HSA's Safety Update #7

COVID-19 Vaccines

(30 December 2020 – 31 October 2021)

Introduction

This is HSA's 7th safety update of the COVID-19 vaccines covering the period from the roll-out of the vaccines on 30 December 2020 to 31 October 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 October 2021)

- A total of 9,953,673 doses of the Pfizer-BioNTech/Comirnaty and Moderna/Spikevax mRNA vaccines have been administered, out of which 13,334 suspected AE reports (0.13% of administered doses) were received. Of these, 634 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 allergic reactions (such as rash, itch, hives and swelling of eyelids, face and lips), dizziness, shortness of breath, chest tightness/discomfort, palpitations, injection site reactions such as pain and swelling and fever. 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), shortness of breath, palpitation, chest tightness/discomfort, fever, dizziness, light headedness and syncope (fainting and temporary loss of consciousness)

- The AEs reported in individuals who had been administered booster doses of the mRNA vaccines were similar to the profile of AEs associated with Dose 1 and Dose 2 of the vaccines and there was no observed increase in frequency of events. These include rash, angioedema (swelling of eyelids, face and lips), chest discomfort, palpitation, shortness of breath, fever, generalised weakness and dizziness.

- 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.

- 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. The risk of myocarditis and pericarditis is observed to be highest in young males aged 30 years and below who received the vaccine. Most of the cases have responded well to treatment and have recovered or were discharged well from hospital.

[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.

- 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 of the event is within the background incidence.

- One hundred and seventy-one suspected AEs (0.08% of doses administered) including fourteen serious ones (0.007% of doses administered) were reported following the administration of 206,722 doses of Sinovac-CoronaVac COVID-19 vaccine.

- Seventeen suspected AEs (0.03% of doses administered) including one serious AE (0.002% of doses administered) were reported with Sinopharm COVID-19 vaccine after 48,697 doses were administered.

- It should be noted that the type and number of reports received for different COVID-19 vaccines are not directly comparable as the vaccines have been used in the vaccination programme for different durations of time. The inactivated COVID-19 vaccines have been administered only to a very small proportion (< 3%) of the population compared to the much larger scale of deployment for the mRNA vaccines.

- Overall, based on the data to date, the benefits of the Pfizer-BioNTech/Comirnaty, Moderna/Spikevax and Sinovac-CoronaVac COVID-19 vaccines approved under the Pandemic Special Access Route continue to outweigh the known risks in a pandemic. HSA will continue to closely 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 and an inactivated COVID-19 vaccine in Singapore under the Pandemic Special Access Route (PSAR) (Table 1).

Table 1. Authorisation of COVID-19 vaccines in Singapore

Vaccines	Authorisation date	Vaccination roll-out date
Pfizer-BioNTech /Comirnaty^ COVID-19 Vaccine*	**14 December 2020**	**30 December 2020**
Moderna/Spikevax^ COVID-19 Vaccine	**3 February 2021**	**12 March 2021**
Sinovac-CoronaVac COVID-19 vaccine	**23 October 2021**	**18 June 2021⁺**

*HSA extended the use of the Pfizer-BioNTech/Comirnaty vaccine to adolescent aged 12-15 years on 18 May 2021
^HSA approved the new brand names Comirnaty and Spikevax for Pfizer-BioNTech and Moderna vaccines respectively on 14 September 2021
⁺Sinovac-Coronovac vaccine was first made available for use in Singapore under the Special Access Route (SAR)[2]

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[3].

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

[2] https://www.hsa.gov.sg/therapeutic-products/register/special-access-routes/SAR-covid19
[3] HSA has appointed four Expert Panels to adjudicate neurological AEs, cardiac AEs, thromboembolic and haematological AEs and severe hypersensitivity reactions such as anaphylaxis.

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. In the case of the inactivated COVID-19 vaccines (Sinovac-CoronaVac and Sinopharm) which were first made available for use (via the SAR) at a later date, these were administered only to a very small proportion (< 3%) of the population compared to the much larger scale of deployment for the mRNA vaccines (Pfizer-BioNTech/Comirnaty and Moderna/Spikevax). 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/Comirnaty and Moderna/Spikevax COVID-19 Vaccines

7 As of 31 October 2021, HSA has received 13,334 suspected AE reports (0.13% of doses administered) associated with the use of Pfizer-BioNTech/Comirnaty and Moderna/Spikevax COVID-19 vaccines (Table 2).

Table 2. Overview of vaccination data and no. of suspected AE reports reported by healthcare professionals for mRNA COVID-19 vaccines (as of 31 October 2021)

	mRNA COVID-19 vaccines (Pfizer-BioNTech/Comirnaty and Moderna/Spikevax)
No. of persons who have received at least Dose 1	**4,640,306**
No. of persons who received two doses*	**4,459,099**
No. of persons who received booster doses	**854,268**
Total no. of doses administered	**9,953,673**
No. of suspected AE reports	**13,334** (**0.13%** of doses administered)
No. of suspected serious[4] AE reports	**634** (**0.006%** of doses administered)

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

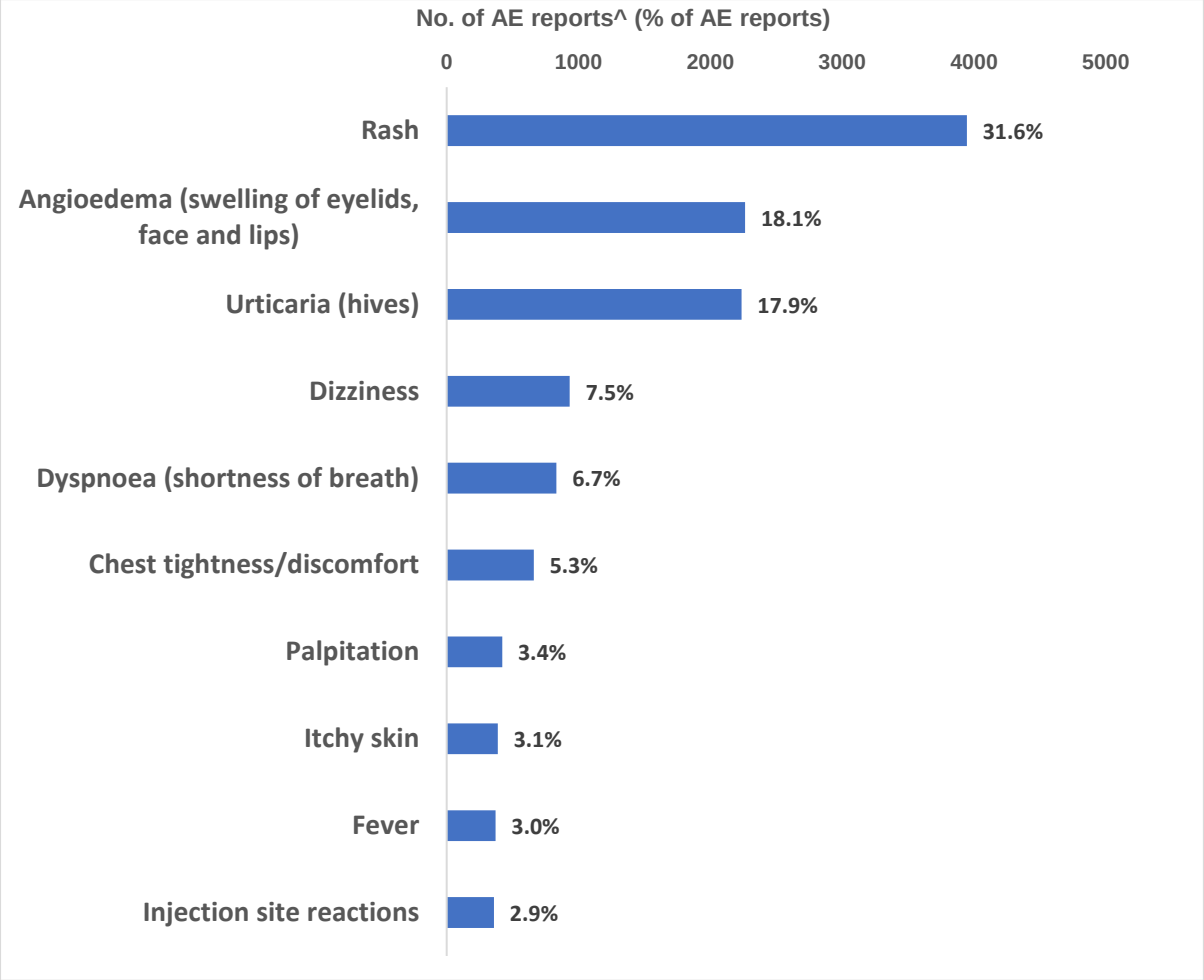
[4] An adverse event is classified as serious when the event resulted in hospitalisation/extended stay in hospital, resulted in a significant reduction in functioning level/disability, resulted in a life-threatening illness (e.g. anaphylaxis) or death, resulted in birth defects or is a medically important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

8 About 78% of the AEs were reported in individuals less than 60 years old. This is in line with the observation in the clinical trials of both vaccines whereby 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 66% 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 allergic reactions (such as rash, itch, hives and swelling of eyelids, face and lips), dizziness, shortness of breath, chest tightness/discomfort, palpitations, injection site reactions such as pain and swelling and fever. 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/Comirnaty and Moderna/Spikevax COVID-19 vaccines (as of 31 October 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 798 AE reports (0.13% of doses administered) associated with the use of Pfizer-BioNTech/Comirnaty or Moderna/Spikevax vaccine in adolescents aged 12-18 years old. The commonly reported AEs include rash, hives, angioedema (swelling of the eyelids, face and lips), shortness of breath, palpitation, 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.

Serious adverse events

11 Of the 13,334 suspected AE reports received, 634 of the reports were assessed as serious. Serious AEs comprised 0.006% of doses administered. The most frequently reported serious AEs were anaphylaxis (86 reports) and other severe allergic reactions (52 reports). Other serious AEs include exacerbation of underlying asthma or autoimmune 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), inflammation of the nerves or blood vessels, muscle injury, joint pain, blood clots, low platelets, tinnitus (ringing in the ears), hearing loss, changes in vision, immune disorders, neurological disorders, 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[5] 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 with booster doses

12 The national COVID-19 booster vaccination programme was rolled out on 15 September 2021 and 854,268 individuals have received the booster doses as at 31 October 2021. HSA has received 200 AE reports (0.02% of doses administered) associated with the use of Pfizer-BioNTech/Comirnaty or Moderna/Spikevax vaccine as booster dose.

13 The commonly reported AEs include rash, angioedema (swelling of the eyelids, face and lips), chest discomfort, palpitation, shortness of breath, fever, generalised weakness and dizziness. There were 10 SAE reports (0.001% of administered doses) describing myocarditis, seizures, blood clots, drop in platelet count, fluid overload and angioedema. Overall, the AE reports with the booster doses described similar AEs associated with Dose 1 and Dose 2 of the mRNA vaccines and there was no observed increase in frequency. As the booster dose programme was recently rolled out, HSA continues to closely monitor the adverse events and will inform the public on any significant events that are observed as well as take relevant regulatory actions as required.

Adverse events of special interest[6]

14 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

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, 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.

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

[6] 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 86 cases of anaphylaxis reported with the Pfizer-BioNTech/Comirnaty and Moderna/Spikevax 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 0.94 per 100,000 doses administered, which is similar to the incidence rates reported overseas.

Myocarditis and pericarditis reports

17 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.[7,8] 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.

18 In our earlier reports, HSA has highlighted a small increased risk of myocarditis and pericarditis following the vaccination of young people in Singapore. HSA has received 86 AE reports of myocarditis and pericarditis following more than 9.9 million doses of mRNA vaccines administered in Singapore. The risk is observed to be highest in younger males aged 30 years and below (incidence rate of 3.69 per 100,000 doses administered) compared to females from the same age group (incidence rate of 0.47 per 100,000 doses administered). Of the 49 cases which occurred in individuals aged 30 years and below, 44 (90%) had occurred in males. It is observed that the risk in females was highest in those aged 20 to 49 years old with an incidence rate of 0.63 per 100,000 doses. All the patients were reported to have recovered or are recovering.

19 The risk of myocarditis and pericarditis is also observed to be higher with Dose 2 of the vaccine, comprising 64% of the reported cases. The incidence rates of myocarditis and pericarditis following Dose 2 of the vaccine are 5.8 per 100,000 doses administered in those aged 12-19 years old, 2.0 per 100,000 doses administered in those aged 20-29 years old, and 0.61 per 100,000 doses administered in those aged 30 years and above.

20 Locally, a higher incidence of myocarditis has been reported with Moderna/Spikevax COVID-19 vaccine (1.29 per 100,000 doses administered) compared to Pfizer-BioNTech/Comirnaty COVID-19 vaccine (0.62 per 100,000 doses administered) in individuals aged 18 years and above who have taken Dose 1 or Dose 2 of the vaccines. However, as the number of reports received locally is small given our small population, currently it cannot be confirmed if there is an increased risk associated with the Moderna/Spikevax COVID-19 vaccine compared to the Pfizer-BioNTech/Comirnaty COVID-19 vaccine. While some countries such as Canada, Sweden, Norway and Finland have reported an increased risk associated with the Moderna/Spikevax COVID-19 vaccine, this observation is not consistently reported globally. HSA will closely monitor the development on this front and keep the public updated on any significant findings.

[7] 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

[8] 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

Heart attacks and strokes

21 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. We will continue to monitor these events closely and update the public if there are significant findings.

Cerebral venous thrombosis reports

22 There have been rare cases of cerebral venous thrombosis (CVT) reported with the Pfizer-BioNTech/Comirnaty and Moderna/Spikevax COVID-19 vaccines, both overseas and locally. CVT is a very rare type of blood clot occurring in the veins of the brain. The yearly background incidence of CVT in the general population is 1.3 to 2.0 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]

23 HSA has received 13 suspected reports of CVT with the Pfizer-BioNTech/Comirnaty and Moderna/Spikevax 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. So far, no overseas regulators have identified CVT as a safety signal with mRNA vaccines.

Bell's Palsy reports

24 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. Most of the patients will generally have complete recovery even without treatment. To date, 109 cases of Bell's Palsy have been reported, with most of the reports being non-serious. The local incidence rate is within the background incidence and data to date does not suggest an increased risk following vaccination.

[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.

Sinovac-CoronaVac Vaccine

25 As of 31 October 2021, HSA has received 171 AE reports (0.08% of administered doses) following the administration of 206,722 doses of Sinovac-CoronaVac COVID-19 vaccine (Table 3). The commonly reported AEs were rash, angioedema, shortness of breath, chest discomfort and dizziness. There were 14 SAEs (0.007% of administered doses), describing Bell's Palsy, blood clots, numbness, muscle spasm, vertigo with tinnitus (ringing of the ears) and serious allergic reactions including anaphylaxis.

Table 3. Overview of vaccination data and no. of suspected AE reports reported by healthcare professionals for Sinovac-CoronaVac Vaccine (as of 31 October 2021)

	Sinovac-CoronaVac COVID-19 Vaccine
No. of persons who have received at least Dose 1	**101,476**
No. of persons who received two doses	**105,246**
Total no. of doses administered	**206,722**
No. of suspected AE reports	**171** (**0.08%** of doses administered)
No. of suspected serious AE reports	**14** (**0.007%** of doses administered)

Other COVID-19 Vaccine on HSA's Special Access Route (SAR)

Sinopharm COVID-19 Vaccine

26 Vaccination for Sinopharm COVID-19 vaccine was rolled out on 30 August 2021. As of 31 October 2021, HSA has received 17 suspected AE reports (0.03% of doses administered) following the administration of 48,697 doses of Sinopharm COVID-19 vaccine. The non-serious AEs include rash, angioedema, shortness of breath, chest discomfort and tinnitus. There was one serious AE report of low platelet count (0.002% of doses administered).

27 Overall, the AEs were consistent with those typically observed following vaccination. HSA will continue to monitor the AEs with Sinopharm COVID-19 vaccine.

Conclusion

28 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/Comirnaty, Moderna/Spikevax and Sinovac-CoronaVac COVID-19 vaccines continue to outweigh the known risks in a pandemic.

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

HEALTH SCIENCES AUTHORITY
SINGAPORE