Analysis of Bell's Palsy Following Vaccination with mRNA (Comirnaty) and inactivated (CoronaVac) SARS-CoV-2 vaccines: a case series and nested case-control study

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Research in Context

Evidence before this study

We searched PubMed and Embase on 1 July, 2021, for articles in English using the search terms “Bell's palsy”, “facial paralysis”, “SARS-CoV-2”, “COVID”, “BNT162b2”, “vaccines”, “Comirnaty” and “CoronaVac”, with no date restrictions. Most of the studies were either case reports or brief research letters and commentaries. There was one case-control study conducted in Israel to evaluate the association of Bell’s Palsy and Comirnaty. These studies and commentaries reported inconsistent findings on the risk of Bell’s Palsy following Comirnaty. No published study on the risk of Bell’s Palsy following CoronaVac was identified.

Added value of this study

This is one of the first population-based studies that evaluated the association between Bell’s palsy and inactivated COVID-19 vaccines. Our study used three different approaches to evaluate the association: including (1) descriptive case series; (2) estimating the Bell’s palsy incidence differences between vaccinated individuals and historical population, and (3) evaluating the risk of Bell’s palsy using territory-wide surveillance data and nested case-control study. Using different study designs, with different underlying assumptions, this study consistently demonstrates a safety signal and overall increased risk of Bell's palsy after CoronaVac vaccination.

Implications of all the available evidence

We found a signal of increased risk of Bell’s palsy following CoronaVac vaccination. The event is rare and transient. In general over 90% of Bell’s palsy cases, not specific to SARS-CoV-2 vaccines, can be resolved within 9 months following prompt corticosteroid treatment. The beneficial and protective effects of the inactivated COVID-19 vaccine far outweigh the

low risk of this generally self-limiting adverse event. Continued surveillance is essential to closely monitor COVID-19 vaccine safety and the prognosis of COVID-19 vaccine related Bell's palsy cases.

Abstract

Background: Bell's palsy is a rare adverse event reported in clinical trials of COVID-19 vaccines. However, no population-based study has assessed the association between the inactivated SARS-CoV-2 vaccines and Bell's palsy.

Methods: We assessed the risk of Bell's palsy within 42 days following vaccination with Comirnaty from Fosun-BioNTech (equivalent to Pfizer-BioNTech) or CoronaVac from Sinovac Biotech (HK) Limited in Hong Kong through voluntary surveillance reporting channel with the Hospital Authority in HK, reporting system from COVID-19 Vaccine Adverse Event Online Reporting system for all healthcare professionals, and territory-wide electronic health records from Clinical Data Analysis and Reporting System (CDARS) in Hospital Authority. We described reported cases of Bell's palsy and estimated age-standardized incidence rates of the clinically confirmed cases. A nested case-control study was also conducted using conditional logistic regression. Cases and controls were matched in 1:4 ratio by age, sex, admission setting and admission date.

Findings: Between 23 February and 4 May 2021, the total number of individuals who received the first dose of CoronaVac was 451,939 and Comirnaty was 537,205. 28 and 16 cases of clinically confirmed Bell's palsy following CoronaVac and Comirnaty, respectively, were reported voluntarily to the Hong Kong Department of Health. The age-standardized incidence rate of clinically confirmed Bell's palsy was 66.9 (95% confidence interval (CI):37.2-96.6) and 42.8 (95% CI:19.4-66.1) per 100,000 person-years for CoronaVac and Comirnaty vaccination, respectively. The age-standardized rate ratios were 2.64 (95% CI:1.67-4.17) and 1.66 (95% CI:0.95-2.91) times higher than the background population rate equivalent to an additional 4.8

cases for CoronaVac and 2.0 cases for Comirnaty per 100,000 people vaccinated. In the nested case-control analysis, 298 cases were matched to 1181 controls, the adjusted odds ratios were 2.39 (95% CI:1.42-4.02) for CoronaVac and 1.76 (95% CI:0.89-3.48) for Comirnaty.

Interpretation: Our findings generate a safety signal and demonstrate overall increased risk of Bell's palsy after CoronaVac vaccination.

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Introduction

Bell's palsy, also known as acute peripheral facial nerve palsy of unknown cause, commonly manifests with sudden onset of unilateral facial paralysis. Bell's palsy is usually transient with 70% of cases recovering within 6 months without treatment[1]. Timely corticosteroid treatment can increase the chance of recovery to more than 90% by 9 months[2]. However, those with incomplete recovery of facial function may experience incomplete eye closure, brow ptosis, and nasal valve collapse[3] that can potentially affect daily life.

Pfizer-BioNTech (Comirnaty) and Moderna coronavirus (COVID-19) vaccines use messenger ribonucleic acid (mRNA) technology, which are currently widely used in different parts of the world. The clinical trials of these vaccines reported seven cases of Bell's palsy in the vaccinated group of 40,000 patients[4]. The US Food and Drug Administration (FDA) did not consider there to be a clear basis upon which to conclude a causal relationship. Therefore, the FDA recommended further surveillance of these vaccines as they have been authorized for widespread emergency use[5,6]. However, acute peripheral facial paralysis was reported as a rare adverse event in the European Medicines Agency-approved Summary of Product Characteristics (product monograph) of Comirnaty[7] and Moderna[8]. In a letter, Cirillo and Doan reported that the observed incidence of Bell's palsy in the mRNA vaccine arms were between 1.5- to 3-times higher than would be expected in the general population[9]. Authors of a commentary and a correspondence postulated that the risk for Bell's palsy might vary with the types of vaccine platform based on the imbalanced risk identified among mRNA vaccine group[4,9]. However, another research letter reported lack of association between facial paralysis with mRNA COVID-19 vaccines when compared to other viral vaccines in a disproportionality analysis[10]. A recently published case-control study conducted in Israel also reported that there is no association between Bell's palsy and Comirnaty[11]. In addition, there is no published information for Bell's palsy on inactivated COVID-19 vaccines that have been used worldwide

(e.g. CoronaVac from Sinovac Life Sciences Company Limited). The World Health Organization (WHO) recommends the safety surveillance and monitoring on Bell's palsy after CoronaVac vaccination[12].

Currently, the Hong Kong (HK) Government Vaccination Programme provides two authorized COVID-19 vaccines: CoronaVac from Sinovac Biotech (HK) Limited (equivalent to Sinovac Life Sciences Company Limited) and Comirnaty (BNT162b2) from Fosun-BioNTech (equivalent to Pfizer-BioNTech). As the drug regulatory authority, the Drug Office of the Department of Health (DH) in HK has implemented a pharmacovigilance system for COVID-19 vaccines that receives reports of Adverse Events Following Immunization (AEFI). In addition, the Expert Committee on Clinical Events Assessment Following COVID-19 Immunization ("Expert Committee") was set up to provide independent clinical adjudication of potential causal links between AEFI and locally authorized COVID-19 vaccines. Bell's palsy is an AEFI listed under intensive monitoring.

This study aims to describe cases reported to the DH and their causality classifications up to 4 May 2021 according to the WHO classification[13]. Second, to estimate the differences in incidence rates for Bell's palsy among vaccinated individuals as compared with historical population rates. Third, to assess the association between COVID-19 vaccination and Bell's palsy using a nested case-control study.

Methods

Case series

Adverse event data were based on voluntary reports received by the DH from all healthcare professionals via the territory-wide COVID-19 Vaccine Adverse Event on-line Reporting System[14] and the established reporting channel with the Hospital Authority (HA), the statutory body which serves as a major publicly-funded healthcare provider[15].

Upon receipt of serious or unexpected AEFI reports, the DH will immediately contact the reporting healthcare professionals for further clinical information. All cases of reported Bell's palsy are then assessed by the Expert Committee. Based on the information provided and subsequent follow-up information if appropriate, the Expert Committee will confirm whether cases are consistent with the clinical diagnosis of Bell's palsy (clinically confirmed cases). With the follow up information, some reported cases were reclassified to other conditions, such as stroke and Ramsay Hunt Syndrome. The Committee conducted causality assessment of clinically confirmed cases according to the WHO classification (Supplementary information 1)[13].

Comparison of incidence rates

HA has a comprehensive electronic health records system for clinical management. Data from the HA electronic health records are de-identified and then transferred daily to Clinical Data Analysis and Reporting System (CDARS) (Supplementary information 2), which has been used for pharmacovigilance studies to evaluate safety of medicine[16-19].

The incidence of clinically confirmed Bell's palsy per 100,000 doses administered were reported. To estimate the background incidence rate of Bell's palsy, incident Bell's palsy events in the same study period [the period from the launch of mass COVID-19 vaccination (23 February 2021 for CoronaVac; 6 March 2021 for Comirnaty) to the date of data analysis (4 May 2021)] between 2010 and 2020 were captured in CDARS. Rollout schedule of the vaccination program is stated in Supplementary Table 1 which includes people with specific types of employment such as healthcare workers, transport service operators and elderly population. Incident Bell's palsy was defined as the first diagnosis in CDARS using the

International Classification of Diseases, Ninth Revision, Clinical Modification codes 351.0, 351.8, and 351.9. Population data for HK between 2010 and 2021 were obtained from the HK Census and Statistics Department. Meanwhile, the number of reported and clinically confirmed cases in case series mentioned above were used for the incident case of Bell's palsy for CoronaVac and Comirnaty. The reported cases with misclassification after assessment by the Expert Committee were excluded in the number of clinically confirmed cases. Population-wide vaccination records were provided by the DH and vaccine recipients were excluded if they were below 18 and 16 years of age for CoronaVac and Comirnaty respectively, because these recipients were likely to be clinical trial participants. Those over 110 years of age were excluded due to potential error in the age recording. Each vaccine recipient was followed up from the date of vaccination to 42 days after the first or second dose or 4 May 2021, whichever was earlier. The 42 days is the upper end of reporting of Bell's palsy case following vaccination in the DH and HA reporting policies.

Nested case-control study

Cases were defined as patients first diagnosed with Bell's palsy in the emergency room and inpatient setting between 23 February and 3 May 2021. These cases were identified using CDARS. Cases with a subsequent diagnosis of stroke or Ramsay Hunt Syndrome were excluded. All other patients attending HA emergency rooms, or if hospitalized during the same period, and without a diagnosis of Bell's palsy were selected as controls. Medical and medication history was also extracted from CDARS. Patients aged less than 18 years were excluded in the analysis as they are unlikely to receive vaccines. Patients with a history of Bell's palsy were also excluded. Four controls were randomly matched with the cases according to sex, age, date of attendance (within three calendar days), and the setting (emergency room or hospitalization). Vaccination status was ascertained by linking CDARS data to COVID-19 vaccination records from DH. Vaccine recipients were defined if patients

received the vaccination on or before the date of first diagnosis with Bell's palsy for the case, and the date of the hospitalization or emergency room visit for the control. Sample size and power estimation can be found in Supplementary Figure 1. We anticipated the sample size would not be sufficient to conduct a direct comparison of CoronaVac and Comirnaty, therefore, such analysis was not conducted. The voluntary surveillance also includes a small number of cases from the private healthcare sector; therefore, the data sources of the case series and case control analysis were slightly different.

Statistical analysis

Comparison of incidence rates

The age-standardized incidence rate for the background incidence rate from 2010 onwards, CoronaVac and Comirnaty in 5-year age intervals against the HK population in 2021 was calculated. The age-standardized incidence rate for CoronaVac and Comirnaty was compared with the background incidence rate in 2020. Subgroup analysis was conducted by sex. Sensitivity analyses were conducted by using the background incidence rate in 2018 and 2019 and the average background incidence rate from 2015 and 2019 rather than in 2020. We also conducted analyses by assuming the actual background incidence rate was 50% higher than reported to account for potential under-reporting in 2020 before COVID-19 vaccines were available and cases from the private healthcare sector. Furthermore, we also excluded Bell's palsy cases with extreme onset time defined as less than 1 day after vaccination.

Nested case-control study

Conditional logistic regression adjusted for patient characteristics, including smoking habit, diabetes mellitus, hypertension, asthma, neoplasms, acute respiratory infections, viral infections, rheumatoid arthritis, stroke, migraine, usage of antiviral drugs, systemic

corticosteroids, antibacterial drugs, immunosuppressants and statins was performed to estimate the adjusted odds ratio for risk of Bell's palsy and vaccination. Subgroup analysis was conducted by sex (male and female) and age (<60; ≥60 years old). Post-hoc analysis was performed by duration between vaccination and diagnosis of Bell's palsy (≤14; >14 days), number of doses (completed 1st dose only; completed both 1st and 2nd doses). Sensitivity analyses were conducted by excluding Bell's palsy cases with extreme onset time defined as less than 1 day after vaccination.

All statistical tests were two sided and P values at the 5% level were considered statistically significant. Statistical analysis was conducted using R version 4.0.3 (www.R-project.org). For quality assurance, two investigators (EW and VY) independently conducted the statistical analyses. We followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement checklists to guide transparent reporting of the case-control study[20].

Role of the funding source

This is a regulatory pharmacovigilance study initiated by the DH and funded via Food and Health Bureau of the Government of the Hong Kong Special Administrative Region. The sponsor of the study had been involved in study design, data collection, data analysis, data interpretation and writing of the report via the DH. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Ethical approval

Ethical approval for this study was granted by the Institutional Review Board of the University of HK/HA HK West Cluster (UW21-149 and UW21-138); and the DH Ethics Committee (LM21/2021).

Results

From the commencement of vaccination programme, 33 and 20 cases of Bell's palsy were reported after CoronaVac and Comirnaty, respectively to DH via passive surveillance system. Supplementary Table 2 describes the demographic, general case description, and causality assessment of reported cases. After assessment by the Expert Committee, 9 of the 53 cases were reclassified as not Bell's palsy cases. Clinical causality adjudication was conducted for 28 cases in CoronaVac and 16 cases in Comirnaty. A total of 42 and 2 cases were classified as B (Indeterminate) and D (inadequate information; Case No: S13 and B7), respectively. For the clinically confirmed cases who received CoronaVac, the median age was 57.5 years(range 26-87years), 67.9%(19/28) were male, 67.9%(19/28) occurred after the first dose, 71.4%(20/28) were left-sided facial paralysis, and 89.3%(25/28) were reported within 21 days after vaccination (Supplementary Figure 2). For the clinically confirmed cases who received Comirnaty, the median age was 47.5 years(range 20-78years), 62.5%(10/16) were male, 50%(8/16) occurred after the first dose, 50%(8/16) were left-sided facial paralysis, and 100%(16/16) were reported within 21 days after vaccination (Supplementary Figure 2).

A total of 776,571 doses of CoronaVac and 785,162 doses of Comirnaty were administered between 23 February 2021 and 4 May 2021, after excluding 55 people aged <18 or >110 years for CoronaVac administration, 230 people aged <16 or >110 years for Comirnaty administration and 294 people with incomplete records. 451,939 and 537,205 individuals received the first dose of CoronaVac and Comirnaty, respectively. Among these, 324,632 (71.8%) and 247,957 (46.2%) individuals received the second dose of CoronaVac and Comirnaty, respectively. The incidence of clinically confirmed Bell's palsy was 3.61 (95% confidence interval[CI]:2.40-5.21) for CoronaVac and 2.04 (95%CI:1.16-3.31) for Comirnaty per 100,000 doses administered. The age-standardized incidence rates for Bell's palsy from 2010 onwards for CoronaVac and Comirnaty in the reporting period are shown in Figures 1 and Table 1. Overall, the age-standardized incidence rate of clinically confirmed Bell's palsy

was 66.9 (95%CI:37.2-96.6) and 42.8 (95%CI:19.4-66.1) per 100,000 person-years for CoronaVac and Comirnaty vaccination, respectively. The age-standardized incidence rate difference compared to the background incidence rate in the same period in 2020 was 41.5 (95%CI:11.7-71.4) and 17.0 (95%CI:-6.6-40.6) per 100,000 person-years, indicating that an additional 4.8 and 2.0 cases per 100,000 people within 42 days of receiving the vaccine for CoronaVac and Comirnaty, respectively. Results were similar in all sensitivity analyses (Supplementary Table 3-6). When we assume that the actual background rate was 50% higher than reported, the overall estimates for CoronaVac and the male subgroup remained statistically significant. Other results are in the same direction but no longer statistically significant (Supplementary Table 7).

Figure 2 shows the selection of cases and controls into the nested case-control study. A total of 298 cases of Bell's palsy were successfully matched to 1181 controls. Table 2 and Supplementary Table 8 summarizes the characteristics of the cases, controls, and all individuals by vaccine exposure. 28 cases and 53 controls received the CoronaVac vaccine; 14 cases and 31 controls got the Comirnaty vaccine. Table 3 shows the adjusted odds ratios of Bell's palsy after vaccination. The results indicated a higher risk of Bell's palsy associated with receiving CoronaVac (adjusted odds ratio: 2.39, 95%CI:1.42–4.02), but non-statistically significant increase in risk of Bell's palsy was observed in those receiving Comirnaty (adjusted odds ratio: 1.76, 95%CI:0.89–3.48). The findings of sex and age subgroup analyses were similar to the main results except for non-statistically significant increase in risk of Bell's palsy in women receiving CoronaVac. Regarding post-hoc analyses on diagnosis interval after vaccination and number of doses, the risk of Bell's palsy in people completed both 1st and 2nd dose of CoronaVac became non-statistically significant increase. The risk in longer than 14 days between Comirnaty vaccination and diagnosis of Bell's palsy in recipients completed both 1st

and 2nd dose of Comirnaty became statistically significant increase (Table 3). Results are consistent in the sensitivity analysis (Supplementary Table 9).

Discussion

This population-based study in HK showed evidence of increased risk of Bell's palsy following CoronaVac vaccination. Notably, Bell's palsy is not listed in the current prescribing information of CoronaVac and no other case reports were identified via our literature search. However, similar to other pharmacoepidemiological studies, we cannot conclude a causal relationship between CoronaVac vaccination and individual Bell's palsy cases purely based on statistical association. A previous study, using the WHO Pharmacovigilance Database, reported no higher risk of facial paralysis in mRNA COVID-19 vaccines compared to other viral and influenza vaccines using a disproportionality analysis of spontaneous adverse drug reaction reports[10]. Another case-control study of 37 patients with acute-onset facial nerve palsy conducted in Israel did not report any significant association with Comirnaty[11]. However, potential signals for Bell's palsy have been reported with several other vaccines including parenteral seasonal influenza vaccines and the influenza H1N1 monovalent pandemic vaccine[4].

Our study showed the average background incidence rate of Bell's palsy in HK was around 27 per 100,000 person-years during the past decade, which is very similar to global estimates that range from 15 to 30 cases per 100,000 person-years[4,21]. A previous ecological analysis using background population rates deduced similar relative risk of 1.5- to 3-times times higher for COVID-19 mRNA vaccines associated with the Bell's palsy compared to our estimation[4,9].

The mechanism of Bell's palsy in patients following vaccination is unclear. One hypothesis linking the trigger of Bell's palsy with autoimmune phenomenon, which is thought to occur via either mimicry of host molecules by the vaccinal antigen or bystander activation of dormant autoreactive T-cells[22]. Other possible mechanisms include reactivation of latent herpes simplex

type 1 infections of the geniculate ganglia of facial nerves[23-25]. It could also be secondary to an immune-mediated segmental demyelination similar to Guillain-Barré syndrome[26,27]. A more biological reason could be explained by the transient interference with peripheral nerve function resulting in facial nerve compression within the facial canal, due to accumulation of the vaccine content, for example the accumulation of LTK63 molecules, or inflammation arising from immune response to LTK63, following a ganglioside binding and retrograde neuronal transport after intranasal delivery of an inactivated vaccine by a genetically detoxified mutant *Escherichia coli* head labile toxin[28]. Inactivated vaccine technology has been widely used to produce vaccines against other viral infections, such as influenza. It is known that inactivated virus consists of a variety of viral antigens which may alter the immune response in a wider group of patients[29]. In contrast, the Comirnaty vaccine might induce innate immune activation and production of interferon proteins by a combined effect of mRNA and lipids[4]. Interferon therapy has been reported to cause facial nerve palsy[30]. While several potential individual pathways including viral, autoimmune reaction or innate immune activation were hypothesized, these mechanisms may be multicausal and unlikely to be applicable to all cases such as onset with varying interval after vaccination. Further investigation should be conducted to verify the mechanism of Bell's palsy following COVID-19 vaccination.

No sex-based difference were observed in recipients of Comirnaty, which is inconsistent when compared with the World Health Organization Pharmacovigilance Database that reported 67.8% of reported cases were female for mRNA COVID-19 vaccines[10]. This discrepancy may be attributable to reporting bias. However, our observations showed that a higher proportion of Bell's palsy cases after CoronaVac vaccination were men, we cannot exclude the possibility of sex differences in the risk of Bell's palsy following CoronaVac vaccination. In addition, we are short in sample size to detect statistically significant results in the subgroup analyses of female according to our sample size calculations. Similarly, we could not rule out the

possibility of the risk of Bell's palsy associated with administration of Comirnaty, including post-hoc analyses of the effect of the duration between vaccination and diagnosis as well as the dose-response. Our post-hoc analyses are underpower which can only serve as exploratory analyses in this study. We detected another potential signal of Comirnaty, however, it did not affect the conclusion of our primary analysis about CoronaVac. More importantly, due to the nature of post-hoc analysis which may introduces biases, over-interpretation of the post-hoc analysis results should be discouraged. Further studies with sufficient sample size are needed to evaluate this potential signal.

Several study limitations should be noted. First, the passive surveillance of Bell's palsy cases relied on voluntary reporting from healthcare professionals, the extent of under-reporting remains unknown. However, under current pandemic situation, the top emergency response level activated by the DH, healthcare professionals would be inclined to report suspicious cases more than the pre-vaccination period, which may result in an increase of reported cases. The results of the sensitivity analyses by assuming the background rates are 50% higher did not change the direction of the estimated incidence rate ratios which further support the robustness of our results. Second, those pre-vaccination reported cases might have false positives, although this would further strengthen the hypothesis of the possible cause of Bell's palsy by vaccinations. However, our background incidence rate in HK was within the range of the global estimation[4,21], it should not affect our interpretation of the results. Third, we were unable to investigate cases of Bell's palsy presenting to private clinics and hospitals. Hence, the background incidence rate may be underestimated, but as stated above, our sensitivity analyses are consistent with our observed rates and they are within the range of the global estimates[4,21]; therefore, the underestimation is likely to be minimal. Fourth, the controls in a nested case-control study may be also misclassified. However, given the low incidence of Bell's palsy (approximately 27 incident events per 100,000 person-years) in HK, the probability of

misclassification in control group should be negligible and have no effect on our results. Fifth, socioeconomic status and education level may be important confounders but not available in the current study. Sixth, the duration of reporting Bell's palsy cases subsequent to COVID-19 vaccines was 42 days in HK voluntary reporting surveillance system, therefore, cases that occurred more than 42 days after vaccination were not captured in this case series study. However, Supplementary Figure 2 showed that most of the clinically confirmed Bell's palsy cases from voluntary reporting surveillance system occurred within 21 days from vaccination. Cases that occurred more than 42 days after vaccination is likely to be the background incidence. Hence, underestimation is not likely. Finally, the current study is limited to the patients with a new diagnosis of Bell's palsy in HK, and thus further studies including patients with previous history of Bell's palsy and in other regions should be warranted to confirm our finding.

Conclusion

Our study shows a signal and overall increased risk of Bell's palsy after CoronaVac vaccination. Nevertheless, Bell's palsy is a rare and transient AEFI. In general over 90% of Bell's palsy cases, not specific to SARS-CoV-2 vaccines, can be resolved within 9 months following prompt corticosteroid treatment. The beneficial and protective effects of the inactivated COVID-19 vaccine far outweigh the risk of this generally self-limiting adverse event. Additional studies are needed in other regions to confirm our findings.

Data sharing statement:

Data will not be available for others as the data custodians have not given permission.

Author contributions:

EYFW, CSLC and ICKW had the original idea for the study, contributed to the development of the study, extracted data from the source database, constructed the study design and the

statistical model, reviewed the literature, and act as guarantors for the study. EYFW, VKCY, FTTL, LG, QY undertook the statistical analysis. EYFW and ICKW wrote the first draft of the manuscript. CSLC, VKCY, LG, QY, RKCC, WCF, VCTM, IFNH, FLFC, LSTC and DL extracted data from the source database and validated case reports and the diagnosis codes from the database. ICKW is the principal investigator and provided oversight for all aspects of this project. FFTL, EWYC, XL, ICHL, BJC, WCF, VCTM, CKL, IFNH and GML provided critical input to the analyses, design and discussion. All authors contributed to the interpretation of the analysis, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

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Conflict of interest:

EYFW has received research grants from the Food and Health Bureau of the Government of the Hong Kong SAR, and the Hong Kong Research Grants Council, outside the submitted work. CSLC has received grants from the Food and Health Bureau of the Hong Kong Government, Hong Kong Research Grant Council, Hong Kong Innovation and Technology Commission, Pfizer, IQVIA, and Amgen; personal fee from Primevigilance Ltd.; outside the submitted work. FTTL has been supported by the RGC Postdoctoral Fellowship under the Hong Kong Research Grants Council and has received research grants from Food and Health Bureau of the

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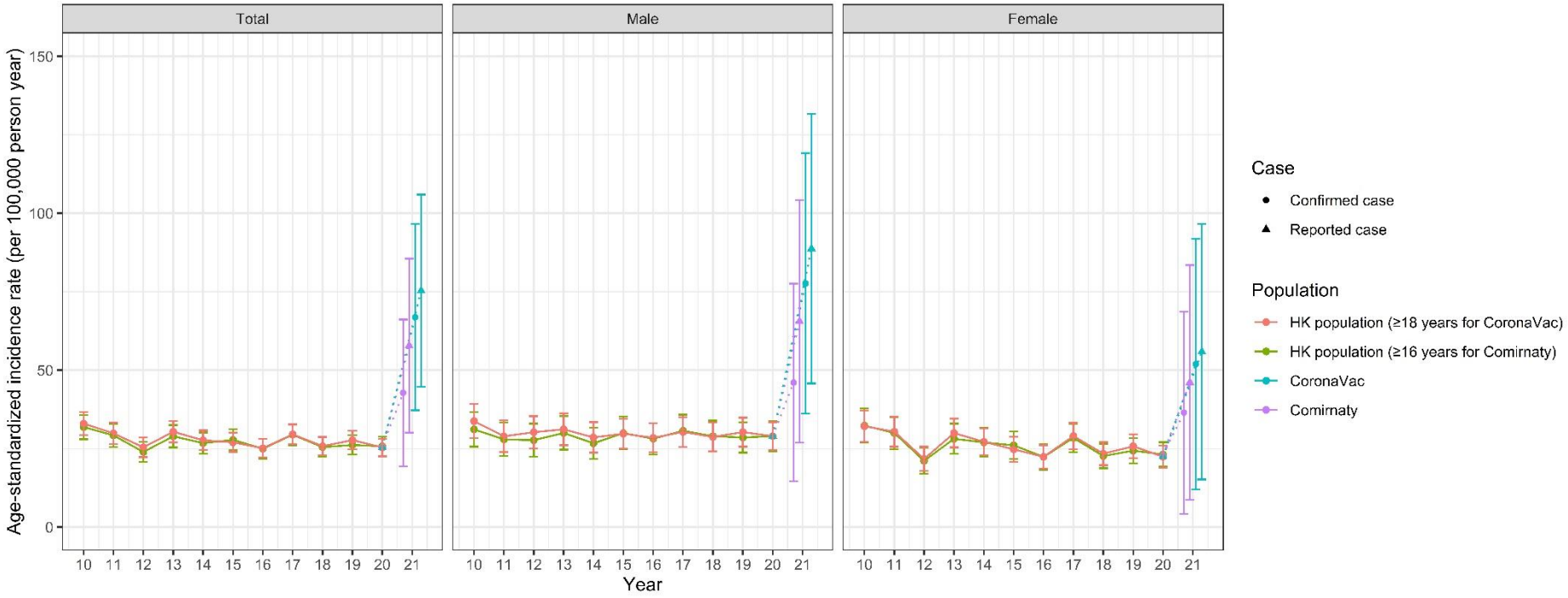
Figure 1. Overall and sex-specific age-standardized incidence rate of Bell's palsy in people after CoronaVac and Comirnaty vaccination and the Hong Kong population (2010 to 2021)



The background incidence rates were calculated using the same reporting period (For CoronaVac, February 23, 2021-May 4, 2021; For Comirnaty, March 6, 2021-May 4, 2021) in 2010-2021. The number of reported and clinically confirmed cases in people exposed to Comirnaty were the same for females. Thus, the lines for reported and clinically confirmed cases in Comirnaty overlap. The bar is 95% confidence interval of the age-standardized incidence rate.

Figure 2. Selection of cases and controls for the nested case-control study

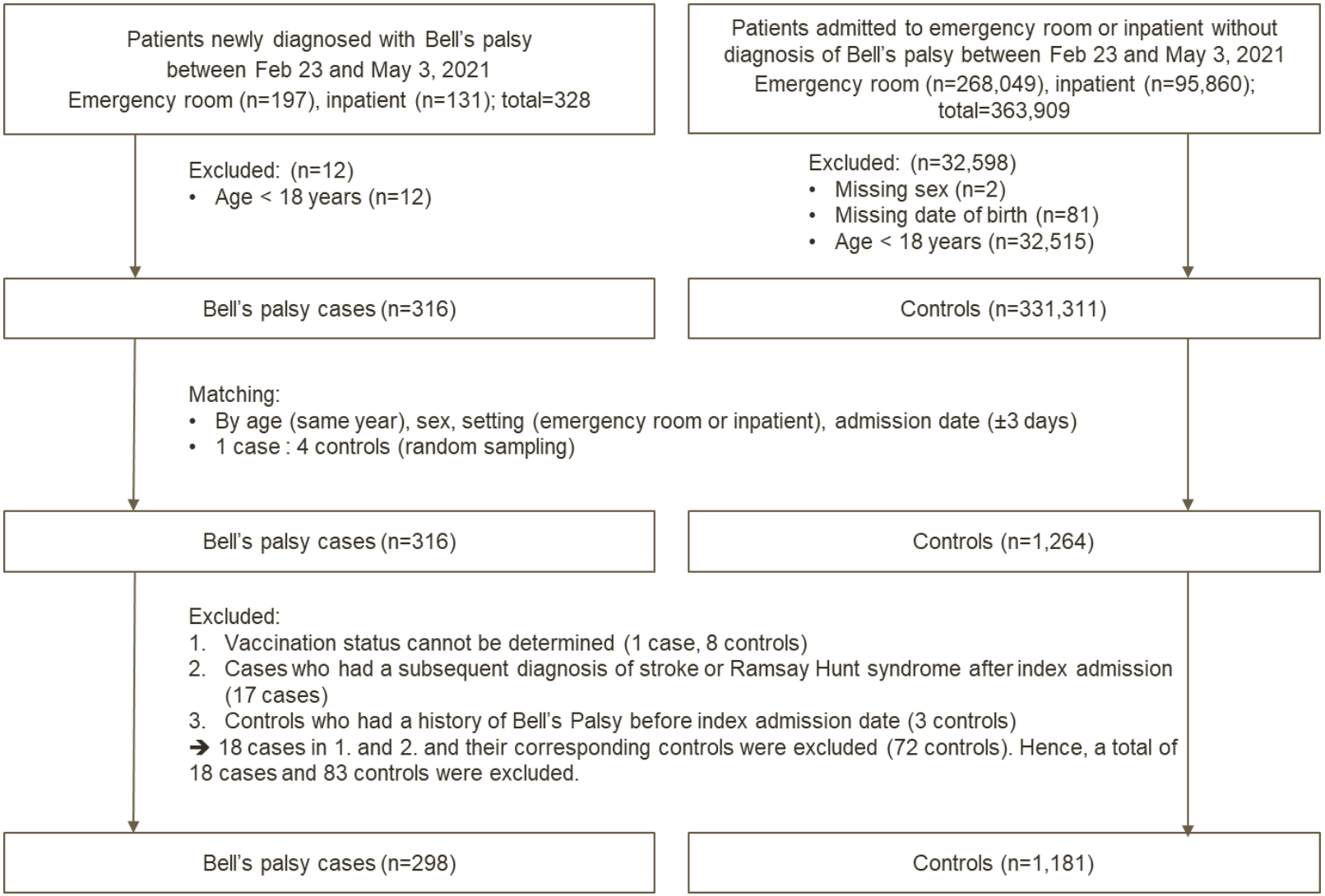


Table 1. Standardized rate ratios of reported and clinically confirmed Bell's palsy cases following vaccination with CoronaVac and Comirnaty by sex

	Age-standardized background incidence rate in 2020† (per 100,000 person-years)	Age-standardized incidence rate (per 100,000 person-years)		Age-standardized incidence rate difference (per 100,000 person-years)		Age-standardized rate ratio (95% CI)	
		Reported	Clinically confirmed	Reported	Clinically confirmed	Reported	Clinically confirmed
CoronaVac							
Total	25.3 (22.6-28.1)	75.3 (44.7-105.9)	66.9 (37.2- 96.6)	49.9 (19.2- 80.7)	41.5 (11.7-71.4)	2.97 (1.95-4.53)	2.64 (1.67-4.17)
Male	29.0 (24.5-33.4)	88.7 (45.7-131.6)	77.6 (36.1-119.2)	59.7 (16.6-102.9)	48.7 (6.9-90.4)	3.06 (1.84-5.09)	2.68 (1.54-4.68)
Female	22.4 (18.9-26.0)	55.9 (15.1- 96.6)	51.9 (11.9- 91.9)	33.4 (-7.4- 74.3)	29.5 (-10.6-69.6)	2.49 (1.18-5.25)	2.31 (1.05-5.08)
Comirnaty							
Total	25.7 (22.7-28.8)	57.8 (30.1- 85.5)	42.8 (19.4- 66.1)	32.1 (4.2- 59.9)	17.0 (-6.6-40.6)	2.25 (1.37-3.68)	1.66 (0.95-2.91)
Male	28.9 (24.1-33.8)	65.5 (26.9-104.2)	46.1 (14.6- 77.5)	36.6 (-2.3- 75.5)	17.1 (-14.7-49.0)	2.26 (1.23-4.18)	1.59 (0.79-3.22)
Female	23.1 (19.2-27.0)	46.1 (8.7- 83.5)	36.4 (4.2- 68.7)	23.0 (-14.6- 60.5)	13.3 (-19.2-45.8)	1.99 (0.87-4.56)	1.58 (0.64-3.88)

†The background incidence rates were calculated using the same reporting period (For CoronaVac, February 23, 2021-May 4, 2021; For Comirnaty, March 6, 2021-May 4, 2021) in 2020.

Table 2. Baseline characteristics of patients in the nested case-control study

Characteristics	**Case patients** (N=298)	**Controls** (N=1181)
Age - mean (SD)	57.3 (17.3)	57.4 (17.2)
Male – no. (%)	158 (53.0)	627 (53.1)
Admission setting – no. (%)		
Inpatient	112 (37.6)	447 (37.8)
Emergency room	186 (62.4)	734 (62.2)
Smoker – no. (%)	2 (0.7)	10 (0.8)
Pre-existing comorbidities† – no. (%)		
Diabetes mellitus	58 (19.5)	198 (16.8)
Hypertension	84 (28.2)	337 (28.5)
Asthma	7 (2.3)	26 (2.2)
Neoplasms	14 (4.7)	151 (12.8)
Acute respiratory infections	1 (0.3)	14 (1.2)
Viral infections	4 (1.3)	2 (0.2)
Rheumatoid Arthritis	1 (0.3)	5 (0.4)
Head trauma	0 (0.0)	0 (0.0)
Stroke	18 (6.0)	69 (5.8)
Guillain–Barré syndrome	0 (0.0)	0 (0.0)
Migraine	2 (0.7)	7 (0.6)
Medication use within 90 days – no. (%)		
Antiviral drugs	13 (4.4)	40 (3.4)
Systemic corticosteroids	19 (6.4)	48 (4.1)
Antibacterial drugs	21 (7.0)	156 (13.2)
Immunosuppressants	1 (0.3)	24 (2.0)
Statins	79 (26.5)	315 (26.7)
Isoniazid	0 (0.0)	3 (0.3)

†For pre-existing comorbidities, diagnosis within 90 days before index date were considered for acute respiratory infections and viral infections, and diagnosis before index date were considered for other diseases.

Table 3. Risk of Bell's palsy among participants in the nested case-control study.

Vaccine and Sex	Case patients (N=298)	Controls (N=1181)	Crude odds ratio (95% CI)	P-value	Adjusted odds ratio (95% CI)	P-value
Total						
Not vaccinated	256	1097	(Ref)		(Ref)	
CoronaVac	28	53	2.451 (1.477 - 4.067)	0.0005	2.385 (1.415 - 4.022)	0.0011
Comirnaty	14	31	2.062 (1.061 - 4.009)	0.033	1.755 (0.886 - 3.477)	0.11
Subgroup analysis						
Male						
Not vaccinated	128	575	(Ref)		(Ref)	
CoronaVac	22	35	3.130 (1.698 - 5.770)	0.0003	2.892 (1.541 - 5.426)	0.0009
Comirnaty	8	17	2.194 (0.915 - 5.259)	0.078	1.970 (0.820 - 4.734)	0.13
Female						
Not vaccinated	128	522	(Ref)		(Ref)	
CoronaVac	6	18	1.411 (0.538 - 3.704)	0.48	1.332 (0.496 - 3.574)	0.57
Comirnaty	6	14	1.869 (0.674 - 5.180)	0.23	1.772 (0.629 - 4.991)	0.28
Age<60						
Not vaccinated	125	540	(Ref)		(Ref)	
CoronaVac	15	28	2.563 (1.262 - 5.204)	0.0092	2.618 (1.272 - 5.388)	0.0090
Comirnaty	10	24	1.833 (0.850 - 3.953)	0.12	1.696 (0.779 - 3.694)	0.18
Age≥60						
Not vaccinated	131	557	(Ref)		(Ref)	
CoronaVac	13	25	2.377 (1.145 - 4.933)	0.020	2.362 (1.097 - 5.086)	0.028
Comirnaty	4	7	3.053 (0.786 - 11.863)	0.11	2.338 (0.515 - 10.611)	0.27

Post-hoc analysis						
Within 14 days between vaccination and diagnosis of Bell's palsy						
Not vaccinated	256	1,023	(Ref)		(Ref)	
CoronaVac	14	20	3.354 (1.520 - 7.402)	0.0027	3.264 (1.455 - 7.318)	0.0041
Comirnaty	6	19	1.271 (0.495 - 3.260)	0.62	1.071 (0.415 - 2.760)	0.89
Longer than 14 days between vaccination and diagnosis of Bell's palsy						
Not vaccinated	256	1,029	(Ref)		(Ref)	
CoronaVac	14	23	2.448 (1.231 - 4.868)	0.011	2.320 (1.124 - 4.789)	0.023
Comirnaty	8	9	3.943 (1.411 - 11.019)	0.0089	3.778 (1.251 - 11.410)	0.019
Completed 1st dose only						
Not vaccinated	256	1,038	(Ref)		(Ref)	
CoronaVac	21	28	3.311 (1.772 - 6.185)	0.0002	3.200 (1.679 - 6.099)	0.0004
Comirnaty	5	18	1.093 (0.397 - 3.011)	0.86	0.853 (0.290 - 2.507)	0.77
Completed 1st and 2nd dose						
Not vaccinated	256	1,014	(Ref)		(Ref)	

CoronaVac	7	19	1.459 (0.592 - 3.599)	0.41	1.453 (0.575 - 3.676)	0.43
Comirnaty	9	12	3.201 (1.287 - 7.962)	0.012	3.162 (1.245 - 8.036)	0.016

Cases and controls were matched according to age, sex, setting, and admission date. Odds ratios for Bell's palsy were estimated by conditional logistic regression adjusted for smoking status, pre-existing comorbidities (diabetes mellitus, hypertension, asthma, neoplasms, rheumatoid arthritis, stroke, migraine, infections in the past 90 days (acute respiratory infections, viral infections), and medication use in the past 90 days (antiviral drugs, systemic corticosteroids, antibacterial drugs, immunosuppressants). The list of confounders in the model for subgroup and post-hoc analyses is shown in the Supplementary table 10. CI denotes confidence interval.

Supplementary Appendix

Supplementary Table 1. Vaccination program priority groups rollout schedule in Hong Kong

Order of expansion	Date of rollout	Vaccination group
First [1]	26 Feb, 2021	• Healthcare workers and staff involved in anti-epidemic work • Persons aged 60 or above and a maximum of 2 carers accompanying elderly people aged above 70 • Residents and staff of residential care homes for the elderly and persons with disabilities • People providing essential public services • People providing cross-boundary transportation or working at control points and ports
Second [2]	8 Mar, 2021	• Staff of food and beverages premises, markets, supermarkets, convenience stores, couriers and takeaway delivery • Staff of local public transport service operators • Registered construction workers • Staff of property management • Teachers and school staff • Staff in the tourism industry • Staff of scheduled premises under the Prevention and Control of Disease
Third [3]	16 Mar, 2021	• People aged between 30 and 59 • Students aged 16 or above studying outside Hong Kong • Domestic helpers
Four [4]	15 Apr, 2021	• People aged 16 to 29 (18 for person receiving Sinovac vaccine)

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2. The Government of the Hong Kong Special Administrative Region. Government expands scope of priority groups and opens more CVCs. Press Releases. 8 Mar 2021 (https://www.info.gov.hk/gia/general/202102/18/P2021021800767.htm?fontSize=1)
3. The Government of the Hong Kong Special Administrative Region. Vaccination priority groups to be expanded to cover people aged 30 or above. Press Releases. 15 Mar 2021 (https://www.info.gov.hk/gia/general/202103/15/P2021031500626.htm?fontSize=1)
4. The Government of the Hong Kong Special Administrative Region. COVID-19 Vaccination Programme opens to persons aged 16 or above. Press Releases. 15 Apr 2021 (https://www.info.gov.hk/gia/general/202104/15/P2021041500565.htm?fontSize=1)

Supplementary Table 2. Characteristics of the reported cases of Bell's palsy to the Department of Health

Case No.	Sex	Age	COVID-19 Vaccine Dose Received	Interval to symptom onset	Side affected	Clinical outcomes (As of 31 May 2021)	Causality assessment (For clinically confirmed Bell's palsy case)†
Clinically confirmed cases after CoronaVac vaccination							
S1	M	69	First	2 hours	Left	Fully recovered with treatment.	B2
S2	M	72	First	6 days	Right	Almost fully recovered with treatment.	B1
S3	M	86	First	13 days	Left	Good recovery with treatment. Mild left angle of mouth weakness at last follow-up on 13 Apr 2021 (28 days after symptom onset.)	B1
S4	M	52	First	16 days	Left	Almost fully recovered with treatment.	B1
S5	M	54	First	8 days	Left	Good recovery with treatment. Slight residual palsy on left corner of mouth at last follow-up on 9 Apr 2021 (24 days after symptom onset).	B1
S6	M	74	First	6 days	Left	Lost to follow up.	B1
S7	M	58	First	17 days	Left	No follow up was scheduled.	B1
S8	M	79	First	14 days	Left	Follow up was scheduled and pending assessment.	B2
S9	M	76	First	14 days	Left	Fully recovered with treatment	B1
S10	M	26	First	1 hour	Left	Almost fully recovered with treatment. Minimal drooping of left angle of mouth at last follow up on 6 May 2021 (43 days after symptom onset).	B2

S11	M	67	Second	3 days	Right	Good recovery with treatment. Facial weakness improved at last follow-up on 5 May 2021 (37 days after symptom onset).	B1
S12	M	48	First	2 days	Left	Lost to follow up.	B1
S13	F	36	Second	3 days	Right	Almost fully recovered without treatment.	D
S14	F	38	First	3 days	Left	Good recovery with treatment. Complete eyelid closure with mild decreased left face movement at last follow-up on 20 May 2021 (51 days after symptom onset).	B1
S15	M	63	Second	1 day	Left	Good recovery with treatment. Facial asymmetry improved at last follow-up on 7 May 2021 (32 days after symptom onset).	B1
S16	F	31	First	19 days	Left	Good recovery with treatment. Complete eyelid closure at last follow-up on 6 May 2021 (29 days after symptom onset).	B1
S17	F	66	Second	2 days	Right	Follow up was scheduled and pending assessment.	B1
S18	F	64	First	1-2 weeks	Left	Good recovery with treatment. Facial asymmetry improved at last follow-up on 4 May 2021 (40-47 days after symptom onset).	B1
S19	M	35	Second	1 day	Right	Good recovery with treatment. Facial weakness improved with complete eyelid closure at last follow-up on 26 Apr 2021 (16 days after symptom onset).	B1
S20	M	44	First	16 days	Right	Good recovery with treatment. Functions of right facial nerve improved at last follow-up on 10 May 2021 (30 days after symptom onset).	B1
S21	F	50	First	17 days	Left	Good recovery with treatment. Facial weakness improved at last follow-up on 28 May 2021 (48 days after symptom onset).	B1
S22	M	35	Second	13 days	Left	Similar left facial weakness at last follow-up on 18 May 2021 (33 days after symptom onset).	B1

S23	F	52	First	26 days	Left	Lost to follow up.	B1
S24	M	59	Second	< 1 day	Left	Fair recovery with treatment. Symptoms slightly improved at last follow up on 5 May 2021 (9 days after symptom onset).	B1
S25	F	57	Second	16 days	Left	Follow up was scheduled on 20 May 2021 and pending follow up information on clinical progress.	B1
S26	M	71	Second	17 days	Left	Follow up was scheduled on 31 May 2021 and pending follow up information on clinical progress.	B1
S27	M	32	First	21 days	Right	Fully recovered with treatment.	B1
S28	F	87	First	42 days	Left	Follow up was scheduled and pending assessment.	B1
Excluded cases after CoronaVac vaccination							
S29	M	57	First	1 day	Left	Attending physician reviewed the case and revised the diagnosis to Ramsay Hunt Syndrome.	
S30	M	55	First	2 days	Not Applicable	Attending physician reviewed the case and considered not Bell's palsy. The case discharged against medical advice and no specific diagnosis was concluded.	
S31	M	56	Second	2 hours	Left	Attending physician reviewed the case and considered not Bell's palsy.	
S32	F	40	First	3 days	Left	Attending physician reviewed the case and revised the diagnosis to rhinitis.	
S33	M	69	Second	28 days	Right	Attending physician reviewed the case and revised the diagnosis to Ramsay Hunt Syndrome.	
Clinically confirmed cases after Comirnaty vaccination							
B1	M	37	First	6 days	Right	Good recovery with treatment. Complete eyelid closure at last follow-up on 20 Apr 2021 (32 days after symptom onset).	B2

B2	F	48	First	18 days	Left	Lost to follow up.	B1
B3	M	58	Second	1 day	Left	Good recovery with treatment. Complete eyelid closure at last follow-up on 14 May 2021 (37 days after symptom onset).	B1
B4	M	46	Second	3 days	Left	Good recovery with treatment. Facial weakness much improved at last follow-up on 5 May 2021 (26 days after symptom onset).	B1
B5	F	65	First	20 days	Right	Good recovery with treatment. Facial weakness much improved at last follow-up on 10 May 2021 (30 days after symptom onset).	B1
B6	F	50	Second	1 day	Left	Almost fully recovered with treatment.	B1
B7	M	33	First	4 days	Left	Lost to follow up	D
B8	M	69	Second	12 days	Left	Good recovery with treatment. Complete eyelid closure at last follow-up on 28 Apr 2021 (8 days after symptom onset).	B1
B9	M	52	Second	14 days	Right	Good recovery with treatment. Lower face asymmetry resolved and only minimal different in forehead wrinkles noted at last follow-up on 20 May 2021 (27 days after symptom onset).	B1
B10	F	46	First	16 days	Right	Good recovery with treatment. Facial weakness improved at last follow-up on 26 Apr 2021 (4 days after symptom onset).	B1
B11	M	54	First	18 days	Right	Good recovery with treatment. Facial weakness improved, complete eyelid closure, forehead wrinkle reappeared at last follow-up on 6 May 2021 (8 days after symptom onset).	B1
B12	M	47	Second	18 days	Right	Lost to follow-up	B1
B13	F	20	Second	17 days	Left	Follow up was scheduled on 13 May 2021 and pending follow up information on clinical progress.	B1
B14	F	42	First	17 days	Right	Lost to follow up.	B1

B15	M	78	First	2 days	Right	Good recovery with treatment. Facial weakness improved at last follow-up on 27 May 2021 (26 days after symptom onset).	B1
B16	M	41	Second	13 days	Left	Fair recovery with treatment. Facial asymmetry improved as reported by the case at last follow-up on 7 May 2021 (13 days after symptom onset).	B1
Excluded cases after Comirnaty vaccination							
B17	M	58	First	1 day	Left	Attending physician reviewed the case and considered not Bell's palsy.	
B18	M	72	First	3 days	Right	Attending physician reviewed the case and revised the diagnosis to ischemic stroke.	
B19	M	71	First	2 days	Right	Attending physician reviewed the case and revised the diagnosis to Ramsay Hunt Syndrome.	
B20	F	71	Second	8 days	Right	Attending physician reviewed the case and revised the diagnosis to Ramsay Hunt Syndrome.	

† WHO classification:
A. Consistent causal association to immunization
• A1. Vaccine product-related reaction; or
• A2. Vaccine quality defect-related reaction; or
• A3. Immunization error-related reaction; or
• A4. Immunization anxiety-related reaction/Immunization stress related response (ISRR).
B. Indeterminate
• B1. Temporal relationship is consistent but there is insufficient definitive evidence that vaccine caused the event (it may be a new vaccine-linked event). This is a potential signal and needs to be considered for further investigation.
• B2. Reviewing factors result in conflicting trends of consistency and inconsistency with causal association to immunization (i.e. it may be vaccine-associated as well as coincidental and it is not possible clearly to favour one or the other).
C. Inconsistent causal association to immunization (coincidental). This could be due to underlying or emerging condition(s) or conditions caused by exposure to something other than vaccine. Events which could have occurred naturally are generally assigned this classification.
D. Case without adequate information for causality conclusion.

Supplementary Table 3. Standardized rate ratios of reported and clinically confirmed Bell's palsy cases following vaccination with CoronaVac and Comirnaty by sex, with reference to 2019

	Age-standardized background incidence rate in 2019 (per 100,000 person-years)	Age-standardized incidence rate (per 100,000 person-years)		Standardized incidence rate difference (per 100,000 person-years)		Standardized rate ratio (95% CI)	
		Reported	Clinically confirmed	Reported	Clinically confirmed	Reported	Clinically confirmed
CoronaVac							
Total	27.7 (24.8-30.7)	75.3 (44.7-105.9)	66.9 (37.2- 96.6)	47.6 (16.8- 78.3)	39.2 (9.3-69.0)	2.72 (1.78-4.14)	2.41 (1.53-3.81)
Male	30.3 (25.6-34.9)	88.7 (45.7-131.6)	77.6 (36.1-119.2)	58.4 (15.2-101.6)	47.4 (5.6-89.2)	2.93 (1.76-4.87)	2.57 (1.47-4.48)
Female	25.7 (21.9-29.6)	55.9 (15.1- 96.6)	51.9 (11.9- 91.9)	30.1 (-10.8- 71.0)	26.2 (-14.0-66.3)	2.17 (1.03-4.56)	2.02 (0.92-4.42)
Comirnaty							
Total	26.2 (23.1-29.3)	57.8 (30.1- 85.5)	42.8 (19.4- 66.1)	31.6 (3.7- 59.5)	16.6 (-7.0-40.2)	2.21 (1.35-3.62)	1.63 (0.93-2.86)
Male	28.5 (23.7-33.4)	65.5 (26.9-104.2)	46.1 (14.6- 77.5)	37.0 (-1.9- 76.0)	17.5 (-14.3-49.4)	2.30 (1.24-4.24)	1.61 (0.80-3.26)
Female	24.3 (20.3-28.4)	46.1 (8.7- 83.5)	36.4 (4.2- 68.7)	21.7 (-15.9- 59.4)	12.1 (-20.4-44.6)	1.89 (0.83-4.33)	1.50 (0.61-3.68)

The background incidence was calculated using the same reporting period (For CoronaVac, February 23, 2021-May 4, 2021; For Comirnaty, March 6, 2021-May 4, 2021) in 2019.

Supplementary Table 4. Standardized rate ratios of reported and clinically confirmed Bell's palsy cases following vaccination with CoronaVac and Comirnaty by sex, with reference to 2018

	Age-standardized background incidence rate in 2018 (per 100,000 person-years)	Age-standardized incidence rate (per 100,000 person-years)		Standardized incidence rate difference (per 100,000 person-years)		Standardized rate ratio (95% CI)	
		Reported	Clinically confirmed	Reported	Clinically confirmed	Reported	Clinically confirmed
CoronaVac							
Total	25.8 (22.9-28.7)	75.3 (44.7-105.9)	66.9 (37.2- 96.6)	49.5 (18.8- 80.3)	41.1 (11.3-71.0)	2.92 (1.92-4.45)	2.60 (1.64-4.10)
Male	28.7 (24.1-33.3)	88.7 (45.7-131.6)	77.6 (36.1-119.2)	60.0 (16.8-103.1)	48.9 (7.2-90.7)	3.09 (1.86-5.14)	2.70 (1.55-4.73)
Female	23.4 (19.7-27.1)	55.9 (15.1- 96.6)	51.9 (11.9- 91.9)	32.5 (-8.4- 73.3)	28.5 (-11.6-68.7)	2.39 (1.13-5.03)	2.22 (1.01-4.87)
Comirnaty							
Total	25.5 (22.4-28.6)	57.8 (30.1- 85.5)	42.8 (19.4- 66.1)	32.3 (4.4- 60.2)	17.3 (-6.3-40.9)	2.27 (1.38-3.72)	1.68 (0.96-2.94)
Male	29.0 (24.0-33.9)	65.5 (26.9-104.2)	46.1 (14.6- 77.5)	36.6 (-2.4- 75.5)	17.1 (-14.8-49.0)	2.26 (1.23-4.18)	1.59 (0.79-3.22)
Female	22.6 (18.7-26.5)	46.1 (8.7- 83.5)	36.4 (4.2- 68.7)	23.5 (-14.1- 61.1)	13.8 (-18.7-46.3)	2.04 (0.89-4.67)	1.61 (0.65-3.97)

The background incidence was calculated using the same reporting period (For CoronaVac, February 23, 2021-May 4, 2021; For Comirnaty, March 6, 2021-May 4, 2021) in 2018.

Supplementary Table 5. Standardized rate ratios of reported and clinically confirmed Bell's palsy cases following vaccination with CoronaVac and Comirnaty by sex, with reference to the average background incidence rate from 2015 to2019.

	Average age-standardized background incidence rate from 2015 to 2019 (per 100,000 person-years)	Age-standardized incidence rate (per 100,000 person-years)		Age-standardized incidence rate difference (per 100,000 person-years)		Age-standardized rate ratio (95% CI)	
		Reported	Clinically confirmed	Reported	Clinically confirmed	Reported	Clinically confirmed
CoronaVac							
Total	27.0 (25.7-28.4)	75.3 (44.7-105.9)	66.9 (37.2- 96.6)	48.3 (17.6- 78.9)	39.8 (10.1-69.6)	2.78 (1.85-4.19)	2.47 (1.58-3.87)
Male	29.6 (27.5-31.7)	88.7 (45.7-131.6)	77.6 (36.1-119.2)	59.1 (16.1-102.1)	48.1 (6.5-89.6)	3.00 (1.84-4.89)	2.62 (1.53-4.50)
Female	25.0 (23.3-26.7)	55.9 (15.1- 96.6)	51.9 (11.9- 91.9)	30.8 (-9.9- 71.6)	26.9 (-13.1-66.9)	2.23 (1.07-4.64)	2.08 (0.96-4.50)
Comirnaty							
Total	26.8 (25.3-28.2)	57.8 (30.1- 85.5)	42.8 (19.4- 66.1)	31.0 (3.3- 58.8)	16.0 (-7.4-39.4)	2.16 (1.33-3.50)	1.60 (0.92-2.77)
Male	29.3 (27.0-31.5)	65.5 (26.9-104.2)	46.1 (14.6- 77.5)	36.3 (-2.5- 75.0)	16.8 (-14.8-48.3)	2.24 (1.23-4.06)	1.57 (0.79-3.13)
Female	24.7 (22.8-26.6)	46.1 (8.7- 83.5)	36.4 (4.2- 68.7)	21.4 (-16.1- 58.8)	11.7 (-20.6-44.0)	1.86 (0.83-4.21)	1.47 (0.61-3.58)

The background incidence rates were calculated using the same reporting period (For CoronaVac, February 23, 2021-May 4, 2021; For Comirnaty, March 6, 2021-May 4, 2021) from 2015 to 2019.

Supplementary Table 6. Standardized rate ratios of reported and clinically confirmed Bell's palsy cases following vaccination with CoronaVac and Comirnaty by sex, excluding Bell's palsy cases with onset time less than 1 day after vaccination.

	Age-standardized background incidence rate in 2020 (per 100,000 person-years)	Age-standardized incidence rate (per 100,000 person-years)		Age-standardized incidence rate difference (per 100,000 person-years)		Age-standardized rate ratio (95% CI)	
		Reported	Clinically confirmed	Reported	Clinically confirmed	Reported	Clinically confirmed
CoronaVac							
Total	25.3 (22.6-28.1)	64.8 (36.8- 92.7)	58.1 (31.0-85.3)	39.4 (11.4-67.5)	32.8 (5.5-60.1)	2.56 (1.64-3.99)	2.29 (1.42-3.71)
Male	29.0 (24.5-33.4)	70.5 (33.5-107.5)	62.4 (26.6-98.2)	41.5 (4.3-78.8)	33.4 (-2.6-69.5)	2.43 (1.41-4.20)	2.15 (1.19-3.90)
Female	22.4 (18.9-26.0)	55.9 (15.1- 96.6)	51.9 (11.9-91.9)	33.4 (-7.4-74.3)	29.5 (-10.6-69.6)	2.49 (1.18-5.25)	2.31 (1.05-5.08)
Comirnaty							
Total	25.7 (22.7-28.8)	57.8 (30.1- 85.5)	42.8 (19.4-66.1)	32.1 (4.2-59.9)	17.0 (-6.6-40.6)	2.25 (1.37-3.68)	1.66 (0.95-2.91)
Male	28.9 (24.1-33.8)	65.5 (26.9-104.2)	46.1 (14.6-77.5)	36.6 (-2.3-75.5)	17.1 (-14.7-49.0)	2.26 (1.23-4.18)	1.59 (0.79-3.22)
Female	23.1 (19.2-27.0)	46.1 (8.7- 83.5)	36.4 (4.2-68.7)	23.0 (-14.6-60.5)	13.3 (-19.2-45.8)	1.99 (0.87-4.56)	1.58 (0.64-3.88)

The background incidence rates were calculated using the same reporting period (For CoronaVac, February 23, 2021-May 4, 2021; For Comirnaty, March 6, 2021-May 4, 2021) in 2020.

Supplementary Table 7. Standardized rate ratios of reported and clinically confirmed Bell's palsy cases following vaccination with CoronaVac and Comirnaty by sex, assuming actual background incidence rates were 50% higher than reported.

	Age-standardized background incidence rate in 2020 (per 100,000 person-years)	Age-standardized incidence rate (per 100,000 person-years)		Age-standardized incidence rate difference (per 100,000 person-years)		Age-standardized rate ratio (95% CI)	
		Reported	Clinically confirmed	Reported	Clinically confirmed	Reported	Clinically confirmed
CoronaVac							
Total	38.0 (34.6-41.4)	75.3 (44.7-105.9)	66.9 (37.2- 96.6)	37.3 (6.5-68.1)	28.9 (-1.0-58.8)	1.98 (1.31-3.00)	1.76 (1.12-2.77)
Male	43.4 (38.0-48.9)	88.7 (45.7-131.6)	77.6 (36.1-119.2)	45.2 (2.0-88.5)	34.2 (-7.7-76.1)	2.04 (1.24-3.37)	1.79 (1.03-3.10)
Female	33.6 (29.3-38.0)	55.9 (15.1- 96.6)	51.9 (11.9- 91.9)	22.2 (-18.7-63.1)	18.3 (-21.9-58.5)	1.66 (0.79-3.48)	1.54 (0.71-3.37)
Comirnaty							
Total	38.6 (34.9-42.3)	57.8 (30.1- 85.5)	42.8 (19.4- 66.1)	19.2 (-8.8-47.2)	4.2 (-19.5-27.8)	1.50 (0.92-2.44)	1.11 (0.64-1.93)
Male	43.4 (37.5-49.3)	65.5 (26.9-104.2)	46.1 (14.6- 77.5)	22.1 (-17.0-61.2)	2.7 (-29.4-34.7)	1.51 (0.82-2.77)	1.06 (0.53-2.13)
Female	34.7 (29.9-39.5)	46.1 (8.7- 83.5)	36.4 (4.2- 68.7)	11.4 (-26.3-49.1)	1.7 (-30.9-34.3)	1.33 (0.58-3.03)	1.05 (0.43-2.57)

The background incidence rates were calculated using the same reporting period (For CoronaVac, February 23, 2021-May 4, 2021; For Comirnaty, March 6, 2021-May 4, 2021) in 2020.

Supplementary Table 8. Baseline characteristics of case and controls in the nested case-control study, stratified by vaccine exposure.

	Cases			**Controls**		
	No vaccine (N=256)	**CoronaVac** (N=28)	**Comirnaty** (N=14)	**No vaccine** (N=1097)	**CoronaVac** (N=53)	**Comirnaty** (N=31)
Age - mean (SD)	57.62 (17.62)	56.76 (15.11)	52.38 (16.35)	57.63 (17.47)	56.47 (12.88)	50.07 (13.62)
Male – no. (%)	128 (50.0)	22 (78.6)	8 (57.1)	575 (52.4)	35 (66.0)	17 (54.8)
Admission setting – no. (%)						
Inpatient	98 (38.3)	8 (28.6)	6 (42.9)	425 (38.7)	14 (26.4)	8 (25.8)
Emergency room	158 (61.7)	20 (71.4)	8 (57.1)	672 (61.3)	39 (73.6)	23 (74.2)
Smoker – no. (%)	2 (0.8)	0 (0.0)	0 (0.0)	10 (0.9)	0 (0.0)	0 (0.0)
Pre-existing comorbidities† – no. (%)						
Diabetes mellitus	55 (21.5)	3 (10.7)	0 (0.0)	189 (17.2)	3 (5.7)	6 (19.4)
Hypertension	79 (30.9)	5 (17.9)	0 (0.0)	319 (29.1)	11 (20.8)	7 (22.6)
Asthma	7 (2.7)	0 (0.0)	0 (0.0)	26 (2.4)	0 (0.0)	0 (0.0)
Neoplasms	14 (5.5)	0 (0.0)	0 (0.0)	147 (13.4)	3 (5.7)	1 (3.2)
Acute respiratory infections	1 (0.4)	0 (0.0)	0 (0.0)	14 (1.3)	0 (0.0)	0 (0.0)
Viral infections	3 (1.2)	0 (0.0)	1 (7.1)	2 (0.2)	0 (0.0)	0 (0.0)
Rheumatoid Arthritis	0 (0.0)	0 (0.0)	1 (7.1)	5 (0.5)	0 (0.0)	0 (0.0)
Head trauma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Stroke	17 (6.6)	1 (3.6)	0 (0.0)	68 (6.2)	1 (1.9)	0 (0.0)
Guillain–Barré syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Migraine	2 (0.8)	0 (0.0)	0 (0.0)	7 (0.6)	0 (0.0)	0 (0.0)
Medication use within 90 days – no. (%)						
Antiviral drugs	12 (4.7)	0 (0.0)	1 (7.1)	35 (3.2)	4 (7.5)	1 (3.2)
Systemic corticosteroids	18 (7.0)	1 (3.6)	0 (0.0)	48 (4.4)	0 (0.0)	0 (0.0)
Antibacterial drugs	20 (7.8)	1 (3.6)	0 (0.0)	156 (14.2)	0 (0.0)	0 (0.0)
Immunosuppressants	1 (0.4)	0 (0.0)	0 (0.0)	24 (2.2)	0 (0.0)	0 (0.0)
Statins	73 (28.5)	5 (17.9)	1 (7.1)	302 (27.5)	8 (15.1)	5 (16.1)

Isoniazid	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)

†For pre-existing comorbidities, diagnosis within 90 days before index date were considered for acute respiratory infections and viral infections, and diagnosis before index date were considered for other diseases.

Supplementary Table 9. Risks of Bell's palsy among participants in the nested case-control study, excluding cases and controls with onset time less than 1 day after vaccination.

	Case patients (N=296)	**Controls (N=1174)**	**Crude odds ratio (95% CI)**	**P-value**	**Adjusted odds ratio (95% CI)**	**P-value**
Total						
Not vaccinated	256	1090	(Ref)		(Ref)	
CoronaVac	26	51	2.362 (1.403 – 3.978)	0.0012	2.296 (1.341 – 3.932)	0.0025
Comirnaty	14	29	2.223 (1.132 – 4.368)	0.02	1.901 (0.949 – 3.81)	0.07
Subgroup analysis						
Male						
Not vaccinated	128	568	(Ref)		(Ref)	
CoronaVac	20	34	2.894 (1.544 – 5.426)	0.0009	2.658 (1.392 – 5.075)	0.0031
Comirnaty	8	15	2.514 (1.023 – 6.178)	0.044	2.234 (0.908 – 5.497)	0.08
Female						
Not vaccinated	128	522	(Ref)		(Ref)	
CoronaVac	6	17	1.507 (0.568 – 3.999)	0.41	1.428 (0.526 – 3.877)	0.48
Comirnaty	6	14	1.882 (0.678 – 5.221)	0.22	1.784 (0.633 – 5.03)	0.27
Age<60						
Not vaccinated	125	533	(Ref)		(Ref)	
CoronaVac	13	27	2.256 (1.078 – 4.72)	0.031	2.295 (1.081 – 4.872)	0.03
Comirnaty	10	22	1.998 (0.914 – 4.368)	0.083	1.803 (0.818 – 3.977)	0.14
Age≥60						
Not vaccinated	131	557	(Ref)		(Ref)	
CoronaVac	13	24	2.507 (1.197 – 5.252)	0.015	2.508 (1.152 – 5.463)	0.021

Comirnaty	4	7	3.095 (0.795 – 12.047)	0.1	2.372 (0.522 – 10.785)	0.26
Post-hoc analysis						
Within 14 days between vaccination and diagnosis of Bell's palsy						
Not vaccinated	256	1,016	(Ref)		(Ref)	
CoronaVac	12	19	2.896 (1.273 - 6.588)	0.0112	2.800 (1.210 - 6.480)	0.0162
Comirnaty	6	17	1.423 (0.545 - 3.713)	0.4716	1.202 (0.458 - 3.156)	0.7082
Larger than 14 days between vaccination and diagnosis of Bell's palsy						
Not vaccinated	256	1,029	(Ref)		(Ref)	
CoronaVac	14	22	2.568 (1.282 - 5.144)	0.0078	2.456 (1.179 - 5.117)	0.016
Comirnaty	8	9	3.962 (1.418 - 11.076)	0.0087	3.785 (1.253 - 11.43)	0.018
Completed 1st dose only						
Not vaccinated	256	1,031	(Ref)		(Ref)	
CoronaVac	19	26	3.183 (1.663 - 6.091)	0.0005	3.081 (1.574 - 6.029)	0.0010
Comirnaty	5	16	1.229 (0.439 - 3.446)	0.69	0.967 (0.322 - 2.904)	0.95
Completed 1st and 2nd dose						
Not vaccinated	256	1014	(Ref)		(Ref)	

CoronaVac	7	19	1.459 (0.592 - 3.599)	0.41	1.457 (0.576 - 3.69)	0.43
Comirnaty	9	12	3.201 (1.287 - 7.962)	0.012	3.162 (1.244 - 8.039)	0.016

Cases and controls were matched according to age, sex, setting, and admission date. Odds ratios for Bell's palsy were estimated by conditional logistic regression adjusted for smoking status, pre-existing comorbidities (diabetes mellitus, hypertension, asthma, neoplasms, rheumatoid arthritis, stroke, migraine, infections in the past 90 days (acute respiratory infections, viral infections), and medication use in the past 90 days (antiviral drugs, systemic corticosteroids, antibacterial drugs, immunosuppressants). The list of confounders in the model for subgroup and post-hoc analyses is shown in the Supplementary table 10. CI denotes confidence interval.

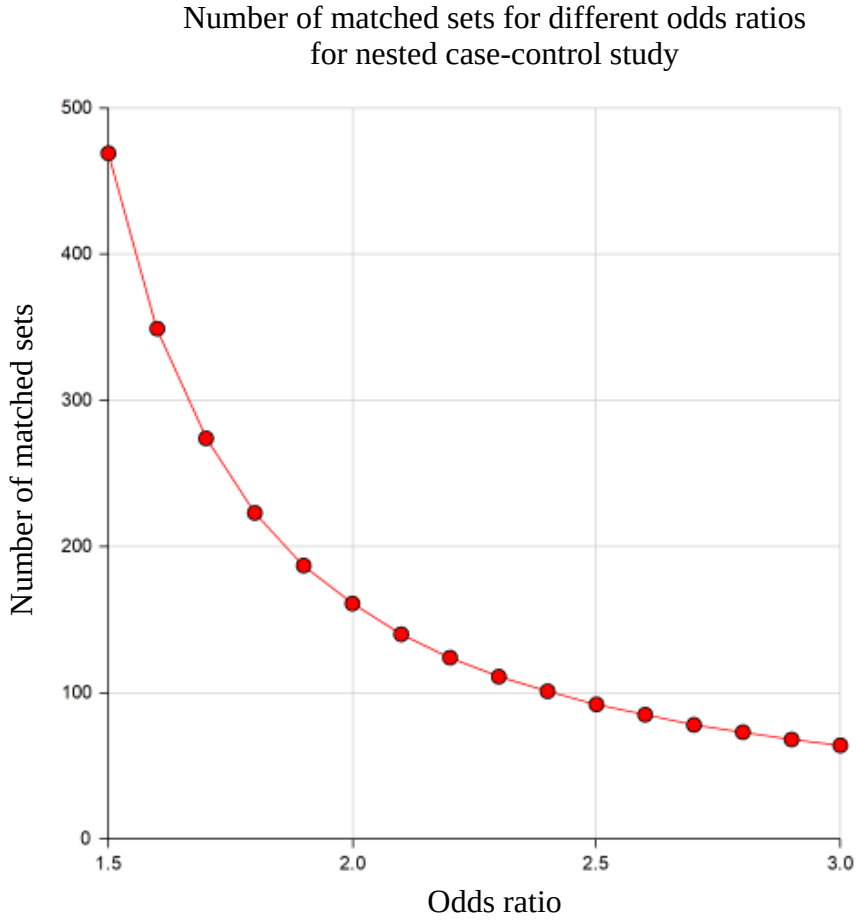
Supplementary table 10. List of confounders in the regression model in the main and sensitivity analysis.

Confounder	Total	Subgroup and post-hoc analysis							
		Male	Female	Age<60	Age≥60	≤14 days between vaccination and diagnosis	> 14 days between vaccination and diagnosis	Completed 1st dose only	Completed 1st and 2nd dose
Smoker	✓	✓	×	✓	✓	✓	✓	✓	✓
Pre-existing comorbidities†									
Diabetes mellitus	✓	✓	✓	✓	✓	✓	✓	✓	✓
Hypertension	✓	✓	✓	✓	✓	✓	✓	✓	✓
Asthma	✓	✓	✓	✓	✓	✓	✓	✓	✓
Neoplasms	✓	✓	✓	✓	✓	✓	✓	✓	✓
Acute respiratory infections	✓	×	✓	✓	×	✓	✓	✓	✓
Viral infections	✓	×	✓	×	✓	✓	✓	✓	✓
Rheumatoid Arthritis	✓	×	✓	✓	×	×	✓	✓	×
Stroke	✓	✓	✓	✓	✓	✓	✓	✓	✓
Migraine	✓	✓	✓	✓	×	✓	✓	✓	✓
Medication use within 90 days									
Antiviral drugs	✓	✓	✓	✓	✓	✓	✓	✓	✓
Systemic corticosteroids	✓	✓	✓	✓	✓	✓	✓	✓	✓

Antibacterial drugs	✓	✓	✓	✓	✓	✓	✓	✓	✓
Immunosuppressants	✓	✓	×	×	✓	✓	✓	✓	✓
Statins	✓	✓	✓	✓	✓	✓	✓	✓	✓

†For pre-existing comorbidities, diagnosis within 90 days before index date were considered for acute respiratory infections and viral infections, and diagnosis before index date were considered for other diseases.
✓ included in the regression model
× not included in the regression model due to due to very rare number in case and control groups (e.g. smoker status was excluded in the regression model in the female subgroup analysis as all female were non-smoker in current study.)

Supplementary Figure 1. Sample size calculation for nested case-control study

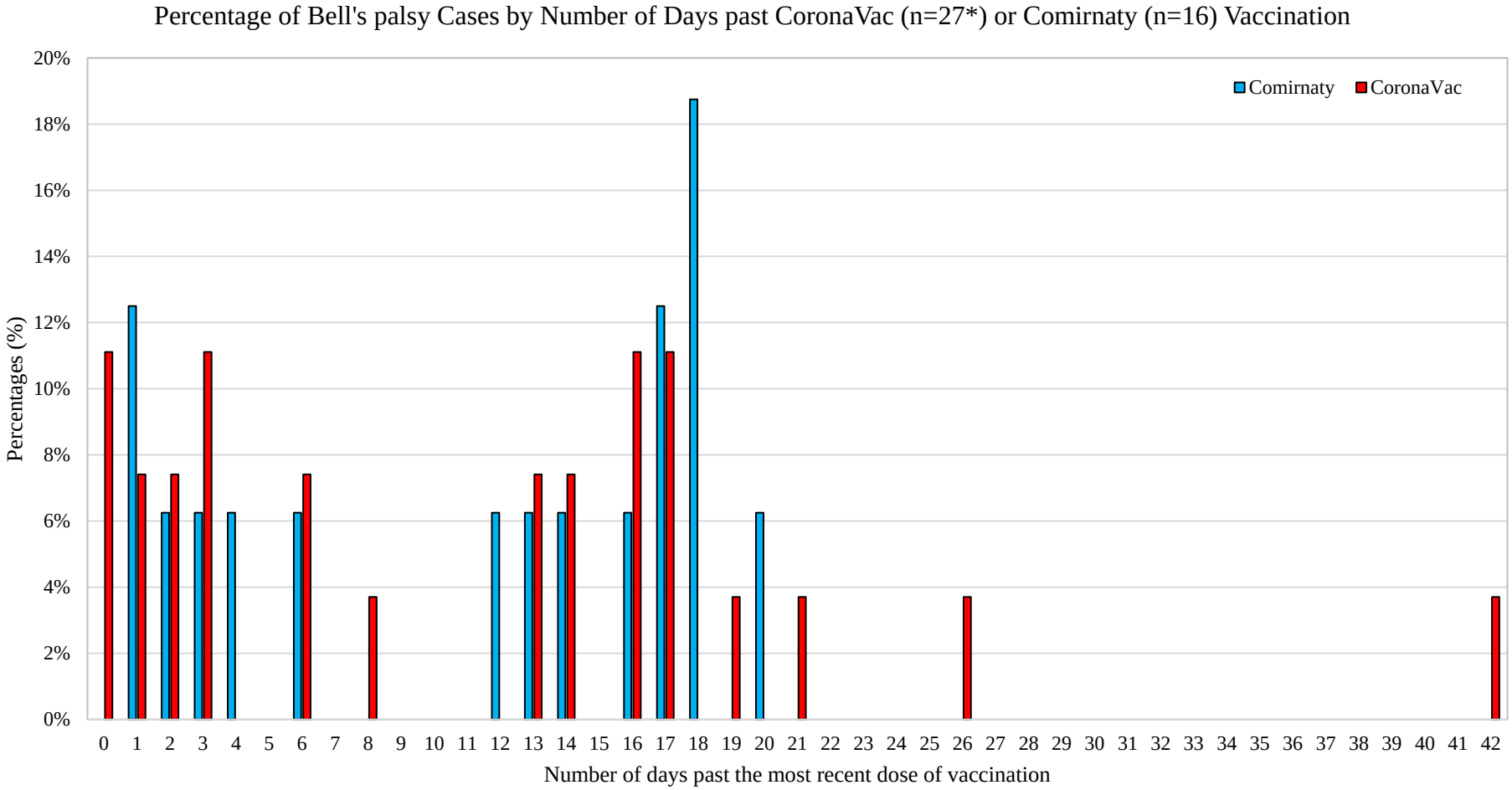


Remark: Assuming 15% of Hong Kong population aged 18 years with vaccination (1 million vaccine recipients among 6.5 million Hong Kong residents aged 18 years) by May 3 2021, the number of matched sets (1 case and 4 controls) ranging from 64 to 469 were required to achieve 80% power to detect the odds ratios from 1.5 to 3 at 0.05 significance level [1-3]. The red points were plotted for odds ratios from 1.5 to 3 by 0.1. The sample size calculation was conducted using the Power Analysis and Sample Size software version 2019 (NCSS, Kaysville, Utah, USA).

References:

1. Lachin, John M. Sample size evaluation for a multiply matched case-control study using the score test from a conditional logistic (discrete Cox PH) regression model. Stat Med, 2008;27:2509-2523.
2. Lachin, John M. Biostatistical Methods: The Assessment of Relative Risks, Second Edition. John Wiley & Sons, 2011.
3. Tang, Yongqiang. Comments on ‘Sample size evaluation for multiply matched case-control study using the score test from a conditional logistic (discrete Cox PH) regression model. Stat Med, 2009;28:175-177.

Supplementary Figure 2. Onset distribution of clinically confirmed Bell's palsy cases by number of days past the most recent dose of vaccination



*Remark: There are 28 clinically confirmed Bell's palsy cases for CoronaVac. However, the onset date in one clinically confirmed Bell's palsy case following CoronaVac vaccination (Case no S18 in the Supplementary Table 2) is uncertain, and thus this case was excluded from the figure.

Supplementary information 1. The details of WHO classification.

The Expert Committee conducted causality assessment of clinically confirmed cases according to the WHO classification[1].

A. Consistent causal association to immunization

• A1. Vaccine product-related reaction; or

• A2. Vaccine quality defect-related reaction; or

• A3. Immunization error-related reaction; or

• A4. Immunization anxiety-related reaction/Immunization stress related response (ISRR).

B. Indeterminate

• B1. Temporal relationship is consistent but there is insufficient definitive evidence that vaccine caused the event (it may be a new vaccine-linked event). This is a potential signal and needs to be considered for further investigation.

• B2. Reviewing factors result in conflicting trends of consistency and inconsistency with causal association to immunization (i.e. it may be vaccine-associated as well as coincidental and it is not possible clearly to favour one or the other).

C. Inconsistent causal association to immunization (coincidental). This could be due to underlying or emerging condition(s) or conditions caused by exposure to something other than vaccine. Events which could have occurred naturally are generally assigned to this classification.

D. Case without adequate information for causality conclusion.

Reference

1. World Health Organization. Causality assessment of an adverse event following immunization (AEFI): user manual for the revised WHO classification. https://apps.who.int/iris/bitstream/handle/10665/259959/9789241513654-eng.pdf?sequence=1&isAllowed=y.

Supplementary information 2. The details information of Clinical Data Analysis and Reporting System.

Hospital Authority has a comprehensive electronic health records system for clinical management. Each resident in Hong Kong has a unique Hong Kong Identity Card Number which allows the HA to create a unique electronic health record for each patient to link up all hospitals, ambulatory clinics, specialist clinics, general out-patients clinics, and emergency rooms. Data from the HA electronic health records are de-identified and pseudo-anonymised data are then transferred daily to Clinical Data Analysis and Reporting System (CDARS). Since 1995, the pseudo-anonymised clinical data from patients who had ever used any of the healthcare services at HA, including demographics, diagnosis, medication dispensing records, outpatient and primary care clinics, emergency room attendances, laboratory tests and hospitalisation details, have been made available on CDARS for research and audit purposes. CDARS has been used for pharmacovigilance studies to evaluate safety of medicine[1-4].

Reference

1. Lau WC, Chan EW, Cheung CL, et al. Association Between Dabigatran vs Warfarin and Risk of Osteoporotic Fractures Among Patients With Nonvalvular Atrial Fibrillation. JAMA 2017; 317(11): 1151-8.
2. Lau WCY, Cheung CL, Man KKC, et al. Association Between Treatment With Apixaban, Dabigatran, Rivaroxaban, or Warfarin and Risk for Osteoporotic Fractures Among Patients With Atrial Fibrillation: A Population-Based Cohort Study. Ann Intern Med 2020; 173(1): 1-9.
3. Man KKC, Chan EW, Ip P, et al. Prenatal antidepressant use and risk of attention-deficit/hyperactivity disorder in offspring: population based cohort study. BMJ 2017; 357: j2350.
4. Man KKC, Lau WCY, Coghill D, et al. Association between methylphenidate treatment and risk of seizure: a population-based, self-controlled case-series study. Lancet Child Adolesc Health 2020; 4(6): 435-43.