



# Safety monitoring of COVID-19 vaccines in Japan

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## Summary

The assessment of the efficacy and safety of coronavirus disease 2019 (COVID-19) vaccines in actual practice is extremely important, and monitoring efforts are being implemented worldwide. In Japan, a joint council in the Ministry of Health, Labour and Welfare is held every two to three weeks to summarise information on the adverse events following COVID-19 vaccination, with careful assessment of individual case safety reports and comparison with background incidence rates. In 2021, the joint council mainly reviewed anaphylaxis, death, myocarditis/pericarditis, and thrombosis with thrombocytopenia syndrome. These activities resulted in several safety-related regulatory actions, including the revision of vaccine package inserts with warnings about myocarditis/pericarditis. International sharing of vaccine safety information, as well as details of the evaluation systems, is important for international discussion and decision-making on better safety monitoring of COVID-19 vaccines.

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## Introduction

Coronavirus disease 2019 (COVID-19) has affected people's lives worldwide, with total casualties being over 5 million by November, 2021.<sup>1</sup> In Japan, the first case of the SARS-CoV-2 infection (COVID-19) was reported on January 15, 2020. By the end of November 2021, there had been five waves of the pandemic, with around 173 million infected patients and approximately 18,000 deaths.<sup>1</sup> The BNT162b2 (Pfizer-BioNTech) was approved in Japan on February 14, 2021, followed by

mRNA-1273 (Moderna/Takeda) and ChAdOx1-S (AstraZeneca) on May 21, 2021. Vaccinations using BNT162b2, mRNA1273, and ChAdOx1-S began on February 17, May 24, and August 1, 2021, respectively. The vaccination coverage has risen dramatically since then. In November 2021, the proportion of people receiving two doses of vaccinations exceeded 75%, indicating that Japan has one of the highest vaccination coverage globally.<sup>2</sup>

Accordingly, safety monitoring of COVID-19 vaccines is increasingly important. In Japan, vaccine safety monitoring has been conducted mainly by the Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA). Since the start of COVID-19 vaccination in Japan, several safety-related regulatory actions have been taken, such as revision of package inserts with warnings of myocarditis/pericarditis.<sup>3,4</sup>

Japan's national strategy for safety monitoring of COVID-19 vaccines is considered to work well, but

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records of the proceedings and results of the analyses have been published almost exclusively in Japanese.<sup>5</sup> Sharing Japan's experiences would be informative to countries that still have low vaccine coverage, and also stimulate international discussions on improved vaccine safety monitoring of COVID-19 vaccines. This report aims to show the Japanese systems of COVID-19 vaccines safety monitoring, analytical results through November 2021, and safety-related regulatory actions by focusing on four outcomes of national and international interest: anaphylaxis, death, myocarditis/pericarditis, and thrombosis with thrombocytopenia syndrome (TTS). Because implementation of the third vaccination 'booster' shot has begun in Japan since December 2021, the statistics in the current report represent the first and second COVID-19 vaccinations.

## Governmental structure for vaccine safety monitoring for COVID-19 vaccines in Japan

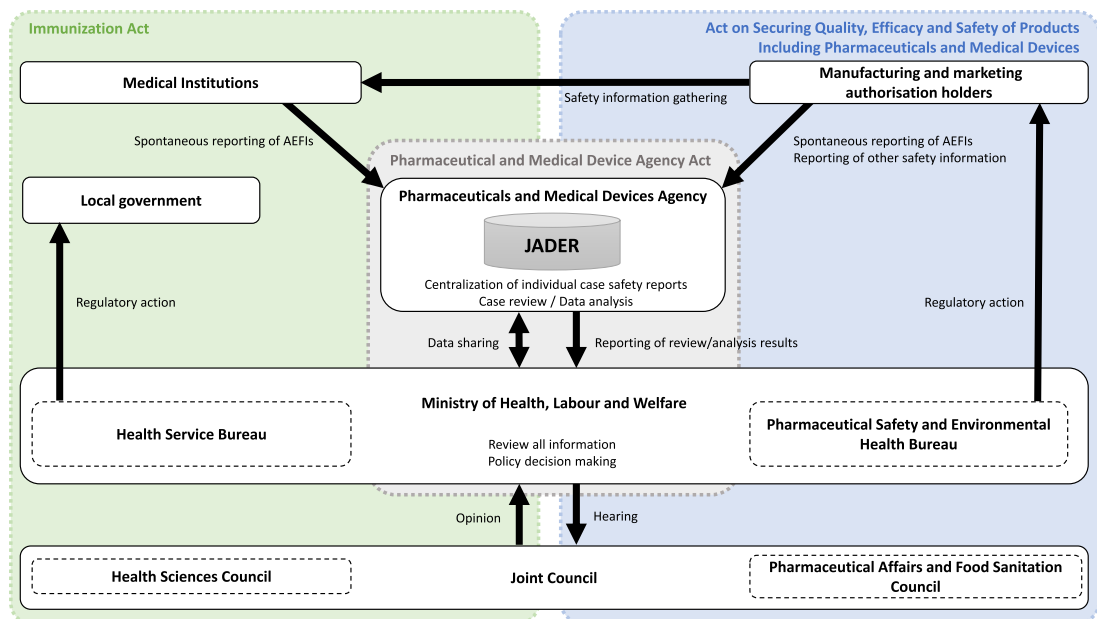
In Japan, safety monitoring of vaccines has been conducted mainly by the MHLW and PMDA under the Immunisation Act<sup>6</sup> and the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices.<sup>7</sup> External review panels have been formed from the Health Sciences Council and the Pharmaceutical Affairs and Food Sanitation Council. This joint council has played a central role in determining safety-related vaccine policy (Figure 1). This joint

council comprises 15 members, including two chairs. The members and chairs are selected by the Minister of the MHLW.

COVID-19 vaccinations have been implemented under the Immunisation Act. In response to the increasing numbers of individual case safety reports (ICSRs) of adverse events following COVID-19 vaccination, the systems of receiving and evaluation reports at PMDA were enhanced, and the frequency of joint council meetings was increased.

## Available data sources for vaccine safety monitoring

*Individual case safety reports (numerator data):* Japanese spontaneous reporting system is designed to accept reports of adverse events following immunisation and detect safety signals of licensed vaccines. There are two types of ICSR in Japan (Figure 1). First, based on the Immunisation Act, healthcare professionals are required to report adverse events following immunisation using a standardised reporting format.<sup>8</sup> The Japanese standardised form includes the basic items similar to the World Health Organisation (WHO)'s reporting form for Adverse Events Following Immunisation.<sup>9</sup> In addition, the questionnaire consistent with Brighton Classification for some specific adverse events is provided separately. Reporting has been mandatory since 2013.<sup>6</sup> Second, the Act on Securing Quality, Efficacy



**Figure 1.** Governmental structure for vaccine safety monitoring in Japan.

AEFIs = adverse events following immunisation, JADER= Japanese Adverse Drug Event Report database, ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

and Safety of Products Including Pharmaceuticals and Medical Devices requires vaccine marketing authorisation holders (MAHs) to report suspected adverse reactions that come to their attention,<sup>7</sup> using the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E2B format.<sup>10</sup> Reporting has been mandatory for MAHs since 1980.<sup>7</sup> All reports from healthcare professionals and MAHs are received, managed, maintained, and assessed by the PMDA based on the Pharmaceuticals and Medical Devices Agency Act.<sup>11</sup>

Reports to the PMDA from healthcare professionals cover adverse events, including minor and severe ones. The PMDA shares the information with each MAH, which conducts further investigation, follows up each case, and reports severe cases back to the PMDA. Therefore, the total number of reports from MAHs is smaller than that from healthcare professionals.

PMDA conducts additional investigations and causality assessments, and reports evaluation results to the MHLW in cooperation with the National Institute of Infectious Diseases. Detailed information of ICSRs for COVID-19 vaccines from MAHs, including unstructured data (e.g., details of clinical encounters), is fully open to the public.<sup>5</sup> Structured data from these reports are available on the PMDA website via the Japanese Adverse Drug Event Report database.<sup>12</sup>

*Vaccination data (denominator data):* As the denominator for estimating the incidence rate of adverse outcomes, the number of COVID-19 vaccinations can be estimated from the Vaccination Record System (VRS) and Vaccination System (V-SYS) data, by brand name, age, sex, dose number, and date. The VRS, established by the Digital Agency,<sup>13</sup> is a system that records the vaccinations for COVID-19 and is managed by municipalities in a cloud-based system provided by the government. Information regarding when, where, and which vaccines were administered is input into the VRS. The V-SYS was established by the MHLW for the government, prefectures, municipalities, and medical institutions to share information and adjust the supply and demand of vaccines. Because of periodic time lags in updating VRS data, the V-SYS data are complementarily used for more accurate and timely estimation of the number of COVID-19 vaccinations.

*Other data sources (background incidence rates):* For comparison with the incidence rate of adverse outcomes among COVID-19 vaccine recipients, mortality rates before the pandemic (i.e., in 2019) were obtained from the National Vital Statistics death data.<sup>14</sup> The background incidence rates of several adverse events, including myocarditis/pericarditis, were calculated using data from the National Database of Health Insurance Claims (NDB).<sup>15</sup> The NDB contains

information on insurance claims from almost all Japanese residents, derived from the universal health insurance system in Japan.

### National strategy of COVID-19 vaccine safety monitoring

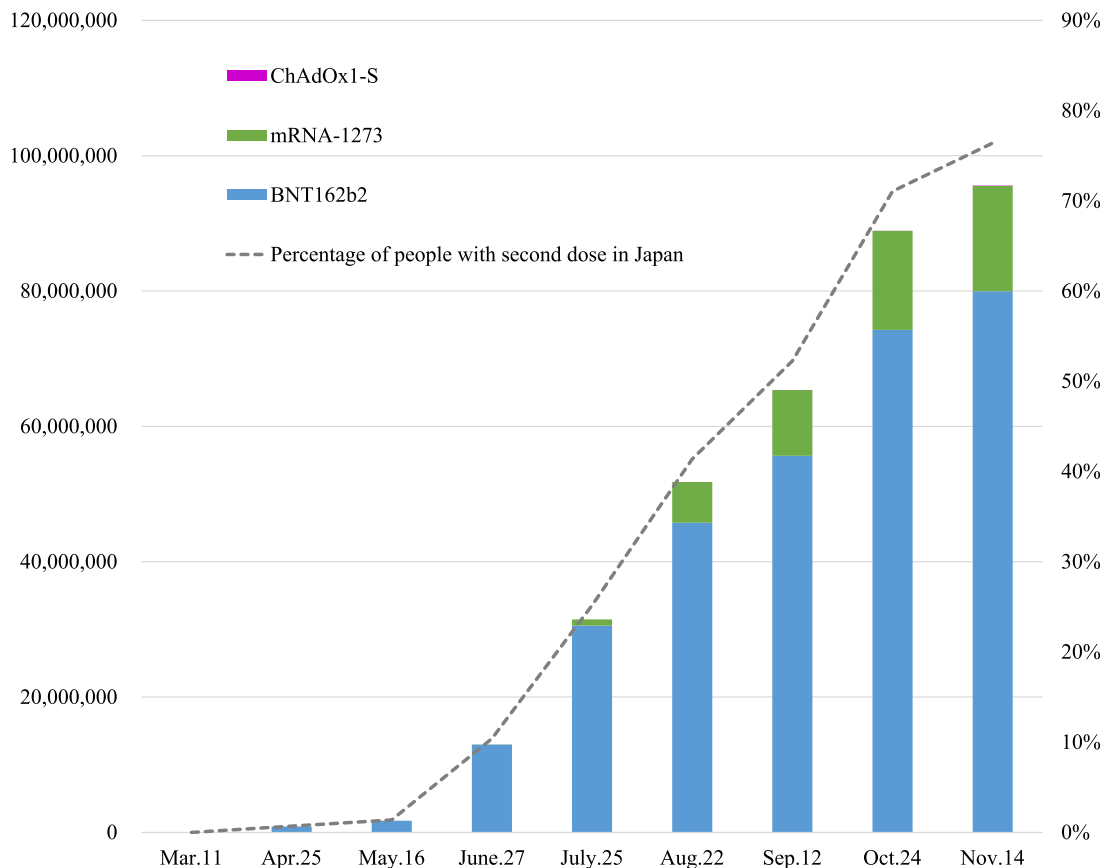
The joint council's strategy for COVID-19 vaccine safety monitoring consists of several steps. The first step is 'signal detection', which is mainly based on the ICSR information. A signal in pharmacovigilance is defined by the WHO; a signal does not indicate a direct causal relationship between a side effect and a medicine but is essentially only a hypothesis that justifies the need for further assessment.<sup>16</sup> Generally, if the accumulated number of ICSRs for a specific adverse event is increasing, especially suggesting causal relationship by qualitative assessment from clinical aspects, the adverse event is considered as a safety signal for the vaccine. As a reinforcement system for COVID-19 vaccines, the PMDA conducts a review and evaluation involving two or more clinical experts in an assessment of all the ICSRs on COVID-19 vaccines, which is then confirmed by the joint council. ICSRs with anaphylaxis, myocarditis/pericarditis, TTS, and other adverse events are formally graded using Brighton classification.<sup>17</sup>

If safety signals of adverse outcomes are detected in the first step, the second step is 'signal strengthening' by a population-level comparison for that outcome. This process compares the incidence rate of the adverse outcome, estimated as the number of reported cases divided by the number of people receiving the COVID-19 vaccine, with its background incidence rates in 2019.

Among the potential serious adverse outcomes associated with COVID-19 vaccines, the joint council agreed that the priority of investigation should be given to anaphylaxis and death, based on reports from other countries, as well as previous experience in 2009 with influenza A/H1N1 vaccinations. Myocarditis/pericarditis and TTS were additionally given priority for detailed investigation, based on the results of the first step as well as international reports.

### Overall trend in the number of COVID-19 vaccinations and individual case safety reports

The vaccination coverage in Japan has risen dramatically since the introduction of vaccines in February 2021 (Figure 2). As of November 14, 2021, among a national population of approximately 125 million, an estimated 99.3 million (79.4%) have received at least one dose and 95.6 million (76.4%) have received two. Of these shots, 83.6% were of BNT162b2, 16.3% of mRNA-1273, and <0.1% of ChAdOx1-S. The age-sex distribution according to the vaccine type is shown in Appendix P 1. People receiving BNT162b2 were older



**Figure 2.** Trend in the cumulative number of people receiving second dose in 2021.

and more likely to be women compared to those receiving mRNA-1273, whereas the majority of people receiving ChAdOx1-S were middle-aged men.

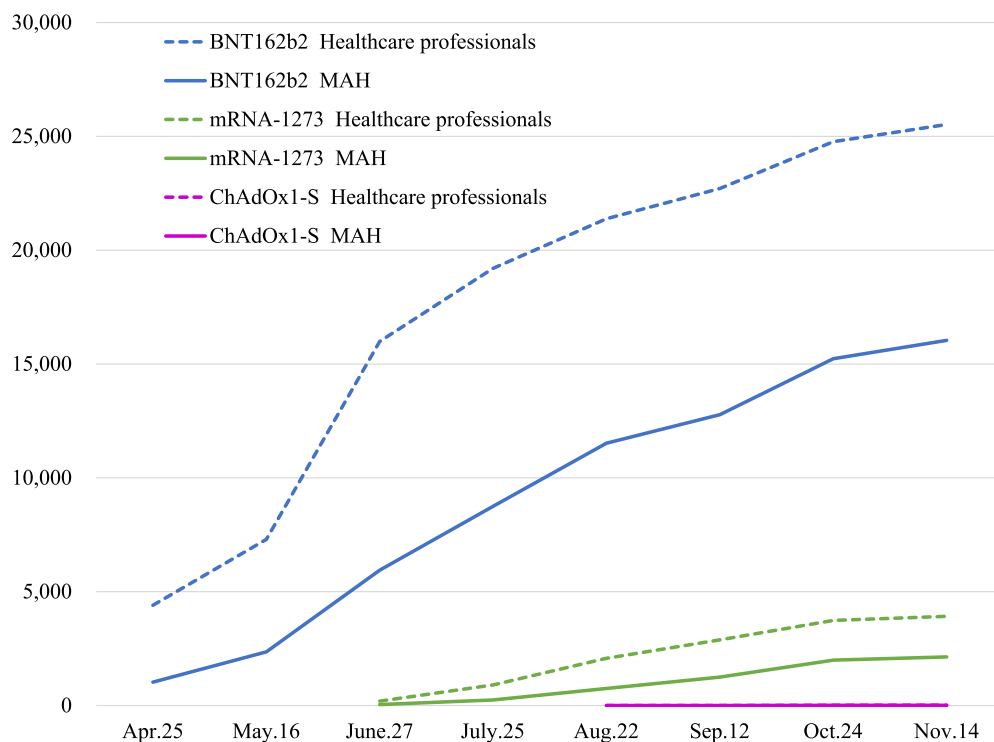
Concurrently, there has been an increasing number of ICSRs from healthcare professionals and MAHs (Figure 3). As of November 14, 2021, there were 25,522 (0.02%) reports from healthcare professionals and 16,040 (0.01%) from the MAH (Pfizer-BioNTech) among 163,059,502 shots of BNT162b2. There were 3,919 (0.01%) reports from healthcare professionals and 2,133 (0.1%) from the MAH (Moderna/Takeda) among 31,768,352 mRNA-1273 shots. The number of reports from healthcare professionals was 12 (0.01%), and the MAH (AstraZeneca) reported 8 (0.01%) among 101,502 shots of ChAdOx1-S. The age distribution of events by vaccine type is presented in Appendix P 2.

### Summary of statistics, interpretation, and regulatory actions for anaphylaxis

**Statistics:** As of November 14, 2021, among 163,059,502 shots of BNT162b2, the MAH (Pfizer/BioNTech) reported 3,012 ICSRs of suspected anaphylaxis, of which 581 were

confirmed as Brighton classifications 1–3 by the expert review panels (4 cases per 1 million shots). Among 31,768,352 shots of mRNA-1273, the MAH (Moderna/Takeda) reported 504 cases of suspected anaphylaxis, of which 50 were confirmed as Brighton classifications 1–3 by the expert panels (1.6 cases per 1 million shots). No cases associated with ChAdOx1-S met Brighton classification levels 1–3. Occurrence tended to be higher in BNT162b2 than in mRNA-1273 in all age and sex groups (Table 1). However, the frequency of reports involving BNT162b2 was highest during the first three months, possibly reflecting the fact that healthcare workers (including many younger females) were among the initial recipients. After May 2021, the frequencies of confirmed anaphylaxis were comparable between BNT162b2 and mRNA-1273 (Appendix P 3).

**Interpretation:** The frequency of anaphylaxis associated with COVID-19 vaccines in Japan is as expected, and comparable to or even lower than that in other developed countries.<sup>18,19</sup> For example, the frequency of reported anaphylaxis in the United States as of the end of July 2021 was 37 out of 7.4 million shots of BNT162b2 (5.0 cases per 1 million shots) and 26 out of 5.31 million shots of mRNA-1273 (4.9 cases per



**Figure 3.** Trend in the cumulative number of individual case safety reports in 2021. MAH=marketing authorisation holder.

1 million shots).<sup>18</sup> As of November 17, 2021, the frequency of reported anaphylaxis in the United Kingdom was 555 out of 45 million shots of BNT162b2 (12.3 cases per 1 million shots) and 43 out of 2.8 million shots of mRNA-1273 (15.4 cases per 1 million shots).<sup>19</sup>

**Regulatory action:** At the approval of the COVID-19 vaccines, anaphylaxis had already been included in the package insert sections on 'ADVERSE REACTIONS' and 'CONTRAINDICATIONS' for people with a history of anaphylaxis. Similar to other countries, to date, no additional safety measures have been implemented in Japan.

### Summary of statistics, interpretation, and regulatory actions for death

**Statistics:** The real-time cumulative number of deaths after COVID-19 vaccination was calculated using deduplicated reports from both healthcare professionals and MAH reports due to the time lag between the two reports. Among the 1,368 deaths (1,315 with BNT162b2, 53 with mRNA-1273, and 0 with ChAdOx1-S), the most common cause of death was ischaemic heart disease ( $n=138$ ), followed by heart failure ( $n=118$ ), and haemorrhagic stroke ( $n=109$ ). However, none of the cases were confirmed by experts as suggesting a causal relationship between vaccination and death.

The proportions of reported death among people with the COVID-19 vaccine were 8.1 and 1.7 cases per 1 million shots (1,315 cases/163,059,502 shots and 53 cases/31,768,352 shots), or 15.8 and 3.3 cases per 1 million people with at least one shot (1,315 cases/83,094,685 people and 53 cases/16,173,124 people) for BNT162b2 and mRNA-1273, respectively. When partitioned by cause of death, the incidence rates of death with ischaemic heart disease (Appendix P 4) or intracranial haemorrhage (Appendix P 5) within 21 days of vaccination were strikingly lower than the background incidence rates in 2019. The distribution of the time interval between vaccination and death is shown in Appendix P 6, suggesting that reporting was more frequent when death was soon after vaccination.

**Interpretation:** It is generally difficult to infer a causal relationship between vaccination and death, especially among older people, because of various potential causes of death. Indeed, the experts confirmed none of the cases as suggesting a causal relationship between vaccination and death. Moreover, the population-level comparisons did not detect an excess risk of death associated with COVID-19 vaccination.

The proportion of reported deaths in Japan is lower than seen in other countries (22.2 cases in the United States,<sup>20</sup> and 13.6 cases in BNT162b2 and 6.8 cases in mRNA-1273 per 1 million shots in the United

|         |         | BNT162b2 |                            | mRNA-1273 |                            |
|---------|---------|----------|----------------------------|-----------|----------------------------|
|         |         | n        | Per 1 million vaccinations | n         | Per 1 million vaccinations |
| Total   |         | 581      | 4                          | 50        | 1.6                        |
| Male    | 10-14y  | 1        | 0.5                        | 0         | 0                          |
|         | 15-19y  | 6        | 1.7                        | 0         | 0                          |
|         | 20-24y  | 9        | 3.5                        | 6         | 2.9                        |
|         | 25-29y  | 6        | 2.1                        | 2         | 1.1                        |
|         | 30-34y  | 11       | 3.4                        | 0         | 0                          |
|         | 35-39y  | 8        | 2.1                        | 3         | 1.5                        |
|         | 40-44y  | 6        | 1.3                        | 0         | 0                          |
|         | 45-49y  | 7        | 1.2                        | 1         | 0.4                        |
|         | 50-54y  | 2        | 0.3                        | 0         | 0                          |
|         | 55-59y  | 5        | 0.9                        | 0         | 0                          |
|         | 60-64y  | 0        | 0                          | 0         | 0                          |
|         | 65-69y  | 6        | 0.9                        | 0         | 0                          |
|         | 70-74y  | 4        | 0.5                        | 0         | 0                          |
|         | 75-79y  | 0        | 0                          | 0         | 0                          |
|         | 80y-    | 2        | 0.3                        | 0         | 0                          |
|         | unknown | 1        | -                          | 0         | -                          |
| Female  | 10-14y  | 2        | 1.1                        | 1         | 8.6                        |
|         | 15-19y  | 7        | 2                          | 2         | 2.5                        |
|         | 20-24y  | 32       | 10.4                       | 6         | 3.4                        |
|         | 25-29y  | 44       | 13                         | 7         | 5                          |
|         | 30-34y  | 42       | 11                         | 9         | 7.2                        |
|         | 35-39y  | 74       | 15.8                       | 2         | 1.6                        |
|         | 40-44y  | 71       | 12.7                       | 3         | 2.3                        |
|         | 45-49y  | 81       | 11.8                       | 2         | 1.3                        |
|         | 50-54y  | 49       | 7.1                        | 3         | 2.3                        |
|         | 55-59y  | 34       | 5.6                        | 1         | 1                          |
|         | 60-64y  | 18       | 2.9                        | 0         | 0                          |
|         | 65-69y  | 19       | 2.7                        | 1         | 2.9                        |
|         | 70-74y  | 8        | 0.9                        | 0         | 0                          |
|         | 75-79y  | 5        | 0.7                        | 0         | 0                          |
|         | 80y-    | 18       | 1.3                        | 0         | 0                          |
|         | unknown | 2        | -                          | 0         | -                          |
| Unknown | -       | 1        |                            | 1         |                            |

**Table 1: The number of individual case safety reports for anaphylaxis from marketing authorization holders confirmed as Brighton classifications 1–3 as of November 14, 2021.**

Kingdom).<sup>19</sup> However, direct comparison between these rates may be affected by different reporting methods between the countries.

As the next step, a large cohort study to compare the mortality of vaccinated and unvaccinated people in Japan may be warranted, as has been conducted elsewhere.<sup>21,22</sup> These observational studies found significantly lower mortality rates in the vaccinated groups compared to those in the unvaccinated groups,<sup>21,22</sup> although the results may be affected by confounding if vaccinated persons tend to be healthier than the unvaccinated.

*Regulatory action:* To date, there has been no safety-related regulatory action in Japan for COVID-19 vaccine-associated deaths. Nonetheless, careful monitoring is ongoing.

## Summary of statistics, interpretation, and regulatory actions for myocarditis/pericarditis

*Statistics:* Since the first case report of myocarditis in March 2021, the number of reported cases of myocarditis or pericarditis has steadily increased in patients receiving BNT162b2 and mRNA-1273. By November 14, 2021, there were 476 reports from the MAHs (281 from Pfizer-BioNTech and 195 from Moderna/Takeda), suggesting the incidence rates of 1.7 and 6.1 cases per 1 million shots (3.4 and 12.1 cases per 1 million people with at least one shot) for BNT162b2 and mRNA-1273, respectively. Of these cases, 20 cases (16 cases for BNT162b2 and 4 cases for mRNA-1273) were followed by death, although the causal relationship between the vaccination and death remained inconclusive by experts.

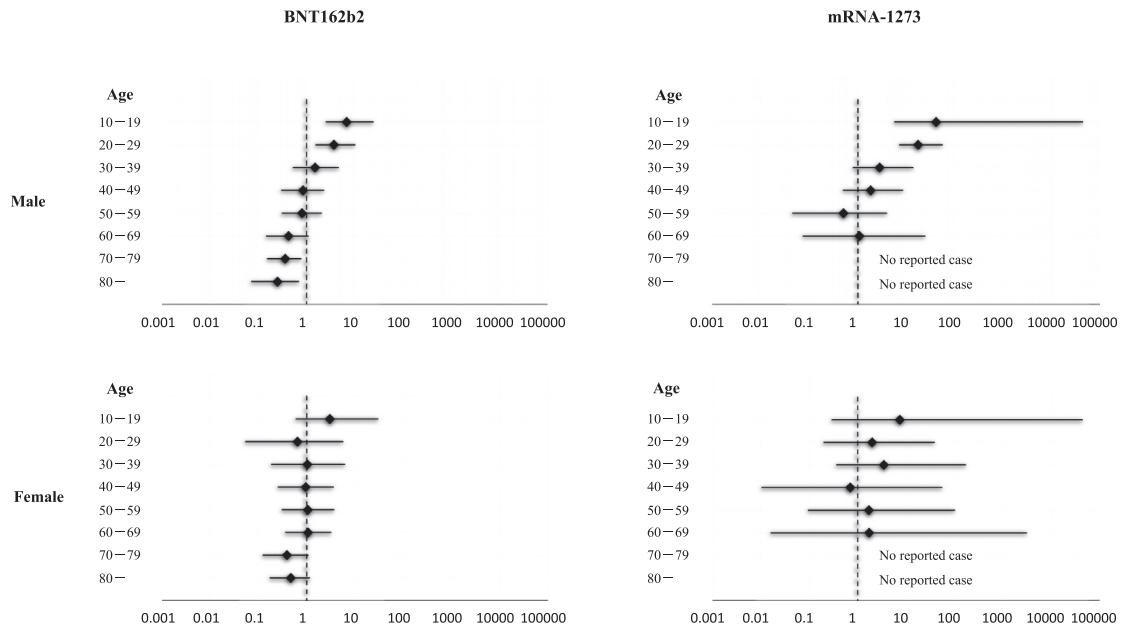
|         |         | BNT162b2 |                            |                       | mRNA-1273 |                            |                       |
|---------|---------|----------|----------------------------|-----------------------|-----------|----------------------------|-----------------------|
|         |         | n        | Per 1 million vaccinations | Per 1 million persons | n         | Per 1 million vaccinations | Per 1 million persons |
| Total   |         | 281      | 1.7                        | 3.4                   | 195       | 6.1                        | 12.1                  |
| Male    | 10-14y  | 15       | 7.7                        | 14.3                  | 3         | 25.3                       | 46.9                  |
|         | 15-19y  | 30       | 8.6                        | 16.4                  | 38        | 45.3                       | 87.6                  |
|         | 20-24y  | 20       | 7.9                        | 14.9                  | 60        | 28.8                       | 56.3                  |
|         | 25-29y  | 18       | 6.3                        | 11.9                  | 37        | 19.9                       | 38.9                  |
|         | 30-34y  | 15       | 4.6                        | 8.8                   | 10        | 5.5                        | 10.7                  |
|         | 35-39y  | 7        | 1.8                        | 3.5                   | 3         | 1.5                        | 3                     |
|         | 40-44y  | 8        | 1.7                        | 3.3                   | 7         | 3.5                        | 6.9                   |
|         | 45-49y  | 7        | 1.2                        | 2.3                   | 7         | 3.1                        | 6                     |
|         | 50-54y  | 6        | 1                          | 2                     | 1         | 0.5                        | 1                     |
|         | 55-59y  | 6        | 1.1                        | 2.2                   | 2         | 1.3                        | 2.6                   |
|         | 60-64y  | 5        | 0.9                        | 1.8                   | 1         | 1.1                        | 2.2                   |
|         | 65-69y  | 10       | 1.5                        | 3                     | 1         | 2.1                        | 4.3                   |
|         | 70-74y  | 10       | 1.2                        | 2.5                   | 0         | 0                          | 0                     |
|         | 75-79y  | 7        | 1.3                        | 2.6                   | 0         | 0                          | 0                     |
|         | 80y-    | 11       | 1.4                        | 2.8                   | 0         | 0                          | 0                     |
|         | unknown | 1        | -                          | -                     | 2         | -                          | -                     |
|         | Female  | 10-14y   | 4                          | 2.2                   | 4.1       | 0                          | 0                     |
| 15-19y  |         | 9        | 2.6                        | 5                     | 3         | 3.7                        | 7.2                   |
| 20-24y  |         | 2        | 0.6                        | 1.2                   | 2         | 1.1                        | 2.2                   |
| 25-29y  |         | 3        | 0.9                        | 1.7                   | 2         | 1.4                        | 2.8                   |
| 30-34y  |         | 3        | 0.8                        | 1.5                   | 4         | 3.2                        | 6.3                   |
| 35-39y  |         | 7        | 1.5                        | 2.9                   | 2         | 1.6                        | 3                     |
| 40-44y  |         | 7        | 1.2                        | 2.4                   | 2         | 1.5                        | 3                     |
| 45-49y  |         | 5        | 0.7                        | 1.4                   | 4         | 2.6                        | 5.2                   |
| 50-54y  |         | 12       | 1.7                        | 3.4                   | 3         | 2.3                        | 4.4                   |
| 55-59y  |         | 5        | 0.8                        | 1.6                   | 0         | 0                          | 0                     |
| 60-64y  |         | 9        | 1.4                        | 2.8                   | 0         | 0                          | 0                     |
| 65-69y  |         | 6        | 0.8                        | 1.7                   | 1         | 2.9                        | 5.7                   |
| 70-74y  |         | 8        | 0.9                        | 1.7                   | 0         | 0                          | 0                     |
| 75-79y  |         | 3        | 0.4                        | 0.9                   | 0         | 0                          | 0                     |
| 80y-    |         | 17       | 1.2                        | 2.5                   | 0         | 0                          | 0                     |
| unknown |         | 5        | -                          | -                     | 0         | -                          | -                     |

**Table 2: The number of individual case safety reports for myocarditis/pericarditis as of November 14, 2021.**

Many of which were reported within 30 days, particularly within 5 days of vaccination (Appendix P 7). As of November 14, 2021, there had not been any reports of myocarditis or pericarditis associated with ChAdOx1-S. Table 2 shows the incidence rate of myocarditis/pericarditis according to age, sex, and vaccine type. Moreover, an observed-to-expected (OE) analysis was conducted using the 2019 NDB background incidence rates for myocarditis/pericarditis (Figure 4). In men in their teens and twenties, the lower 95% confidence interval limit of the OE ratio was above 1.0 for both BNT162b2 and mRNA-1273; this trend was more pronounced for mRNA-1273: the OE ratio was 6.8 and 3.7, and 41.1 and 17.4 in their teens and twenties, for BNT162b2 and mRNA-1273, respectively, while their confidence intervals overlapped. Stratified by the number of doses, the risk was larger following the second dose than the first dose (Appendix P 8).

*Interpretation:* Increasing amounts of data suggest that the incidence of reported myocarditis/pericarditis after mRNA vaccination is significantly higher than the background incidence rates for men in their teens and twenties. This finding is in line with many reports from other countries suggesting that mRNA vaccines may increase the risk of myocarditis/pericarditis in younger men.<sup>23–27</sup> For example, in Israel, the overall incidence rate of myocarditis after vaccination of BNT162b2 was 21.3 cases per 1 million people with at least one shot, whereas the highest incidence rate was observed in men aged 16–29 years (106.9 cases per 1 million).<sup>24</sup> In addition, the current analysis may be the first to suggest a higher risk of myocarditis/pericarditis from mRNA-1273 than from BNT162b2 in men in their teens and twenties.

*Regulatory actions:* As of July 7, 2021, based on the increasing number of ICSRs from Japan and several



**Figure 4.** Result of observed-to-expected ratio analysis of myocarditis and pericarditis by age and sex.

The risk period was set as seven days (i.e., observed cases in each subgroup were counted only during the risk window of seven days from the date of each vaccination). The background incidence rate in each subgroup was calculated using the National Database of Health Insurance Claims data (NDB), including the International Classification of Diseases 10<sup>th</sup> revision codes suggesting myocarditis/pericarditis and the population census data. The expected cases were calculated by multiplying the background incidence rate by the follow-up period (calculated by multiplying the total number of COVID-19 vaccinations by seven days).

scientific reports from other countries such as the United States,<sup>28</sup> the package inserts of both BNT162b2 and mRNA-1273 vaccines were updated in the 'IMPORTANT PRECAUTIONS' and 'OTHER PRECAUTIONS' sections.<sup>29</sup> The relevant MHLW web pages instructed vaccine recipients or their caregivers to seek medical attention immediately if they experience or notice any symptoms suggestive of myocarditis or pericarditis.

On October 15, 2021, the joint council concluded that the risk of myocarditis/pericarditis from mRNA vaccines, particularly mRNA-1273, is specifically increased in men in their teens and twenties. The council decided to suggest that those who had received the first dose of mRNA-1273 could choose BNT162b2 for their second dose. However, the council also emphasised that people should not be discouraged from receiving COVID-19 vaccines, considering the balance between the relatively small risk of myocarditis, and the benefit of preventing COVID-19, which is known to induce myocarditis much more frequently than the vaccination itself. These messages were immediately sent to the public via the mass media.

On December 3, 2021, the package inserts of both the BNT162b2 and mRNA-1273 vaccines were further updated to list myocarditis/pericarditis as one of the clinically significant adverse reactions in the 'ADVERSE REACTION' section.<sup>3,4</sup>

## Summary of statistics, interpretation, and regulatory actions for thrombosis with thrombocytopenia syndrome

The ChAdOx1-S vaccine was approved in Japan on May 21, 2021, but its use in the community was delayed due to concerns expressed internationally about the potential risk of TTS and other thrombotic events.<sup>30</sup> Actual use of ChAdOx1-S in Japan began in August 2021, while encouraging reporting of TTS through the ICSRs. However, as of November 14, 2021, there had been only one reported case of TTS following 101,502 shots to 56,832 people. This case occurred in a 48-year-old man without a history of relevant comorbidities, and was classified as Brighton classification 1. The risk of TTS had already been included in the first version of the ChAdOx1 package insert, and no additional regulatory action has been taken. Careful monitoring is ongoing.

## Discussion and conclusions

Spontaneous reporting of adverse events by healthcare professionals and MAHs, and other national data sources is well established in Japan. This has enabled the government to conduct immediate evaluation, information sharing, and data analysis, leading to effective safety monitoring of COVID-19 vaccines. The conference minutes and statistics of every meeting were immediately open to the public on the MHLW of Japan



website,<sup>5</sup> which can be accessed by the general people and mass media. This timely approach is expected to increase vaccine confidence among Japanese people.

Although safety monitoring systems may differ across countries, broadly sharing monitoring information on COVID-19 vaccination, and how the data are used in decision making, will stimulate international discussion for the enhanced safety monitoring of COVID-19 vaccines. Moreover, the details of the adverse outcomes associated with COVID-19 vaccinations in Japan would be informative to other countries with low vaccine coverage, especially countries in Asia, as there may be ethnic differences in the effectiveness and safety of the COVID-19 vaccinations.

In many developed countries, in addition to spontaneous reporting systems for signal detection, active monitoring using large electronic medical information databases (including vaccination data) has been conducted for signal strengthening. For example, the United States Vaccine Safety Datalink, a collaboration between health plans and the Centers for Disease Control and Prevention for active safety monitoring, has conducted weekly monitoring of 23 serious outcomes, including death, haemorrhagic and ischaemic stroke, thromboembolism, myocarditis, and anaphylaxis, since December 14, 2020.<sup>23,31</sup> In comparing the incidence of events one to 21 days postvaccination with 22 to 42 days postvaccination, the study had not found any safety concerns until June 26, 2021, when analyses began detecting indications of myocarditis in people aged 12–39 years.<sup>23</sup> There are other examples of observational studies using such databases, including descriptive analyses estimating the incidence of an outcome among vaccinated persons,<sup>26</sup> the OE analysis,<sup>21</sup> a matched cohort study,<sup>27</sup> and a self-controlled case series.<sup>32</sup>

The analyses found a statistically significant difference between the background incidence rate of myocarditis/pericarditis and that among people receiving the mRNA vaccines. Further, the analyses found the possibility of differences in the incidence rates for people who had received different types of mRNA vaccines. This was particularly true for men in their teens and twenties, and resulted in prompt safety-related regulatory action. Ideally, this finding should be further confirmed by additional studies, such as a matched cohort study. Ongoing efforts to link different nationwide databases (e.g., NDB and vaccination data) by the government and vaccination information and medical claims data in local municipalities, will help enable such studies.

There were several limitations to the statistical and analytical results presented in the current paper. First, the numbers and incidence rates of adverse events following immunization (defined as any adverse events following vaccination, with or without a causal relationship) could be underestimated by using the spontaneous reporting data, which may suffer from under-

reporting. Therefore, comparison of the statistics in the current paper with those estimated in other data sources is warranted as soon as these data are available for analysis; however, the different data sources have their own limitations (e.g., small sample size of active surveillance data to identify rare outcomes, such as myocarditis/pericarditis and TTS, and misclassification or overdiagnosis in the administrative claims data). Notably, in the OE analysis for myocarditis/pericarditis, the incidence rate based on the ICSRs (possibly underestimated) was significantly larger than the background incidence rate calculated from the administrative claims data in NDB (possibly overestimated) in men in their teens and twenties. Secondly, most of the vaccinations so far have been with mRNA vaccines (BNT162b2 or mRNA1273) in Japan, and the experiences of viral vector vaccines for COVID-19 (such as ChAdOx1-S) have been small. Furthermore, the statistics in the current report represent only the first and second COVID-19 vaccinations, whereas implementation of the third vaccination ‘booster’ shot has begun since December 2021 in Japan. Thus, data on the booster shots and types of vaccines other than mRNA vaccines should be analysed and reported in the near future.

Safety monitoring of emerging vaccines and timely regulatory actions are important for public health. If the safety of a vaccine is found to be questionable after analysis of accumulating data, the most radical safety-related regulatory action may be to pause vaccination in the community. Less radical actions include informing people about the risk through measures such as revised package inserts and medication guides. While the final benefit-risk assessments of vaccination may be up to individuals, governments are expected to provide the general public with the best information available, and may sometimes need to take regulatory action for the public good. National experiences of COVID-19 vaccination should be shared internationally and utilised to further improve the safety monitoring system of vaccines.

In conclusion, Japan is conducting safety monitoring of COVID-19 vaccines at the national level. So far, the process is considered to be working well, and has led to regulatory actions regarding vaccine-associated risks of myocarditis/pericarditis. The Japanese government is continually working to enhance the quality, timely collection, and analysis of available data to monitor this and other health risks.

#### Author contributions

TY, MI, and CI drafted the manuscript TY, DF, MN, and TT had full access to and verified all the data in the study and were responsible for data acquisition, analysis, and interpretation and drafting of the manuscript. TN substantially contributed to the analysis of the National Database of Health Insurance Claims data for the background incidence rates of myocarditis/

pericarditis. HU, NK, and TI contributed significantly to the observed-to-expected analysis. NY, ST, AO, TM, KN, and SH contributed substantially to the interpretation of data and drafting of the manuscript. All authors had final responsibility for the decision to submit the manuscript for publication.

## Data sharing

The data for this report are available to the public on the webpage (Japanese language only) of the Ministry of Health, Labour and Welfare of Japan ([https://www.mhlw.go.jp/stf/shingi/shingi-kousei\\_284075.html](https://www.mhlw.go.jp/stf/shingi/shingi-kousei_284075.html)).

## Declaration of interests

AO receives grants from Eisai Co., Ltd, SHIONOGI & CO., LTD., Takeda Pharmaceutical Co, Eli Lilly Japan K. K., Chugai Pharmaceutical Co., Ltd., and Pfizer Japan Inc. All other authors declare no competing interests.

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## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.lanwpc.2022.100442](https://doi.org/10.1016/j.lanwpc.2022.100442).

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