and symmetrical; ECG: RRS at 70 cpm, no repolarization disorder Chest x-ray: RAS. Bio: CRP <0, no hyperleuco, too much <0, correct kidney and liver function TTE: undilated LV of conserved global systolic function, homogeneous segmental kinetics, minimal MI, undilated OG, normal mitral profile, CD preserved, Straight cavities not dilated, IT minimal, PAPs at 19 + 3 = 22mmHg, VCI fine pericardial detachment of 5-6mm compared to the right cavities visible in parasternal long axis and below costal => acute pericarditis in front of typical pain + pericardial effusion. Treated with: colchicine 0.5m + aspirin 1g \* 3 / day + esomeprazole for 15 days. ETT in 7 days Rest + 3-week work stoppage. Recovery In progress. Last ultrasound of the heart on day 30 which still showed a slight pericardial effusion. Always painful at the slightest work stoppage extended until day 45 25 with the same drug treatment. Resolving. *Causality possible but confounded by previous history of pericarditis following influenza.*

**Case 6** 40-49y M. smoker, overweight. No known history of covid19. Three months after receiving the 2nd dose of the Comirnaty vaccine, he presented mid-thoracic pain that wakes him up in the early morning , radiated to the right shoulder, back, neck and jaw that increased with movements and deep

inspiration. ECG: ST elevation leading to suspicion of AMI, normal ultrasensitive troponins. Amb hemogram with slight leukocytosis ( $12.35 \times 10^3 / \text{microl}$  [4.40 - 11.30] and slight neutrophilia (absolute  $8.59 \times 10^3 / \text{microl}$  [1.70 - 6.50]). Echocardiogram (9/4) ruled out effusion. Diagnosis acute pericarditis. Treatment with Colchicine. The patient is still on sick leave, fatigue persists with little effort and discomfort centrothoracic, oppressive type and with radiation on the back for weeks. Resolving. *Causality possible, but evidence not strong due to long TTO of 3 months.*

**Case 7** 50-59y F. Date of injection: day 0 Dose: D2. Adverse effects: fever with myalgia and chest pain 12 hours after the injection. Go to the emergency room the next day, an ECG and an ultrasound cardiac confirm the diagnosis of pericarditis. No history of COVID-19. PCR test history: yes, test performed on day 1 and negative result Allergic history: no. **Not recovered.** *Causality possible due to suggestive TTO and absence other etiologies.*

**Case 8** 50-59y F with no medical history or family history. At the time of the second dose episode of hypotension, dizziness. To the 15 days after the second dose of Pfizer's COVID19 vaccine initiates mild symptoms of chest discomfort, not fever. Symptoms are intensified until requiring medical attention and sick leave from four weeks. Still symptomatic, in recovery. Did have NOT had a SARS-Cov-2 infection at any time. An echocardiogram was performed which was normal, in the physical examination the presence of a pericardial rubbing. Analytical with a slight increase in CPK-MB. Treatment with colchicine 0.5 mg / day for 3 months, Ibuprofen in a descending regimen for 5 weeks (from every 6h to every 12h) and bisoprolol 1.25 mg every 24h. Still in recovery, she was sick for 5 weeks, and she is currently working, but without intense hourly loads. Resolving. *Causality possible due to TTO and absence of other etiologies.*

**Case 9** 60-69y F. No history of COVID. Improvement with ibuprofen 400mg. Resolving. *Insufficiently documented.*

**Case 10** 70-79y M. 1st dose No history of COVID, not tested. Pericarditis with chest pain, without details, being resolved. *Insufficiently documented.*

**Case 11** 80+y M. History of hypertension 4-5 years ago, enalapril / hydrochlorothiazide 1/24 h. TAS 140,150 mmHg. Dyslipidemia 6 years simvastatin. Epilepsy 2008 episodes (5-6 during an afternoon) consisting of a feeling of instability, and inability to speak for a few seconds, during that day he was with underlying language disorder that gradually resolved. It was oriented as of epileptic origin and valproic onset without new episodes. Normal MRI and EEG study (no reports available). In treatment 7-8 years, general medical control until 2014 approx. Reboot dysesthesia and dysgeusia symptoms in 2017 being cataloged as comitiality. In treatment with levetiracetam. Diabetes mellitus 2021 being treated with insulin + metformin. No allergies. No toxic habits. Possible incipient cognitive impairment in a patient with heart attacks lacunar in the TAC and emotional lability, although it maintains the autonomy for the ABVD in treatment with aspirin 150mg / 24h. Sertraline 100mg / 24h. AAS 100mg / day. Functional, mental situation: preserved FFSS. Physical situation: independent. No covid 19 antecedent. Diagnosed Acute idiopathic pleuropericarditis. Treated with oral colchicine and ibuprofen, it relieves chest pain and fever, improving the general condition. ECG has not shown significant pericardial effusion or signs of hemodynamic compromise. Treatment by anti-inflammatory and evolutionary control within a period of about 2 weeks. Resolving. *Causality assessment hampered by multiple comorbidities (hypertension, dyslipidemia, epilepsy, T2DM).*

**Case 12** 30-39y M lateral Acute Coronary Syndrome ST + in a patient who smokes. Absence of lesion in coronography. Troponin cycle: 3.4 ng / L. Normal ETT. ECG, laboratory and clinical criteria in favor of acute dry pericarditis. Therapy with aspirin, colchicine and proton pump inhibitor. No known allergies. Mother breast cancer and father kidney tumor. Cardiovascular risk factors: Tobacco: yes. No diabetes, hypertension or dyslipidemia. No family cardiac inheritance: (no early infarction, no sudden death).



Concomitant medication: Buprenorphine 1.2mg: 0.8mg-0-0.4mg; Paroxetine 30 mg: 1.5-0-0. **Not recovered.** *Causality possible.*

**Case 13** 40-49y F with history of Pericarditis in 2010, Obesity. Comedication irbesartan/hydrochlorothiazide 150 mg/12.5mg 1 cpr / day. Vaccination date: day 0 dose 2. Within 12 hours onset of pericarditis which necessitated going to the emergency room with chest discomfort, feeling of dyspnea of progressive onset with an upsurge in the morning at 3:00 a.m. ECG: normoaxial sinus tachycardia. Cardio review concluded treatment like pericarditis (aspirin 1000 mg 2 cpr / day, COLCHICINE for 2 months). Patient returned home with supervision instructions and is recovering. *Confounded by history of pericarditis.*

**Case 14** 40-49y M with history of hypercholesterolemia, familial type 2 diabetes received on day 0, Dose 2. Presented with pericarditis sicca accompanied by stiffness, headache and tinnitus on the day after vaccination. Covid19 TEST: negative. SEVERITY: yes (outpatient hospitalization time to make the necessary assessments for the diagnosis). MEDICALLY CONFIRMED: yes. day 1, i.e. the day after the second COMIRNATY \* injection, onset of chest pain radiating to the left arm, occurring at 11:30 am. Being on a hospital site, the patient immediately consults cardiology. Chest pain is continuous, increased when breathing and lying down, calmed when sitting. Dyspnea on exertion. No throbbing. Aches, associated headaches and tinnitus. Clinical examination found BP at 141/87 mmHg, HR at 112 bpm, clear pulmonary auscultation, no sign of right heart failure nor left. Resolving. *Causality possible due to short TTO, but confounded by underlying hypercholesterolemia and T2DM.*

**Case 15** 60-69y F received the 2nd dose, on day 0. Medical history included mitral valve prolapse. No prior history of allergies to medications, food, or other products. Prior to vaccination, the patient was not diagnosed with COVID-19. Concomitant medications included sertraline and bromazepam. First dose 22 days before the first dose. The patient experienced pericarditis on day 34. The adverse event resulted in emergency room/department or urgent care. Unspecified treatment was received for the adverse event. Since the vaccination, the patient had not been tested for COVID-19. The outcome of the event was recovering. *Causality possible but assessment hampered by underlying condition, comedication, limited information.*

**Case 16** 60-69 y M. No history of COVID. Not tested. Not considered to be at risk of developing a severe form of Covid-19 disease. Experienced pericarditis one day following 1<sup>st</sup> dose. Resolved. *Insufficiently documented case.*

**Case 17** 70-79y M with history of diabetes and arterial hypertension. Without previous COVID-19 infection (test day 18). Received 2<sup>nd</sup> dose on day 0, onset on day 3 of chest pain, dyspnea on exertion, biological inflammatory syndrome with CRP at 164 mg / l. Diagnosis of pericarditis (10 mm) on cardiac ultrasound. Required hospitalization. Pericarditis 3 days after a 2nd dose of Comirnaty. Day 108, reception of the CR of the cardiac ultrasound: presence of a circumferential pericardial effusion of 5-6 mm, without sign of compression. VG undilated. LVEF = 66%. Small restrictive mitral insufficiency. OG little dilated. Aortic sclerosis without significant stenosis. Cavities straight lines not dilated. PAPS = 38 mmHg. **Not Recovered.** *Causality possible, but confounded by medical history.*

**Case 18** 80+y F. received her first dose on day 0. No information on concomitant medication or medical history. On day 10, the patient developed PERICARDITIS. Results from ELECTROCARDIOGRAM, day 10, and examination of the patient's pain at the hospital was compatible with the diagnosis. COVID-19 VIRUS TEST, day 10, taken upon admission was negative). The patient's outcome was Recovering/resolving, at the time of the report. The case was considered to be Serious. *Causality possible, but assessment hampered by limited details.*

**Case 19** 30-39y F. reported by a consumer. The patient's height was reported as 170 cm and weight was reported as 57 kg. On day 0, the patient received her 1st dose of Comirnaty for active immunisation. On day 11, she developed postvaccination pericarditis. As a corrective therapy the patient received colchicine, nurofen, vitamin C and magnesium. Withdrawal is not applicable because the administration has been completed. At the time of reporting, the outcome was: not recovered. In the reporter's opinion the events were related to Comirnaty. The patient has been tested for SARS-CoV-2 infection (negative PCR on day 0). The patient had no symptoms associated with COVID-19 before or after vaccination. The patient described herself as healthy and without a relevant personal medical history prior to vaccination. Concomitant medication: no. The adverse reactions were assessed as "life threatening" by the primary reporter. **Not Recovered.** *Causality possible, due to TTO and absence of confounding factors or etiologies.*

**Case 20** 60-69 y M. Admitted to emergency room. Patient vaccinated with 2 doses of covid 19 vaccine. Last dose 2 weeks ago. Patient experienced 3 days after the second dose with asthenia, lack of appetite, no fever, no headache, no vomiting, or diarrhea, but feeling of dyspnea, no chest pain or palpitations. For 1 week. After that he returned to work, but about 16 hours ago he started again with asthenia and a feeling of suffocation. He says that yesterday he began to feel dyspnea while walking at a slow pace. The patient reports not having previously suffered from COVID 19. He does not report other symptoms. Normal bowel habit. He reports very yellow and smelly urine about 4 days ago. BEG, BHYP, COC, normal colored, eupneic at rest, tolerates decubitus, currently afebrile, walks. AC: rhythmic at a good rhythm without murmurs or extra tones currently. AP: MVC no other super-added noises ABD: globular, RHA +, deoresible, no masses or meglia are palpable, not painful, blumberg, and wallhy negative. No signs of peritoneal irritation. MMII: no edema or signs of DVT. TA right arm: 187/101; TA left arm: 181/96; Chest X-ray: good technique, bone frame without alterations. Pulmonary parenchyma without infiltrates or condensations. Normal ICT. No breast pinching costofrenics. - ECG: sinus rhythm at 70bpm, narrow QRS, normal PR, normal axis, I do not currently observe acute repolarization alterations; Normal blood count of the 3 series; Coagulation: dimer 895; Biochemistry: CK 279, normal remainder including troponin and proBNP; GSV: pH 7.4, bicarbonate 28.4, pCO2 47.3. Stable while in minimal care, but high blood pressure figures persist despite alprazolam and captopril. Diagnosis: Dyspnea (Referral diagnosis at discharge); Post-vaccination pericarditis? (Diagnosis of referral at discharge). Treatment: Enalapril 10 mg / 24 hours; Ibuprofen 400 mg / 8 hours; Relative rest, especially avoiding efforts and controlling salt in the diet. Control and monitoring by family doctor, monitoring of ECG and blood pressure. Resolving. *Causality possible due to TTO and absence of other etiologies.*

**Case 21** 30-39y F with medical history of celiac disease, diagnosed in 2008 (on gluten-free diet; Celiac disease had not been checked for two years); E.coli (which was treated with antibiotics); lymphocytosis; and lip herpes, all three from 2009 to an unknown date; COVID infection in Nov2020; and aphtha; quinsy (treated with amoxicillin/clavulanic acid, azithromycin, and pantoprazole); anaemia; iron deficiency; enlarged lymph nodes; diseases of the upper respiratory tract; infectious mononucleosis, not otherwise specified (nos); chlamydia infection; mycoplasma infection; stomatitis; chronic atrophic gastritis; reactive arthropathy; autoimmune thyroiditis; and flour sensitivity, all from an unknown date and unknown if ongoing. No known allergies.

On same day of receiving 1<sup>st</sup> dose the patient experienced heart pain, fainting, muscle pain, hand shaking, subfebrility, chills, waking up at night, watery sweat, jumping blood pressure and pulse, dizziness/feeling of fainting, tiredness, weakness, and pale face.

Diagnosis was reported as Tachycardia; Acute pericarditis; Pericarditis in other diseases classified elsewhere; Load tolerance functions (moderate problem); Health preservation (moderate problem); Load tolerance functions (moderate problem); Health preservation (moderate problem); NYHA functional class; NYHA functional class.



In November symptoms typical of possible COVID infection, but test was not done. In December negative antibody test was done. Since receiving the first Pfizer vaccine she has tachycardia, sweating, mild burning sensation throughout the body, shortness of breath, reduced SpO2 (lowest value was 84%), continuous subfebrility, weakness, heart pain, hand tremor, extremely volatile heart rate and blood pressure, dizziness, feeling of fainting, sore throat, due to which several examinations were performed, she was also treated at a hospital. After the vaccination she was bedridden.

On day 19 cardiac ultrasound was performed due to permanent subfebrility, with which significant deviation was not found. The Emergency Care Unit did not see significant deviation on the chest image, troponin, CKMB, CRP, WBC did not show deviation. AG rapid test was negative. She was discharged home.

On day 21 cervical ultrasound examination was performed with double carotid, with which the thyroid gland, the salivary gland, the cervical soft tissues and arteries did not show deviation, with abdominal and lesser pelvis examination only a 0.6 mm cortical cyst was found in the upper third of the right kidney.

On day 20, Covid-19 PCR test was negative. Day 21, 3 weeks after the vaccination high antibody level can be detected. ( 3124.3 AU/ ml) On day 21, serum Ferritin, TSH, coeliac disease screening tests were negative. Interleukin 6 and procalcitonin negative. Opinion: post-covid syndrome that activated due to the vaccination.

On day 27 she was treated due to collaptiform sickness. Ag rapid test was negative. On day 27 she was admitted to the hospital where PCR negative, for Chlamydia, Mycoplasma, CMV serology blood was collected, the need for cranial MR, chest CT was considered.

On day 32 the cardiologist concluded based on pericardial fluid behind the atriums. 11 mm. Based on the seen report Diagnosis: pericarditis.

Due to assumed post-covid syndrome (it was never confirmed by COVID 19 test), for the inhibition of cytokine activity / reduction of systemic inflammation fluvoxamine treatment was recommended.

Based on the information provided by the reporter, it appears unlikely that subject vaccine contributed to the event of angina pectoris. The reported event may likely represent intercurrent medical condition. Based on available information, a possible contributory role of the subject product, BNT162B2 vaccine, cannot be excluded for the other reported events due to temporal relationship. There is limited information provided in this report. Recovered. *Causality is possible.*

**Case 22** 50-59y M with history of myocardial infarction on Sep 2020. No history of COVID (not tested) received Dose 2 on day 0. On day 10 patient experienced Chest pain not very intense but lasting about 1 month. Hospitalized for assessment on day 37. Based on Coronary angiography; Echocardiography: diagnosis of pericarditis. Patient is recovered. *Causality possible but confounded by recent MI.*

**Case 23** 70-79y F with history of Hypothyroidism, Type 2 diabetes mellitus, Lymphoma, Breast cancer. No COVID. Received 1<sup>st</sup> dose on day 0 and developed pericarditis on day 6. COVID PCR negative. **Not Recovered.** *Insufficient information for assessment.*

**Case 24** 50-59 year F required hospitalization, but AEs were not considered life-threatening and are resolving. Pericarditis diagnosed by heart ultrasound, 8mm pericardial fluid, chest pain, most pronounced in the supine position. Asthma attack-allergy 1 day post-vaccination asthma attack, throat swelling, drowsiness, hypoxxygenemia and loss of event memory, call an ambulance and stay in first aid for 12 hours. Repeated asthma attacks in first aid for 8 hours after, approximately every half hour. Since then, daily minor attacks of asthma, shortness of breath after a few minutes of walking or talking, fatigue and weakness. *A causal role of the vaccine in either pericarditis or exacerbation of asthma, or both (e.g. via a synergistic effect), is possible due to the suggestive TTO. However the causality assessment is*

hampered by overlap in symptoms (e.g. chest pain, shortness of breath) between an asthma attack and pericarditis.

**Case 25** 60-69 year M, history of hypertension (no details available). AEs resolving. vaccinated with Comirnaty (second dose) and 15 days later, she presented with signs and symptoms of pericarditis (chest pain, difficulty in breathing and tachycardia) and pericardial friction. Based on ultrasound scan, a small amount of fluid in posterior pericardiac area was found. Neither SARS-CoV-2 test nor virological tests were performed. No medical record of recent infection. He received medrol 16mg and he is in recovery. No hospitalisation was required. She was sent to laboratory tests whose results are not known yet. *Causality possible due to TTO and absence of other etiologies.*

**Case 26** 80+ year F with history of hypoacusis, osteoarthritis (no details). No history of COVID, not tested. AE Pericarditis with chest pain, without details, being resolved. Two days after first dose patient experienced bilateral pleural effusion (twice; caused or prolonged hospitalization), pericarditis (caused or prolonged hospitalization), fever (caused or prolonged hospitalization), dyspnoea (caused or prolonged hospitalization), thorax pain (caused or prolonged hospitalization) following first dose. Treatment: Pleural effusion is treated with Pleurapunction (twice) and prednisone. The patient is recovering from dyspnoea, is recovering from fever, is recovering from pericarditis, is recovering from pleural effusion and is recovering from thorax pain. No other causes were found. CT scan: no pulmonary embolism, bilateral pleural effusion with atelectase, pericardial effusion of pericarditis. Serology for pericarditis not known at time of reporting. Cardiac ultrasound showed good function, however with atrial fibrillation, all around pericardial effusion with fibrine (0,7 posterior left ventricle, 1 cm anterior right ventricle); good kinetics left ventricle, estimated LVEF 60%; small left ventricle; bi-atrial dilatation (RA 94,4 ml); respiratory sputum move; inflow variation MV with AF; E' lateral almost like E' mediaal (13,5 cm/sec vs 13,7 cm/sec). Small VCI, spontaneous collaps. Blood test: CRP up to 260; auto-immune investigation ANA and ANCA negative. Serology very low positive for *C. burnetti* others negative and considered as no cause for pericarditis by the reporter. *Causality possible, due to short TTO, absence of confounding factors and other etiologies.*

**Case 27** 80+ year F with history of T2DM and COVID-19. Pericarditis **not resolved**. Type II diabetes, Medication: Metformin 850 (1-0-1); Atorvastatin 10 (0-0-1). COVID infection in Sep 20. Screening PCR diagnosis on Sep, 20. The patient was initially asymptomatic. The patient later presented low-grade fever (only 1 day) and recurrent episodes of palpitations (he did not value them). The patient was discharged and began to work - PCR NEGATIVE. On day 0 received the first dose of the vaccine (Pfizer) and noticed pain in the place where the vaccine was inoculated. Received the second dose of the vaccine on day 22. In the interval between doses, the patient had general discomfort for several days, but no tracing was done. Admitted to the emergency room on day 48 for retrosternal chest pain with 5 days of evolution. The pain was not accompanied by vegetative symptoms, it worsened with lying down and relieved with sitting. The patient did not present other respiratory, urinary symptoms, gastrointestinal, skin or bone joint. A complementary investigation was performed in the emergency room and the patient was admitted with the diagnosis of acute pericarditis, medicated with ASA and colchicine. *Causality possible, but confounded by T2DM and preceding COVID infection.*

**Case 28** 80+ year M required hospitalization, but AEs were not considered life-threatening. Pericarditis has resolved. History of hypertension, hyperuricemia. Right amaurosis fugax secondary to embolism due to right internal carotid stenosis (1999). Acute idiopathic pericarditis in 2004. In Jan/2020 with a diagnosis of exertional angina, percutaneous coronary angioplasty was performed on a 98% lesion of the proximal circumflex with a 2.5x40 sirolimus stent implant. Good result with disappearance of the injury. Comedication: Pantoprazole 20mg / 24h, monthly Calcifediol, Clopidogrel 75mg / 24h, ASA 100mg / 24h, long acting isosorbide mononitrate 60mg / 24h, Atenolol 25mg / 24h, Rosuvastatin 20mg

/ 24h. Resolved. *A causal role of the vaccine is possible, but the evidence is weak based on the patients relevant medical history and confounding cardiac comorbidities.*

**Case 29** 80+ year M with history of cardiac failure (no details available). Following 2<sup>nd</sup> dose patient presented with prolonged chest pain which gave way spontaneously. There is an inflammatory syndrome and an ECG compatible with pericarditis. The ETT shows a good LV and a minimal pericardial lamina opposite the apex of the right ventricle. If the cycle troponin is negative, the cardiologist recommends treating with aspirin / colchicine as pericarditis. The troponin T hs is at 14.8 pg / ml (<14) and 2 hours later it is at 14.4 pg / ml. It is also noted a CRP at 87 mg / L and monocytes at 1.26 G / L (0.23-0.71). The diagnosis retained is that of pericarditis and the patient was able to return home the same day with a prescription of aspirin 1000 mg. (DL-lysine acetylsalicylate) at a dosage of 1 sachet 3 times a day in decreasing doses and colchicine at a dosage of 0.5 mg per day in the morning and evening for 3 months. Pericarditis is resolving. *Causality is possible.*

**Case 30** 20-29 year M. Pericarditis recovered. This spontaneous non-serious report was received from a Consumer or other non-health professional. No relevant medical history reported. No concomitant medication reported. On day 0 the patient experienced Myocarditis NOS, Pericarditis. The patient's outcome was: not recovered/not resolved for Myocarditis NOS, not recovered/not resolved for Pericarditis.

The diagnosis was initially made in the emergency room, for which no documentation is available, only the diagnosis. There was a re-presentation in the practice on day 52 with unspecific complaints, but echocardiographic and laboratory improvement of perimyocarditis.

The first symptoms of myocarditis occurred on day 0 as left thoracic pain. The patient is considered recovered but should continue to take it easy. The patient had undergone a COVID infection (in Nov 2020). No other infection documented in the immediate period.

The diagnosis of "myocarditis" was established on the basis of

- Clinical symptoms: left thoracic pain, fatigue.
- Blood tests (please specify): severely elevated troponin
- Echocardiography, electrocardiogram, cardio - MRI: initial echo > pericardial effusion, confirmation of findings in cardio MRI (perimyocarditis posterior/lateral wall), ECG with ST elevation inferior, in addition coronarangiography, CT thorax, Autoimmune diseases are not known in the medical history.

*Causality is possible due to TTO and absence of other etiologies. However it is noted that the patient has had COVID.*

**Case 31** 30-39 year F. Chest pain, pericarditis, pyrexia not resolved. The patient on day 37 reports: ADR and date onset ADR: chest pain in a mild but "pungent" form and fever (max 37.5 ° C) occurred after about 15 days from the vaccine; severe chest pain started on day 0; following the diagnosis of pericarditis Action taken: day 0: access to the emergency room (diagnosis of intercostal pain); Exams instrumental: CT scan: pericardial and pleural effusion; Thoracic MRI, echocardiogram and cardiological consultation: mild pericarditis Other diseases concomitants: Atopic dermatitis Concomitant therapies: norgestrel acetate/estradiol cp (for contraception); Dupilumab 300 mg 1f / 2weeks from October 2020 (last administration 2 weeks before the vaccine) Dupilumab discontinued, on the recommendation of the cardiologist, (around day 15) Therapy: ibuprofen 3 v / day Outcome: no still resolved - Ethnic origin (Caucasian (white)). *Causality is possible due to TTO and absence of other etiologies.*

**Case 32** 40-49 year F with history of pre-eclampsia, tooth infection, Type IIa hyperlipidaemia. Recent tooth and lung infection (COVID PCR negative). Pericarditis 12 days after 2<sup>nd</sup> dose. pericarditis resolving. *Causality possible but confounded by recent infections.*

Case 33 40-49 year F vaccinated on day 0 with the COMIRNATY vaccine and who developed pericarditis on day 6. Ultrasound shows good LV function without HVG. No valve disease. Pericardial effusion of small circumferential abundance. **Viral pericarditis** to be treated with anti-inflammatory drugs with PPI for one month and ultrasound control. The ultrasound check on day 21 shows clinically an improvement under anti-inflammatory treatment. On the ultrasound level, there is still a circumferential pericardial effusion but markedly reduced compared to the initial examination which was almost disappeared next to the left cavities and essentially persists next to the right cavities. There is no impact on the cavities straight. Very good left ventricular function, absence of any valve disease. on day 41, The patient received a further consultation to check her pericardial effusion by echocardiography. Very good left ventricular function found. No valve abnormality. On the other hand, the pericardial effusion persists while remaining of low abundance, mainly next to the cavities. straight lines without any impact on them. The patient remains asthenic with episodes of tachycardia. Despite an improvement on nonsteroidal anti-inflammatory drugs, the situation is not completely resolved. Prescription of colchicine 1 / d for one months and blood tests with inflammatory markers. on 05/15 the chest CT found a circumferential pericardial effusion of average abundance, of fluid density, without calcification: compatible with pericarditis. Multiple subpleural and fissural nodular formations which may correspond to intrapulmonary nodes, some of atypical morphology (non-polygonal): to be rechecked in 3 to 6 months.

Undergoing improvement as of 10/05/2021. *Possible viral infection is a more likely explanation.*

**Case 34** 40-49 year M with history of chronic kidney disease, testicular metastatic cancer (no details) required hospitalization, but AEs were not considered life-threatening. Presented with pericarditis 17 days after vaccination with covid-19 vaccine (Comirnaty), first dose. Hospitalized with acute chest pain and hypotension. CT scan and echocardiography found possible hemopericardium. Patient with metastatic testicular cancer from before, with stable disease and no treatment at the moment. Pericarditis resolving. *Confounded by underlying morbidity chronic kidney disease and metastatic cancer.*

**Case 35** 60-69 year F with history of hypothyroidism. Received 1st vaccination on day 0 presented on day 6 for consultation following the onset of chest pain without fever. Day 7: onset of fever and chills leading to suspicion of a urinary and pulmonary infection. Initiation of antibiotic therapy by levofloxacin. Day 8: CRP 182 mg / L; Day 10: normal chest x-ray; Day 12: CRP 49 mg / L; 23/04/2021: chest CT scan showing pericardial effusion with pleural effusion slide and diffuse pulmonary micro-opacities. Initiation of treatment with aspirin 1 g 3x / d. Day 27: cardiac ultrasound showing improvement in cardiac effusion. Day 28: regression of chest pain but persistence of chest tightness and fatigue. Infectious serologies and autoimmunity assessment in progress. Evolution: recovering Conclusion: patient who presented with pericarditis 6 days after vaccination with COMIRNATY (COVID-19 vaccine). *Possibly confounded by underlying hypothyroidism and urinary and pulmonary infection.*

**Case 36** 80+ year F with history of COVID-19 and cognitive disorder (no details) required hospitalization. First dose on day 0. On day 13, admission to the Emergency Department with the persistence of constrictive chest pain at rest and with the effort radiating into the shoulders and increased on inspiration, accompanied by dyspnea (initially without oxygen desaturation) at the slightest effort evolving since day 9 No associated ENT, pulmonary or digestive infectious manifestations. No fever. Absence of particular abnormality on the ionic, renal, hepatic and hematological level apart from an inflammatory syndrome. Cardiac: NT proBNP 900 IU / L - troponin negative - D-Dimer 3200 IU / L. HIV, Cosackie, Echovirus negative serologies; PCR Covid19 negative; Parvo B19 serology positive for IgG and IgM, but parvoB19 viral load negative. Trans-thoracic echocardiography of day 20: "Circumferential pericardial effusion of average abundance, non-compressive, measured at maximum at 20 mm opposite the lateral wall of the LV, 6 mm at the apex of the LV, 13 mm latero-RV. No significant respiratory variation in flow aortic and mitral. No dilation of the right cavities. OG dilated (volume 49 ml / m<sup>2</sup>). LVEF 60%. No significant valve disease".

Reporter Comments: @ CT TAP of day 20: "Bilateral pleural effusion of low abundance seeming partially partitioned on the left. No thickening plural. No suspicious lung nodule. Circumferential pericardial effusion measured up to 2 cm with fine thickening and pericardial enhancement. [?] "

Thoracic CT angiography on day 22: "Absence of pulmonary embolism. Stability of the circumferential pericardial effusion of great abundance. Increase in bilateral septate pleural effusion predominantly on the left ". ECG without special feature

Treatment: initiation of aspirin on day 13 then addition of colchicine on day 15 to reduce chest pain and dyspnea. "Probabilistic" anti-tuberculosis quadruple therapy (negative quantiferon. Direct negative sputum BK): Rifampicin/Isoniazid/Pyrazinamide + Ethambutol since day 32 Pleuropericarditis resolving.

*In the absence of another currently identified cause, TTO does not exclude causal role of vaccine in the occurrence of this pleuropericarditis.*

**Case 37** 80+ year M with history of B-cell lymphoma (MALT type, no details), atrial fibrillation, pneumonia, benign prostatic hyperplasia, urinary incontinence, inguinal hernia, pyelonephritis, fall, cerebral infarction, cardiac failure, constipation chronic. Comedication includes Metoprolol, Rivaroxaban, Furosemide, dutasteride/tamsulosin, mirabegron, lactulose. After 1<sup>st</sup> dose patient developed productive cough and symptoms gradually increased, before an acute deterioration 8 days following 1<sup>st</sup> dose. The patient was admitted to hospital in a condition of systemic inflammation, with affection of several organ systems: Lung affection with severe hypoxaemia, pleuritis with pleural effusion, basal slight opacity and atelectases, some thickening of the bronchi, but no other pulmonary pathology. Need for O2 supply- Kidney affection with creatinine 124-150 umol/L, eGFR 45-37, nephritis sedimentation with several cylinder types. Urine albumin/creatinine-ratio shows light microalbuminuria. Decreased appetite, repeated retching/vomiting after food intake. Pericarditis with pericardial effusion, increasing pericardial fluid with need of pericardial drainage. After drainage at a different hospital, where the patient was admitted for 3 days, the patient's condition spontaneously improved, with decreasing inflammation according to CRP. Performed left sided pleural drainage 3 days later, with further gradual respiratory improvement without laboured breathing and adequate oxygen saturation, where the need for O2 supply disappeared. After initiation of prednisolone treatment, CRP decreased further, general condition improved, the patient became mobilised and also had improved appetite with normalised dietary intake.

Rheumatologist stated that there was no indication of rheumatic disease, and that a large proportion of men of this age have high anti-SSA, slightly elevated RF. Imaging procedures showed that there are no indication of aortitis. Other causalities sought were bacterial infection, systemic reaction after viral disease, but no evidence were found to establish this. Negative antibodies for Covid-19 and parvovirus B-19, normal immunoglobulins, no indication of M component in protein electrophoresis. Differential diagnosis to post-infectious systemic inflammation, severe systemic reaction after Covid-19 vaccination was considered.

The patient had not experienced any adverse reactions or symptoms directly after the vaccination, but it is not clear when the cough symptoms started relative to vaccination. The patient had seen an ambulatory physician and taken a COVID-19 VIRUS TEST before admission to hospital. The patient's symptoms gradually increased, before an acute deterioration, when the patient was admitted to hospital with airway symptoms, biochemical inflammation. The patient was initially treated with penicillin/gentamycin (5 days treatment) and Cefotaxime (6 days treatment), but experienced only minor clinical and biochemical effect. The patient' condition spontaneously improved the last week prior to the report, and a clinical and biochemical improvement was also observed after the patient started treatment with prednisolone 60 mg/day, 22 days after the hospital admission.



The patient's outcome was Recovering/resolving, at the time of the report. The case was considered to be serious. *Causality is possible but underlying medical condition and hampers assessment. In addition it is not clear when the cough symptoms started relative to vaccination.*

**Case 38** 60-69 year M with glaucoma, sleep apnoea syndrome, mitral valve repair (no details). Pericarditis resolving. First dose on day 0, 2nd dose on day 21. Presented on day 24 with dyspnea on exertion which has increased since January following the first injection. Patient describes a clear worsening for 48-72 hours. Dyspnea revealing circumferential pericardial effusion in pre-tamponade, in a patient who underwent mitral and tricuspid plasty a year ago on Barlow's disease.

> Percutaneous pericardial drainage bringing back hemorrhagic fluid. Non-compressive sub-centimetric residual pericardial effusion, with scheduled close ultrasound control.

> TAP CT finding an isolated infra-mediastinal lymphadenopathy not very specific in the acute inflammatory context which will motivate a control CT scan, and caecal thickening without satellite image

> Possible pericarditis reaction secondary to recent vaccine injection.

Treatment with Colchicine 0.5 mg for three months then discontinue. Prohibition of all physical and sporting activity for at least 1 month.

*Causality possible, but confounding by underlying cardiac condition Barlow's disease and recent surgery (mitral valve repair).*

#### **Comment PRAC Rapporteur:**

In summary, in 5 out of these 38 cases without reported confounding medical history/comorbidity or alternative aetiologies (according to coding in EV) the pericarditis was not resolved. In the majority of cases however (33 out of 38), the pericarditis is resolving or has resolved following treatment.

In 12 out of 38 cases due to the absence of confounding medical history/comorbidity or alternative aetiologies a causal relation between pericarditis and Comirnaty cannot be excluded and is possible.

However it is noted that despite of the coding in EudraVigilance, 20 out of 38 case narratives do report relevant comorbidities (*i.e.* hypertension, T2DM, cardiac failure, COVID-19, recent tooth and lung infections, chronic kidney disease, hypothyroidism and urinary and pulmonary infection, metastatic cancer, B-cell lymphoma, history of pericarditis, Barlow's disease, mitral valve repair), which hampers firm conclusions regarding a causal relation between the vaccine and pericarditis.

#### *Cases with confounding medical history, morbidities, other aetiologies*

16 cases (and 1 duplicate ) reported relevant confounders:

**Case 40** 60-69 y M with a 10 years history of recurrent pericarditis

**Case 39** 40-49 y F with oncology -related pericarditis

**Case 41** 40-49 y M with viral myocarditis (TnT: 40ng/L, à 32 ng/l)

**Case 42** 70-79 y F who was CMV IgG positive

**Case 43** 70-79 y F with history of Tuberculosis

**Case 44** 70-79 y M with recurrent pericarditis since September 2018, last episode in Nov 2020 and under colchicine since then

**Case 45** 20-29 y F with pseudo-flu like illness

EU-EC-10007767115 30-39 y F with concurrent Covid-19 infection

EU-EC-10008625805 30-39 y F with Previous history of pericarditis and current symptoms same as previous pericarditis

**Case 46** 30-39y M with history of aortic valve replacement and pericarditis

**Case 47** 40-49y F with history of Sjogren's Syndrome

**Case 48** 50-59y M with pericarditis of infectious etiology

**Case 49** 50-59y M with history of a long flu episode in Dec 2020

**Case 50** 60-69y F with history of lung carcinoma

**Case 51** 70-79y F with possible viral etiology

**Case 52** age unknown F with COVID-19

In 15 out of 16 cases symptoms are resolving.

In addition to the cases above 12 cases had a possible history of COVID-19

**Case 53** 80+y M

**Case 54** 30-39y F

**Case 55** 30-39y F

**Case 56** 30-39y M

**Case 57** 60-69y M

**Case 58** 80+y F

**Case 59** 30-39y M

**Case 60** 60-69y M

**Case 36** 80+y F

**Case 52** unknown age F

**Case 61** 50-59y F

**Case 62** 50-59y F

### 3.1.3. Latest O/E analysis Myocarditis by gender – DLP 13 June 2021 by EMA

EMA colleagues independently performed an O/E analysis on the cases from EEA countries reporting following vaccination with COVID-19 vaccines (Comirnaty, Moderna and AstraZeneca) as available in EudraVigilance (shared with the PRAC Rapporteur on 28 June 2021), which is included below.

#### MYOCARDITIS, ONLY

The EMA noted the following:

- **Incidence rates** for main analysis from **ACCESS – ARS**:
  - **Rates for myocarditis** have just been received from ACCESS. Previously, only the rates for myocarditis and pericarditis combined were available. The new rates are based on myocarditis diagnosis (pericarditis might also be present)
  - The myocarditis diagnosis is likely to be made in secondary care, so there is a risk of underreporting in primary care records. **ARS** (Tuscany region) incorporates outcomes from both primary and secondary care
  - Sensitivity analysis with rates from **THIN UK** (primary care records), which provides a much lower estimate of the risk (~ 1/4 of ARS rates for age < 30)
- **Exposure** data: from ECDC + gender distribution and breakdown of ECDC 25-49 group into 25-29, 30-39, 40-49 from MSs (data up to 6<sup>th</sup> Jun for both ECDC and MSs)

- **Observed** cases from EV: HLT Infectious myocarditis and HLT Noninfectious myocarditis (incl. myopericarditis)

### Myocarditis in Males (using ACCESS-ARS background incidence rates)

Information on TTO was missing in 17 cases, and TTO was >42 days in 7 cases.

Legend	
<b>OE point est. &gt; 1</b>	<b>OE point est. &gt; 1 and lower bound of 95% CI &gt; 1</b>

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

### Myocarditis in Females (using ACCESS-ARS background incidence rates)

Information on TTO was missing in 8 cases, and TTO was > 42d in 3 cases.

Legend	
<b>OE point est. &gt; 1</b>	<b>OE point est. &gt; 1 and lower bound of 95% CI &gt; 1</b>

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

### EMA Considerations on the OE results – Myocarditis

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

- **OE ratio > 2 in the male 18-24 group for all three vaccines** and statistically significant for Comirnaty
- OE ratio ~ 1 in the male 25-29 group for Comirnaty
- More fragmented picture in the female group: OE ratio > 1 for Comirnaty 18-24;
- **Sensitivity analysis** uses much lower rates (THIN UK), therefore OE ratio > 9 in male 18-24 and OE ratio > 2 in male 25-29 for all three vaccines

The EMA noted the following **Caveats** of the analysis:



- The OE analysis should be treated as a tool for signal detection rather than signal validation. The comparison of EV event rates with those observed in healthcare records should be interpreted cautiously, for contextualisation only
- The extent of underreporting in EV is not known (presumably low for serious events such as myocarditis)
- The analysis did not include the age group 15-17 because of the lack of exposure data from ECDC/MSs; 6 cases of myocarditis were reported to EV, 5 for Comirnaty (of which 4 from DE)

## MYOCARDITIS AND PERICARDITIS COMBINED

The EMA noted the following:

- **Incidence rates** for main analysis from **ACCESS – ARS**:
  - **Updated rates for ARS** have just been received from ACCESS. The new rates are considerably higher than the previous ones (new: ~ 30 per 100,000 vs previous: ~ 10 per 100,000)
  - Clarifications on the rate variations along with updated rates from other ACCESS databases yet to be received
  - The myocarditis and pericarditis diagnoses are likely to be made in secondary care, so there is a risk of underreporting in primary care records. **ARS** incorporates outcomes from both primary and secondary care
  - Sensitivity analysis with rates from **THIN UK** (primary care records), which provides a lower estimate of the risk (~ 1/2 of the ARS rates for age < 30)
- **Exposure** data: from ECDC + gender distribution and breakdown of ECDC 25-49 group into 25-29, 30-39, 40-49 from MSs (data up to 6<sup>th</sup> Jun for both ECDC and MSs)
- **Observed** cases from EV: HLT Infectious myocarditis, HLT Noninfectious myocarditis (incl. myopericarditis), HLT Infectious pericarditis, HLT Noninfectious pericarditis

### Myocarditis and Pericarditis in Males (using ACCESS-ARS background incidence rates)

Information on TTO was missing in 23 cases, and TTO was > 42d in 12 cases.

Legend

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

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

### Myocarditis and Pericarditis in Females (using ACCESS-ARS background incidence rates)

Information on TTO was missing in 20 cases, and TTO was > 42d in 8 cases.

Legend

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

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

**EMA Considerations on the OE results – Myocarditis and Pericarditis**

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

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

**Final considerations on both OE analyses**

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

The PRAC Rapporteur fully endorses the evaluation and conclusion of the analysis by the EMA.

### 3.1.4. PRAC Rapporteur discussion and conclusion

Cumulatively until 31 May 2021 the MAH identified (Worldwide) **358** reports coded Myocarditis AEs; **296** coded Pericarditis, including **25** reports reporting both PTs (Myocarditis and Pericarditis).

Cumulative exposure worldwide from the receipt of the first temporary authorisation for emergency supply on 01 December 2020 through 31 May 2021 is **542,013,978 estimated administered doses** (6<sup>th</sup> MSSR).

**MYOCARDITIS** Brighton's collaboration (BC) criteria:

**BC level 1:** 24 cases. Age ranged <18-69 (median: 34, mean: 37.96) years: 11 cases 18-30 years age group, 9 cases in the 31-65 year age group, 3 cases in the above 65 year age group, and in 1 case, there was no age reported. More reports in males (15) than in females (8); gender was not reported in 1 case

**BC level 2:** 37 cases. Age ranged between <18-89 years; there were 27 males and 10 females.

**BC level 3:** 42 cases

**BC level 4:** 245 cases.

**BC level 5:** 10 cases.

The MAH only has presented a causality assessment of the fatal cases. An evaluation of causality and outcome of the events, especially in sufficiently documented cases not reporting alternative aetiologies, confounding medical history or underlying conditions should still be provided (**Question 1 not resolved, see RfSI**).

Following the **PRAC Rapporteur's review** of EEA cases without another identifiable cause and plausible time-to-onset, a role of the vaccine in causing (acute) myocarditis is considered possible. Nevertheless, causality assessment is hampered by the confounding medical history and comorbidities/conditions (*e.g.* COVID-19, diabetes, heart disease, including previous myocarditis). The MAH should still provide a discussion regarding the possible mechanisms (if any) explaining the observation that O/E ratios were higher for Dose 2 compared to Dose 1 (**RfSI**).

#### **Observed/Expected analysis myocarditis**

The MAH did not provide the requested age strata under 25 years of age: **12-15, 16-19, 20-24**. This is **not acceptable** as the current signal is strongest in those age groups. Moreover, the same predominance within these age groups is consistent in several other O/E analysis conducted by Israel, USA, UK and the WHO. **Question 2 is not resolved.**

The MAH did not include an O/E analysis without an assumed risk window given the substantial challenges and assumptions required to estimate total age-, sex- or dose-specific person years of exposure for the strata and subsequent limitations in interpretation of O/E using an unrestricted risk window. This is accepted as the O/E ratio probably is lower than using a 14 or 21 d risk window.

The MAH performed a more refined O/E analysis based on the **available data** in US, EU and globally (including the cases from Israel). A separate O/E analysis of the cases from Israel was also provided.

For the EU/US analysis, no O/E ratios were greater than 1. O/E ratios for both the age- gender-stratified and dose-stratified analyses were highest for the 14-day risk window, with similar patterns

but numerically lower ratios using the 21-day risk window. Ratios were highest in the 12-24 age group for both males and females, with a slightly higher ratio in females.

The MAH noted that the background rate for males for this age group is more than 4 times higher than the background rate for females. Although ratios did not exceed 1 for any of the age-gender strata, the upper limit of the 95% CI exceeded 1 for females in the 12-24 years stratum. Ratios were higher for Dose 2 compared to Dose 1.

The Global O/E analysis, which includes cases from Israel, showed similar patterns as the EU/US analysis. The ratio was again highest in the 12-24 age group, although in contrast to the EU/US data, the ratio was higher among males in this age group. The O/E was greater than 1 for the 12-24 year old male stratum for the 14-day risk window, with the lower limit of the 95% CI exceeding 1. The upper limit of the 95% CI exceeded 1 for the 12-24 year old female stratum for the 14-day risk window. Ratios were higher for Dose 2 compared to Dose 1.

Regarding the Israeli cases, which appear to be the main driver of the global O/E ratio just above 1 within the 12-24 years of age group (males and females), the MAH noted that no cases were assessed as BC level 1. Two (2) cases were assessed as BC level 2, 10 as BC level 3, 88 as BC level 4, and 2 as BC level 5. Three (3) of these cases had a fatal outcome (see below). In addition cases of myocarditis reported by Israel lacked supporting evidence of imaging and/or laboratory values to make a definitive assessment.

The results of the MAH O/E analyses (EU/US and globally) are different from the results of the O/E analyses with a data cut off of 13 June 2021 performed by EMA. *I.e.* the O/E analyses with a 14d risk window showed a higher number of myocarditis cases than expected in males aged 18-24 (O/E ratio and lower 95% CI limit above 1). For females 18-24 and 25-49, the O/E ratio was above 1 but the lower limit of the 95% CI was not.

The MAH performed separate O/E analyses of the Israeli cases and concluded that in both the age-gender-stratified and dose-stratified analyses, the O/E ratios were highest for the 14-day risk window, with similar patterns but numerically lower ratios using the 21-day risk window.

Ratios were highest in the 12-24 age group for both males and females, with a higher ratio in males. Using a 14-day risk window, ratios exceeded 1 for Males 12-24 years, Males 25-49 year, Males 70-79 years, Females 12-24 years, Females 25-49 years, and Females 50-59 years. Dose stratified O/E exceeded 1 for both Dose 1 and Dose 2, although the ratio was higher for dose 2.

Based on the total number of cases from Israel (n=102) included in the O/E analysis, it is noted that the MAH opted for a conservative approach (*i.e.* also including 88 out of 102 cases not meeting BC level 1-3), which is supported and valid approach for trend/signal identification purposes.

The MAH's analyses of the data from Israel are in line with the previously observed trends in O/E analyses, not only by the MAH, but also those conducted independently by EMA, WHO and other authorities (Israel, US, UK). **The overall picture seems to consistently point to a higher than expected reporting rate of myocarditis within the younger age group, with a predominance in men and following the second dose.**

## PERICARDITIS

The MAH used the European Association for Cardio-Thoracic Surgery (EACTS) criteria<sup>17</sup> for evaluation of the status of pericarditis. This is accepted.

The MAH only has presented a causality assessment of the fatal cases. An evaluation of causality in all cases, especially those not reporting alternative aetiologies, confounding medical history or underlying conditions should still be provide (**Question 1 not resolved, see RfSI**).

Following the **PRAC Rapporteur's review** a causal role of the vaccine is possible based on analysis of the spontaneously reported EEA cases without another identifiable cause and plausible (short) time-to-onset. However, many cases were confounded by relevant medical history, confounding underlying conditions or risk factors. A causal role of the vaccine in the 4 fatal cases, cannot be ruled out, but seems unlikely due to advanced age of the patients with considerable comorbidities (*i.e.* COVID, meningioma, sepsis, CVA, colorectal cancer, bladder cancer, chronic kidney disease, Acute Myeloid Leukemia, neoplasm).

### **Observed expected analysis pericarditis**

As no background rates of pericarditis are provided by the ACCESS/VAC4EU initiative and age- and gender-specific rates of pericarditis were not identified in the literature, a constant background rate of 18.0/100,000 PY is considered acceptable for signal detection purposes.

However the MAH should still present the data in the age strata (12-15, 16-19, 20-24) as requested previously. **Question 2 is not resolved.**

None of the O/E analyses had a ratio greater than 1.

For the EU/US analysis, both the age- gender-stratified and dose-stratified analyses the O/E ratios were higher for the 14-day risk window ([Table 9](#)), with similar patterns but numerically lower ratios using the 21-day risk window ([Table 11](#)).

Ratios were highest in the 12-24 age group for males and 25-49 age group for females. The upper level of the 95% CI did not exceed 1 for any of the age-gender strata; ratios were higher for dose 2 compared to dose 1.

The MAH noted that global O/E analysis ([Table 10](#) and [Table 12](#)), which include cases from Israel, demonstrated the similar patterns as EU/US only.

Based on the currently available evidence a causal relation between Comirnaty and pericarditis is considered weak. Nevertheless, note that clearly separating pericarditis from myocarditis is challenging as the term pericarditis can refer to inflammation of the pericardium and myocarditis. Both can occur together in clinical practice, and hence the term myopericarditis is used. Sometimes myopericarditis is used interchangeably with perimyocarditis. In the EEA cases of myocarditis, cases reporting both myocarditis and pericarditis have been included (17 cases of perimyocarditis and 16 cases of myopericarditis).

Pending the MAH's response to the outstanding issues and additional analyses the signal for pericarditis should remain open.

In addition the MAH should continue to closely monitor any new cases and notify the Rapporteur in case of unexpected trends or findings.

### **Pathogenic mechanism**

The MAH provided a discussion on possible mechanisms by which the vaccine may cause myocarditis, including Multisystem inflammatory syndrome in children (MIS/MIS-C) as alternative aetiology.

In summary, at the moment a causal relationship between the vaccine and the reported myocarditis and pericarditis cannot be refuted.

Irrespective of vaccination, myocarditis may be due to numerous of causes including viral or bacterial infection, autoimmune, genetic, metabolic (*e.g.*, diabetes mellitus) and toxic factors. As generally cases of myocarditis are thought to have infectious causes, the incidence could vary depending on local epidemiology.

Vaccine-associated myocarditis has been reported with several vaccines (*e.g.*, influenza, smallpox, tetanus toxoid, diphtheria/poliomyelitis/tetanus, HBV, MENcn-C), although diagnostic endomyocardial biopsies are rare. An endocardial biopsy from a case of myocarditis associated with inactivated influenza vaccine demonstrated lymphocytic myocarditis, indicating a viral or delayed-type hypersensitivity mechanism.

Based on randomised clinical trial data at the moment there is no suggestion that myocarditis or pericarditis would be a risk causally related to vaccination with Comirnaty. However, the RCT was not powered to detect very rare adverse events and the younger age groups were relatively less well represented.

Nonclinical data thus far have not observed clear (mechanistic) evidence supportive of Vaccine-induced and immune-mediated myocarditis or pericarditis:

- In rats administered doses of up to 100 µg BNT162b2 intramuscularly (IM) once weekly for 3 times there was no microscopic evidence of myocarditis or pericarditis at the end of either the dosing or recovery phases
- In nonhuman primates administered BNT162b2 at doses of up to 100 µg IM twice 3 weeks apart followed by SARS-CoV-2 challenge, there was no evidence of myocarditis, pericarditis, or MIS at 7-8, 14-15, or 21-23 days post challenge
- Biodistribution studies in rats using bio-luminescent labelled LNP did not identify the heart as a site of LNP distribution

Nevertheless, eosinophilic myocarditis is considered a hypersensitivity myocarditis and is associated with increased peripheral eosinophils in most patients. Nonclinical studies in rats administered BNT162b2 had transient slight increases in eosinophils along with a prominent neutrophilic response (resolved at the end of recovery period) and were interpreted to be the result of generalized myeloid cell stimulation rather than a hypersensitivity reaction. This may suggest a possible pathogenic mechanism.

Amino-acid sequence homology search for molecular mimicry/autoimmune targets did not identify any membrane-expressed heart-specific proteins with homology to the spike protein.

Systemic exposure to the expressed spike protein antigen is expected to be very low, and thus binding of the protein to ACE2 receptors leading to an off-target immune response to the antigen-receptor complex is considered highly unlikely, particularly in tissues with low ACE-2 expression.

At the moment no obvious parallels can be drawn from the limited data characterizing the immune responses in MIS-C and the known immunologic reactions following vaccination.

The MAH's discussion is accepted.

## Product information

**Question 5 is not resolved.** The MAH should update the product information and risk management plan and submit a draft DHPC.

### 3.2. Rapporteur's proposed recommendation

The overall benefit-risk remains unchanged. However, as an immediate step amendment of the product information is warranted, which should be communicated by a DHPC. The MAH should submit a draft DHPC and communication plan by 1 July 2021.

Furthermore, the MAH should adequately address the outstanding topics listed in **Section 3.3 List of outstanding issues**, (below), timetable to be agreed during the July 2021 PRAC plenary meeting.

#### Regarding Myocarditis

A causal role of the vaccine is considered possible based on the analysis of the spontaneously reported EEA cases without another identifiable cause and plausible time-to-onset.

Despite the uncertainties regarding expected background rates and some differences with earlier O/E analyses (e.g. due to differences in chosen background rates, risk window, number of observed cases etc) the most recent MAH and EMA analyses are **not** refuting the signal, rather are in line with the previously observed trends in O/E analyses, not only by the MAH, but also those conducted independently by EMA, WHO and other authorities (Israel, US, UK). The overall pattern seems to consistently point to an higher than expected reporting rate of myocarditis within the younger age group, with a predominance in men and following the second dose.

In our view these findings must be adequately reflected in the product information (*i.e.* SmPC Section 4.4 Warnings and precautions, and PL accordingly) in order to increase HCP and vaccinee awareness, enabling early detection and adequate management as warranted.

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

Dissemination of a DHPC is considered warranted.

At present, a definite causal relationship between myocarditis and vaccine administration has not been established. Causality assessment of the spontaneously reported cases generally was hampered by insufficient documentation, confounding medical history, underlying conditions, or risk factors, hence inclusion as adverse reaction in SmPC section 4.8, in addition to section 4.4, is not supported as yet.

#### Regarding Pericarditis

A causal role of the vaccine is possible based on analysis of the spontaneously reported EEA cases without another identifiable cause and plausible (short) time-to-onset. However, many cases were confounded by relevant medical history, confounding underlying conditions or risk factors. Taken together with the results from the current O/E analyses which do not identify a higher than expected incidence rate of pericarditis, the evidence supporting a causal role of the vaccine is considered weak. In the majority of cases, the pericarditis is resolving or has resolved following treatment.



### **3.3. PRAC Rapporteur proposed product information update**

#### **Summary of Product Characteristics (SmPC)**

##### **Section 4.4 Warnings and Precautions**

Very rare cases of myocarditis have been observed following vaccination with Comirnaty.

These cases occurred predominantly in adolescents and young adults, more often in males than females, more often after the second dose of the vaccine, and typically within 14 days after vaccination (after the 2<sup>nd</sup> dose mostly within 6 days). These are typically mild cases and individuals tend to recover within a short time following standard treatment and rest.

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

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

The **Patient Information Leaflet** should be amended accordingly.

##### **Section 2:**

Very rare cases of myocarditis (inflammation of the heart) have been reported after vaccination with Comirnaty. The cases have primarily occurred within two weeks following vaccination and occurred more often after the 2<sup>nd</sup> vaccination, then within 6 days. Most cases were mild and individuals recovered within a short time following standard treatment and rest. Those vaccinated should be alert to signs of myocarditis, such as breathlessness, palpitations and chest pain, and seek medical attention should these occur.

### **3.4. UPDATED List of outstanding issues (following PRAC discussion):**

#### **Myocarditis and Pericarditis**

1. **Initial Question 1 is not resolved.** It is reiterated that the MAH should provide a causality assessment (including a summary and number of cases with **vaccine-relatedness** assessed as probable, possible, unlikely, unassessable etc) and outcome of the events (e.g. hospitalization, life-threatening, or death) for each case, in particular for those cases (including any new cases) which are sufficiently documented and not reporting alternative etiologies, confounding medical history or underlying conditions. In addition, taking into account the totality of the available data, including relevant publications, the MAH should provide a discussion regarding:
  - a) Possible mechanism(s) that could explain the observation that O/E ratios were higher for Dose 2 compared to Dose 1.
  - b) Risk factors, with the aim to implement measures to mitigate the risk. If appropriate, PI updates should be proposed.



- c) Recommendations for administration of the second dose, in case of the occurrence of myocarditis/pericarditis following the first dose.
2. **Initial Question 2 is not resolved.** Focus of further analyses should be on the younger group, where the confounding is much less present. Considering the shift of the immunization campaigns to the younger population the MAH should increase their efforts to closely monitor O/E trends in this population and provide the requested age strata under 25 years of age: 12-15, 16-19, 20-24 as the current signal is strongest in those age groups.
  3. The MAH should confirm (or otherwise justify) that no restriction/selection was made on BC level diagnostic certainty (i.e. only including at least BC level 3 [possible] myocarditis cases). In principle, including all BC level cases (also BC level 4-5, i.e. cases not meeting BC level 1-3) in the O/E analysis is supported, as a conservative approach. In addition, the MAH should clarify which and how many of the BC level cases have been included (per stratum), especially in the strata that show an O/E ratio near or above 1.
  4. **Question 5 is not resolved.** In the updated RMP, the following points should be addressed:
    - Propose how to further characterise the new important risks, including evaluation of the outcome (mild/severe/sequelae), in ongoing and future studies.
    - The MAH should discuss if the need and possibility to perform specific studies to investigate risk factors for myocarditis and pericarditis after Comirnaty administration with the aim to implement measures to mitigate the risk.

### **3.5. Comments from other PRAC members (MS) and MAH(s)**

#### MS1 comments:

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

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

The dissemination of a DHPC is also supported.

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

#### **Section 4.4 Warnings and Precautions**

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

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

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

#### **Section 4.8**

“Myocarditis” “Pericarditis” in SOC: “Cardiac disorder” with frequency “unknown”

MS2 comments:

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

In accordance with MS4 comments, and based on currently available information, besides an update of the SmPC section 4.4, an update of Section 4.8 is warranted for both myocarditis and pericarditis, in line with MHRA, CDC and Health Canada label updates.

We also agree with the proposal from MS3 for the MAH to discuss if there are appropriate RMMs that could be identified in younger population at higher risk or studies to identify them.

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

MS3 comments:

We would like to make the following considerations to this signal AR:

We consider that, based on the evidence available, a causal association between Comirnaty and Myocarditis is at least a reasonable possibility, so besides an update of the SmPC section 4.4, an update of Section 4.8 is warranted.

In line with our proposal for Spikevax, the MAH should discuss if there are RMMs that could be identified in this younger population at higher risk of myocarditis, or specific studies to identify them (i.e. testing a lower vaccination dose?).

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

MS4 comments:

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

*Myocarditis*

As a causal relationship between myocarditis is considered at least a reasonable possibility, the proposed update of section 4.4 to include myocarditis is endorsed. As outlined in the SmPC guideline ([https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-2/c/smpc\\_guideline\\_rev2\\_en.pdf](https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf)), ‘any adverse reaction described in this section or known to result from conditions mentioned here should also be included in section 4.8’. A corresponding update of section 4.8 is therefore considered warranted.

*Pericarditis*

The outstanding questions with regards to pericarditis is acknowledged.

As pointed out by the PRAC Rapporteur, clearly separating pericarditis from myocarditis is challenging, as the term pericarditis can refer to inflammation of the pericardium and myocarditis. In addition, myocarditis and pericarditis share clinical features and pathomechanisms. Therefore, inclusion of both terms in section 4.4 and 4.8 is considered warranted, in line with the label updates from MHRA, CDC and Health Canada.

MS5 comments:

We agree that RMP should be updated in order to include myocarditis and pericarditis in summary of safety concerns and to further characterize both events in the ongoing and planned studies in the PhV plan, with particular attention to age stratification and risk profile identification. A DHPC is strongly supported.

**Myocarditis:** the PRAC Rapp proposal to update section 4.4 of SmPC to include myocarditis is endorsed, as the causal role of the vaccine is considered possible. The unresolved outstanding issues are acknowledged. However, based on current evidences, myocarditis should also be included in section 4.8.

**Pericarditis:** we agree that O/E analyses do not identify a higher than expected incidence rate of pericarditis. However, the assessment of spontaneous reports cannot exclude a possible causative role of the vaccine. Moreover, according to PRAC Rapporteur, clearly separating pericarditis from myocarditis is challenging, since both conditions share some pathophysiological mechanisms and some cases of myopericarditis and perimyocarditis have also been reported. Thus, we support the proposal to also include the term pericarditis in section 4.4 and 4.8.

MS6 comments:

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

We support the proposal to update section 4.4 with a warning on myocarditis. We acknowledge that the proposed text regarding the characterisation of cases as typically mild, with recovery in a short timeframe following standard treatment and rest, is consistent with the clinical experience reported in the US and in Israel. We note, however, from the assessment that detailed information on the clinical course of cases is not provided. Therefore, we consider that the wording should more closely reflect the outcome data available from assessment of EEA cases and suggest modifications to the text, similar to the wording implemented by the FDA. We consider that further clarification on the clinical course of cases reported to date in terms of their severity, treatments administered and time to recovery would be helpful to inform the appropriate wording of this text describing the nature of the cases in the product information.

We agree that it is challenging to separate pericarditis from myocarditis as they may occur together and there is an overlap in clinical features. While we acknowledge that the strength of evidence of a causal relationship between Comirnaty and pericarditis is currently weaker than for myocarditis, we consider that based on the available data the warning in section 4.4 of the SmPC should include reference to pericarditis in addition to myocarditis.

Furthermore, we are of the view that the available data suggest a reasonable possibility of a causal association between Comirnaty and both myocarditis and pericarditis, therefore, we suggest that these terms are included as adverse reactions in section 4.8 of the SmPC.

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

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

SmPC section 4.4:

### **Myocarditis and pericarditis**

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

These cases **of myocarditis** occurred predominantly in adolescents and young adults, more often in males than females, more often after the second dose of the vaccine, **and typically a few days after vaccination**, and typically within 14 days after vaccination (after the 2nd dose mostly within 6 days). These are typically mild cases and individuals tend to recover within a short time following standard treatment and rest. **Available data suggest resolution of symptoms within a short timeframe, however, information on potential long-term sequelae is not yet available.**

Healthcare professionals should be alert to the signs and symptoms of myocarditis **and pericarditis**.

Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis such as (acute and persisting) chest pain, ~~sometimes with accompanying fever and shortness of breath,~~ **or palpitations.**

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

PL section 2:

Very rare cases of myocarditis (**inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart)** inflammation of the heart) have been reported after vaccination with Comirnaty. The cases **of myocarditis** have primarily occurred within two weeks following vaccination and **mainly occurred a few days after vaccination and** occurred more often after the 2nd vaccination. **Most cases have occurred in younger men,** then within 6 days. Most cases were mild and individuals recovered within a short time following standard treatment and rest. Those vaccinated should be alert to signs of myocarditis, **You should urgently seek medical attention if you experience new onset of symptoms** such as **chest pain,** breathlessness, **or feelings of having a fast-beating, fluttering, or pounding heart.** and chest pain, and seek medical attention should these occur.

Comments MS7:

The PRAC Rapporteur is thanked for a comprehensive report. The overall conclusions are endorsed. However, since some of the reported cases of myocarditis were serious, we would like to propose some minor additional information to the warning in section 4.4 of the SmPC. Furthermore, we find that there is sufficient evidence for a causal relationship between myocarditis and vaccination with Comirnaty, and thus support inclusion of myocarditis in section 4.8.

### **SmPC Section 4.4**

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

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

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

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

### **Package Leaflet**

We propose a shortened information for the package leaflet to keep the information concise.

### **Section 2:**

Very rare cases of myocarditis (inflammation of the heart) have been reported after vaccination with Comirnaty. The cases have primarily occurred within two weeks following vaccination and occurred more often after the 2<sup>nd</sup> vaccination, ~~then within 6 days. Most cases were mild and individuals recovered within a short time following standard treatment and rest. Those vaccinated~~ **Following vaccination, you** should be alert to signs of myocarditis, such as breathlessness, palpitations and chest pain, and seek medical attention should these occur.

### **Comment PRAC Rapporteur:**

All seven MSs noted that based on the available evidence both myocarditis **and pericarditis** should be included in section 4.4 **and 4.8**. This is consistent with the recent label updates from Health Canada, FDA and MHRA. Ideally EU labeling should be aligned between mRNA COVID-19 vaccines.

Please note that from the comments it is not clear whether MS3 and MS7 also propose labelling of pericarditis in 4.8.

MS6 and MS7 comments on proposed PI wording are considered in the final proposed wording.

### MS8 comments:

All OCs raised by the PRAC Rapporteur are agreed. Furthermore, the updating of section 4.4 of the current SmPC regarding the risk of myocarditis is also agreed as well as a communication via a DHPC to HCPs.

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

### MS9 comment:

We support the Rapp's recommendation based on currently assessed data to include a warning into SmPC section 4.4. We propose to include a symptom of myocarditis "palpitations" into SmPC as well (similarly to the PIL update).

A DHPC to disseminate a quick information is mostly supported.

MS10 comment:

We fully endorse the Rapporteurs' Report regarding the above mentioned procedure and have no additional comments.

**Comment PRAC Rapporteur:**

Full endorsements from additional three MSs (only 4.4 update and mentioning myocarditis only) are appreciated.

MS8 suggestion that an *ad-hoc* expert group of cardiologists would be very helpful for the next steps of this signal is endorsed. Indeed, the causality is especially complex to analyse and none of the mechanisms put forward by the MAH to explain the occurrence of myocarditis after mRNA vaccine immunization have been validated. This AHEG might also be helpful to reflect on risk minimisation measures.

MS9 proposal to include a symptom of myocarditis "palpitations" into SmPC as well (similarly to the PIL update) is endorsed.

### **3.6. Updated rapporteur's proposed recommendation**

The overall benefit-risk remains unchanged. However, as an immediate step amendment of the product information is warranted, which should be communicated by a DHPC. The MAH should submit a draft DHPC and communication plan by 1 July 2021.

Furthermore, the MAH should adequately address the outstanding topics listed in Section 3.3 List of outstanding issues, timetable to be agreed during the July 2021 PRAC plenary meeting.

Based on comments received from other PRAC members and NL cardiology experts the PRAC (and labelling in other jurisdictions) rapporteur is recommending the following:

#### **Regarding Myocarditis**

A causal role of the vaccine is considered **at least reasonably** possible based on the analysis of the spontaneously reported EEA cases without another identifiable cause and plausible time-to-onset.

Despite the uncertainties regarding expected background rates and some differences with earlier O/E analyses (*e.g.* due to differences in chosen background rates, risk window, number of observed cases etc) the most recent MAH and EMA analyses are not refuting the signal, rather are in line with the previously observed trends in O/E analyses, not only by the MAH, but also those conducted independently by EMA, WHO and other authorities (Israel, US, UK). The overall pattern seems to consistently point to a higher than expected reporting rate of myocarditis within the younger age group, with a predominance in men and following the second dose.

In our view these findings must be adequately reflected in the product information (*i.e.* SmPC Sections 4.4 Warnings and precautions, **and 4.8 Adverse reactions**, and PL accordingly) in order to increase HCP and vaccinee awareness, enabling early detection and adequate management as warranted.

Also, myocarditis and pericarditis are considered as important **identified** risks and should be further characterized in the ongoing and planned studies in the PhV plan, as appropriate. The RMP should be updated accordingly.

In the updated RMP, the following points should be taken into consideration:

- propose how to further characterise the new important risks, including evaluation of the outcome (mild/severe/sequelae), in ongoing and future studies.
- The MAH should discuss if there are RMMs that could be identified in the younger population (including the adolescent population) at higher risk of myocarditis or pericarditis, or the possibility to perform specific studies to investigate this.

Dissemination of a DHPC is considered warranted.

The submitted data are not conclusive, mainly because of the confounding factors and the often poor documentation. In addition, myocarditis and pericarditis are specified separately, while the definition of pericarditis is more specific, and also easier to recognize by the symptoms and ultrasound abnormalities (combination of pain, pericardial rubbing and/or pericardial fluid) than that of myocarditis (according to Brighton's collaboration criteria), where actually no symptom is specific and the chance of confounding is only greater. This confounding is especially important in the elderly, where no conclusion is actually possible about causality (probably not even after further questioning with the MAH). Focus of further analyses should be on the younger group, where the confounding is much less present. To that extent, further stratification on age and dose with further analysis of the O/E ratio is crucial.

### Regarding Pericarditis

A causal role of the vaccine is possible based on analysis of the spontaneously reported EEA cases without another identifiable cause and plausible (short) time-to-onset. However, many cases were confounded by relevant medical history, confounding underlying conditions or risk factors. Taken together with the results from the current O/E analyses which do not identify a higher than expected incidence rate of pericarditis, the evidence supporting a causal role of the vaccine is considered weak. In the majority of cases, the pericarditis is resolving or has resolved following treatment.

Nevertheless, it is challenging to separate pericarditis from myocarditis as they may occur together and there is an overlap in clinical features. While we acknowledge that the strength of evidence of a causal relationship between Comirnaty and pericarditis is currently weaker than for myocarditis, we consider that based on the available data the warning in section 4.4 **and 4.8** of the SmPC should **include reference to pericarditis in addition to myocarditis**. In the DHPC, pericarditis should be included in addition to myocarditis.

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

### Section 4.4 Warnings and Precautions

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

These cases occurred predominantly in adolescents and young adults, more often in males than females, more often after the second dose of the vaccine, and typically within 14 days after vaccination (after the 2<sup>nd</sup> dose mostly within 6 days). **Currently, there is no indication that the cases have had a more severe course than otherwise seen for myocarditis. However, information on potential long-term sequelae is not yet available.** ~~These are typically mild cases and individuals tend to recover within a short time following standard treatment and rest.~~



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

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

#### **SmPC 4.8**

#### **"Myocarditis" and "Pericarditis" in SOC: "Cardiac disorder" with frequency "unknown"**

The **Patient Information Leaflet** should be amended accordingly.

#### **Section 2:**

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 Comirnaty. The cases have primarily occurred within two weeks following vaccination and occurred more often after the 2<sup>nd</sup> vaccination, then mostly within 6 days. Most cases were mild and individuals recovered within a short time following standard treatment and rest. **Following vaccination, you**~~These vaccinated~~ should be alert to signs of myocarditis, such as breathlessness, palpitations and chest pain, and seek medical attention should these occur.

#### **Section 4:**

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

### ***3.7. Adopted PRAC recommendation***

Having considered the available evidence from the data provided by the Marketing Authorisation Holder (MAH) and from the EudraVigilance database, including data from clinical trials, post-marketing experience, the literature and from observed to expected analyses, the PRAC has agreed that based on the evidence assessed, a causal association between COVID-19 mRNA vaccine (nucleoside-modified) Comirnaty and myocarditis/pericarditis is considered of at least a reasonable possibility. The PRAC has agreed that the MAH for Comirnaty (BioNTech Manufacturing GmbH) should address the below recommendation:

#### **1. Product information update**

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

#### **Summary of Product Characteristics**

#### **Section 4.4 – Special warnings and precautions for use:**

##### Myocarditis and pericarditis

Very rare cases of myocarditis and pericarditis have been observed following vaccination with Comirnaty. These cases have primarily occurred within 14 days following vaccination, more often after the second

vaccination, and more often in younger men. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

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

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

#### **Section 4.8 – Undesirable effects:**

“Myocarditis” and “Pericarditis” in SOC: “Cardiac disorders” with frequency “unknown”

#### **Package Leaflet:**

#### **Section 2 - What you need to know before you are given Comirnaty**

##### **Warnings and precautions**

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

#### **Section 4 - Possible side effects**

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

#### 2. Direct healthcare professional communication (DHPC)

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

#### 3. Request for supplementary information (RfSI)

The MAH should provide answers to the below List of Questions by 02/08/2021.

##### List of Questions (myocarditis and pericarditis)

1. Initial Question 1 is not resolved. It is reiterated that the MAH should provide a causality assessment (including a summary and number of cases with vaccine-relatedness assessed as probable, possible, unlikely, un-assessable, etc.) and outcome of the events (e.g. hospitalization, life-threatening, or death) for each case, in particular for those cases (including any new cases) which are sufficiently documented and not reporting alternative etiologies, confounding medical history or underlying conditions. In addition, taking into account the totality of the available data, including relevant publications, the MAH should provide a discussion regarding:

- a) Possible mechanism(s) that could explain the observation that O/E ratios were higher for Dose 2 compared to Dose 1.
  - b) Recommendations for administration of the second dose, in case of the occurrence of myocarditis/pericarditis following the first dose.
2. Initial Question 2 is not resolved. Focus of further analyses should be on the younger group, where the confounding is much less present. Considering the shift of the immunization campaigns to the younger population the MAH should increase their efforts to closely monitor observed/expected (O/E) trends in this population and provide the requested age strata under 25 years of age: 12-15, 16-19, 20-24 as the current signal is strongest in those age groups.
  3. The MAH should confirm (or otherwise justify) that no restriction/selection was made on BC level diagnostic certainty (i.e. only including at least BC level 3 [possible] myocarditis cases). In principle, including all BC level cases (also BC level 4-5, i.e. cases not meeting BC level 1-3) in the O/E analysis is supported, as a conservative approach. In addition, the MAH should clarify which and how many of the BC level cases have been included (per stratum), especially in the strata that show an O/E ratio near or above 1.

The PRAC will assess the answers to the above List of Questions within a 30-days timetable.

#### 4. Risk management plan (RMP) update

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

- a) Propose how to further characterise the new important risk, including evaluation of the outcomes (e.g. mild/severe/sequelae);
- b) Discuss any risk factors that could be identified, as well as the need and possibility to perform specific studies to investigate risk factors for myocarditis and pericarditis after Comirnaty administration with the aim to implement measures to mitigate the risk. If appropriate, PI updates should be proposed.
- c) Assure long term follow up of myocarditis and pericarditis cases in order to better characterize long term consequences.
- d) Number of young patients included in the studies should assure timely characterisation of the risk in this population of special interest.

## 4. Additional evidence

### 4.1. Assessment of MAH response to RfSI

#### Question 1

Initial Question 1 is not resolved. It is reiterated that the MAH should provide a causality assessment (including a summary and number of cases with vaccine-relatedness assessed as probable, possible, unlikely, un-assessable etc) and outcome of the events (e.g. hospitalization, life-threatening, or death) for each case, in particular for those cases (including any new cases) which are sufficiently

documented and not reporting alternative etiologies, confounding medical history or underlying conditions. In addition, taking into account the totality of the available data, including relevant publications, the MAH should provide a discussion regarding:

- a. Possible mechanism(s) that could explain the observation that O/E ratios were higher for Dose 2 compared to Dose 1.
- b. Recommendations for administration of the second dose, in case of the occurrence of myocarditis/pericarditis following the first dose.

### **MAH response to Question 1**

In alignment with GVP Module VI and ICH Guideline E2A for regulatory reporting purposes, all spontaneous reports notified by healthcare professionals or consumers are considered suspected adverse reactions unless the reporters specifically state that they believe the events to be unrelated or that a causal relationship can be excluded. That said, we have independently analyzed the cases of **Myocarditis**, defined as per Brighton Collaboration (BC) Levels 1 to 3 cumulatively through 31 May 2021 (103 cases: 24 BC Level 1, 37 BC level 2, and 42 BC level 3 out of the 357 Myocarditis cases reported during that period after more than 300 million doses administered worldwide) for completeness of their etiological workup in order to confirm existing or alternate etiologies leading up to the Myocarditis diagnosis.

This assessment was divided into:

#### A – Thorough etiological workup

- Clinical Exam findings and cardiac imaging (cardiac magnetic resonance [CMR] or echocardiography) and/or electrophysiology (ECG)
- Known dose sequence
- Known time to onset

And at least two of the following:

- Blood testing such as Troponin, CRP, CBC, ALT, AST, etc.
- Viral panel such as EBV, VZV, HIV, HBV, HCV, etc.
- SARS-CoV-2 N nucleoprotein serology or PCR

#### B – Partially complete etiological workup

- Clinical exam findings and Cardiac imaging (CMR or echocardiograph ) and/or electrophysiology (ECG)
- Known dose sequence
- Known time to onset

And at least one of the following:

- Blood testing such as Troponin, CRP, CBC, ALT, AST, etc.
- Viral panel such as EBV, VZV, HIV, HBV, HCV, etc.
- SARS-CoV-2 N nucleoprotein serology or PCR

#### C – Incomplete etiological workup

One of the following or more is missing:

- Clinical exam findings Cardiac imaging (CMR or echocardiograph ) and/or electrophysiology (ECG)
- Known dose sequence
- Known time to onset

Out of the 103 cases, 16 had a complete, 58 a partially complete, and 29 an incomplete etiological work-up. Thus, very few reports provide sufficient information to reasonably assess if an alternate etiology was present, even within these **myocarditis** cases that met BC 1 to 3.

For the 16 cases with thorough etiological work-up, 7 were BC level 1, 8 BC level 2 and 1 BC level 3. Four had previous history of COVID-19 infection, 2 had other viral infections, including EBV, HSV, and parvovirus (one who had history of both COVID-19 and other viral infections). Two (2) had history of myocarditis and pericarditis. Altogether, this information indicates that 8 out of these 16 patients may have had other causative factors for myocarditis rather than the vaccine itself, a conclusion possible because of the thorough etiological workup. The other 8 cases either did not have a relevant medical history or other alternate etiologies were provided in the report. Out of the total 357 Myocarditis cases, 9 had a fatal outcome (described in detail in our response to the EMA PRAC on 22 June 2021), 118 were of unknown outcome, 102 were unrecovered, 71 were recovering, 47 were recovered/resolved and 10 were recovered with sequelae.

A clear causal relationship between the vaccine and the reported cases of myocarditis and pericarditis and a clear mechanism have not been determined by the MAH. Possible speculative mechanisms may include delayed-type hypersensitivity. One hypothetical possibility, based on historical information, is eosinophilic myocarditis, given previous reports of similar conditions following MEN<sub>en-C</sub> and HBV vaccines<sup>5,6,7,8</sup>. In the case of a prime-boost vaccination platform, the subsequent administration may lead to a cytokine – related and/or eosinophil-mediated amplification of such an in vivo reaction. However, as this has not been identified in the context of the COVID-19 vaccines, it is also speculative. On the other hand, previous dormant viral infection may be a possible cause of the pathogenesis of myocarditis (Bears M et al. *Factors associated with myocardial SARS-CoV-2 infection, myocarditis, and cardiac inflammation in patients with COVID-19*. Mod Pathol 2021 Jul;34(7):1345-1357). Indeed few of the cases of confirmed myocarditis identified in our database had either a history of COVID19 and/or other viral infections.

It may also be speculated that the changes in underlying infections with non-covid viral illnesses as well as social distancing/ behavioral changes that may occur following vaccination in an individual or group of individuals, may contribute to changing incidence and distribution of myocarditis and pericarditis (Gomez GB et al. *Uncertain effects of the pandemic on respiratory viruses*. Science. 2021 Jun 4;372(6546):1043-1044). While an O/E analysis without an assumed risk window was not conducted given the substantial challenges and assumptions required to estimate total age-, sex- or dose-specific person-years of vaccination (exposure) for the strata and given the subsequent limitations in interpretation of O/E using an unrestricted risk window, a constant ratio of administration by gender was assumed globally, which may not reflect the actual distribution (it could potentially over- or underestimate the expected counts in any given stratum).

It remains the MAH's position that while there may be an association between vaccination and the occurrence of **myocarditis**, a causal relationship with the vaccine itself has not yet been established. It is worth noting that the risk of acquiring myocarditis from COVID19 infection is significantly higher than that of acquiring the condition following vaccination. Given that the benefit/risk ratio remains favorable in all approved age groups, the MAH continues to recommend/support the administration of both doses in sequence and schedule as approved by the HAs, always in the context of individual benefit/risk.

**Comment PRAC Rapporteur:**

The MAH's response concerning causality assessment is noted.

No new cases were discussed with this response as the MAH analysed cases of Myocarditis up to 31 May 2021. However, the MAH submitted their response document on 30 July 2021 and consequently there is a two month lag time. This is not considered acceptable in view of the fact that vaccination campaigns in Europe now have progressed to the younger age cohorts and the ADR under assessment seems to occur more frequently in younger populations. Consequently, recent data may be of particular interest. The MAH is urged to provide more recent data in future submissions. It is noted that for the MSSRs there is a 15 day period between DLP and submission. The MAH is expected to achieve a similar period for signal procedures that comprise less data than the MSSRs, unless otherwise stated in the PRAC request for supplementary information.

The MAH mentions as possible mechanism by which Comirnaty could cause myocarditis that with a prime-boost vaccination platform, the subsequent administration may lead to a cytokine – related and/or eosinophil-mediated amplification of such an in vivo reaction. In addition, the MAH hypothesized that previous dormant viral infection, changes in underlying infections with non-covid viral illnesses as well as social distancing/ behavioral changes that may occur following vaccination, may contribute to changing incidence and distribution of myocarditis and pericarditis, which is acknowledged. At present no definite conclusions can be drawn regarding pathogenic mechanisms and any new information in this regard should be presented and discussed in MSSRs and PSURs.

Note that it would be of interest and helpful to better understand why cases of myocarditis and pericarditis are only being observed following mRNA COVID-19 vaccination (Bibhuti B et al. *Myocarditis and Pericarditis Following mRNA COVID-19 Vaccination: What Do We Know So Far?* Children 2021,8,607). The MAH should discuss this publication in the next MSSR.

Currently there are no mechanism(s) demonstrated that explains the observation that O/E ratios were higher for the second dose compared to the first dose. In addition, there are currently no new data to substantiate changed recommendations for administration of the *second* dose, in case of the occurrence of myocarditis/pericarditis following the *first* dose. Hence, no changes to the current PI are recommended.

Further characterization of myocarditis and pericarditis (important identified risks per EU RMP, see section 3.6 in this report) – including but not limited to e.g. age stratification, risk profile of the vaccinee, occurrence of the event after first or second dose, severity of the events – should be addressed in the ongoing and planned additional pharmacovigilance studies per EU RMP. Please refer to **section 4.2** of this report for Rapporteur's proposed recommendation.

Note that on 16 July 2021, Brighton Collaboration issued [update](#) case definitions for myocarditis and pericarditis (Annex 2 and 3 in this report).

## Question 2

Initial Question 2 is not resolved. Focus of further analyses should be on the younger group, where the confounding is much less present. Considering the shift of the immunization campaigns to the younger population the MAH should increase their efforts to closely monitor O/E trends in this population and provide the requested age strata under 25 years of age: 12-15, 16-19, 20-24 as the current signal is strongest in those age groups.

## MAH response to Question 2

For the 7<sup>th</sup> Summary Monthly Safety Report (SMSR), the MAH has provided O/E within age strata under 25 years of age to reduce potential confounding. We have provided O/E within two strata:  $\leq 17$  years and 18 to 24 years. The  $\leq 17$ -year age group includes all cases reported in persons 17 and under, and the expected number of cases is based on exposure estimates derived from reported vaccine administration information in persons 17 and younger. The  $\leq 17$  years category was selected due to inconsistent reporting of vaccination within these smaller age categories across the countries that provide administration information by age.

Additionally, ACCESS reports age and sex specific background rates for the 0 to 19-year-old and 20 to 29-year-old age categories. In the 7<sup>th</sup> SMSR, the MAH calculated the O/E using a range of background rates. The low and high estimates used age-gender specific rates based on ACCESS rates derived from electronic health records. Using these estimates, the expected rate in 0 to 19-year-olds is roughly 2 to 5 times lower than the rate in the 20 to 29-year-olds. When the 0 to 19-year-old background rates are assumed for the O/E using both the low and high estimates, the O/E ratio is markedly higher in the 17 years and under category than in the 18 to 24-year-old category. However, the magnitude of O/E calculated using a medium rate estimate, which was derived from the literature and assumed constant across all age groups, were more similar between the 2 age categories. This suggests that use of a constant background rate derived from all ages for the 0 to 19-year-old age group could confound the myocarditis O/E analysis. The MAH will continue to seek sources of information specific to the age-categories of interest and incorporate this information in the O/E.

**Comment PRAC Rapporteur:**

The MAH provided the O/E age strata under 25 years of age within two strata:  $\leq 17$  years and 18 to 24 years. Tables presenting Observed to Expected (O/E) analysis of myocarditis in EEA and US are included in the MAH's 7<sup>th</sup> SMSR Appendix 5.1.

Age strata under 25 years of age are reproduced here:

**EEA – 14-day risk window**

**Table 13. Observed to Expected (O/E) Analysis of Myocarditis in European Economic Area Countries, 14-day Risk Window, Cumulative**

Stratification	Person Years	Obs Cases	Low				Mid				High			
			Bkgd rate <sup>15</sup>	Exp Cases	O/E Ratio	95% CI	Bkgd rate <sup>25</sup>	Exp Cases	O/E Ratio	95% CI	Bkgd rate <sup>8</sup>	Exp Cases	O/E Ratio	95% CI
Males $\leq 17$ years	26,459	5	0.95	0.3	19.892	6.459, 46.421	4.40	1.2	4.295	1.395, 10.023	9.58	2.5	1.973	0.640, 4.603
Males 18-24 years	167,707	30	5.38	9.0	3.325	2.243, 4.747	4.40	7.4	4.066	2.743, 5.804	23.75	39.8	0.753	0.508, 1.075
Females $\leq 17$ years	29,836	1	1.00	0.3	3.352	0.085, 18.674	4.40	1.3	0.762	0.019, 4.244	2.05	0.6	1.635	0.041, 9.109
Females 18-24 years	189,116	7	0.65	1.2	5.694	2.289, 11.733	4.40	8.3	0.841	0.338, 1.733	5.14	9.7	0.720	0.290, 1.484

**US – 14-day risk window**

**Table 14. Observed to Expected (O/E) Analysis of Myocarditis in the United States, 14-day Risk Window, Cumulative**

Stratification	Person Years	Obs Cases	Low				Mid				High			
			Bkgd rate <sup>15</sup>	Exp Cases	O/E Ratio	95% CI	Bkgd rate <sup>25</sup>	Exp Cases	O/E Ratio	95% CI	Bkgd rate <sup>8</sup>	Exp Cases	O/E Ratio	95% CI
Males $\leq 17$ years	158,747	25	0.95	1.5	16.577	10.728, 24.471	4.40	7.0	3.579	2.316, 5.284	9.58	15.2	1.644	1.064, 2.427
Males 18-24 years	260,346	22	5.38	14.0	1.571	0.984, 2.378	4.40	11.5	1.921	1.204, 2.908	23.75	61.8	0.356	0.223, 0.539
Females $\leq 17$ years	179,013	2	1.00	1.8	1.117	0.135, 4.036	4.40	7.9	0.254	0.031, 0.917	2.05	3.7	0.545	0.066, 1.969
Females 18-24 years	293,581	6	0.65	1.9	3.144	1.154, 6.844	4.40	12.9	0.464	0.170, 1.011	5.14	15.1	0.398	0.146, 0.865

**EEA – 21-day risk window**



**Table 15. Observed to Expected (O/E) Analysis of Myocarditis in European Economic Area Countries, 21-day Risk Window, Cumulative**

Stratification	Person Years	Obs Cases	Low				Mid				High			
			Bkgd rate <sup>15</sup>	Exp Cases	O/E Ratio	95% CI	Bkgd rate <sup>25</sup>	Exp Cases	O/E Ratio	95% CI	Bkgd rate <sup>8</sup>	Exp Cases	O/E Ratio	95% CI
Males ≤17 years	36,028	5	0.95	0.3	14.608	4.743, 34.091	4.40	1.6	3.154	1.024, 7.361	9.58	3.5	1.449	0.470, 3.381
Males 18-24 years	234,288	30	5.38	12.6	2.380	1.606, 3.398	4.40	10.3	2.910	1.963, 4.154	23.75	55.6	0.539	0.364, 0.770
Females ≤17 years	40,628	1	1.00	0.4	2.461	0.062, 13.714	4.40	1.8	0.559	0.014, 3.117	2.05	0.8	1.201	0.030, 6.690
Females 18-24 years	264,197	7	0.65	1.7	4.076	1.639, 8.399	4.40	11.6	0.602	0.242, 1.241	5.14	13.6	0.515	0.207, 1.062

**US – 21-day risk window**

**Table 16. Observed to Expected (O/E) Analysis of Myocarditis in the United States, 21-day Risk Window, Cumulative**

Stratification	Person Years	Obs Cases	Low				Mid				High			
			Bkgd rate <sup>15</sup>	Exp Cases	O/E Ratio	95% CI	Bkgd rate <sup>25</sup>	Exp Cases	O/E Ratio	95% CI	Bkgd rate <sup>8</sup>	Exp Cases	O/E Ratio	95% CI
Males ≤17 years	234,737	25	0.95	2.2	11.211	7.255, 16.549	4.40	10.3	2.421	1.566, 3.573	9.58	22.5	1.112	0.719, 1.641
Males 18-24 years	384,968	22	5.38	20.7	1.062	0.666, 1.608	4.40	16.9	1.299	0.814, 1.966	23.75	91.4	0.241	0.151, 0.364
Females ≤17 years	264,703	2	1.00	2.6	0.756	0.092, 2.729	4.40	11.6	0.172	0.021, 0.620	2.05	5.4	0.369	0.045, 1.331
Females 18-24 years	434,113	6	0.65	2.8	2.126	0.780, 4.628	4.40	19.1	0.314	0.115, 0.684	5.14	22.3	0.269	0.099, 0.585

As noted by the MAH, the O/E ratio is markedly higher in the ≤ 17 years category than in the 18-24 years category, predominantly in males. The MAH however did not provide a review and analysis of myocarditis in the 7<sup>th</sup> MSSR. As commented in the AR for the 7<sup>th</sup> MSSR, in the next MSSR, the cumulative review of myocarditis should contain causality assessment per case and review of clinical data and data from literature. The MAH has been further requested to investigate the potential mechanism and discuss whether changes to the product information are warranted. In addition, the MAH should perform an O/E analysis, with sensitivity analysis to compensate for backlog cases.

The current warning that (very rare) cases of myocarditis and pericarditis have been observed following vaccination with the product more often in younger men is still considered adequate at this stage. The MAH commits to closely monitor O/E trends in the younger age groups. The ongoing and planned additional pharmacovigilance studies per EU RMP will be further characterize these risks.

Issue considered **resolved**, however will continue to be monitored in the MSSR, PSUR and RMP.

**Question 3**

The MAH should confirm (or otherwise justify) that no restriction/selection was made on BC level diagnostic certainty (i.e. only including at least BC level 3 [possible] myocarditis cases). In principle, including all BC level cases (also BC level 4-5, i.e. cases not meeting BC level 1-3) in the O/E analysis is supported, as a conservative approach. In addition, the MAH should clarify which and how many of the BC level cases have been included (per stratum), especially in the strata that show an O/E ratio near or above 1.

**MAH response to Question 3**

In the 6<sup>th</sup> SMSR, all cases of myocarditis were included as observed cases in the O/E calculation without respect to Brighton Collaboration (BC) criteria assessment.

**Table 1** presents the distribution of myocarditis cases by BC level per age stratum. In the 7<sup>th</sup> SMSR, depending on the background rate assumed, any excess in observed cases is in men and women younger than 50 years of age. In the case review, in the 12 to 15-year-old age group, no case met BC level 1 to 3. In the 16 to 19, 20 to 24, and 25 to 49-year-old age categories, roughly 30% met BC level 1 to 3 (similar in the 50+ age categories).

**Table 1. Myocarditis: Distribution of Brighton Collaboration categories by age group**

	12-15 yrs		16-19 yrs		20-24 yrs		25-49 yrs		50-59 yrs		60-69 yrs		70+ yrs		Unknown age	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
<b>BC1</b>	0	0%	1	2%	2	3%	15	10%	1	3%	4	22%	0	0%	1	6%
<b>BC2</b>	0	0%	6	13%	7	10%	17	12%	4	10%	0	0%	3	12%	0	0%
<b>BC3</b>	0	0%	7	15%	9	13%	12	8%	6	15%	2	11%	6	23%	0	0%
<b>BC4</b>	2	100%	32	68%	48	72%	96	67%	28	72%	11	61%	15	58%	13	81%
<b>BC5</b>	0	0%	1	2%	1	1%	3	2%	0	0%	1	6%	2	8%	2	13%
<b>Total</b>	2	100%	47	100%	67	100%	143	100%	39	100%	18	100%	26	100%	16	100%

**Comment PRAC Rapporteur:**

The MAH confirmed that all cases of myocarditis were included as observed cases in the O/E calculation without respect to BC criteria assessment.

In addition, the MAH presented distribution of myocarditis cases by BC level per age stratum. Regarding the younger age group (12 – 15 years), no case met BC level 1 to 3. Please refer to the PRAC Rap conclusion upon review of the 7<sup>th</sup> SMSR (circulated 5 August 2021) that there was no indication of new safety information concerning Use in adolescents aged 12-15 years, including cases of myocarditis and pericarditis.

Issue considered **resolved**.

**Question 4**

**Risk management plan (RMP) update**

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

- a) Propose how to further characterise the new important risk, including evaluation of the outcomes (e.g. mild/severe/sequelae);
- b) Discuss any risk factors that could be identified, as well as the need and possibility to perform specific studies to investigate risk factors for myocarditis and pericarditis after Comirnaty administration with the aim to implement measures to mitigate the risk. If appropriate, PI updates should be proposed.
- c) Assure long term follow up of myocarditis and pericarditis cases in order to better characterize long term consequences.
- d) Number of young patients included in the studies should assure timely characterisation of the risk in this population of special interest.

#### **MAH response to Question 4**

The MAH will revise the RMP in order to address the PRAC's comments in the pharmacovigilance plan studies. In particular, pending agreement with the Agency, the MAH is planning to submit a Type II variation to update the RMP in the first week of August. The proposed strategy to address the requested RMP changes has been shared beforehand with the PRAC Rapporteur.

#### **Comment PRAC Rapporteur:**

The MAH submitted a type II variation (II/0059) including update of the RMP which is currently under assessment (II/0059).

Issue considered **resolved**.

#### **4.2. Rapporteur's proposed recommendation**

In conclusion, no new data or information have been provided to substantiate changed recommendations for administration of the *second* dose, in case myocarditis and/or pericarditis occurred in vaccinees following the *first* dose.

As the MAH provided their response to the RfSI and the data submitted do not change the conclusions reached by PRAC previously (i.e. updates to the PI and RMP), no further changes to the PI are warranted at this stage. Based on the current assessment, the signal can be closed now that myocarditis and pericarditis are included as important identified risks in the RMP and will be further characterised accordingly and reported about in the MSSRs and PSURs.

#### **4.3. Comments from other PRAC members and MAH(s)**

MS11, MS8, MS5, MS7

We fully endorse the PRAC Rapp Assessment Report and have no further comments.

MS4

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

The Rapporteur conclude that no new data has been provided to substantiate changed recommendations for administration of the second dose, in case myocarditis and/or pericarditis occurred in vaccinees following the first dose. As the MAH only analysed cases of Myocarditis up to 31 May 2021, the Rapporteurs request for the MAH to provide more recent data in future submissions is endorsed.

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

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

#### **Comment PRAC Rapporteur:**

The comments of endorsement are noted.

The proposal from MS5 to update SmPC section 4.4 seems to be based on public health bodies rather than scientific data. Before an advice not to administer a second dose to vaccinees who experienced myocarditis/pericarditis would be included in the product information, careful consideration should be given to the consequences of such an advice. Since only the mRNA COVID-19 vaccines are authorised in children from 12-18 year old and the adenovector COVID-19 vaccines are no longer administered to the non-elderly or not at all in several EU countries, an advice not to administer a second dose would essentially deprive vaccinees from effective protection against COVID-19. This is considered undesirable, especially for people at higher risk of severe COVID-19. Furthermore, it is currently unclear whether persons with a history of myocarditis/pericarditis are at increased risk of myocarditis/pericarditis after vaccination with Comirnaty. Lastly, the proposed wording does not include actionable recommendations to HCPs: it is unclear for which information should be waited before administering a second dose and it is unclear what clinical circumstances should be taken into account. Therefore, we consider that the current wording (see also section 3.7 in this report) is deemed sufficient at this stage. The Rapporteur's proposed recommendation – see section 4.2 in this report – still remains.

#### **4.4. Updated rapporteur's proposed recommendation**

Not applicable. Please refer to section 4.2 in this report.

#### **4.5. Adopted PRAC recommendation**

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

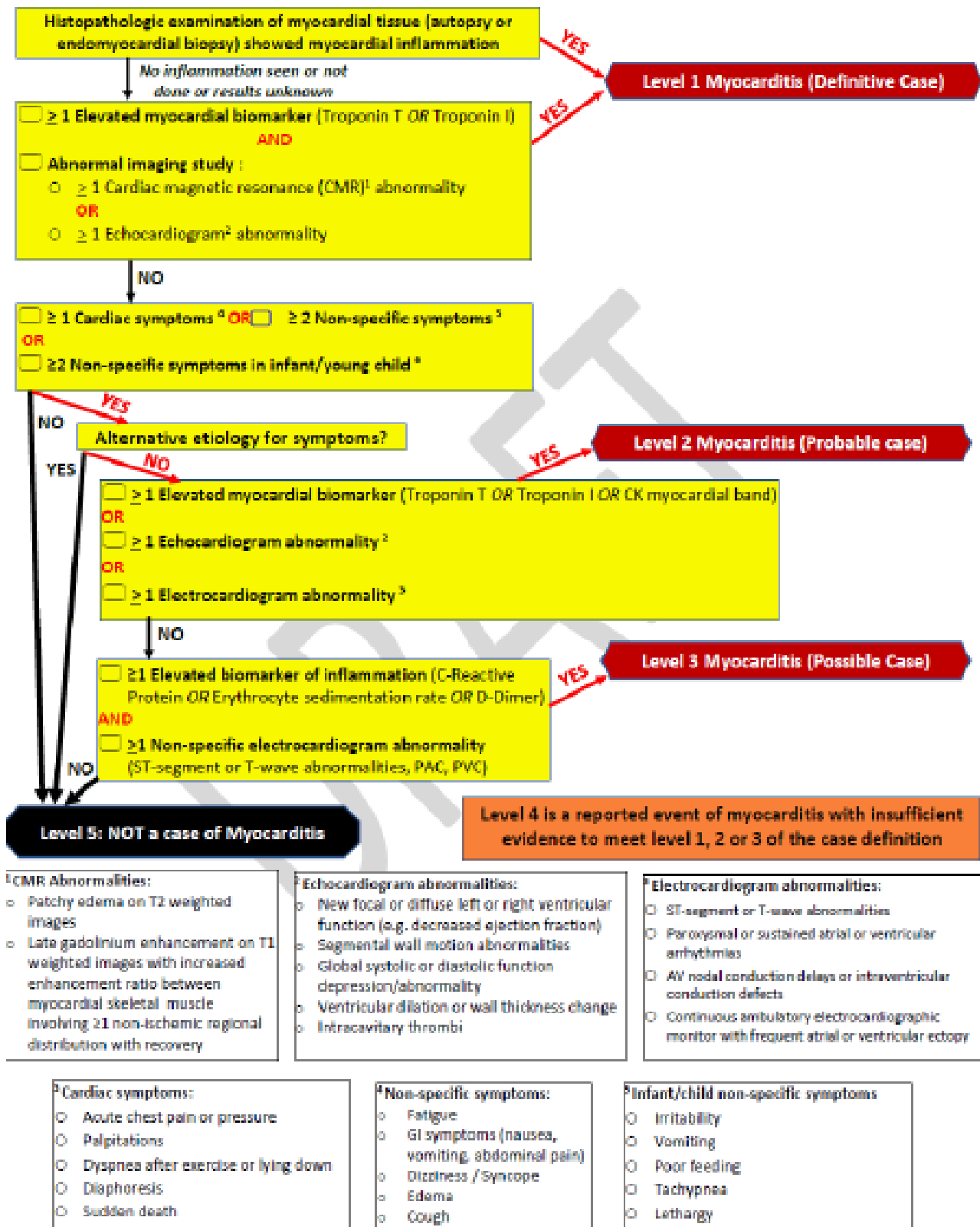
The PRAC has agreed that the signal can therefore be closed, and that the MAH for Comirnaty (BioNTech Manufacturing GmbH) should continuously monitor this topic within the MSSR-submissions. As soon as new relevant information becomes available, the MAH should further characterise this risk and suggest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

## **5. References**

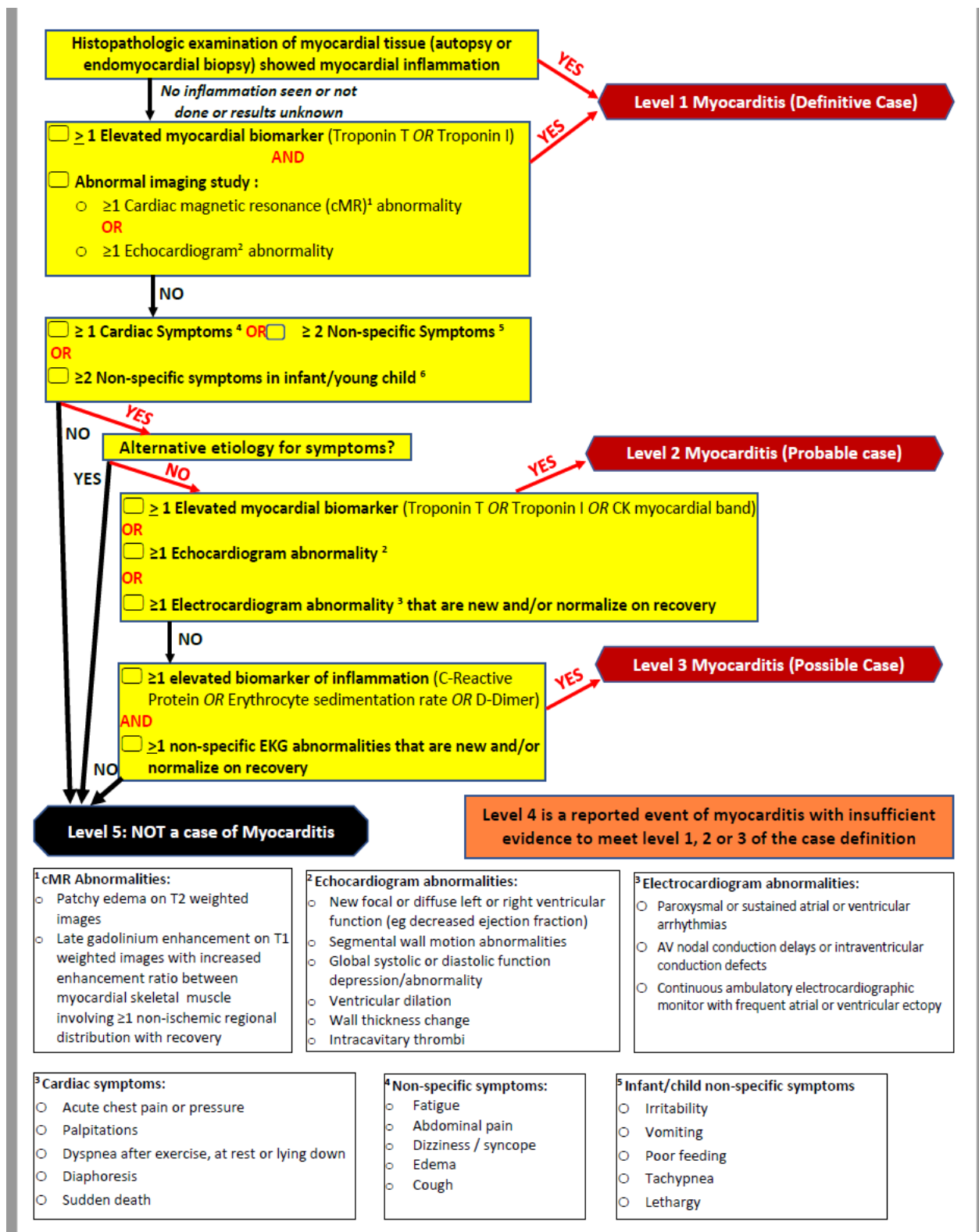
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# Annex 1: Brighton's Collaboration Criteria (v1.4.2\_30-May-2021)



## Annex 2: Brighton's Collaboration Criteria Myocarditis V 1.5.0 16 July 2021





# Annex 3: Brighton's Collaboration Criteria Pericarditis V 1.0.0 15 July 2021

