HSA's Safety Update #5

COVID-19 Vaccines

(30 December 2020 – 31 August 2021)

Introduction

This is HSA's 5th safety update of the COVID-19 vaccines covering the period from the roll-out of the vaccines on 30 December 2020 to 31 August 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 31 August 2021)

- A total of 8,716,085 doses of the Pfizer-BioNTech and Moderna mRNA vaccines have been administered, out of which 11,737 suspected AE reports (0.13% of administered doses) were received. Of these, 498 reports (0.006% of administered doses) were classified as serious AEs.

- The most commonly reported AEs were consistent with those typically observed following vaccination. They include dizziness, shortness of breath, chest tightness/discomfort, palpitations, injection site reactions such as pain and swelling, fever and allergic reactions (such as rash, itch, hives and swelling of eyelids, face and lips). These typically resolve within a few days. 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, angioedema (swelling of the eyelids, face and lips), chest tightness/discomfort, shortness of breath, fever, dizziness and light-headedness. Syncope (fainting and temporary loss of consciousness) has also been reported, 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. Myocarditis and pericarditis are not heart attacks, which are usually caused by blockage of the blood vessels that supply the heart. Review of the local reports showed an increased risk of myocarditis and pericarditis, particularly after Dose 2 of the vaccines. The risk is observed to be higher in young males aged 30 years and below. Most of the cases have responded well to treatment and have recovered or were discharged well from hospital. To mitigate the risk of myocarditis/pericarditis, the period of abstinence from strenuous exercise or physical activity after vaccination is extended to two weeks instead of one week.

- It is important to note that heart attacks and strokes occur naturally within our population, regardless of whether 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.

- Cases of Bell's Palsy (facial muscle weakness caused by inflammation of the facial nerve) have also been observed in some vaccine recipients. Generally, patients will recover completely even without treatment. The incidence rate is within the background incidence.

- Ninety AEs including five serious ones have been received for the Sinovac-CoronaVac COVID-19 vaccine following its placement under the Special Access Route on 2 June 2021.

- 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.

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].

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

How to interpret the data

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 background 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.

Pfizer-BioNTech and Moderna COVID-19 Vaccines

7 As of 31 August 2021, HSA has received 11,737 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 reported by healthcare professionals for COVID-19 vaccines (as of 31 August 2021)

	COVID-19 Vaccines (Pfizer-BioNTech and Moderna)
No. of persons who have received at least Dose 1	**4,515,469**
No. of persons who received two doses*	**4,200,616**
Total no. of doses administered	**8,716.085**
No. of suspected AE reports	**11,737** (**0.13%** of doses administered)
No. of suspected serious[3] AE reports	**498** (**0.006%** 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.

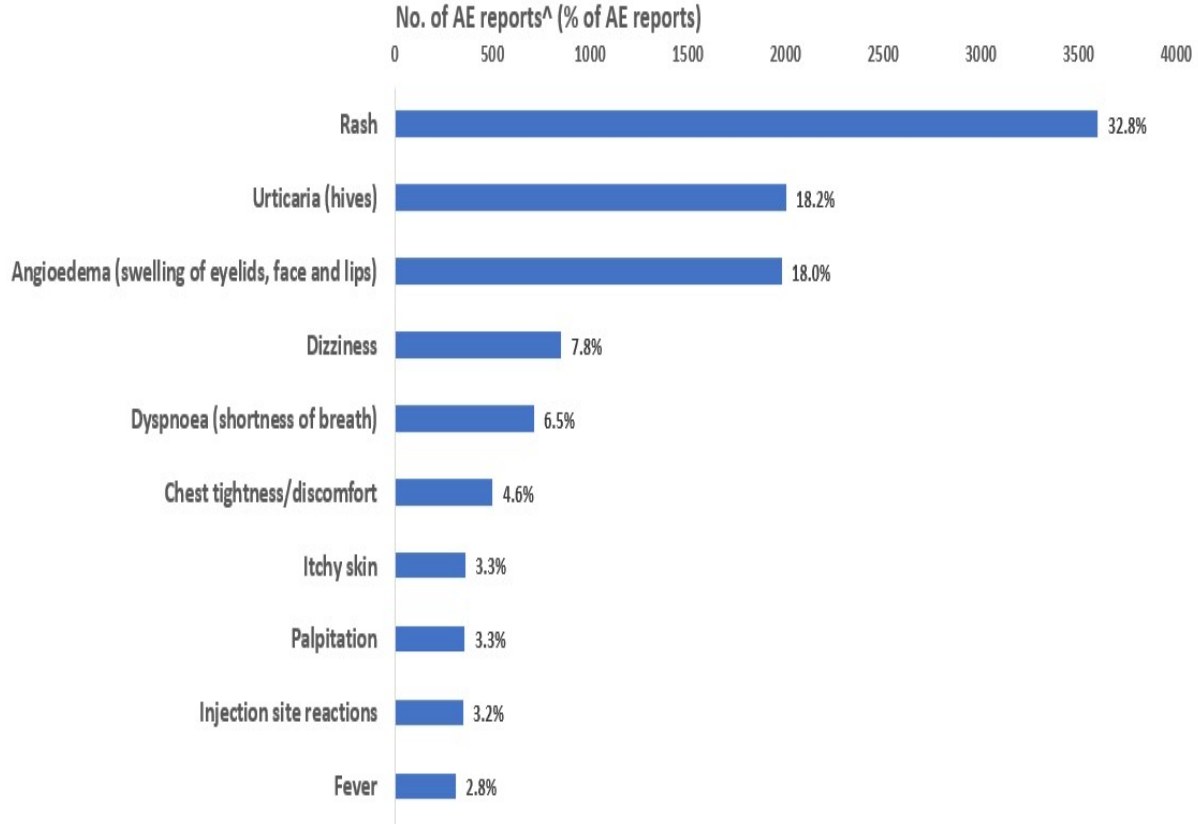
[3] An adverse event is classified as serious when the event resulted in hospitalisation/extended stay in hospital, resulted in a significant reduction in functioning level/disability, resulted in a life-threatening illness (e.g. anaphylaxis) or death, resulted in birth defects or is a medically important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

8 About 80% 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 67% 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 dizziness, shortness of breath, chest tightness/discomfort, palpitations, injection site reactions such as pain and swelling, fever 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 COVID-19 vaccines (as of 31 August 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 491 AE reports (0.08% of doses administered) associated with the use of Pfizer-BioNTech or Moderna vaccine in adolescents aged 12 to 18 years old. The commonly reported AEs include rash, hives, angioedema (swelling of the eyelids, face and lips), shortness of breath, chest tightness/discomfort, fever, 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 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. Patients will generally recover quickly if they lie down, and symptoms typically resolve after 5 minutes. Locally, 26 reports of syncope among adolescents aged 12 to 18 years old have been reported to HSA. The local rate of syncope in this age group is about 4.5 per 100,000 doses, which is similar to the rate from overseas reports. Safeguards have been implemented to mitigate this risk, which include vaccinating those who are anxious or with needle phobia while lying down, and vaccine recipients are also advised to drink, eat and rest well before coming for their vaccination.

Serious adverse events

12 Of the 11,737 suspected AE reports received, 498 of the reports were assessed as serious. Serious AEs comprised 0.006% of doses administered. The most frequently reported serious AEs were anaphylaxis (72 reports) and other severe allergic reactions (49 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, seizures (fits), muscle injury and joint pain, blood clots, low platelets, tinnitus (ringing in the ears), changes in vision, increase in liver enzymes, thyroid gland dysfunction, abnormal renal function, menstrual disorder, severe skin reactions 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.

Adverse events of special interest[5]

13 An adverse event of special interest (AESI) is a 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 to detect any increase over baseline incidences.

Anaphylaxis reports

14 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, which 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.

15 There were 72 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 0.87 per 100,000 doses administered, which is similar to the incidence rates reported overseas.

[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

Myocarditis and pericarditis reports

16 An increased risk of myocarditis and pericarditis (inflammation of the heart muscles and outer lining of the heart, respectively) associated with the mRNA vaccines have been observed 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] Majority of the individuals who develop myocarditis or pericarditis 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.

17 HSA has received 65 local reports of myocarditis and pericarditis following more than 8.5 million doses of mRNA vaccines administered in Singapore. Forty cases (62%) occurred in those below 30 years of age, out of which 36 (90%) occurred in males. Forty-three (66%) cases were reported after Dose 2 of the mRNA vaccines. While most of the cases were reported to occur within a week after receiving the vaccine, 12 (18%) of these had occurred more than a week after vaccination. Majority of the cases responded well to treatment and have recovered or discharged well from the hospital. Our review of the local reports showed an increased risk of myocarditis and pericarditis, particularly after Dose 2 of the vaccines (incidence rate of 1.06 per 100,000 doses administered). The risk is observed to be higher in younger males aged 30 years and below (incidence rate of 4.84 per 100,000 doses administered after Dose 2). These are within the incidence rates of myocarditis reported overseas. HSA will continue to monitor this risk closely and take regulatory actions as necessary.

18 Following HSA's above review, the Expert Committee on COVID-19 Vaccination (EC19V) has updated its advisory on 16 September 2021, that vaccine recipients, in particular adolescents and those of younger age, should avoid strenuous exercise or physical activity for two weeks following any dose of the mRNA vaccine and to seek medical attention if they develop symptoms of myocarditis and pericarditis. MOH has also advised doctors to be vigilant in detecting myocarditis and pericarditis in vaccinated persons and to clinically manage them accordingly.

Heart attacks and strokes

19 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. 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.

Cerebral venous thrombosis reports

20 There have been rare cases of cerebral venous thrombosis (CVT) reported with the Pfizer-BioNTech and Moderna COVID-19 vaccines, both overseas and locally. CVT is a very rare type of blood clot occurring in the veins of the brain, which can happen naturally

[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

regardless of whether people have been vaccinated. Some of the possible risk factors of CVT include a medical history of blood clotting disorder, head trauma and the use of medicines such as oral contraceptives and hormonal replacement therapies.[8] Patients with CVT are generally treated with anticoagulants (blood thinning medicines) for a few months. The yearly background incidence of CVT in the general population is 1.3 to 2 per 100,000 persons. CVT has also been reported to be associated with COVID-19 infection at an incidence of 8.4 per 100,000 infections in a local study.[9]

21 HSA has received 10 suspected reports of CVT with the Pfizer-BioNTech and Moderna COVID-19 vaccines. None of the cases had a fatal outcome. The number of cases of CVT reported is small and with observed fluctuations in the yearly background incidence rates locally, it cannot be determined if there is an increased incidence of CVT associated with the use of the mRNA vaccines. HSA is monitoring this event closely and reviewing the reported cases with our expert panels. So far, no overseas regulators have identified CVT as a safety signal with mRNA vaccines. It is important to note that the CVT cases reported locally are not associated with thrombocytopenia (low platelet levels) and are different in clinical presentation from the overseas cases of CVT with thrombocytopenia that has been reported with the AstraZeneca and Janssen (Johnson & Johnson) COVID-19 vaccines. We will continue to monitor this event closely and update if there are significant findings.

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 Ninety-six cases of Bell's Palsy have been reported, with most of the reports being non-serious. The local incidence rate is estimated to be 2.4 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.

Sinovac-CoronaVac COVID-19 vaccine

24 Sinovac-CoronaVac COVID-19 vaccine was placed on HSA's Special Access Route[10] (SAR) on 2 June 2021 and vaccinations started at designated Public Health Preparedness Clinics (PHPCs) on 18 June 2021. As of 31 August 2021, HSA has received a total of 90 AE reports, including five serious reports, following the administration of 168,439 doses of Sinovac-CoronaVac vaccine. The serious AEs included one report each of Bell's Palsy, serious allergic reaction and vertigo with ringing of the ears and two reports of anaphylaxis. Overall, the AEs were consistent with those typically observed following vaccination. HSA will continue to monitor the AEs with Sinovac-CoronaVac vaccine.

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[8] Saposnik, Gustavo et al. "Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association." Stroke vol. 42,4 (2011): 1158-92. doi:10.1161/STR.0b013e31820a8364

[9] Koh JS, De Silva DA, Quek AML, et al. Neurology of COVID-19 in Singapore. *J Neurol Sci*. Nov 15, 2020; 418:117118. doi: 10.1016/j.jns.2020.117118.

[10] https://www.hsa.gov.sg/therapeutic-products/register/special-access-routes/SAR-covid19

Conclusion

25 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.

26 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.

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