HSA's Safety Update #3

Pfizer-BioNTech and Moderna COVID-19 Vaccines

(30 December 2020 – 30 June 2021)

Introduction

This is HSA's third safety update of the mRNA COVID-19 vaccines covering the period from the roll-out of the vaccines on 30 December 2020 to 30 June 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.

Summary (as of 30 June 2021)

- A total of 5,470,425 doses of the mRNA vaccines have been administered, out of which 6,606 suspected AE reports (0.12% of administered doses) were received. Of these, 252 reports (0.005% of administered doses) were classified as serious AEs.

- The most commonly reported AEs were consistent with those typically observed following vaccination. They include injection site reactions such as pain and swelling, 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). Among the serious AE reports, the most frequently reported AEs were anaphylaxis and other severe allergic reactions.

- In the age group of 12 to 18 years, the most commonly reported AEs include rash, hives, shortness of breath, dizziness, light-headedness and syncope. Syncope (fainting and temporary loss of consciousness) is not uncommon with vaccination, particularly in this age group, and it is generally triggered by anxiety and fear of pain during the vaccination process, rather than by the vaccines. The local incidence rate for syncope in this age group is similar to overseas reports.

- Rare instances of anaphylaxis, a severe life-threatening allergic reaction, have been linked to the COVID-19 vaccines. It is a known adverse reaction associated with vaccines in general. The incidence rate of anaphylaxis locally is similar to those reported overseas.

[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

- Rare cases of myocarditis and pericarditis have been reported with mRNA COVID-19 vaccines both overseas and locally. They are caused by inflammation of the heart muscles and outer lining of the heart, respectively. In most cases, the inflammation is mild. Myocarditis and pericarditis are not heart attacks, which are usually caused by blockage of the blood vessels that supply the heart. HSA received 12 reports of myocarditis and pericarditis after close to 5.5 million doses of vaccines were administered. Seven were reported in males aged below 30 years. While most of the cases reported previously occurred after Dose 2 of the vaccine, HSA has also received 6 cases that occurred after Dose 1. Although there is a small increased risk of myocarditis and pericarditis in the younger age groups, the local incidence rate remains low. All the cases in the younger age group responded well to treatment and had recovered or were discharged well from hospital.

- It is important to note that heart attacks and strokes occur naturally within our population, regardless of whether or not people are vaccinated. The frequency of heart attacks and strokes in vaccinated persons locally is within the background incidence rates, 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.

- Cases of Bell's Palsy (facial muscle weakness which will generally recover completely even without treatment) have also been observed in some vaccine recipients. The incidence rate is within the background incidence.

- 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

*HSA extended the use of the Pfizer-BioNTech COVID-19 Vaccine to adolescents aged 12-15 years on 18 May 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

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

4 AEs are reported by healthcare professionals to HSA when they suspect that the AEs may be associated with the vaccine. This does not necessarily mean that the vaccine has caused the AEs. 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.

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 79% of the doses administered in our population, most of the AEs reported were associated with the Pfizer-BioNTech COVID-19 vaccine. As of 30 June 2021, HSA has received 6,606 suspected AE reports (0.12% 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 30 June 2021)

	COVID-19 Vaccines (Pfizer-BioNTech and Moderna)
No. of persons who have received at least Dose 1	**3,365,594**
No. of persons who received two doses*	**2,104,831**
Total no. of doses administered	**5,470,425**
No. of suspected AE reports	**6,606** (**0.12%** of doses administered)
No. of suspected serious[3] AE reports	**252** (**0.005%** 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.

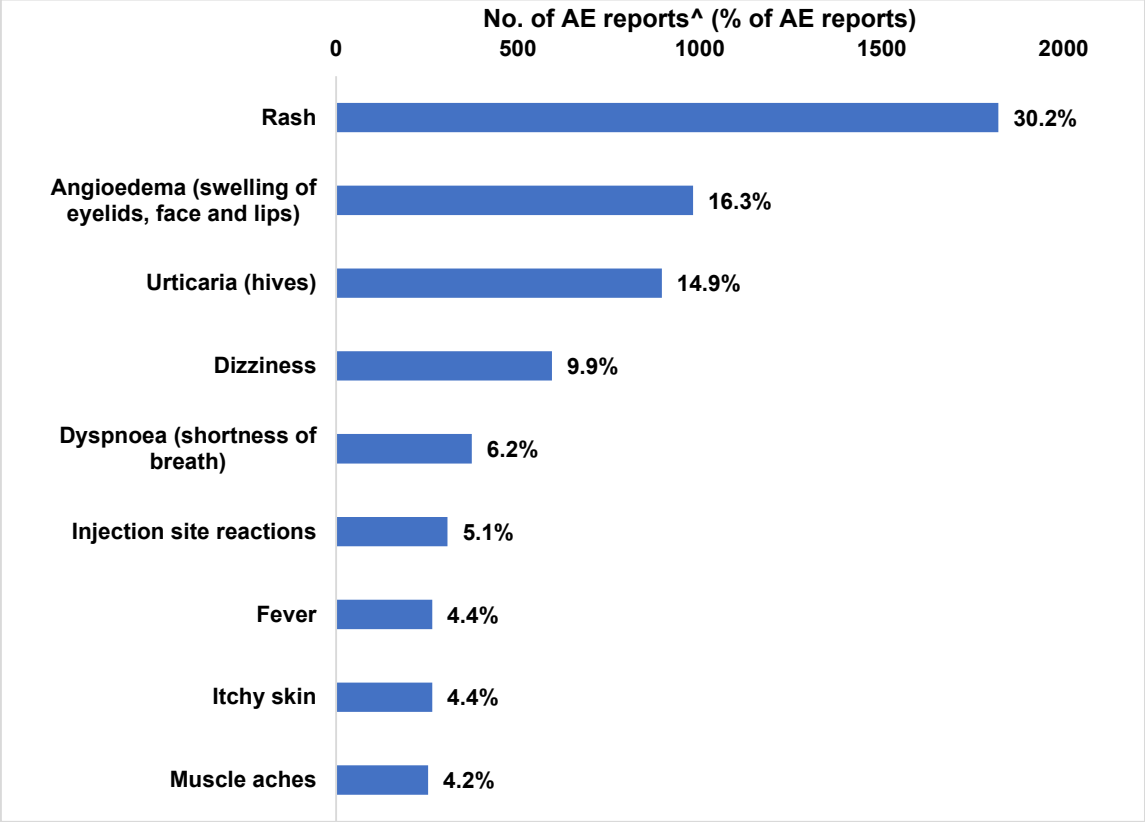
[3] An adverse event is classified as serious when the event resulted in hospitalisation/extended stay in hospital, resulted in a significant reduction in functioning level/disability, resulted in a life-threatening illness (e.g. anaphylaxis) or death, resulted in birth defects or is a medically important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

8 About 73% 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 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, 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 those reported overseas.

Figure 1. Most commonly reported AEs associated with the use of Pfizer-BioNTech and Moderna vaccines (as of 30 June 2021)



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

10 Since the roll out of the vaccination programme in students aged 12 years and above on 3 June 2021, HSA has received 129 AE reports associated with the use of Pfizer-BioNTech vaccine (0.06% of doses administered) in adolescents aged 12 to 18 years old. The commonly reported AEs include rash, hives, shortness of breath, dizziness, light headedness and syncope (fainting and temporary loss of consciousness). These reported AEs generally resolved within a few days, and they are also in line with the events reported overseas.

11 Syncope (fainting and temporary loss of consciousness) occurring after vaccination is not uncommon in adolescents and has been reported with the Pfizer-BioNTech COVID-19 vaccine both overseas and locally. It is generally triggered by the vaccination process, such

as anxiety about the injection and fear of pain, and not by the vaccines. Some of the symptoms include light headedness, weakness, nausea, dimming of vision, ringing in the ears and sweating. Syncope can occur very suddenly, and the individual may appear pale-faced, feel faint, have rapid or irregular heart rate and muscle twitching or jerky movements. Patients will generally recover quickly if they lie down, and symptoms typically resolve after 5 minutes.

12 Locally, 17 reports of syncope among adolescents aged 12 to 18 years old have been reported to HSA, and most of the individuals recovered well after about five minutes. The local rate of syncope in this age group is about 7.4 per 100,000 doses, which is similar to the rate from overseas reports. Safeguards have been implemented to mitigate this risk. Those who are anxious or have needle phobia can be vaccinated while lying down. Those who develop symptoms are advised to either place their head between their knees if they are sitting down or lie down and elevate their feet. These measures would help prevent them from falling down and injuring themselves. Vaccine recipients are also advised to drink, eat and rest well before coming for their vaccination.

Serious adverse events

13 Of the 6,606 suspected AE reports received, 252 of the reports were assessed as serious. Serious AEs comprised 0.005% of doses administered. The most frequently reported serious AEs were anaphylaxis (42 reports) and other severe allergic reactions (32 reports). Other serious AEs include exacerbation of underlying asthma condition, breathing difficulty, fast heart rate, an increase or decrease in blood pressure, chest discomfort and pain, pericarditis or myocarditis (inflammation of the heart muscles and the outer lining of the heart, respectively), syncope, 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.

Adverse events of special interest[5]

14 An adverse event of special interest (AESI) is a pre-specified medically significant event that has been observed historically with other vaccines, of which some examples include anaphylaxis, Bell's Palsy, myocarditis and pericarditis. Hence, HSA is closely monitoring the occurrence of such adverse events.

Anaphylaxis reports

15 Anaphylaxis is a rare and potentially life-threatening allergic reaction that can occur following vaccination in certain susceptible individuals. Safeguards have been implemented to mitigate this risk. Measures include pre-vaccination screening, observing all vaccinated persons for 30 minutes after vaccination and ensuring that all 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.

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

16 There were 42 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 0.81 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.

17 MOH and the Expert Committee on COVID-19 Vaccination (EC19V) had on 5 June 2021 recommended that individuals with anaphylaxis or allergic reactions to other drugs, food, insect stings, or unknown trigger (idiopathic) can be vaccinated with the mRNA vaccines after careful study of the data globally and locally. From 6 June 2021 to 25 June 2021, HSA had received 8 cases of anaphylaxis and the incidence rate is 0.89 per 100,000 doses administered for these 8 cases. Hence, the overall anaphylaxis incidence rate is similar to the rate of 0.85 per 100,000 doses administered reported in HSA's second safety report published on 11 June 2021. About 32,000 individuals were previously not able to take the mRNA vaccines due to severe allergies. As of 25 June 2021, about 13,000 individuals in this group were vaccinated and four of them developed anaphylaxis within 30 minutes of the post-vaccination observation period. These individuals could have some increased risk of anaphylaxis as they are generally more reactive to potential allergens. All four have since recovered as they were attended to promptly at the vaccination centres.

Myocarditis and pericarditis reports

18 There have been rare cases of myocarditis and pericarditis (inflammation of the heart muscles and outer lining of the heart, respectively) reported with the vaccines, both overseas and locally. While myocarditis and pericarditis have many different causes, 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. Myocarditis and pericarditis are separate and distinct from heart attacks. Heart attacks are generally caused by blockage of the blood vessels supplying the heart. In myocarditis and pericarditis, the blood vessels usually appear normal.[6,7] The individuals who develop myocarditis or pericarditis generally respond well to treatment and recover. Locally, the background incidence of myocarditis or pericarditis leading to hospitalisation is estimated to be about 5 to 7 in 100,000 persons per year, or about 280 to 400 cases a year.

19 Locally, HSA has received 12 reports of myocarditis and pericarditis as of 30 June 2021, after close to 5.5 million doses of vaccines were administered. Five of the cases occurred in adults aged 30 years old and above (3 males and 2 females) and is within the baseline incidence rate. Seven of the cases involved males aged below 30 years old and this exceeds the expected numbers for this age group, based on background incidence rates. While most of the cases reported previously occurred after Dose 2 of the vaccine, HSA had also received reports of 6 cases that occurred after Dose 1. Most of the cases were reported to have occurred within a week after receiving the vaccine. Although there is a small increased risk of myocarditis and pericarditis, the local incidence rate remains low. The overall local incidence rate is 0.22 per 100,000 doses administered, and the incidence rate in males below 30 years old is 1.24 per 100,000 doses administered. All the cases in the younger age group below 30 years old responded well to treatment and had recovered or were discharged well from the hospital.

[6] Yilmaz A, Mahrholdt H, Athanasiadis A, et al. Coronary vasospasm as the underlying cause for chest pain in patients with PVB19 myocarditis. Heart 2008; 94:1456-63

[7] Lim Y, Singh D, Loh PH, Poh KK. Multivessel coronary artery spasm in pericarditis. Singapore Med J. 2018;59(11):611-613. doi:10.11622/smedj.2018138

20 The small increased risk in myocarditis and pericarditis in young males is consistent with what has been observed in the US and Israel, which are the two major users of the mRNA vaccines. Both countries are continuing with the vaccination of their adolescent group (12 years and above) to protect the individuals from getting infected with COVID-19 and suffering poorer outcomes when infected. On 11 June 2021, EC19V released an advisory for vaccine recipients to avoid strenuous physical activity for one week following the second dose of the vaccine and to seek medical attention if they develop symptoms of myocarditis and pericarditis. MOH also advised doctors to be vigilant in detecting myocarditis and pericarditis in vaccinated persons and to clinically manage them accordingly. 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 latest assessment, which includes the small increased risk of myocarditis and pericarditis occurring after the first dose of the vaccine. HSA is also working with the companies of the mRNA vaccines to include the information on myocarditis and pericarditis in the local product information of the vaccines. We will continue to monitor this risk closely and take regulatory actions as necessary.

Heart Attacks and Strokes

21 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.

Bell's Palsy reports

22 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.

23 Sixty-two cases of Bell's Palsy have been reported, with most of the reports being non-serious. The local incidence rate is estimated to be 2.3 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.

Conclusion

24 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. HSA's current assessment is that the benefits of the Pfizer-BioNTech and Moderna COVID-19 vaccines continue to outweigh the known risks in a pandemic.

25 HSA and MOH will continue to monitor the safety profile of the COVID-19 vaccines closely, especially anaphylaxis, myocarditis and pericarditis risks, take the necessary regulatory actions, and update members of the public of any significant safety concerns detected with the vaccines.