mRNA (BNT162b2) COVID-19 vaccination increased risk of Bell's palsy: a nested case control and self-controlled case series study

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Summary

There is an overall increased risk of Bell's palsy following BNT162b2 vaccination, particularly

within the first 14 days after the second dose, but absolute risk was low. The benefits from

COVID-19 vaccination still outweigh the small risk of Bell's palsy.

Abstract

Background

Observable symptoms of Bell's palsy following vaccinations may arouse concern over the safety profiles of novel COVID-19 vaccines in the general public. However, there are only a few studies on Bell's palsy following mRNA COVID-19 vaccination with inconclusive findings. This study aimed to update the previous analysis on the risk of Bell's palsy following mRNA (BNT162b2) COVID-19 vaccination.

Methods

This study included cases aged ≥16-years-old with a new diagnosis of Bell's palsy within 28 days after BNT162b2 vaccinations from the population-based electronic health records in Hong Kong, using a nested case-control and self-controlled case series (SCCS) analyses were employed. The association between Bell's palsy and BNT162b2 was evaluated using conditional logistic and Poisson regression in nested case-control and SCCS analysis, respectively.

Results

A total of 54 individuals were newly diagnosed with Bell's palsy after BNT162b2 vaccinations. The incidence of Bell's palsy was 1.58 (95% CI:1.19-2.07) per 100,000 doses administered. The nested case-control analysis showed significant association between BNT162b2 vaccinations and Bell's palsy (Adjusted OR: 1.543, 95%CI:1.123 - 2.121), with up to 1.112 excess events per 100,000 people receiving two doses of BNT162b2. An increased risk of Bell's palsy was observed during the first 14 days after the second dose of BNT162b2 in both nested case-control

(Adjusted OR: 2.325, 95%CI:1.414 – 3.821) and SCCS analysis (Adjusted IRR=2.44,

95%CI:1.32-4.50).

Conclusion

There is an overall increased risk of Bell's palsy following BNT162b2 vaccination, particularly

within the first 14 days after the second dose, but the absolute risk was very low.

Introduction

Our previous local study revealed an overall increased risk of Bell's palsy associated with CoronaVac vaccinations (Odds ratio: 2.39;95% confidence interval (CI):1.42-4.02), but a non-significantly increased risk after mRNA BNT162b2 vaccination (Odds ratio: 1.76;95% CI:0.89-3.48), which may be attributed to the insufficient number of events reported[1]. Despite its rare occurrence, observable symptoms of Bell's palsy following vaccinations may arouse concern over the safety profiles of novel COVID-19 vaccines in the general public, devaluing their motivation to take up the COVID-19 vaccines. Currently, the clinical trial of BNT162b2 reported imbalanced incidence of Bell's palsy between vaccinated and control groups (four cases of Bell's palsy in the vaccinated group and none in the control group)[2]. There are only a few studies on Bell's palsy following mRNA COVID-19 vaccination, including observational studies and ecological studies[1, 3-9]. The findings from these studies remained inconclusive. Hence, the actual risk of Bell's palsy after mRNA COVID-19 vaccinations remains unclear. Several international organizations have recommended the monitoring of mRNA COVID-19 vaccine recipients for Bell's palsy[2, 10, 11]. More importantly, none of these studies have evaluated the impact of the first and second doses on the risk of Bell's palsy. A retrospective cohort study showed a non-significant increased risk of Bell's palsy associated with BNT162b2 vaccination (Rate ratio: 1.32;95% CI:0.92-1.86), but suggested that the association of Bell's palsy may be linked to the increased risk of herpes zoster infection after BNT162b2 vaccination (Risk ratio, 1.43;95% CI,1.20-1.73)[8]. As suggested in a commentary, the controversial findings on the association between Bell's palsy and various types of COVID-19 vaccines requires more comprehensive evidence on the safety of COVID-19 vaccines[12].

This study aimed to update our previous analysis on the risk of Bell's palsy following

BNT162b2 vaccination[1], by extending the inclusion period from May 4 to July 31, 2021.

Methods

Study design and data sources

Two study designs, including nested case control and self-controlled case series, were applied in

this study. We analyzed the data in the clinical management system from the Hospital Authority

(HA), which has been used previously to conduct the study on the risk of Bell's palsy after

COVID-19 vaccinations and other COVID-19 pharmacovigilance studies[1, 13-26]. Currently,

the COVID-19 Vaccination programme led by the Government of HKSAR authorized

BNT162b2 vaccine (from Fosun–BioNTech [equivalent to Pfizer–BioNTech]; Mainz, Germany)

and CoronaVac vaccine for emergency use. Individuals could freely choose BNT162b2 or

CoronaVac vaccines as their first dose, and are restricted to receive the same vaccine as their

second dose except if there is a clinical reason approved by a clinician e.g. anaphylaxis. The

rollout schedule of the vaccination programme since March 6, 2021 is shown in the

Supplementary Table 1. Vaccination status was ascertained by linking data from clinical

management system to COVID-19 vaccination records from the Department of Health (DH),

The Government of the HKSAR. Incident Bell's palsy was defined as the first diagnosis in the

database using the International Classification of Diseases, ninth revision, clinical modification

codes 351.0, 351.8, and 351.9.

Nested case-control analysis

Cases were defined as patients with a first primary diagnosis of Bell's palsy in the emergency room or inpatient setting between March 6 and July 31, 2021. Patients attending HA emergency rooms or hospitalized during the same period without being diagnosed with Bell's palsy were selected as controls. Patients aged below 16 years, those with a history of Bell's palsy or vaccination of CoronaVac were excluded from the analysis. Up to ten controls were randomly matched with each case according to sex, age, Charlson comorbidity index , and date of attendance of emergency room or hospitalization. Vaccine recipients were defined as patients who received the first or second dose of vaccine on or 28 days before the date of first diagnosis of Bell's palsy for cases, and the date of the hospitalization or emergency room visit for controls.

Self-controlled case series analysis

The SCCS has been applied in several studies of evaluation of COVID-19 vaccine safety[27-33]. Individuals who were aged 16 or above and had at least one episode of Bell's palsy in the emergency room or as a primary diagnosis in the hospital admission records between March 6 and July 31, 2021 were included in the analysis. Patients with vaccination of CoronaVac during the observation period were excluded. To satisfy the assumptions of SCCS, we applied extension of SCCS model including unvaccinated individuals with Bell's palsy and considered first incidence of a specific AESI during observation period. Details are shown in the Supplementary Information.

The individual observation period started on March 6, 2021 and ended on July 31, 2021. We divided the observation period into five discrete periods: 1) day 0-13 after first dose, 2) day 14-27 after first dose (i.e. day 14 to day 27 for people with single dose only; day 14 to the day

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before the second dose but up to 27 days for people with two doses of vaccination), 3) day 0-13 after second dose, 4) day 14-27 after second dose, and 5) baseline period (i.e. any other periods that do not fall into the above risk windows). A graphical representation of the study design timeline of a single hypothetical participant is illustrated in Figure 1. Some eligible individuals did not receive the second dose of the vaccinations within the observation period so the time after risk window 2 were considered as baseline period.

A total of 88 matched sets (one case and ten controls) and 71 was required for the nested case-control and SCCS analyses, respectively. A detailed sample size calculation for nested case-control and SCCS analyses is provided in Supplementary Figures 1 and 2.

Statistical analysis

Nested case-control analysis

Conditional logistic regression was applied to estimate the association between the vaccine and risk of Bell's palsy, with the adjustment for patient characteristics, including smoking status, medical history (diabetes mellitus, hypertension, asthma, neoplasms, acute respiratory infections, viral infections, rheumatoid arthritis, stroke or systemic embolism, Guillain-Barré syndrome, migraine and herpes zoster infection), and medication use in the past 90 days (antiviral drugs, systemic corticosteroids, antibacterial drugs, immunosuppressants, lipid lowering agents). Adjusted odds ratio (OR) and 95% confidence interval (CI) were calculated to quantify the risk of Bell's palsy. Events before and after the second dose were individually analyzed in two additional analyses. Subgroup analysis was conducted according to sex (male and female) and age groups (<60; ≥60 years old).

Self-controlled case series analysis

SCCS extension for event dependent exposure was applied using the R function "eventdepenexp" in the R-package "SCCS"[34]. Season of the year was adjusted in monthly categories. The adjusted incidence rate ratio (IRR) and its corresponding 95% CIs were estimated by comparing the rates of Bell's palsy in different risk windows with that in baseline period using conditional Poisson regression.

In both nested case-control and SCCS analyses, we conducted a sensitivity analysis by excluding patients with a subsequent diagnosis of stroke or Ramsay Hunt Syndrome after incident diagnosis of Bell's palsy to avoid any potential risk of misdiagnosis of Bell's palsy. As suggested by a recent study, herpes zoster infection is one of the potential causes of facial-nerve palsy[8]. Hence, another sensitivity analysis was conducted by excluding patients with a history of herpes zoster infection or were prescribed antiviral medications in the past 90 days prior to the incident diagnosis of Bell's palsy. Finally, we also excluded the patients with COVID-19 infection during the observation period in order to minimize the effect of COVID-19 infection. Post-hoc analysis by extending the risk periods to 42 days to investigate the risk of Bell's palsy in 28-41 days after vaccination was performed.

All statistical tests were two-sided and p values of less than 0.05 were considered significant. Statistical analysis was conducted using R version 4.0.3. At least two investigators (EYFW, VWSN, YW, VKCY and MF) independently did the statistical analyses for each study design for quality assurance.

Ethical approval

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

Results

After excluding 1) 45 people with different vaccine types between first and second doses, 2) 1,655 people with second dose record but without first dose record, and 3) 16 people with inconsistent duplicated records, 1,957,612 individuals have been recorded to have received their first dose of BNT162b2 between March 6 and July 31, 2021. Amongst them, 1,451,858 (74.2%) individuals received both doses of BNT162b2. A total of 3,409,470 doses of BNT162b2 were administered. The number of first diagnosis of Bell's palsy within 28 days after first or second dose of BNT162b2 vaccinations was 54 out of 80 cases (67.5%) after vaccination (Figure 2). Hence, the incidence of Bell's palsy was 1.58 (95% CI:1.19-2.07) per 100,000 doses of BNT162b2 vaccine administered.

Nested case-control analysis

The selection flow for cases and matched controls is summarized in Figure 3. A total of 517 cases and 4,945 matched controls were identified. The characteristics of cases and controls by vaccine exposure are shown in Supplementary Table 2 and 3. There were 54 cases and 348 controls receiving BNT162b2. There were significant positive associations between vaccination group and Bell's palsy (Adjusted OR: 1.543;95% CI:1.123-2.121;Table 2). Findings from the

additional analyses demonstrated a significantly increased risk during the first 14 days following the second dose (Adjusted OR: 2.325;95% CI:1.414-3.821) of BNT162b2 vaccination. However, the risk of Bell's palsy was not significantly increased in the 0-13 and 14-27 days after first dose and 14-27 days after second dose of BNT162b2 vaccine. Results from the subgroup and sensitivity analyses reported similar findings (see Supplementary Tables 4-7).

Self-controlled case series analysis

A total of 529 patients who had their incident primary diagnosis of Bell's palsy either at the inpatient or emergency setting were included in the analysis (Figure 3). The patients' demographics and baseline comorbidities were summarized in Supplementary Table 8.

Compared to the baseline period, the risk of Bell's palsy was approximately 2.4-fold higher during the first 14 days after the second dose of BNT162b2 vaccination (IRR=2.44;95% CI:1.32-4.50) while no association was found in other risk windows. The details of the results are illustrated in Table 2. Results of the sensitivity analyses remained robust and did not change the overall findings (Supplementary Table 9).

Post-hoc analysis

The nested case control analysis showed an insignificant risk of Bell's palsy 28-41 days after first or second dose (Supplementary Table 10). The SCCS analysis showed a significant risk of Bell's palsy in 28-41 days after first dose (IRR: 13.54;95% CI:1.93-94.87) but not after second dose (Supplementary Table 11). The reason is clear that 95% of vaccine recipients received second dose within 28 days after first dose in the current study. Since only one event occurred in this period, it

was sufficient to produce a significant result due to a very short follow-up time (0.64 person-years in 28-41 days after first dose and without the second dose).

Discussion

The risk of Bell's palsy was found to increase following BNT162b2 vaccination using both between and within individual comparison study designs. Based on the incidence of Bell's palsy of 3.16 (2*1.58) per 100,000 people vaccinated with two doses and the relative risks of 1.543 in nested case-control analysis, there is an excess 1.112 events per 100,000 people receiving two doses of BNT162b2. To the best of our knowledge, our study is the first to investigate the risk of Bell's palsy following the first and second doses of BNT162b2 vaccine. We observed a higher risk in first 14 days after the second dose compared to the other risk period using two different methods. Although the booster dose of COVID-19 vaccines is already rolled out to increase the levels of immunity against new variants of COVID-19 in several countries, there are still uncertainties as to whether the booster dose would uplift the risk and thus lay down concerns in public health. It is important to conduct further studies to evaluate the risk of Bell's palsy before vaccination of booster dose is fully implemented in the general public.

While the randomized controlled trials of BNT162b2 obtained higher incidence of Bell's palsy in vaccinated group compared to control group and did not yield statistical significant results, the United States Food and Drug Administration(FDA) stated in the report that the frequency of the observed incident was similar to the background rate[2]. However, the result was not adjusted for the follow-up time, and thus the conclusion is debatable[4]. Nevertheless, the FDA did not exclude the possibility of a causal relationship and urged further study on the risk of Bell's palsy

after vaccination in larger population[2]. Randomized controlled trials often recruit relatively healthy individuals due to stringent inclusion criteria, and thus findings may not be fully generalizable to more diverse populations. Furthermore, the limited size of the study population may not provide sufficient power to reveal outcomes of rare occurrence. Although a disproportionality analysis using the WHO Pharmacovigilance Database later revealed that the reporting rate of facial paralysis incidence after mRNA COVID-19 vaccination was not higher than that in other viral vaccines[6], previous studies showed a positive association between Bell's palsy and some viral vaccines such as parenteral seasonal influenza vaccines and the influenza A (H1N1) inactivated monovalent pandemic vaccine[35, 36]. Besides, this database relied on self-reported cases by healthcare professionals and the public, it lacked the capacity to take other confounding risk factors into account. Hence, this indirect evidence may not conclude the risk of Bell's palsy between people with and without mRNA COVID-19 vaccination. Another small nested case-control study which conducted on 37 patients who developed Bell's palsy following vaccinations (of which 21 patients received BNT162b2 vaccine) with 74 matched controls (44 patients received BNT162b2 vaccine) in Israel also showed no association between Bell's palsy and BNT162b2[37]. A further cohort study using Israel population reported a non-significant increased risk of Bell's palsy after BNT162b2 vaccination with a risk ratio of 1.32 (95% CI:0.92-1.86), but they acknowledged that the results may be limited to confounding and selection bias[8]. Another cohort study in the United States showed no association (Adjusted rate ratio:1.00;95% CI:0.86-1.17) between risk of Bell's palsy and mRNA vaccines (BNT162b2/ mRNA-1273)[9], but their study was limited to low statistical power[9]. The SCCS analysis performed in this study can eliminate both measured and unmeasured time-invariant confounding factors, such as family history, genetic factors and underlying disease severity.

Moreover, our study with larger sample size and number of events possessed sufficient power to detect the lowest OR of 1.3 in nested case-control analysis and the lowest IRR of 2.0 in SCCS analysis. Indeed, a previous ecological analysis deduced similar relative risk of 1.5- to 3-times higher for COVID-19 mRNA vaccines associated with the risk of Bell's palsy compared to our estimation[3, 4]. Given the similar relative risk and trend in dose analysis from different study designs, results from this study should provide robust evidence.

The exact pathophysiology of Bell's palsy remains unclear. It has been speculated that the cause may be due to a combination of factors including autoimmune reaction, viral and innate immune activation[1]. An evaluation of COVID-19 vaccine immunogenicity in Hong Kong showed that the antibody concentrations increased substantially following both the first and second doses of BNT162b2[38]. Such drastic increase in antibody concentrations caused by the triggering of immune system may potentially lead to the development of Bell's palsy. A recent cohort study in Israel suggested that BNT162b2 increased the risk of herpes zoster infection, which is a potential cause of facial-nerve palsy[8]. However, in our study, no patient was diagnosed with herpes zoster infection between the date of first dose and the date of incident diagnosis of Bell's palsy. The results of the sensitivity analysis by excluding patients with a history of herpes zoster or were previously prescribed antiviral drugs showed similar findings as the primary analyses in both study designs. Hence, herpes zoster cannot explain the association between Bell's palsy and BNT162b2 vaccines in our study.

There are several limitations that need to be acknowledged in this study. The HA clinical management system only captures patients who have used HA services, e.g. public hospitals and

emergency room. However, HA covers over 70% of hospitalizations. Besides, HA is the major healthcare service provider of affordable care, and thus the vast majority of the patients were likely to be included in our study. Apart from the database limitation, there are some limitations on the study designs. Firstly, the control group in a nested case-control analysis may be misclassified and potentially bias the results. However, the incidence of Bell's palsy with the estimation of approximately 27 new cases per 100,000 person-years in Hong Kong is relatively low[1], therefore the chance of misclassification in control group should be minimal and would not affect our estimates. Secondly, like other observational studies using between-individual comparisons, there might be some important unmeasured confounders (e.g. socioeconomic status and educational level), which could bias the results. However, SCCS as a within-individual comparison, can eliminate both measured and unmeasured time-invariant confounding factors, the results from both study designs are similar and support the robustness of the results. Lastly, the arrangement of booster dose of COVID-19 vaccinations was not yet rolled out during the inclusion period in this study. Besides, our study only included patients with a new diagnosis of Bell's palsy in Hong Kong. Moreover, due to short observation period, seasonal association cannot be evaluated. Hence, further studies are warranted by including booster dose of vaccination, patients with history of Bell's palsy, longer observational period and in other populations with different ethnicities to confirm the generalizability of our findings.

Conclusion

This study found an overall increased risk of Bell's palsy following BNT162b2 vaccinations, particular in the first 14 days after vaccination. It appears that herpes zoster infection cannot explain the association between Bell's palsy and COVID-19 vaccinations in our study. As Bell's

palsy is a rare and largely self-limiting adverse event, the benefits from COVID-19 vaccination still outweigh the small risk of Bell's palsy. However, continuous monitoring of the adverse events related to COVID-19 vaccines should be conducted.

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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, VWSN, WY, VKCY, MF conducted statistical analysis. EYFW, VWSN and ICKW wrote the first draft of the manuscript. EYFW, CSLC, VWSN, WY and VKCY 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. VWSN, ICHL, WY, VKCY, MF, FTTL, EWYC, XL, CKHW, RKCC, BJC, WCF, AYLL, CKL, LSTC, DL, KKL, IFNH, CSL 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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Figure legends

Figure 1. Pictorial illustration of a hypothetical patient in the self-controlled case series analysis

Figure 2. Distribution of the time of onset of Bell's palsy after the most recent dose of

BNT162b2 vaccination

Figure 3. Flowchart of inclusion and exclusion criteria in the nested case-control analysis and

self-controlled case series analysis

Table 1. Risk of Bell's palsy among patients in the nested case-control analysis

	Case (N=517)	Control (N=4945)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Total				
Not vaccinated	463	4597		
BNT162b2	54	348	1.559 (1.136 - 2.141)	1.543 (1.123 - 2.121)
Additional analysis				
Events after first dose and before second dose				
0-13 days				
Not vaccinated	463	4292		
BNT162b2	18	104	1.491 (0.889 - 2.5)	1.471 (0.876 - 2.468)
14-27 days				
Not vaccinated	463	4222		
BNT162b2	8	49	1.382 (0.647 - 2.953)	1.354 (0.634 - 2.891)
Events after second dose				
0-13 days				
Not vaccinated	463	4337		
BNT162b2	22	91	2.315 (1.411 - 3.799)	2.325 (1.414 - 3.821)
14-27 days				
Not vaccinated	463	4205		
BNT162b2	6	56	0.884 (0.373 - 2.097)	0.871 (0.366 - 2.073)

Cases and controls were matched according to age, sex, admission date and Charlson Comorbidity Index. Odds ratios for Bell's palsy events were estimated by conditional logistic regression adjusted for smoking status, medical history (diabetes mellitus, hypertension, asthma, neoplasms, acute respiratory infections, viral infections, rheumatoid arthritis, stroke or systemic embolism, Guillain-Barré syndrome, migraine, and herpes zoster) and medication use in the past 90 days (antiviral drugs, systemic corticosteroids, antibacterial drugs, immunosuppressants, lipid lowering agents). CI denotes confidence interval.

Table 2. Results of self-controlled case series analysis

Risk periods	Number of events	Person-years	Incidence rate ratio† (95% CI)
Extension for the SCCS model: Event-dependent exposure			
BNT162b2 (n=529)			
0 to 13 days after first dose	18	4.51	1.21 (0.66-2.20)
14 to 27 days after first dose	8	2.74	1.18 (0.49-2.83)
0 to 13 days after second dose	22	3.00	2.44 (1.32-4.50)
14 to 27 days after second dose	6	2.52	0.97 (0.37-2.58)
Baseline	475	201.58	--

†Incidence rate ratio was conducted by conditional Poisson regression and adjusted with seasonal effect. CI=Confidence interval;