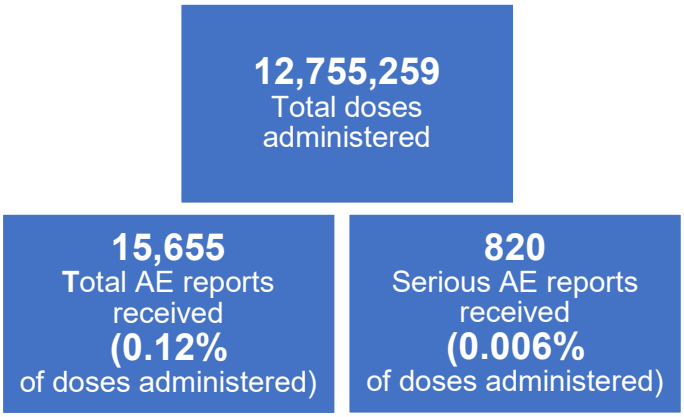
HSA's Safety Update #10

COVID-19 Vaccines

(30 December 2020 – 31 January 2022)

Introduction

Summary of key statistics for mRNA vaccines, Pfizer/Comirnaty vaccine and Moderna/SpikeVax vaccine (as of 31 January 2022)



This is HSA's 10th safety update of the COVID-19 vaccines covering the period from the roll-out of the vaccines on 30 December 2020 to 31 January 2022. 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. HSA has assessed that the reporting rate of AEs and serious AEs of 0.12% and 0.006% of administered doses, respectively have remained stable since the roll-out of the COVID-19 vaccines and the overall benefits of the COVID-19 vaccines in preventing COVID-19 and serious complications associated with COVID-19 far outweigh any currently known AEs.

2 Vaccination is the most effective way to reduce deaths and severe illness from COVID-19 infection. A national immunisation programme has been underway since early December 2020. HSA has authorised two mRNA COVID-19 vaccines (Pfizer-BioNTech/Comirnaty Vaccine and Moderna/Spikevax Vaccine), an inactivated COVID-19 vaccine (Sinovac-CoronaVac Vaccine) and a protein-based COVID-19 vaccine (Nuvaxovid Vaccine) for use in Singapore.

3 All vaccines and medicines may cause side effects or adverse events (AEs). As with all other vaccines, HSA closely monitors the safety of the COVID-19 vaccines and has actively encouraged healthcare professionals to report AEs to HSA. This is the most intense safety monitoring ever conducted by HSA and the relevant measures are taken to ensure that the vaccines remain safe for use. HSA reviews the submitted AE reports, in consultation with our

[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.

expert panels[2]. It is important to note that the AEs reported do not necessarily mean that the vaccine has caused these AEs as they may be 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. Overall, based on the data to date, the benefits of the Pfizer-BioNTech/Comirnaty, Moderna/Spikevax and Sinovac-CoronaVac COVID-19 vaccines continue to outweigh the known risks when used in a pandemic.

Summary (as of 31 January 2022)

- **The incidences of AEs and serious AEs have remained stable at 0.12% and 0.006% of administered doses, respectively. The reporting rate of AEs and serious AEs have remained stable since 18 April 2021.** A total of 12,755,259 doses of the Pfizer-BioNTech/Comirnaty and Moderna/Spikevax mRNA vaccines have been administered, out of which 15,655 suspected AE reports were received. The vast majority of reported AEs are not serious.

- **Similar to other vaccines, the COVID-19 vaccines may cause AEs and the most commonly reported AEs generally resolved within a few days.** The most commonly reported AEs (e.g., muscle aches, allergic reactions, fever) are consistent with those typically observed following vaccination, such as with the flu vaccination.

- **In the age group of 5 to 11 years, the incidence rates of AEs and SAEs are similar to that observed in adolescents and adults at 0.12% and 0.004% of administered doses, respectively**. No cases of myocarditis or pericarditis have been reported in this age group.

- **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**. Myocarditis is a rare adverse event with vaccination. Fifteen cases of myocarditis and pericarditis have been reported following 3.19 million booster doses (0.5 per 100,000 doses administered). Most cases are mild, with individuals reported to have recovered or are recovering.

- Rare instances of anaphylaxis, a severe life-threatening allergic reaction, have occurred after administering the COVID-19 vaccines. The local incidence rate of anaphylaxis reported with mRNA vaccines has remained low and stable at an estimated 0.89 per 100,000 doses administered. No anaphylaxis reports have been reported with booster doses.

- Rare cases of myocarditis and pericarditis have been reported with various COVID-19 vaccines both overseas and locally. They are caused by inflammation of the heart muscles and outer lining of the heart, respectively. The overall incidence for the primary series has remained stable, at 1.08 per 100,000 doses. As with other countries, these events occur more frequently in younger males below 30 years old, and more often with Dose 2. Most cases are mild, with individuals reported to have recovered or are recovering. Overall, reports of myocarditis and pericarditis following mRNA vaccination are rare. COVID-19 infection is also known to be associated with myocarditis. In one study, the extra myocarditis events in the month following vaccination was estimated to be between 1 and 10 per million persons, which is substantially lower than the 40 extra events per million persons observed following COVID-19 infection.

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

- Cases of cerebral venous thrombosis (CVT) have been reported with the Pfizer-BioNTech/Comirnaty and Moderna/Spikevax COVID-19 vaccines, both overseas and locally. Although HSA's analysis found a small increase in incidence of CVT with mRNA vaccines, which translates to about 1 additional case of CVT per million doses, the incidence remains rare. The risk of CVT after COVID-19 infection is much higher than CVT after mRNA vaccination, and the benefits of vaccination continue to outweigh the small increased risk of CVT.

- Two hundred and ninety-nine suspected AEs (0.08% of doses administered) including twenty-two serious AEs (0.006% of doses administered) were reported following the administration of 369,083 doses of Sinovac-CoronaVac COVID-19 vaccine.

- Forty-one suspected AEs (0.05% of doses administered) including six serious AEs (0.007% of doses administered) were reported with Sinopharm COVID-19 vaccine after 89,350 doses were administered.

- 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 (3.6%) 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 continue to outweigh the known risks when used in a pandemic.

Background

4 Vaccination is the most effective way to reduce deaths and severe illness from COVID-19. A national immunisation programme has been underway since early December 2020. All vaccines and medicines may cause side effects or adverse events (AEs). These AEs need to be continuously balanced against the expected benefits in preventing illness.

5 HSA has granted interim authorisation for two mRNA COVID-19 vaccines, an inactivated COVID-19 vaccine and a protein-based COVID-19 vaccine in Singapore under the Pandemic Special Access Route (PSAR) (Table 1). On 10 December 2021, the interim authorisation for Pfizer-BioNTech/Comirnaty COVID-19 vaccine was transitioned to product registration.

Table 1. Authorisation of COVID-19 vaccines in Singapore

Vaccines	Authorisation date	Vaccination roll-out date
Pfizer-BioNTech /Comirnaty^ Vaccine*	14 December 2020	30 December 2020
Moderna/Spikevax^ Vaccine	3 February 2021	12 March 2021
Sinovac-CoronaVac Vaccine	23 October 2021	18 June 2021+
Nuvaxovid Vaccine	3 February 2022	-

*HSA extended the use of the Pfizer-BioNTech/Comirnaty vaccine to adolescents aged 12-15 years on 18 May 2021 and to children aged 5-11 years old on 10 December 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)[3]

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

mRNA COVID-19 Vaccines

6 As of 31 January 2022, HSA has received 15,655 suspected AE reports (0.12% of doses administered) associated with the use of Pfizer-BioNTech/Comirnaty and Moderna/Spikevax COVID-19 vaccines.

Table 2. Overview of vaccination data and no. of suspected AE reports reported by healthcare professionals for mRNA COVID-19 vaccines (as of 31 January 2022)

	Pfizer-BioNTech/Comirnaty	Moderna/Spikevax	Total
No. of persons who have received at least the first dose	3,900,748	1,028,271	**4,929,019**
No. of persons who received two doses*	3,739,585	892,161	**4,631,746**
No. of persons who received booster doses	2,200,751	993,743	**3,194,494**
Total no. of doses administered	9,841,084	2,914,175	**12,755,259**
No. of suspected AE reports	12,770 (0.13% of doses administered)	2,885 (0.10% of doses administered)	**15,655 (0.12% of doses administered)**
No. of suspected serious[4] AE reports	664 (0.007% of doses administered)	156 (0.005% of doses administered)	**820 (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.

Commonly reported adverse events

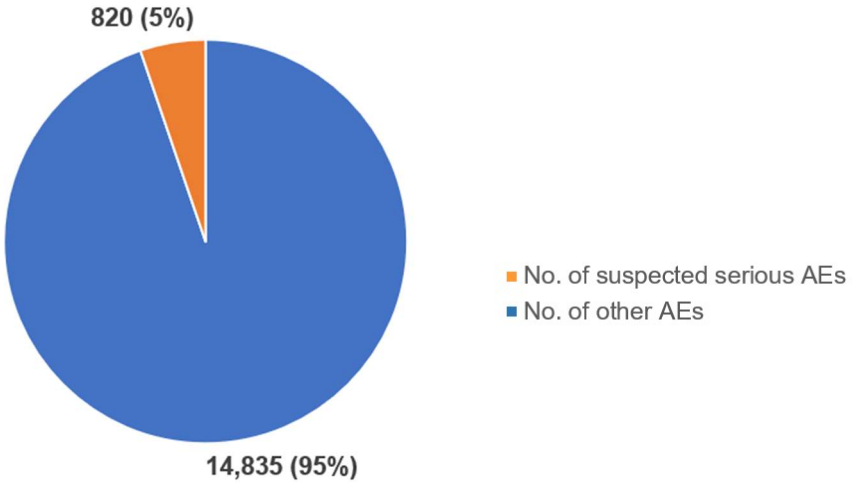
7 The most commonly reported AEs are consistent with those typically observed following vaccination such as with the flu vaccine. These include allergic reactions (such as rash, itch, hives and swelling of eyelids, face and lips), dizziness, shortness of breath, chest discomfort/pain, palpitations, fever, headache, muscle aches and injection site reactions such as pain and swelling. These reported AEs generally resolved within a few days.

Serious adverse events

8 The reporting rate of serious AEs has remained stable (between 0.004% to 0.007%). Of the 15,655 suspected AE reports received for the mRNA vaccines (Pfizer-BioNTech/Comirnaty and Moderna/Spikevax), 820 of the reports were assessed as serious (Figure 1). Serious AEs comprised 0.006% of doses administered. Of the reports received which include information on outcome, many of the suspected AEs had resolved or were resolving at the time of reporting.

[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.

Figure 1. No. of suspected serious AEs and other AE reports with the use of mRNA COVID-19 vaccines



The most frequently reported serious AEs were anaphylaxis (88 reports) and other severe allergic reactions (55 reports). Other serious AEs include:

- immunological - rheumatoid arthritis and other autoimmune conditions;
- cardiovascular - chest pain, drop or increase in blood pressure, irregular heartbeat, tachycardia (fast heart rhythm), myocarditis and pericarditis (inflammation of the heart muscles and the outer lining of the heart, respectively);
- neurological – migraine, nerve damage or dysfunction resulting in numbness or tingling / pricking sensation, muscle or limb weakness and pain in the affected area, syncope, seizures (fits), inflammation of the brain tissues, Bell's Palsy (facial muscle weakness or paralysis) and cerebral venous thrombosis (CVT);
- haematological involving the blood cells - low platelets and blood clots;
- musculoskeletal - joint inflammation or pain and muscle injury;
- dermatological - severe skin reactions, eczema flare and skin blisters;
- renal - reduced kidney function and inflammation of the kidney;
- visual inflammation and visual disturbances;
- tinnitus (ringing in the ears) and hearing loss;
- respiratory - exacerbation of underlying asthma and breathing difficulties and
- other SAEs such as increase in liver enzymes, appendicitis, thyroid gland dysfunction, menstrual disorders, 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.

Adverse events in children 5 to 11 years old

9 On 27 December 2021, the COVID-19 vaccination programme was rolled out to children aged 5 to 11 years old.[∞] Two hundred and eighty AE reports were received (0.12% out of 238,253 administered doses) in this age group. The reporting rates of SAEs in this age group is similar to that observed in adolescents and adults at 0.004% of administered doses. No cases of myocarditis or pericarditis have been reported so far. The commonly reported AEs are also similar to that observed in adolescents (12-17 years old) and include angioedema

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

∞ Pfizer-BioNTech/Comirnaty vaccine is approved for use in individuals aged 5 years and above, while Moderna/Spikevax vaccine is authorised for use in individuals aged 18 years and above

(swelling of eyelids, face or lips), hives, dizziness, fever, rash, chest discomfort/pain, palpitations and shortness of breath. While there were 10 serious AE reports amongst children aged 5 to 11 years, describing seizures (fits), appendicitis, drop in blood pressure, allergic reaction, abnormal renal function and swelling of small blood vessels, this does not necessarily mean that the vaccine has caused these serious AEs as they may be related to an underlying or undiagnosed disease or it may be coincidental that they occurred around the same time that the vaccine was given. HSA is closely monitoring the AEs reported in children and is assessing them in the context of background incidence rates.

Adverse events with booster doses

10 The national COVID-19 booster vaccination programme was rolled out on 15 September 2021 and 3,194,494 individuals have received the booster doses as of 31 January 2022. 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. HSA has received 553 AE reports (0.03 % of doses administered) associated with the use of Pfizer-BioNTech/Comirnaty vaccine and 289 AE reports (0.03% of doses administered) with the Moderna/Spikevax vaccine as booster doses. There were 73 SAE reports (0.002% of administered doses), of which 15 cases were myocarditis and pericarditis reported to HSA following more than 3.19 million booster doses administered.

Adverse events of special interest[6]

11 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, myocarditis, pericarditis and cerebral venous thrombosis. Hence, HSA is closely monitoring the occurrence of such AEs to detect any increase over background incidences.

Anaphylaxis reports

12 The incidence rate of anaphylaxis reported locally with the vaccines has remained low and stable at an estimated 0.89 per 100,000 doses administered. There were 88 cases of anaphylaxis reported with the Pfizer-BioNTech/Comirnaty and Moderna/Spikevax vaccines. All the patients were reported to have recovered after medical treatment. The number of cases of anaphylaxis associated with Dose 2 is lower than with Dose 1 for the mRNA vaccines. To date, HSA has not received any cases of anaphylaxis associated with the booster dose.

Myocarditis and pericarditis reports

13 Myocarditis and pericarditis (inflammation of the heart muscles and outer lining of the heart, respectively) associated with the mRNA vaccines have been reported 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

[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

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.

14 Reports of myocarditis and pericarditis following mRNA vaccination are rare and the overall incidence for the primary vaccination dose series has remained stable at 1.08 per 100,000 doses. HSA has received 115 AE reports of myocarditis and pericarditis following more than 12.7 million doses of mRNA vaccines administered. As reported overseas, these events occur more frequently in younger males below 30 years old, and more often with Dose 2. Most cases are mild, with individuals reported to have recovered or are recovering. It should be noted that COVID-19 infection is also known to be associated with myocarditis. In one study, the extra myocarditis events in the month following vaccination were estimated to be between 1 and 10 per million persons, which is substantially lower than the 40 extra events per million persons observed following COVID-19 infection.[9]

15 Aside from mRNA vaccines, myocarditis and pericarditis have also been reported with other vaccines, such as viral vector vaccines (i.e., Janssen/Johnson & Johnson and Oxford/AstraZeneca COVID-19 vaccines) internationally. Locally, one case of myocarditis with Sinovac-Coronavac vaccine has been reported.

Heart attacks and strokes

16 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

17 There have been rare cases of cerebral venous thrombosis (CVT) reported with the Pfizer-BioNTech/Comirnaty and Moderna/Spikevax vaccines, both overseas and locally. The incidence of CVT has stabilised and remains rare. CVT involves blood clots occurring in the veins of the brain, which can happen naturally regardless of whether people have been vaccinated. HSA has received 13 suspected reports of CVT with the Pfizer-BioNTech/Comirnaty and Moderna/Spikevax COVID-19 vaccines, out of more than 12.7 million doses that has been administered. HSA's analysis has found a small increase in incidence of CVT with mRNA vaccines from expected baseline incidence locally, which translates to about 1 additional case of CVT per million doses. It is important to note that COVID-19 infections can also lead to CVT. Comparatively, based on local data, the additional number of CVT cases with COVID-19 infection is about 30 per million infected persons. Considering that the risk of CVT after COVID-19 infection is much higher than CVT after mRNA vaccination, the benefits of vaccination continue to outweigh the small increased incidence of CVT.

---

[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

[9] Patone, M., Mei, X.W., Handunnetthi, L. *et al.* Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. *Nat Med* (2021). https://doi.org/10.1038/s41591-021-01630-0

Non-mRNA COVID-19 vaccines

1) Sinovac-CoronaVac Vaccine [authorised under PSAR]

18 As of 31 January 2022, HSA has received 299 AE reports (0.08% of administered doses) following the administration of 369,083 doses of Sinovac-CoronaVac vaccine (Table 3). The commonly reported AEs were rash, hives, angioedema, shortness of breath, chest discomfort and dizziness. Twenty-two serious AEs were reported (0.006% of administered doses). There were twelve reports of anaphylaxis and all the cases had occurred in individuals who had previous allergic reactions with the mRNA vaccines or had multiple drug allergies. The other 10 serious AE reports include myocarditis, Bell's Palsy, blood clots, numbness, muscle spasms, tachycardia, hypertension, vertigo with tinnitus (ringing of the ears) and serious allergic reactions.

Table 3. Overview of vaccination data and no. of suspected AE reports reported by healthcare professionals for Sinovac-CoronaVac Vaccine (as of 31 January 2022)

	Sinovac-CoronaVac COVID-19 Vaccine
No. of persons who have received at least Dose 1	**151,674**
No. of persons who received two doses	**141,252**
No. of persons who received three doses	**76,157**
Total no. of doses administered	**369,083**
No. of suspected AE reports	**299** (**0.08%** of doses administered)
No. of suspected serious AE reports	**22** (**0.006%** of doses administered)

2) Sinopharm COVID-19 Vaccine (supplied via HSA's Special Access Route)

19 Vaccination for Sinopharm vaccine was rolled out on 30 August 2021. As of 31 January 2022, HSA has received 41 suspected AE reports (0.05% of doses administered) following the administration of 89,350 doses of Sinopharm vaccine. The non-serious AEs include rash, angioedema, shortness of breath, numbness, syncope, chest discomfort and tinnitus. There were six serious AE reports (0.007 % of doses administered) of low platelet count, syncope with muscle jerks, frequent palpitations, chest pain with visual disturbance, flare of rheumatoid arthritis and relapse of thyroid dysfunction.

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

Conclusion

21 Vaccines are the best way to protect people from COVID-19 and have already saved many lives. All vaccines and medicines may cause side effects or AEs. As with all vaccines and medicines, HSA closely monitors the safety of the COVID-19 vaccines.

22 Based on the local AE reports received, most of the AEs are largely expected with vaccination and reflect what has been reported globally. HSA's current assessment is that the overall benefits of the Pfizer-BioNTech/Comirnaty, Moderna/Spikevax and Sinovac-CoronaVac COVID-19 vaccines in preventing COVID-19 and serious complications associated with COVID-19 far outweigh any currently known adverse events.

23 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

Interpretation of the data

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 of local AE reports from healthcare professionals, public self-reported AEs, epidemiological studies, literature and overseas reports) has to be considered before drawing any evidence-based conclusions on the safety of the vaccine.

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 (3.6%) 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.

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.