Risks of Myocarditis and Pericarditis Following Vaccination with SARS-CoV-2 mRNA Vaccines in Japan: An Analysis of Spontaneous Reports of Suspected Adverse Events

Hidetaka Kobayashi1 · Sayoko Fukuda2 · Rina Matsukawa1 · Yumi Asakura1 · Yuri Kanno1 · Tomohiro Hatta1 · Yurina Saito1 · Yuki Shimizu1 · Shuichi Kawasaki1 · Mari Kihara1 · Natsumi Kinoshita1 · Hikari Umeda1 · Tatsuya Noda3 · Tomoaki Imamura3 · Yuichi Nishioka3 · Toshihiro Yamaguchi4 · Shuichiro Hayashi4 · Toyotaka Iguchi1

Received: 16 May 2022 / Accepted: 30 September 2022 / Published online: 30 October 2022
© The Author(s), under exclusive licence to The Drug Information Association, Inc 2022

Abstract

Objective To identify the risks of myocarditis or pericarditis after vaccination with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccines in Japan.

Methods We conducted an observed-to-expected analysis (OE analysis) of spontaneous reports of suspected adverse events from pharmaceutical companies, calculating rate ratios with myocarditis and pericarditis after the vaccination of the mRNA vaccines Comirnaty (BNT162b2) and Spikevax (mRNA-1273) and expected rate of myocarditis and pericarditis in the population before the COVID-19 pandemic. These reports dated from 17/2/2021 to 14/11/2021 and from 22/5/2021 to 14/11/2021 for Comirnaty and Spikevax, respectively. The observed-to-expected ratios (OE ratios) for each vaccine were estimated by age groups and sex.

Results We identified 281 and 195 cases of myocarditis or pericarditis for Comirnaty and Spikevax, respectively, which were administrated 163,059,502 and 31,768,352 doses for Comirnaty and Spikevax until the 14th of November 2021, respectively. The OE ratios were statistically significantly higher in adolescent and young adult males in their age of teens and twenties after the second dose in a two-dose series [Comirnaty in teens male: 6.15 (95% CI, 2.26–21.98), Comirnaty in twenties male: 2.86 (95% CI, 1.13–8.38), Spikevax in teens male: 41.59 (95% CI, 5.64–43,281.94), Spikevax in twenties male: 16.84 (95%CI, 6.77–57.49)].

Conclusions Risks of myocarditis and pericarditis following SARS-CoV-2 mRNA vaccines in Japan seems to be significantly elevated for adolescent and young adult males.

Keywords COVID-19 · Myocarditis · Pericarditis · mRNA Vaccines · Observed-to-expected analysis

Introduction

In Japan, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccines Comirnaty and Spikevax (previously known as COVID-19 Vaccine Moderna) were approved for marketing on 14/2/2021 and 21/5/2021, respectively, while vaccination started on 17/2/2021 and 22/5/2021, respectively. Vaccine safety surveillance in Japan is performed by the Ministry of Health, Labour and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (PMDA) under the Immunization act[1] and the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices[2]. Medical institutions report suspected adverse events following immunization (AEFIs) adverse in accordance with the...
Myocarditis and pericarditis are very rare diseases. Myocarditis and Pericarditis are inflammatory heart diseases.

When inflammation induced by some cause affects myocardium, the condition is diagnosed as myocarditis, whereas when inflammation affects epicardium, the condition is diagnosed as pericarditis. The clinical diagnosis of myocarditis is made on imaging findings which suggest inflammation of myocardium. Imaging modality for diagnosis includes echocardiogram, cardiac MRI, and myocardial scintigram. Definitive diagnosis of myocarditis is confirmed by pathological findings of inflammation in myocardium. Endomyocardial biopsy or autopsy is needed to perform pathological diagnosis [2]. The clinical diagnosis of myocarditis is made on imaging findings which suggest inflammation of epicardium. Imaging modality for diagnosis includes electrocardiogram, echo-cardiogram and cardiac MRI. Definitive diagnosis of pericarditis is confirmed by pathological findings of inflammation in myocardium. Pericardial biopsy or autopsy is needed to perform pathological diagnosis [2]. Before the COVID-19 pandemic, they were recognized as illnesses generally occurring after viral and bacterial infections as well as exposure to radiation and drugs, while it was not known whether such diseases could be caused by vaccines. Their diagnosis is complicated by the fact that clinical symptoms and most laboratory findings are non-specific and a differential diagnosis would be needed to distinguish them from other conditions. The prognosis is mostly good, however, some very severe cases with rapid progression may occur [6].

Although the biological mechanisms involved in the development of myocarditis or pericarditis following vaccination against SARS-CoV-2 have not been yet elucidated [7], warnings and regulations about myocarditis and pericarditis have already been issued for mRNA vaccines in several countries [8–11]. For example, Pharmacovigilance Risk Assessment Committee (PRAC), which is responsible for the evaluation of drug safety in the European Medicines Agency (EMA), conducted a detailed review of myocarditis in the European Economic Area (EEA) in 145 cases after vaccination of Comirnaty and 19 cases after Spikevax, as well as 138 cases of pericarditis after the use of Comirnaty and a review of reports of 19 cases that developed after the use of Spikevax in the EEA. As of May 31, 2021, approximately 177 million doses of Comirnaty and 20 million doses of Spikevax had been administered in the EEA. As a result, they concluded that on July 9, 2021, myocarditis and pericarditis could occur in very rare cases after vaccination with Comirnaty and Spikevax. They listed myocarditis and pericarditis as a new adverse reaction in the product information for these vaccines, and recommended that a warning be provided to raise awareness among health care professionals [8]. Nevertheless, so far no population-based study to assess this relation in Japan due to the lack of precise data about the incidence of myocarditis and pericarditis in non-vaccinated individuals and the inability of the system to
connect spontaneous reports of adverse events with health care data of vaccinated persons. In addition, it is also unclear whether there are ethnic differences in myocarditis and pericarditis after SARS-CoV-2 mRNA vaccination.

Therefore, this study aims to fill this knowledge gap and identify the relation between the occurrence of myocarditis or pericarditis and SARS-CoV-2 vaccination in Japan.

Methods

Data Source of Observed Cases

To identify the number of cases of myocarditis and pericarditis after vaccination, we used the documents published by the Joint Committee on Adverse Events of Vaccines and Drug Safety of Pharmaceutical Affairs and Food Safety of the Ministry of Health, Labour, and Welfare in Japan [12]. These documents cover all adverse events reported in Japan. The number of cases used in this study is based on spontaneous reports received from pharmaceutical companies between the 17th of February 2021 and 14th of November 2021. The number of vaccinations (Table 1) was also obtained from the published documents of the Joint Committee.

Definition of Background Rate: Incidence in the General Population

The incidence of myocarditis and pericarditis in the general population before the COVID-19 pandemic could be found in the documents published by the Joint committee [12], and was calculated using the National Database of Health Insurance Claims and Specific Health Check-ups of Japan (NDB) and the data of population estimates in the Portal Site of Official Statistics of Japan run by the Ministry of Internal Affairs and Communication [13]. To define the number of myocarditis and pericarditis cases as numerator of the background rate, NDB was used, while to calculate the denominator, the data of the estimated population in the Portal Site was used because of limited data availability. NDB is a national database run by the government, which contains national health insurance claims data and specific health check data. Almost all 127 million Japanese citizens belong to this health insurance system, thus this database covers almost all Japanese population. To calculate the incidence, personal identifier (ID0 variable), date, age group, sex, diagnosis codes according to the International Classification of Diseases (ICD-10) were extracted from NDB.

In order to identify a more accurate the number of case, suspected diagnosis codes were excluded. The incidence of myocarditis and pericarditis was classified in two groups, i.e., narrow and broad. The "narrow" group was defined by the diagnosis of acute myocarditis or acute pericarditis, while the "broad" group dealt with the diagnosis of myocarditis or pericarditis with the exception of those induced by radiation and neoplasm as well as chronic conditions.

Definition of the Outcome: Observed Cases

The outcome of myocarditis and pericarditis among vaccinated individuals was defined according to the MedDRA code Ver24.1 system as follows: Myocarditis (10028606/Myocarditis, 10014961/Eosinophilic myocarditis, 10083635/Giant cell myocarditis, 10064539/Autoimmune myocarditis, and 10082606/Immune-mediated myocarditis) and Pericarditis (10034484/Pericarditis, 10079058/Autoimmune pericarditis, and 10059361/Pleuropericarditis). When at least one of these codes occurred in a spontaneous report, it was counted as a case of myocarditis or pericarditis. The incidence of myocarditis is combined with that of pericarditis because the two diseases are very similar inflammatory conditions that can coexist. In fact, some case reports contained these two events at the same time and making it difficult to conclude whether the inflammation was limited only to the myocardium or pericardium. When myocarditis and pericarditis appear in a same spontaneous report, we counted as one case.

Statistical Method: OE Analysis

To assess the relation between SARS-CoV-2 vaccination and myocarditis or pericarditis, we used an observed-to-expected analysis (OE analysis). In this analysis, we calculated rate ratios with the observed rates of myocarditis and pericarditis after the vaccination of SARS-CoV-2 vaccines and the expected rate, which is the incidence of myocarditis and pericarditis in the general population before the COVID-19 pandemic calculated with Japanese Health insurance claims data NDB. According to the guidelines on good pharmacovigilance of the European Medicines Agency, this type of analysis is useful for population-based vaccination programs that require immediate decisions on safety concerns. Furthermore, it is also useful for the evaluation of signals in case of lack of reliable epidemiological data [14]. The formula for calculating the OE ratio and Poisson confidential interval (riskα = 5%), which was used in this study, is shown below:

\[
OE_{\text{ratio}} = \frac{\text{Observed cases}(a)}{\text{Personyearpar}100,000(c_1)} / \frac{\text{Expected cases}(b)}{\text{Personyearpar}100,000(c_2)}
\]
The ratios were estimated by age group every 10 years from 10–19 to 80+ years and based on sex. A 14-day risk window was selected for the estimation. The general population incidence of the narrow definition was used, and subjects whose date of onset of adverse events was not

\begin{equation}
OE_{\text{ratio} \ CI} = \left( \frac{c_2}{c_1} \right) \left( \frac{a}{b+1} \right) \frac{1}{F_{a/2,2b+1,2a}} \left( \frac{c_2}{c_1} \right) \left( \frac{a+1}{b} \right) F_{a/2(a+1),2b}
\end{equation}

\( c_1 = c_2 = \text{number of vaccine} \times \text{Risk window} \)

\( \frac{\text{day}}{365.2425/100,000} \)

\( b = \text{background rate (Person year per 100,000)} \times c_2 \)

Table 1 Number of vaccinations using COVID-19 mRNA vaccines in Japan (From 17th of February 2021 to 14th of November 2021)

| Comirnaty | 12–19 | 20–29 | 30–39 | 40–49 | 50–59 | 60–69 |
|-----------|-------|-------|-------|-------|-------|-------|
| 1st dose  |       |       |       |       |       |       |
| Male      | 2,872,854 | 2,852,280 | 3,703,367 | 5,419,628 | 5,702,254 | 6,129,070 |
| Female    | 2,790,385 | 3,391,311 | 4,402,039 | 6,393,544 | 6,581,720 | 6,745,140 |
| Unknown   | 1927  | 4831  | 6471  | 9397  | 10,070 | 10,428 |
| Total     | 5,665,166 | 6,248,422 | 8,111,877 | 11,822,569 | 12,294,044 | 12,884,638 |
| 2nd dose  |       |       |       |       |       |       |
| Male      | 2,555,822 | 2,561,369 | 3,408,923 | 5,151,780 | 5,534,662 | 6,067,439 |
| Female    | 2,473,955 | 3,082,276 | 4,088,289 | 6,089,327 | 6,363,346 | 6,655,197 |
| Unknown   | 2514  | 4542  | 6168  | 9453  | 10,174 | 10,464 |
| Total     | 5,032,291 | 5,648,187 | 7,503,380 | 11,250,560 | 11,908,182 | 12,733,100 |

| Spikevax  | 1st dose |       |       |       |       |       |
|-----------|----------|-------|-------|-------|-------|-------|
| Male      | 501,258  | 1,989,181 | 1,926,608 | 2,189,300 | 2,189,300 | 1,819,728 |
| Female    | 477,527  | 1,588,792 | 1,290,674 | 1,453,561 | 1,453,561 | 1,171,070 |
| Unknown   | 3330     | 4061   | 1674  | 2242  | 1939   | 524   |
| Total     | 982,115  | 3,582,034 | 3,218,956 | 3,645,103 | 3,645,103 | 2,992,737 |
| 2nd dose  |       |       |       |       |       |       |
| Male      | 458,685  | 1,925,424 | 1,861,732 | 2,113,447 | 1,761,575 | 675,965 |
| Female    | 445,505  | 1,539,243 | 1,243,384 | 1,398,770 | 1,131,493 | 455,309 |
| Unknown   | 2482     | 4000   | 1588  | 2096  | 1857   | 511   |
| Total     | 906,672  | 3,468,667 | 3,106,704 | 3,514,313 | 3,514,313 | 2,894,925 |

| Comirnaty | 70–79 | 80–89 | 90–99 | 100- | Unknown | Total |
|-----------|-------|-------|-------|------|--------|-------|
| 1st dose  |       |       |       |      |        |       |
| Male      | 6,792,838 | 3,395,698 | 564,385 | 8597 | 58     | 37,441,029 |
| Female    | 8,019,904 | 5,203,963 | 1,607,207 | 63,818 | 95     | 45,199,126 |
| Unknown   | 9301   | 5903  | 2131  | 91   | 393,981 | 454,531 |
| Total     | 14,822,043 | 8,605,564 | 2,173,723 | 72,506 | 394,134 | 83,094,686 |
| 2nd dose  |       |       |       |      |        |       |
| Male      | 6,772,200 | 3,382,574 | 559,964 | 8433 | 54     | 36,003,220 |
| Female    | 7,988,112 | 5,180,448 | 1,593,399 | 62,779 | 102    | 43,577,230 |
| Unknown   | 9349   | 5930  | 2,163 | 91   | 323,518 | 384,366 |
| Total     | 14,769,661 | 8,568,952 | 2,155,526 | 71,303 | 323,674 | 79,964,816 |

| Spikevax  | 1st dose |       |       |      |        |       |
|-----------|----------|-------|-------|------|--------|-------|
| Male      | 245,727  | 38,780 | 3054  | 17   | 24     | 9,405,607 |
| Female    | 199,408  | 43,401 | 5758  | 94   | 33     | 6,697,251 |
| Unknown   | 16      | 3     | 2     | 0    | 56,471 | 70,262 |
| Total     | 445,151  | 82,184 | 8814  | 111  | 56,528 | 16,173,120 |
| 2nd dose  |       |       |       |      |        |       |
| Male      | 242,382  | 38,113 | 2971  | 19   | 17     | 9,080,330 |
| Female    | 196,324  | 42,491 | 5586  | 85   | 17     | 6,458,207 |
| Unknown   | 16      | 2     | 2     | 0    | 44,134 | 56,688 |
| Total     | 438,722  | 80,606 | 8559  | 104  | 44,168 | 15,595,225 |

\( c_1 = c_2 = \text{number of vaccine} \times \text{Risk window} \)

\( \frac{\text{day}}{365.2425/100,000} \)

\( b = \text{background rate (Person year per 100,000)} \times c_2 \)
reported were excluded. Different analyses were performed based on the number of doses, which were distinguished in three groups: 1st dose, 2nd dose, and 1st + 2nd doses.

This statistical analysis was conducted with Microsoft Office Excel 2016 and performed between November 15 and December 2, 2021.

Sensitivity Analysis

The estimated ratios are uncertain due to the number observed, diagnostic certainty of adverse events, exposure levels, and incidence in the general population [14]. We therefore performed sensitivity analyses calculating OE ratios in different condition from OE analysis at the levels of the risk window, definition of incidence in the general population, and number of observations.

This sensitivity analysis follows the same methodology as the main analysis described in the previous section, except for the following changes in the analysis conditions. We applied the risk window at 7, 14, and 21 days for Comirnaty, and 7, 14, and 28 days for Spikevax considering the interval between two injections and the time of onset of myocarditis or pericarditis after vaccination that we observed from the spontaneous reports. We also performed analyses with the broad definition of incidence in the general population. In addition, we performed analyses including subjects who did not have the day of occurrence of the adverse event. Finally, we performed 72 sets of analyses (Table 2) including the main analysis.

Microsoft Office Excel 2016 was used for the analyses, which was performed between November 15 and December 2, 2021.

All analyses in this study were performed as a public health obligation and not as a research activity.

Results

Descriptive Data

The number of vaccinations in Japan with both vaccines from 17th of February 2021 until the 14th of November 2021 corresponded to 163,059,502 (1st dose: 83,094,686, 2nd dose: 79,964,816) and 31,768,352 doses (1st dose: 16,173,120, 2nd dose: 15,595,225) for Comirnaty and Spikevax, respectively (Table 1). Comirnaty comprised 83.7% of mRNA vaccines vaccinated in Japan during this period. Those vaccinated with Comirnaty were older and more likely to be female than those vaccinated with Spikevax. We identified 281 cases of myocarditis or pericarditis for Comirnaty and 195 cases for Spikevax among the spontaneous reports dating between the 17th of February 2021 and 14th of November 2021 (Table 3).

As for the proportion of sex among the cases, it was higher for males than females for both vaccines (Comirnaty: 61.9%, Spikevax: 88.2%). For male age groups, adolescents and young adults, especially in the 12–19 and 20–29 age groups, exhibited more cases than other generations for both vaccines. As for the date of the onset of cases, the majority of cases occurred up to day 7 for both vaccines.

OE Analysis

Table 4 and Figs. 1 and 2 illustrate the main results of the OE analyses. For the two vaccines, the lower 95% confidential interval (CI) of the OE ratios were higher than 1 in males in 10–19 years (OE ratio: Comirnaty 6.15 [2.26–21.98], Spikevax 41.59 [5.64–43,281.94]) and 20–29 years (OE ratio: Comirnaty 2.86 [1.13–8.38], Spikevax 16.84 [6.77–57.49]) at the 2nd dose analysis. At the 1st + 2nd doses analysis, it was higher than 1 in males in 10–19 years (OE ratio: 20.53 [4.70–295.10]) and 20–29 years (OE ratio: 8.81 [4.59–19.00]) for Spikevax, but only in 10–19 years (OE ratio: 3.62 [1.73–8.36]) for Comirnaty. Compared to males, there is nothing in the lower 95% confidential intervals of the OE ratios which is greater than 1 in females for all 3 analyses and in males for the 1st dose analysis. As age decreased, the estimated OE ratios generally increased for both vaccines in both sexes.

Sensitivity Analyses

Table 5 shows the summary of results for sensitivity analyses comparing principal analyses. The details of the results of the sensitivity analyses are showed in Appendix 1–11. The ranges of OE ratios in each condition of sensitivity analyses were generally similar to those of the main analyses; the lower values of the CI of the OE ratios were higher than 1 in young males for both vaccines, especially at the 2nd dose for all testing conditions. While a trend toward higher OE ratios with shorter risk window was observed in comparing between the principal analysis and the sensitivity analysis, and in some of the analysis conditions with a 7-day risk window, there were cases in which the lower CI of the OE ratio exceeded 1 in males in 30–39 years for both vaccines, the patterns in differences between the two vaccines and relationships between age or sex and OE ratios did not significantly differ between the main and sensitivity analyses.

Discussion

The conducted OE analysis showed a statistical relation between vaccination and occurrence of myocarditis and pericarditis, especially in adolescent and young adult males with the second dose of either Comirnaty or Spikevax.
Practical Implication

In other countries, the following measures against myocarditis and pericarditis have been taken. In the U.S. package inserts for both Comirnaty and Spikevax, myocarditis is listed in section "6.2 Post-Authorization Experience" as an adverse reaction that was identified after marketing [15, 16]. Furthermore, the package inserts in the U.K. and Europe, as of May 2022, list myocarditis as an very rare adverse reaction (< 1/10,000) in "4.8 Undesirable effects" for both Comirnaty and Spikevax. Furthermore, in the package inserts for both Comirnaty and Spikevax [17–20] in the U.S., the U.K., and the EU, the section "5 WARNINGS AND PRECAUTIONS" or "4.4 Special warnings and precautions for use" lists that cases of post-vaccination myocarditis are more under 40 years at the second dose of Spikevax compared to other approved mRNA vaccines for Covid-19[16]. Furthermore, the package inserts in the U.K. and Europe, as of May 2022, list myocarditis as an very rare adverse reaction (< 1/10,000) in "4.8 Undesirable effects" for both Comirnaty and Spikevax. Furthermore, in the package inserts for both Comirnaty and Spikevax [17–20] in the U.S., the U.K., and the EU, the section "5 WARNINGS AND PRECAUTIONS" or "4.4 Special warnings and precautions for use" lists that cases of post-vaccination myocarditis are more

Table 2 Condition of 72 sets of OE analyse

| Definition of myocarditis/ Pericarditis | Risk window (day)* | Cases with unknown onset data | Dose number | Table |
|----------------------------------------|--------------------|------------------------------|-------------|-------|
| Principal analyse                       |                    |                              |             |       |
| Narrow                                 | 14                 | Not include                  | 1st + 2nd dose | Table 4 |
| Narrow                                 | 14                 | Not include                  | 1st dose    |        |
| Narrow                                 | 14                 | Not include                  | 2nd dose    |        |
| Sensitivity analyse                    |                    |                              |             |       |
| Narrow                                 | 14                 | Include                      | 1st + 2nd dose | Appendix 1 |
| Narrow                                 | 14                 | Include                      | 1st dose    |        |
| Narrow                                 | 14                 | Include                      | 2nd dose    |        |
| Broad                                  | 14                 | Not include                  | 1st + 2nd dose | Appendix 2 |
| Broad                                  | 14                 | Not include                  | 1st dose    |        |
| Broad                                  | 14                 | Not include                  | 2nd dose    |        |
| Broad                                  | 14                 | Include                      | 1st + 2nd dose | Appendix 3 |
| Broad                                  | 14                 | Include                      | 1st dose    |        |
| Broad                                  | 14                 | Include                      | 2nd dose    |        |
| Narrow                                 | 21 or 28           | Not include                  | 1st + 2nd dose | Appendix 4 |
| Narrow                                 | 21 or 28           | Not include                  | 1st dose    |        |
| Narrow                                 | 21 or 28           | Not include                  | 2nd dose    |        |
| Narrow                                 | 21 or 28           | Include                      | 1st + 2nd dose | Appendix 5 |
| Narrow                                 | 21 or 28           | Include                      | 1st dose    |        |
| Narrow                                 | 21 or 28           | Include                      | 2nd dose    |        |
| Broad                                  | 21 or 28           | Not include                  | 1st + 2nd dose | Appendix 6 |
| Broad                                  | 21 or 28           | Not include                  | 1st dose    |        |
| Broad                                  | 21 or 28           | Not include                  | 2nd dose    |        |
| Broad                                  | 21 or 28           | Include                      | 1st + 2nd dose | Appendix 7 |
| Broad                                  | 21 or 28           | Include                      | 1st dose    |        |
| Broad                                  | 21 or 28           | Include                      | 2nd dose    |        |
| Narrow                                 | 7                  | Not include                  | 1st + 2nd dose | Appendix 8 |
| Narrow                                 | 7                  | Not include                  | 1st dose    |        |
| Narrow                                 | 7                  | Not include                  | 2nd dose    |        |
| Narrow                                 | 7                  | Include                      | 1st + 2nd dose | Appendix 9 |
| Narrow                                 | 7                  | Include                      | 1st dose    |        |
| Narrow                                 | 7                  | Include                      | 2nd dose    |        |
| Broad                                  | 7                  | Not include                  | 1st + 2nd dose | Appendix 10 |
| Broad                                  | 7                  | Not include                  | 1st dose    |        |
| Broad                                  | 7                  | Not include                  | 2nd dose    |        |
| Broad                                  | 7                  | Include                      | 1st + 2nd dose | Appendix 11 |
| Broad                                  | 7                  | Include                      | 1st dose    |        |
| Broad                                  | 7                  | Include                      | 2nd dose    |        |

*Risk window: 21 days for Comirnaty, 28 days for Spikevax
frequently reported in young males and after the second dose of vaccination. In addition to the OE analysis results, we compared the results of studies and measures taken in other countries [4–7, 15–20], whose results showed a similar tendency in the age and sex of individuals with a the risk of myocarditis or pericarditis after the vaccination, and we determined that myocarditis and pericarditis are risks that require attention after mRNA vaccination in Japan because of the report of severe cases of these diseases leading to cardiogenic shock, cardiac tamponade, or sudden death. On the basis of this evaluation, as of December the 3rd 2021, the package inserts of both Comirnaty and Spikevax were further updated to list myocarditis and pericarditis as “SERIOUS ADVERSE REACTIONS”, and also the Ministry of Health, Labour and Welfare (MHLW) imposed an obligation for the medical institutions to report adverse reactions as myocarditis and pericarditis. Furthermore, in the IMPORTANT PRECAUTIONS section, the sentence “Although the causal relationship with this vaccine is unknown, cases of myocarditis and pericarditis have been reported following inoculation with this vaccine” was replaced by “Myocarditis, pericarditis may occur” To the Clinically Significant Adverse Reactions section, myocarditis and pericarditis were also added. In the OTHER PRECAUTIONS section, the sentence “Although the causal relationship is unknown” was removed, and the information that myocarditis and pericarditis occur especially following the second inoculation of the vaccine was added.

We performed an OE analysis to identify the relation between mRNA vaccines against COVID-19 and myocarditis or pericarditis because of the following reasons: (1) Post-vaccination myocarditis and pericarditis have been attracting attention in Japan and abroad, and the accumulation of cases including several serious cases have been observed in Japan; (2) The Reporting OR was also calculated to be high, although we have the limitation of using individual
Table 4  Results of the observed-to-expected analysis—Principal analyses (Risk window: 14 days; Definition of background incidence: narrow; Subjects: excluded those whose date of onset of adverse events is unknown)

| Age Group | Comirnaty 1st + 2nd dose | Male | | Spikevax 1st + 2nd dose | Female | | Comirnaty 1st dose | Male | | Spikevax 1st dose | Female | | Comirnaty 2nd dose | Male | | Spikevax 2nd dose | Female |
|-----------|-------------------------|------|------|-------------------------|--------|------|-------------------------|--------|------|-------------------------|--------|------|-------------------------|--------|
| 10–19 years | Observed case | O/E ratio | 95% CI | Observed case | O/E ratio | 95% CI | Observed case | O/E ratio | 95% CI | Observed case | O/E ratio | 95% CI | Observed case | O/E ratio | 95% CI |
| 35 | 3.62 | [1.73–8.36] | | 35 | 20.53 | [4.70–295.10] | | 8 | 1.72 | [0.48–7.18] | | 3 | 3.69 | [0.25–4710.74] |
| 20–29 years | 26 | 1.85 | [0.93–3.84] | | 90 | 8.81 | [4.59–19.00] | | 2 | 0.32 | [0.03–1.80] | | 3 | 0.99 | [0.13–7.40] |
| 30–39 years | 11 | 0.75 | [0.31–1.76] | | 12 | 1.53 | [0.57–4.45] | | 4 | 0.51 | [0.11–1.97] | | 4 | 1.72 | [0.26–19.06] |
| 40–49 years | 12 | 0.56 | [0.25–1.20] | | 8 | 0.92 | [0.31–2.75] | | 8 | 0.64 | [0.23–1.67] | | 3 | 1.05 | [0.14–9.43] |
| 50–59 years | 10 | 0.4 | [0.17–0.87] | | 2 | 0.25 | [0.03–1.30] | | 9 | 0.68 | [0.26–1.71] | | 2 | 0.85 | [0.06–11.69] |
| 60–69 years | 9 | 0.27 | [0.11–0.58] | | 2 | 0.54 | [0.05–4.14] | | 9 | 0.53 | [0.21–1.27] | | 1 | 0.86 | [0.01–67.48] |
| 70–79 years | 13 | 0.23 | [0.12–0.43] | | 0 | – | – | | 8 | 0.26 | [0.10–0.58] | | 0 | – | – |
| 80+ years | 7 | 0.17 | [0.07–0.39] | | 0 | – | – | | 9 | 0.26 | [0.11–0.56] | | 0 | – | – |

| Age Group | Observed case | O/E ratio | 95% CI | Observed case | O/E ratio | 95% CI | Observed case | O/E ratio | 95% CI | Observed case | O/E ratio | 95% CI | Observed case | O/E ratio | 95% CI |
|-----------|-----------------|-----------|--------|-----------------|-----------|--------|-----------------|-----------|--------|-----------------|-----------|--------|-----------------|-----------|--------|
| 10–19 years | Observed case | O/E ratio | 95% CI | Observed case | O/E ratio | 95% CI | Observed case | O/E ratio | 95% CI | Observed case | O/E ratio | 95% CI | Observed case | O/E ratio | 95% CI |
| 7 | 1.37 | [0.37–5.46] | | 1 | 1.12 | [0.01–2013.77] | | 5 | 2.03 | [0.35–21.34] | | 0 | – | – |
| 20–29 years | 7 | 0.95 | [0.29–3.16] | | 6 | 1.16 | [0.30–4.82] | | 2 | 0.61 | [0.05–5.35] | | 1 | 0.65 | [0.01–19.76] |
| 30–39 years | 3 | 0.39 | [0.07–1.68] | | 2 | 0.5 | [0.05–3.87] | | 4 | 0.99 | [0.19–5.33] | | 3 | 2.54 | [0.22–133.20] |
| 40–49 years | 5 | 0.46 | [0.12–1.45] | | 1 | 0.23 | [0.00–2.28] | | 4 | 0.62 | [0.13–2.62] | | 2 | 1.36 | [0.08–80.52] |
| 50–59 years | 4 | 0.32 | [0.08–1.04] | | 1 | 0.25 | [0.01–2.52] | | 4 | 0.59 | [0.13–2.40] | | 0 | – | – |
| 60–69 years | 5 | 0.3 | [0.09–0.85] | | 0 | – | – | | 6 | 0.7 | [0.20–2.26] | | 1 | 1.69 | [0.02–3046.18] |
| 70–79 years | 9 | 0.32 | [0.13–0.71] | | 0 | – | – | | 5 | 0.32 | [0.09–0.94] | | 0 | – | – |
| 80+ years | 5 | 0.25 | [0.07–0.68] | | 0 | – | – | | 6 | 0.35 | [0.11–0.93] | | 0 | – | – |

| Age Group | Observed case | O/E ratio | 95% CI | Observed case | O/E ratio | 95% CI | Observed case | O/E ratio | 95% CI | Observed case | O/E ratio | 95% CI | Observed case | O/E ratio | 95% CI |
|-----------|-----------------|-----------|--------|-----------------|-----------|--------|-----------------|-----------|--------|-----------------|-----------|--------|-----------------|-----------|--------|
| 10–19 years | 28 | 6.15 | [2.26–21.98] | | 34 | 41.59 | [5.64–43,281.94] | | 3 | 1.38 | [0.16–16.47] | | 3 | 7.64 | [0.08–79.68] |
| 20–29 years | 19 | 2.86 | [1.13–8.38] | | 84 | 16.84 | [6.77–57.49] | | 0 | – | – | | 2 | 1.35 | [0.01–68.91] |
| 30–39 years | 8 | 1.14 | [0.36–3.69] | | 10 | 2.6 | [0.73–12.72] | | 0 | – | – | | 1 | 0.88 | [0.01–55.67] |
| 40–49 years | 7 | 0.67 | [0.22–1.96] | | 7 | 1.64 | [0.42–7.64] | | 4 | 0.65 | [0.14–2.75] | | 1 | 0.71 | [0.01–101.51] |
| 50–59 years | 6 | 0.49 | [0.15–1.42] | | 1 | 0.26 | [0.01–2.84] | | 5 | 0.76 | [0.19–2.89] | | 2 | 1.72 | [0.10–101.51] |
| 60–69 years | 4 | 0.24 | [0.06–0.75] | | 2 | 1.09 | [0.08–24.10] | | 3 | 0.36 | [0.06–1.48] | | 0 | – | – |
| 70–79 years | 4 | 0.14 | [0.04–0.41] | | 0 | – | – | | 3 | 0.2 | [0.04–0.69] | | 0 | – | – |
| 80+ years | 2 | 0.1 | [0.01–0.41] | | 0 | – | – | | 3 | 0.18 | [0.03–0.61] | | 0 | – | – |

Bold values mean that the lower 95% confidential interval (CI) of the OE ratios were higher than 1
※1…does not include the cases for which sex is unknown
※2…not possible to calculate because the number of expected cases is very small
Figure 1  OE ratios of myocarditis and pericarditis of receipt of 1st dose of Comirnaty and Spikevax by age group and gender.

Figure 2  OE ratios of myocarditis and pericarditis of receipt of 2nd dose of Comirnaty and Spikevax by age group and gender.
data among vaccinated people. Under the Immunisation Act, we have the Adverse Drug Reaction reporting system (clause 12). All reports of death and serious cases and some adverse events of special interest (anaphylaxis and others), which are sent to PMDA, were investigated and causality between vaccination and each event was discussed based on opinions from clinical experts. As a result of the causality assessment by experts, almost all cases were concluded to be unassessable or unclassified. In general, the reasons for the difficulty in assessing the causality of vaccination and AEFI are as follows: (1) Vaccines are often administered to healthy individuals, and background information on underlying diseases is lacking, (2) There are few events that can be explained based on the pharmacological effects of the vaccine itself, and in many cases it is difficult to evaluate the causality of events that occur after vaccination based on pharmacological mechanisms, (3) It is not possible to distinguish drug adverse events from accidental events or complications and events induced by concomitant medications. In addition to the above, the following factors are specific to cases of myocarditis and pericarditis: these diseases are very rare and have not been known to be caused by any vaccines.

### Table 5 Summary of results for sensitivity analyses comparing principal analyse

| Definition of myocarditis/Pericarditis | Risk window (day) | Cases with unknown onset data | Dose number | Age group and gender whose lower CI of OE ratio is greater than 1 | Details of result in |
|--------------------------------------|-------------------|-------------------------------|-------------|---------------------------------------------------------------|---------------------|
| Principal analysis                    | Narrow            | Not include                   | 1st + 2nd dose | Male:10–19  Male:10–19,20–29 | Table 4             |
|                                      | Narrow            | Not include                   | 1st dose     | None  None                                                     |
|                                      | Narrow            | Not include                   | 2nd dose     | Male:10–19,20–29  Male:10–19,20–29 |
| Sensitivity analysis                  | Narrow            | Include                       | 1st + 2nd dose | Male:10–19  Male:10–19,20–29 | Appendix 1         |
|                                      | Narrow            | Include                       | 1st dose     | None  None                                                     |
|                                      | Narrow            | Include                       | 2nd dose     | Male:10–19,20–29  Male:10–19,20–29 |
|                                      | Broad             | Not include                   | 1st + 2nd dose | Male:10–19  Male:10–19,20–29 | Appendix 2         |
|                                      | Broad             | Not include                   | 1st dose     | None  None                                                     |
|                                      | Broad             | Not include                   | 2nd dose     | Male:10–19,20–29  Male:10–19,20–29 |
|                                      | Broad             | Include                       | 1st + 2nd dose | Male:10–19  Male:10–19,20–29 | Appendix 3         |
|                                      | Broad             | Include                       | 1st dose     | None  None                                                     |
|                                      | Broad             | Include                       | 2nd dose     | Male:10–19,20–29  Male:10–19,20–29 |
|                                      | Narrow            | 21 or 28                      | Not include  | 1st + 2nd dose | Male:10–19  Male:10–19,20–29 | Appendix 4         |
|                                      | Narrow            | 21 or 28                      | Not include  | 1st dose     | None  None                                                     |
|                                      | Narrow            | 21 or 28                      | Not include  | 2nd dose     | Male:10–19  Male:10–19,20–29 | Appendix 5         |
|                                      | Narrow            | 21 or 28                      | Include       | 1st + 2nd dose | Male:10–19  Male:10–19,20–29 | Appendix 5         |
|                                      | Narrow            | 21 or 28                      | Include       | 1st dose     | None  None                                                     |
|                                      | Narrow            | 21 or 28                      | Include       | 2nd dose     | Male:10–19,20–29  Male:10–19,20–29 |
|                                      | Broad             | 21 or 28                      | Not include  | 1st + 2nd dose | Male:10–19  Male:10–19,20–29 | Appendix 6         |
|                                      | Broad             | 21 or 28                      | Not include  | 1st dose     | None  None                                                     |
|                                      | Broad             | 21 or 28                      | Not include  | 2nd dose     | Male:10–19,20–29  Male:10–19,20–29 |
|                                      | Broad             | Include                       | 1st + 2nd dose | Male:10–19  Male:10–19,20–29 | Appendix 7         |
|                                      | Broad             | Include                       | 1st dose     | None  None                                                     |
|                                      | Broad             | Include                       | 2nd dose     | Male:10–19,20–29  Male:10–19,20–29 |
|                                      | Narrow            | 7                             | Not include  | 1st + 2nd dose | Male:10–19,20–29  Male:10–19,20–29 |
|                                      | Narrow            | 7                             | Not include  | 1st dose     | None  None                                                     |
|                                      | Narrow            | 7                             | Not include  | 2nd dose     | Male:10–19,20–29  Male:20–29,30–39 |
|                                      | Narrow            | 7                             | Include       | 1st + 2nd dose | Male:10–19,20–29  Male:10–19,20–29 | Appendix 9 |
|                                      | Narrow            | 7                             | Include       | 1st dose     | None  None                                                     |
|                                      | Narrow            | 7                             | Include       | 2nd dose     | Male:10–19,20–29  Male:20–29,30–39 |
|                                      | Broad             | 7                             | Not include  | 1st + 2nd dose | Male:10–19,20–29  Male:10–19,20–29 | Appendix 10       |
|                                      | Broad             | 7                             | Not include  | 1st dose     | None  None                                                     |
|                                      | Broad             | 7                             | Not include  | 2nd dose     | Male:10–19,20–29  Male:10–19,20–29 |
|                                      | Broad             | 7                             | Include       | 1st + 2nd dose | Male:10–19,20–29  Male:10–19,20–29 | Appendix 11       |
|                                      | Broad             | 7                             | Include       | 1st dose     | None  None                                                     |
|                                      | Broad             | 7                             | Include       | 2nd dose     | Male:10–19,20–29  Male:10–19,20–29 |

*Risk window: 21 days for Comirnaty, 28 days for Spikevax*
Comparison with the Situation of Other Countries

The reported rates of myocarditis and pericarditis after the second dose of mRNA COVID-19 vaccines were 3.2 and 1.3 cases per million doses in Japan for Comirnaty, respectively. 13.2 and 2.7 cases for Spikevax, respectively (as of June 12, 2022). In the U.S., this reporting rate is 3.7 cases per million doses of vaccination, which is calculated based on all number of vaccinations using Comirnaty and Spikevax combined [21]. Although the reporting rate in Japan is not comparable to that in the U.S. due to differences in the method of collecting adverse reaction reports after vaccination, we cannot conclude that the reporting rate in Japan is more extreme than that in the U.S. This is the reason for the bias in our analysis. We judge it unlikely that this reporting rate situation has a significant influence on our results as a bias in our analysis.

Furthermore, when we compare the calculated OE ratios to overseas situations, our results are consistent with the results of analyses or reports by EMA, CDC, and Public Health Ontario at the subgroup level that presents a significant risk of myocarditis or pericarditis [8–10]. A group of FDA has effectuated an OE analysis of myocarditis and pericarditis after vaccination of Comirnaty and Spikevax using several health care insurance claim database [22]. Table 6 shows comparison of results of OE analysis between FDA study and ours. Despite differences in the age categories used in the analysis, there were similarities in that young men were at higher risk of post-vaccine myocarditis and pericarditis for both vaccines compared to other sexes and age groups. In contrast, the results of a case–control study by the EPI-PHARE team in France, which was effectuated using a single database of the national health insurance, differed from our and other analyses. The results of the study conducted in France showed that the risk of myocarditis occurred not only in young males but also young females, who exhibited a statistically significant risk (OR at the second dose after up to 7 days of vaccination: Comirnaty 11.4 [95%CI: 4.5–28.6], Spikevax 40.6 [95%CI: 9.9–166.4]) [23]. For this study, the health insurance data from the total population were used when they detected cases of myocarditis or pericarditis after vaccination. Their case detection therefore seems to be more comprehensive than that of our study. This explains why it is possible to have more cases of myocarditis or pericarditis after the vaccination in Japan than those detected in the spontaneous reports of suspected adverse events. This factor may be the reason for the difference between the French study and our analysis. On the other hand, considering that our analysis is based on a large sample size of approximately 200 million doses of mRNA vaccine, we are awaiting the results of further analysis in the immediate future.

Limitations and Strengths of This Analyses

It should be noted that this study has some limitations. Firstly, our analysis is based on several different databases, with different definitions between the observed cases, which are identified in spontaneous reports of suspected adverse events, and the expected cases in the general population, which are identified in the NDB. At the moment, we do not have an infrastructure for the evaluation of myocarditis/pericarditis cases of both vaccinated and non-vaccinated individuals using a single database. Secondly, we did not use a criterion that can specify the level of diagnostic precision when we identified the cases. We only considered the diagnosis code for the definition of the observed and expected cases, and we were unable to evaluate the clinical presentations and the results of diagnostic tests in more detail. This is responsible for some diagnostic uncertainty. However, when calculating the expected cases in the NDB, the accuracy of the data was ensured as far as possible by removing the suspected disease codes and using a unique Patient-Matching Technique to remove duplicates. Thirdly, as we used spontaneous reports, there is a possibility of underestimation of the incidence of adverse events. To overcome these concerns and verify the robustness of the main analysis, we performed the sensitivity analyses under many analysis conditions. We believe that this study is the best possible estimation considering the present data collection system in Japan.

Despite these limitations, this study has the following strengths. Our analysis is the first large SARS-CoV-2 mRNA vaccine analysis of approximately 200 million doses for east Asian population. While some medicines have shown ethnic differences in efficacy and safety between Japanese and the others, we can show that this new modality of mRNA vaccines have no ethnic differences between Japan and overseas in terms of safety against myocarditis and pericarditis, comparing to the analysis in North America and the EU. In addition, it is very meaningful that the pharmacoepidemiologic assessment was conducted as a complement to the limiting factors of individual case assessment, and was used as one of the factors to decide whether or not to take a regulatory action in a timely manner. Since there are several limitations to the interpretation of the OE analysis, it would be desirable to use a single database for further evaluation, but this will require infrastructure development and a tremendous amount of time to create it. In the tense situation...
Table 6  Comparison of results of OE analysis

| Number of vaccine doses | Wong et al. [22] |
|-------------------------|------------------|
| Comirnaty               | Spikevax         |
| 163,059,502             | 31,768,353       |
| DP2                     | 159,435          |
| DP3                     | 262,536          |
| DP4                     | 209,473          |
of the COVID-19 pandemic, rapidity is also critical in risk management of vaccines, and this our OE analysis is the best that can be achieved at present in Japan.

**Conclusion**

In conclusion, a large-scale study was conducted that confirmed a statistically significant association between the development of myocarditis or pericarditis and the two available mRNA vaccines against SARS-CoV-2 in adolescent and young adult males in Japan. However, considering the vaccine effectiveness, the efficacy in preventing severe disease and the frequency of these adverse events, the benefit-risk ratio for the risk of myocarditis and pericarditis identified in this study remains positive.

**Author Contributions**

HK, SF, RM, YA, YK, TH, YS, TN, TI, YN, TY, and YS handled, analyzed, and double checked the data; SK, MK, NK, SH, TI, and HK wrote the manuscript. All authors read and approved the final version.

**Funding**

No funding was received for this research.

**Declarations**

**Conflict of Interest**

All authors declared no competing interests.

**Ethical Approval**

Not applicable in waiver of the ethics committee of PMDA, approved by the Ethics Committee of Nara Medical University (No. 2831. 2020/10/30).

**Other Declarations**

The views expressed in the discussion part of this article are those of the authors and do not necessarily reflect the official views of Pharmaceuticals and Medical Devices Agency.

**Consent to Participate**

All authors declare to consent to participate in the research.

**Consent for Publication**

All authors declare to consent the publication of the article.

**Supplementary Information**

The online version contains supplementary material available at https://doi.org/10.1007/s43441-022-00466-1.

**References**

1. Immunization Act (Act No. 68 of 1948) (Amendment Act No. 75 of 2020) [in Japanese] [Accessed 18 Aug 2022]. Available from: https://elaws.e-gov.go.jp/document?lawid=323AC0000000068
2. Act on securing quality, efficacy and safety of products including pharmaceuticals and medical devices (Act No. 145 of 1960) (Amendment Act No. 63 of 2019) [in Japanese]. [Accessed 18 Aug 2022]. Available from: https://elaws.e-gov.go.jp/document?lawid=335AC0000000145
3. CDC. Clinical Considerations: Myocarditis after mRNA COVID-19 Vaccines | CDC [Internet]. 2022 [Accessed 10 Dec 2021]. Available from: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html
4. Matta A, Kunadharaju R, Osman M, et al. Clinical presentation and outcomes of myocarditis post mrna vaccination: a meta-analysis and systematic review. Cureus [Internet]. 2021 Nov 3 [Accessed 18 Aug 2022];13(11). Available from: https://www.cureus.com/articles/75720-clinical-presentation-and-outcomes-of-myocarditis-post-mrna-vaccination-a-meta-analysis-and-systematic-review
5. Lane S, Yeomans A, Shakir S. Reports of myocarditis and pericarditis following mRNA COVID-19 vaccination: a systematic review of spontaneously reported data from the UK, Europe and the USA and of the scientific literature. BMJ Open. 2022;12(5):e059223.
6. Group JJW. Guidelines for diagnosis and treatment of myocarditis (JCS 2009). Circ J. 2011;75(3):734–43.
7. Mevorach D, Anis E, Cedar N, et al. Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel. N Engl J Med. 2021;385(23):2140–9.
8. EMA. Comirnaty and Spikevax: possible link to very rare cases of myocarditis pericarditis [Internet]. European Medicines Agency. 2021 [Accessed 21 Dec 2021]. Available from: https://www.ema.europa.eu/en/news/comirnaty-sparkvax-possible-link-very-rare-cases-myocarditis-pericarditis
9. CDC. Myocarditis and Pericarditis After mRNA COVID-19 Vaccination [Internet]. Centers for Disease Control and Prevention. 2020 [Accessed 21 Dec 2021]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/myocarditis.html
10. Public Health Ontario. Adverse events following immunization (AEFIs) for COVID-19 in Ontario: December 13, 2020 to December 12, 2021. [Accessed 21 Dec 2021]. Available from: https://www.publichealthontario.ca/-/media/documents/ncov/epi/covid-19-aefi-report.pdf?sc_lang=en
11. Haute Autorité de santé. Covid-19 : la HAS précise la place de Spikevax® dans la stratégie vaccinale [Internet]. Haute Autorité de Santé [in French]. [Accessed 18 Dec 2021]. Available from: https://www.has-sante.fr/jcms/p_3297260/fr/covid-19-la-has-prefere-la-place-de-spikevax-dans-la-strategie-vaccinale
12. Ministry of Health, Labour and Welfare. Joint Committee on Adverse events of Vaccines and Drug Safety of Pharmaceutical Affairs and Food Safety. Material for the Side Effect Subcommittee of the Immunization and Vaccine Section Meeting in the Health Science Council (the 73rd meeting), and the 2021 Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council (the 23rd meeting) (joint meeting) [Internet] [Accessed 21 Dec 2021].
13. Ministry of Internal Affairs and Communications. Population Estimates | All | Browse Statistics [Internet]. Portal Site of Official Statistics of Japan. [Accessed 21 Dec 2021]. Available from: https://www.e-stat.go.jp/en/stat-search?page=1&toukei=00200524

14. EMA. Good pharmacovigilance practices [Internet]. European Medicines Agency. 2018 [Accessed 21 Dec 2021]. Available from: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices

15. FDA. Comirnaty and Pfizer-BioNTech COVID-19 Vaccine [Internet]. FDA; 2022 [Accessed 18 Aug 2022]. Available from: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/comirnaty-and-pfizer-biontech-covid-19-vaccine

16. FDA. Spikevax and Moderna COVID-19 Vaccine [Internet]. FDA. FDA; 2022 [Accessed 18 Aug 2022]. Available from: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/spikevax-and-moderna-covid-19-vaccine

17. EMA. Comirnaty [Internet]. European Medicines Agency. 2020 [Accessed 18 Aug 2022]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty

18. EMA. Spikevax (previously COVID-19 Vaccine Moderna) [Internet]. European Medicines Agency. 2021 [Accessed 18 Aug 2022]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/spikevax

19. MHRA. Summary of Product Characteristics Comirnaty 30 micrograms/dose concentrate for age 12+ (purple cap) [Internet]. GOV.UK. [Accessed 18 Aug 2022]. Available from: https://www.gov.uk/government/publications/regulatory-approval-of-pfizer-biontech-vaccine-for-covid-19/summary-of-product-characteristics-for-covid-19-vaccine-pfizerbiontech

20. MHRA. Summary of Product Characteristics for Spikevax [Internet]. GOV.UK. [Accessed 18 Aug 2022]. Available from: https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-moderna/information-for-healthcare-professionals-on-covid-19-vaccine-moderna

21. Tom S. Update on myocarditis following mRNA COVID-19 vaccination [Internet]. CDC; 2022 Jun. [Accessed 18 Aug 2022]. Available from: https://www.cdc.gov/media/159007/download

22. Wong HL, Hu M, Zhou CK, et al. Risk of myocarditis and pericarditis after the COVID-19 mRNA vaccination in the USA: a cohort study in claims databases. Lancet. 2022;399(10342):2191–9.

23. Le Vu S, Bertrand M, Jabagi MJ, et al. Age and sex-specific risks of myocarditis and pericarditis following Covid-19 messenger RNA vaccines. Nat Commun. 2022;13(1):3633.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.