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Bell's palsy following vaccination with mRNA (BNT162b2) and inactivated (CoronaVac) SARS-CoV-2 vaccines: a case series and nested case-control study

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For the Chinese translation of the abstract see **Online** for appendix 1

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Summary

Background Bell's palsy is a rare adverse event reported in clinical trials of COVID-19 vaccines. However, to our knowledge no population-based study has assessed the association between the inactivated SARS-CoV-2 vaccines and Bell's palsy. The aim of this study was to evaluate the risk of Bell's palsy after BNT162b2 and CoronaVac vaccination.

Methods In this case series and nested case-control study done in Hong Kong, we assessed the risk of Bell's palsy within 42 days following vaccination with BNT162b2 (Fosun–BioNTech [equivalent to Pfizer–BioNTech]) or CoronaVac (from Sinovac Biotech, Hong Kong) using data from voluntary surveillance reporting with the Hospital Authority, the COVID-19 Vaccine Adverse Event Online Reporting system for all health-care professionals, and the Hospital Authority's territory-wide electronic health records from the Clinical Data Analysis and Reporting System. We described reported cases of Bell's palsy among vaccine recipients (aged 18–110 years for CoronaVac and aged 16–110 years for BNT162b2). We compared the estimated age-standardised incidence of clinically confirmed cases among individuals who had received the CoronaVac or BNT162b2 vaccination (up to 42 days before presentation) with the background incidence in the population. A nested case-control study was also done using conditional logistic regression to estimate the odds ratio (OR) for risk of Bell's palsy and vaccination. Cases and controls were matched (1:4) by age, sex, admission setting, and admission date.

Findings Between February 23 and May 4, 2021, 451 939 individuals received the first dose of CoronaVac and 537 205 individuals received the first dose of BNT162b2. 28 clinically confirmed cases of Bell's palsy were reported following CoronaVac and 16 cases were reported following BNT162b2. The age-standardised incidence of clinically confirmed Bell's palsy was 66·9 cases per 100 000 person-years (95% CI 37·2 to 96·6) following CoronaVac vaccination and 42·8 per 100 000 person-years (19·4 to 66·1) for BNT162b2 vaccination. The age-standardised difference for the incidence compared with the background population was 41·5 (95% CI 11·7 to 71·4) for CoronaVac and 17·0 (–6·6 to 40·6) for BNT162b2, equivalent to an additional 4·8 cases per 100 000 people vaccinated for CoronaVac and 2·0 cases per 100 000 people vaccinated for BNT162b2. In the nested case-control analysis, 298 cases were matched to 1181 controls, and the adjusted ORs were 2·385 (95% CI 1·415 to 4·022) for CoronaVac and 1·755 (0·886 to 3·477) for BNT162b2.

Interpretation Our findings suggest an overall increased risk of Bell's palsy after CoronaVac vaccination. However, 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.

Funding The Food and Health Bureau of the Government of the Hong Kong Special Administrative Region, China.

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 patients 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, patients with incomplete recovery of facial function might have incomplete eye closure, brow ptosis, and nasal valve collapse,[3] which can potentially affect daily life.

The BNT162b2 (international non-proprietary name tozinameran; Pfizer–BioNTech) and mRNA-1273 (international non-proprietary name elasomeran; Moderna) COVID-19 vaccines use mRNA technology, and are currently widely used in different parts of the world. Two clinical trials of these vaccines reported seven cases of Bell's palsy in the vaccinated group of 35 000 patients.[4,5] The US Food and Drug Administration (FDA) did not consider there to be a clear basis on which to conclude a causal relationship. Therefore, the FDA recommended further surveillance of these vaccines as they have been

Research in context

Evidence before this study

We searched PubMed and Embase on July 1, 2021, for articles published 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 done in Israel to evaluate the association of Bell's Palsy with BNT162b2 (international non-proprietary name tozinameram; Pfizer–BioNTech). These studies and commentaries reported inconsistent findings on the risk of Bell's Palsy following BNT162b2 vaccination. No published studies on the risk of Bell's palsy following CoronaVac vaccination was identified.

Added value of this study

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

Implications of all the available evidence

We found an increased risk of Bell's palsy following CoronaVac vaccination. Our findings suggest that the event is rare. In general, more than 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 for patients with COVID-19 vaccine-related Bell's palsy.

authorised for widespread emergency use.[4,5] 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 BNT162b2[6] and mRNA-1273.[7] In a letter, Cirillo and Doan reported that the observed incidence of Bell's palsy in the mRNA vaccine groups was 1·5–3 times higher than would be expected in the general population.[8] Authors of a commentary and a letter postulated that the risk for Bell's palsy might vary with the type of vaccine platform based on the imbalanced risk identified among mRNA vaccine groups.[8,9] However, another research letter reported no association between facial paralysis and mRNA COVID-19 vaccines when compared with other viral vaccines in a disproportionality analysis.[10] A case-control study done in Israel also reported no association between Bell's palsy and BNT162b2.[11] Additionally, to our knowledge, there are no published data on Bell's palsy and inactivated COVID-19 vaccines that have also been used worldwide (eg, CoronaVac; Sinovac Life Sciences). WHO recommends safety surveillance and monitoring for Bell's palsy after CoronaVac vaccination.[12]

Currently, the Hong Kong Government Vaccination Programme provides two authorised COVID-19 vaccines for emergency use: CoronaVac (from Sinovac Biotech [equivalent to Sinovac Life Sciences]; Beijing, China) and BNT162b2 (from Fosun–BioNTech [equivalent to Pfizer–BioNTech]; Mainz, Germany). As the drug regulatory authority, the Drug Office of the Department of Health in Hong Kong has implemented a pharmacovigilance system for COVID-19 vaccines that receives reports of adverse events following immunisation. Additionally, the Expert Committee on Clinical Events Assessment Following COVID-19 Immunization (herein referred to as the Expert Committee) was set up to provide independent clinical adjudication of potential causal links between adverse events following immunisation and locally authorised COVID-19 vaccines. Bell's palsy is listed under intensive monitoring as an adverse event following immunisation.

This study aimed to describe cases of Bell's palsy reported to the Department of Health in Hong Kong and their causality classifications between Feb 23 and May 4, 2021, according to the WHO classification.[13] We also aimed to estimate the difference in incidence of Bell's palsy among COVID-19-vaccinated individuals compared with the incidence in the historical population and to assess the association between COVID-19 vaccination and Bell's palsy using a nested case-control study.

Methods

Study design and data sources

For the case series study, we used adverse event data from voluntary reports received by the Department of Health from all health-care professionals in Hong Kong via the territory-wide COVID-19 Vaccine Adverse Event online Reporting System[14] and the established reporting channel with the Hospital Authority, the statutory body that serves as a major publicly funded health-care provider.[15] For the nested case-control study, we used the Hospital Authority comprehensive electronic health records system that is established for clinical management. Data from the Hospital Authority electronic health records are de-identified and transferred daily to Clinical Data Analysis and Reporting System (CDARS; appendix 2 p 22), which has been used for pharmacovigilance studies to evaluate safety of medicine.[16–19] Further details on the data extracted from CDARS are included in the following sections. COVID-19 vaccination records were also obtained from the Department of Health.

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See **Online** for appendix 2

All clinical data were anonymised; therefore, the regulations in Hong Kong did not require us to obtain consent from participants. This project was approved by the institutional review boards in the Department of Health and Hospital Authority, which allowed us to use anonymised data for this study. Ethical approval for this study was granted by the institutional review board of the University of Hong Kong and the Hospital Authority Hong Kong West Cluster (UW21-149 and UW21-138), and by the Department of Health Ethics Committee (LM21/2021).

Procedures

Upon receipt of reports of serious or unexpected adverse events following immunisation, the Department of Health immediately contacts the reporting health-care professionals for further clinical information. All reported cases of 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 confirms whether cases are consistent with the clinical diagnosis of Bell's palsy (clinically confirmed cases). Using the follow-up information, some reported cases of Bell's palsy are reclassified to other conditions, such as stroke and Ramsay Hunt syndrome. The Expert Committee assesses causality of clinically confirmed cases according to the WHO classification (appendix 2 p 21).[13]

The case series included all Bell's palsy events from the launch of mass COVID-19 vaccination (Feb 23, 2021, for CoronaVac; March 6, 2021, for BNT162b2) to the date of data analysis (May 4, 2021). Population-wide vaccination records were provided by the Department of Health, and vaccine recipients were excluded if they were younger than 18 years for CoronaVac and if they were younger than 16 years for BNT162b2 because these recipients were likely to be clinical trial participants. Those older than 110 years were excluded because of potential error in the age recording. Any patients with Bell's palsy presented to the Hospital Authority or reported to the Department of Health within 42 days after the first or second vaccine dose or until May 4, 2021, whichever was earlier, were included in the analyses.

For the incidence comparison, the incidence of clinically confirmed Bell's palsy cases per 100 000 vaccine doses administered was calculated. To estimate the background incidence of Bell's palsy, Bell's palsy events were extracted from CDARS for the same study period as for each vaccination programme (February 23–May 4 for CoronaVac; March 6–May 4 for BNT162b2) for each year between 2010 and 2020. The rollout schedule of the vaccination programme, which includes people with specific types of employment such as health-care workers, transport service operators, as well as people aged 60 years or older, is shown in appendix 2 (p 1). 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 Hong Kong between 2010 and 2021 were obtained from the Hong Kong Census and Statistics Department. The number of reported and clinically confirmed cases from the case series were used for the incidence of Bell's palsy following vaccination with CoronaVac and BNT162b2. Reported cases with misclassification after assessment by the Expert Committee were excluded from the number of clinically confirmed cases.

For the nested case-control study, cases were defined as patients first diagnosed with Bell's palsy in the emergency room and inpatient setting between Feb 23 and May 3, 2021. These cases were identified using CDARS. Cases with a subsequent diagnosis of stroke or Ramsay Hunt syndrome were excluded. All other patients attending Hospital Authority emergency rooms, or who were admitted to hospital during the same period, and without a diagnosis of Bell's palsy were selected as controls. Medical and medication history were also extracted from CDARS. Patients younger than 18 years were excluded from the case-control study as they were unlikely to have received vaccines. Patients with a history of Bell's palsy were also excluded. Four controls were randomly matched with each case according to sex, age (same year), date of hospital attendance (within 3 calendar days), and the setting (emergency room or hospital admission). Vaccination status was ascertained by linking CDARS data to the COVID-19 vaccination records from the Department of Health. For the cases, vaccine recipients were defined as patients who received the vaccination on or before the date of first diagnosis with Bell's palsy, and for the controls, as patients who received the vaccination on or before the date of the hospital admission or emergency room visit. The voluntary surveillance by the Department of Health includes a small number of cases from the private health-care sector, which were included in the cases series and incidence comparison. For the nested case-control study, only the public health-care data could be included in the analysis because of data privacy rules preventing access to detailed clinical histories; therefore, the data sources of the case series and case-control analysis were slightly different.

Statistical analysis

The background incidence of Bell's palsy for the Hong Kong population from 2010 onwards and the incidence following vaccination with CoronaVac or BNT162b2 in 2021 were calculated (both age-standardised in 5-year age intervals). The age-standardised incidence of Bell's palsy following CoronaVac or BNT162b2 vaccination was then compared with the background incidence in 2020 to calculate the age-standardised incidence difference and rate ratio. We also calculated the incidence difference per 100 000 people within 42 days after vaccination. Subgroup analysis was done by sex (male *vs* female). Sensitivity analyses were done using the background incidence from 2018 and 2019 and the average background incidence

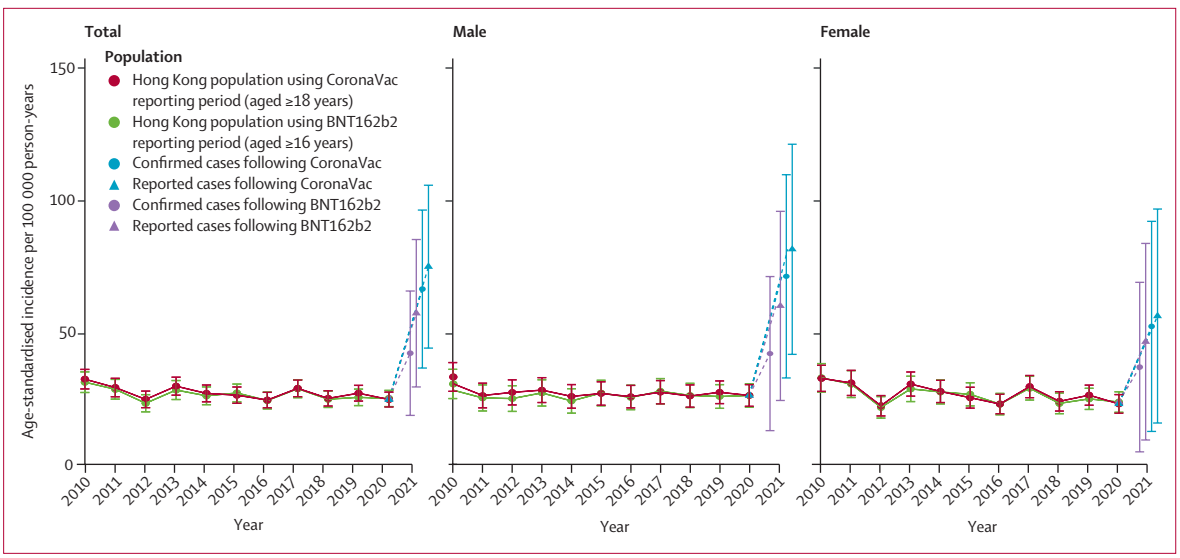

Figure 1: **Overall and sex-specific age-standardised incidence of Bell's palsy in people after CoronaVac and BNT162b2 vaccination and in the background population in Hong Kong**

The background incidence was calculated using the same reporting period in 2010–20 as for each vaccination programme in 2021 (for CoronaVac, Feb 23–May 4; for BNT162b2, March 6–May 4). In the female group, the number of reported and clinically confirmed cases in people exposed to BNT162b2 were the same. Thus, the lines for reported and clinically confirmed cases in BNT162b2 overlap. The error bars are 95% CI of the age-standardised incidence.

from 2015 and 2019, rather than in 2020. We also did an analysis assuming that the actual background incidence was 50% higher than reported to account for potential under-reporting in 2020 before COVID-19 vaccines were available and to account for possible cases from the private health-care sector that were not included in the original analysis. A sensitivity analysis was also done excluding Bell's palsy cases with extreme onset time defined as less than 1 day after vaccination.

For the nested case-control study, sample size and power estimation calculations are shown in appendix 2 (p 19). We anticipated that the size of the sample from the current available data would not be sufficient to do a direct comparison of Bell's palsy incidence following vaccination with CoronaVac and BNT162b2; therefore, such an analysis was not done. Conditional logistic regression adjusted for patient characteristics, including smoking status, diabetes, hypertension, asthma, neoplasms, acute respiratory infections in the past 90 days, viral infections in the past 90 days, rheumatoid arthritis, stroke, migraine, and use in the past 90 days of antiviral drugs, systemic corticosteroids, antibacterial drugs, immunosuppressants, and statins was used to estimate the adjusted odds ratio (OR) for risk of Bell's palsy and vaccination. Subgroup analysis was done by sex (male *vs* female) and age (<60 years old *vs* ≥60 years old). Post-hoc analysis was done by time between vaccination and diagnosis of Bell's palsy (≤14 days *vs* >14 days), number of doses (completed first dose only *vs* completed both first and second doses). Sensitivity analyses were done 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 of less than 0·05 were considered significant. Statistical analysis was done using R version 4.0.3. For quality assurance, two investigators (EYFW and VKCY) independently did 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 was a regulatory pharmacovigilance study initiated by the Department of Health and funded via the Food and Health Bureau of the Government of the Hong Kong Special Administrative Region. The sponsor of the study was involved in study design, data collection, data analysis, data interpretation and writing of the report via the Department of Health.

Results

From the commencement of each vaccination programme to May 4, 2021, 33 cases of Bell's palsy were reported after CoronaVac vaccination and 20 cases were reported after BNT162b2 vaccination to the Department of Health via the passive surveillance system. The demographic data, general case description, and causality assessment of the reported cases are shown in appendix 2 (pp 2–6). After assessment by the Expert Committee, nine of the 53 cases were reclassified as not being Bell's palsy. Clinical causality adjudication was done for 28 of the cases following CoronaVac vaccination and for 16 of the cases following BNT162b2 vaccination. Overall, 42 cases were classified as B (indeterminate) and two cases were classified as D

	Age-standardised background incidence in 2020* per 100 000 person-years (95% CI)	Age-standardised incidence per 100 000 person-years (95% CI)		Age-standardised incidence difference per 100 000 person-years (95% CI)		Age-standardised rate ratio (95% CI)	
		Reported	Clinically confirmed	Reported	Clinically confirmed	Reported	Clinically confirmed
CoronaVac							
Total	25·3 (22·6 to 28·1)	75·3 (44·7 to 105·9)	66·9 (37·2 to 96·6)	49·9 (19·2 to 80·7)	41·5 (11·7 to 71·4)	2·97 (1·95 to 4·53)	2·64 (1·67 to 4·17)
Male	29·0 (24·5 to 33·4)	88·7 (45·7 to 131·6)	77·6 (36·1 to 119·2)	59·7 (16·6 to 102·9)	48·7 (6·9 to 90·4)	3·06 (1·84 to 5·09)	2·68 (1·54 to 4·68)
Female	22·4 (18·9 to 26·0)	55·9 (15·1 to 96·6)	51·9 (11·9 to 91·9)	33·4 (–7·4 to 74·3)	29·5 (–10·6 to 69·6)	2·49 (1·18 to 5·25)	2·31 (1·05 to 5·08)
BNT162b2							
Total	25·7 (22·7 to 28·8)	57·8 (30·1 to 85·5)	42·8 (19·4 to 66·1)	32·1 (4·2 to 59·9)	17·0 (–6·6 to 40·6)	2·25 (1·37 to 3·68)	1·66 (0·95 to 2·91)
Male	28·9 (24·1 to 33·8)	65·5 (26·9 to 104·2)	46·1 (14·6 to 77·5)	36·6 (–2·3 to 75·5)	17·1 (–14·7 to 49·0)	2·26 (1·23 to 4·18)	1·59 (0·79 to 3·22)
Female	23·1 (19·2 to 27·0)	46·1 (8·7 to 83·5)	36·4 (4·2 to 68·7)	23·0 (–14·6 to 60·5)	13·3 (–19·2 to 45·8)	1·99 (0·87 to 4·56)	1·58 (0·64 to 3·88)

*The background incidence was calculated using the same reporting period in 2020 as for each vaccination programme in 2021 (for CoronaVac, Feb 23–May 4; for BNT162b2, March 6–May 4).

Table 1: **Standardised rate ratios of reported and clinically confirmed Bell's palsy cases following vaccination with CoronaVac and BNT162b2**

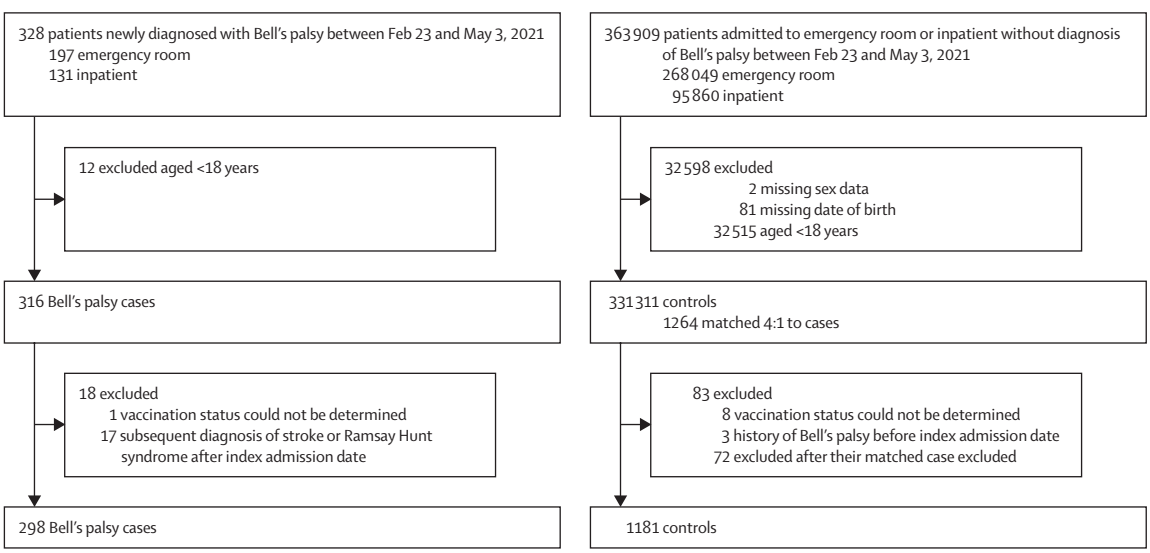

Figure 2: **Selection of cases and controls for the nested case-control study**

(inadequate information; case numbers S13 and B7). For patients with clinically confirmed cases of Bell's palsy following CoronaVac vaccination, the median age was 57·5 years (IQR 42·5–69·5), 19 (68%) of 28 were male, nine (32%) were female, 19 (68%) had confirmed Bell's palsy after the first vaccine dose, 20 (71%) had left-sided facial paralysis, and 25 (89%) had Bell's palsy reported within 21 days after vaccination (appendix 2 pp 2–6). For patients with clinically confirmed Bell's palsy who received BNT162b2, the median age was 47·5 years (IQR 41·8–55·0), ten (63%) of 16 were male, six (38%) were female, eight (50%) had confirmed Bell's palsy after the first vaccine dose, eight (50%) had left-sided facial paralysis, and 16 (100%) had Bell's palsy reported within 21 days after vaccination (appendix 2 pp 2–6).

776 571 doses of CoronaVac and 785 162 doses of BNT162b2 were administered between Feb 23 and May 4, 2021, not including 55 people younger than 18 years or older than 110 years who received CoronaVac, 230 people younger than 16 years or older than 110 years who received BNT162b2, and 294 people with incomplete records. 451 939 individuals received the first dose of CoronaVac, of whom 324 632 (71·8%) also received the second dose. 537 205 individuals received the first dose of BNT162b2, of whom 247 957 (46·2%) also received the second dose. The incidence of clinically confirmed Bell's palsy was 3·61 cases per 100 000 doses administered (95% CI 2·40–5·21) for CoronaVac and 2·04 cases per 100 000 doses administered (1·16–3·31) for BNT162b2. The age-standardised incidence for Bell's palsy from 2010 onwards for CoronaVac and BNT162b2 in the reporting period is shown in figure 1 and table 1. The age-standardised incidence differences compared with the background incidence in the same period in 2020, indicate that there were an additional 4·8 cases per 100 000 people within 42 days of receiving the CoronaVac

vaccination and an additional 2·0 cases per 100 000 people within 42 days of receiving the BNT162b2 vaccination (table 1). Results were similar in all sensitivity analyses (appendix 2 pp 7–10). In the analysis assuming that the actual background incidence was 50% higher than reported, the overall estimates of the age-standardised rate ratio for CoronaVac and the male subgroup were significant (appendix 2 p 11). Results for the other subgroups were not significant (appendix 2 p 11).

The selection of cases and controls into the nested case-control study is shown in figure 2. The characteristics of the cases, controls, and all individuals by vaccine exposure are shown in table 2 and appendix 2 (pp 12–13). 28 patients with Bell's palsy and 53 controls received the CoronaVac vaccine; 14 patients with Bell's palsy and 31 controls received the BNT162b2 vaccine. Receiving CoronaVac was associated with a significantly increased risk of Bell's palsy whereas receiving BNT162b2 was not associated with a significantly increased risk compared with the control group (table 3). The findings of the sex and age subgroup analyses were similar to the main results except that there was no increased risk of Bell's palsy in women receiving CoronaVac compared with the control group (table 3). The results of the post-hoc analyses on diagnosis interval after vaccination and the number of doses received are shown in table 3. There was no increase in the risk of Bell's palsy in people who received both doses of CoronaVac, but the risk following both doses of BNT162b2 was significantly higher than in the control group. The risk was also significantly higher in individuals for whom there was longer than 14 days between either CoronaVac or BNT162b2 vaccination and Bell's palsy diagnosis, compared with the control group (table 3). The results of the sensitivity analysis were consistent with the primary analysis (appendix 2 pp 14–16).

	Case patients (n=298)	Controls (n=1181)
Age, years	59·8 (45·5–68·8)	59·9 (45·4–69·1)
Male	158 (53%)	627 (53%)
Female	140 (47%)	554 (47%)
Admission setting		
Inpatient	112 (38%)	447 (38%)
Emergency room	186 (62%)	734 (62%)
Smoker	2 (1%)	10 (1%)
Pre-existing comorbidities*		
Diabetes	58 (20%)	198 (17%)
Hypertension	84 (28%)	337 (29%)
Asthma	7 (2%)	26 (2%)
Neoplasms	14 (5%)	151 (13%)
Acute respiratory infections	1 (<1%)	14 (1%)
Viral infections	4 (1%)	2 (<1%)
Rheumatoid arthritis	1 (<1%)	5 (<1%)
Head trauma	0	0
Stroke	18 (6%)	69 (6%)
Guillain-Barré syndrome	0	0
Migraine	2 (1%)	7 (1%)
Medication use within 90 days		
Antiviral drugs	13 (4%)	40 (3%)
Systemic corticosteroids	19 (6%)	48 (4%)
Antibacterial drugs	21 (7%)	156 (13%)
Immunosuppressants	1 (<1%)	24 (2%)
Statins	79 (27%)	315 (27%)
Isoniazid	0	3 (<1%)

Data are median (IQR) or n (%). *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 2: **Baseline characteristics of patients in the nested case-control study**

Discussion

The findings of this population-based study in Hong Kong showed an 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 on the basis of statistical association. A previous study, using the WHO Pharmacovigilance Database and a disproportionality analysis of spontaneous adverse drug reaction reports, reported no higher risk of facial paralysis following mRNA COVID-19 vaccination than with other viral vaccines (including influenza) according to the WHO Anatomical Therapeutic Chemical Classification System.[10] Another case-control study of 37 patients with acute-onset facial nerve palsy done in Israel did not report any significant association with BNT162b2 vaccination.[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.[9]

Our study showed the average background incidence of Bell's palsy in Hong Kong was around 27 cases 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.[9,21] A previous ecological analysis using the incidence in the background population found the relative risk of Bell's palsy was 1·5–3 times higher following COVID-19 mRNA vaccines than in the background population, a risk similar to that found in our study.[8,9]

The mechanism of Bell's palsy in patients following vaccination is unclear. One hypothesis links the trigger of Bell's palsy with an 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] Bell's palsy

	Number of case patients (n=298)	Number of controls (n=1181)	Crude odds ratio (95% CI)	p value	Adjusted odds ratio (95% CI)	p value
Total						
Not vaccinated	256 (86%)	1097 (93%)	1 (ref)	..	1 (ref)	..
CoronaVac	28 (9%)	53 (4%)	2·451 (1·477–4·067)	0·0005	2·385 (1·415–4·022)	0·0011
BNT162b2	14 (5%)	31 (3%)	2·062 (1·061–4·009)	0·033	1·755 (0·886–3·477)	0·11
Subgroup analysis						
Male						
Not vaccinated	128 (81%)	575 (92%)	1 (ref)	..	1 (ref)	..
CoronaVac	22 (14%)	35 (6%)	3·130 (1·698–5·770)	0·0003	2·892 (1·541–5·426)	0·0009
BNT162b2	8 (5%)	17 (3%)	2·194 (0·915–5·259)	0·078	1·970 (0·820–4·734)	0·13
Female						
Not vaccinated	128 (91%)	522 (94%)	1 (ref)	..	1 (ref)	..
CoronaVac	6 (4%)	18 (3%)	1·411 (0·538–3·704)	0·48	1·332 (0·496–3·574)	0·57
BNT162b2	6 (4%)	14 (3%)	1·869 (0·674–5·180)	0·23	1·772 (0·629–4·991)	0·28
Age younger than 60 years						
Not vaccinated	125 (83%)	540 (91%)	1 (ref)	..	1 (ref)	..
CoronaVac	15 (10%)	28 (5%)	2·563 (1·262–5·204)	0·0092	2·618 (1·272–5·388)	0·0090
BNT162b2	10 (7%)	24 (4%)	1·833 (0·850–3·953)	0·12	1·696 (0·779–3·694)	0·18
Age 60 years and older						
Not vaccinated	131 (89%)	557 (95%)	1 (ref)	..	1 (ref)	..
CoronaVac	13 (9%)	25 (4%)	2·377 (1·145–4·933)	0·020	2·362 (1·097–5·086)	0·028
BNT162b2	4 (3%)	7 (1%)	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 (93%)	1023 (96%)	1 (ref)	..	1 (ref)	..
CoronaVac	14 (5%)	20 (2%)	3·354 (1·520–7·402)	0·0027	3·264 (1·455–7·318)	0·0041
BNT162b2	6 (2%)	19 (2%)	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 (92%)	1029 (97%)	1 (ref)	..	1 (ref)	..
CoronaVac	14 (5%)	23 (2%)	2·448 (1·231–4·868)	0·011	2·320 (1·124–4·789)	0·023
BNT162b2	8 (3%)	9 (1%)	3·943 (1·411–11·019)	0·0089	3·778 (1·251–11·410)	0·019
Completed first dose only						
Not vaccinated	256 (91%)	1038 (96%)	1 (ref)	..	1 (ref)	..
CoronaVac	21 (7%)	28 (3%)	3·311 (1·772–6·185)	0·0002	3·200 (1·679 ·6·099)	0·0004
BNT162b2	5 (2%)	18 (2%)	1·093 (0·397–3·011)	0·86	0·853 (0·290–2·507)	0·77
Completed first and second dose						
Not vaccinated	256 (94%)	1014 (97%)	1 (ref)	..	1 (ref)	..
CoronaVac	7 (3%)	19 (2%)	1·459 (0·592–3·599)	0·41	1·453 (0·575–3·676)	0·43
BNT162b2	9 (3%)	12 (1%)	3·201 (1·287–7·962)	0·012	3·162 (1·245–8·036)	0·016

The list of confounders in the model for subgroup and post-hoc analyses is shown in appendix 2 (pp 17–18).

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

could also be secondary to an immune-mediated segmental demyelination similar to Guillain-Barré syndrome.[26,27] 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 that might alter the immune response in a wider group of patients.[28] By contrast, the BNT162b2 vaccine might induce innate immune activation and production of interferon proteins by a combined effect of mRNA and lipids.[9] Interferon therapy has been reported to cause facial nerve palsy.[29] Although several potential individual pathways including viral, autoimmune reaction, or innate immune activation have been hypothesised as causing Bell's palsy after COVID-19 vaccination, these

mechanisms might be multicausal and are unlikely to be applicable to all cases (such as onset with varying intervals after vaccination). Further investigation should be done to verify the mechanism of Bell's palsy following COVID-19 vaccination.

No sex-based differences were observed in recipients of BNT162b2, which is inconsistent with the WHO Pharmacovigilance Database that reported that 67·8% of patients who developed Bell's palsy following mRNA COVID-19 vaccination were female.[10] This discrepancy might be attributable to reporting bias. However, our observations showed that a higher proportion of patients with Bell's palsy after CoronaVac vaccination were men, and we cannot exclude the possibility of sex differences in the risk of Bell's palsy following CoronaVac vaccination. In addition, our sample size was too small to detect significant results in the subgroup analyses of female patients. Our post-hoc analyses detected potential signals in both CoronaVac and BNT162b2. This does not affect the results of our primary analysis; however, we cannot rule out the possibility of the risk of Bell's palsy associated with administration of BNT162b2. It is worth noting that our post-hoc analyses were underpowered to test the association between COVID-19 vaccine dose-response and Bell's palsy. Therefore, they should only serve as exploratory analyses in this study. More importantly, because of the nature of post-hoc analysis, which might introduce biases, over-interpretation of these results should be discouraged. Further studies with a sufficient sample size are needed to evaluate the association between Bell's palsy and COVID-19 vaccine dose-response.

Several limitations of our study should be noted. First, the passive surveillance of Bell's palsy cases relied on voluntary reporting from health-care professionals and the extent of under-reporting is unknown. However, in the current pandemic situation with the top emergency response level activated by the Department of Health, health-care professionals might be more inclined to report suspicious cases than in the prevaccination period, which might result in an increased number of reported cases. Additionally, the results of the sensitivity analyses 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, cases reported in the prevaccination period might include false positives, although this would further strengthen the hypothesis of the possible cause of Bell's palsy by vaccinations. However, the background incidence in Hong Kong was within the range of the global estimation,[9,21] and it should not affect our interpretation of the results. Third, we were unable to investigate patients presenting with Bell's palsy to private clinics and hospitals; therefore, the background incidence might be underestimated. However, as already stated, our sensitivity analyses are consistent with our observed incidence and they are within the range of the global estimates;[9,21] therefore, the underestimation is likely to be minimal. Fourth, the controls in the nested case-control study might be also misclassified. However, given the low incidence of Bell's palsy (approximately 27 incident events per 100 000 person-years) in Hong Kong, the probability of misclassification in the control group should be negligible and have no effect on our results. Fifth, socioeconomic status and education level might be important confounders, which we did not account for as these data were not available. Sixth, the duration of reporting of Bell's palsy cases subsequent to COVID-19 vaccination was 42 days in the Hong Kong voluntary reporting surveillance system. Therefore, cases that occurred more than 42 days after vaccination were not captured in this case series study. However, most of the clinically confirmed Bell's palsy cases from the voluntary reporting surveillance system occurred within 21 days after vaccination. Cases that occurred more than 42 days after vaccination are likely to be background incidents; therefore, underestimation is unlikely. Finally, the current study is limited to the patients with a new diagnosis of Bell's palsy in Hong Kong, and thus further studies including patients with a history of Bell's palsy and patients in other regions should be done to confirm our findings.

In conclusion, our study shows an overall increased risk of Bell's palsy after CoronaVac vaccination but not after BNT162b2 vaccination. Nevertheless, Bell's palsy is a rare and transient adverse event following immunisation. In general, more than 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.

Contributors

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, and QY did 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. AYLL and KKL provided critical input to the discussion. EYFW, CSLC, and ICKW have accessed and verified the data used in the study. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

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

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