Adverse event reporting and Bell's palsy risk after COVID-19 vaccination – Authors’ Reply

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Selection bias may overestimate the risk of Bell’s palsy following COVID-19 vaccination – Reply

Chang et al. suggested that the possibility of selection bias in our nested case-control study could be due to potential control subjects (i.e., patients admitted to emergency rooms or hospital wards) being older than all subjects eligible for vaccination in the general population\textsuperscript{1}. However, as we used a matched case-control study design, this concern is irrelevant. As stated in our methods, we matched each case with a control using the exact year of age in our analysis. Hence, the hypothetical example for potential selection bias referred to by Chang et al. does not apply to our study.

We acknowledge that the health condition of subjects eligible for vaccination may be relatively healthier compared to our control subjects. A possible reason is that relatively healthy individuals with high-risk occupations were given priority for vaccination in the rollout schedule of the vaccination programme in Hong Kong, which is included in our article\textsuperscript{2}. We addressed this in our analysis by adjusting baseline characteristics including comorbidities and concurrent medications use. Therefore, such characteristics should not have had a significant effect on our results or conclusions. To further address Chang et al.’s concern on the difference in baseline characteristics between cases and controls\textsuperscript{1}, we conducted further post-hoc sensitivity analysis by excluding control subjects with neoplasms or exposure to antibacterial drugs, where there were substantial differences between cases and controls (neoplasm: 5\% vs 13\%; antibacterial drugs: 7\% vs 13\% in Table 2 in our published study\textsuperscript{2}). Table 1 showed that the results were similar with the main findings, which further supports the robustness of our study.

As in the case for all observational study, the effect of unmeasured confounding in our nested case-control study cannot be completely ruled out. In recent years, the self-controlled case series (SCCS) method has become a popular alternative study design for drug safety studies\textsuperscript{3}. It was specifically developed to evaluate vaccine safety with the advantage of reduced unmeasured confounding through the comparisons within individuals\textsuperscript{4,5}. Due to the small number of events and a short follow-up period in our previous study, we were unable to apply such a method. We appreciate Chang et al.’s interest in our study, and as stated in our paper, further study should be warranted to confirm our findings.

\textit{(current words: 372; max.: 400)}

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Conflict of interest:

ICKW reports research funding outside the submitted work from Amgen, Bristol-Myers Squibb, Pfizer, Janssen, Bayer, GSK, Novartis, the Hong Kong RGC, and the Hong Kong Health and Medical Research Fund, National Institute for Health Research in England, European Commission, National Health and Medical Research Council in Australia, and also...
received speaker fees from Janssen and Medice in the previous 3 years. He is also an independent non-executive director of Jacobson Medical in Hong Kong. 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. XL has received research grants from the Food and Health Bureau of the Government of the Hong Kong SAR, research and educational grants from Janssen and Pfizer; internal funding from University of Hong Kong; consultancy fee from Merck Sharp & Dohme, unrelated to this work. EWYC reports honorarium from Hospital Authority, grants from Research Grants Council (RGC, Hong Kong), grants from Research Fund Secretariat of the Food and Health Bureau, grants from National Natural Science Fund of China, grants from Wellcome Trust, grants from Bayer, grants from Bristol-Myers Squibb, grants from Pfizer, grants from Janssen, grants from Amgen, grants from Takeda, grants from Narcotics Division of the Security Bureau of HKSAR, outside the submitted work.

Reference

1. Chang KC, Kong FY. Selection bias may overestimate the risk of Bell’s palsy following COVID-19 vaccination. The Lancet Infectious Diseases 2021.
2. Wan EYF, Chui CSL, Lai FTT, et al. Bell’s palsy following vaccination with mRNA (BNT162b2) and inactivated (CoronaVac) SARS-CoV-2 vaccines: a case series and nested case-control study. The Lancet Infectious Diseases 2021.
Table 1. Sensitivity analysis excluding control subjects with neoplasms or antibacterial drugs used in the nested case-control study.

<table>
<thead>
<tr>
<th></th>
<th>Number of case patients (N=295&lt;sup&gt;†&lt;/sup&gt;)</th>
<th>Number of controls (N=908)</th>
<th>Crude odds ratio (95% CI)</th>
<th>P-value</th>
<th>Adjusted odds ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not vaccinated</td>
<td>253 (86%)</td>
<td>828 (91%)</td>
<td>(Ref)</td>
<td>(Ref)</td>
<td></td>
<td>(Ref)</td>
</tr>
<tr>
<td>CoronaVac</td>
<td>28 (9%)</td>
<td>50 (6%)</td>
<td>2.049 (1.221 - 3.438)</td>
<td>0.0066</td>
<td>2.196 (1.293 - 3.728)</td>
<td>0.0036</td>
</tr>
<tr>
<td>BNT162b2</td>
<td>14 (5%)</td>
<td>30 (3%)</td>
<td>1.636 (0.842 - 3.178)</td>
<td>0.15</td>
<td>1.745 (0.888 - 3.430)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

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, rheumatoid arthritis, stroke, migraine, infections in the past 90 days (acute respiratory infections), and medication use in the past 90 days (antiviral drugs, systemic corticosteroids, immunosuppressants).

<sup>†</sup>Three cases were excluded as the corresponding controls were excluded due to neoplasms or antibacterial drugs used.