HSA's Safety Update #2

Pfizer-BioNTech and Moderna COVID-19 Vaccines

(30 December 2020 – 23 May 2021)

Introduction

This is HSA's second safety update of the mRNA COVID-19 vaccines covering the period from the roll-out of the vaccines on 30 December 2020 to 23 May 2021. It provides an overview of the reports by healthcare professionals of ***suspected adverse events*** [1] ***(AEs)*** associated with COVID-19 vaccines to the Health Sciences Authority (HSA) and our current assessment of these AEs. It follows HSA's first update published on 6 May 2021.

Summary (as of 23 May 2021)

- A total of 4,704 suspected AE reports (0.13% of administered doses) were received, with 157 reports (0.004% of administered doses) classified as serious AEs after assessment. A total of 3,680,368 doses have been administered. Among the serious AE reports, the most frequently reported AEs were anaphylaxis and other severe allergic reactions.

- The most commonly reported AEs were consistent with those typically observed following vaccination. They include injection site reactions such as pain and swelling (including delayed reactions also known as "COVID arm"), dizziness, fever, muscle aches and pain, headache, shortness of breath and allergic reactions (such as rash, itch, hives and swelling of eyelids, face and lips). These are also in line with the events described in the COVID-19 vaccines product information.

- Cases of myocarditis and pericarditis (inflammation of the heart muscles and outer lining of the heart, respectively) have been reported with COVID-19 vaccines both overseas and locally. Myocarditis and pericarditis have many causes and most are due to viral infections and immunological reactions. In most cases, the inflammation is mild. We have received 6 reports of myocarditis and pericarditis, of which 4 were in males less than 30 years of age. While the local numbers are small, and within the upper end of the expected range for this age group, based on background incidence, the pattern of occurrence after Dose 2 of mRNA vaccines and in young men (between 18 and 30 years old) is consistent with what has been observed in the US and Israel so far. HSA will continue to monitor this potential safety issue closely.

- Rare instances of anaphylaxis, a severe life-threatening allergic reaction have been linked to the COVID-19 vaccines, a known adverse reaction associated with vaccines in general. The incidence rate of anaphylaxis locally is similar to those reported overseas. Cases of Bell's Palsy (facial muscle weakness which will generally recover completely even without treatment), an adverse event of special interest (AESI), have also been observed in some vaccine recipients. The incidence rate is within the background incidence.

[1] An adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product (including vaccines) but does not necessarily have a causal relationship with this treatment/vaccination

- It is important to note that heart attacks and strokes occur naturally within our population, regardless of whether people are vaccinated or not. The frequency of heart attacks and strokes in vaccinated persons locally is within the background incidence, and to date, there is no evidence that the vaccines can directly cause these events. No deaths from heart attacks, strokes or any other causes suspected to be associated with the vaccines have been reported locally.

- Overall, based on the data to date, the benefits of the Pfizer-BioNTech and Moderna COVID-19 vaccines continue to outweigh the known risks in a pandemic. HSA will continue to actively monitor the safety profile of the COVID-19 vaccines and relevant regulatory actions will be taken to safeguard public health when warranted.

Background

2 HSA has granted interim authorisation for two mRNA COVID-19 vaccines in Singapore under the Pandemic Special Access Route (PSAR) (Table 1).

Table 1. Authorisation and vaccination roll-out dates for COVID-19 vaccines in Singapore

Vaccine name	Authorisation date	Vaccination roll-out date
Pfizer-BioNTech COVID-19 Vaccine	14 December 2020	30 December 2020
Moderna COVID-19 Vaccine	3 February 2021	12 March 2021

3 As with all other vaccines, HSA actively monitors the safety of the COVID-19 vaccines to ensure that the benefits of the vaccines continue to outweigh the risks. This is achieved through AE monitoring systems to detect any potential safety concerns so that relevant measures can be taken to ensure that the vaccines remain safe for use. HSA reviews the submitted adverse event reports, in consultation with our expert panels[2].

How to interpret the data

4 AEs are reported by healthcare professionals to HSA when they suspect that the AE may be associated with the vaccine. This does not necessarily mean that the vaccine has caused the AE. In some instances, these AEs are related to an underlying or undiagnosed disease or the natural progression of an underlying disease. It may be coincidental that the event occurred around the same time when the vaccine was given but is not caused by the vaccine. The causality based on isolated cases of individual events usually cannot be established as many illnesses cause the same symptoms and signs, and there are generally no confirmatory tests for diagnosing an AE. Hence, AEs are assessed and interpreted in the context of baseline incidence rates of such occurrences (i.e., historical rates in our general population unexposed to the COVID-19 vaccines). While each individual report is carefully reviewed, the totality of data from all sources (e.g. mechanistic actions, clinical assessments, epidemiological studies and literature) has to be considered before drawing any evidence-based conclusions on the safety of the vaccine.

[2] HSA has appointed three Expert Panels to adjudicate neurological AEs, cardiac AEs and severe hypersensitivity reactions such as anaphylaxis.

5 The type and number of reports received for the different COVID-19 vaccines are not directly comparable as the vaccines may have been used in the vaccination programme for different lengths of time, and may have been administered to different numbers of people, with different underlying medical conditions and across different settings. Similarly, the AE numbers or rates between countries should not be directly compared as the usage of the vaccines may be different and the AE reporting systems are often also different.

6 The description of suspected AEs in this update reflects the available information known at the time by HSA. These data may undergo changes as more information on individual reports becomes available through follow-up, and as more data are reported and evaluated.

Overview of adverse event reports

7 In Singapore, the Pfizer-BioNTech COVID-19 vaccine was rolled out for use on 30 December 2020, followed by the Moderna COVID-19 vaccine on 12 March 2021. As the former had been deployed over a longer period and comprised 83% of the doses administered in our population, most of the AEs reported were associated with the Pfizer-BioNTech COVID-19 vaccine. As of 23 May 2021, HSA has received 4,704 suspected AE reports (0.13% of doses administered) associated with the use of Pfizer-BioNTech and Moderna COVID-19 vaccines (Table 2).

Table 2. Overview of vaccination data and no. of suspected AE reports received for COVID-19 vaccines (as of 23 May 2021)

	COVID-19 Vaccines (Pfizer-BioNTech and Moderna)
No. of persons who have received at least the first dose	**2,084,704**
No. of persons who received two doses*	**1,595,664**
Total no. of doses administered	**3,680,368**
No. of suspected AE reports	**4,704** (**0.13%** of doses administered)
No. of suspected serious[3] AE reports	**157** (**0.004%** of doses administered)

* The full vaccination regimen for Pfizer-BioNTech and Moderna COVID-19 vaccines comprises 2 doses. The no. of persons who received two doses includes those who had received the first dose.

8 About 68% of the AEs were reported in individuals less than 60 years old. It was noted that in the clinical trials of both vaccines, persons younger than 60 years of age tend to experience more reactogenic AEs than those aged 60 years and above. Generally, younger individuals have more active immune responses and may experience more AEs to the

[3] An adverse event is classified as serious when the event resulted in hospitalisation/extended stay in hospital, resulted in a significant reduction in functioning level/disability, resulted in a life-threatening illness (e.g. anaphylaxis) or death, resulted in birth defects or is a medically important event.

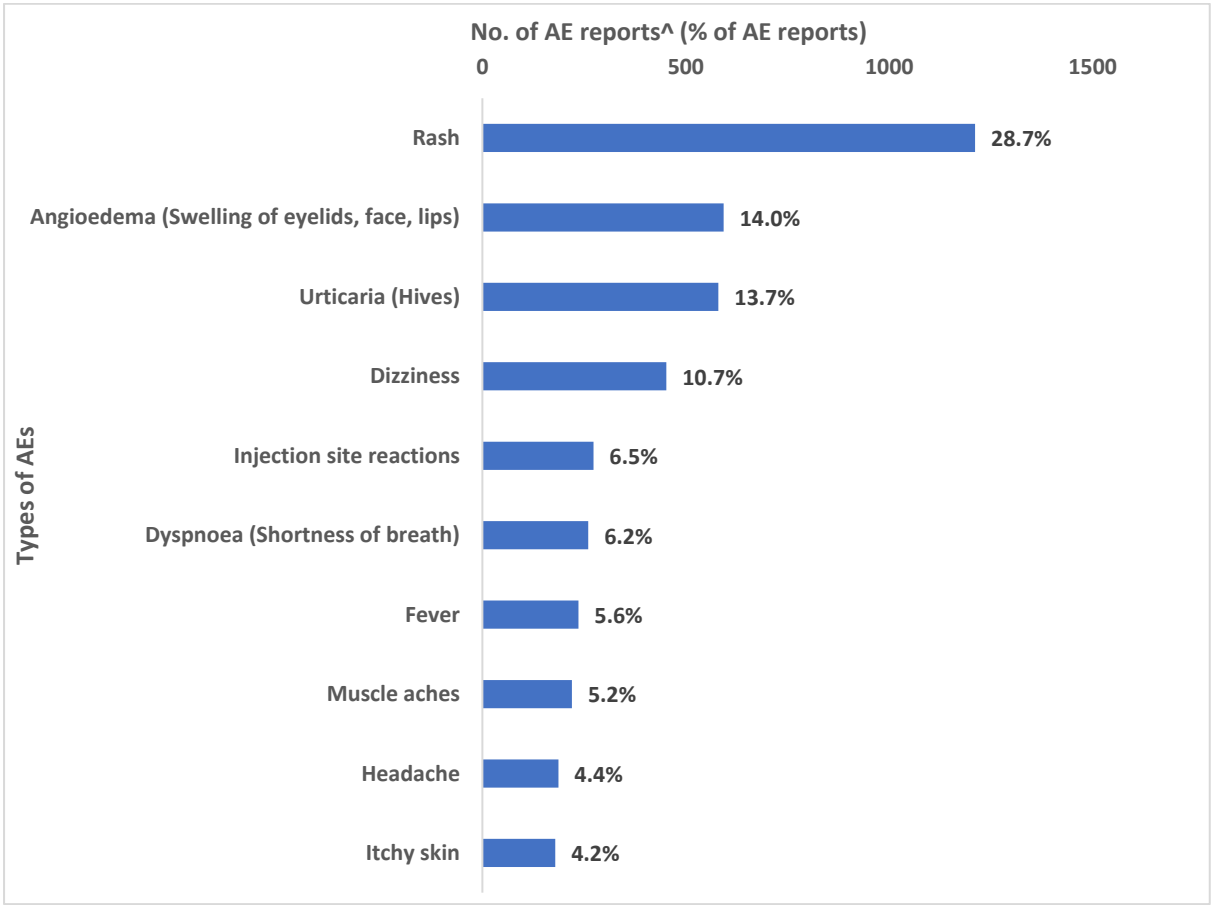
vaccines. This is part of the body's natural response to build immunity against COVID-19 infection. About 64% of the AEs were reported in females.

Commonly reported adverse events

9 The most commonly reported AEs (Figure 1) are consistent with those typically observed following vaccination. These include injection site reactions such as pain and swelling, dizziness, fever, muscle aches, headache, shortness of breath and allergic reactions (such as rash, itch, hives and swelling of eyelids, face and lips). These reported AEs generally resolved within a few days. These AEs are also in line with the events described in the COVID-19 vaccines product information and those reported overseas.

10 For the reports of injection site reactions, some of the cases presented as delayed reactions (also called "COVID arm"). These have been reported to occur as red, itchy, swollen or painful patch of rash at the injection site several days or up to a week or more after vaccination. This delayed reaction has also been observed in other countries, and it generally resolves on its own within a few days. Notwithstanding such injection site reactions, vaccine recipients may still go for their second vaccination dose.

Figure 1. Most commonly reported AEs associated with the use of Pfizer-BioNTech and Moderna vaccines (as of 23 May 2021)



^ *Each report may describe more than 1 adverse event*

Serious adverse events

11 Of the 4,704 suspected AE reports received, 157 of the reports were assessed as serious. Serious AEs comprised 0.004% of doses administered. Among the serious reports, the most frequently reported AEs were anaphylaxis and other severe allergic reactions. There were 26 reports of anaphylaxis and 23 reports of severe allergic reactions. Other serious AEs include breathing difficulty, fast heart rate, an increase or decrease in blood pressure, chest discomfort and pain, syncope (fainting), limb numbness, weakness or pain, changes in vision, increase in liver enzymes, joint pain, seizures (fits), tinnitus (ringing in the ears) and infections. These serious AEs are being closely monitored by HSA. Background disease incidence[4] or underlying medical conditions are taken into consideration when determining if the vaccine had any contributory role to these events. Most of the individuals who developed serious AEs were reported to have recovered or are recovering. No deaths suspected to be associated with the vaccines or any other causes have been reported locally.

12 A greater frequency of heart attacks and strokes has not been observed in vaccinated persons locally. It is important to note that heart attacks and strokes can occur naturally within our population, regardless of whether people are vaccinated or not. Due to the large numbers of people being vaccinated, it is expected that, by coincidence, some individuals may experience other medical events such as heart attacks and strokes in the days or weeks after vaccination which may not be related to the vaccination.

13 There have been cases of myocarditis and pericarditis (inflammation of the heart muscles and the outer lining of the heart, respectively) reported with the vaccines, both overseas and locally. Myocarditis and pericarditis have many different causes, and most are due to viral infections and immunological reactions. The typical symptoms are chest pain, shortness of breath, and fast heartbeat. In most cases, the inflammation is mild. The affected individuals generally respond well to treatment and recover. In general, the background incidence of myocarditis or pericarditis leading to hospitalisation is estimated to occur in about 5 to 7 in 100,000 persons per year in the local population, or about 280 to 400 cases a year.

14 Israel (which is using the Pfizer-BioNTech vaccine) has very recently announced that there may be a probable link between the second vaccine dose and the onset of myocarditis in young males aged 16 to 30 years in its population. The link was found to be stronger among the younger age group of 16 to 19 years old. To date, no other country has flagged out a similar causal link, although the US Centre for Disease Control and prevention (CDC) has reported that they have observed more cases of myocarditis and pericarditis in male patients between 16 and 24 years of age, especially after Dose 2 of mRNA vaccines. Nonetheless, they have stressed that investigations are ongoing, and they have not made any conclusion about a causal link. Globally, regulatory authorities, including Israel and the US, continue to recommend vaccination in the age group of 16 to 30 years to protect individuals from getting infected with COVID-19 and getting a poorer outcome from COVID-19 infection.

15 Locally, HSA has received 6 such reports as of 7 June 2021. Two cases occurred in adults (one male and one female) above 40 years of age and is within the baseline incidence rate. Four involved young males aged between 18 and 30 years. This is at the upper end of the expected range for this age group, based on background incidence rates. Most of the cases were reported to have occurred within a few days after receiving the second dose of the vaccine. All have recovered or have been discharged well from hospital.

[4] The incidence of new cases of disease in a population over a specified period of time in the absence of vaccination

16 While the local numbers are small, the pattern of occurrence after Dose 2 and in young men is consistent with what has been observed in the US and Israel, which are the 2 major users of the mRNA vaccines. Individuals who developed myocarditis and pericarditis responded well to treatment and recovered. Vaccination protects individuals and those around them from the risk of COVID-19 illness and its potential serious, life-threatening complications. Overall, the benefits of the Pfizer-BioNTech and Moderna COVID-19 vaccines continue to outweigh the known risks of COVID-19 disease and its severe complications in a pandemic. HSA has informed MOH and EC19V of our assessment. We will also continue to monitor this closely and take the relevant and necessary regulatory actions.

Adverse events of special interest[5]

17 An adverse event of special interest (AESI) is a pre-specified medically significant event that has been observed historically with other vaccines. Anaphylaxis and Bell's Palsy are examples of AESIs that have been reported historically with the use of other vaccines. Hence, HSA is closely monitoring the occurrence of such adverse events.

Anaphylaxis reports

18 Anaphylaxis is a rare and potentially life-threatening allergic reaction that can occur following vaccination in certain susceptible individuals. Safeguards have been put in-place to mitigate this risk. These include pre-vaccination screening, observing all vaccinated persons for 30 minutes after vaccination and ensuring that all the vaccination centres are medically equipped and staffed by qualified medical professionals at all times to provide medical treatment in the rare event that they are needed.

19 There were 26 cases of anaphylaxis reported with the Pfizer-BioNTech and Moderna COVID-19 vaccines. All the patients were reported to have recovered after medical treatment. The incidence rate of anaphylaxis reported locally with the vaccines is about 0.85 per 100,000 doses administered. This is similar to the incidence rates reported overseas of around 0.5 to 2 per 100,000 doses administered.

Bell's Palsy reports

20 Bell's Palsy, also known as peripheral facial nerve palsy, is caused by inflammation of the facial nerve. It is a condition that causes temporary weakness or paralysis of the facial muscles. It was reported in the clinical trials of the Pfizer-BioNTech and Moderna COVID-19 vaccines, but the numbers were assessed to be within background incidences. Most of the patients will generally have complete recovery even without treatment.

21 Forty-five cases of Bell's Palsy have been reported, with most of the reports being non-serious. The local incidence rate is estimated to be 3.35 per 100,000 persons per month, which is within the background incidence of 1.1 to 4.4 per 100,000 persons per month prior to the introduction of vaccination.

[5] Definition of AESI adapted from World Health Organization (WHO), Dec 2020. *COVID-19 Vaccines: Safety Surveillance Manual*[online] [24 Mar 2021 viewed]. Available from: https://www.who.int/publications/i/item/10665338400

Conclusion

22 Based on the local AE reports received, most of the AEs are largely expected with vaccination and reflect what has been reported in the clinical trials. Based on HSA's assessment, the benefits of the Pfizer-BioNTech and Moderna COVID-19 vaccines continue to outweigh the known risks in a pandemic.

23 HSA and MOH will continue to monitor the safety profile of the COVID-19 vaccines closely and update members of the public of any significant safety concerns detected with the vaccines.

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