Safety Monitoring of COVID-19 Vaccines in Hong Kong

This report contains data of adverse event reports between 26 February 2021 and 23 December 2023

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1. COVID-19 vaccines and pharmacovigilance system in Hong Kong

Authorization of COVID-19 vaccines for emergency use

The COVID-19 pandemic caused a significant disease burden in Hong Kong and worldwide. To reduce the impacts of COVID-19 on health and society, vaccines against COVID-19 is considered an important public health tool for containing the pandemic. According to the World Health Organization ("WHO"), the rapid development of vaccines against COVID-19 represent a fundamental step towards ending the pandemic, protecting health systems and helping to restore global economies.

In December 2020, the Prevention and Control of Disease (Use of Vaccines) Regulation, Cap. 599K ("the Regulation") was enacted to provide the legal framework for bringing

in COVID-19 vaccines which satisfy the criteria of safety, efficacy and quality for emergency use under public health emergency. The two platforms of COVID-19 vaccines authorized for use in Hong Kong have been rigorously evaluated by the Advisory Panel on COVID-19 Vaccines ("Advisory Panel") established under the Regulation. Current scientific evidence indicates that the benefits of the two platforms of COVID-19 vaccines outweigh their risks for use as active immunization to prevent COVID-19 caused by SARS-CoV-2 virus. The vaccines not only protect individuals from COVID-19 infection, available data also support that the vaccines could reduce the seriousness of the COVID-19 even if infected.

With the two COVID-19 vaccines authorized for emergency use under the Regulation, the Government COVID-19 Vaccination Programme commenced on 26 February 2021. The authorization has been lapsed on 23 December 2023 when the Regulation expired on the same day. This report consolidates the safety monitoring of the COVID-19 vaccines authorized under the Regulation.

During the above period, i.e. between 26 February 2021 and 23 December 2023, the Government Vaccination Programme provided two different platforms of COVID-19 vaccines, which were authorized in accordance with the Regulation. They were:

1. Inactivated virus technology platform - CoronaVac COVID-19 Vaccine (Vero Cell), Inactivated by Sinovac Biotech (Hong Kong) Limited; and

2. mRNA technology platform - Comirnaty COVID-19 mRNA Vaccine (BNT162b2) Concentrate for Dispersion for Injection (including 30mcg/dose for 12 years of age and older, 10mcg/dose for children aged 5 to 11 years, and 3mcg/dose for toddlers aged 6 months to less than 5 years old) and Comirnaty Original/Omicron BA.4-5 dispersion for injection COVID-19 mRNA Vaccine by Fosun Pharma in collaboration with the German drug manufacturer BioNTech, collectively known as "Comirnaty".

Pharmacovigilance system for COVID-19 vaccination

Pursuant to the requirements of the Regulation to monitor any adverse event that occurs to the recipient associated with the administration of the relevant vaccine, the Department of Health ("DH") has put in place a pharmacovigilance system for COVID-19 vaccination, which included passive surveillance, stimulated passive surveillance, active surveillance and sentinel surveillance. **The main purpose of the pharmacovigilance system is to detect signals of possible side effects of the vaccines.** The Director of Health also appointed the Expert Committee on Clinical Events Assessment Following COVID-19 Immunization ("Expert Committee") to provide independent assessment of potential causal link between AEFIs and COVID-19 vaccines used in Hong Kong and to provide expert advice to the Government on safety-related matters. The membership and the terms of reference of the Expert Committee are provided under Annex 1.

Passive Surveillance and Stimulated Passive Surveillance

To monitor the safety of the COVID-19 vaccines, the DH has established an on-line reporting system (link click **here**) and the reporting channel with the Hospital Authority ("HA") to receive reports of Adverse Events Following Immunization ("AEFIs")[1] related to the COVID-19 vaccines used in Hong Kong from healthcare professionals, including doctors, dentists, pharmacists, nurses and Chinese medicine practitioners, and pharmaceutical industries. In addition, healthcare professionals are encouraged to report 16 items of serious or unexpected AEFIs (link click **here**) for close monitoring of the safety of the vaccines. To enhance the vaccine recipients' awareness, Fact Sheets with information about common side effects of the COVID-19 vaccines and reporting mechanism of AEFIs were prepared for vaccine recipients' reference. Letters had been sent to relevant healthcare professional associations and organizations to solicit their

[1] According to World Health Organization, Adverse Events Following Immunization ("AEFIs") refers to any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine.

assistance in encouraging the reporting of any serious or unexpected AEFIs of COVID-19 vaccine to the DH.

Active Surveillance and Sentinel Surveillance

The DH also partners with the University of Hong Kong ("HKU") to conduct an active and sentinel surveillance programme for AEFIs and Adverse Events of Special Interest ("AESIs")[2] related to COVID-19 vaccines, i.e. the COVID-19 vaccines Adverse events Response and Evaluation Programme ("CARE Programme"). Through big-data analysis and scientific studies designed when indicated, the CARE Programme would provide more data on the safety profile of the COVID-19 vaccines[3]. This programme comprises four parts:

Part 1: To provide background incidence of AESIs including but not limited to rare or serious adverse events. Before the commencement of the vaccination programme, the age and sex-specific incidences of these AESIs were estimated and the likely frequency of putative adverse events expected from the background incidence were reported.

Part 2: To establish an early warning mechanism by conducting active surveillance identifying AESI among patients of the HA through automated search of clinical records of HA and conduct causality assessment. Private sector was also engaged to participate.

Part 3: To conduct a variety of analytical studies, including cohort, case-control and self-controlled studies, by linking the DH vaccination records and the HA records and possibly private hospital clinical records, for examining any possible association between the occurrence of AESI and vaccination.

Part 4: To conduct intensive monitoring on a group of consented recipients through regular contacts to ascertain details of adverse events inclusive of common adverse events including injection site inflammation, headache and others, and it ensures the capturing

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[2] According to the World Health Organization, Adverse Event of Special Interest ("AESI") is a pre-identified and predefined medically-significant event that has the potential to be causally associated with a vaccine product that needs to be carefully monitored and confirmed by further specific studies. The list of AESI is available at https://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/adr_reporting/index.html

[3] Further information about the CARE Programme is available at https://www.hkcare.hku.hk/copy-of-care-programme .

of data on these common mild adverse events which normally do not warrant contact with a healthcare professional.

Handling of AEFI reports

Upon receipt of reports on the 16 items of serious or unexpected AEFIs, the DH will contact the healthcare professionals whom reported the AEFI for further information. According to the established mechanism, all important cases will be considered by the Expert Committee while all other serious or unexpected AEFI cases will be assessed by DH based on the causality assessment algorithm of the WHO[4]. **The ultimate goal of causality assessment is to detect signals of possible side effects of the vaccines[5].**

When causality assessment is finished, the DH will inform the causality assessment result to the reporting healthcare professional within two weeks so that the healthcare professional could follow up with his/her patient accordingly. The DH would not contact vaccine recipients directly in relation to AEFI reports. Vaccine recipients or their family members may contact the reporting healthcare professional if they want to know the causality assessment result.

According to the risk communication plan on clinical events following immunization endorsed by the Expert Committee, reports on safety monitoring of COVID-19 vaccines have been published on the Government's designated website since the commencement of the Government COVID-19 Vaccination Programme and updated periodically.

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[4] WHO Causality assessment of an adverse event following immunization (AEFI) (CausalityAssessmentAEFI_EN.pdf (who.int))

[5] More information about how AEFI reports are handled is available at https://www.chp.gov.hk/en/features/106959.html.

2. The work of the Expert Committee

The Expert Committee, consisting of experts in cardiology, forensic pathology, haematology, immunology & allergy, infectious disease, microbiology, neurology, paediatrics, pharmacology, etc., was established in January 2021. Since then, the Expert Committee had convened 30 meetings, conducted (together with DH) causality assessments for more than 4,100 AEFI or AESI reports, and published 25 reports on safety monitoring of COVID-19 vaccines in Hong Kong. In addition, the Coroner's Court has made requests for expert opinion on certain cases involving reportable death. To respond to these requests, the Expert Committee had prepared a total of eight reports to the Coroner's Court accordingly.

Identified Bell's palsy as potential signal

In the first few months of the Government COVID-19 Vaccination Programme, the Expert Committee identified Bell's palsy as a potential signal of side effect of the CoronaVac vaccine (Bell's palsy is a listed side effect of Comirnaty vaccine)[6]. The Expert Committee requested the HKU to further analyse the association between Bell's palsy and the vaccine under the CARE programme. Analysis of the HKU confirmed a signal of increased risk of Bell's palsy after receiving CoronaVac vaccine but the benefit of the vaccine continues to outweigh the risks. The study was also published in The Lancet Infectious Diseases[7]. The findings from the analysis together with relevant case reports were reported to the Advisory Panel and also provided to the supplier of the vaccine for considering appropriate action. Subsequently, the supplier of CoronaVac vaccines had applied for listing Bell's palsy as its very rare adverse reaction under the Regulation in

[6] Bell's palsy is also one of the side effects of Comirnaty vaccine. Such information has already been included in its Vaccination Fact Sheet before the commencement of the Government Vaccination Programme.

[7] Article available at https://www.sciencedirect.com/science/article/pii/S1473309921004515.

July 2021. Upon approval of the application, the Government updated the Vaccination Fact Sheet for CoronaVac on 12 July 2021.

Monitoring events of myocarditis and pericarditis

During the same period, the Expert Committee noted that there were local reports as well as reports from overseas drug regulatory authorities about cases of myocarditis and pericarditis within 14 days following vaccination of Comirnaty, especially among younger vaccine recipients and more often after the second dose of vaccination. On 5 July 2021, the Expert Committee endorsed the inclusion of myocarditis and pericarditis in the list of serious or unexpected AEFI to enhance monitoring. The DH and HKU have also closely monitored adverse events of myocarditis or pericarditis among adolescents who received Comirnaty. Subsequently, the supplier of Comirnaty had applied for updating the products' package insert to include myocarditis and pericarditis as its adverse reactions under the Regulation. Upon approval of the application, the Government updated the Vaccination Fact Sheet for Comirnaty on 20 July 2021 and provided relevant health education to the public accordingly.

In addition, the Expert Committee had reported the above findings to the DH and Advisory Panel. The information was subsequently discussed by the Scientific Committee on Vaccine Preventable Diseases and the Scientific Committee on Emerging the Zoonotic Diseases under the Centre for Health Protection of the DH together with the then Chief Executive's expert advisory panel. Having considered the risk of myocarditis and pericarditis among adolescents following vaccination of Comirnaty, experts recommended to adjust the vaccination schedules of Comirnaty for adolescents in September 2021 and December 2021 respectively to minimize such side effects[8]. Since

[8] Consensus Interim Recommendations of the Joint Scientific Committees are available at https://www.chp.gov.hk/files/pdf/consensus_interim_recommendations_on_the_use_of_covid19_vaccines_in_hk_15sept21.pdf and

the adjustments of the vaccination schedules, reports of myocarditis and pericarditis among adolescents have decreased significantly. Relevant studies had also been published in peer-reviewed journals[9].

Accomplishment of the CARE Programme

Under the CARE Programme, the HKU has conducted more than 70 pharmacoepidemiologic studies, consolidated the background incidence of 28 clinical conditions, and engaged 4,213 people for the intensive monitoring cohort study to evaluate more commonly experienced adverse reactions. In the past 3 years, over 44 scholarly journal articles have been published in peer-reviewed journals. A complete list of published articles is presented at Annex 2. Of note, the CARE team published the first analytic study in the world to provide real-world evidence of an elevated risk of Bell's palsy following CoronaVac vaccination, which necessitated the addition of Bell's palsy as a very rare adverse reaction in the product insert. The team was also the first in the world to use real-world data to analytically test for and confirm the overall elevated risk of myocarditis following Comirnaty vaccination. This finding had direct implications and impacts on the Government's policies on mass vaccination, particularly among adolescents for whom the recommended primary dosing interval was extended to reduce the risk of myocarditis. From the data, the team confirmed a significant decline of myocarditis cases following the introduction of such a policy and showed a significantly reduced risk of myocarditis and potentially better vaccine effectiveness with an extended dosing interval. The team conducted numerous studies on various disease groups and

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https://www.chp.gov.hk/files/pdf/consensus_interim_recommendations_on_the_use_of_comirnaty_vaccines_23dec.pdf.

[9] "Myocarditis following COVID-19 BNT162b2 vaccination among adolescents in Hong Kong" (https://jamanetwork.com/journals/jamapediatrics/fullarticle/2789584) and "Impact of a delayed second dose of mRNA vaccine (BNT162b2) and inactivated SARS-CoV-2 vaccine (CoronaVac) on risks of all-cause mortality, emergency department visit, and unscheduled hospitalization" (https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-022-02321-4).

successfully established the safety profile of the vaccines in patients with multimorbidity, various immunological diseases, and cancer, apart from many other pre-existing conditions.

With the rapid development of the COVID-19 vaccines, proactive safety monitoring of these vaccines is of paramount importance. The Expert Committee has successfully identified signals of side effects of the vaccines with local data and analysis. The information has assisted the Government to fine-tune the vaccination schedules and the public education strategies to reduce the adverse effects of the vaccines in a timely manner. This also ensures the success of the vaccination programme and the overall battle against the pandemic. Continuous monitoring of the Expert Committee has also found that the vaccines authorized for emergency use are generally safe, which is also in line with the assessments of the WHO as well as other drug regulatory authorities around the globe.

3. Summary of AEFI reports received between 26 February 2021 and 23 December 2023

Under the Government vaccination programme between 26 February 2021 and 23 December 2023, there were about 20,916,600 doses of COVID-19 vaccines administered. During the same period, the Department of Health had received a total of 8,139 AEFI reports [reporting rate: 0.04% (38.9 cases per 100,000 doses administered)].

CoronaVac vaccine

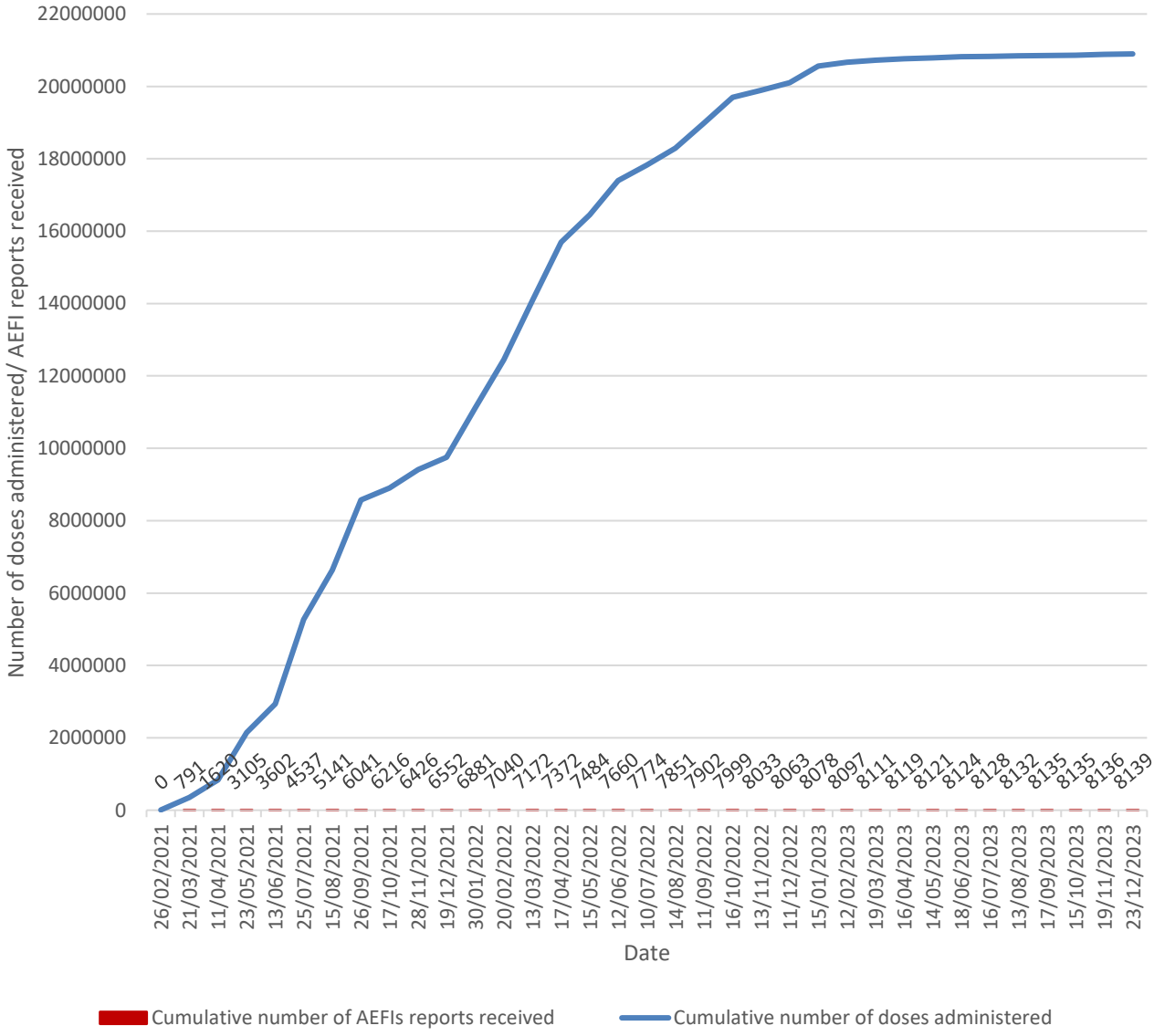
Cumulative number of doses of COVID-19 vaccine administered	**About 8,927,000**
Cumulative number of AEFI reports received [Reporting rate (cases per 100,000 doses administered)]	**3,407 [0.04% (38.2)]**

Comirnaty vaccine

Cumulative number of doses of COVID-19 vaccine administered	**About 11,989,600**
Cumulative number of AEFI reports received [Reporting rate (cases per 100,000 doses administered)]	**4,732 [0.04% (39.5)]**

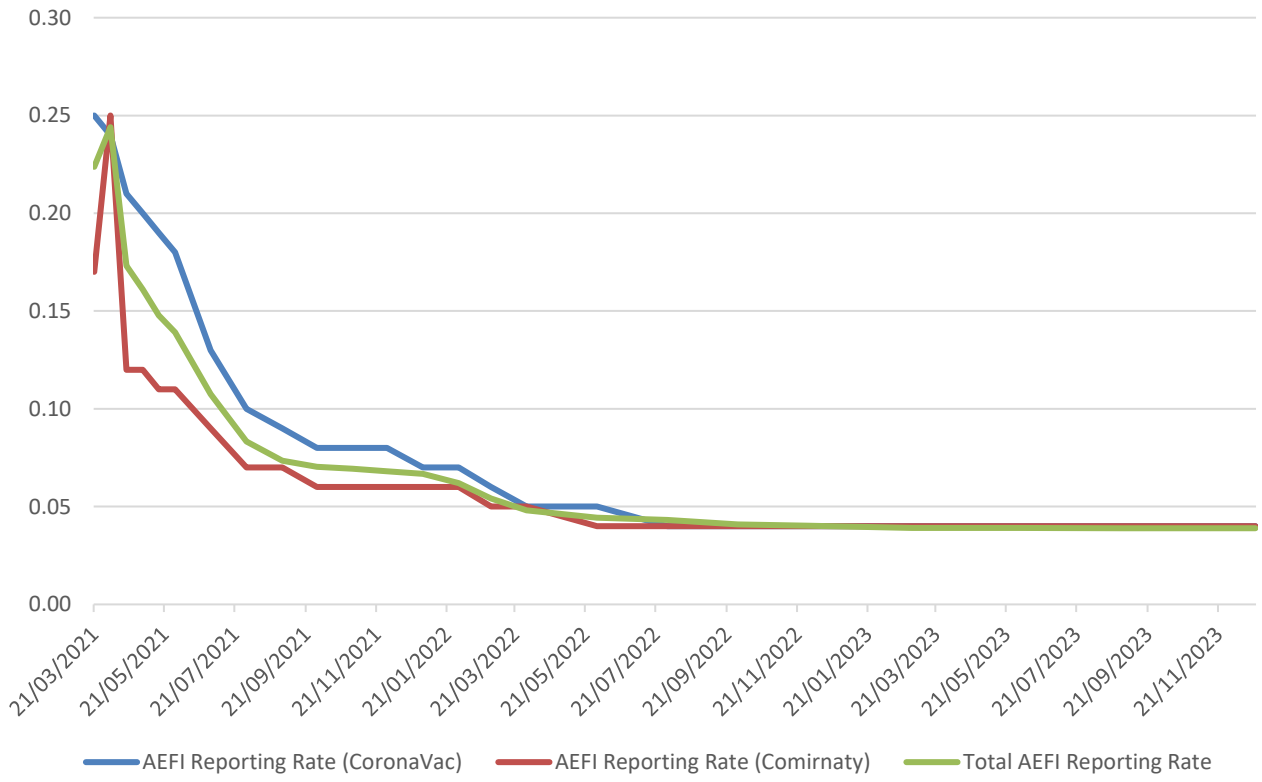
The cumulative number of doses of COVID-19 vaccines administered and the cumulative number of AEFI reports received from the commencement of the COVID-19 vaccination programme up to 23 December 2023 are shown in Figure 1:

Figure 1. Cumlative number of doses of COVID-19 vaccines administered and cumulative number of AEFI reports received during the Government Vaccination Programme



The initial AEFI reporting rate was up to 0.25% in the first month of the Government Vaccination Programme, probably due to general awareness of healthcare professionals in contributing AEFI reports for safety monitoring. This rate dropped over time and was steady at a rate of 0.04% since mid-2022, it is believed that the healthcare professionals were getting familiar with the safety profile and side effects of the vaccines as well as gaining experience in contributing to the newly introduced pharmacovigilance system for the emergency use of vaccines. This AEFI reporting rate is comparable to that in other jurisdictions[10]. The AEFI reporting rates during the Government Vaccination Programme up to 23 December 2023 are presented in Figure 2:

Figure 2. AEFI Reporting Rate (%) up to 23 December 2023



[10] AEFI reporting rates from selected countries (including Australia, Canada, United Kingdom and United States of America) ranged from 0.04% to 0.2%.

The age distribution of AEFI reports received from the commencement of the COVID-19 vaccination programme up to 23 December 2023 are shown below:

Between 26 February 2021 and 23 December 2023	Doses administered	AEFI reporting rate (cases per 100,000 doses administered)
19 years and below	2,305,500	0.03% (27.9)
20-29 years	2,198,100	0.04% (37.4)
30-39 years	3,215,500	0.04% (37.5)
40-49 years	3,555,100	0.04% (39.4)
50-59 years	3,668,900	0.04% (40.2)
60-69 years	3,325,500	0.04% (43.7)
70 years and above	2,648,000	0.04% (42.1)

During the same period (i.e. between 26 February 2021 and 23 December 2023), the DH received 8,139 AEFI reports related to CoronaVac vaccine and Comirnaty vaccine. Summary of these cases are shown as follows:

	CoronaVac	Comirnaty	Total
Serious or unexpected AEFI reports*	1,900	1,647	3,547
Other reports	1,507	3,085	4,592
Total	3,407	4,732	8,139

* Serious or unexpected AEFI reports include 16 items as endorsed by the Expert Committee (see page 3), these include deaths and hospitalization cases.

Other Reports

Apart from those reports involving serious or unexpected AEFI, 4,592 other reports were received between 26 February 2021 and 23 December 2023.

Based on the 1,507 AEFI reports associated with CoronaVac, the most frequently reported events are:

Description of Events	Number of Events*
1. Dizziness	283
2. Chest discomfort	281
3. Rash	189
4. Chest pain	185
5. Palpitation	146
6. Headache	134
7. Numbness	79
8. Shortness of breath	67
9. Hypertension	64
10. Fever	59
11. Vomiting	45
12. Weakness	34
13. Vertigo	33
14. Nausea	33
15. Urticaria	32
16. Malaise	27
17. Allergic reaction	25
18. Loss of consciousness	22
19. Itchy rash	20
20. Herpes zoster	19

*One report may have more than one event.

Based on the 3,085 AEFI reports associated with Comirnaty, the most frequently reported events are:

Description of Events	Number of Events*
1. Dizziness	844
2. Chest discomfort	771
3. Chest pain	421
4. Palpitation	398
5. Rash	333
6. Headache	285
7. Fever	282
8. Numbness	175
9. Shortness of breath	172
10. Nausea	128
11. Vasovagal attack	92
12. Hypertension	82
13. Loss of consciousness	72
14. Vomiting	69
15. Sweating	68
16. Syncope	67
17. Urticaria	59
18. Malaise	51
19. Itchy rash	49
20. Myalgia	47

*One report may have more than one event.

4. Specific reports

Anaphylaxis/ anaphylactoid reactions

From the commencement of the vaccination programme up to 23 December 2023, the DH had received a total of 53 AEFI reports of suspected anaphylaxis or anaphylactoid reactions with history of COVID-19 vaccination. Having reviewed available clinical data of these cases, only 22 reports were considered as anaphylaxis or anaphylactoid reactions [reporting rate: 0.0001% (0.1 cases per 100,000 doses administered)]. Among these, 5 reports were assessed as having consistent causal association to immunization, no report was assessed as having indeterminate causal association to immunization and 17 reports were assessed as not associated with immunization.

According to the product information of the vaccines, anaphylaxis is one of the adverse reactions of the vaccines reported from clinical trials. People with previous severe allergic reactions to COVID-19 vaccines should not receive COVID-19 vaccination, unless advised by specialists in Immunology and Allergy.

Bell's palsy

From the commencement of the vaccination programme up to 23 December 2023, the DH had received a total of 689 AEFI reports of suspected Bell's palsy with history of COVID-19 vaccination. Having reviewed available clinical data of these cases, 668 reports were considered as Bell's palsy [reporting rate: 0.003% (3.2 cases per 100,000 doses administered)] (313 cases received CoronaVac vaccine and 355 cases received Comirnaty vaccine). Among these 668 cases, 627 reports were assessed as having consistent causal association to immunization, 16 reports were assessed as having indeterminate causal association to immunization and 14 reports were assessed as not associated with immunization.

Bell's palsy (acute peripheral facial paralysis) is a common neurologic disorder. Majority of the patients will have complete recovery even without treatment and early use of a short course of treatment within 3 days of symptoms onset will further enhance the recovery rate. According to the information collected by the HKU from HA, in 2018, 2019 and 2020, there were on average 1,764 new cases of Bell's palsy recorded for people of 3-year-old or above each year. Bell's palsy is listed as one of the rare adverse reactions of Comirnaty. The Expert Committee identified Bell's palsy as a potential signal of side effect of CoronaVac vaccine in the first few months following commencement of the vaccination programme. HKU assisted in conducting further analysis and the findings were provided to the supplier of the vaccine. Subsequently, the vaccine supplier applied for listing Bell's palsy as a very rare adverse reaction of CoronaVac in July 2021.

Death

From the commencement of the vaccination programme up to 23 December 2023, the DH had received a total of 120 death reports of AEFI [reporting rate: 0.0006% (0.57 cases per 100,000 doses administered)] with history of COVID-19 vaccination within 14 days before they passed away[11], involving 79 males and 41 females between 34 and 101 years old. Among the death cases reported, 78 of them received CoronaVac vaccine and 42 received Comirnaty vaccine.

The Expert Committee conducted causality assessment of individual cases based on the algorithm of the WHO and all available information, including the medical conditions and history of the patient with relevant clinical data, vaccine information and autopsy findings. **There is no case identified as having causal relationship with the COVID-19 vaccination.** The Expert Committee had concluded the causality assessment for all of

[11] Death cases with COVID-19 vaccination history of more than 14 days and no clinical evidence to indicate association with vaccine would be captured and analyzed by the HKU under the CARE Programme as AESI.

the above death cases and considered 118 cases were inconsistent with COVID-19 vaccination (i.e. no causal relationship) and 2 cases[12] as indeterminate (i.e. causal relationship could not be established).

The Expert Committee had reviewed all available data, including the local mortality data, and considered that all reported death cases do not show any causal relationship with the vaccines. Death cases outside the reporting criteria for AEFI[13], including death of all causes and sudden death as listed AESI, were actively monitored and analyzed under the CARE Programme conducted by the HKU; no unusual pattern has been identified.

Guillain-Barre syndrome

From the commencement of the vaccination programme up to 23 December 2023, the DH had received a total of 26 AEFI reports of suspected Guillain-Barre syndrome (GBS)

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[12] One of the death cases involved an 83-year-old man who passed away five days after receiving the first dose of CoronaVac vaccine in May 2022. Preliminary autopsy revealed ischaemic heart disease. In the final autopsy report, the cause of death as shown by the autopsy appears to be acute myocarditis. Investigations could not identify the cause of acute myocarditis. From literatures and overseas data so far, there is no evidence indicating that the vaccination could cause acute myocarditis. Moreover, studies conducted by HKU under the CARE Programme also did not find any association between CoronaVac vaccination and myocarditis. Nevertheless, based on the available information, the Expert Committee considered that a causal relationship between the death and vaccination could not be established. Another death case involved a 74-year-old male who passed away on the same day after receiving the first dose of Comirnaty vaccine in November 2021. Preliminary autopsy revealed coronary artery disease. In the final autopsy report, the cause of death as shown by the autopsy appears to be anaphylaxis and ischaemic heart disease. However, according to available information, the deceased did not experience discomfort during the observation period after vaccination and there was no sign of anaphylaxis attack during resuscitation. In addition, the condition of ischaemic heart disease of the deceased was very severe, which was considered as a significant condition contributing to the death. On the basis of the above, the Expert Committee considered that a causal relationship between the death and vaccination could not be established.

[13] Death cases with vaccination history of more than 14 days (unless with evidence of association with COVID-19 vaccine) or cases with obvious cause(s) of death, other than vaccination, are outside the reporting criteria for AEFI. These cases were included in the HKU's CARE Programme for big-data analysis.

with history of COVID-19 vaccination. Having reviewed available clinical data of these cases, only 21 reports were considered as GBS AEFI [reporting rate: 0.0001% (0.1 cases per 100,000 doses administered)]. Among these, no report was assessed as having consistent causal association to immunization, 11 reports were assessed as having indeterminate causal association to immunization and 7 reports were assessed as not associated with immunization.

GBS is a rare neurological disorder causing paralysis and even respiratory difficulties. Most people recover completely but some have chronic weakness. GBS can develop following a variety of infections, including influenza. GBS was identified as a possible adverse event requiring specific safety monitoring activities.

According to the data provided by the HA to the Centre for Health Protection[14], the average number of newly admitted GBS cases to HA for the past ten years (2012 – 2021) was 57.5 cases per year. In 2022, there were 36 cases of newly admitted GBS. So far, there was no evidence indicating that the GBS cases exceed the background incidence.

Myocarditis/ Pericarditis

From the commencement of the vaccination programme up to 23 December 2023, the DH had received a total of 241 AEFI reports of suspected myocarditis with vaccination received within 14 days before symptoms onset or suspected pericarditis. Having reviewed available clinical data of these cases, 225 reports were considered as myocarditis or pericarditis involving 176 males and 49 females aged between 9 and 88; 16 cases received CoronaVac vaccine and 209 cases received Comirnaty vaccine [reporting rate: 0.0017% (1.7 cases per 100,000 doses administered)], including 48 male and 8 female adolescents aged 5 to 15 [reporting rate: 0.008%]. Among these 225 cases, 148 reports were assessed as having consistent causal association to immunization, 29

[14] Information available at: https://www.chp.gov.hk/en/features/26736.html.

reports were assessed as having indeterminate causal association to immunization and 38 reports were assessed as not associated with immunization.

Myocarditis and pericarditis refer to the inflammation of the heart muscle and the inflammation of the tissue surrounding the heart respectively. According to the information collected by the HKU from HA, in 2018, 2019 and 2020, there were on average 846 new cases of myocarditis recorded for people of 3-year-old or above each year. The Expert Committee noted that there were local reports as well as reports from overseas drug regulatory authorities about cases of myocarditis and pericarditis within 14 days following vaccination of Comirnaty, especially among younger vaccine recipients and more often after the second dose of vaccination. The DH and HKU also closely monitored adverse events of myocarditis or pericarditis among adolescents. Subsequently, the supplier of Comirnaty had applied for updating the products' package insert to include myocarditis and pericarditis as its adverse reactions in July 2021. The Government also adjusted the vaccination schedule of Comirnaty for adolescents based on the above findings.

Thrombocytopenia

From the commencement of the vaccination programme up to 23 December 2023, the DH had received a total of 37 AEFI reports of suspected thrombocytopenia or thrombosis with thrombocytopenia syndrome with history of COVID-19 vaccination. Having reviewed available clinical data of these cases, only 29 reports were considered as thrombocytopenia [reporting rate: 0.0001% (0.1 cases per 100,000 doses administered)]. Among these, no report was assessed as having consistent causal association to immunization, 6 reports were assessed as having indeterminate causal association to immunization and 22 reports were assessed as not associated with immunization.

Thrombocytopenia refers to an abnormally low platelet count. The cause of thrombocytopenia following immunization is not known and clinically apparent thrombocytopenia after immunization is rare. According to the information collected by the HKU from HA, in 2018, 2019 and 2020, there were on average 2,074 new cases of thrombocytopenia recorded for people of 3-year-old or above each year. Currently, there is no evidence to indicate the COVID-19 vaccines authorized for use in Hong Kong are associated with thrombocytopenia.

5. Summary of causality assessments of serious or unexpected AEFI

AEFI causality assessment

Causality assessment is a systematic review of data about an AEFI case. It aims to determine the likelihood of a causal association between the event and the vaccine received. The quality of the causality assessment depends upon various factors including effectiveness and quality of investigation, availability of adequate medical and laboratory data, access to background information, etc.

According to the "Causality assessment of an Adverse Event Following Immunization (AEFI)" issued by the WHO (see Note 2 above), causality assessment of AEFI could be classified into:

A. Consistent with causal association to immunization: - This may be further classified into vaccine product-related reaction, vaccine quality defect-related reaction, immunization error-related reaction, and immunization anxiety-related reaction.

B. Indeterminate:- This may either be "temporal relationship is consistent but there is insufficient definitive evidence for vaccine causing event" or "qualifying factors result in conflicting trends of consistency and inconsistency with causal association to immunization".

C. Inconsistent with causal association to immunization:- That is, coincidental, underlying or emerging condition(s), or condition(s) caused by exposure to something other than vaccine.

D. Unclassifiable:- That is, adequate information not available for causality assessment.

Causality assessment conducted by the Expert Committee and the DH

Since the commencement of the Government Vaccination Programme, the Expert Committee and the DH have conducted causality assessment for over 4,100 AEFI or AESI reports. Among these, 3,545 were serious of unexpected AEFI reports with a total of 5,000 events[15]. The causality assessments of these 5,000 events are as follows:

Causality assessment classification	CoronaVac	Comirnaty	Total
A. Consistent with causal association to immunization*	486	671	1,157
B. Indeterminate	126	161	287
C. Inconsistent with causal association to immunization	1,546	957	2,503
D. Unclassifiable	589	464	1,053
Total	2,747	2,253	5,000

* Events were only vaccine product-related reactions or immunization anxiety-related reactions. None of these events were vaccine quality defect-related reaction or immunization error-related reaction.

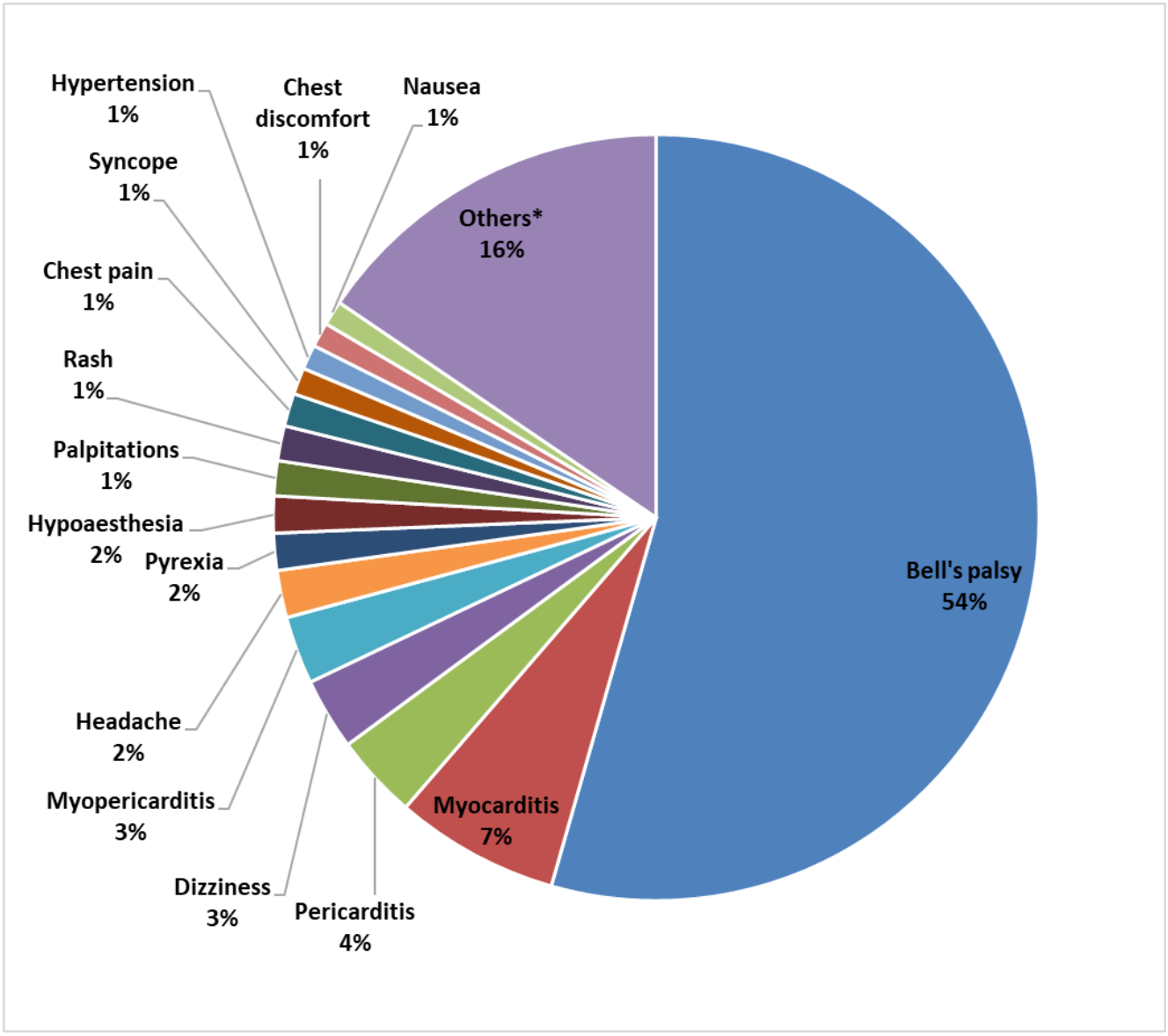
Events assessed as having consistent causal association to immunization

Distributions of assessed events that were classified as consistent with causal association to immunization are presented below. A total of 1,157 events were concluded under this classification. These events were mainly known side effects of the COVID-19 vaccines or related to immunization anxiety. Majority of these events were Bell's palsy,

[15] Causality assessment is event-based. If one AEFI report has more than one event, causality assessment for each event would be conducted.

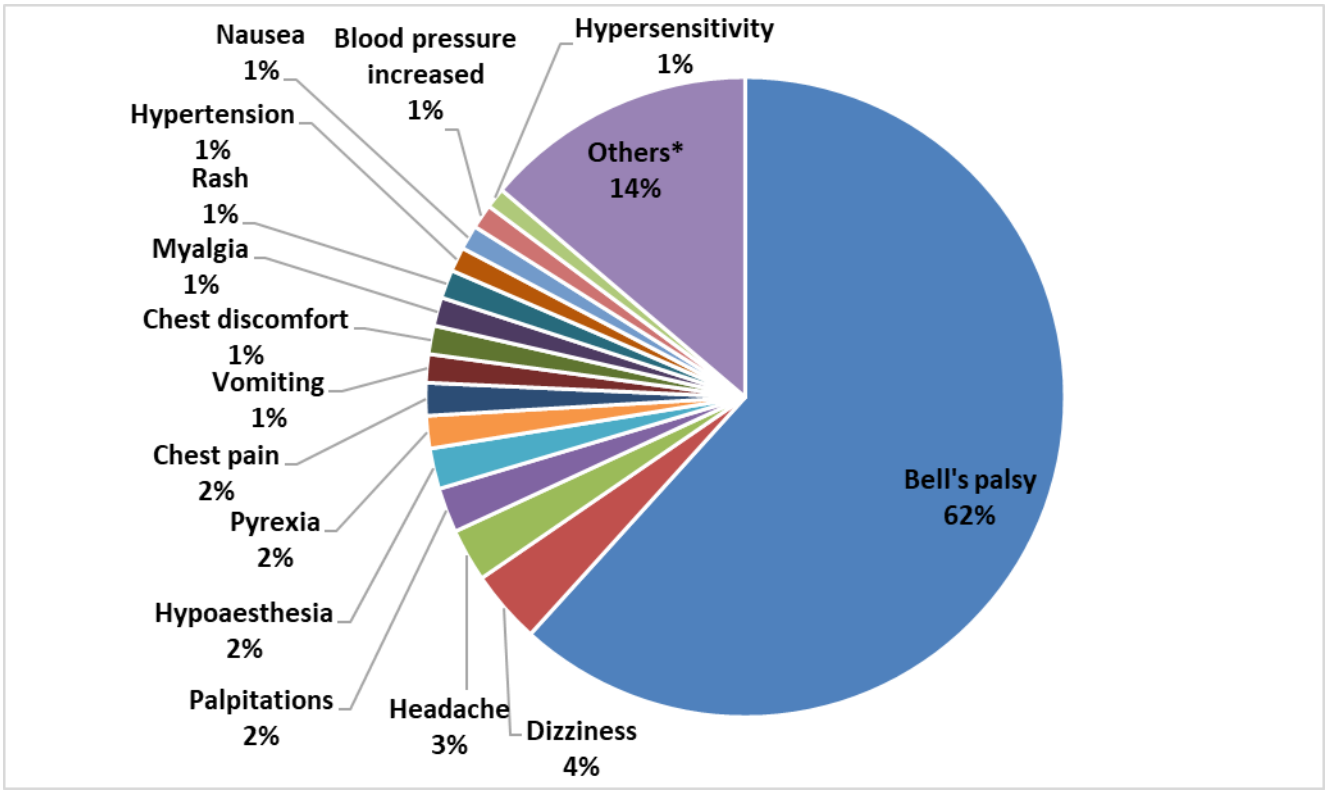
myocarditis and pericarditis. Events less than 1% are grouped as “Others”, which include asthenia, hypersensitivity, loss of consciousness, myalgia, vomiting, etc.

Distribution of Assessed Events classified as A (consistent with causal association to immunization) among Serious Cases (n=1,157)

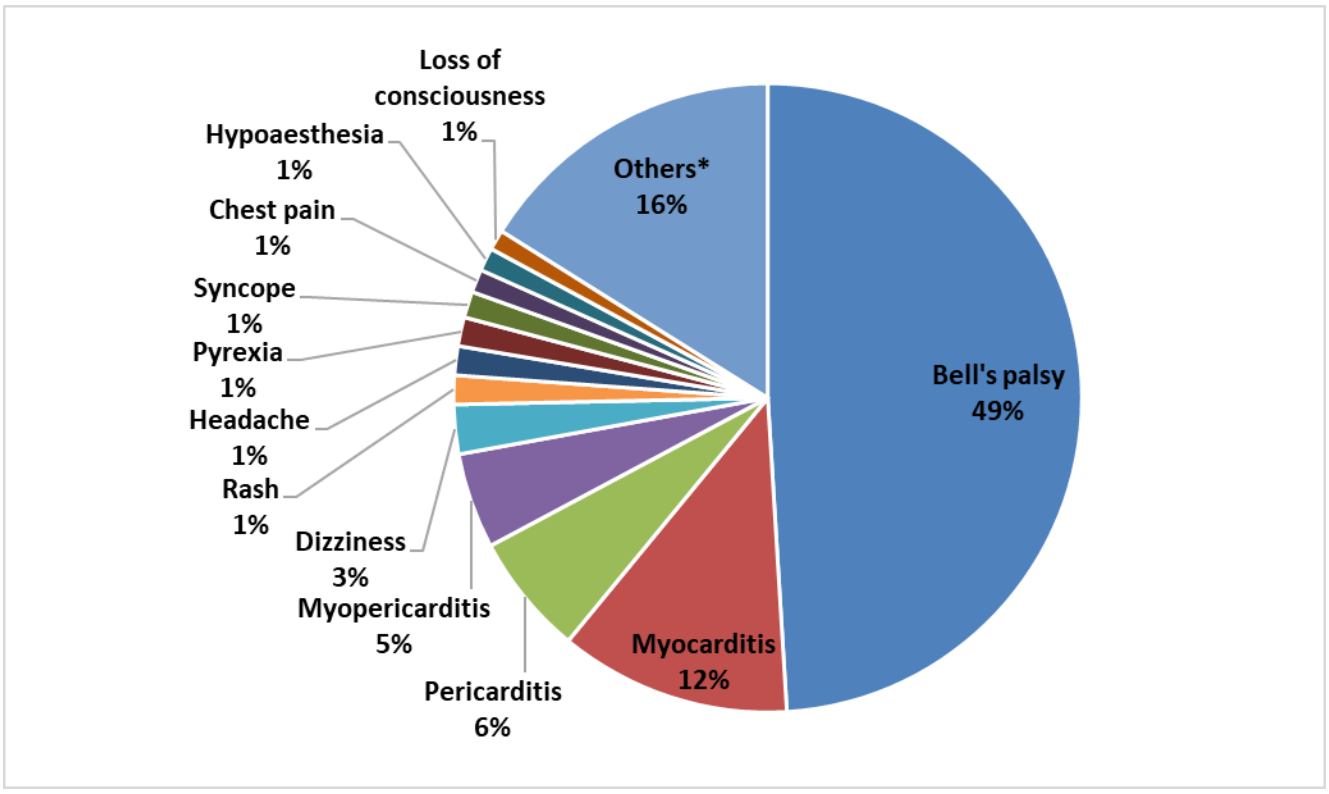


**Those events less than 1% are classified as Others*

Distribution of Assessed Events classified as A among Cases received **CoronaVac** vaccine (n=486)



Distribution of Assessed Events classified as A among Cases received **Comirnaty** vaccine (n=671)



**Those events less than 1% are classified as Others*

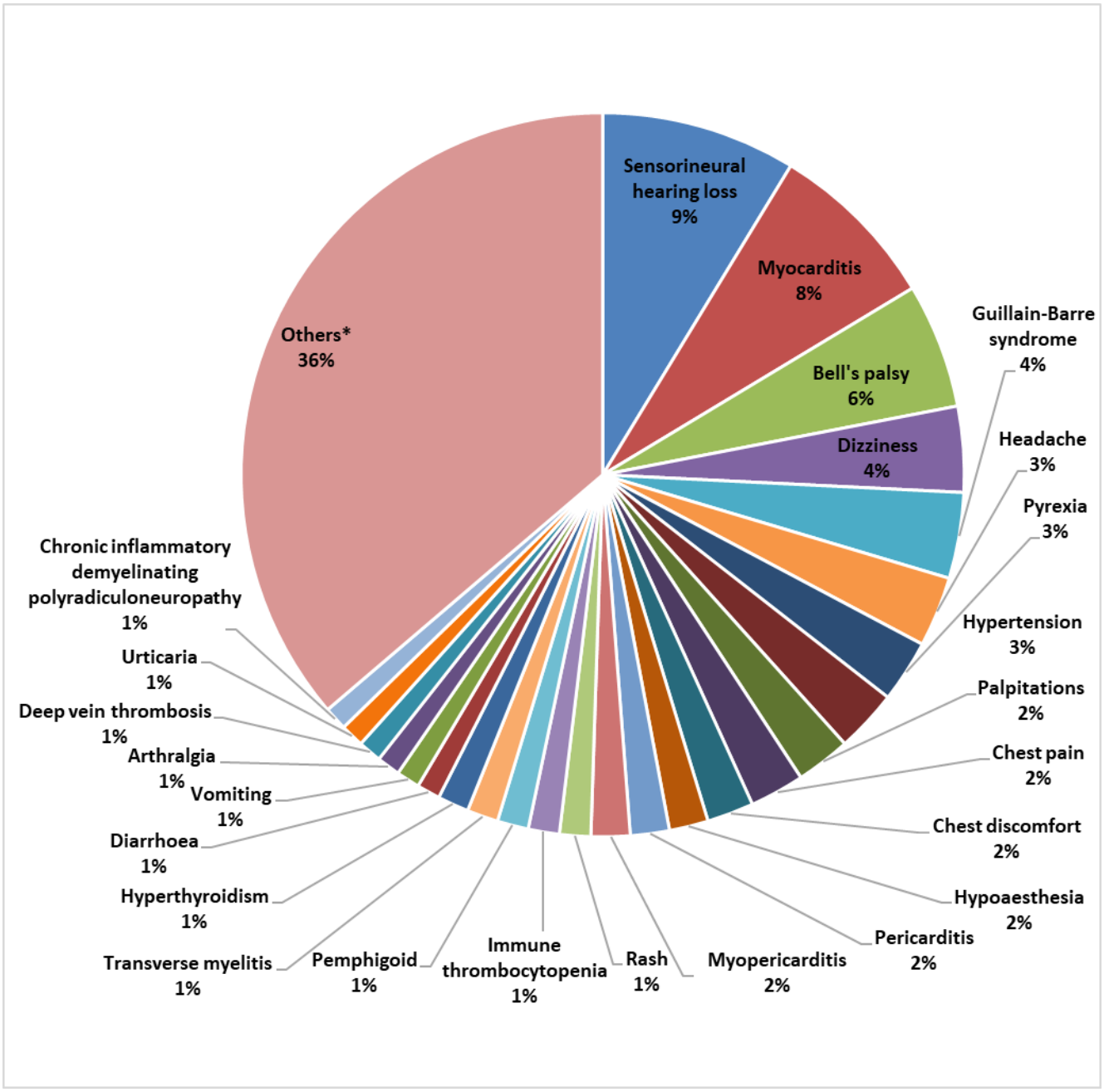
Events assessed as having indeterminate causal association to immunization

Distributions of assessed events that were classified as indeterminate with causal association to immunization are presented below. A total of 287 events were concluded under this classification. These events may present trend of consistency with causal association to immunization but either without definitive evidence for causal relationship or with information showing inconsistent causal association to immunization. Majority of these events were hearing loss, myocarditis, Bell's palsy, dizziness and Guillain-Barre syndrome ("GBS"). WHO also noted that there were reports of hearing loss following COVID-19 vaccine immunization; however, WHO considered that there are only limited data and further monitoring is required[16]. Events related to myocarditis and Bell's palsy mainly involved inconsistent temporal relationship. For GBS, several countries have been monitoring the relationship between COVID-19 vaccines (in particular Comirnaty and other mRNA platform vaccines) and GBS, but there is no evidence that the vaccines cause an increased risk of GBS[17]. Events less than 1% are grouped as "Others", which include allergy to vaccine, myalgia, thrombocytopenia, upper abdominal pain, etc.

[16] A comprehensive review from WHO Newsletter published in 2022 available at: https://iris.who.int/bitstream/handle/10665/351326/9789240042452-eng.pdf?sequence=1.

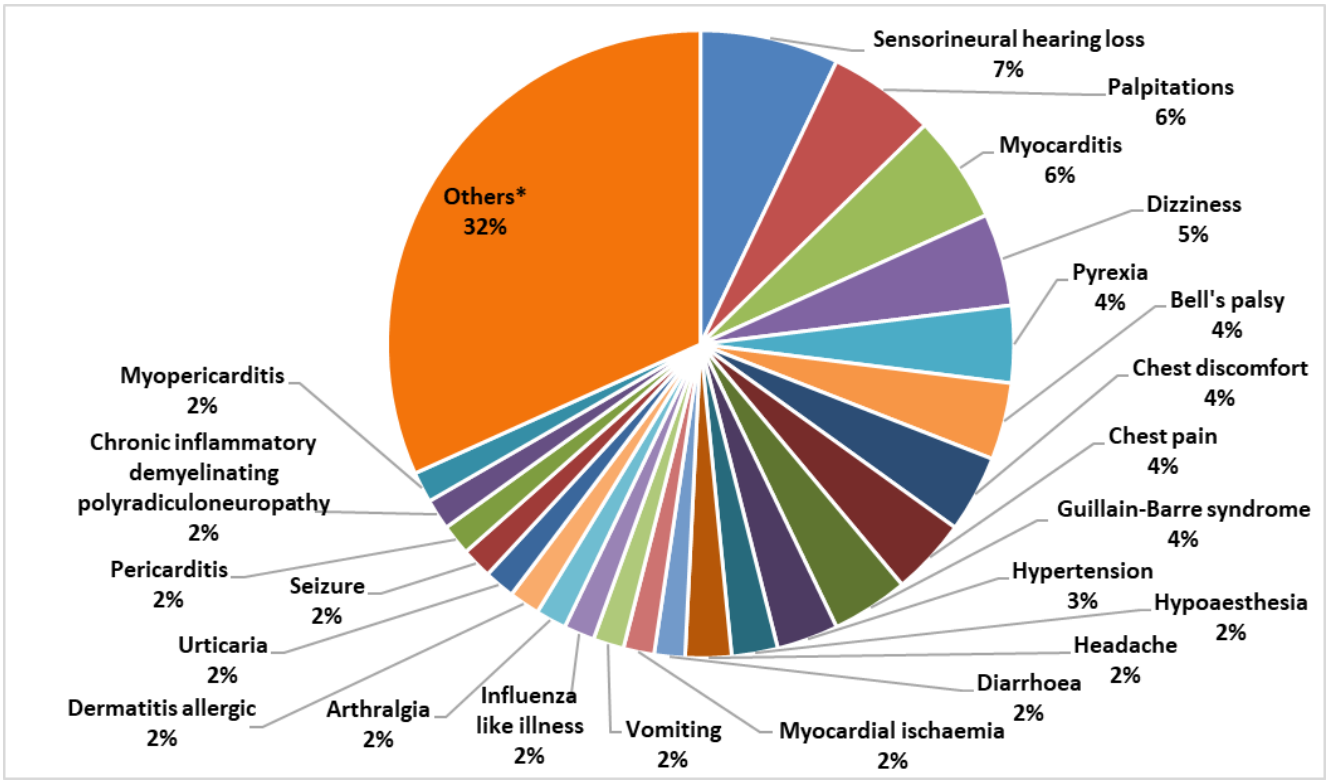
[17] A summary report from WHO Newsletter published in 2022 available at: https://iris.who.int/bitstream/handle/10665/362661/9789240057883-eng.pdf?sequence=1.

Distribution of Assessed Events classified as B (indeterminate causal association to immunization) among Serious and Unexpected Cases (n=287)

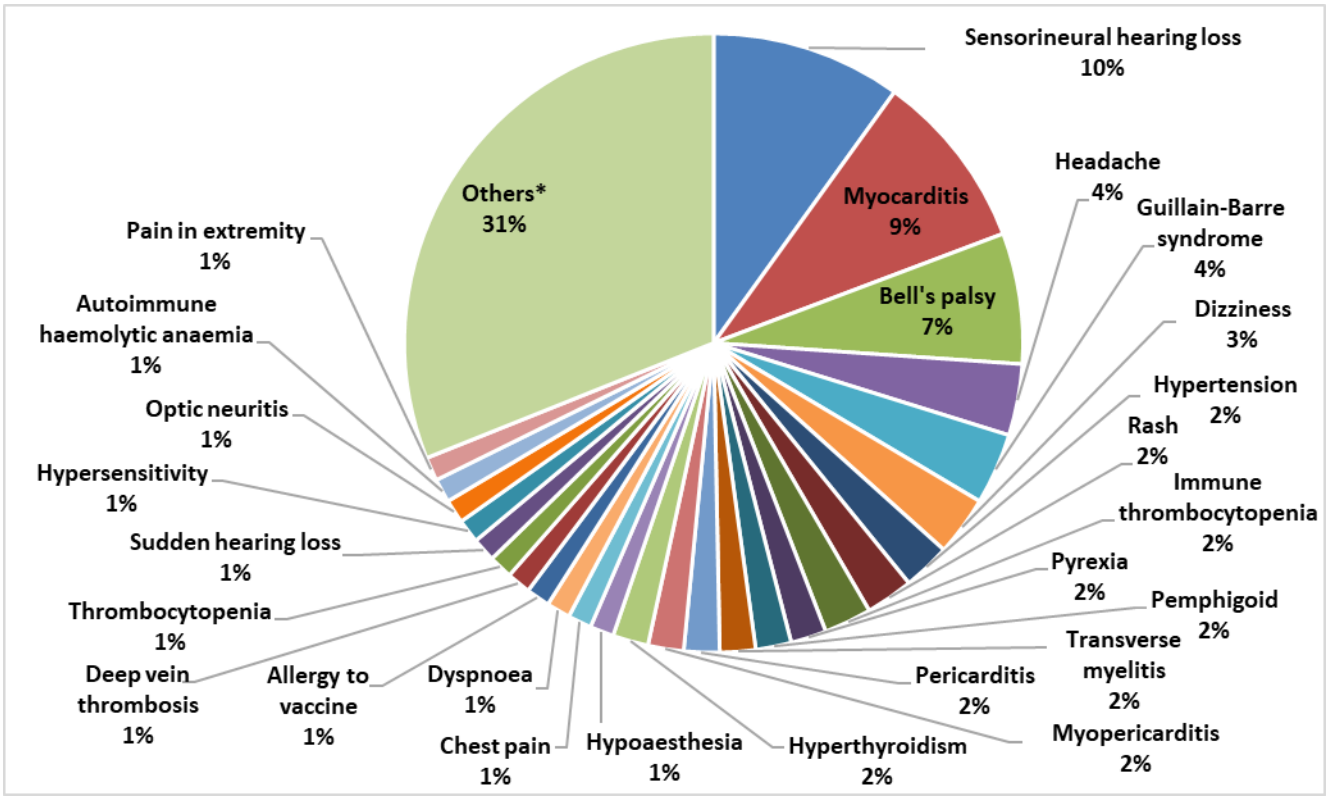


**Those events less than 1% are classified as Others*

Distribution of Assessed Events classified as B among Cases received CoronaVac vaccine (n=126)



Distribution of Assessed Events classified as B among Cases received Comirnaty vaccine (n=161)



**Those events less than 1% are classified as Others*

Events assessed as having inconsistent causal association to immunization or unclassifiable

A total of 2,503 events were assessed as having inconsistent causal association to immunization, i.e. not associated with immunization based on WHO causality assessment algorithm. Since these events were considered as coincidental, they may cover a wide range of diseases or clinical conditions.

Separately, causality assessment of 1,053 events could not be concluded based on WHO algorithm mainly because there was inadequate information. Reasons may include lack of clinical and/or laboratory data, unconfirmed diagnosis of the events, lack of responses from reporting clinicians, failure of the patients to seek medical attention at the time of onset, etc.

6. Conclusion

The COVID-19 pandemic has a huge impact to the global public health. Rapid development of COVID-19 vaccines was crucial to restore the world to normalcy but at the same time posed an unprecedent challenge to drug regulation. The Government quickly enacted the Prevention and Control of Disease (Use of Vaccines) Regulation, Cap. 599K as a response to the emergency situation. A robust pharmacovigilance system plays an essential role to ensure the COVID-19 vaccines authorized for emergency use are properly monitored to safeguard the public.

The Expert Committee has been working tirelessly for the past three years to assess thousands of AEFI reports. Although many of these reported events may not have causal association with COVID-19 vaccines, the Expert Committee has identified signals of side effects of these vaccines and made appropriate recommendations to reduce the side effects of vaccination.

With billions of COVID-19 vaccines, including the vaccines authorized for emergency use in Hong Kong, administered worldwide, there is ample information about the safety and efficacy of these vaccines. Drug regulatory authorities, including the Pharmacy and Poisons Board of Hong Kong, around the world consider these vaccines as safe, efficacious and of quality, and have been approving them under their existing legal framework. These vaccines no longer require the Prevention and Control of Disease (Use of Vaccines) Regulation for emergency authorization.

Upon the expiration of the Regulation on 23 December 2023, the work of the Expert Committee to monitor the safety of the COVID-19 vaccines authorized for emergency use has also come to an end. The Expert Committee wishes to extend its appreciation to all healthcare professionals in Hong Kong, particularly those who have reported AEFIs, as their contributions are indispensable for the functioning of the Expert Committee. The

monitoring of COVID-19 vaccines authorized for emergency use has now been concluded. Nevertheless, the pharmacovigilance system maintained by the DH will continue to monitor the safety of pharmaceutical products being used in Hong Kong to safeguard public health.

The Expert Committee on Clinical Events Assessment Following COVID-19 Immunization

29 December 2023

Annex 1

Expert Committee on Clinical Events Assessment Following COVID-19 Immunization
Member List

Co-convenors:	Prof HUNG Fan-ngai, Ivan
	Dr LEE Cheuk-kwong
Members:	Prof CHAN Kay-sheung, Paul
	Dr CHAN Yat-sun, Joseph (Appointed on 29 March 2021)
	Dr CHIU Shui-seng, Susan (Resigned on 30 June 2022)
	Dr FONG Wing-chi
	Dr LEE Kang-yin, Michael (Appointed on 29 March 2021)
	Dr LEE Shing-cheung, Benjamin
	Prof LEUNG Ting-fan (Appointed on 1 July 2022)
	Dr LI Philip Hei
	Prof MOK Chung-tong, Vincent
	Prof WONG Chi-kei, Ian
Representatives from the DH:	Controller, Centre for Health Protection, DH (or his representative)
	Consultant (Forensic Pathology) in-charge, DH
	Assistant Director (Drug), DH
	Assistant Director (Health Sciences and Technology), DH
	Experts from other specialties (e.g. geriatric medicine, nephrology, respiratory medicine) will be invited on needed basis

Terms of Reference for the Expert Committee on Clinical Events Assessment Following COVID-19 Immunization

(a) Assessment of potential causal links between Adverse Events Following Immunization (AEFIs) and COVID-19 vaccines;

(b) Monitoring AEFIs data for identification of potential signals of previously unidentified COVID-19 vaccine related adverse events;

(c) Reviewing serious AEFIs and providing expert opinion;

(d) Advising the Secretary for Health and the Advisory Panel on COVID-19 Vaccines on AEFIs, and

(e) Advising the Director of Health on COVID-19 vaccines and immunization safety-related matters.

Annex 2

List of articles published by the University of Hong Kong under the CARE Programme

1. Bell's palsy following vaccination with mRNA (BNT162b2) and inactivated (CoronaVac) SARS-CoV-2 vaccines: a case series and nested case-control study; *The Lancet Infectious Diseases (https://doi.org/10.1016/S1473-3099(21)00451-5)*
2. Two-dose Covid-19 vaccination and possible arthritis flare among patients with rheumatoid arthritis in Hong Kong; *Annals of the Rheumatic Diseases (*http://doi.org/10.1136/annrheumdis-2021-221571*)*
3. Adverse event reporting and Bell's palsy risk after COVID-19 vaccination - Authors' reply; *The Lancet Infectious Diseases (*https://doi.org/10.1016/S1473-3099(21)00631-9*)*
4. Epidemiology of Acute Myocarditis/Pericarditis in Hong Kong Adolescents Following Comirnaty Vaccination; *Clinical Infectious Diseases (*https://doi.org/10.1093/cid/ciab989*)*
5. Comparing self-reported reactogenicity between adolescents and adults following the use of BNT162b2 (Pfizer-BioNTech) messenger RNA Covid-19 vaccine: a prospective cohort study; *International Journal of Infectious Diseases (*https://doi.org/10.1016/j.ijid.2021.12.354*)*
6. Post-Covid-19-vaccination adverse events and healthcare utilization among individuals with or without previous SARS-CoV-2 infection; *Journal of Internal Medicine (*https://doi.org/10.1111/joim.13453*)*
7. Multimorbidity and adverse events of special interest associated with Covid-19 vaccines in Hong Kong; *Nature Communications (*https://doi.org/10.1038/s41467-022-28068-3*)*
8. Carditis After COVID-19 Vaccination With a Messenger RNA Vaccine and an Inactivated Virus Vaccine; *Annals of Internal Medicine (*https://doi.org/10.7326/M21-3700*)*
9. COVID-19 vaccines and risks of hematological abnormalities: Nested case–control and self-controlled case series study; *American Journal of Hematology (*https://doi.org/10.1002/ajh.26478*)*
10. Herpes zoster related hospitalization after inactivated (CoronaVac) and mRNA (BNT162b2) SARS-CoV-2 vaccination: A self-controlled case series and nested case-

control study; *The Lancet Regional Health - Western Pacific* *(*https://doi.org/10.1016/j.lanwpc.2022.100393*)*

11. Self-reported reactogenicity of CoronaVac (Sinovac) compared with Comirnaty (Pfizer-BioNTech): a prospective cohort study with intensive monitoring; *Vaccine* *(*https://doi-org.eproxy.lib.hku.hk/10.1016/j.vaccine.2022.01.062*)*
12. Lack of inflammatory bowel disease flare-up following two-dose BNT162b2 vaccine: a population-based cohort study; *Gut (*http://doi.org/10.1136/gutjnl-2021-326860*)*
13. Myocarditis Following COVID-19 BNT162b2 Vaccination Among Adolescents in Hong Kong; *JAMA Pediatrics (*http://doi.org/10.1001/jamapediatrics.2022.0101*)*
14. Impact of a delayed second dose of mRNA vaccine (BNT162b2) and inactivated SARS-CoV-2 vaccine (CoronaVac) on risks of all-cause mortality, emergency department visit, and unscheduled hospitalization; *BMC Medicine* *(*https://doi.org/10.1186/s12916-022-02321-4*)*
15. Adverse Events of Special Interest Following the Use of BNT162b2 in Adolescents: A Population-Based Retrospective Cohort Study; *Emerging Microbes & Infections* *(*https://doi.org/10.1080/22221751.2022.2050952*)*
16. Autoimmune conditions following mRNA (BNT162b2) and inactivated (CoronaVac) COVID-19 vaccination: A descriptive cohort study among 1.1 million vaccinated people in Hong Kong; *Journal of Autoimmunity* *(*https://doi.org/10.1016/j.jaut.2022.102830*)*
17. Safety of inactivated and mRNA COVID-19 vaccination among patients treated for hypothyroidism: a population-based cohort study; *Thyroid* *(*https://doi.org/10.1089/thy.2021.0684*)*
18. Safety of two-dose COVID-19 vaccination (BNT162b2 and CoronaVac) in adults with cancer: a territory-wide cohort study; *Journal of Hematology & Oncology* *(*https://doi.org/10.1186/s13045-022-01265-9)
19. Messenger RNA Coronavirus Disease 2019 (COVID-19) Vaccination With BNT162b2 Increased Risk of Bell's Palsy: A Nested Case-Control and Self-Controlled Case Series Study; *Clinical Infectious Diseases* *(*https://doi.org/10.1093/cid/ciac460*)*
20. Adverse events of special interest and mortality following vaccination with mRNA (BNT162b2) and inactivated (CoronaVac) SARS-CoV-2 vaccines in Hong Kong: A retrospective study; *PLOS Medicine (*https://doi.org/10.1371/journal.pmed.1004018*)*
21. Association between BNT162b2 or CoronaVac COVID-19 vaccines and major adverse cardiovascular events among individuals with cardiovascular disease; *Cardiovascular Research (*https://doi.org/10.1093/cvr/cvac068*)*

22. Thromboembolic events and hemorrhagic stroke after mRNA (BNT162b2) and inactivated (CoronaVac) covid-19 vaccination: A self-controlled case series study; *eClinicalMedicine (*https://doi.org/10.1016/j.eclinm.2022.101504*)*
23. Safety of an inactivated, whole-virion COVID-19 vaccine (CoronaVac) in people aged 60 years or older in Hong Kong: a modified self-controlled case series; *The Lancet Healthy Longevity (*https://doi.org/10.1016/S2666-7568(22)00125-8*)*
24. Risk of acute liver injury following the mRNA (BNT162b2) and inactivated (CoronaVac) COVID-19 vaccines; *Journal of Hepatology (*https://doi.org/10.1016/j.jhep.2022.06.032*)*
25. The effectiveness and safety of mRNA (BNT162b2) and inactivated (CoronaVac) COVID-19 vaccines among individuals with chronic kidney diseases; *Kidney International (*https://doi.org/10.1016/j.kint.2022.07.018*)*
26. mRNA (BNT162b2) and Inactivated (CoronaVac) COVID-19 Vaccination and Risk of Adverse Events and Acute Diabetic Complications in Patients with Type 2 Diabetes Mellitus: A Population-Based Study; *Drug safety (*https://doi.org/10.1007/s40264-022-01228-6*)*
27. Association between the risk of seizure and COVID-19 vaccinations: A self-controlled case-series study; *Epilepsia (*https://doi.org/10.1111/epi.17436*)*
28. Risk of thyroid dysfunction associated with mRNA and inactivated COVID-19 vaccines: a population-based study of 2.3 million vaccine recipients; *BMC Medicine (*https://doi.org/10.1186/s12916-022-02548-1*)*
29. Risk of glomerular diseases, proteinuria and hematuria following mRNA (BNT162b2) and inactivated (CoronaVac) SARS-CoV-2 vaccines; *Nephrology Dialysis Transplantation (*https://doi.org/10.1093/ndt/gfac292*)*
30. Prognosis of myocarditis developing after mRNA COVID-19 vaccination compared with viral myocarditis; *Journal of the American College of Cardiology (*https://doi.org/10.1016/j.jacc.2022.09.049*)*
31. Tuberculosis following two-dose SARS-CoV-2 vaccination with messenger RNA vaccine (BNT162b2) and inactivated virus vaccine (CoronaVac); *Journal of Infection (*https://doi.org/10.1016/j.jinf.2022.12.016*)*
32. Molnupiravir and nirmatrelvir–ritonavir reduce mortality risk during post-acute COVID-19 phase; *Journal of Infection (*https://doi.org/10.1016/j.jinf.2023.02.029*)*
33. Sex-based differences in risk of ischaemic stroke or systemic embolism after BNT162b2 or CoronaVac COVID-19 vaccination in patients with atrial fibrillation: a self-controlled case series and nested case-control study; *European Heart Journal (*https://doi.org/10.1093/ehjcvp/pvad015*)*

34. Effectiveness of Molnupiravir and Nirmatrelvir–Ritonavir in Hospitalized Patients With COVID-19; *Annals of internal medicine (*https://doi.org/10.7326/M22-3057*)*
35. Risk of carditis after three doses of vaccination with mRNA (BNT162b2) or inactivated (CoronaVac) covid-19 vaccination: a self-controlled cases series and a case–control study; *The Lancet Regional Health - Western Pacific (*https://doi.org/10.1016/j.lanwpc.2023.100745*)*
36. Risk of Adverse Events and Delirium after COVID-19 Vaccination in Patients Living with Dementia; *Journal of the American Medical Directors Association (*https://doi.org/10.1016/j.jamda.2023.04.003*)*
37. Long-term post-acute sequelae of COVID-19 infection: a retrospective, multi-database cohort study in Hong Kong and the UK; *eClinicalMedicine (*https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(23)00177-3/fulltext*)*
38. Post-acute sequelae of COVID-19 in older persons: multi-organ complications and mortality; *Journal of Travel Medicine (*https://doi.org/10.1093/jtm/taad082*)*
39. Incidence of diabetes following COVID-19 vaccination and SARS-CoV-2 infection in Hong Kong: A population-based cohort study; *PLOS Medicine (*https://doi.org/10.1371/journal.pmed.1004274*)*
40. Association between BNT162b2 and CoronaVac vaccination and risk of CVD and mortality after COVID-19 infection: A population-based cohort study; *Cell Reports Medicine (*https://doi.org/10.1016/j.xcrm.2023.101195*)*
41. Effectiveness of molnupiravir vs nirmatrelvir-ritonavir in non-hospitalised and hospitalised patients with COVID-19: a target trial emulation study; *eClinicalMedicine (*https://doi.org/10.1016/j.eclinm.2023.102225*)*
42. Long-term effects of coronavirus disease 2019 on diabetes complications and mortality in people with diabetes: Two cohorts in the UK and Hong Kong; *Diabetes, Obesity and Metabolism (*https://doi.org/10.1111/dom.15279*)*
43. Elevated risk of multimorbidity post-COVID-19 infection: protective effect of vaccination; *QJM: An International Journal of Medicine (*https://doi.org/10.1093/qjmed/hcad236*)*
44. Effectiveness and Respiratory Adverse Events Following Inactivated and mRNA COVID-19 Vaccines in Patients with COPD and Asthma: A Chinese Population-Based Study; *Drug Safety (*https://doi.org/10.1007/s40264-023-01364-7 *)*